



(86) Date de dépôt PCT/PCT Filing Date: 2015/12/14
(87) Date publication PCT/PCT Publication Date: 2016/06/23
(85) Entrée phase nationale/National Entry: 2017/06/16
(86) N° demande PCT/PCT Application No.: US 2015/065497
(87) N° publication PCT/PCT Publication No.: 2016/100184
(30) Priorités/Priorities: 2014/12/16 (US62/092,702);
2015/05/28 (US62/167,706)

(51) Cl.Int./Int.Cl. *A61K 31/519* (2006.01),
A61P 25/22 (2006.01)
(71) Demandeur/Applicant:
AXOVANT SCIENCES GMBH, CH
(72) Inventeurs/Inventors:
ACHARYA, RAKSHA, US;
BURNETT, DUANE A., US;
BURSAVICH, MATTHEW GREGORY, US;
COOK, ANDREW SIMON, US;
HARRISON, BRYCE ALDEN, US;
KOENIG, GERHARD, US;
MCRINER, ANDREW J., US
(74) Agent: RIDOUT & MAYBEE LLP

(54) Titre : COMPOSES AMIDE DE QUINUCLIDINE A SUBSTITUANTS GEMINAL, EN TANT QU'AGONISTES DES
RECEPTEURS NICOTINIQUES DE L'ACETYLCHOLINE ?
(54) Title: GEMINAL SUBSTITUTED QUINUCLIDINE AMIDE COMPOUNDS AS AGONISTS OF ALPHA-7 NICOTINIC
ACETYLCHOLINE RECEPTORS

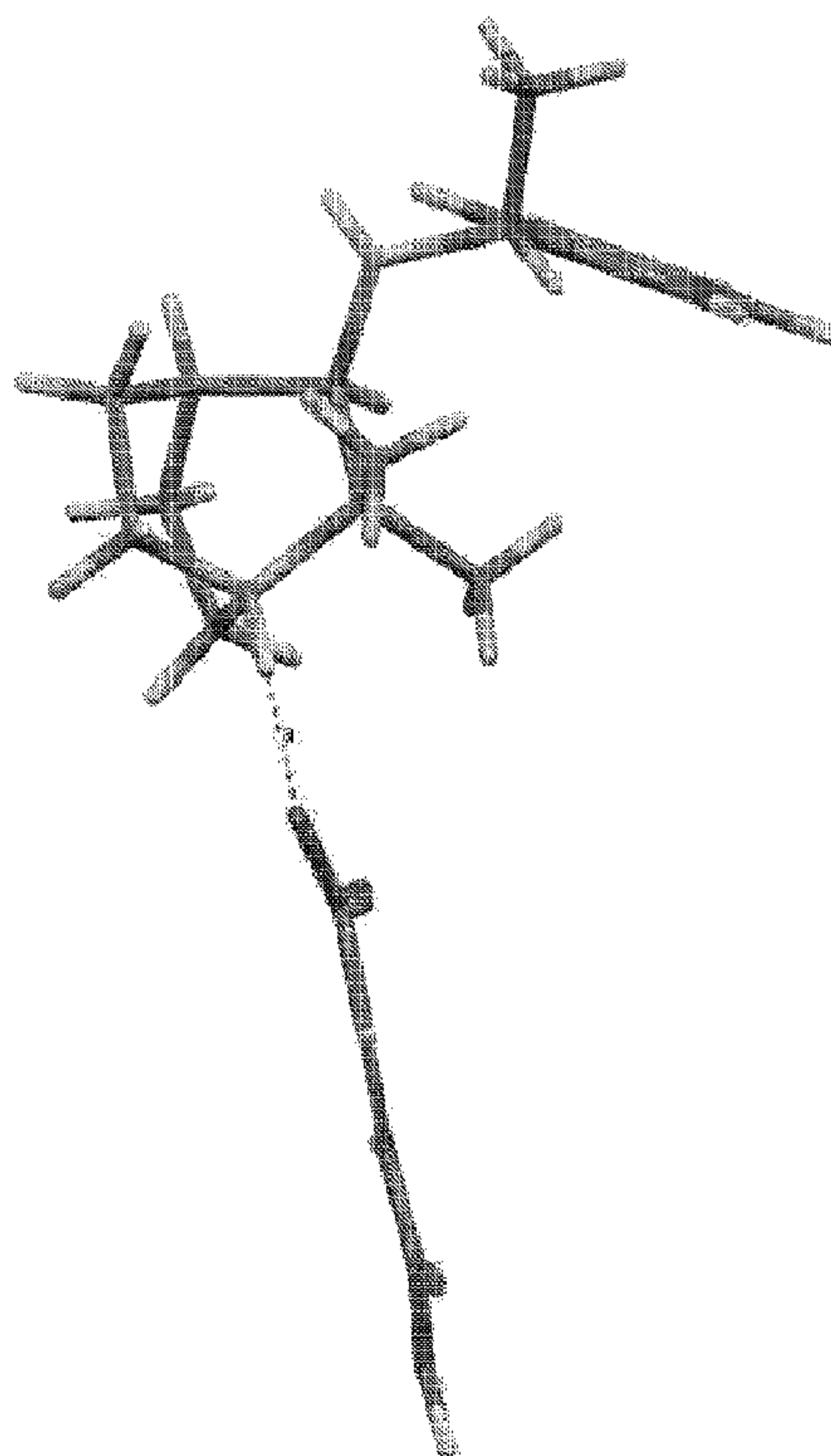


FIGURE 1

(57) Abrégé/Abstract:

The present invention relates to novel geminal substituted quinuclidine amide compounds, and pharmaceutical compositions of the same, that are suitable as agonists or partial agonists of $\alpha 7$ - nAChR, and methods of preparing these compounds and compositions, and the use of these compounds and compositions in methods of maintaining, treating and/or improving cognitive function. In particular, methods of administering the compound or composition to a patient in need thereof, for example a patient with a cognitive deficiency and/or a desire to enhance cognitive function, that may derive a benefit therefrom.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau(10) International Publication Number
WO 2016/100184 A1(43) International Publication Date
23 June 2016 (23.06.2016)

- (51) International Patent Classification:
A61K 31/519 (2006.01) *A61P 25/22* (2006.01)
- (21) International Application Number:
PCT/US2015/065497
- (22) International Filing Date:
14 December 2015 (14.12.2015)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
62/092,702 16 December 2014 (16.12.2014) US
62/167,706 28 May 2015 (28.05.2015) US
- (71) Applicant: **FORUM PHARMACEUTICALS, INC.**
[US/US]; 225 Second Avenue, Waltham, MA 02451 (US).
- (72) Inventors: **ACHARYA, Raksha**; 2 Glen Ora Drive, Bedford, MA 01730 (US). **BURNETT, Duane, A.**; 19 Sherman Bridge Road, Wayland, MA 01778 (US). **BURSAVICH, Matthew, Gregory**; 172 Damon Road, Needham, MA 02494 (US). **COOK, Andrew, Simon**; 9

October Lane, Stow, MA 01775 (US). **HARRISON, Bryce, Alden**; 7 Old Wood Road, Framingham, MA 01701 (US). **KOENIG, Gerhard**; 1662 Commonwealth Avenue, Newton, MA 02465 (US). **MCRINER, Andrew, J.**; 31 Lynde Street, Melrose, MA 02176 (US).

(74) Agents: **SHARER, Paul, L.** et al.; Jones Day, 222 East 41st Street, New York, NY 10017 (US).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH,

[Continued on next page]

(54) Title: GEMINAL SUBSTITUTED QUINUCLIDINE AMIDE COMPOUNDS AS AGONISTS OF ALPHA-7 NICOTINIC ACETYLCHOLINE RECEPTORS

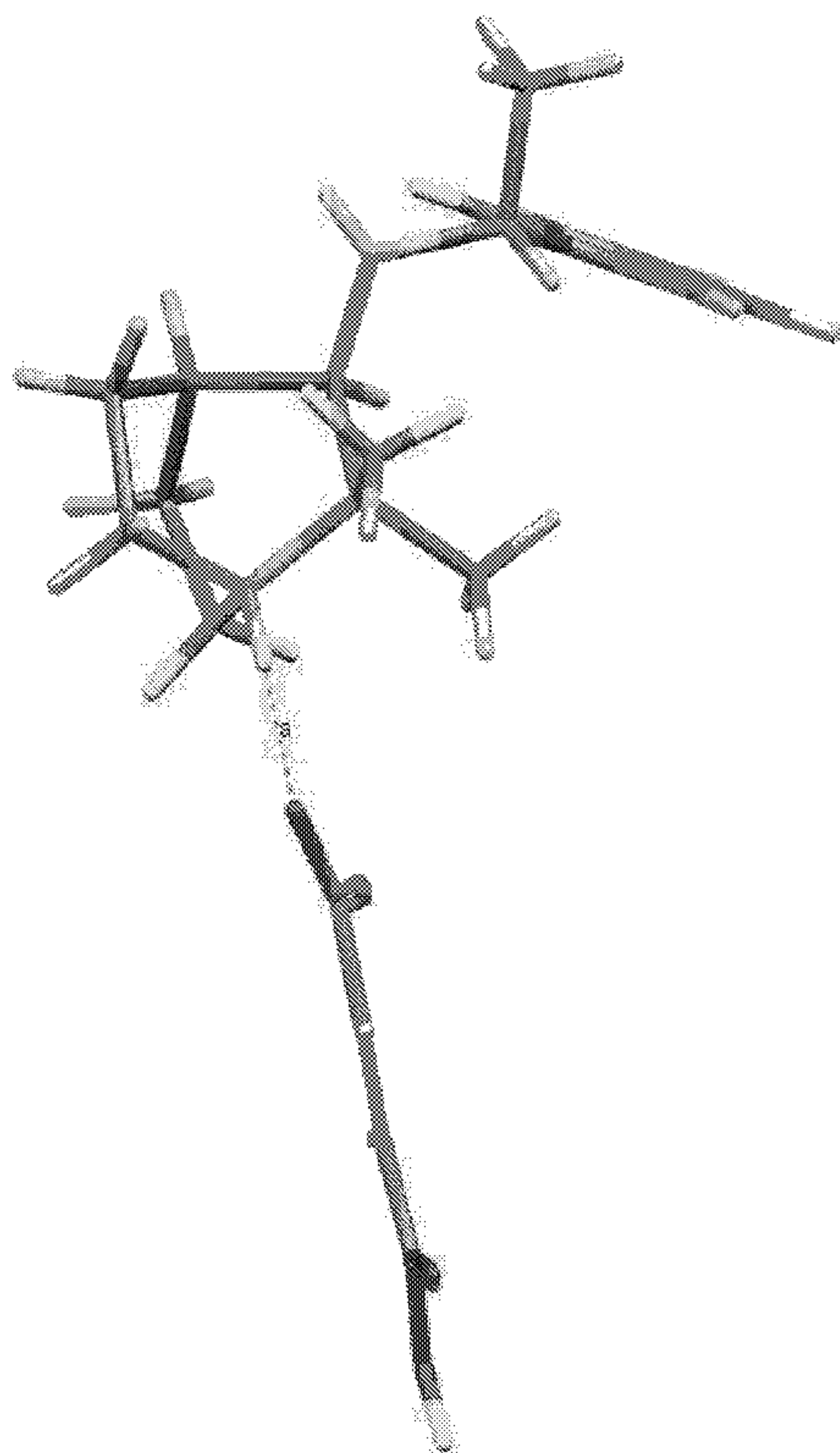


FIGURE 1

(57) Abstract: The present invention relates to novel geminal substituted quinuclidine amide compounds, and pharmaceutical compositions of the same, that are suitable as agonists or partial agonists of $\alpha 7$ - nAChR, and methods of preparing these compounds and compositions, and the use of these compounds and compositions in methods of maintaining, treating and/or improving cognitive function. In particular, methods of administering the compound or composition to a patient in need thereof, for example a patient with a cognitive deficiency and/or a desire to enhance cognitive function, that may derive a benefit therefrom.

WO 2016/100184 A1

WO 2016/100184 A1

GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

DEMANDE OU BREVET VOLUMINEUX

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NOTE POUR LE TOME / VOLUME NOTE:

**GEMINAL SUBSTITUTED QUINUCLIDINE AMIDE COMPOUNDS AS AGONISTS OF
ALPHA-7 NICOTINIC ACETYLCHOLINE RECEPTORS**

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority from U.S. Provisional Application No. 62/092,702, filed December 16, 2014, and from U.S. Provisional Application No. 62/167,706, filed May 28, 2015. Each of the foregoing related applications, in their entirety, are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to novel geminal substituted quinuclidine amide compounds, and pharmaceutical compositions of the same, that are suitable as agonists or partial agonists of $\alpha 7$ -nAChR, and methods of preparing these compounds and compositions, and the use of these compounds and compositions in methods of maintaining, treating and/or improving cognitive function. In particular, methods of administering the compound or composition to a patient in need thereof, for example a patient with a cognitive deficiency and/or a desire to enhance cognitive function, that may derive a benefit therefrom.

BACKGROUND OF THE INVENTION

[0003] The prevalence of cognitive disease, for example dementia in North America, is approximately 6 to 10% of the population, with Alzheimer's disease accounting for a substantial portion of these cases. Many forms of cognitive disease represent a steadily growing medical and social problem of our aging societies around the World. Some believe the main pathological features may relate to intraneuronal neurofibrillary tangles, formation of amyloid beta plaques and/or neurodegeneration of mainly cholinergic and, in later stages, also serotonergic, noradrenergic, and other neurons, resulting in deficiencies of acetylcholine and other neurotransmitters. Some theories suggest that the gradual development of an acetylcholine signaling deficiency may be responsible for the early clinical manifestations of cognitive disease. Consequently, some believe that compounds that improve cholinergic functioning, such as acetylcholine esterase inhibitors may ameliorate the cognitive deficits in patients with cognitive disease. The most widely used acetylcholine esterase inhibitor is donepezil hydrochloride (Aricept®).

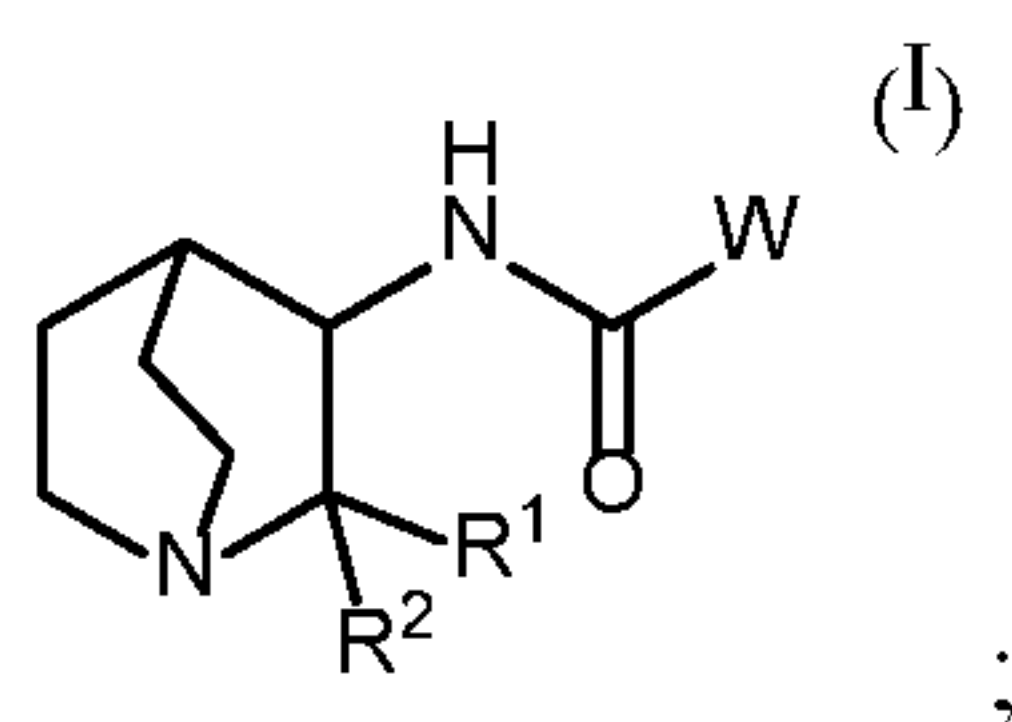
[0004] Nicotinic acetylcholine receptors (nAChR) form a large family of ion channels which are activated by the messenger acetylcholine which is produced in the body (Galzi and Changeux, Neuropharmacol. 1995, 34, 563-582). A functional nAChR consists of five subunits which may be different (certain combinations of $\alpha 1-9$ and $\beta 1-4, \gamma, \delta, \epsilon$ subunits) or identical ($\alpha 7-9$). This leads to the formation of a diversity of subtypes which differ in the distribution in the muscles, the nervous system

and other organs (McGehee and Role, *Annu. Rev. Physiol.* 1995, 57, 521-546). Activation of nAChR leads to influx of cations into the cell and to stimulation of nerve cells or muscle cells. Selective activation of individual nAChR subtypes restricts this stimulation to the cell types which have a corresponding subtype and is thus able to avoid unwanted side effects such as, for example, stimulation of nAChR in the muscles. Clinical experiments with nicotine and experiments in various animal models indicate that central nicotinic acetylcholine receptors are involved in learning and memory processes (e.g. Rezvani and Levin, *Biol. Psychiatry* 2001, 49, 258-267). Nicotinic acetylcholine receptors of the $\alpha 7$ subtype ($\alpha 7$ nAChR) have a particularly high concentration in regions of the brain which are important for learning and memory, such as the hippocampus and the cerebral cortex (Séguéla et al., *J. Neurosci.* 1993, 13, 596-604). The $\alpha 7$ nAChR has a particularly high permeability for calcium ions, modulates neurotransmission, influences the growth of axons and, in this way, modulates neuronal plasticity (Broide and Leslie, *Mol. Neurobiol.* 1999, 20, 1-16).

[0005] WO 2003/055878 describes a variety of agonists of the $\alpha 7$ nAChR said to be useful for improving cognition. WO 2003/055878 suggests that certain agonists of the $\alpha 7$ nAChR are useful for improving perception, concentration, learning or memory, especially after cognitive impairments like those occurring for example in situations/diseases/syndromes such as mild cognitive impairment, age-associated learning and memory impairments, age-associated memory loss, Alzheimer's disease, schizophrenia and certain other cognitive disorders.

BRIEF SUMMARY OF THE INVENTION

[0006] An aspect of the invention provides a geminal substituted quinuclidine amide compound represented by Formula (I):



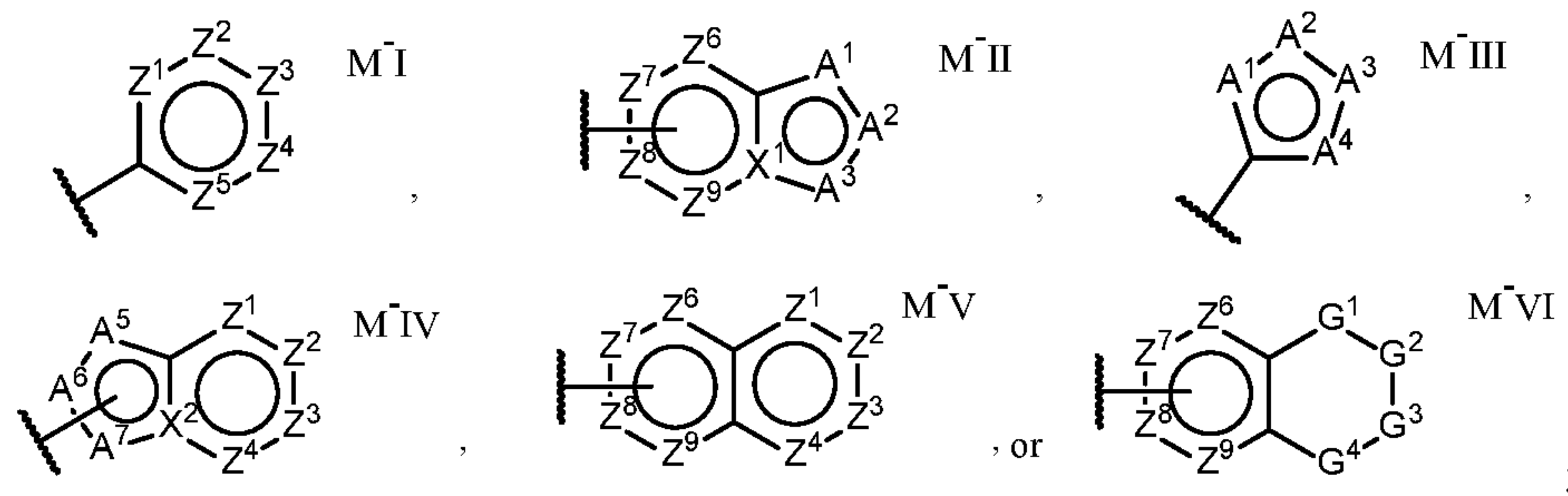
wherein:

- R¹ and R² independently represent a branched or unbranched C₁-C₄-alkyl radical; or the C(R¹)(R²) moiety forms a (3-4 membered)-carbocycle, wherein R¹ and R² taken together represent a C₂-C₃-alkyl di-radical; wherein the C₁-C₄-alkyl radical and the C₂-C₃-alkyl di-radical may be substituted with up to 4 radical substituents comprising: -D, -F, -Cl, -Br, -I, -CN, CH₃, CH₂CH₃, =O, -OR³, or -OCF₃;
- R³ independently represents -H; a branched or unbranched C₁-C₄-alkyl radical; C₃-C₄-cycloalkyl radical; wherein the C₁-C₄-alkyl radical and the C₃-C₄-cycloalkyl radical may be substituted with up to 4 radical

substituents comprising: $-\text{D}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{CN}$, $=\text{O}$, $-\text{OH}$, $-\text{OC}_1\text{-C}_4\text{-alkyl}$ or $-\text{OCF}_3$; and

W

represents a moiety represented by ring system M-I, M-II, M-III, M-IV, M-V, or M-VI:



wherein:

Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 independently represent N or CR^4 ; with the proviso that no more than two of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are N;

R^4 independently represents $-\text{H}$; $-\text{D}$; $-\text{F}$; $-\text{Cl}$; $-\text{Br}$; $-\text{I}$; $-\text{CN}$; $-\text{NO}_2$; $-\text{OR}^5$; $-\text{N}(\text{R}^5)(\text{R}^6)$; $-\text{SO}_2(\text{CH}_2)_m\text{R}^5$; $-(\text{CO})(\text{CH}_2)_m\text{R}^5$; $-(\text{CO})\text{N}(\text{R}^5)(\text{R}^6)$; $-\text{OCF}_3$; a $\text{C}_1\text{-C}_6\text{-alkyl}$ radical; a $\text{C}_1\text{-C}_6\text{-haloalkyl}$ radical; a $\text{C}_3\text{-C}_6\text{-cycloalkyl}$ radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; or a heteroaryl radical; or when adjacent members of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 is $(\text{CR}^4)(\text{CR}^4)$, the $(\text{CR}^4)(\text{CR}^4)$ may form a cycle such that the adjacent R^4 substituents taken together represents a (3-6 membered)-heteroalkyl di-radical with at least one ring atom of the (3-6 membered)-heteroalkyl di-radical selected from the group consisting of oxygen, nitrogen, and sulfur, with the proviso that when the at least one ring atom is nitrogen, the nitrogen is substituted with $-\text{H}$, a branched or unbranched $\text{C}_1\text{-C}_4\text{-alkyl}$ radical, a $\text{C}_3\text{-C}_4\text{-cycloalkyl}$ radical, $-(\text{CO})$ -branched or unbranched $\text{C}_1\text{-C}_4\text{-alkyl}$, or $-(\text{SO}_2)$ -branched or unbranched $\text{C}_1\text{-C}_4\text{-alkyl}$, wherein the $\text{C}_1\text{-C}_4\text{-alkyl}$ radical and the $\text{C}_3\text{-C}_4\text{-cycloalkyl}$ radical may be substituted with up to 4 radical substituents comprising: $-\text{D}$, halogen, $=\text{O}$, $-\text{OH}$, $-\text{OC}_1\text{-C}_4\text{-alkyl}$ or $-\text{OCF}_3$, and with the further proviso that when the at least one ring atom is sulfur, the sulfur may substituted with 0 or 2 $=\text{O}$; wherein the $\text{C}_1\text{-C}_6\text{-alkyl}$ radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, the heteroaryl radical, and the alkyl portion of the (3-6 membered)-heteroalkyl di-radical, may be substituted with up to 4 radical substituents comprising: $-\text{D}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}^5$, $-(\text{CH}_2)_m\text{OR}^5$, $-\text{N}(\text{R}^5)(\text{R}^6)$, $-(\text{CH}_2)_m\text{N}(\text{R}^5)(\text{R}^6)$, $-\text{SO}_2(\text{CH}_2)_m\text{R}^5$, $-(\text{CO})(\text{CH}_2)_m\text{R}^5$, $-(\text{CO})\text{N}(\text{R}^5)(\text{R}^6)$, $-\text{OCF}_3$, a branched or unbranched $\text{C}_1\text{-C}_4\text{-alkyl}$ radical, or a $\text{C}_3\text{-C}_4\text{-cycloalkyl}$ radical;

- C₆-alkyl radical, a C₃-C₆-cycloalkyl radical, a C₁-C₆-hydroxyalkyl radical, or a C₁-C₆-haloalkyl radical;
- R⁵ and R⁶ independently represent -H; a branched or unbranched C₁-C₆-alkyl radical; a C₃-C₆-cycloalkyl radical; or the N(R⁵)(R⁶) moiety forms a cycle, wherein R⁵ and R⁶ taken together represent a C₂-C₆-alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;
- Z⁶, Z⁷, Z⁸, and Z⁹ independently represent N or CR⁷; with the proviso that no more than two of Z⁶, Z⁷, Z⁸, and Z⁹ are N;
- R⁷ independently represents -H; -D; -F; -Cl; -Br; -I; -CN; -NO₂; -OR⁸; -N(R⁸)(R⁹); -SO₂(CH₂)_mR⁸; -(CO)(CH₂)_mR⁸; -(CO)N(R⁸)(R⁹); -OCF₃; a C₁-C₆-alkyl radical; a C₁-C₆-haloalkyl radical; a C₃-C₆-cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; a heteroaryl radical; or the bond directly attaching the W moiety with the carbonyl moiety; wherein the C₁-C₆-alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: -D, -F, -Cl, -Br, -I, -CN, -NO₂, -OR⁸, -(CH₂)_mOR⁸, -N(R⁸)(R⁹), -(CH₂)_mN(R⁸)(R⁹), -SO₂(CH₂)_mR⁸, -(CO)(CH₂)_mR⁸, -(CO)N(R⁸)(R⁹), -OCF₃, a branched or unbranched C₁-C₆-alkyl radical, a C₃-C₆-cycloalkyl radical, a C₁-C₆-hydroxyalkyl radical, or a C₁-C₆-haloalkyl radical;
- R⁸ and R⁹ independently represent -H; a branched or unbranched C₁-C₆-alkyl radical; a C₃-C₆-cycloalkyl radical; or the N(R⁸)(R⁹) moiety forms a cycle, wherein R⁸ and R⁹ taken together represent a C₂-C₆-alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;
- X¹ independently represents N or C;
- A¹, A², A³ and A⁴ independently represent N; NR¹⁰; N(CH₂)_mR¹⁰; O; S; or CR¹¹; with the proviso that only one A¹, A², A³ and A⁴ is NR¹⁰, O, or S; with the further proviso that when X¹ is N, then A¹, A², and A³ independently represent N or CR¹¹;
- R¹⁰ independently represents -H; -D; -SO₂(CH₂)_mR¹²; -(CO)(CH₂)_mR¹²; -(CO)N(R¹²)(R¹³); a C₁-C₆-alkyl radical; a C₁-C₆-haloalkyl radical; a C₃-C₆-cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; or a heteroaryl radical; wherein the C₁-C₆-alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: -D, -F, -Cl, -Br, -I, -CN, -NO₂, -OR¹², -(CH₂)_mOR¹², -N(R¹²)(R¹³), -(CH₂)_mN(R¹²)(R¹³), -SO₂(CH₂)_mR¹², -(CO)(CH₂)_mR¹³, -(CO)N(R¹²)(R¹³),

- OCF₃, a branched or unbranched C₁-C₆-alkyl radical, a C₃-C₆-cycloalkyl radical, a C₁-C₆-hydroxyalkyl radical, or a C₁-C₆-haloalkyl radical;
- R¹¹** independently represents –H; –D; –F; –Cl; –Br; –I; –CN; –NO₂; –OR¹²; –N(R¹²)(R¹³); –SO₂(CH₂)_mR¹²; –(CO)(CH₂)_mR¹²; –(CO)N(R¹²)(R¹³); –OCF₃; a C₁-C₆-alkyl radical; a C₁-C₆-haloalkyl radical; a C₃-C₆-cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; or a heteroaryl radical; wherein the C₁-C₆-alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: –D; –F; –Cl; –Br; –I; –CN; –NO₂; –OR¹²; –(CH₂)_mOR¹²; –N(R¹²)(R¹³); –(CH₂)_mN(R¹²)(R¹³); –SO₂(CH₂)_mR¹²; –(CO)(CH₂)_mR¹²; –(CO)N(R¹²)(R¹³); –OCF₃; a branched or unbranched C₁-C₆-alkyl radical, a C₃-C₆-cycloalkyl radical, or a C₁-C₆-haloalkyl radical;
- R¹² and R¹³** independently represent –H; a branched or unbranched C₁-C₆-alkyl radical; a C₃-C₆-cycloalkyl radical; or the N(R¹²)(R¹³) moiety forms a cycle, wherein R¹² and R¹³ taken together represent a C₂-C₆-alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;
- X²** independently represents N or C;
- A⁵, A⁶, and A⁷** independently represent N; NR¹⁴; N(CH₂)_mR¹⁴; O; S; or CR¹⁵; with the proviso that only one A⁵, A⁶, and A⁷ is NR¹⁴, O, or S; with the further proviso that when X² is N, then A⁵, A⁶, and A⁷ independently represent N or CR¹⁵;
- R¹⁴** independently represents –H; –D; –(CH₂)_mN(R¹⁶)(R¹⁷); –SO₂(CH₂)_mR¹⁶; –(CO)(CH₂)_mR¹⁶; –(CO)N(R¹⁶)(R¹⁷); a C₁-C₆-alkyl radical; a C₁-C₆-haloalkyl radical; a C₃-C₆-cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; a heteroaryl radical; or the bond directly attaching the W moiety with the carbonyl moiety; wherein the C₁-C₆-alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: –D, –F, –Cl, –Br, –I, –CN, –NO₂, –OR¹⁶, –(CH₂)_mOR¹⁶, –N(R¹⁶)(R¹⁷), –(CH₂)_mN(R¹⁶)(R¹⁷), –SO₂(CH₂)_mR¹⁶, –(CO)(CH₂)_mR¹⁶, –(CO)N(R¹⁶)(R¹⁷), –OCF₃, a branched or unbranched C₁-C₆-alkyl radical, a C₃-C₆-cycloalkyl radical, or a C₁-C₆-haloalkyl;
- R¹⁵** independently represents –H; –D; –F; –Cl; –Br; –I; –CN; –NO₂; –OR¹⁶; –N(R¹⁶)(R¹⁷); –SO₂(CH₂)_mR¹⁶; –(CO)(CH₂)_mR¹⁶; –(CO)N(R¹⁶)(R¹⁷); –OCF₃; a C₁-C₆-alkyl radical; a C₁-C₆-haloalkyl radical; a C₃-C₆-cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl

radical; a heteroaryl radical; or the bond directly attaching the W moiety with the carbonyl moiety; wherein the C₁-C₆-alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: –D; –F; –Cl; –Br; –I; –CN; –NO₂; –OR¹⁶; –(CH₂)_mOR¹⁶; –N(R¹⁶)(R¹⁷); –(CH₂)_mN(R¹⁶)(R¹⁷); –SO₂(CH₂)_mR¹⁶; –(CO)(CH₂)_mR¹⁶; –(CO)N(R¹⁶)(R¹⁷); –OCF₃; a branched or unbranched C₁-C₆-alkyl radical, a C₃-C₆-cycloalkyl radical, or a C₁-C₆-haloalkyl radical;

R¹⁶ and R¹⁷ independently represent –H; a branched or unbranched C₁-C₆-alkyl radical; a C₃-C₆-cycloalkyl radical; or the N(R¹⁶)(R¹⁷) moiety forms a cycle, wherein R¹⁶ and R¹⁷ taken together represent a C₂-C₆-alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;

G¹, G², G³, and G⁴ independently represent C(R¹⁸)(R¹⁸); N(R¹⁹); –N(CH₂)_mR¹⁸; O; S; SO₂; or (C=O); with the proviso that no more than two of G¹, G², G³, and G⁴ represent N(R¹⁹); –N(CH₂)_mR¹⁸; O; S; SO₂; or (C=O);

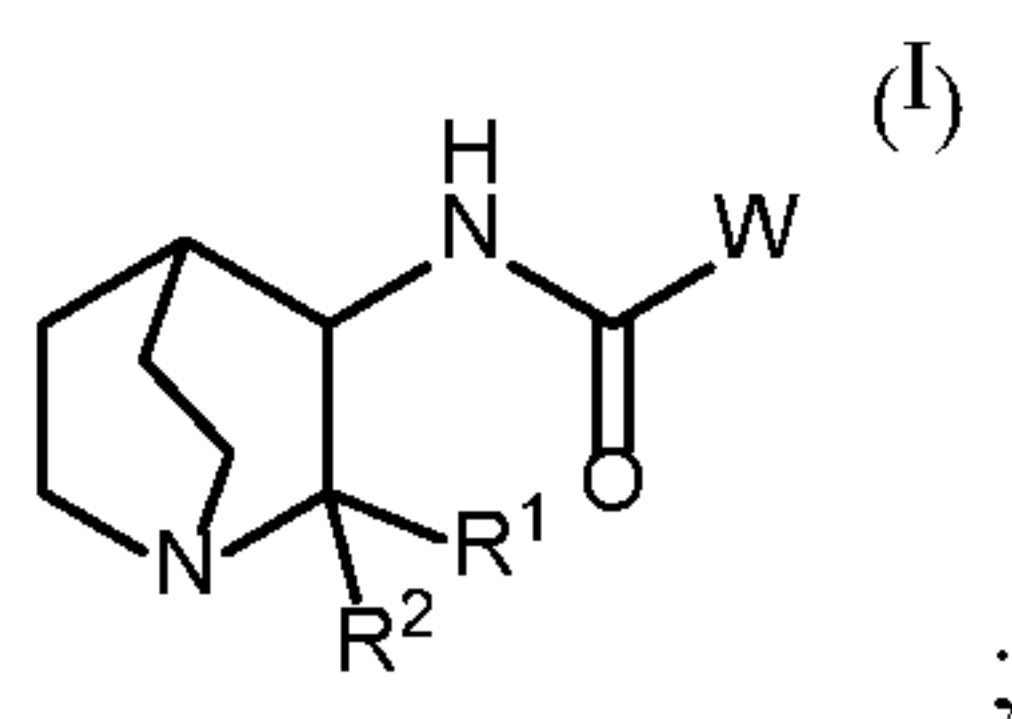
R¹⁸ independently represents –H; –D; –F; –Cl; –Br; –I; –CN; –NO₂; –OR¹⁹; –N(R¹⁹)(R²⁰); –SO₂(CH₂)_mR¹⁹; –(CO)(CH₂)_mR¹⁹; –(CO)N(R¹⁹)(R²⁰); –OCF₃; a C₁-C₆-alkyl radical; a C₁-C₆-haloalkyl radical; a C₃-C₆-cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; or a heteroaryl radical; wherein the C₁-C₆-alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: –D; –F; –Cl; –Br; –I; –CN; –NO₂; –OR¹⁹; –(CH₂)_mOR¹⁹; –N(R¹⁹)(R²⁰); –(CH₂)_mN(R¹⁹)(R²⁰); –SO₂(CH₂)_mR¹⁹; –(CO)(CH₂)_mR¹⁹; –(CO)N(R¹⁹)(R²⁰); –OCF₃; a branched or unbranched C₁-C₆-alkyl radical, a C₃-C₆-cycloalkyl radical, or a C₁-C₆-haloalkyl radical; and

R¹⁹ and R²⁰ independently represent –H; a branched or unbranched C₁-C₆-alkyl radical; a C₃-C₆-cycloalkyl radical; or the N(R¹⁹)(R²⁰) moiety forms a cycle, wherein R¹⁹ and R²⁰ taken together represent a C₂-C₆-alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical; or the C(R¹⁹)(R²⁰) moiety forms a cycle, wherein R¹⁹ and R²⁰ taken together represent a C₂-C₆-alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;

m independently represents an integer from 1 to 6;

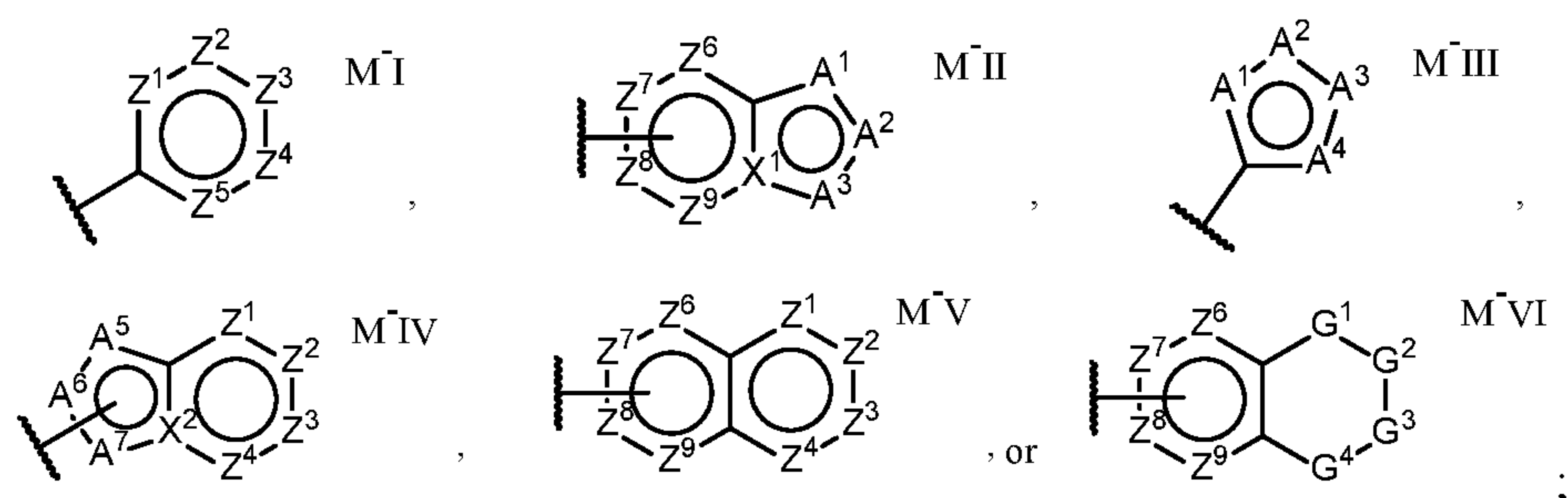
or a single stereoisomer or a pharmaceutically acceptable salt thereof.

[0007] An aspect of the invention provides a geminal substituted quinuclidine amide compound represented by Formula (I):



wherein:

- R^1 and R^2 independently represent a branched or unbranched C_1 - C_4 -alkyl radical; or the $C(R^1)(R^2)$ moiety forms a (3-4 membered)-carbocycle, wherein R^1 and R^2 taken together represent a C_2 - C_3 -alkyl di-radical; wherein the C_1 - C_4 -alkyl radical and the C_2 - C_3 -alkyl di-radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, CH_3 , CH_2CH_3 , $=O$, $-OR^3$, or $-OCF_3$;
- R^3 independently represents $-H$; a branched or unbranched C_1 - C_4 -alkyl radical; C_3 - C_4 -cycloalkyl radical; wherein the C_1 - C_4 -alkyl radical and the C_3 - C_4 -cycloalkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $=O$, $-OH$, $-OC_1$ - C_4 -alkyl or $-OCF_3$;
- W represents a moiety represented by ring system M-I, M-II, M-III, M-IV, M-V, or M-VI:



- Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 independently represent N or CR^4 ; with the proviso that no more than two of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are N;
- R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^5$; $-N(R^5)(R^6)$; $-SO_2(CH_2)_mR^5$; $-(CO)(CH_2)_mR^5$; $-(CO)N(R^5)(R^6)$; $-OCF_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; or a heteroaryl radical; wherein the C_1 - C_6 -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^5$, $-(CH_2)_mOR^5$, $-N(R^5)(R^6)$, $-(CH_2)_mN(R^5)(R^6)$, $-SO_2(CH_2)_mR^5$, $-(CO)(CH_2)_mR^5$, $-(CO)N(R^5)(R^6)$, $-OCF_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, a C_1 - C_6 -hydroxyalkyl radical, or a C_1 - C_6 -haloalkyl radical;

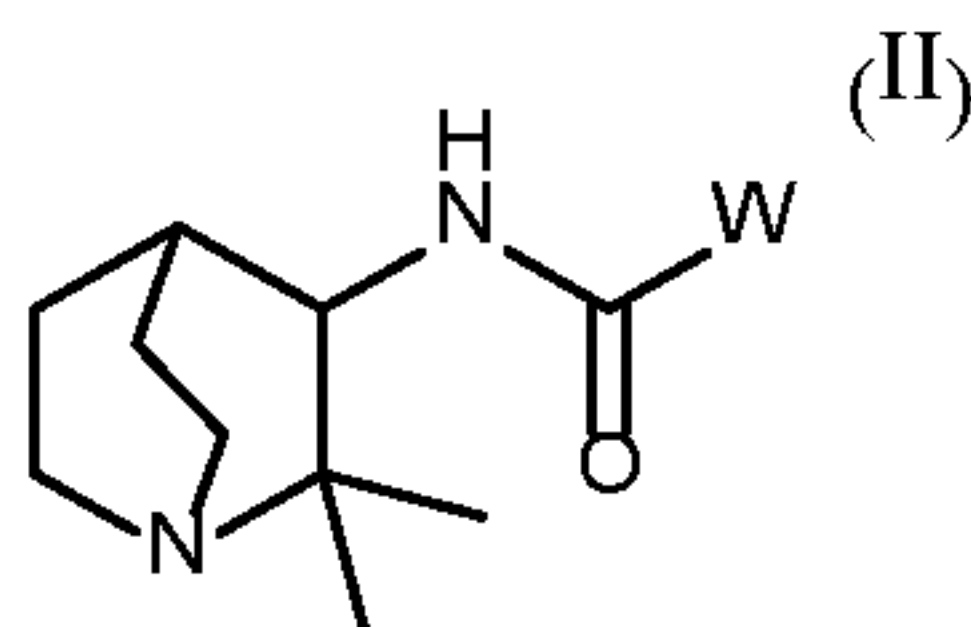
- R^5 and R^6 independently represent $-H$; a branched or unbranched C_1 - C_6 -alkyl radical; a C_3 - C_6 -cycloalkyl radical; or the $N(R^5)(R^6)$ moiety forms a cycle, wherein R^5 and R^6 taken together represent a C_2 - C_6 -alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;
- Z^6 , Z^7 , Z^8 , and Z^9 independently represent N or CR^7 ; with the proviso that no more than two of Z^6 , Z^7 , Z^8 , and Z^9 are N ;
- R^7 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^8$; $-N(R^8)(R^9)$; $-SO_2(CH_2)_mR^8$; $-(CO)(CH_2)_mR^8$; $-(CO)N(R^8)(R^9)$; $-OCF_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; a heteroaryl radical; or the bond directly attaching the W moiety with the carbonyl moiety; wherein the C_1 - C_6 -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^8$, $-(CH_2)_mOR^8$, $-N(R^8)(R^9)$, $-(CH_2)_mN(R^8)(R^9)$, $-SO_2(CH_2)_mR^8$, $-(CO)(CH_2)_mR^8$, $-(CO)N(R^8)(R^9)$, $-OCF_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, a C_1 - C_6 -hydroxyalkyl radical, or a C_1 - C_6 -haloalkyl radical;
- R^8 and R^9 independently represent $-H$; a branched or unbranched C_1 - C_6 -alkyl radical; a C_3 - C_6 -cycloalkyl radical; or the $N(R^8)(R^9)$ moiety forms a cycle, wherein R^8 and R^9 taken together represent a C_2 - C_6 -alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;
- X^1 independently represents N or C ;
- A^1 , A^2 , A^3 and A^4 independently represent N ; NR^{10} ; $N(CH_2)_mR^{10}$; O ; S ; or CR^{11} ; with the proviso that only one A^1 , A^2 , A^3 and A^4 is NR^{10} , O , or S ; with the further proviso that when X^1 is N , then A^1 , A^2 , and A^3 independently represent N or CR^{11} ;
- R^{10} independently represents $-H$; $-D$; $-SO_2(CH_2)_mR^{12}$; $-(CO)(CH_2)_mR^{12}$; $-(CO)N(R^{12})(R^{13})$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; or a heteroaryl radical; wherein the C_1 - C_6 -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^{12}$, $-(CH_2)_mOR^{12}$, $-N(R^{12})(R^{13})$, $-(CH_2)_mN(R^{12})(R^{13})$, $-SO_2(CH_2)_mR^{12}$, $-(CO)(CH_2)_mR^{13}$, $-(CO)N(R^{12})(R^{13})$, $-OCF_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, a C_1 - C_6 -hydroxyalkyl radical, or a C_1 - C_6 -haloalkyl radical;

- R^{11} independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^{12}$; $-N(R^{12})(R^{13})$; $-SO_2(CH_2)_mR^{12}$; $-(CO)(CH_2)_mR^{12}$; $-(CO)N(R^{12})(R^{13})$; $-OCF_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; or a heteroaryl radical; wherein the C_1 - C_6 -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^{12}$; $-(CH_2)_mOR^{12}$; $-N(R^{12})(R^{13})$; $-(CH_2)_mN(R^{12})(R^{13})$; $-SO_2(CH_2)_mR^{12}$; $-(CO)(CH_2)_mR^{12}$; $-(CO)N(R^{12})(R^{13})$; $-OCF_3$; a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, or a C_1 - C_6 -haloalkyl radical;
- R^{12} and R^{13} independently represent $-H$; a branched or unbranched C_1 - C_6 -alkyl radical; a C_3 - C_6 -cycloalkyl radical; or the $N(R^{12})(R^{13})$ moiety forms a cycle, wherein R^{12} and R^{13} taken together represent a C_2 - C_6 -alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;
- X^2 independently represents N or C;
- A^5 , A^6 , and A^7 independently represent N; NR^{14} ; $N(CH_2)_mR^{14}$; O; S; or CR^{15} ; with the proviso that only one A^5 , A^6 , and A^7 is NR^{14} , O, or S; with the further proviso that when X^2 is N, then A^5 , A^6 , and A^7 independently represent N or CR^{15} ;
- R^{14} independently represents $-H$; $-D$; $-(CH_2)_mN(R^{16})(R^{17})$; $-SO_2(CH_2)_mR^{16}$; $-(CO)(CH_2)_mR^{16}$; $-(CO)N(R^{16})(R^{17})$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; a heteroaryl radical; or the bond directly attaching the W moiety with the carbonyl moiety; wherein the C_1 - C_6 -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^{16}$, $-(CH_2)_mOR^{16}$, $-N(R^{16})(R^{17})$, $-(CH_2)_mN(R^{16})(R^{17})$, $-SO_2(CH_2)_mR^{16}$, $-(CO)(CH_2)_mR^{16}$, $-(CO)N(R^{16})(R^{17})$, $-OCF_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, or a C_1 - C_6 -haloalkyl;
- R^{15} independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^{16}$; $-N(R^{16})(R^{17})$; $-SO_2(CH_2)_mR^{16}$; $-(CO)(CH_2)_mR^{16}$; $-(CO)N(R^{16})(R^{17})$; $-OCF_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; a heteroaryl radical; or the bond directly attaching the W moiety with the carbonyl moiety; wherein the C_1 - C_6 -alkyl radical, the (3-6

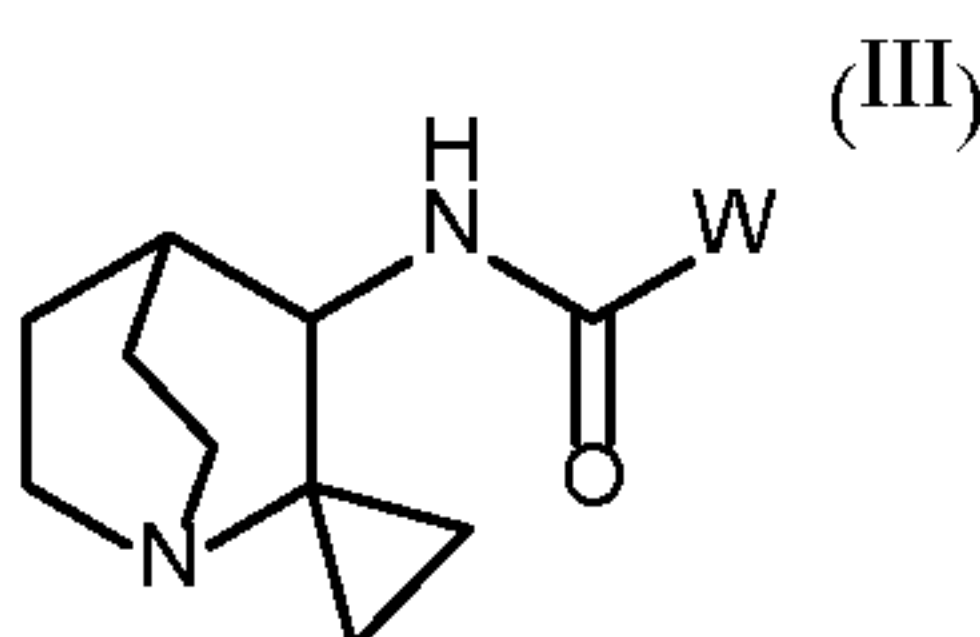
	membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: –D; –F; –Cl; –Br; –I; –CN; –NO ₂ ; –OR ¹⁶ ; –(CH ₂) _m OR ¹⁶ ; –N(R ¹⁶)(R ¹⁷); –(CH ₂) _m N(R ¹⁶)(R ¹⁷); –SO ₂ (CH ₂) _m R ¹⁶ ; –(CO)(CH ₂) _m R ¹⁶ ; –(CO)N(R ¹⁶)(R ¹⁷); –OCF ₃ ; a branched or unbranched C ₁ -C ₆ -alkyl radical, a C ₃ -C ₆ -cycloalkyl radical, or a C ₁ -C ₆ -haloalkyl radical;
R ¹⁶ and R ¹⁷	independently represent –H; a branched or unbranched C ₁ -C ₆ -alkyl radical; a C ₃ -C ₆ -cycloalkyl radical; or the N(R ¹⁶)(R ¹⁷) moiety forms a cycle, wherein R ¹⁶ and R ¹⁷ taken together represent a C ₂ -C ₆ -alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;
G ¹ , G ² , G ³ , and G ⁴	independently represent C(R ¹⁸)(R ¹⁸); N(R ¹⁹); –N(CH ₂) _m R ¹⁸ ; O; S; SO ₂ ; or (C=O); with the proviso that no more than two of G ¹ , G ² , G ³ , and G ⁴ represent N(R ¹⁹); –N(CH ₂) _m R ¹⁸ ; O; S; SO ₂ ; or (C=O);
R ¹⁸	independently represents –H; –D; –F; –Cl; –Br; –I; –CN; –NO ₂ ; –OR ¹⁹ ; –N(R ¹⁹)(R ²⁰); –SO ₂ (CH ₂) _m R ¹⁹ ; –(CO)(CH ₂) _m R ¹⁹ ; –(CO)N(R ¹⁹)(R ²⁰); –OCF ₃ ; a C ₁ -C ₆ -alkyl radical; a C ₁ -C ₆ -haloalkyl radical; a C ₃ -C ₆ -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; or a heteroaryl radical; wherein the C ₁ -C ₆ -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: –D, –F, –Cl, –Br, –I, –CN, –NO ₂ , –OR ¹⁹ , –(CH ₂) _m OR ¹⁹ , –N(R ¹⁹)(R ²⁰), –(CH ₂) _m N(R ¹⁹)(R ²⁰), –SO ₂ (CH ₂) _m R ¹⁹ , –(CO)(CH ₂) _m R ¹⁹ , –(CO)N(R ¹⁹)(R ²⁰), –OCF ₃ , a branched or unbranched C ₁ -C ₆ -alkyl radical, a C ₃ -C ₆ -cycloalkyl radical, or a C ₁ -C ₆ -haloalkyl radical; and
R ¹⁹ and R ²⁰	independently represent –H; a branched or unbranched C ₁ -C ₆ -alkyl radical; a C ₃ -C ₆ -cycloalkyl radical; or the N(R ¹⁹)(R ²⁰) moiety forms a cycle, wherein R ¹⁹ and R ²⁰ taken together represent a C ₂ -C ₆ -alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical; or the C(R ¹⁹)(R ²⁰) moiety forms a cycle, wherein R ¹⁹ and R ²⁰ taken together represent a C ₂ -C ₆ -alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;
m	independently represents an integer from 1 to 6;

or a single stereoisomer or a pharmaceutically acceptable salt thereof.

[0008] An aspect of the invention relates to the amide compound represented by Formula (I), wherein R¹ and R² independently represent an unbranched C₁-alkyl radical and said compound is represented by Formula (II):



[0009] An aspect of the invention relates to an amide compound represented by Formula (I), wherein R^1 and R^2 taken together represent a C_2 -alkyl di-radical and said compound is represented by Formula (III):



[0010] An aspect of the invention relates to a single stereoisomer of the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof.

[0011] An aspect of the invention relates to a single enantiomer or a single diastereomer of the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof.

[0012] An aspect of the invention relates to a pharmaceutical composition comprising the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; and at least one pharmaceutically acceptable carrier, excipient or diluent.

[0013] An aspect of the invention relates to a method comprising administering to a patient in need thereof an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising an effective dose of the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[0014] Another aspect of the invention provides a method of treating a patient in need thereof, comprising: administering to the patient an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising an effective dose of the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[0015] Another aspect of the invention provides a method of maintaining, treating, curing and/or improving at least one cognitive function in a patient in need thereof, comprising: administering to the patient an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising an effective dose of the amide compound represented by Formula (I),

Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[0016] Another aspect of the invention provides a method of maintaining, treating, curing and/or improving at least one cognitive function in a patient in need thereof, comprising: administering to the patient an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising an effective dose of the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[0017] Another aspect of the invention provides a method of treating a patient diagnosed as having a cognitive impairment, comprising: administering to the an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient an effective dose of a pharmaceutical composition comprising the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[0018] Another aspect of the invention provides a method of treating a patient in need thereof, comprising: administering to the patient, for example, a patient diagnosed with having a cognitive impairment, Limited Cognitive Impairment, Mild Cognitive Impairment, Alzheimer's disease, and/or schizophrenia, an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising an effective dose of the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent; such that the patient may derive a benefit therefrom.

[0019] Another aspect of the invention provides a method of treating one or more symptoms associated with a cognitive impairment, comprising administering to a patient an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising an effective dose of the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent; wherein the patient suffers from, or has been diagnosed as having, a cognitive impairment.

[0020] Another aspect of the invention provides a method of improving cognition of a patient in need thereof, comprising: administering to the patient an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising an effective dose of the amide compound

represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[0021] Another aspect of the invention provides a method of improving cognition in a patient suffering from a cognitive impairment, such as a cognitive impairment associated with either schizophrenia or Alzheimer's disease, for example mild Alzheimer's disease, moderate Alzheimer's disease, severe Alzheimer's disease, or mild-to-moderate Alzheimer's disease, comprising administering an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising an effective dose of the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[0022] Another aspect of the invention provides a method of treating a patient suffering from, diagnosed with having, or suffers from one or more symptoms associated with, a cognitive impairment, for example, Alzheimer's disease, dementia of an Alzheimer's type, MCI, LCI, or schizophrenia, comprising: administering to the patient an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising an effective dose of the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent. For example, the method of treating a patient suffering from, diagnosed with having, or suffers from one or more symptoms associated with, a cognitive impairment, may provide said patient at least one of the following: (i) treats, minimizes progression of, prevents the deterioration of, or reduces the rate of deterioration of, one or more symptoms associated with the cognitive impairment; (ii) treats the cognitive impairment; (iii) improves cognition in said cognitively impaired patient; (iv) improves one or more behavioral symptoms associated with the cognitive impairment; (v) provides a pro-cognitive effect; (vi) provides a pro-cognitive effect in at least one of the following: visual motor, learning, delayed memory, or executive function, or (vii) provides a positive effect on clinical function in said cognitively impaired patient.

[0023] Another aspect of the invention provides a method of treating a patient previously treated, or currently being treated, with an AChEI, that is suffering from, or has been diagnosed with having, a cognitive impairment, for example, Alzheimer's disease, dementia of an Alzheimer's type, MCI, LCI, or schizophrenia, comprising: administering to the patient an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising an effective dose of the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluents;

wherein the method improves one or more symptoms associated with the cognitive impairment in the previously, or currently, AChEI treated patient.

[0024] Another aspect of the invention provides a method of treating a patient suffering from, or diagnosed with having a cognitive impairment, comprising: administering to the patient an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising an effective dose of the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent; wherein the method provides a positive effect on cognition or a positive effect on clinical function in said cognitively impaired patient, and wherein said patient has been previously treated or is currently being treated with an AChEI.

[0025] Another aspect of the invention provides a method of improving cognition in a patient diagnosed as having a probable cognitive disease, comprising: administering to the patient an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient an effective dose of a pharmaceutical composition comprising the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[0026] Another aspect of the invention provides a method of improving or substantially improving one or more symptoms in a cognitive disease patient, comprising: administering to the patient an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient an effective dose of a pharmaceutical composition comprising the effective dose of the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[0027] Another aspect of the invention provides a method of slowing the rate of deterioration of at least one symptom in a cognitive disease patient, comprising: administering to the patient an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient the pharmaceutical composition comprising the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[0028] Another aspect of the invention provides a method of treating one or more symptoms associated with a cognitive disease in a patient suffering therefrom, comprising: administering to the patient an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient an effective dose of a pharmaceutical composition comprising the amide compound represented by Formula (I), Formula

(II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent

[0029] Another aspect provides a method of minimizing or substantially halting the rate of progression of one or more cognitive diseases in a patient suffering from a cognitive disease, comprising: administering to the patient an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient an effective dose of a pharmaceutical composition comprising the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[0030] Another aspect of the invention provides a method of substantially stopping or reversing progression of one or more cognitive diseases, in a patient suffering therefrom, comprising: administering to the patient an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient an effective dose of a pharmaceutical composition comprising the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[0031] Another aspect of the invention provides a method of treating dementia, comprising: administering to a patient in need thereof an effective amount of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient an effective dose of a pharmaceutical composition comprising the effective amount of the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent; wherein said effective amount is administered in an effective dose.

[0032] Another aspect of the invention provides a method of treating dementia, comprising: administering to a patient in need thereof an effective amount of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient an effective dose of a pharmaceutical composition comprising the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[0033] Another aspect of the invention provides a method of treating dementia, comprising: administering to a patient in need thereof an effective amount of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, wherein the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, is administered in the form of a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier, excipient or diluent.

[0034] Another aspect of the invention provides a method of treating dementia, comprising: administering to a patient in need thereof an effective amount of an amide compound represented by

Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient an effective dose of a pharmaceutical composition comprising the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent; wherein the pharmaceutical composition is in the form of a tablet.

[0035] Another aspect of the invention provides a method of treating a patient having a cognitive disease and being administered an acetylcholine esterase inhibitor, comprising: administering to a patient in need thereof an effective amount of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient an effective dose of a pharmaceutical composition comprising an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent; wherein the treatment comprises halting the administration of the acetylcholine esterase inhibitor prior to treating with the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof.

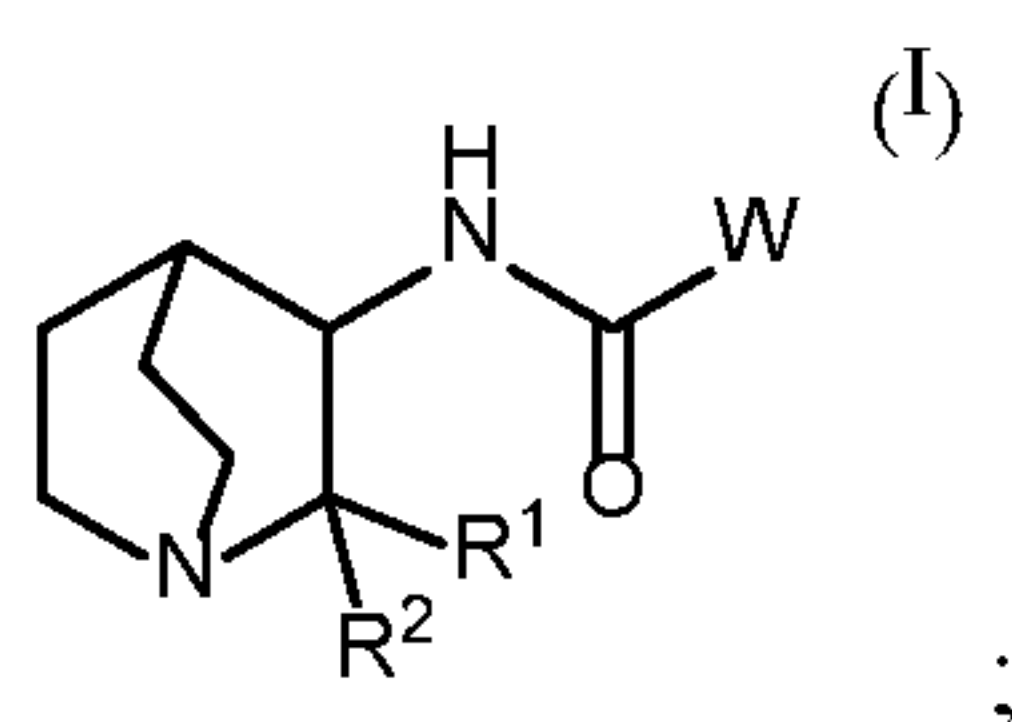
BRIEF DESCRIPTION OF THE DRAWINGS

[0036] **Figure 1:** Illustrates a 3-D representation of the formed crystal of (*R*)-2,2-dimethyl-N-((*R*)-1-phenylethyl)quinuclidin-3-amine fumarate.

[0037] **Figure 2:** Illustrates a 3-D representation of the formed crystal of (*R*)-N-((*R*)-1-phenylethyl)-1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-amine bis(4-methylbenzenesulfonate).

DETAILED DESCRIPTION OF THE INVENTION

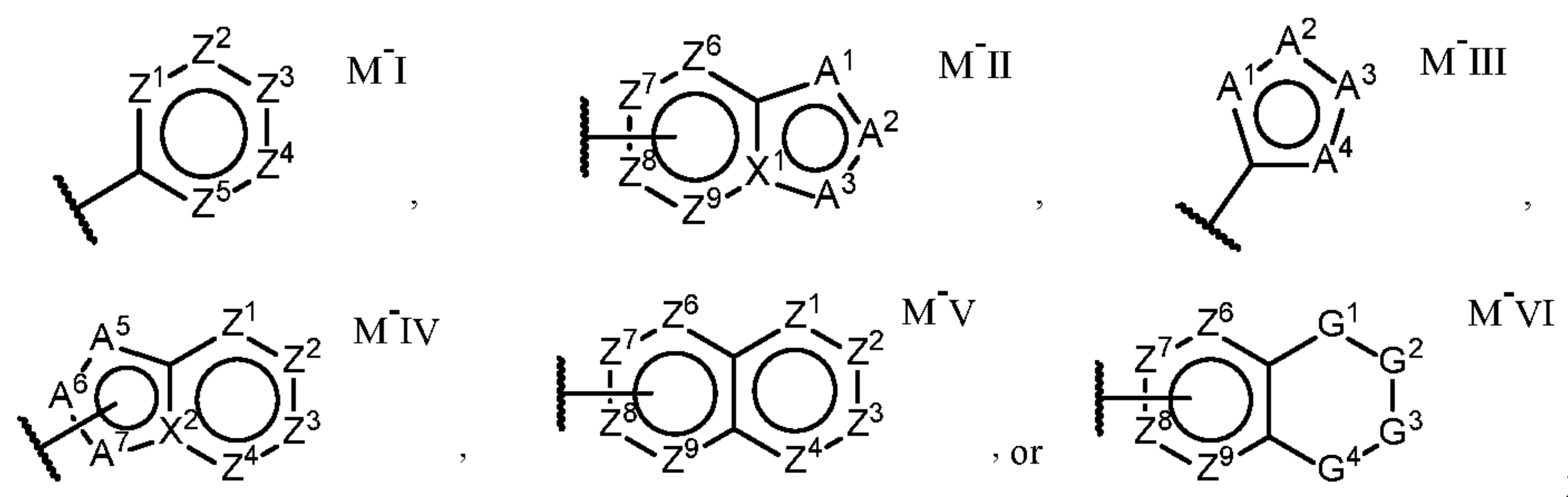
[0038] An embodiment of the present invention provides a geminal substituted quinuclidine amide compound represented by Formula (I):



wherein:

R^1 and R^2 independently represent a branched or unbranched C_1 - C_4 -alkyl radical; or the $C(R^1)(R^2)$ moiety forms a (3-4 membered)-carbocycle, wherein R^1 and R^2 taken together represent a C_2 - C_3 -alkyl di-radical; wherein the C_1 - C_4 -alkyl radical and the C_2 - C_3 -alkyl di-radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, CH_3 , CH_2CH_3 , $=O$, $-OR^3$, or $-OCF_3$;

- R^3 independently represents $-H$; a branched or unbranched C_1 - C_4 -alkyl radical; C_3 - C_4 -cycloalkyl radical; wherein the C_1 - C_4 -alkyl radical and the C_3 - C_4 -cycloalkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $=O$, $-OH$, $-OC_1$ - C_4 -alkyl or $-OCF_3$; and
- W represents a moiety represented by ring system M-I, M-II, M-III, M-IV, M-V, or M-VI:



wherein:

- Z^1, Z^2, Z^3, Z^4 , and Z^5 independently represent N or CR^4 ; with the proviso that no more than two of Z^1, Z^2, Z^3, Z^4 , and Z^5 are N;
- R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^5$; $-N(R^5)(R^6)$; $-SO_2(CH_2)_mR^5$; $-(CO)(CH_2)_mR^5$; $-(CO)N(R^5)(R^6)$; $-OCF_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; or a heteroaryl radical; or when adjacent members of Z^1, Z^2, Z^3, Z^4 , and Z^5 , is $(CR^4)(CR^4)$, the $(CR^4)(CR^4)$ may form a cycle such that the adjacent R^4 substituents taken together represents a (3-6 membered)-heteroalkyl di-radical with at least one ring atom of the (3-6 membered)-heteroalkyl di-radical selected from the group consisting of oxygen, nitrogen, and sulfur, with the proviso that when the at least one ring atom is nitrogen, the nitrogen is substituted with $-H$, a branched or unbranched C_1 - C_4 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, $-(CO)$ -branched or unbranched C_1 - C_4 -alkyl, or $-(SO_2)$ -branched or unbranched C_1 - C_4 -alkyl, wherein the C_1 - C_4 -alkyl radical and the C_3 - C_4 -cycloalkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, halogen, $=O$, $-OH$, $-OC_1$ - C_4 -alkyl or $-OCF_3$, and with the further proviso that when the at least one ring atom is sulfur, the sulfur may substituted with 0 or 2 $=O$; wherein the C_1 - C_6 -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, the heteroaryl radical, and the alkyl portion of the (3-6 membered)-heteroalkyl di-radical, may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^5$, $-$

- $(\text{CH}_2)_m\text{OR}^5$, $-\text{N}(\text{R}^5)(\text{R}^6)$, $-(\text{CH}_2)_m\text{N}(\text{R}^5)(\text{R}^6)$, $-\text{SO}_2(\text{CH}_2)_m\text{R}^5$, $-(\text{CO})(\text{CH}_2)_m\text{R}^5$, $-(\text{CO})\text{N}(\text{R}^5)(\text{R}^6)$, $-\text{OCF}_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, a C_1 - C_6 -hydroxyalkyl radical, or a C_1 - C_6 -haloalkyl radical;
- R^5 and R^6 independently represent $-\text{H}$; a branched or unbranched C_1 - C_6 -alkyl radical; a C_3 - C_6 -cycloalkyl radical; or the $\text{N}(\text{R}^5)(\text{R}^6)$ moiety forms a cycle, wherein R^5 and R^6 taken together represent a C_2 - C_6 -alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;
- Z^6 , Z^7 , Z^8 , and Z^9 independently represent N or CR^7 ; with the proviso that no more than two of Z^6 , Z^7 , Z^8 , and Z^9 are N ;
- R^7 independently represents $-\text{H}$; $-\text{D}$; $-\text{F}$; $-\text{Cl}$; $-\text{Br}$; $-\text{I}$; $-\text{CN}$; $-\text{NO}_2$; $-\text{OR}^8$; $-\text{N}(\text{R}^8)(\text{R}^9)$; $-\text{SO}_2(\text{CH}_2)_m\text{R}^8$; $-(\text{CO})(\text{CH}_2)_m\text{R}^8$; $-(\text{CO})\text{N}(\text{R}^8)(\text{R}^9)$; $-\text{OCF}_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; a heteroaryl radical; or the bond directly attaching the W moiety with the carbonyl moiety; wherein the C_1 - C_6 -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-\text{D}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}^8$, $-(\text{CH}_2)_m\text{OR}^8$, $-\text{N}(\text{R}^8)(\text{R}^9)$, $-(\text{CH}_2)_m\text{N}(\text{R}^8)(\text{R}^9)$, $-\text{SO}_2(\text{CH}_2)_m\text{R}^8$, $-(\text{CO})(\text{CH}_2)_m\text{R}^8$, $-(\text{CO})\text{N}(\text{R}^8)(\text{R}^9)$, $-\text{OCF}_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, a C_1 - C_6 -hydroxyalkyl radical, or a C_1 - C_6 -haloalkyl radical;
- R^8 and R^9 independently represent $-\text{H}$; a branched or unbranched C_1 - C_6 -alkyl radical; a C_3 - C_6 -cycloalkyl radical; or the $\text{N}(\text{R}^8)(\text{R}^9)$ moiety forms a cycle, wherein R^8 and R^9 taken together represent a C_2 - C_6 -alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;
- X^1 independently represents N or C ;
- A^1 , A^2 , A^3 and A^4 independently represent N ; NR^{10} ; $\text{N}(\text{CH}_2)_m\text{R}^{10}$; O ; S ; or CR^{11} ; with the proviso that only one A^1 , A^2 , A^3 and A^4 is NR^{10} , O , or S ; with the further proviso that when X^1 is N , then A^1 , A^2 , and A^3 independently represent N or CR^{11} ;
- R^{10} independently represents $-\text{H}$; $-\text{D}$; $-\text{SO}_2(\text{CH}_2)_m\text{R}^{12}$; $-(\text{CO})(\text{CH}_2)_m\text{R}^{12}$; $-(\text{CO})\text{N}(\text{R}^{12})(\text{R}^{13})$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; or a heteroaryl radical; wherein the C_1 - C_6 -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-\text{H}$; $-\text{D}$; $-\text{F}$; $-\text{Cl}$; $-\text{Br}$; $-\text{I}$; $-\text{CN}$; $-\text{NO}_2$; $-\text{OR}^{12}$; $-(\text{CH}_2)_m\text{OR}^{12}$; $-\text{N}(\text{R}^{12})(\text{R}^{13})$; $-(\text{CH}_2)_m\text{N}(\text{R}^{12})(\text{R}^{13})$; $-\text{SO}_2(\text{CH}_2)_m\text{R}^{12}$; $-(\text{CO})(\text{CH}_2)_m\text{R}^{12}$; $-(\text{CO})\text{N}(\text{R}^{12})(\text{R}^{13})$; $-\text{OCF}_3$; a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, a C_1 - C_6 -hydroxyalkyl radical, or a C_1 - C_6 -haloalkyl radical;

- D, -F, -Cl, -Br, -I, -CN, -NO₂, -OR¹², -(CH₂)_mOR¹², -N(R¹²)(R¹³), -(CH₂)_mN(R¹²)(R¹³), -SO₂(CH₂)_mR¹², -(CO)(CH₂)_mR¹³, -(CO)N(R¹²)(R¹³), -OCF₃, a branched or unbranched C₁-C₆-alkyl radical, a C₃-C₆-cycloalkyl radical, a C₁-C₆-hydroxyalkyl radical, or a C₁-C₆-haloalkyl radical;
- R¹¹ independently represents -H; -D; -F; -Cl; -Br; -I; -CN; -NO₂; -OR¹²; -N(R¹²)(R¹³); -SO₂(CH₂)_mR¹²; -(CO)(CH₂)_mR¹²; -(CO)N(R¹²)(R¹³); -OCF₃; a C₁-C₆-alkyl radical; a C₁-C₆-haloalkyl radical; a C₃-C₆-cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; or a heteroaryl radical; wherein the C₁-C₆-alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: -D; -F; -Cl; -Br; -I; -CN; -NO₂; -OR¹²; -(CH₂)_mOR¹²; -N(R¹²)(R¹³); -(CH₂)_mN(R¹²)(R¹³); -SO₂(CH₂)_mR¹²; -(CO)(CH₂)_mR¹²; -(CO)N(R¹²)(R¹³); -OCF₃; a branched or unbranched C₁-C₆-alkyl radical, a C₃-C₆-cycloalkyl radical, or a C₁-C₆-haloalkyl radical;
- R¹² and R¹³ independently represent -H; a branched or unbranched C₁-C₆-alkyl radical; a C₃-C₆-cycloalkyl radical; or the N(R¹²)(R¹³) moiety forms a cycle, wherein R¹² and R¹³ taken together represent a C₂-C₆-alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;
- X² independently represents N or C;
- A⁵, A⁶, and A⁷ independently represent N; NR¹⁴; N(CH₂)_mR¹⁴; O; S; or CR¹⁵; with the proviso that only one A⁵, A⁶, and A⁷ is NR¹⁴, O, or S; with the further proviso that when X² is N, then A⁵, A⁶, and A⁷ independently represent N or CR¹⁵;
- R¹⁴ independently represents -H; -D; -(CH₂)_mN(R¹⁶)(R¹⁷); -SO₂(CH₂)_mR¹⁶; -(CO)(CH₂)_mR¹⁶; -(CO)N(R¹⁶)(R¹⁷); a C₁-C₆-alkyl radical; a C₁-C₆-haloalkyl radical; a C₃-C₆-cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; a heteroaryl radical; or the bond directly attaching the W moiety with the carbonyl moiety; wherein the C₁-C₆-alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: -D, -F, -Cl, -Br, -I, -CN, -NO₂, -OR¹⁶, -(CH₂)_mOR¹⁶, -N(R¹⁶)(R¹⁷), -(CH₂)_mN(R¹⁶)(R¹⁷), -SO₂(CH₂)_mR¹⁶, -(CO)(CH₂)_mR¹⁶, -(CO)N(R¹⁶)(R¹⁷), -OCF₃, a branched or unbranched C₁-C₆-alkyl radical, a C₃-C₆-cycloalkyl radical, or a C₁-C₆-haloalkyl;
- R¹⁵ independently represents -H; -D; -F; -Cl; -Br; -I; -CN; -NO₂; -OR¹⁶; -N(R¹⁶)(R¹⁷); -SO₂(CH₂)_mR¹⁶; -(CO)(CH₂)_mR¹⁶; -(CO)N(R¹⁶)(R¹⁷); -

OCF₃; a C₁-C₆-alkyl radical; a C₁-C₆-haloalkyl radical; a C₃-C₆-cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; a heteroaryl radical; or the bond directly attaching the W moiety with the carbonyl moiety; wherein the C₁-C₆-alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: –D; –F; –Cl; –Br; –I; –CN; –NO₂; –OR¹⁶; –(CH₂)_mOR¹⁶; –N(R¹⁶)(R¹⁷); –(CH₂)_mN(R¹⁶)(R¹⁷); –SO₂(CH₂)_mR¹⁶; –(CO)(CH₂)_mR¹⁶; –(CO)N(R¹⁶)(R¹⁷); –OCF₃; a branched or unbranched C₁-C₆-alkyl radical, a C₃-C₆-cycloalkyl radical, or a C₁-C₆-haloalkyl radical;

R¹⁶ and R¹⁷ independently represent –H; a branched or unbranched C₁-C₆-alkyl radical; a C₃-C₆-cycloalkyl radical; or the N(R¹⁶)(R¹⁷) moiety forms a cycle, wherein R¹⁶ and R¹⁷ taken together represent a C₂-C₆-alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;

G¹, G², G³, and G⁴ independently represent C(R¹⁸)(R¹⁸); N(R¹⁹); –N(CH₂)_mR¹⁸; O; S; SO₂; or (C=O); with the proviso that no more than two of G¹, G², G³, and G⁴ represent N(R¹⁹); –N(CH₂)_mR¹⁸; O; S; SO₂; or (C=O);

R¹⁸ independently represents –H; –D; –F; –Cl; –Br; –I; –CN; –NO₂; –OR¹⁹; –N(R¹⁹)(R²⁰); –SO₂(CH₂)_mR¹⁹; –(CO)(CH₂)_mR¹⁹; –(CO)N(R¹⁹)(R²⁰); –OCF₃; a C₁-C₆-alkyl radical; a C₁-C₆-haloalkyl radical; a C₃-C₆-cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; or a heteroaryl radical; wherein the C₁-C₆-alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: –D; –F; –Cl; –Br; –I; –CN; –NO₂; –OR¹⁹; –(CH₂)_mOR¹⁹; –N(R¹⁹)(R²⁰); –(CH₂)_mN(R¹⁹)(R²⁰); –SO₂(CH₂)_mR¹⁹; –(CO)(CH₂)_mR¹⁹; –(CO)N(R¹⁹)(R²⁰); –OCF₃; a branched or unbranched C₁-C₆-alkyl radical, a C₃-C₆-cycloalkyl radical, or a C₁-C₆-haloalkyl radical; and

R¹⁹ and R²⁰ independently represent –H; a branched or unbranched C₁-C₆-alkyl radical; a C₃-C₆-cycloalkyl radical; or the N(R¹⁹)(R²⁰) moiety forms a cycle, wherein R¹⁹ and R²⁰ taken together represent a C₂-C₆-alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical; or the C(R¹⁹)(R²⁰) moiety forms a cycle, wherein R¹⁹ and R²⁰ taken together represent a C₂-C₆-alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;

m independently represents an integer from 1 to 6;

or a single stereoisomer or a pharmaceutically acceptable salt thereof.

[0039] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-I. In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-I, wherein, for example, the Z^1 represents N, and Z^2 , Z^3 , Z^4 , and Z^5 each independently represent CR^4 ; Z^2 represents N, and Z^1 , Z^3 , Z^4 , and Z^5 each independently represent CR^4 ; Z^3 represents N, and Z^1 , Z^2 , Z^4 , and Z^5 each independently represent CR^4 ; Z^1 and Z^2 each represent N, and Z^3 , Z^4 , and Z^5 each independently represent CR^4 ; Z^1 and Z^3 each represent N, and Z^2 , Z^4 , and Z^5 each independently represent CR^4 ; Z^1 and Z^4 each represent N, and Z^2 , Z^3 , and Z^5 each independently represent CR^4 ; Z^1 and Z^5 each represent N, and Z^2 , Z^3 , and Z^4 each independently represent CR^4 ; Z^2 and Z^3 each represent N, and Z^1 , Z^4 , and Z^5 each independently represent CR^4 ; or Z^2 and Z^4 each represent N, and Z^1 , Z^3 , and Z^5 each independently represent CR^4 .

[0040] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-I, wherein at least one or two of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 , represent CR^4 with said R^4 representing $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^5$; $-N(R^5)(R^6)$; $-SO_2(CH_2)_mR^5$; $-(CO)(CH_2)_mR^5$; $-(CO)N(R^5)(R^6)$; $-OCF_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; or a (3-6 membered)-heterocycloalkyl radical; wherein the C_1 - C_6 -alkyl radical and the (3-6 membered)-heterocycloalkyl radical, may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^5$, $-(CH_2)_mOR^5$, $-N(R^5)(R^6)$, $-(CH_2)_mN(R^5)(R^6)$, $-SO_2(CH_2)_mR^5$, $-(CO)(CH_2)_mR^5$, $-(CO)N(R^5)(R^6)$, $-OCF_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, or a C_1 - C_6 -haloalkyl radical.

[0041] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-I, wherein the at least one or two of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 , represent CR^4 with said R^4 representing $-F$; $-Cl$; $-Br$; $-I$; or $-CN$.

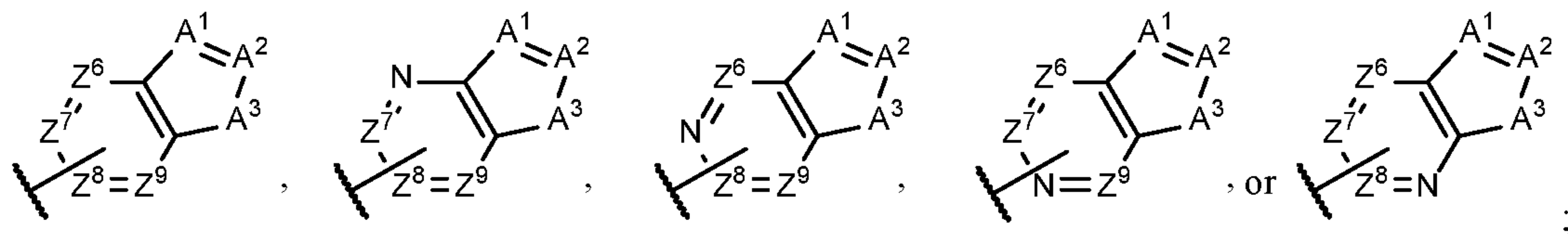
[0042] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-I, wherein the at least one or two of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 , represent CR^4 with said R^4 representing an aryl radical or a heteroaryl radical; wherein the aryl radical and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^5$, $-(CH_2)_mOR^5$, $-N(R^5)(R^6)$, $-(CH_2)_mN(R^5)(R^6)$, $-SO_2(CH_2)_mR^5$, $-(CO)(CH_2)_mR^5$, $-(CO)N(R^5)(R^6)$, $-OCF_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, or a C_1 - C_6 -haloalkyl radical.

[0043] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-I, wherein Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 , each independently represent CR^4 with said R^4 representing $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-OCH_3$; $-OCF_3$; a C_1 - C_3 -alkyl radical; $-CF_3$; or a C_3 - C_4 -cycloalkyl radical; wherein the C_1 - C_3 -alkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, a branched or unbranched C_1 - C_3 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, or a C_1 - C_3 -haloalkyl radical. For example,

in certain embodiments, Z^1 , Z^2 , Z^4 , and Z^5 independently represent CR^4 with said R^4 representing $-H$ or $-D$; and Z^3 independently represents CR^4 with said R^4 representing $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-OCH_3$; $-OCF_3$; a C_1 - C_3 -alkyl radical; $-CF_3$; or a C_3 - C_4 -cycloalkyl radical; wherein the C_1 - C_3 -alkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, a branched or unbranched C_1 - C_3 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, or a C_1 - C_3 -haloalkyl radical.

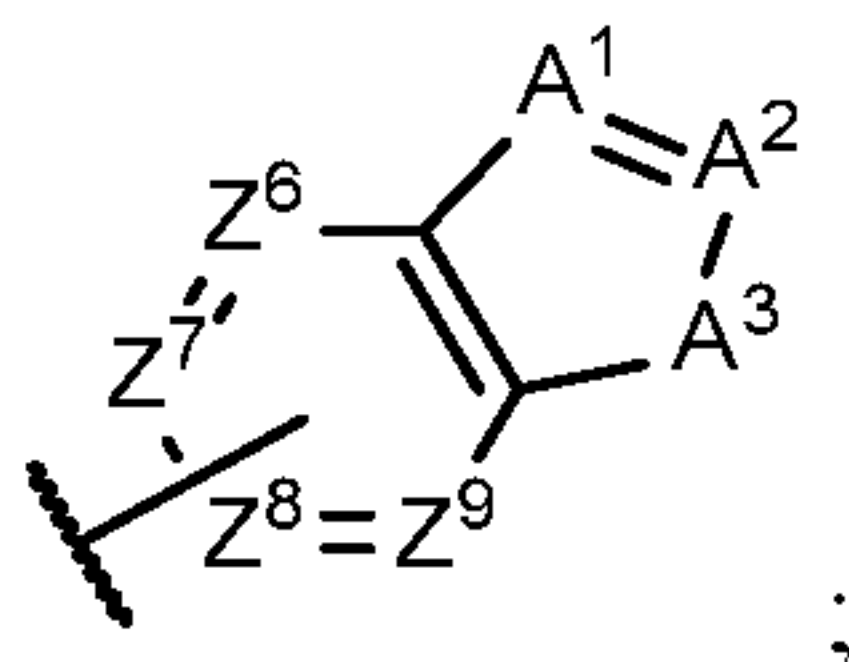
[0044] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-I, wherein Z^1 , Z^2 , Z^4 , and Z^5 independently represent CR^4 with said R^4 representing $-H$ or $-D$; and Z^3 independently represents CR^4 with said R^4 representing $-Cl$; $-OCH_3$; $-OCF_3$; a C_1 - C_3 -alkyl radical; $-CF_3$; or a C_3 - C_4 -cycloalkyl radical.

[0045] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II. In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II, wherein X^1 represents C. For example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II, wherein M-II represents a moiety represented by one of the following:



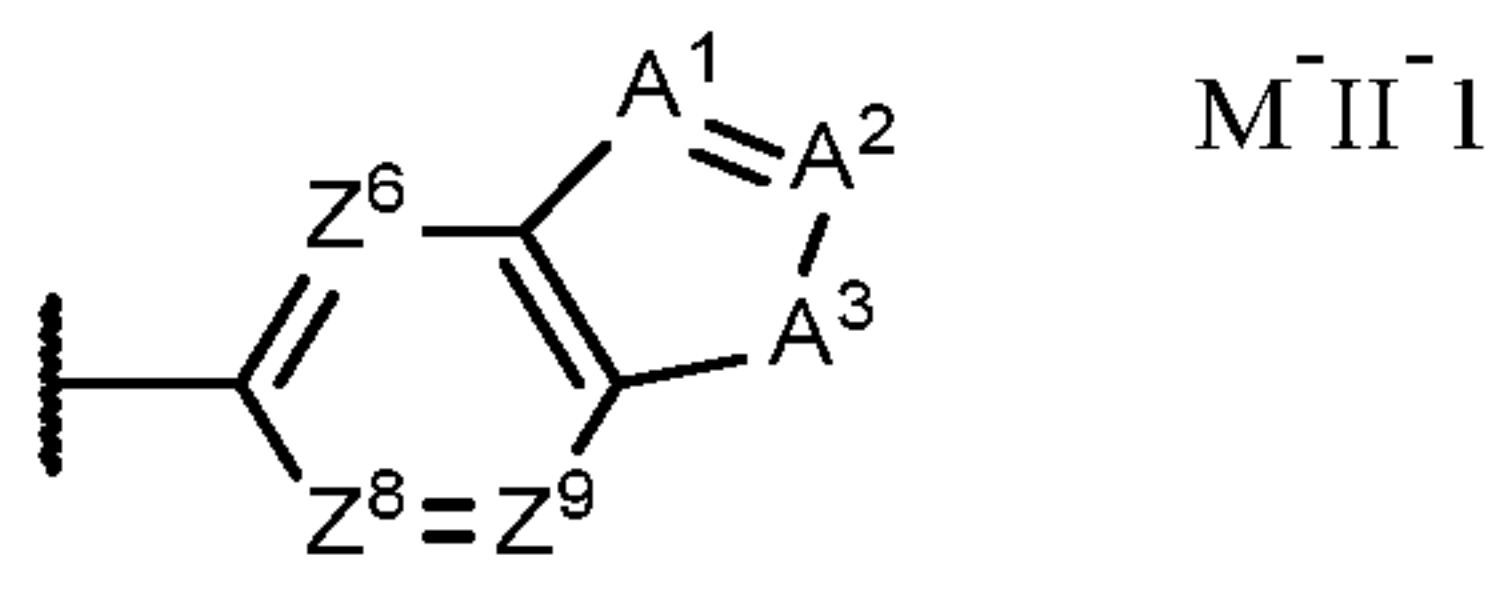
wherein A^1 and A^2 independently represent N or CR^{11} , and A^3 independently represents NR^{10} , O, or S. In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II, wherein either Z^6 or Z^7 represents CR^7 with said R^7 representing the bond directly attaching the W moiety with the carbonyl moiety, or wherein either Z^8 or Z^9 represents CR^7 with said R^7 representing the bond directly attaching the W moiety with the carbonyl moiety.

[0046] For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II with X^1 representing C, wherein M-II represents a moiety represented by:



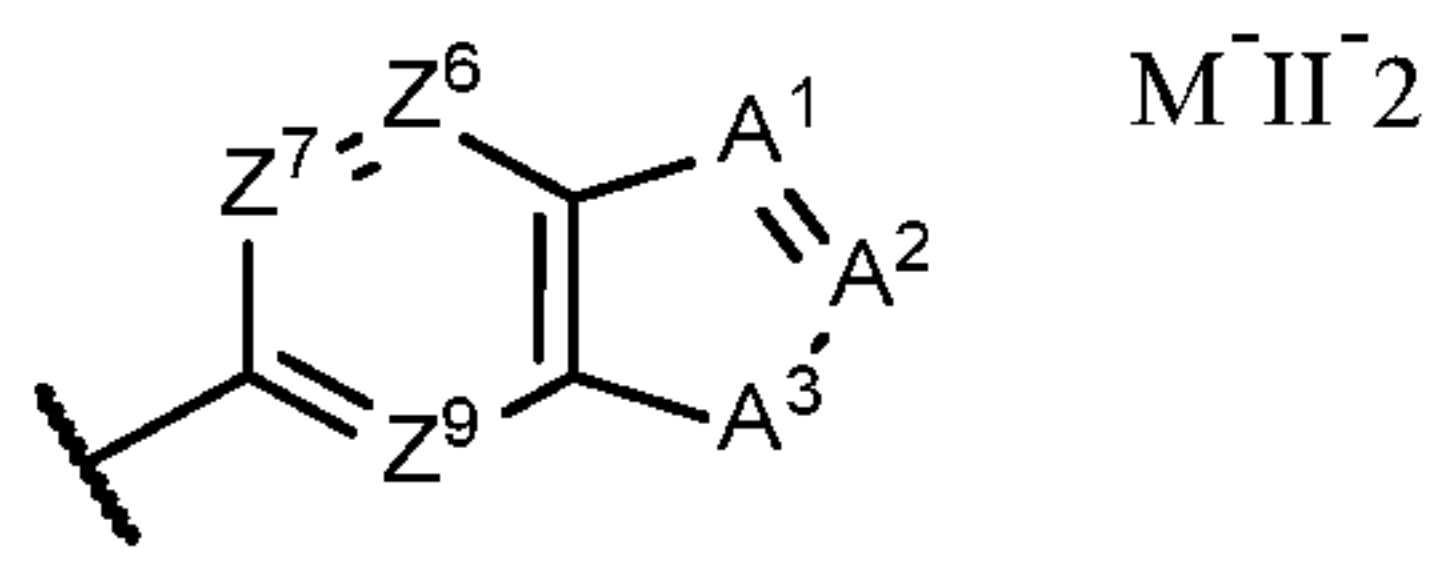
wherein A^1 and A^2 independently represent N or CR^{11} ; A^3 independently represents NR^{10} , O, or S; and Z^6 , Z^7 , Z^8 , and Z^9 represent CR^7 , with one of said R^7 of Z^6 , Z^7 , Z^8 , and Z^9 representing the bond directly attaching the W moiety with the carbonyl moiety.

[0047] In certain embodiments, for example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II-1 with X^1 representing C, said R^7 of Z^7 represents the bond directly attaching the W moiety with the carbonyl moiety:



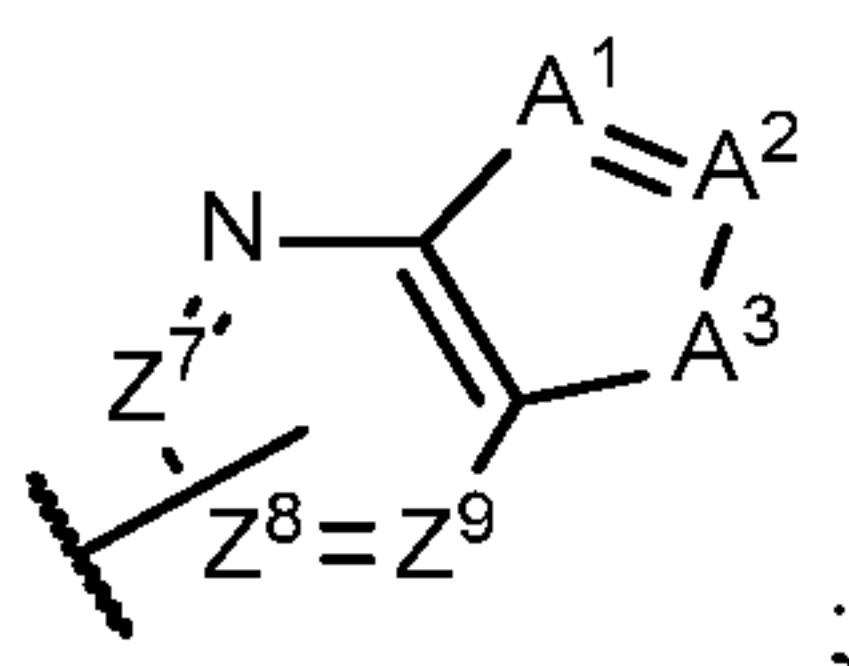
wherein A^1 and A^2 independently represent N or CR^{11} ; A^3 independently represents NR^{10} , O, or S; and Z^6 , Z^8 , and Z^9 independently represent CR^7 . For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II-1, wherein A^1 and A^2 independently represent CR^{11} , and A^3 represents NR^{10} , O, or S, such as wherein A^1 and A^2 independently represent CR^{11} , for example A^1 and A^2 independently represent wherein R^{11} independently represents $-H$, $-F$, $-Cl$, a C_1 - C_4 -alkyl radical, $-CF_3$, or a C_3 - C_4 -cycloalkyl radical, and A^3 represents O; or wherein A^1 represents N and A^2 represents CR^{11} , and A^3 represents NR^{10} , O, or S.

[0048] In certain embodiments, for example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II-2 with X^1 representing C, said R^7 of Z^8 represents the bond directly attaching the W moiety with the carbonyl moiety:



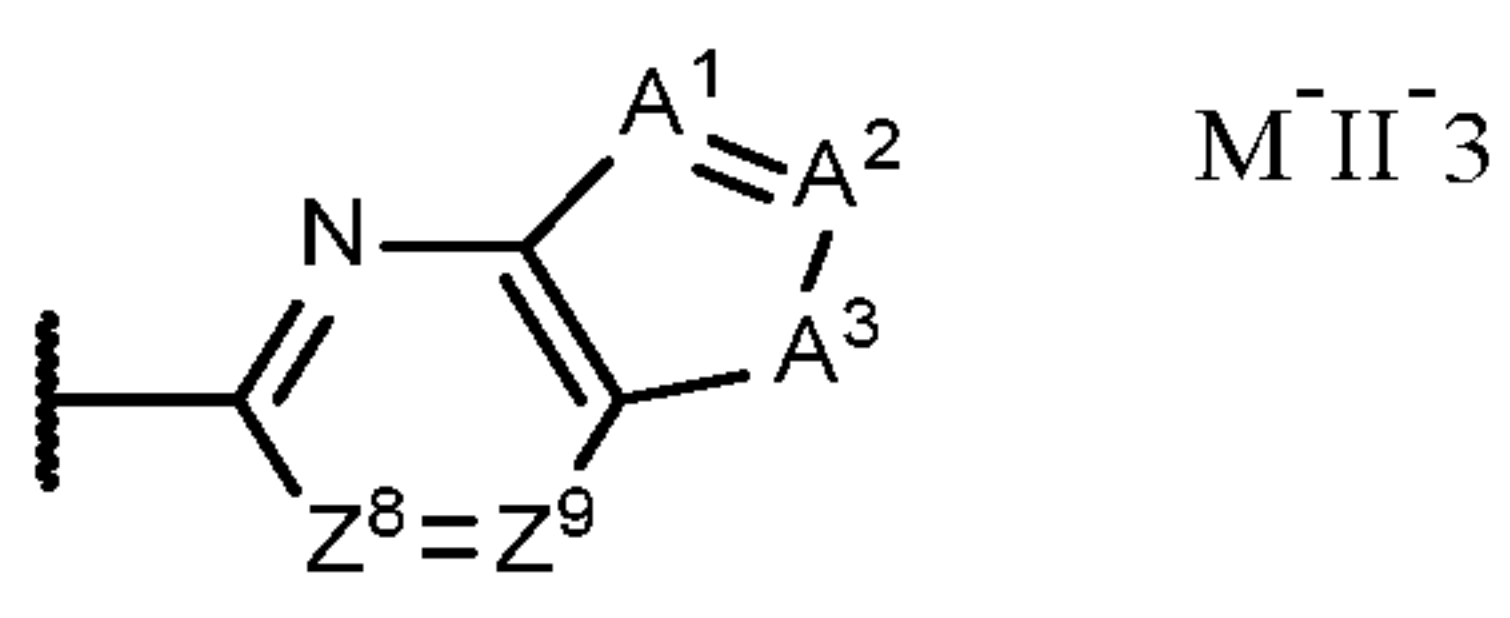
wherein A^1 and A^2 independently represent N or CR^{11} ; A^3 independently represents NR^{10} , O, or S; and Z^6 , Z^7 , and Z^9 independently represent CR^7 . For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II-2, wherein A^1 and A^2 independently represent CR^{11} , and A^3 represents NR^{10} , O, or S, such as wherein A^1 and A^2 independently represent CR^{11} , for example A^1 and A^2 independently represent wherein R^{11} independently represents $-H$, $-F$, $-Cl$, $-Br$, $-CN$, $-OR^{12}$, $-OCF_3$, a C_1 - C_4 -alkyl radical, $-CF_3$, or a C_3 - C_4 -cycloalkyl radical, and A^3 represents NR^{10} , O, or S; or wherein A^1 represents N and A^2 represents CR^{11} , and A^3 represents NR^{10} , O, or S.

[0049] For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II with X^1 representing C, wherein M-II represents a moiety represented by:



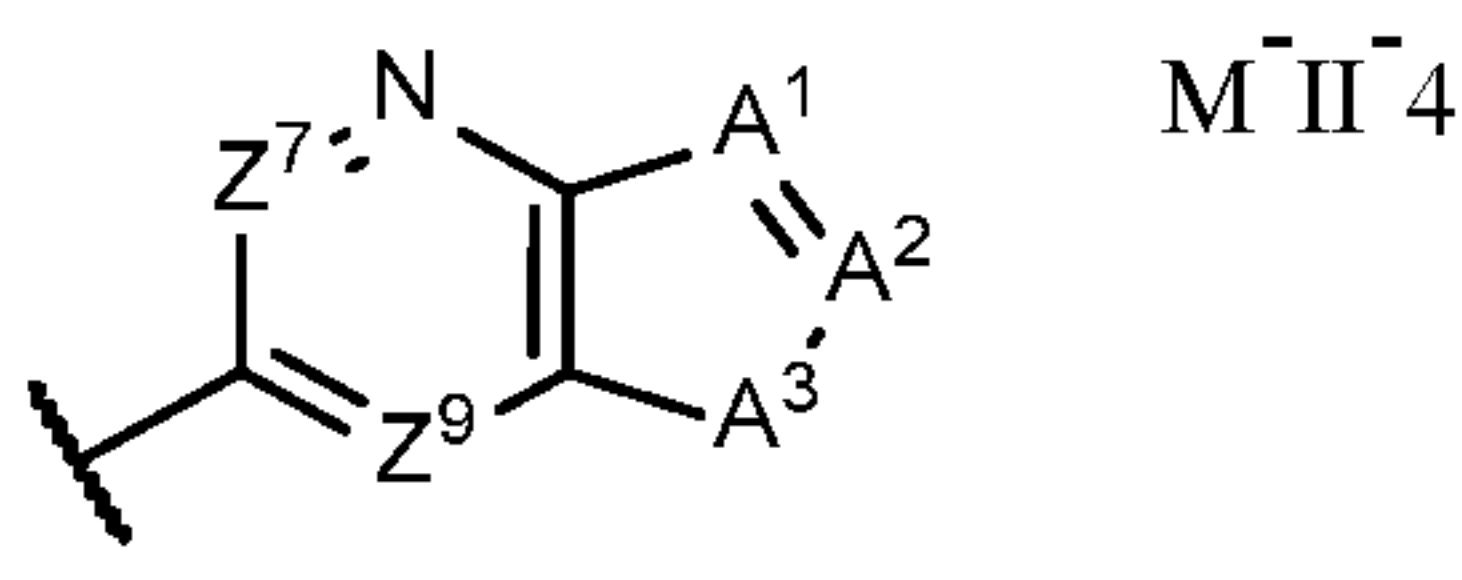
wherein A^1 and A^2 independently represent N or CR^{11} ; A^3 independently represents NR^{10} , O, or S; and Z^7 , Z^8 , and Z^9 independently represent CR^7 , with one of said R^7 of Z^7 , Z^8 , and Z^9 representing the bond directly attaching the W moiety with the carbonyl moiety.

[0050] In certain embodiments, for example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II-3 with X^1 representing C, said R^7 of Z^7 represents the bond directly attaching the W moiety with the carbonyl moiety:



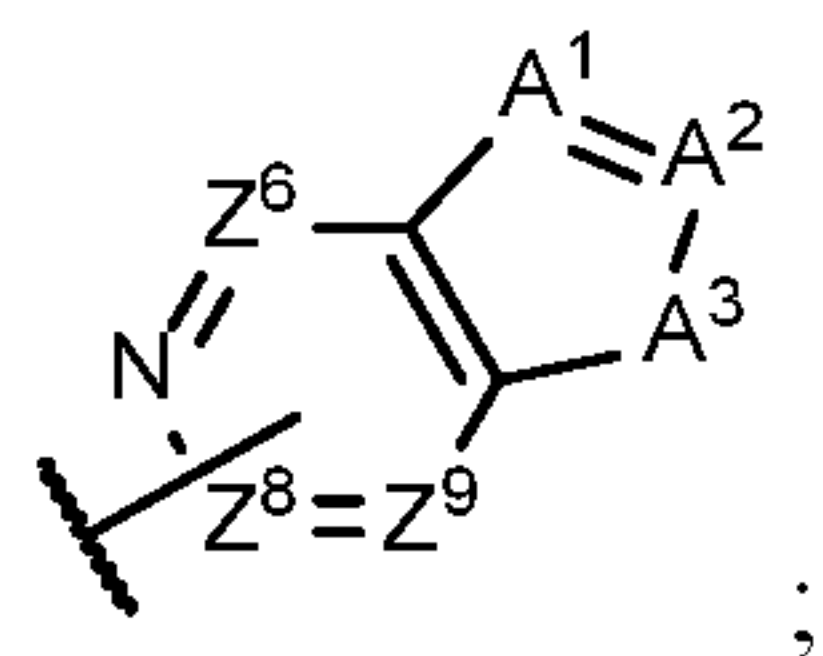
wherein A^1 and A^2 independently represent N or CR^{11} ; A^3 independently represents NR^{10} , O, or S; and Z^8 and Z^9 independently represent CR^7 . For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II-3, wherein A^1 and A^2 independently represent CR^{11} , and A^3 represents NR^{10} , O, or S; or wherein A^1 represents N and A^2 represents CR^{11} , and A^3 represents NR^{10} , O, or S.

[0051] In certain embodiments, for example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II-4 with X^1 representing C, said R^7 of Z^8 represents the bond directly attaching the W moiety with the carbonyl moiety:



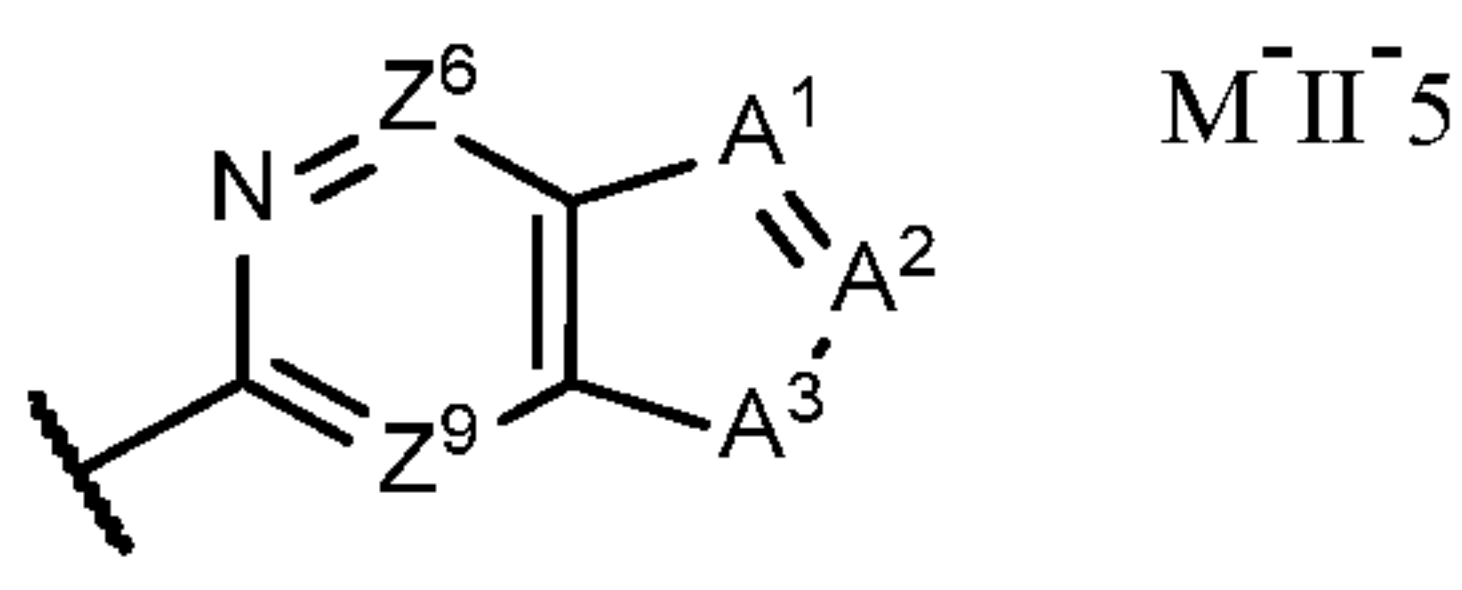
wherein A^1 and A^2 independently represent N or CR^{11} ; A^3 independently represents NR^{10} , O, or S; and Z^7 and Z^9 independently represent CR^7 . For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II-4, wherein A^1 and A^2 independently represent CR^{11} , and A^3 represents NR^{10} , O, or S; or wherein A^1 represents N and A^2 represents CR^{11} , and A^3 represents NR^{10} , O, or S.

[0052] For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II with X^1 representing C, wherein M-II represents a moiety represented by:



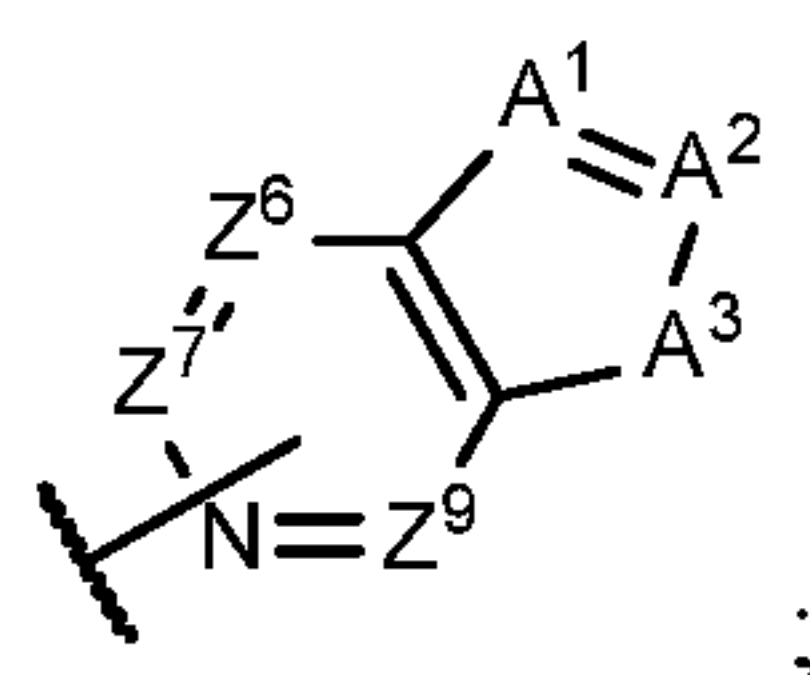
wherein A^1 and A^2 independently represent N or CR^{11} ; A^3 independently represents NR^{10} , O, or S; and Z^6 , Z^8 , and Z^9 independently represent CR^7 , with one of said R^7 of Z^6 , Z^8 , and Z^9 representing the bond directly attaching the W moiety with the carbonyl moiety.

[0053] In certain embodiments, for example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II-5 with X^1 representing C, said R^7 of Z^8 represents the bond directly attaching the W moiety with the carbonyl moiety:



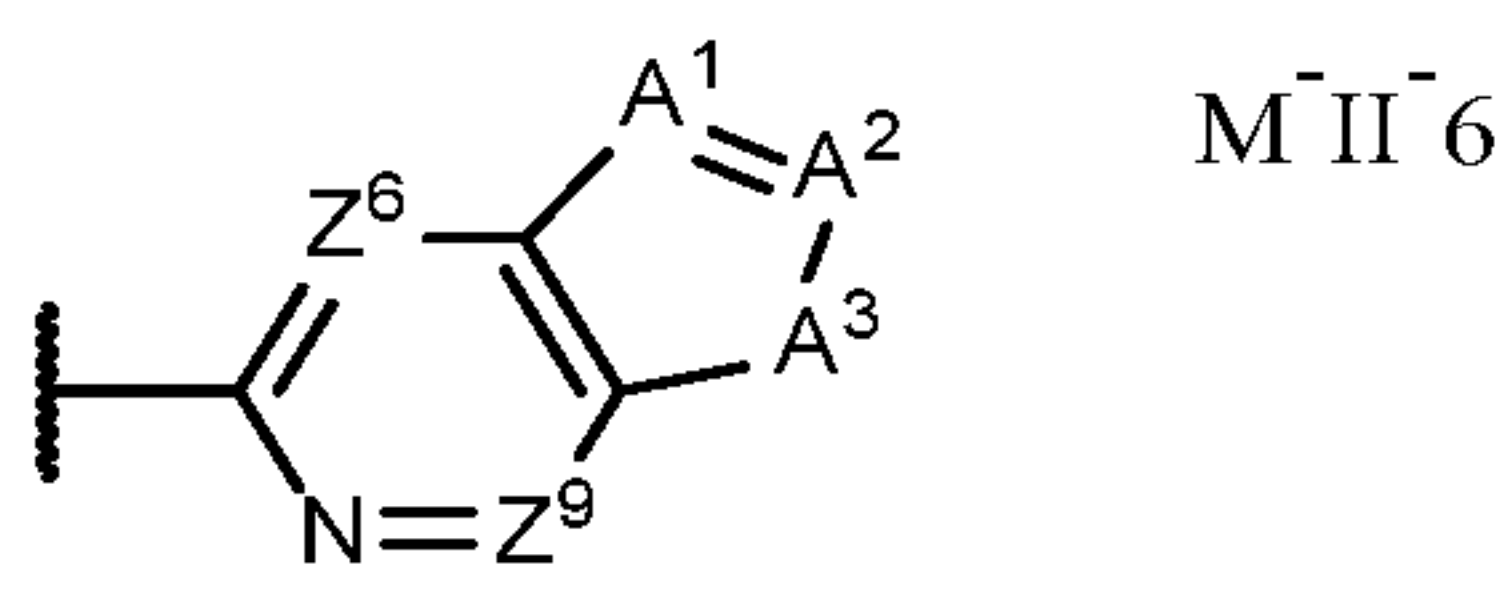
wherein A^1 and A^2 independently represent N or CR^{11} ; A^3 independently represents NR^{10} , O, or S; and Z^6 and Z^9 independently represent CR^7 . For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II-5, wherein A^1 and A^2 independently represent CR^{11} , and A^3 represents NR^{10} , O, or S; or wherein A^1 represents N and A^2 represents CR^{11} , and A^3 represents NR^{10} , O, or S.

[0054] For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II with X^1 representing C, wherein M-II represents a moiety represented by:



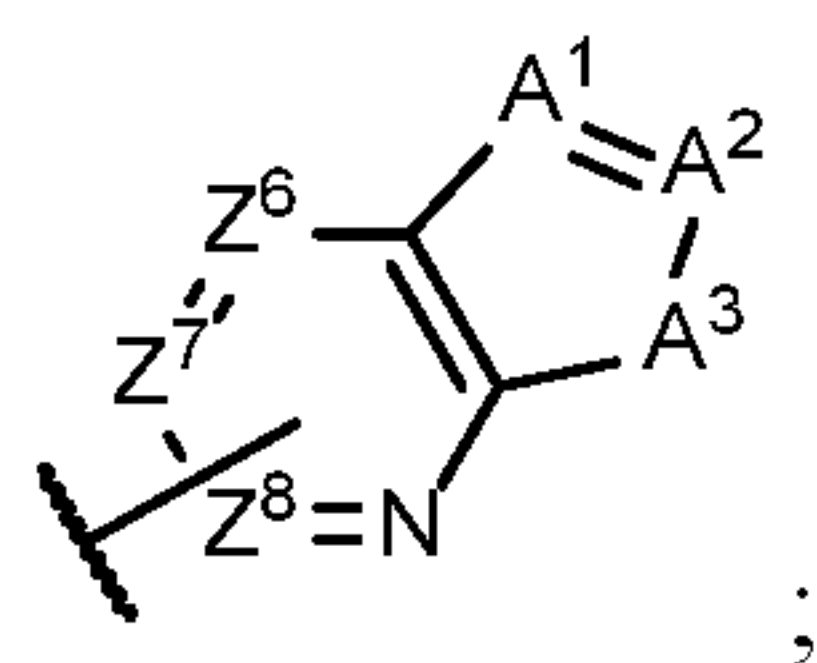
wherein A^1 and A^2 independently represent N or CR^{11} ; A^3 independently represents NR^{10} , O, or S; and Z^6 , Z^7 , and Z^9 independently represent CR^7 , with one of said R^7 of Z^6 , Z^7 , and Z^9 representing the bond directly attaching the W moiety with the carbonyl moiety.

[0055] In certain embodiments, for example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II-6 with X^1 representing C, said R^7 of Z^7 represents the bond directly attaching the W moiety with the carbonyl moiety:



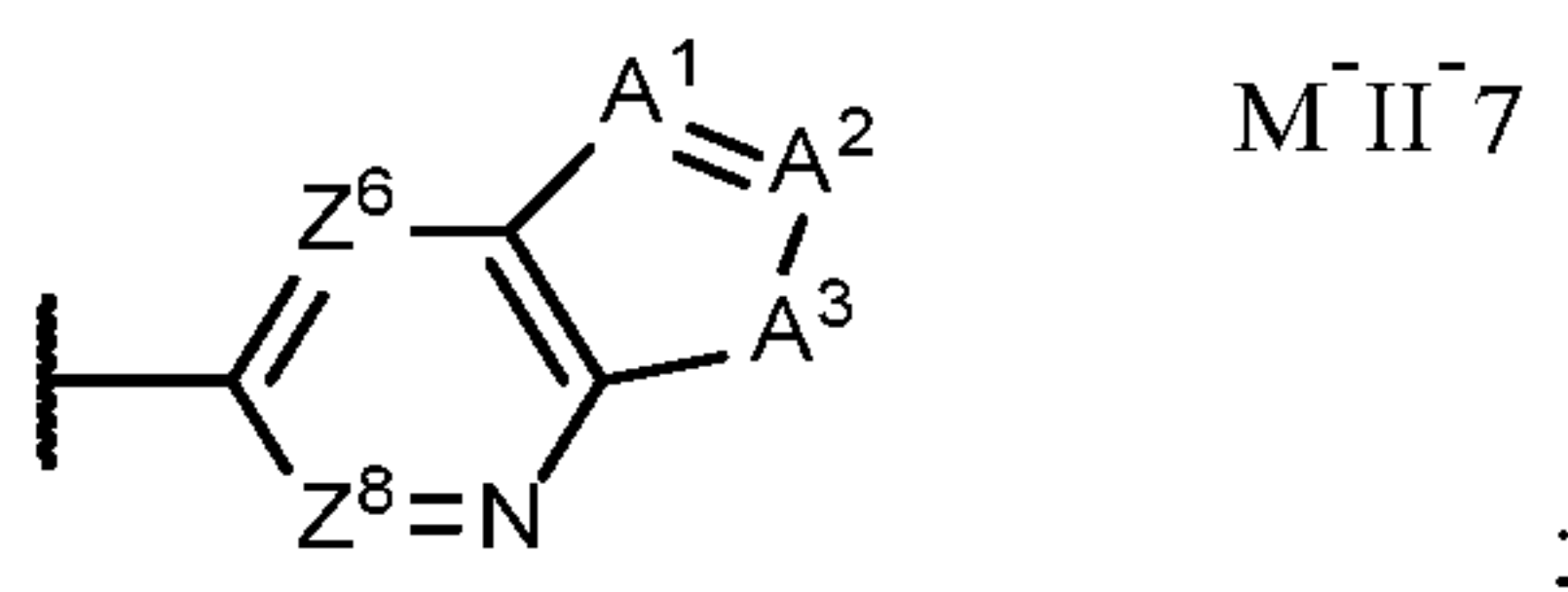
wherein A^1 and A^2 independently represent N or CR^{11} ; A^3 independently represents NR^{10} , O, or S; and Z^6 and Z^9 independently represent CR^7 . For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II-6, wherein A^1 and A^2 independently represent CR^{11} , for example, wherein R^{11} independently represents $-H$, $-F$, $-Cl$, $-OCF_3$, a C_1 - C_4 -alkyl radical, $-CF_3$, or a C_3 - C_4 -cycloalkyl radical, such as wherein R^{11} independently represents $-H$, and A^3 represents NR^{10} , O, or S, for example, wherein A^3 represents O; or wherein A^1 represents N and A^2 represents CR^{11} , and A^3 represents NR^{10} , O, or S.

[0056] For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II with X^1 representing C, wherein M-II represents a moiety represented by:



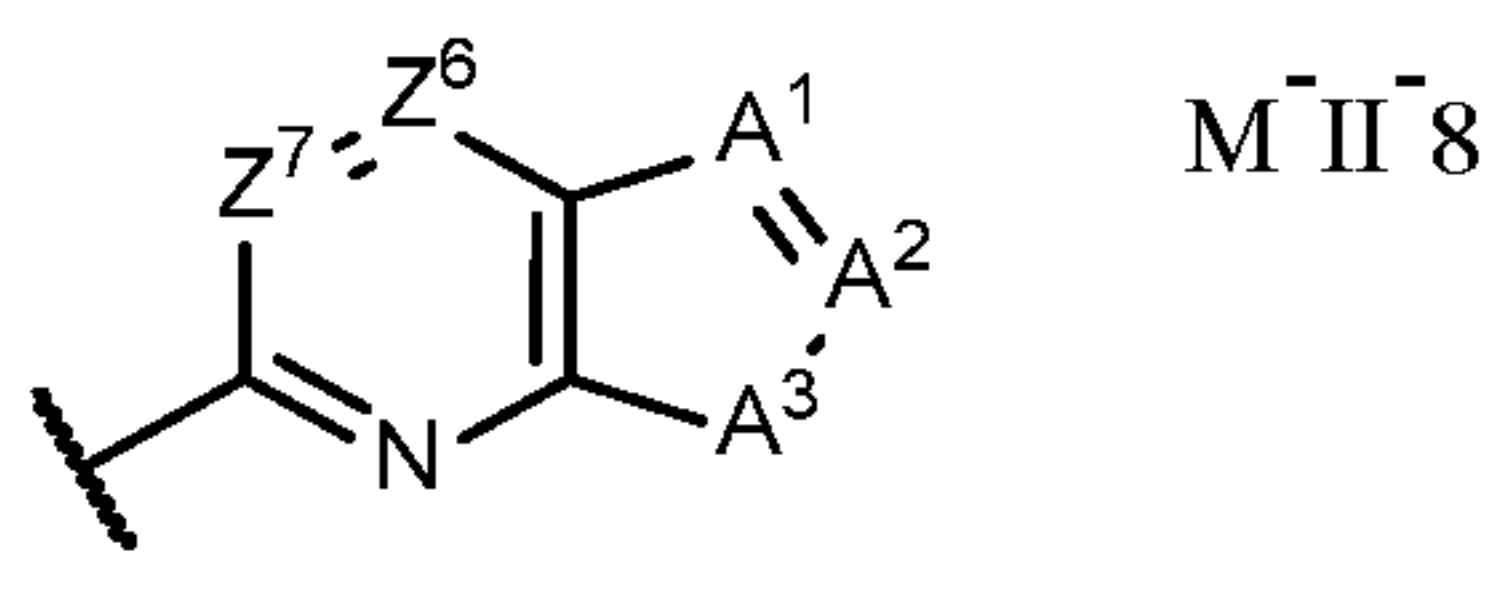
wherein A^1 and A^2 independently represent N or CR^{11} ; A^3 independently represents NR^{10} , O, or S; and Z^6 , Z^7 , and Z^8 independently represent CR^7 , with one of said R^7 of Z^6 , Z^7 , and Z^8 representing the bond directly attaching the W moiety with the carbonyl moiety.

[0057] In certain embodiments, for example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II-7 with X^1 representing C, said R^7 of Z^7 represents the bond directly attaching the W moiety with the carbonyl moiety:



wherein A^1 and A^2 independently represent N or CR^{11} ; A^3 independently represents NR^{10} , O, or S; and Z^6 and Z^8 independently represent CR^7 . For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II-7, wherein A^1 and A^2 independently represent CR^{11} , and A^3 represents NR^{10} , O, or S; or wherein A^1 represents N and A^2 represents CR^{11} , and A^3 represents NR^{10} , O, or S.

[0058] In certain embodiments, for example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II-8 with X^1 representing C, said R^7 of Z^8 represents the bond directly attaching the W moiety with the carbonyl moiety:



wherein A^1 and A^2 independently represent N or CR^{11} ; A^3 independently represents NR^{10} , O, or S; and Z^6 and Z^7 independently represent CR^7 . For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II-8, wherein A^1 and A^2 independently represent CR^{11} , and A^3 represents NR^{10} , O, or S; or wherein A^1 represents N and A^2 represents CR^{11} , and A^3 represents NR^{10} , O, or S.

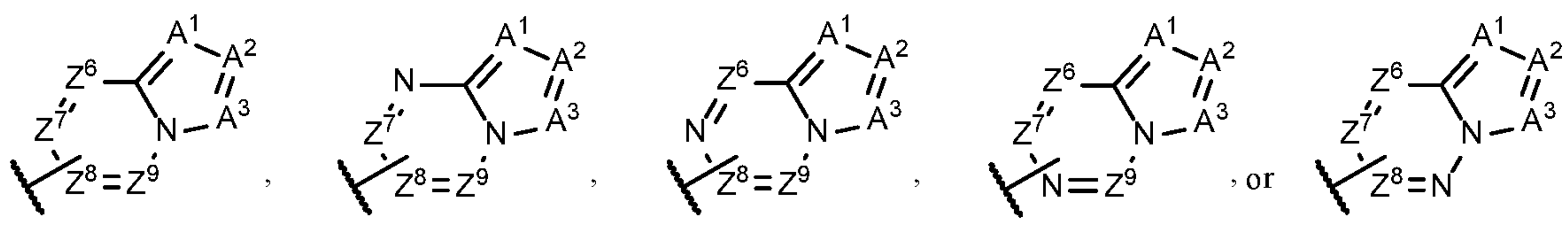
[0059] In certain embodiments, for example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by any one of ring systems M-II-1 to M-II-8, wherein R^7 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-OR^8$; $-OCF_3$; a

C₁-C₆-alkyl radical; a C₁-C₆-haloalkyl radical; a C₃-C₆-cycloalkyl radical; wherein the C₁-C₆-alkyl radical may be substituted with up to 4 radical substituents comprising: -D, -F, -Cl, -Br, -I, -CN, -NO₂, -OR⁸, -(CH₂)_mOR⁸, a branched or unbranched C₁-C₆-alkyl radical, a C₃-C₆-cycloalkyl radical, a C₁-C₆-hydroxyalkyl radical, or a C₁-C₆-haloalkyl radical; for example, wherein R⁷ independently represents -H or -D.

[0060] In certain embodiments, for example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by any one of ring systems M-II-1 to M-II-8, wherein R¹¹ independently represents -H; -F; -Cl; -Br; -I; -CN; -OR¹²; -(CH₂)_mOR¹²; -OCF₃; a C₁-C₆-alkyl radical; a C₁-C₆-haloalkyl radical; or a C₃-C₆-cycloalkyl radical; for example, wherein R¹¹ independently represents -H; -F; -Cl; -Br; -I; -CN; -OR¹²; -(CH₂)_mOR¹²; -OCF₃; a C₁-C₄-alkyl radical; or a C₁-C₂-haloalkyl radical; for example, wherein R¹¹ independently represents -H; -F; -Cl; -Br; -I; -CN; -OR¹²; -OCF₃; a C₁-C₄-alkyl radical; -CF₃; or a C₃-C₄-cycloalkyl radical.

[0061] In certain embodiments, for example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by any one of ring systems M-II-1 to M-II-8, wherein R¹² independently represents -H, a branched or unbranched C₁-C₄-alkyl radical, or a C₃-C₆-cycloalkyl radical.

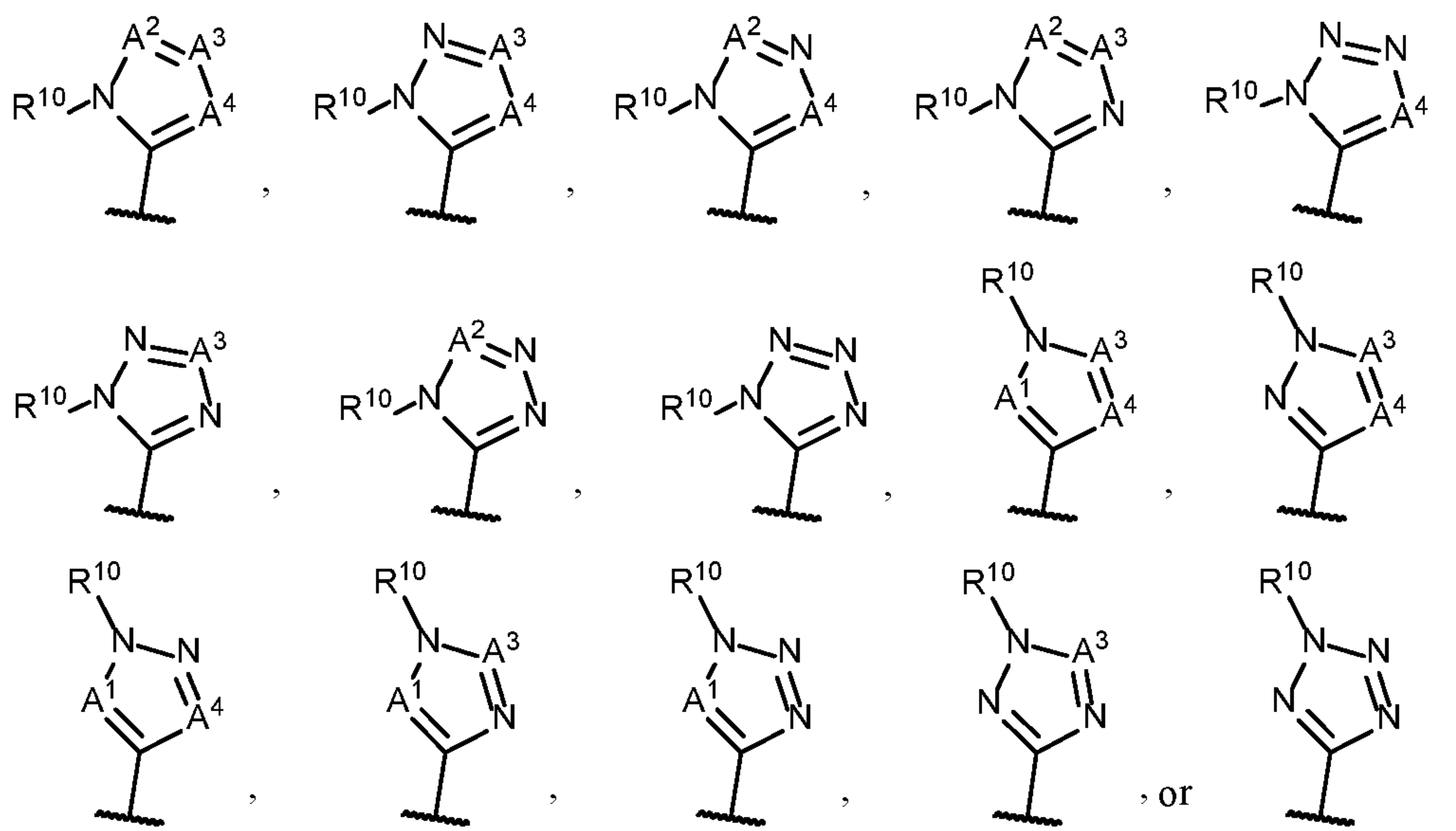
[0062] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II. In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II, wherein X¹ represents N. For example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II, wherein M-II represents a moiety represented by one of the following:



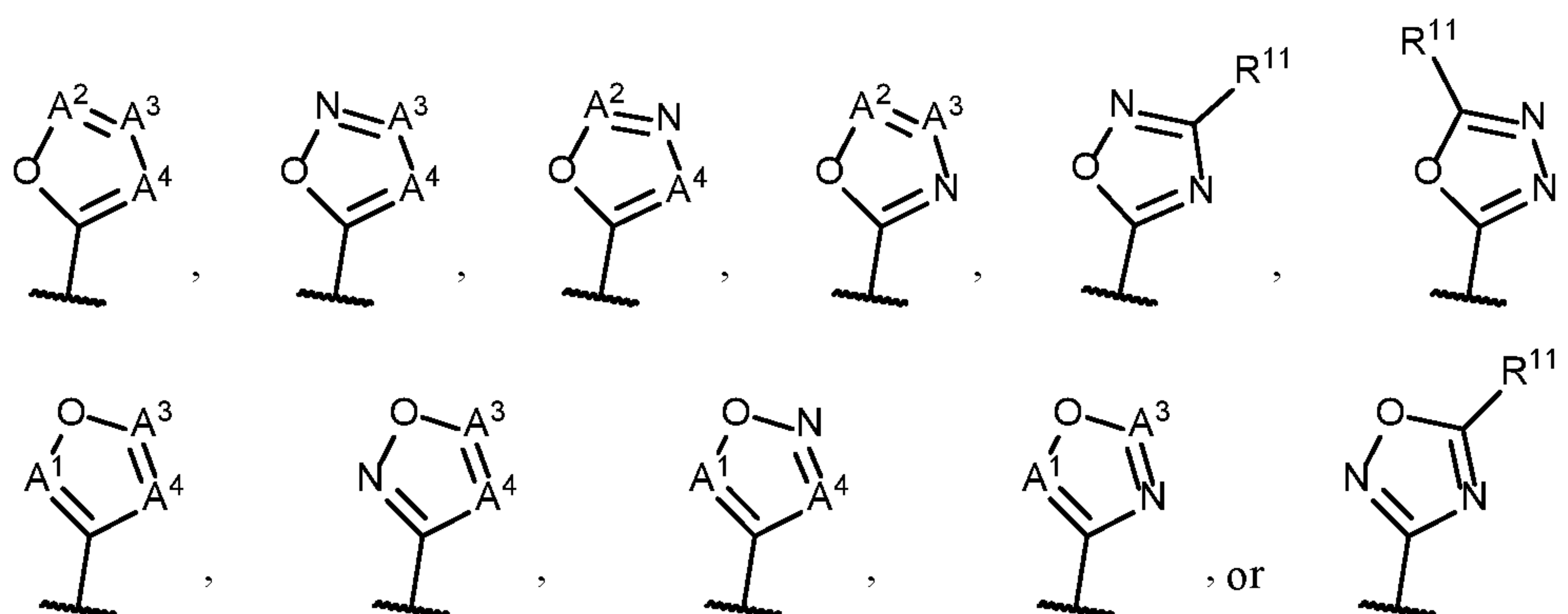
wherein A¹, A², and A³, independently represent N or CR¹¹. In certain embodiments, for example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II, wherein A¹ independently represents CR¹¹; and A² and A³ independently represent N or CR¹¹; for example, wherein A² independently represents CR¹¹; and A¹ and A³ independently represent N or CR¹¹; for example, wherein A³ independently represents CR¹⁰; and A¹ and A² independently represent N or CR¹¹; or in certain embodiments, for example, wherein each of A¹, A², and A³, represents N. In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II, wherein either Z⁶ or Z⁷ represents CR⁷ with said R⁷ representing the bond directly attaching the

W moiety with the carbonyl moiety, or wherein either Z^8 or Z^9 represents CR^7 with said R^7 representing the bond directly attaching the W moiety with the carbonyl moiety.

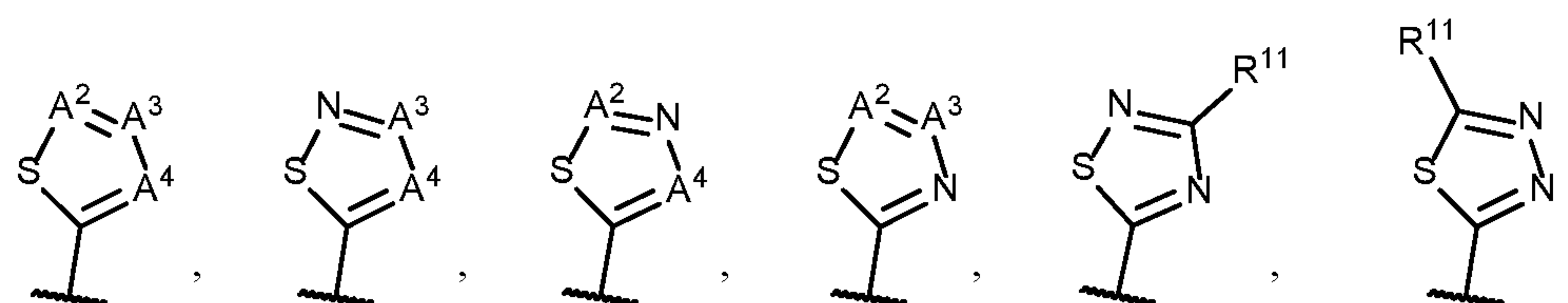
[0063] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-III. In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-III, wherein M-III represents a moiety represented by one of the following ring systems:

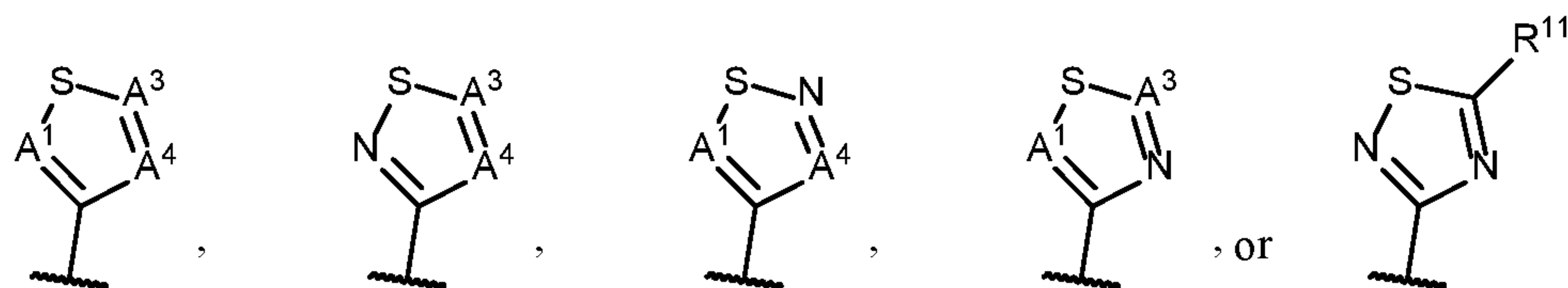


[0064] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-III, wherein M-III represents a moiety represented by one of the following:

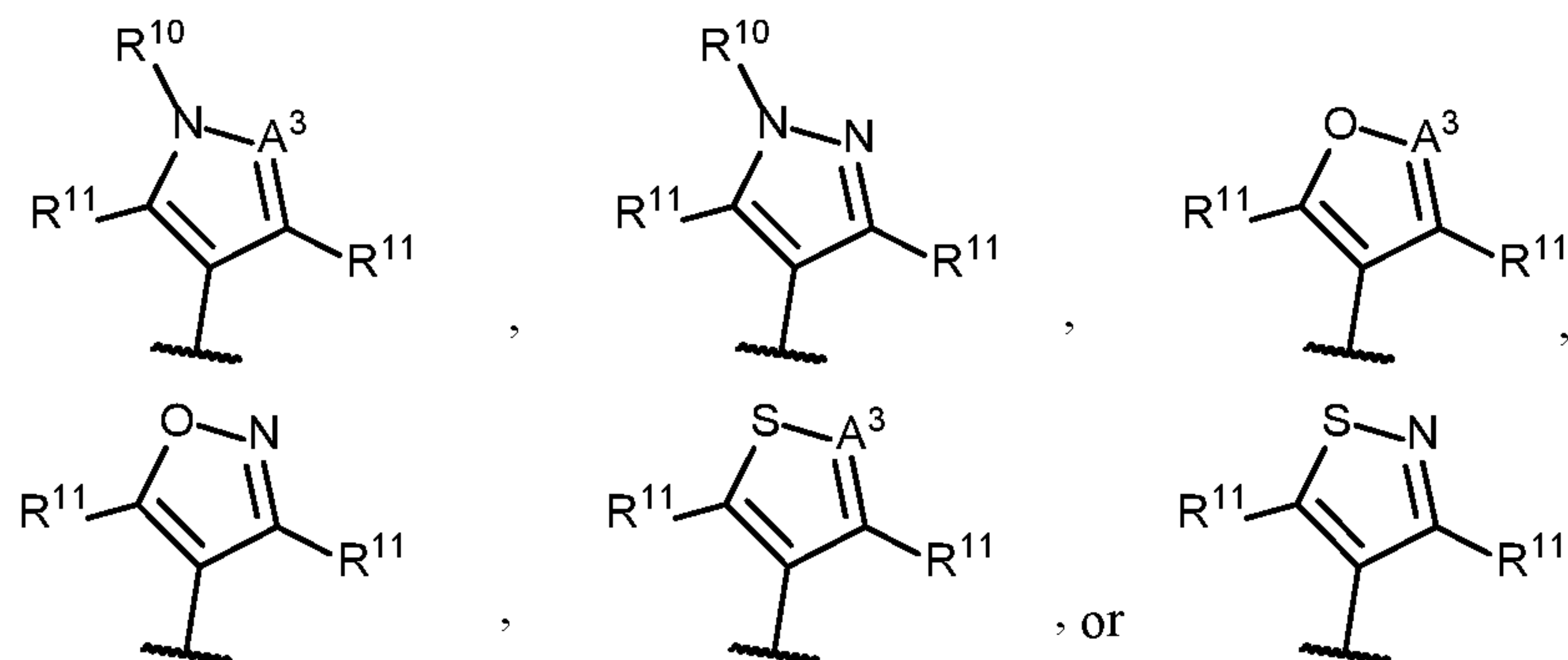


[0065] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-III, wherein M-III represents a moiety represented by one of the following:



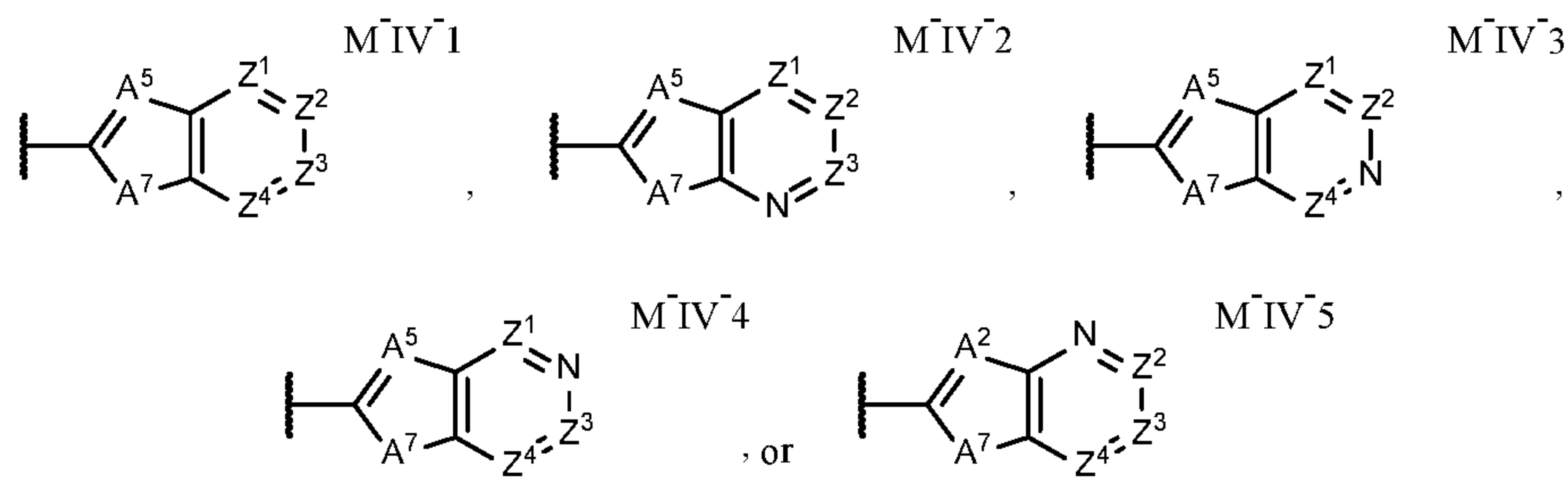


[0066] For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-III, wherein M-III represents a moiety represented by one of the following:



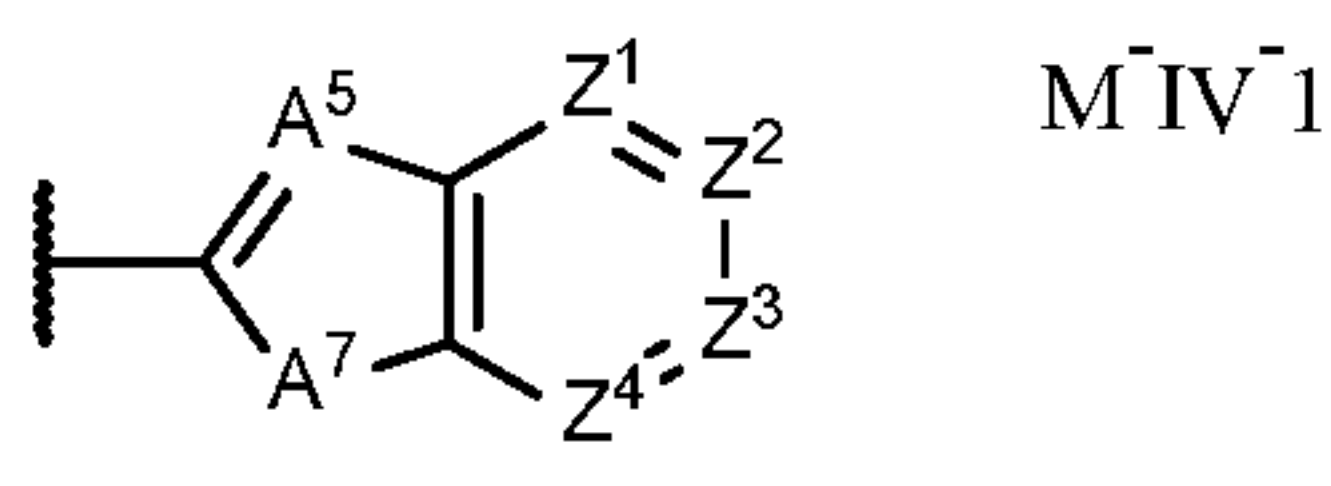
[0067] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV.

[0068] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein X^2 represents C. For example, the amide compound represented by Formula (I), (II), or (III), comprising W representing the moiety represented by the ring system M-IV, may comprise a moiety represented by one of the following:



wherein A^5 represents N or CR^{15} , preferably A^5 represents CR^{15} , wherein R^{15} preferably represents $-H$; and A^7 represents NR^{14} , $N(CH_2)_mR^{14}$, O, or S, preferably A^7 represents O or S.

[0069] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein M-IV represents a moiety represented by ring system M-IV-1:



wherein Z^1 , Z^2 , Z^3 , and Z^4 independently represent CR^4 . For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the

moiety represented by the ring system M-IV-1, wherein A^5 represents N or CR^{15} , preferably A^5 represents CR^{15} , wherein R^{15} preferably represents $-H$; and A^7 represents NR^{14} , $N(CH_2)_mR^{14}$, O, or S, preferably A^7 represents O or S; and wherein R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^5$; $-N(R^5)(R^6)$; $-SO_2(CH_2)_mR^5$; $-OCF_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; or a heteroaryl radical; wherein the C_1 - C_6 -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^5$, $-N(R^5)(R^6)$, $-SO_2(CH_2)_mR^5$, $-OCF_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, a C_1 - C_6 -hydroxyalkyl radical, or a C_1 - C_6 -haloalkyl radical. For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV-1, wherein R^5 and R^6 independently represent $-H$; a branched or unbranched C_1 - C_3 -alkyl radical; or a C_3 - C_6 -cycloalkyl radical.

[0070] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein M-IV represents a moiety represented by ring system M-IV-1, wherein A^5 represents N or CR^{15} , preferably A^5 represents CR^{15} , wherein R^{15} preferably represents $-H$; and A^7 represents NR^{14} , $N(CH_2)_mR^{14}$, O, or S, preferably A^7 represents O or S; and wherein Z^1 and Z^2 independently represent CH ; and Z^3 and Z^4 independently represent CR^4 , wherein R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-CN$; $-OR^5$; $-N(R^5)(R^6)$; $-SO_2(CH_2)_mR^5$; $-OCF_3$; a C_1 - C_4 -alkyl radical; $-CF_3$; a C_3 - C_4 -cycloalkyl radical; a 6 membered-heterocycloalkyl radical; or a heteroaryl radical; wherein the C_1 - C_4 -alkyl radical, the 6 membered-heterocycloalkyl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^5$, $-N(R^5)(R^6)$, $-SO_2(CH_2)_mR^5$, $-OCF_3$, a branched or unbranched C_1 - C_4 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, a C_1 - C_4 -hydroxyalkyl radical, or a C_1 - C_2 -haloalkyl radical.

[0071] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein M-IV represents a moiety represented by ring system M-IV-1, wherein A^5 represents N or CR^{15} , preferably A^5 represents CR^{15} , wherein R^{15} preferably represents $-H$; and A^7 represents NR^{14} , $N(CH_2)_mR^{14}$, O, or S, preferably A^7 represents O or S; and wherein Z^1 , Z^2 , and Z^4 independently represent CH ; and Z^3 independently represent CR^4 , wherein R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-CN$; $-OR^5$; $-N(R^5)(R^6)$; $-SO_2(CH_2)_mR^5$; $-OCF_3$; a C_1 - C_4 -alkyl radical; $-CF_3$; a C_3 - C_4 -cycloalkyl radical; a 6 membered-heterocycloalkyl radical; or a heteroaryl radical; wherein the C_1 - C_4 -alkyl radical, the 6 membered-heterocycloalkyl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^5$, $-N(R^5)(R^6)$, $-SO_2(CH_2)_mR^5$, $-OCF_3$, a branched or unbranched C_1 - C_4 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, a C_1 - C_4 -hydroxyalkyl radical, or a C_1 - C_2 -haloalkyl radical.

[0072] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein M-IV represents a moiety represented by ring system M-IV-1, wherein A^5 represents N or CR^{15} , preferably A^5 represents CR^{15} , wherein R^{15} preferably represents $-H$; and A^7 represents NR^{14} , $N(CH_2)_mR^{14}$, O, or S, preferably A^7 represents O or S; and wherein Z^1 , Z^2 , and Z^4 independently represent CH; and Z^3 independently represent CR^4 , wherein R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-OR^5$; $-N(R^5)(R^6)$; $-OCF_3$; a C_1 - C_4 -alkyl radical; $-CF_3$; or a C_3 - C_4 -cycloalkyl radical; wherein the C_1 - C_4 -alkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, a branched or unbranched C_1 - C_4 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, a C_1 - C_4 -hydroxyalkyl radical, or a C_1 - C_2 -haloalkyl radical; and wherein R^5 and R^6 independently represent $-H$; a branched or unbranched C_1 - C_3 -alkyl radical; or a C_3 - C_6 -cycloalkyl radical.

[0073] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein M-IV represents a moiety represented by ring system M-IV-1, wherein A^5 represents N or CR^{15} , preferably A^5 represents CR^{15} , wherein R^{15} preferably represents $-H$; and A^7 represents NR^{14} , $N(CH_2)_mR^{14}$, O, or S, preferably A^7 represents O or S, for example, A^7 represents S; and wherein Z^1 , Z^2 , and Z^4 independently represent CH; and Z^3 independently represent CR^4 , wherein R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-OCH_3$; $-NH_2$; $-CH_3$; $-CF_3$; or a cyclopropyl radical, for example, wherein R^4 independently represents $-H$, $-D$, $-F$, $-Cl$, $-Br$, $-OCH_3$, $-CH_3$, or a cyclopropyl radical.

[0074] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein M-IV represents a moiety represented by ring system M-IV-1, wherein A^5 represents N or CR^{15} , preferably A^5 represents CR^{15} , wherein R^{15} preferably represents $-H$; and A^7 represents NR^{14} , $N(CH_2)_mR^{14}$, O, or S, preferably A^7 represents O or S; and wherein Z^1 , Z^2 , and Z^3 independently represent CH; and Z^4 independently represent CR^4 , wherein R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-CN$; $-OR^5$; $-N(R^5)(R^6)$; $-SO_2(CH_2)_mR^5$; $-OCF_3$; a C_1 - C_4 -alkyl radical; $-CF_3$; a C_3 - C_4 -cycloalkyl radical; a 6 membered-heterocycloalkyl radical; or a heteroaryl radical; wherein the C_1 - C_4 -alkyl radical, the 6 membered-heterocycloalkyl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^5$, $-N(R^5)(R^6)$, $-SO_2(CH_2)_mR^5$, $-OCF_3$, a branched or unbranched C_1 - C_4 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, a C_1 - C_4 -hydroxyalkyl radical, or a C_1 - C_2 -haloalkyl radical.

[0075] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein M-IV represents a moiety represented by ring system M-IV-1, wherein A^5 represents N or CR^{15} , preferably A^5 represents CR^{15} , wherein R^{15} preferably represents $-H$; and A^7 represents NR^{14} , $N(CH_2)_mR^{14}$, O, or S, preferably A^7 represents O or S; and wherein Z^1 , Z^2 , and Z^3 independently represent CH; and Z^4 independently represent CR^4 , wherein R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-OR^5$; $-$

$N(R^5)(R^6)$; $-OCF_3$; a C_1 - C_4 -alkyl radical; $-CF_3$; or a C_3 - C_4 -cycloalkyl radical; wherein the C_1 - C_4 -alkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, a branched or unbranched C_1 - C_4 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, a C_1 - C_4 -hydroxyalkyl radical, or a C_1 - C_2 -haloalkyl radical; and wherein R^5 and R^6 independently represent $-H$; a branched or unbranched C_1 - C_3 -alkyl radical; or a C_3 - C_6 -cycloalkyl radical.

[0076] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein M-IV represents a moiety represented by ring system M-IV-1, wherein A^5 represents N or CR^{15} , preferably A^5 represents CR^{15} , wherein R^{15} preferably represents $-H$; and A^7 represents NR^{14} , $N(CH_2)_mR^{14}$, O, or S, preferably A^7 represents O or S; and wherein Z^1 , Z^2 , and Z^3 independently represent CH; and Z^4 independently represent CR^4 , wherein R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-OCH_3$; $-NH_2$; $-CH_3$; $-CF_3$; or a cyclopropyl radical.

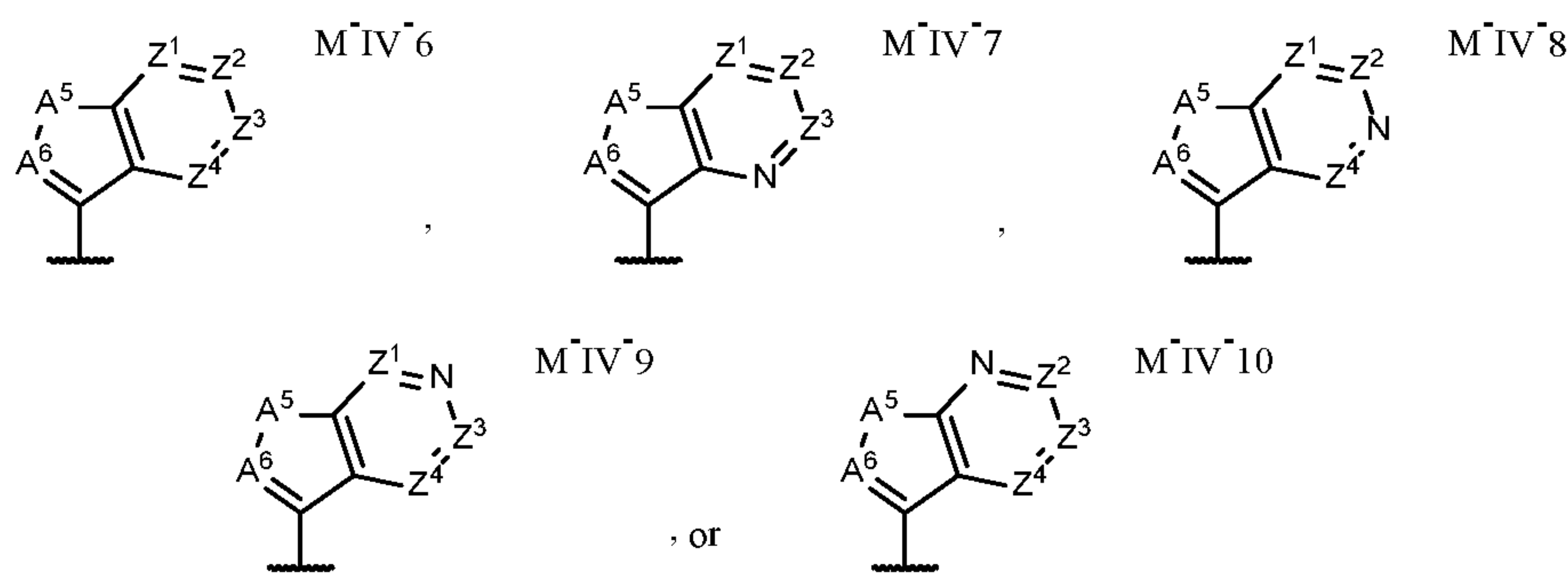
[0077] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein M-IV represents a moiety represented by ring system M-IV-1, wherein A^5 represents N or CR^{15} , preferably A^5 represents CR^{15} , wherein R^{15} preferably represents $-H$; and A^7 represents NR^{14} , $N(CH_2)_mR^{14}$, O, or S, preferably A^7 represents O or S; and wherein Z^1 , Z^2 , and Z^3 independently represent CH; and Z^4 independently represent CR^4 , wherein R^4 independently represents $-F$; $-Cl$; $-OCH_3$; $-CH_3$; $-CF_3$; or a cyclopropyl radical.

[0078] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein M-IV represents a moiety represented by ring system M-IV-1, wherein A^5 represents N or CR^{15} , preferably A^5 represents CR^{15} , wherein R^{15} preferably represents $-H$; and A^7 represents NR^{14} , $N(CH_2)_mR^{14}$, O, or S, preferably A^7 represents O or S; and wherein Z^1 , Z^2 , and Z^3 independently represent CH; and Z^4 independently represent CR^4 , wherein R^4 independently represents $-H$; $-F$; $-Cl$; $-CN$; $-OCH_3$; $-OCH_2CH_3$; $-OCF_3$; or a cyclopropyl radical, for example, wherein R^4 independently represents $-H$; $-F$; $-CN$; $-OCH_2CH_3$; $-OCF_3$; or a cyclopropyl radical.

[0079] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein M-IV represents a moiety represented by ring system M-IV-1, wherein A^5 represents N or CR^{15} , preferably A^5 represents CR^{15} , wherein R^{15} preferably represents $-H$; and A^7 represents NR^{14} , $N(CH_2)_mR^{14}$, O, or S, preferably A^7 represents O or S; and wherein Z^1 independently represents CH; Z^2 independently represents CR^4 , wherein R^4 independently represents $-H$ or $-F$; Z^3 independently represents CR^4 , wherein R^4 independently represents $-H$; $-D$; $-Cl$; $-Br$; $-OCH_3$; $-CH_3$; or a cyclopropyl radical; and Z^4 independently represents CR^4 , wherein R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-CN$; $-OCH_2CH_3$; $-OCF_3$; or a cyclopropyl radical; for example, wherein Z^1 and Z^2 independently represent

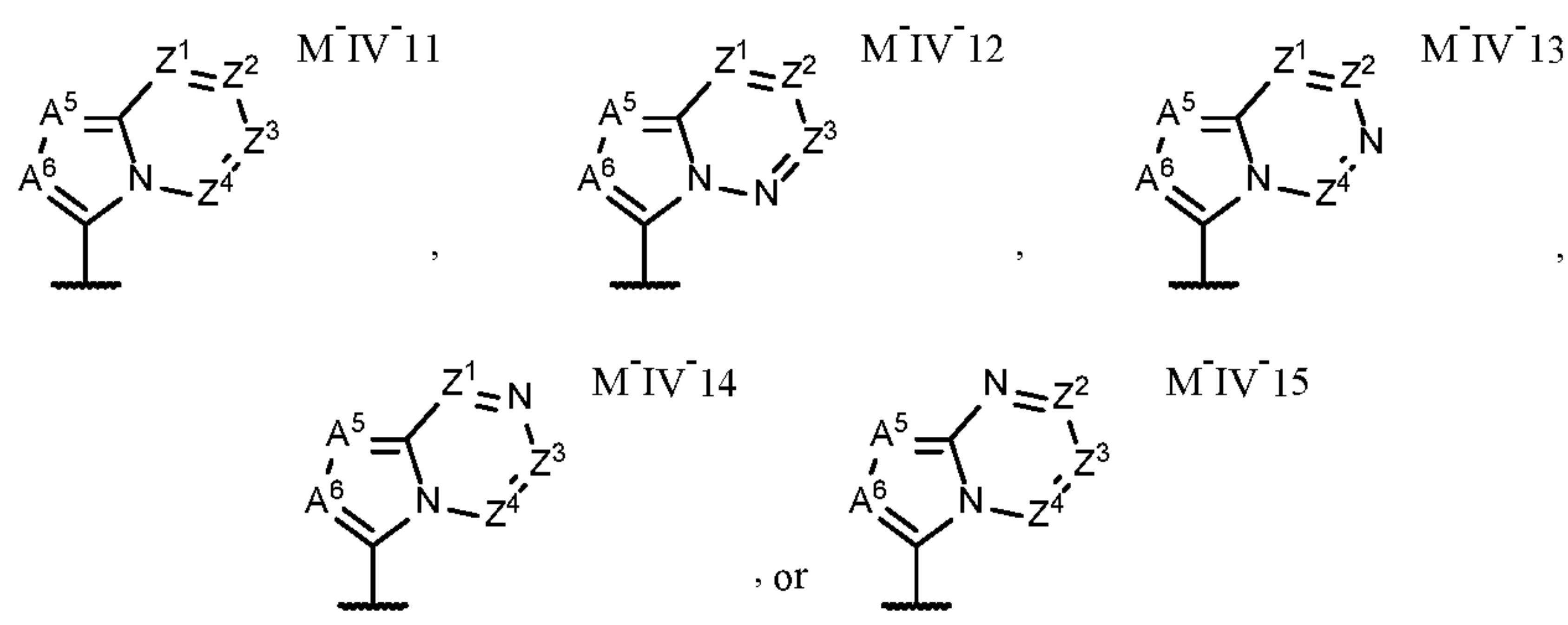
CH; Z^3 independently represents CR^4 , wherein R^4 independently represents $-Cl$ or $-CH_3$; and Z^4 independently represents CR^4 , wherein R^4 independently represents $-F$ or $-Cl$.

[0080] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein X^2 represents C. For example, the amide compound represented by Formula (I), (II), or (III), comprising W representing the moiety represented by the ring system M-IV, may comprise a moiety represented by one of the following:



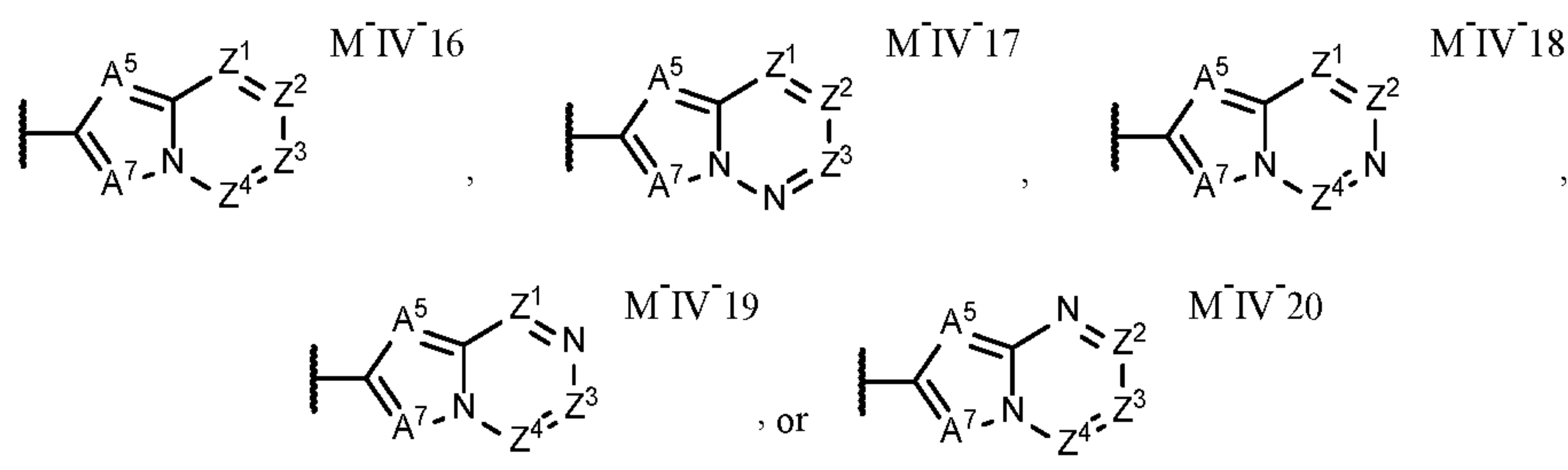
wherein A^5 represents NR^{14} ; O; or S, preferably A^5 represents O or S.

[0081] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein X^2 represents N. For example, the amide compound represented by Formula (I), (II), or (III), comprising W representing the moiety represented by the ring system M-IV, may comprise a moiety represented by one of the following:



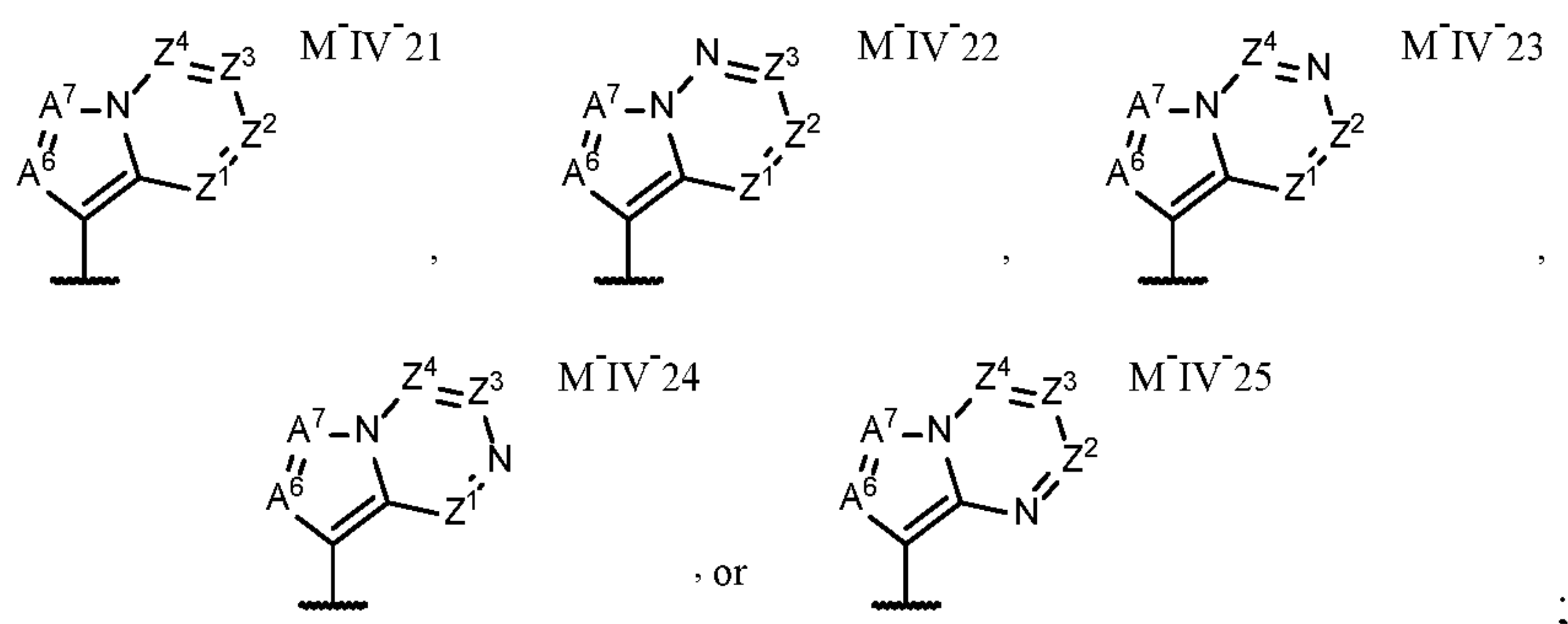
wherein A^5 and A^6 independently represent N or CR^{15} , preferably A^5 and A^6 represents CR^{15} , wherein R^{15} preferably represents $-H$.

[0082] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein X^2 represents N. For example, the amide compound represented by Formula (I), (II), or (III), comprising W representing the moiety represented by the ring system M-IV, may comprise a moiety represented by one of the following:



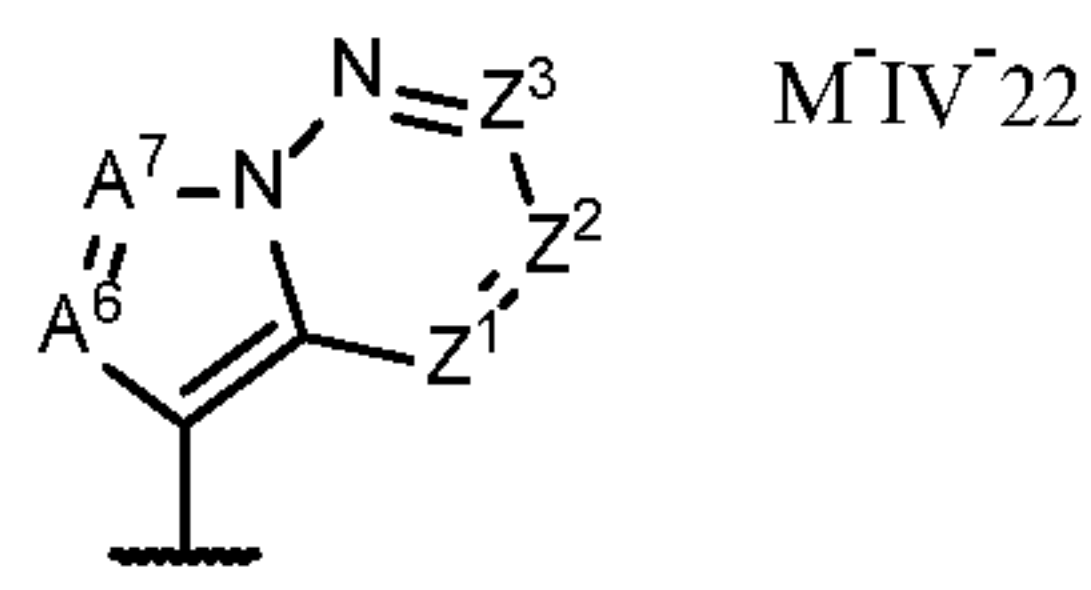
wherein A⁵ and A⁷ independently represent N or CR¹⁵.

[0083] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein X² represents N. For example, the amide compound represented by Formula (I), (II), or (III), comprising W representing the moiety represented by the ring system M-IV, may comprise a moiety represented by one of the following:



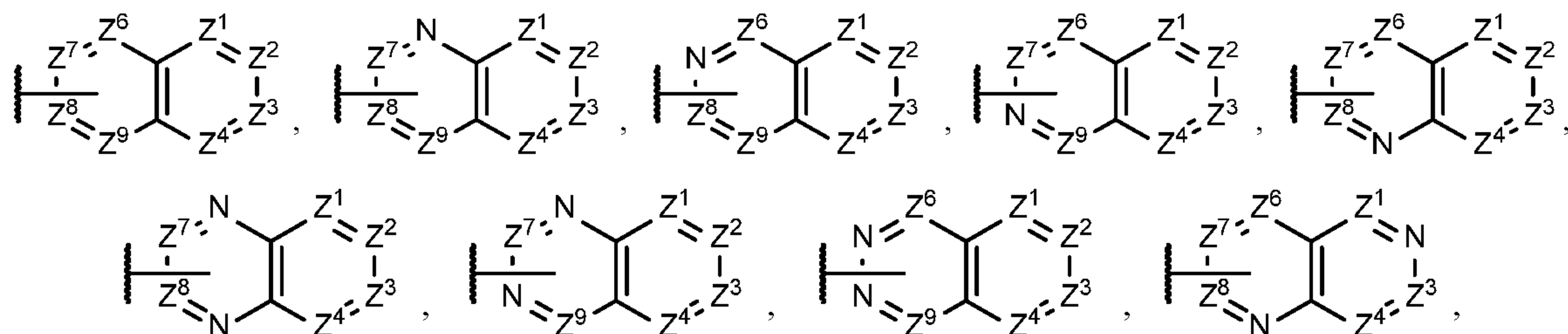
wherein A⁶ and A⁷ independently represent N or CR¹⁵.

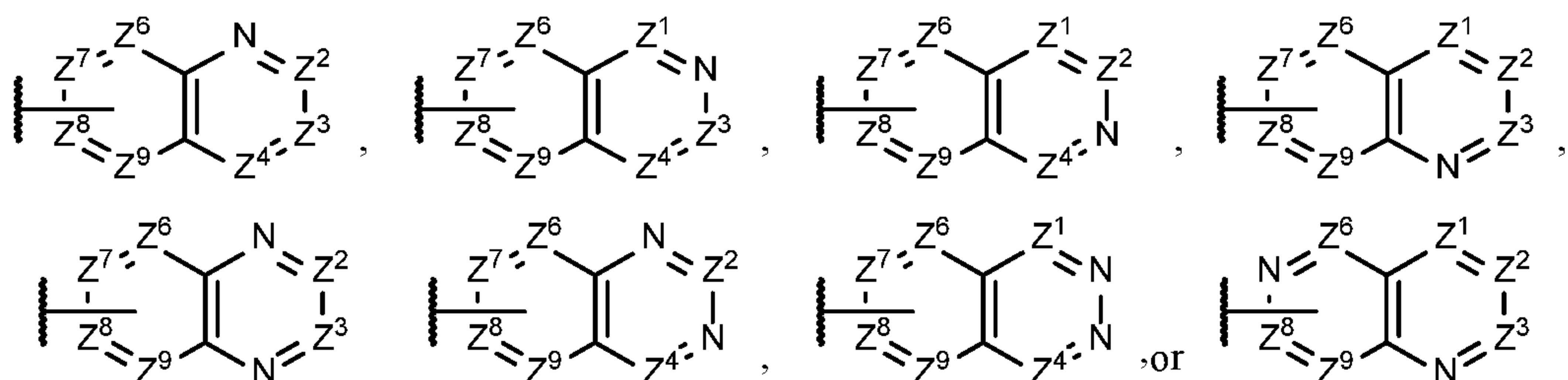
[0084] For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV-22:



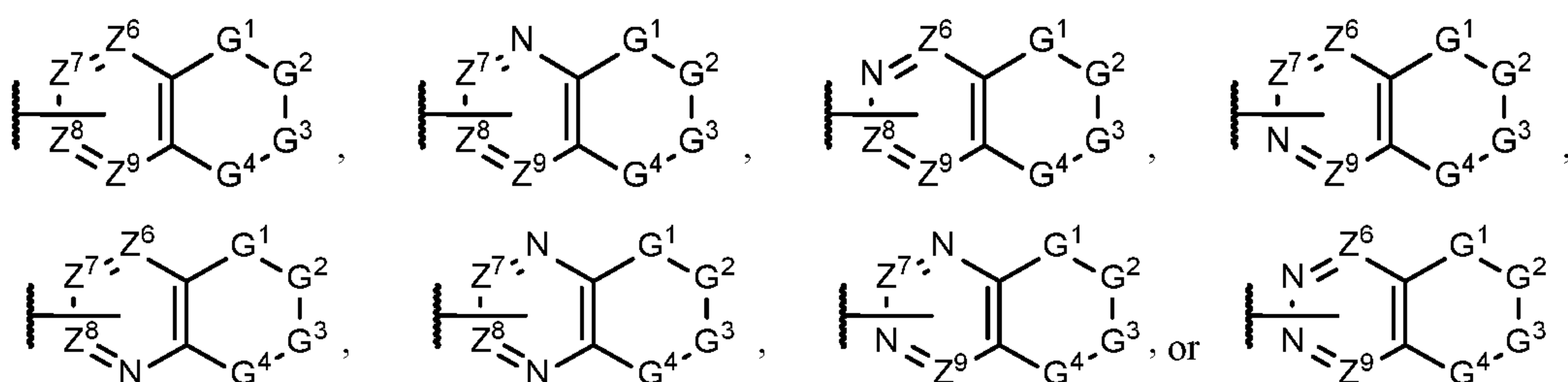
wherein Z¹, Z², and Z³ independently represent CR⁴; A⁶ represents CR¹⁵; and A⁷ represents N.

[0085] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-V. For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-V, wherein M-V represents a moiety represented by one of the following:

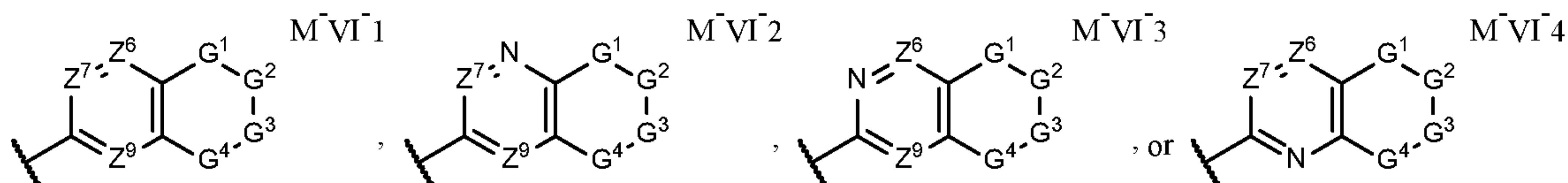




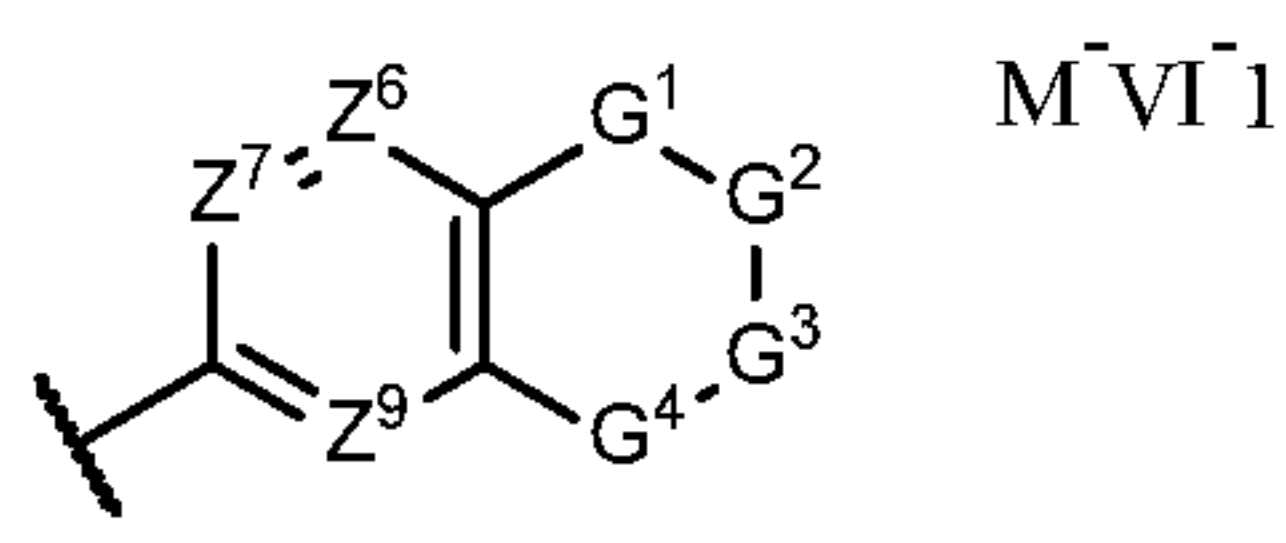
[0086] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-VI. For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-VI, wherein M-VI represents a moiety represented by one of the following:



[0087] In certain embodiments, for example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-VI, wherein M-VI represents a moiety represented by one of the following:

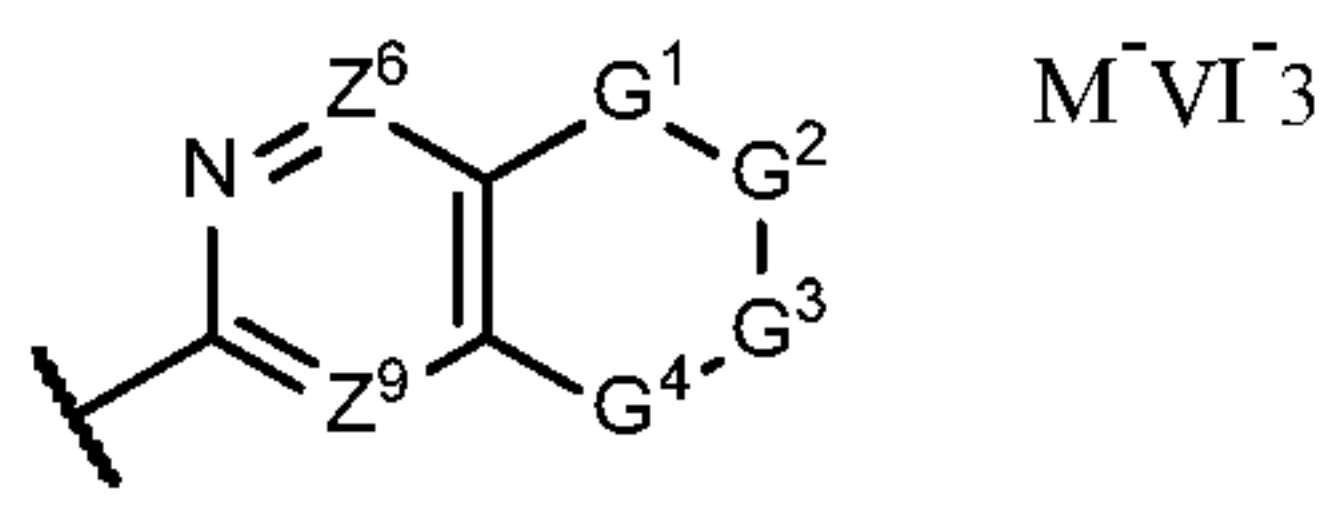


[0088] In certain embodiments, for example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-VI, wherein M-VI represents a moiety represented by ring system M-VI-1:



wherein Z^6 , Z^7 , and Z^9 independently represent CR^7 . For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-VI-1, wherein G^1 and G^4 independently represent $-NH$ or O ; and G^2 and G^3 independently represent $C(R^{18})(R^{18})$; for example, wherein G^1 and G^4 independently represent O ; and G^2 and G^3 independently represent $C(R^{18})(R^{18})$, wherein R^{18} independently represents $-H$.

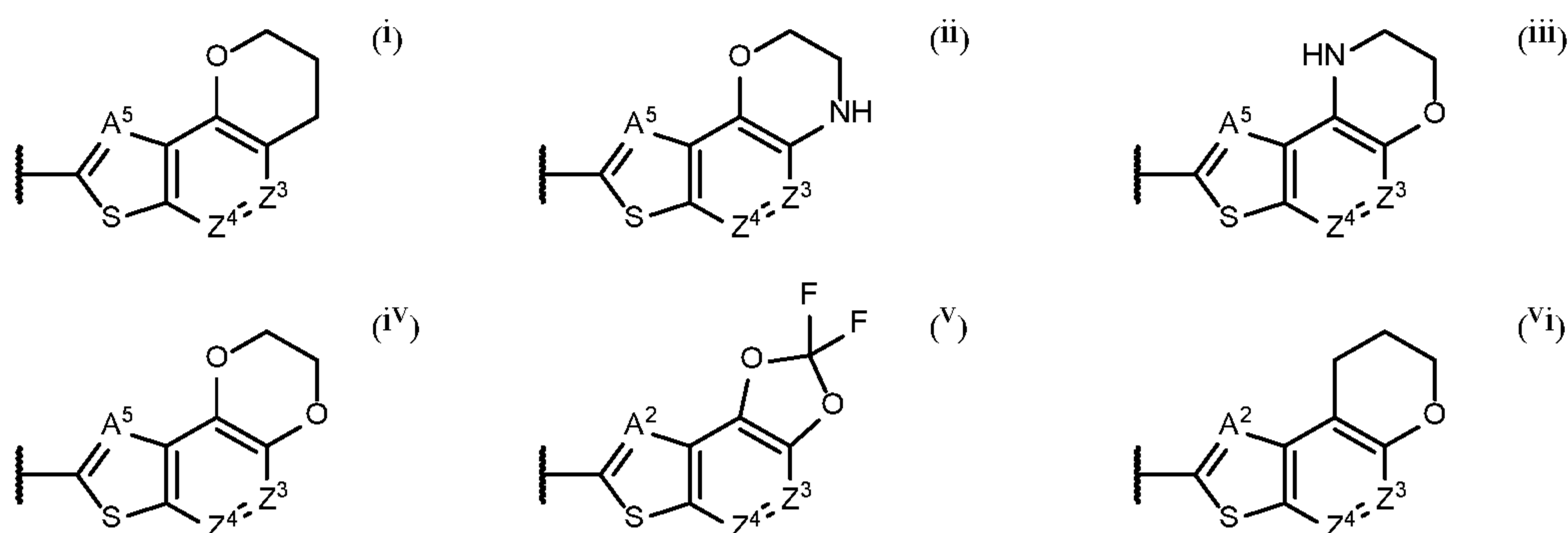
[0089] In certain embodiments, for example, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-VI, wherein M-VI represents a moiety represented by ring system M-VI-3:



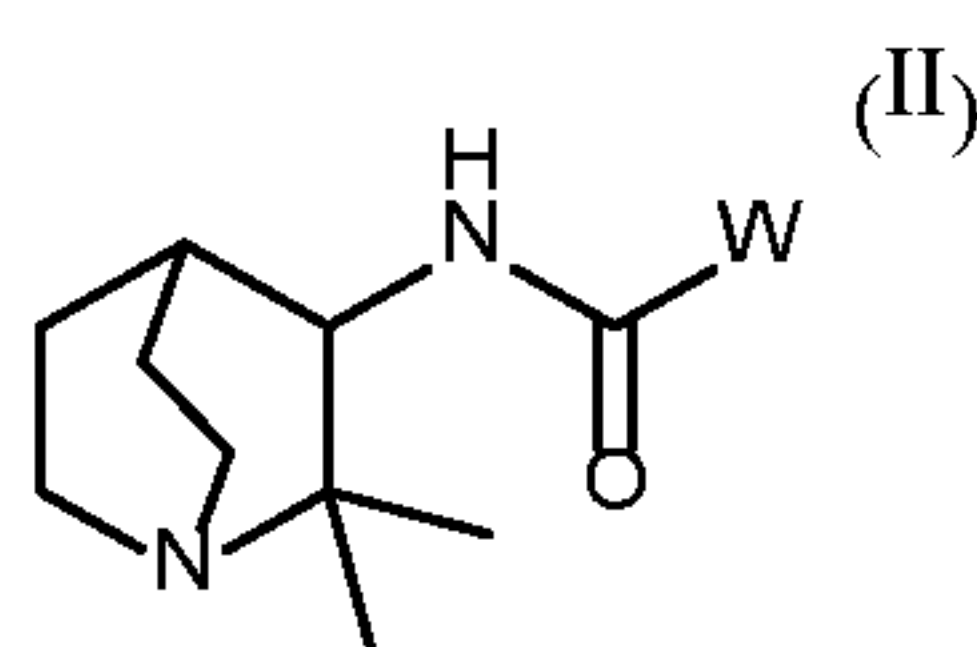
wherein Z^6 and Z^9 independently represent CR^7 . For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-VI-1, wherein G^1 and G^4 independently represent $-NH$ or O ; and G^2 and G^3 independently represent $C(R^{18})(R^{18})$; for example, wherein G^1 and G^4 independently represent O ; and G^2 and G^3 independently represent $C(R^{18})(R^{18})$, wherein R^{18} independently represents $-H$.

[0090] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-I, M-IV, or M-V, wherein adjacent members of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 , is $(CR^4)(CR^4)$, and the $(CR^4)(CR^4)$ forms a cycle such that the adjacent R^4 substituents taken together represents a (3-6 membered)-heteroalkyl di-radical with at least one ring atom of the (3-6 membered)-heteroalkyl di-radical selected from the group consisting of oxygen, nitrogen, and sulfur, with the proviso that when the at least one ring atom is nitrogen, the nitrogen is unsubstituted (specifically is $-N(H)-$) or is substituted with a branched or unbranched C_1 - C_4 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, $-(CO)$ -branched or unbranched C_1 - C_4 -alkyl, or $-(SO_2)$ -branched or unbranched C_1 - C_4 -alkyl, wherein the C_1 - C_4 -alkyl radical and the C_3 - C_4 -cycloalkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, halogen, $=O$, $-OH$, $-OC_1$ - C_4 -alkyl or $-OCF_3$, and with the further proviso that when the at least one ring atom is sulfur, the sulfur may substituted with 0 or 2 $=O$; and wherein the alkyl portion of said (3-6 membered)-heteroalkyl di-radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-OR^5$, $-(CH_2)_mOR^5$, $-N(R^5)(R^6)$, $-(CH_2)_mN(R^5)(R^6)$, $-SO_2(CH_2)_mR^5$, $-(CO)(CH_2)_mR^5$, $-(CO)N(R^5)(R^6)$, $-OCF_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, a C_1 - C_6 -hydroxyalkyl radical, or a C_1 - C_6 -haloalkyl radical. For example, in certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-I, M-IV, or M-V, wherein adjacent members of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 , is $(CR^4)(CR^4)$, such as adjacent members Z^1 and Z^2 is $(CR^4)(CR^4)$, adjacent members Z^2 and Z^3 is $(CR^4)(CR^4)$, adjacent members Z^3 and Z^4 is $(CR^4)(CR^4)$, or adjacent members Z^4 and Z^5 is $(CR^4)(CR^4)$, and the $(CR^4)(CR^4)$ forms a cycle such that the adjacent R^4 substituents taken together represents a (3-6 membered)-heteroalkyl di-radical with at least one ring atom of the (3-6 membered)-heteroalkyl di-radical selected from the group consisting of oxygen, nitrogen, and sulfur, for example, at least two ring atoms of the (3-6 membered)-heteroalkyl di-radical are independently selected from the group consisting of oxygen, nitrogen, and sulfur, with the proviso that when the at least one ring atom is, or at least two ring atoms are independently, nitrogen, then the nitrogen is unsubstituted (specifically is $-N(H)-$) or is substituted with a branched or unbranched C_1 - C_4 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, $-(CO)$ -branched or unbranched C_1 - C_4 -alkyl, or $-(SO_2)$ -branched or unbranched C_1 - C_4 -alkyl, wherein the C_1 - C_4 -alkyl radical and the C_3 - C_4 -cycloalkyl radical

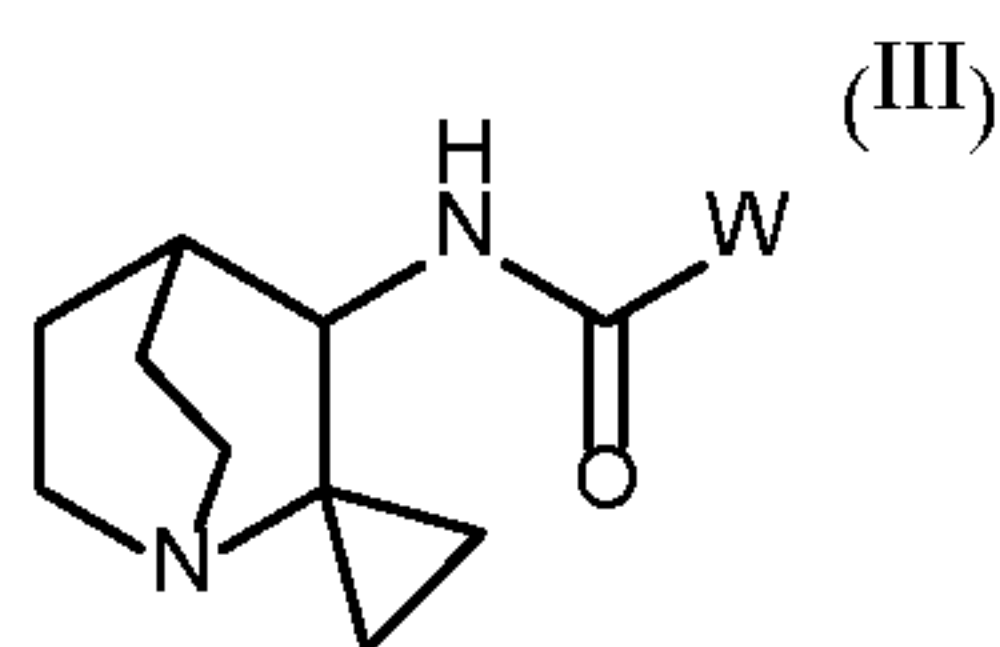
may be substituted with up to 4 radical substituents comprising: $-D$, halogen, $=O$, $-OH$, $-OC_1-C_4$ -alkyl or $-OCF_3$. For example, in certain embodiments, adjacent members of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 , is $(CR^4)(CR^4)$, and the $(CR^4)(CR^4)$ forms a cycle such that the adjacent R^4 substituents taken together represents a (3-6 membered)-heteroalkyl di-radical, and the (3-6 membered)-heteroalkyl di-radical comprises: $-OCH_2CH_2CH_2-$, $-OCH_2CH_2N(H)-$, $-OCH_2CH_2N(C_1-C_4\text{-alkyl})-$, such as $-OCH_2CH_2N(Me)-$; $-CH_2CH_2CH_2N(CO)(C_1-C_4\text{-alkyl})-$, $-N(H)CH_2CH_2O-$, $-N(C_1-C_4\text{-alkyl})CH_2CH_2O-$, such as $-N(Me)CH_2CH_2O-$; $-OCH_2CH_2O-$; $-OCF_2O-$; or $-CH_2CH_2CH_2O-$. For purposes described herein, when the (3-6 membered)-heteroalkyl di-radical is specified, it is both referenced and attached on the ring system M-I, M-IV, or M-V, in order from lowest to highest of adjacent members of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 . For example, by way of illustration, the resulting ring system of W representing the moiety represented by the ring system M-IV-1, wherein A^7 is S, and the adjacent members Z^1 and Z^2 is $(CR^4)(CR^4)$, and the $(CR^4)(CR^4)$ forms a cycle such that the adjacent R^4 substituents taken together represents a (3-6 membered)-heteroalkyl di-radical, and the (3-6 membered)-heteroalkyl di-radical is: (i) $-OCH_2CH_2CH_2-$, (ii) $-OCH_2CH_2N(H)-$; (iii) $-N(H)CH_2CH_2O-$; (iv) $-OCH_2CH_2O-$; (v) $-OCF_2O-$; or (vi) $-CH_2CH_2CH_2O-$, would be represented by the following structures:



[0091] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), for example, may comprise the W representing the moiety represented by the ring system M-I to M-VI, wherein R^1 and R^2 independently represent an unbranched C_1 -alkyl radical, and said compound is represented by Formula (II):



[0092] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), for example, may comprise the W representing the moiety represented by the ring system M-I to M-VI, wherein R^1 and R^2 taken together represent a C_2 -alkyl di-radical and said compound is represented by Formula (III):



[0093] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise racemic mixture of enantiomers, a mixture of diastereomers, a single enantiomer, or a single diastereomer, of the compound, or a pharmaceutically acceptable salt thereof. In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise a mixture of tautomers, substantially a single tautomer form, or a single tautomer form, such as a tautomer contained within W, for example, a tautomer may be contained within a W containing a heteroaryl ring nitrogen adjacent to a heteroaryl ring carbon substituted with a hydroxyl group.

[0094] The chemical names and structure diagrams used herein to describe the compounds of the present invention, supra and infra, were created with the use of ChemBioDraw Ultra® Version 12.0 (available from CambridgeSoft Corp., Cambridge, Mass.).

[0095] In certain embodiments, specific examples of the amide compound represented by Formula (I) may include, collectively or individually, the compounds listed below, and single enantiomers and pharmaceutically acceptable salts thereof:

N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 4-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzamide;
 7-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;
 6-cyano-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;
 6-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 5-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 5,6-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-5-methylbenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-5-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 5-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-5-methoxybenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-c]pyridine-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzo[b]thiophene-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzo[b]thiophene-6-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-1H-indole-6-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)pyrazolo[1,5-b]pyridazine-3-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-b]pyridine-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)benzo[d]thiazole-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)benzofuran-6-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]oxazole-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]oxazole-6-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]thiazole-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]thiazole-6-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-b]pyridine-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)furo[3,2-b]pyridine-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzofuran-5-carboxamide;
 2-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzofuran-5-carboxamide;
 3-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-c]pyridine-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-morpholinobenzo[b]thiophene-2-carboxamide;
 6-(4,4-difluoropiperidin-1-yl)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 6-bromo-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-isopropoxybenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-(methylsulfonyl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-nitrobenzo[b]thiophene-2-carboxamide;
 6-amino-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methoxybenzo[b]thiophene-2-carboxamide;
 7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

4-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;

7-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-nitro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-amino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

5-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

5,6-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

5-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-5-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

5-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

5-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxamide;

3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-5-carboxamide;

3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1*H*-indole-6-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrazolo[1,5-b]pyridazine-3-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*b*]pyridine-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-5-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-6-carboxamide;

2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-5-carboxamide;

2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-6-carboxamide;

2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-5-carboxamide;

2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-6-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-*b*]pyridine-5-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[3,2-*b*]pyridine-5-carboxamide;

2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

3-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-5-carboxamide;

1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-6-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-c]pyridine-5-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(1*H*-1,2,3-triazol-1-yl)benzo[b]thiophene-2-carboxamide;

6-morpholino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-(4,4-difluoropiperidin-1-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-bromo-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-isopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-(methylsulfonyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(tetrahydro-2*H*-pyran-4-yl)benzo[b]thiophene-2-carboxamide;

7-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide; and

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide.

[0096] In certain embodiments, specific examples of the amide compound represented by Formula (I) may include, collectively or individually, the compounds listed below, and single enantiomers and pharmaceutically acceptable salts thereof:

2-amino-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-d]pyrimidine-6-carboxamide;

6,7-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-fluorobenzo[b]thiophene-2-carboxamide;
 6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;
 7-cyano-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6,7-difluorobenzo[b]thiophene-2-carboxamide;
 7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-isopropylbenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-1H-indole-2-carboxamide;
 6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-5-fluoro-6-methoxybenzo[b]thiophene-2-carboxamide;
 6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-5,7-difluorobenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-methylbenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;
 7-(dimethylamino)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)isoquinoline-3-carboxamide;
 7-(tert-butyl)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-phenylbenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-(1-methylcyclopropyl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-ethoxybenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-ethoxybenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-propoxybenzo[b]thiophene-2-carboxamide;
 6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-methoxy-6-methylbenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-1H-indazole-3-carboxamide;
 7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-methoxybenzo[b]thiophene-2-carboxamide;
 7-cyano-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-(methoxymethyl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-3,4-dihydro-2H-thieno[3,2-h]chromene-8-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-8,9-dihydro-7H-thieno[2,3-f]chromene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[b]thiophene-6-carboxamide;
 2-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide;
 6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-methylbenzo[b]thiophene-2-carboxamide;
 2-amino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-d]pyrimidine-6-carboxamide;
 6,7-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 6-chloro-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 7-chloro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 7-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 7-chloro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 7-chloro-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 6-cyclopropyl-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 7-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 6,7-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-2-carboxamide;
 7-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-2-carboxamide;

7-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-isopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-c]pyridine-2-carboxamide;

6-chloro-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

5-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

5,6-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-5,7-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

7-(dimethylamino)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-(methylsulfonyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-morpholino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)isoquinoline-3-carboxamide;

2-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

7-(tert-butyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-(2-hydroxypropan-2-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-phenyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(1-(trifluoromethyl)cyclopropyl)benzo[b]thiophene-2-carboxamide;

7-(1-methylcyclopropyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-propoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-methoxy-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indazole-3-carboxamide;

1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-6-carboxamide;

7-cyclopropyl-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-fluoro-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-cyano-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-(methoxymethyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-(methoxymethyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-3,4-dihydro-2H-thieno[3,2-h]chromene-8-carboxamide;

2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-8,9-dihydro-7H-thieno[2,3-f]chromene-2-carboxamide;

6-chloro-7-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-6-carboxamide;

6-(tert-butyl)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-(1H-1,2,3-triazol-1-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-(oxetan-3-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-methoxy-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

6-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)-7-fluorobenzo[b]thiophene-2-carboxamide;

7-chloro-6-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide;

6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzofuran-2-carboxamide;

7-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzofuran-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)benzo[d]oxazole-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-1H-benzo[d]imidazole-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-*c*]pyridine-2-carboxamide;

3,4-dichloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzamide;

N-(2,2-dimethylquinuclidin-3-yl)-4-methoxy-3-methylbenzamide;

N-(2,2-dimethylquinuclidin-3-yl)imidazo[1,2-*a*]pyrazine-6-carboxamide;;

N-(2,2-dimethylquinuclidin-3-yl)-5,6-difluorobenzo[b]thiophene-2-carboxamide;;

N-(2,2-dimethylquinuclidin-3-yl)-7-(methylsulfonyl)benzo[b]thiophene-2-carboxamide;;

N-(2,2-dimethylquinuclidin-3-yl)-7-morpholinobenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)quinoline-3-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)quinoline-7-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)quinoline-6-carboxamide;

2-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-(2-hydroxypropan-2-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-(1-(trifluoromethyl)cyclopropyl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-1H-indole-5-carboxamide;
 6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-6-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indazole-3-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-3-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-6-carboxamide;
 6-(dimethylamino)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-(methoxymethyl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;
 6-(tert-butyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;
 6-(oxetan-3-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 7-chloro-6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-2-carboxamide;
 1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-2-carboxamide;
 1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-2-carboxamide;
 3,4-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;
 4-methoxy-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)imidazo[1,2-a]pyrazine-6-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-3-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-7-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-6-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-5-carboxamide;

6-cyclopropyl-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-5-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-6-carboxamide;

2,2-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d][1,3]dioxole-5-carboxamide;

1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indazole-3-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-3-carboxamide;

1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-5-carboxamide;

6-(dimethylamino)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide.

N-(2,2-dimethylquinuclidin-3-yl)-7-(oxetan-3-yl)benzo[b]thiophene-2-carboxamide;

6-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

7-(oxetan-3-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide; and

6-cyclopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide.

[0097] In certain embodiments, specific examples of the amide compound represented by Formula (I) may include, collectively or individually, the single enantiomers listed below, and pharmaceutically acceptable salts thereof:

7-cyclobutyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

7-cyclobutyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide;

7-cyclopropyl-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

7-cyclopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-cyclopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-methylbenzo[b]thiophene-2-carboxamide;

6-fluoro-7-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-chloro-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

4-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-7-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;

6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

7-cyano-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;

6-chloro-7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-7-cyano-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

7-(tert-butoxy)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

7-(tert-butoxy)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydro-1H-thieno[2',3':3,4]benzo[1,2-b][1,4]oxazine-8-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-2,3-dihydro-1H-thieno[2',3':3,4]benzo[1,2-b][1,4]oxazine-8-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydro-1H-thieno[2',3':3,4]benzo[1,2-b][1,4]oxazine-8-carboxamide;

1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydro-1H-thieno[2',3':3,4]benzo[1,2-b][1,4]oxazine-8-carboxamide;

2-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide;

2-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;
 7-(difluoromethyl)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 7-(difluoromethyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 7-(oxetan-3-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-(oxetan-3-yl)benzo[b]thiophene-2-carboxamide;
 6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-isopropoxybenzo[b]thiophene-2-carboxamide;
 7-cyclobutoxy-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-ethoxybenzo[b]thiophene-2-carboxamide;
 6-chloro-7-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 7-cyano-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 6-chloro-7-isopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 6-chloro-7-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 7-cyclobutoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 6,7-dimethyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-ethoxy-6-fluorobenzo[b]thiophene-2-carboxamide;
 7-isopropoxy-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 7-ethoxy-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;
 7-cyclopropyl-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-isopropoxy-6-methylbenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-ethoxy-6-methylbenzo[b]thiophene-2-carboxamide;
 7-ethoxy-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6,7-dimethylbenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-5-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;

5-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[3,2-c]pyridine-6-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)thieno[3,2-c]pyridine-6-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydrothieno[3,2-g]benzofuran-7-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydrothieno[3,2-g]benzofuran-7-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-5,7-difluorobenzo[b]thiophene-2-carboxamide;

5,7-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-chloro-N-(2,2-dimethylquinuclidin-3-yl)pyrrolo[1,2-c]pyrimidine-3-carboxamide;

7-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrrolo[1,2-c]pyrimidine-3-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)pyrrolo[1,2-c]pyrimidine-3-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;

6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;

6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-3,4-dihydro-2H-thieno[3',2':5,6]benzo[1,2-b][1,4]oxazine-8-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-4-methyl-3,4-dihydro-2H-thieno[3',2':5,6]benzo[1,2-b][1,4]oxazine-8-carboxamide;

6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-2,2-difluorothieno[2',3':3,4]benzo[1,2-d][1,3]dioxole-7-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-3,4-dihydro-2H-thieno[3',2':5,6]benzo[1,2-b][1,4]oxazine-8-carboxamide;

4-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-3,4-dihydro-2H-thieno[3',2':5,6]benzo[1,2-b][1,4]oxazine-8-carboxamide;

6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

2,2-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2',3':3,4]benzo[1,2-d][1,3]dioxole-7-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7,8-dihydrothieno[2,3-e]benzofuran-2-carboxamide;

6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7,8-dihydrothieno[2,3-e]benzofuran-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

5,7-difluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

7-cyclopropyl-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-cyclopropyl-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-chloro-5-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

4-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

3-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

2-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

4-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

7-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-5,7-difluoro-6-methylbenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-methoxy-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;

7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-5-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-4-fluorofuro[2,3-c]pyridine-5-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-3-fluorofuro[2,3-c]pyridine-5-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-2-fluorofuro[2,3-c]pyridine-5-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-4-methylfuro[2,3-c]pyridine-5-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-methylfuro[2,3-c]pyridine-5-carboxamide;

7-(1-fluorocyclopropyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6,8-dihydrothieno[2,3-e]isobenzofuran-2-carboxamide;

7-cyclopropoxy-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-cyclopropoxy-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-7-cyclopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;

5,6-difluoro-7-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

3-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrrolo[1,2-a]pyrazine-3-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrrolo[1,2-c]pyrimidine-3-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)indolizine-6-carboxamide;

6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrrolo[1,2-a]pyrazine-3-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-pyrrolo[3,2-c]pyridine-6-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-(1-fluorocyclopropyl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6,8-dihydrothieno[2,3-e]isobenzofuran-2-carboxamide;

7-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;

7-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 6-chloro-7-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-5,6-difluoro-7-methylbenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-3-methylfuro[2,3-c]pyridine-5-carboxamide;
 3-chloro-N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-c]pyridine-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)pyrrolo[1,2-a]pyrazine-3-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)indolizine-6-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-methylpyrrolo[1,2-a]pyrazine-3-carboxamide; and
 N-(2,2-dimethylquinuclidin-3-yl)-1H-pyrrolo[3,2-c]pyridine-6-carboxamide;

[0098] In certain embodiments, specific examples of the amide compound represented by Formula (I) may include, collectively or individually, the compounds listed below, and single enantiomers and pharmaceutically acceptable salts thereof:

N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 6-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-c]pyridine-5-carboxamide;
 7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;
 6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-6-carboxamide;
 2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;
 6-bromo-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 7-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 6,7-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 6-chloro-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 7-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 7-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;
 5-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 7-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide; and
 2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide.

[0099] In certain embodiments, specific examples of the amide compound represented by Formula (I) may include, collectively or individually, the single enantiomers listed below, and pharmaceutically acceptable salts thereof:

(R)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-4-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzamide;
 (S)-4-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzamide;
 (R)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;

(S)-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;
 (R)-6-cyano-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-cyano-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;
 (R)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-5-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-5-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-5,6-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-5,6-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-5-methylbenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-5-methylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-5-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-5-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (R)-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-5-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-5-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-5-methoxybenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-5-methoxybenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-c]pyridine-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-c]pyridine-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzo[b]thiophene-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzo[b]thiophene-5-carboxamide;

(R)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzo[b]thiophene-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzo[b]thiophene-6-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-1H-indole-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-1H-indole-6-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)pyrazolo[1,5-b]pyridazine-3-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)pyrazolo[1,5-b]pyridazine-3-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-b]pyridine-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-b]pyridine-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]thiazole-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]thiazole-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-6-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]oxazole-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]oxazole-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]oxazole-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]oxazole-6-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]thiazole-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]thiazole-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]thiazole-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]thiazole-6-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-b]pyridine-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-b]pyridine-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)furo[3,2-b]pyridine-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)furo[3,2-b]pyridine-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzofuran-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzofuran-5-carboxamide;
 (R)-2-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 (S)-2-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzofuran-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzofuran-5-carboxamide;
 (R)-3-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 (S)-3-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-c]pyridine-5-carboxamide;

(S)-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-c]pyridine-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-morpholinobenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-morpholinobenzo[b]thiophene-2-carboxamide;
 (R)-6-(4,4-difluoropiperidin-1-yl)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-(4,4-difluoropiperidin-1-yl)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-6-bromo-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-bromo-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-isopropoxybenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-isopropoxybenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-(methylsulfonyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-(methylsulfonyl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-nitrobenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-nitrobenzo[b]thiophene-2-carboxamide;
 (R)-6-amino-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-amino-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methoxybenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methoxybenzo[b]thiophene-2-carboxamide;
 (R)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (S)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-4-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;
 (S)-4-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;
 (R)-7-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-7-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-nitro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-nitro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-amino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-amino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-5-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-5,6-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5,6-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-5-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-5-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-5-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-5-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-5-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxamide;

(*R*)-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-5-carboxamide;

(*S*)-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-5-carboxamide;

(*R*)-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

(*S*)-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-6-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-6-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrazolo[1,5-b]pyridazine-3-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrazolo[1,5-b]pyridazine-3-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-b]pyridine-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-b]pyridine-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-5-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-5-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-6-carboxamide;

(S)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-6-carboxamide;
 (R)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-5-carboxamide;
 (S)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-5-carboxamide;
 (R)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-6-carboxamide;
 (S)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-6-carboxamide;
 (R)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-5-carboxamide;
 (S)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-5-carboxamide;
 (R)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-6-carboxamide;
 (S)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-6-carboxamide;
 (R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-b]pyridine-5-carboxamide;
 (S)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-b]pyridine-5-carboxamide;
 (R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[3,2-b]pyridine-5-carboxamide;
 (S)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[3,2-b]pyridine-5-carboxamide;
 (R)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;
 (S)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;
 (R)-2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;
 (S)-2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;
 (R)-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;
 (S)-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

(*R*)-3-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

(*S*)-3-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

(*R*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-5-carboxamide;

(*S*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-5-carboxamide;

(*R*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-6-carboxamide;

(*S*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-6-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-c]pyridine-5-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-c]pyridine-5-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(1H-1,2,3-triazol-1-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(1H-1,2,3-triazol-1-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-morpholino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-morpholino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-(4,4-difluoropiperidin-1-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-(4,4-difluoropiperidin-1-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-bromo-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-bromo-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-isopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-isopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-(methylsulfonyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-(methylsulfonyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide; and

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide.

[00100] In certain embodiments, specific examples of the amide compound represented by Formula (I) may include, collectively or individually, the single enantiomers listed below, and pharmaceutically acceptable salts thereof:

(*R*)-2-amino-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-d]pyrimidine-6-carboxamide;

(*S*)-2-amino-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-d]pyrimidine-6-carboxamide;

(*R*)-6,7-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6,7-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-fluorobenzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-fluorobenzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide;

(*S*)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(trifluoromethyl)benzo[*b*]thiophene-2-carboxamide;

(*R*)-7-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[*b*]thiophene-2-carboxamide;

(*S*)-7-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[*b*]thiophene-2-carboxamide;

(*R*)-7-cyano-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide;

(*S*)-7-cyano-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[*b*]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[*b*]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6,7-difluorobenzo[*b*]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6,7-difluorobenzo[*b*]thiophene-2-carboxamide;

(*R*)-7-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide;

(*S*)-7-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-isopropylbenzo[*b*]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-isopropylbenzo[*b*]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethoxy)benzo[*b*]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethoxy)benzo[*b*]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(tetrahydro-2H-pyran-4-yl)benzo[*b*]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(tetrahydro-2H-pyran-4-yl)benzo[*b*]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-1H-indole-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-1H-indole-2-carboxamide;

(*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[*b*]thiophene-2-carboxamide;

(*S*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[*b*]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-fluoro-6-methoxybenzo[*b*]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-fluoro-6-methoxybenzo[*b*]thiophene-2-carboxamide;

(*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-5,7-difluorobenzo[*b*]thiophene-2-carboxamide;

(*S*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-5,7-difluorobenzo[*b*]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-methylbenzo[*b*]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-methylbenzo[*b*]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(2,2,2-trifluoroethyl)benzo[*b*]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(2,2,2-trifluoroethyl)benzo[*b*]thiophene-2-carboxamide;

(*R*)-7-(dimethylamino)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide;

(*S*)-7-(dimethylamino)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(thiazol-2-yl)benzo[*b*]thiophene-2-carboxamide;

(S)-N-(2,2-dimethylquinuclidin-3-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)isoquinoline-3-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)isoquinoline-3-carboxamide;
 (R)-7-(tert-butyl)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-7-(tert-butyl)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-phenylbenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-phenylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-(1-methylcyclopropyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-(1-methylcyclopropyl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-ethoxybenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-ethoxybenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-ethoxybenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-ethoxybenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-propoxybenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-propoxybenzo[b]thiophene-2-carboxamide;
 (R)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide;
 (S)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxy-6-methylbenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxy-6-methylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-1H-indazole-3-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-1H-indazole-3-carboxamide;
 (R)-7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (S)-7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-methoxybenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-methoxybenzo[b]thiophene-2-carboxamide;
 (R)-7-cyano-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (S)-7-cyano-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-(methoxymethyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-(methoxymethyl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-3,4-dihydro-2H-thieno[3,2-h]chromene-8-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-3,4-dihydro-2H-thieno[3,2-h]chromene-8-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-8,9-dihydro-7H-thieno[2,3-f]chromene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-8,9-dihydro-7H-thieno[2,3-f]chromene-2-carboxamide;

(R)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[b]thiophene-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[b]thiophene-6-carboxamide;
 (R)-2-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide;
 (S)-2-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide;
 (R)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-methylbenzo[b]thiophene-2-carboxamide;
 (S)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-methylbenzo[b]thiophene-2-carboxamide;
 (R)-2-amino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-d]pyrimidine-6-carboxamide;
 (S)-2-amino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-d]pyrimidine-6-carboxamide;
 (R)-6,7-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6,7-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-6-chloro-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-chloro-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (S)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (R)-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (S)-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (R)-7-chloro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-7-chloro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-7-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-7-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-7-chloro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-chloro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-chloro-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-chloro-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-cyclopropyl-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-cyclopropyl-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6,7-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6,7-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-2-carboxamide;

(*S*)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-2-carboxamide;

(*R*)-7-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-2-carboxamide;

(*S*)-7-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-2-carboxamide;

(*R*)-7-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-isopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-isopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*c*]pyridine-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*c*]pyridine-2-carboxamide;

(*R*)-6-chloro-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-5-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-5,6-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5,6-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-5,7-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-5,7-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-(dimethylamino)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-(dimethylamino)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-(methylsulfonyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-(methylsulfonyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-morpholino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-morpholino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)isoquinoline-3-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)isoquinoline-3-carboxamide;

(*R*)-2-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

(*S*)-2-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

(*R*)-7-(tert-butyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-(tert-butyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-(2-hydroxypropan-2-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-(2-hydroxypropan-2-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-phenyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-phenyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(1-(trifluoromethyl)cyclopropyl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(1-(trifluoromethyl)cyclopropyl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-(1-methylcyclopropyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-(1-methylcyclopropyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-propoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-propoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-methoxy-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-methoxy-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indazole-3-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indazole-3-carboxamide;

(*R*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-6-carboxamide;

(*S*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-6-carboxamide;

(*R*)-7-cyclopropyl-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclopropyl-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-fluoro-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-fluoro-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-cyano-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyano-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-(methoxymethyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-(methoxymethyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-(methoxymethyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-(methoxymethyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-3,4-dihydro-2H-thieno[3,2-h]chromene-8-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-3,4-dihydro-2H-thieno[3,2-h]chromene-8-carboxamide;

(*R*)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

(*S*)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

(*R*)-2-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

(*S*)-2-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-8,9-dihydro-7H-thieno[2,3-f]chromene-2-carboxamide;

(*S*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-8,9-dihydro-7H-thieno[2,3-f]chromene-2-carboxamide;

(*R*)-6-chloro-7-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-7-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-6-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-6-carboxamide;

(*R*)-6-(tert-butyl)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-(tert-butyl)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(1H-1,2,3-triazol-1-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(1H-1,2,3-triazol-1-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(oxetan-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(oxetan-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methoxy-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methoxy-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)-7-fluorobenzo[b]thiophene-2-carboxamide;

(*S*)-6-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)-7-fluorobenzo[b]thiophene-2-carboxamide;

(*R*)-7-chloro-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-chloro-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide;

(*R*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-2-carboxamide;

(*S*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-2-carboxamide;

(*R*)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-2-carboxamide;

(*S*)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]oxazole-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]oxazole-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-1H-benzo[d]imidazole-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-1H-benzo[d]imidazole-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-c]pyridine-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-c]pyridine-2-carboxamide;

(*R*)-3,4-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzamide;

(*S*)-3,4-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-4-methoxy-3-methylbenzamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-4-methoxy-3-methylbenzamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)imidazo[1,2-a]pyrazine-6-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)imidazo[1,2-a]pyrazine-6-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-5,6-difluorobenzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-5,6-difluorobenzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-(methylsulfonyl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-7-(methylsulfonyl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-morpholinobenzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-7-morpholinobenzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)quinoline-3-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)quinoline-3-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)quinoline-7-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)quinoline-7-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)quinoline-6-carboxamide;

(S)-N-(2,2-dimethylquinuclidin-3-yl)quinoline-6-carboxamide;
 (R)-2-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 (S)-2-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-(2-hydroxypropan-2-yl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-(2-hydroxypropan-2-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-(1-(trifluoromethyl)cyclopropyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-(1-(trifluoromethyl)cyclopropyl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-1H-indole-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-1H-indole-5-carboxamide;
 (R)-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide;
 (S)-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-6-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indazole-3-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indazole-3-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-3-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-3-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-6-carboxamide;
 (R)-6-(dimethylamino)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-(dimethylamino)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-(methoxymethyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-(methoxymethyl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

(*R*)-6-(tert-butyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-(tert-butyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*R*)-6-(oxetan-3-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-(oxetan-3-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-chloro-6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-chloro-6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-2-carboxamide;

(*R*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-2-carboxamide;

(*S*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-2-carboxamide;

(*R*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-2-carboxamide;

(*S*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-2-carboxamide;

(*R*)-3,4-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;

(*S*)-3,4-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;

(*R*)-4-methoxy-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;

(*S*)-4-methoxy-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)imidazo[1,2-a]pyrazine-6-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)imidazo[1,2-a]pyrazine-6-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-3-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-3-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-7-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-7-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-6-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-6-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-5-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-5-carboxamide;

(*R*)-6-cyclopropyl-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-cyclopropyl-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-5-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-5-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-6-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-6-carboxamide;

(*R*)-2,2-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d][1,3]dioxole-5-carboxamide;

(*S*)-2,2-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d][1,3]dioxole-5-carboxamide;

(*R*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indazole-3-carboxamide;

(*S*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indazole-3-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-3-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-3-carboxamide;

(*R*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-5-carboxamide;

(*S*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-5-carboxamide;

(*R*)-6-(dimethylamino)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-(dimethylamino)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide.

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-(oxetan-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-7-(oxetan-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-(oxetan-3-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-(oxetan-3-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-cyclopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide; and

(*S*)-6-cyclopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide.

[00101] In certain embodiments, specific examples of the amide compound represented by Formula (I) may include, collectively or individually, the single enantiomers listed below, and pharmaceutically acceptable salts thereof:

(*R*)-7-cyclobutyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclobutyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-cyclobutyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclobutyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide;

(*R*)-7-cyclopropyl-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclopropyl-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-cyclopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-cyclopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-cyclopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-methylbenzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-methylbenzo[b]thiophene-2-carboxamide;

(*R*)-6-fluoro-7-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-fluoro-7-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-chloro-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-chloro-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-4-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-4-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-7-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-7-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;

(*S*)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;

(*R*)-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*S*)-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-cyano-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;

(*S*)-7-cyano-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-7-cyano-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-7-cyano-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-(tert-butoxy)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-(tert-butoxy)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-(tert-butoxy)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

- (*S*)-7-(tert-butoxy)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
- (*R*)-N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydro-1H-thieno[2',3':3,4]benzo[1,2-b][1,4]oxazine-8-carboxamide;
- (*S*)-N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydro-1H-thieno[2',3':3,4]benzo[1,2-b][1,4]oxazine-8-carboxamide;
- (*R*)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-2,3-dihydro-1H-thieno[2',3':3,4]benzo[1,2-b][1,4]oxazine-8-carboxamide;
- (*S*)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-2,3-dihydro-1H-thieno[2',3':3,4]benzo[1,2-b][1,4]oxazine-8-carboxamide;
- (*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydro-1H-thieno[2',3':3,4]benzo[1,2-b][1,4]oxazine-8-carboxamide;
- (*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydro-1H-thieno[2',3':3,4]benzo[1,2-b][1,4]oxazine-8-carboxamide;
- (*R*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydro-1H-thieno[2',3':3,4]benzo[1,2-b][1,4]oxazine-8-carboxamide;
- (*S*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydro-1H-thieno[2',3':3,4]benzo[1,2-b][1,4]oxazine-8-carboxamide;
- (*R*)-2-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide;
- (*S*)-2-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide;
- (*R*)-2-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;
- (*S*)-2-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;
- (*R*)-7-(difluoromethyl)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
- (*S*)-7-(difluoromethyl)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
- (*R*)-7-(difluoromethyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
- (*S*)-7-(difluoromethyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
- (*R*)-7-(oxetan-3-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
- (*S*)-7-(oxetan-3-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
- (*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-(oxetan-3-yl)benzo[b]thiophene-2-carboxamide;
- (*S*)-N-(2,2-dimethylquinuclidin-3-yl)-7-(oxetan-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-isopropoxybenzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-isopropoxybenzo[b]thiophene-2-carboxamide;

(*R*)-7-cyclobutoxy-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclobutoxy-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-ethoxybenzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-ethoxybenzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-7-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-7-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-cyano-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyano-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-7-isopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-7-isopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-7-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-7-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-cyclobutoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclobutoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6,7-dimethyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6,7-dimethyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-ethoxy-6-fluorobenzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-7-ethoxy-6-fluorobenzo[b]thiophene-2-carboxamide;

(*R*)-7-isopropoxy-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-isopropoxy-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-ethoxy-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-ethoxy-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;

(*R*)-7-cyclopropyl-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclopropyl-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-isopropoxy-6-methylbenzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-7-isopropoxy-6-methylbenzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-ethoxy-6-methylbenzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-7-ethoxy-6-methylbenzo[b]thiophene-2-carboxamide;

(*R*)-7-ethoxy-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-ethoxy-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-6,7-dimethylbenzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-6,7-dimethylbenzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-5-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-5-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;

(*R*)-5-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[3,2-*c*]pyridine-6-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[3,2-*c*]pyridine-6-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)thieno[3,2-*c*]pyridine-6-carboxamide;

(S)-N-(2,2-dimethylquinuclidin-3-yl)thieno[3,2-c]pyridine-6-carboxamide;
(R)-N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydrothieno[3,2-g]benzofuran-7-carboxamide;
(S)-N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydrothieno[3,2-g]benzofuran-7-carboxamide;
(R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydrothieno[3,2-g]benzofuran-7-carboxamide;
(S)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydrothieno[3,2-g]benzofuran-7-carboxamide;
(R)-N-(2,2-dimethylquinuclidin-3-yl)-5,7-difluorobenzo[b]thiophene-2-carboxamide;
(S)-N-(2,2-dimethylquinuclidin-3-yl)-5,7-difluorobenzo[b]thiophene-2-carboxamide;
(R)-5,7-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(S)-5,7-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)pyrrolo[1,2-c]pyrimidine-3-carboxamide;
(S)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)pyrrolo[1,2-c]pyrimidine-3-carboxamide;
(R)-7-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrrolo[1,2-c]pyrimidine-3-carboxamide;
(S)-7-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrrolo[1,2-c]pyrimidine-3-carboxamide;
(R)-N-(2,2-dimethylquinuclidin-3-yl)pyrrolo[1,2-c]pyrimidine-3-carboxamide;
(S)-N-(2,2-dimethylquinuclidin-3-yl)pyrrolo[1,2-c]pyrimidine-3-carboxamide;
(R)-N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;
(S)-N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;
(R)-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;
(S)-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;
(R)-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;
(S)-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;
(R)-N-(2,2-dimethylquinuclidin-3-yl)-3,4-dihydro-2H-thieno[3',2':5,6]benzo[1,2-b][1,4]oxazine-8-carboxamide;
(S)-N-(2,2-dimethylquinuclidin-3-yl)-3,4-dihydro-2H-thieno[3',2':5,6]benzo[1,2-b][1,4]oxazine-8-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-4-methyl-3,4-dihydro-2H-thieno[3',2':5,6]benzo[1,2-b][1,4]oxazine-8-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-4-methyl-3,4-dihydro-2H-thieno[3',2':5,6]benzo[1,2-b][1,4]oxazine-8-carboxamide;

(*R*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-2,2-difluorothieno[2',3':3,4]benzo[1,2-d][1,3]dioxole-7-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-2,2-difluorothieno[2',3':3,4]benzo[1,2-d][1,3]dioxole-7-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-3,4-dihydro-2H-thieno[3',2':5,6]benzo[1,2-b][1,4]oxazine-8-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-3,4-dihydro-2H-thieno[3',2':5,6]benzo[1,2-b][1,4]oxazine-8-carboxamide;

(*R*)-4-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-3,4-dihydro-2H-thieno[3',2':5,6]benzo[1,2-b][1,4]oxazine-8-carboxamide;

(*S*)-4-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-3,4-dihydro-2H-thieno[3',2':5,6]benzo[1,2-b][1,4]oxazine-8-carboxamide;

(*R*)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-2,2-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2',3':3,4]benzo[1,2-d][1,3]dioxole-7-carboxamide;

(*S*)-2,2-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2',3':3,4]benzo[1,2-d][1,3]dioxole-7-carboxamide;

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7,8-dihydrothieno[2,3-*e*]benzofuran-2-carboxamide;

(*S*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7,8-dihydrothieno[2,3-*e*]benzofuran-2-carboxamide;

(*R*)-6-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(thiazol-2-yl)benzo[*b*]thiophene-2-carboxamide;

(*S*)-6-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(thiazol-2-yl)benzo[*b*]thiophene-2-carboxamide;

(*R*)-6-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(thiazol-2-yl)benzo[*b*]thiophene-2-carboxamide;

(*S*)-6-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(thiazol-2-yl)benzo[*b*]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7,8-dihydrothieno[2,3-*e*]benzofuran-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7,8-dihydrothieno[2,3-*e*]benzofuran-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-(thiazol-2-yl)benzo[*b*]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-(thiazol-2-yl)benzo[*b*]thiophene-2-carboxamide;

(*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(thiazol-2-yl)benzo[*b*]thiophene-2-carboxamide;

(*S*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(thiazol-2-yl)benzo[*b*]thiophene-2-carboxamide;

(*R*)-5,7-difluoro-6-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide;

(*S*)-5,7-difluoro-6-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide;

(*R*)-6-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[*b*]thiophene-2-carboxamide;

(*S*)-6-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[*b*]thiophene-2-carboxamide;

(*R*)-7-cyclopropyl-5-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide;

(*S*)-7-cyclopropyl-5-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide;

(*R*)-6-cyclopropyl-5-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide;

(*S*)-6-cyclopropyl-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-chloro-5-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-chloro-5-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-4-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

(*S*)-4-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

(*R*)-3-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

(*S*)-3-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

(*R*)-2-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

(*S*)-2-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

(*R*)-4-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

(*S*)-4-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

(*R*)-7-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

(*S*)-7-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-5,7-difluoro-6-methylbenzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-5,7-difluoro-6-methylbenzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-6-methoxy-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-6-methoxy-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*R*)-7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;

(*R*)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-5-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;

(*S*)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-5-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-4-fluorofuro[2,3-*c*]pyridine-5-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-4-fluorofuro[2,3-*c*]pyridine-5-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-3-fluorofuro[2,3-*c*]pyridine-5-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-3-fluorofuro[2,3-*c*]pyridine-5-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-2-fluorofuro[2,3-*c*]pyridine-5-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-2-fluorofuro[2,3-*c*]pyridine-5-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-4-methylfuro[2,3-*c*]pyridine-5-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-4-methylfuro[2,3-*c*]pyridine-5-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-methylfuro[2,3-*c*]pyridine-5-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-7-methylfuro[2,3-*c*]pyridine-5-carboxamide;

(*R*)-7-(1-fluorocyclopropyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-(1-fluorocyclopropyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6,8-dihydrothieno[2,3-*e*]isobenzofuran-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6,8-dihydrothieno[2,3-*e*]isobenzofuran-2-carboxamide;

(*R*)-7-cyclopropoxy-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclopropoxy-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-cyclopropoxy-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclopropoxy-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-7-cyclopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-7-cyclopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;

(*S*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;

(*R*)-5,6-difluoro-7-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5,6-difluoro-7-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-*c*]pyridine-5-carboxamide;

(*S*)-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-*c*]pyridine-5-carboxamide;

(*R*)-3-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-*c*]pyridine-5-carboxamide;

(*S*)-3-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-*c*]pyridine-5-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrrolo[1,2-*a*]pyrazine-3-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrrolo[1,2-*a*]pyrazine-3-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrrolo[1,2-*c*]pyrimidine-3-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrrolo[1,2-*c*]pyrimidine-3-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)indolizine-6-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)indolizine-6-carboxamide;

(*R*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrrolo[1,2-*a*]pyrazine-3-carboxamide;

(*S*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrrolo[1,2-*a*]pyrazine-3-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-pyrrolo[3,2-*c*]pyridine-6-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-pyrrolo[3,2-*c*]pyridine-6-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-(1-fluorocyclopropyl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-7-(1-fluorocyclopropyl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-6,8-dihydrothieno[2,3-*e*]isobenzofuran-2-carboxamide;

(S)-N-(2,2-dimethylquinuclidin-3-yl)-6,8-dihydrothieno[2,3-e]isobenzofuran-2-carboxamide;
 (R)-7-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;
 (S)-7-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;
 (R)-7-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (S)-7-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (R)-6-chloro-7-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-chloro-7-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(2,2,2-trifluoroethoxy)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-5,6-difluoro-7-methylbenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-5,6-difluoro-7-methylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylfuro[2,3-c]pyridine-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylfuro[2,3-c]pyridine-5-carboxamide;
 (R)-3-chloro-N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-c]pyridine-5-carboxamide;
 (S)-3-chloro-N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-c]pyridine-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)pyrrolo[1,2-a]pyrazine-3-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)pyrrolo[1,2-a]pyrazine-3-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)indolizine-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)indolizine-6-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-1H-pyrrolo[3,2-c]pyridine-6-carboxamide; and
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-1H-pyrrolo[3,2-c]pyridine-6-carboxamide;

[00102] In certain embodiments, specific examples of the amide compound represented by Formula (I) may include, collectively or individually, the single enantiomers listed below, and pharmaceutically acceptable salts thereof:

(R)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-benzo[b]thiophene-2-carboxamide;

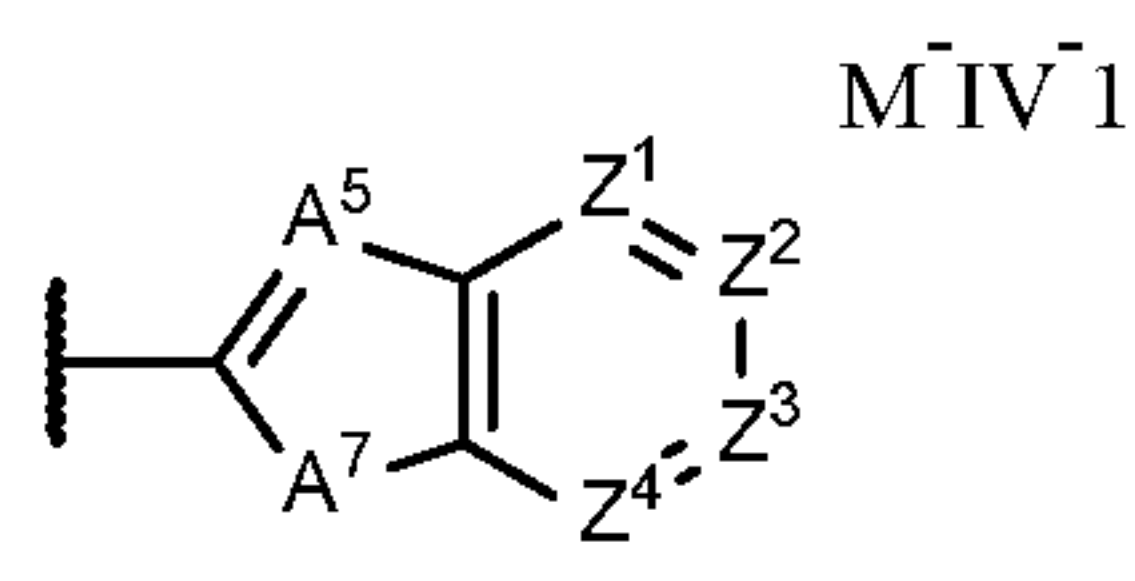
(R)-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 (R)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-c]pyridine-5-carboxamide;
 (R)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;
 (R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;
 (R)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;
 (R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-6-carboxamide;
 (R)-2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;
 (R)-6-bromo-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-7-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-6,7-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-6-chloro-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-7-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-7-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*R*)-5-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide; and

(*R*)-2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide.

[00103] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-IV, wherein M-IV represents a moiety represented by ring system M-IV-1:



wherein Z^1 , Z^2 , Z^3 , and Z^4 independently represent CR^4 ; A^5 represents CR^{15} ; and A^7 represents S; and may include, collectively or individually, the single enantiomers listed below, and pharmaceutically acceptable salts thereof:

- (*R*)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
- (*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-benzo[b]thiophene-2-carboxamide;
- (*R*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
- (*R*)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
- (*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;
- (*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
- (*R*)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
- (*R*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
- (*R*)-6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
- (*R*)-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
- (*R*)-6-bromo-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
- (*R*)-7-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
- (*R*)-6,7-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

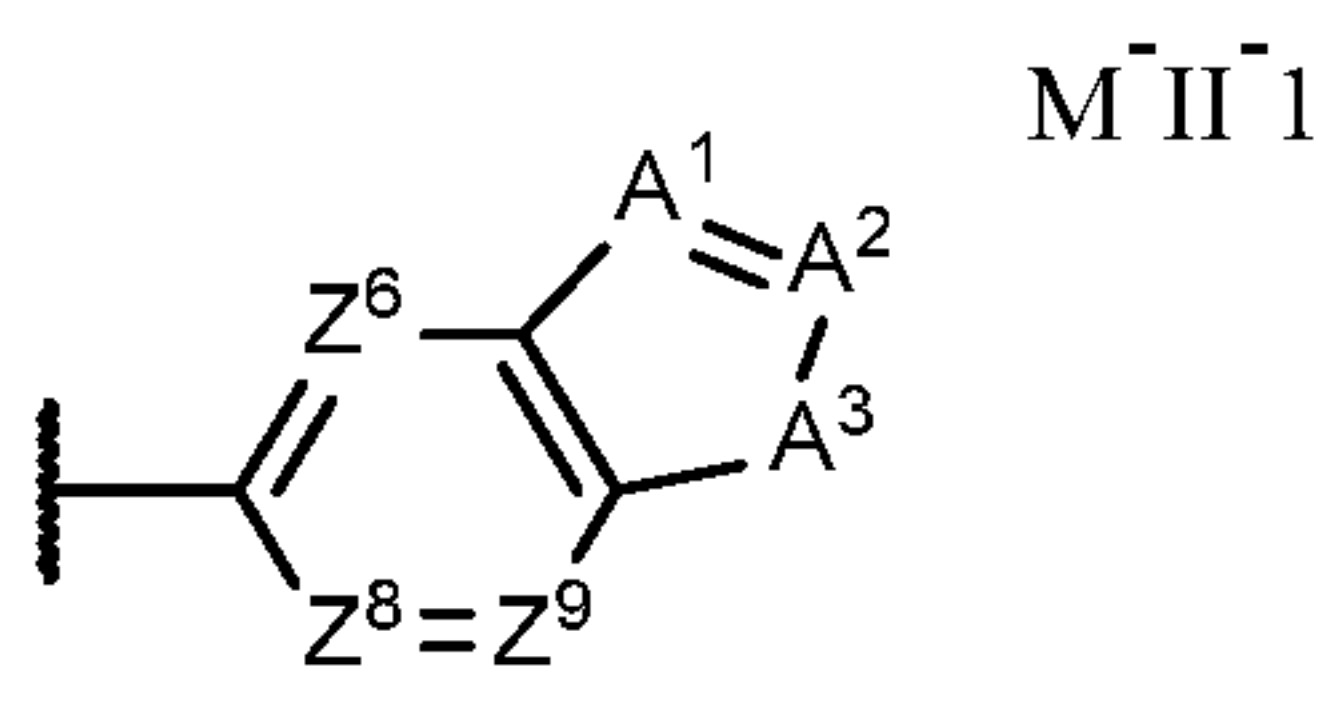
(*R*)-7-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*R*)-5-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide; and

(*R*)-7-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide.

[00104] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II, wherein M-II represents a moiety represented by ring system M-II-1:



wherein A¹ and A² independently represent CR¹¹; A³ represents O; and Z⁶, Z⁸, and Z⁹ independently represent CR⁷;

and may include, collectively or individually, the single enantiomers listed below, and pharmaceutically acceptable salts thereof:

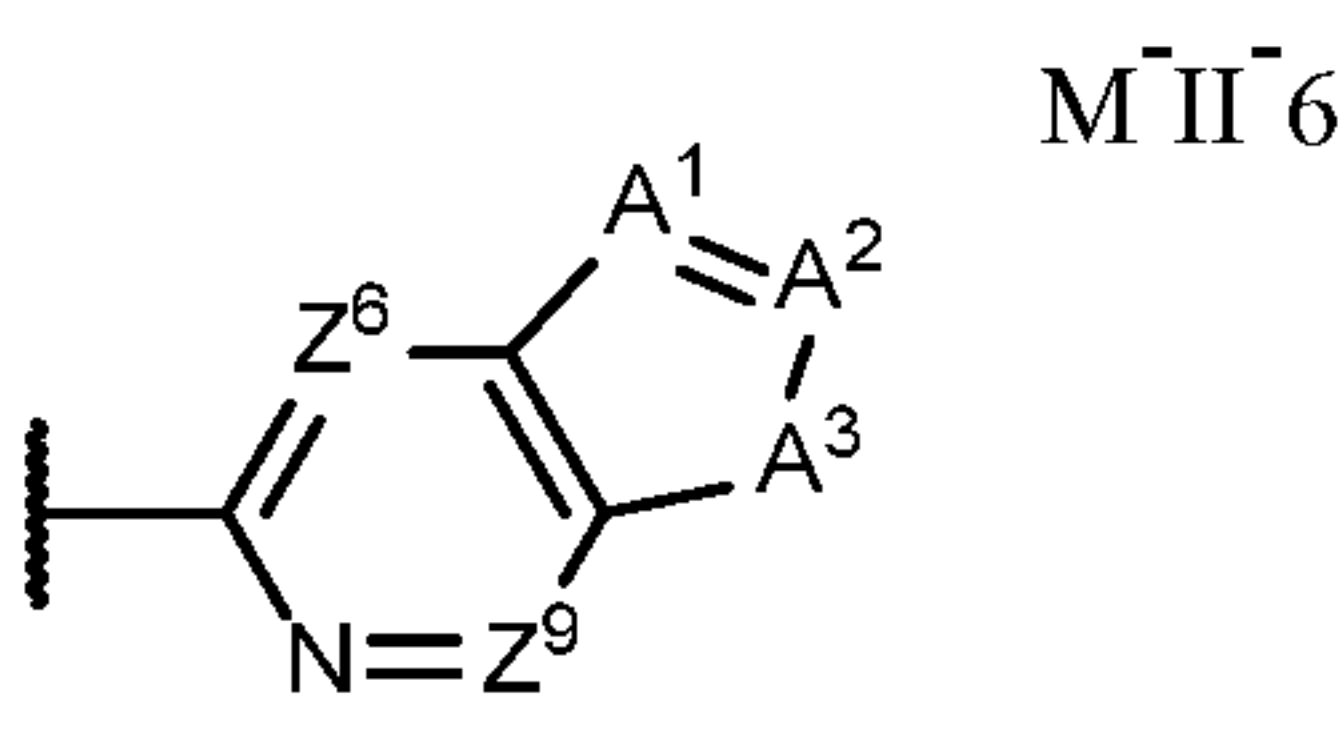
(*R*)-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

and

(*R*)-2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide.

[00105] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II, wherein M-II represents a moiety represented by ring system M-II-6:



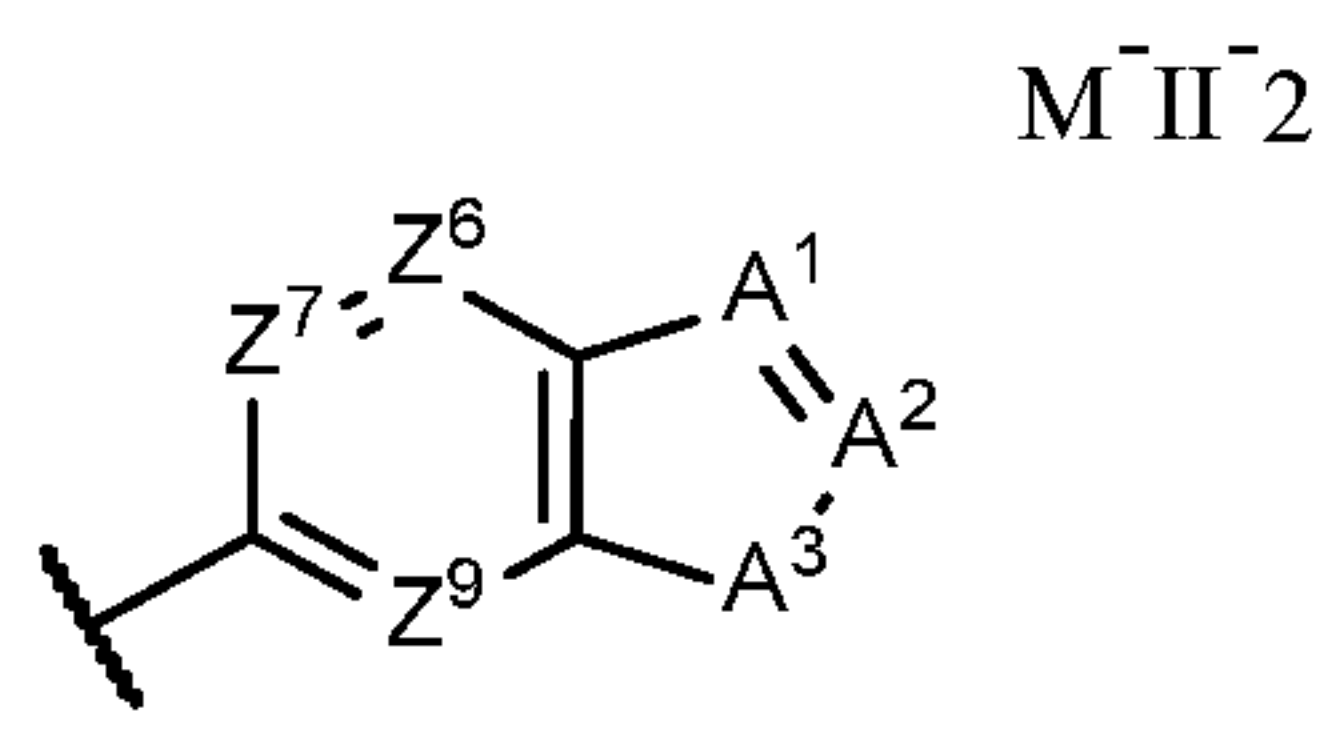
wherein A¹ and A² independently represent CR¹¹; A³ represents O; and Z⁶ and Z⁹ independently represent CR⁷;

and may include, collectively or individually, the single enantiomers listed below, and pharmaceutically acceptable salts thereof:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)furo[2,3-*c*]pyridine-5-carboxamide; and

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-*c*]pyridine-5-carboxamide.

[00106] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II, wherein M-II represents a moiety represented by ring system M-II-2:

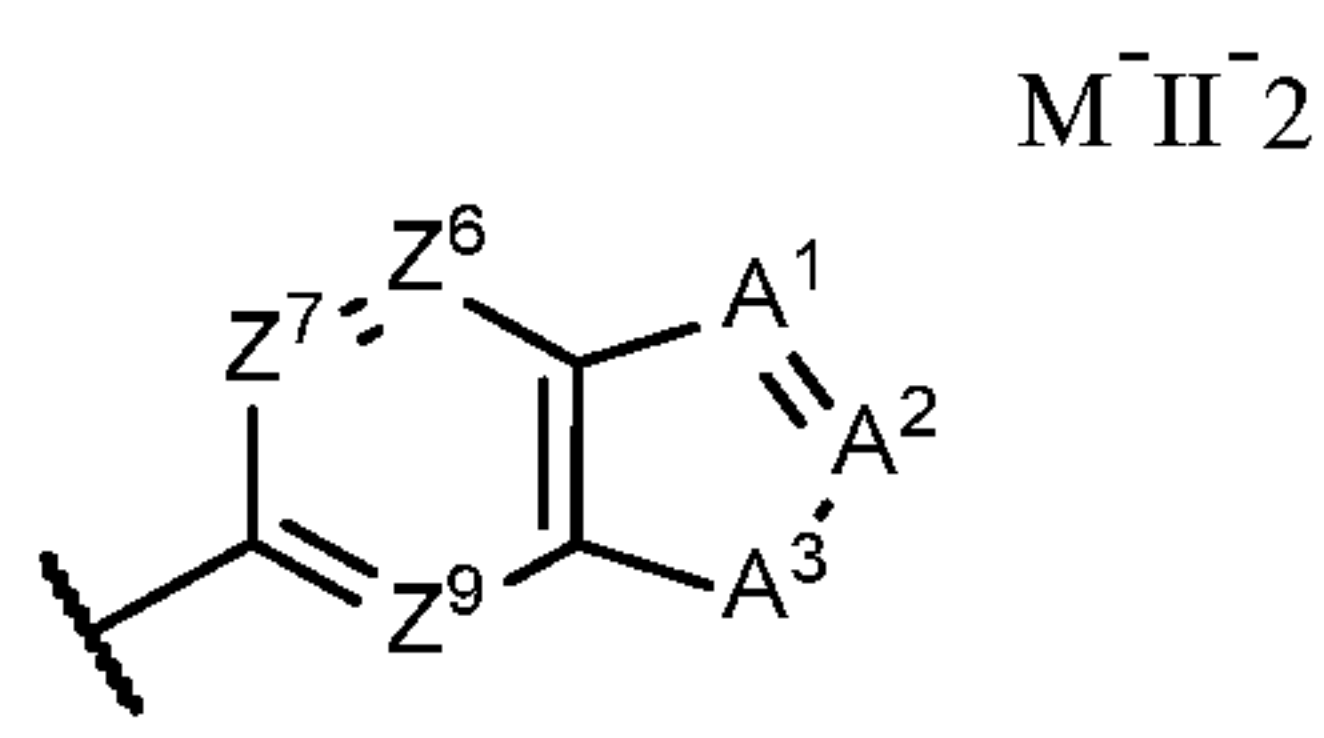


wherein A¹ and A² independently represent CR¹¹; A³ represents NR¹⁰; and Z⁶, Z⁷, and Z⁹ independently represent CR⁷;

and may include, collectively or individually, the single enantiomer listed below, and pharmaceutically acceptable salts thereof:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-6-carboxamide.

[00107] In certain embodiments, the amide compound represented by Formula (I), (II), or (III), may comprise the W representing the moiety represented by the ring system M-II, wherein M-II represents a moiety represented by ring system M-II-2:



wherein A¹ and A² independently represent CR¹¹; A³ represents S; and Z⁶, Z⁷, and Z⁹ independently represent CR⁷;

and may include, collectively or individually, the single enantiomer listed below, and pharmaceutically acceptable salts thereof:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-6-carboxamide; and

(*R*)-2-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-6-carboxamide.

[00108] As used herein, the term “treating” (or “treat” or “treatment”), unless otherwise specified, includes the generally accepted meaning which encompasses improving, modifying, decreasing, prohibiting, preventing, restraining, minimizing, slowing, halting, stopping, curing, and/or reversing a symptom associated with a disease and/or a disease. Treatment may include both therapeutic and prophylactic administration. For example, treatment of a cognitive impairment, in a patient diagnosed

as having a cognitive impairment, may include, but is not limited to, curing the cognitive impairment, preventing the deterioration of one or more symptoms associated with the cognitive impairment; improving cognition in a patient suffering from the cognitive impairment, slowing the progression of the cognitive impairment and/or modifying the cognitive impairment.

[00109] As used herein, the term “effective dose” (or “dose”), unless otherwise specified, is understood to include a therapeutically acceptable dose, a therapeutically acceptable amount, a therapeutically effective dose, a therapeutically effective amount, a pharmaceutically acceptable dose, a pharmaceutically acceptable amount, a pharmaceutically effective dose, or a pharmaceutically effective amount.

[00110] As used herein, the term “cognitive impairment,” unless otherwise specified, includes at least one of the following: Limited Cognitive Impairment (LCI), Mild Cognitive Impairment (MCI), Alzheimer’s disease (or dementia of an Alzheimer’s-type) or a particular stage of Alzheimer’s disease, inclusive of pre-Alzheimer’s disease, early Alzheimer’s disease, mild Alzheimer’s disease, moderate Alzheimer’s disease, severe Alzheimer’s disease, pre-Alzheimer’s-to-mild Alzheimer’s disease, mild-to-moderate Alzheimer’s disease, moderate-to-severe Alzheimer’s disease, schizophrenia (for example, paranoid type schizophrenia, disorganized type schizophrenia, catatonic type schizophrenia, undifferentiated type schizophrenia), schizophreniform disorder, schizoaffective disorder, delusional disorder, positive symptoms of schizophrenia, negative symptoms of schizophrenia, or schizophrenia with dementia.

[00111] Alzheimer’s disease may include, unless otherwise specified, any of the sub-diagnostic categories used to characterize the type or degree of cognitive impairment in a patient for treatment purposes. A commonly referenced diagnostic scale for characterizing the degree of cognitive impairment for a patient with Alzheimer’s disease includes the 3-stage Alzheimer Disease Model. The 3-stages consist of: mild stage (also referred to as “early Alzheimer’s disease” or “mild Alzheimer's disease” or “early stage Alzheimer’s disease” or “mild dementia of an Alzheimer's-type”), moderate stage (also referred to as “middle Alzheimer’s disease” or “moderate Alzheimer's disease” or “middle stage Alzheimer’s disease” or “moderate dementia of an Alzheimer's-type”), and severe stage (also referred to as “late Alzheimer’s disease” or “severe Alzheimer's disease” or “late stage Alzheimer’s disease” or “severe dementia of an Alzheimer's-type”). For patients with a condition that has not progressed to the point of mild stage Alzheimer’s disease, they may be diagnosed as having pre-Alzheimer’s disease. It is also not uncommon for treatment purposes to characterize stages together, such as pre-Alzheimer’s disease-to-mild stage Alzheimer’s disease, mild-to-moderate Alzheimer’s disease, or moderate-to-severe Alzheimer’s disease. Another useful diagnostic scale that is used in characterizing the degree of cognitive impairment for a patient having Alzheimer’s disease is the Seven Stage Alzheimer’s Disease Model (sometimes known as the “Seven Stage Global Deterioration Scale” or the “Reisberg Scale”). This diagnostic scale divides the progression of the cognitive disorder associated with Alzheimer’s disease as follows: Stage 1-no

Alzheimer's disease (generally characterized by absence of impairment, no impairment, or normal function), Stage 2-pre-Alzheimer's disease (generally characterized by minimal impairment, normal forgetfulness, or very mild cognitive decline), Stage 3-early-stage Alzheimer's disease (generally characterized by a noticeable cognitive decline, early confusional/mild cognitive impairment, or mild cognitive decline), Stage 4-early-stage/mild Alzheimer's disease (also referred to as late confusional/mild Alzheimer's, and generally characterized by moderate cognitive decline), Stage 5-middle-stage/moderate Alzheimer's (also referred to as early dementia/moderate Alzheimer's disease and generally characterized by moderately severe cognitive decline), Stage 6-middle dementia/moderately severe Alzheimer's disease (also referred to as middle-stage/moderate to late-stage/severe Alzheimer's disease and generally characterized by severe cognitive decline), and Stage 7-late-stage/severe Alzheimer's disease (also referred to as severe dementia or failure-to-thrive, and generally characterized by very severe cognitive decline). It is also not uncommon for treatment purposes to characterize stages together, such as pre-Alzheimer's disease-to-mild stage Alzheimer's disease, mild-to-moderate Alzheimer's disease, or moderate-to-severe Alzheimer's disease. As used herein, unless otherwise specified, Alzheimer's disease includes all of the above named diagnostic categories or disease characterizations. It is also not uncommon for a physician to categorize any one or more of the above noted states of Alzheimer's disease as being probable, for example, probable mild-to-moderate Alzheimer's disease or probable severe Alzheimer's disease, when their diagnosis does not include, for example a physical biopsy or other definitive analysis.

[00112] Mild Cognitive Impairment (MCI) is considered by some to be an intermediate stage between normal aging and the onset of Alzheimer's disease. For example, MCI may be characterized by persistent forgetfulness, but may lack some or many of the more debilitating symptoms of Alzheimer's disease. Another set of criteria that may characterize a patient as having mild cognitive impairment suitable for treatment includes a patient that meets the following: 1) memory complaints corroborated by an informant, 2) objective memory impairment for age and education, 3) normal general cognitive function, 4) intact activities of daily living, and 5) the patient does not meet criteria for dementia. In general, a patient characterized as having mild cognitive impairment may not yet have a clinical cognitive deficit. Mild cognitive impairment may also be distinguished from senile dementia in that mild cognitive impairment involves a more persistent and troublesome problem of memory loss for the age of the patient. On the clinical diagnostic scale, mild cognitive impairment is followed, in increased severity, by Alzheimer's disease.

[00113] Limited Cognitive Impairment (LCI) describes a cognitive impairment (*i.e.*, symptoms or conditions), which precedes mild cognitive impairment on a clinical diagnostic scale, and includes any chronic or temporary impairment in cognition, learning or memory that prevents or reduces the ability of a patient from achieving their individual potential in these areas. For example, LCIs may include minor impairments to memory associated with focus and concentration (*e.g.*, accuracy and

speed of learning and recalling information), working memory (*e.g.*, used in decision making and problem solving), cognition, focus, mental quickness, and mental clarity.

[00114] The term “stereoisomer” refers to a molecule capable of existing in more than one spatial atomic arrangement for a given atomic connectivity (*e.g.*, enantiomers, meso compounds, and diastereomers). As used herein, the term “stereoisomer” means either or both enantiomers and diastereomers.

[00115] The amide compounds of the present invention represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, may contain one or more stereogenic centers. Accordingly, compounds of this invention can exist as either individual stereoisomers or mixtures of two or more stereoisomers. A compound of the present invention will include both mixtures (*e.g.*, racemic mixtures) and also individual respective stereoisomers that are substantially free from another possible stereoisomer. The term “substantially free of other stereoisomers” as used herein means less than 25% of other stereoisomers, less than 10% of other stereoisomers, less than 5% of other stereoisomers, less than 2% of other stereoisomers, or less than “X”% of other stereoisomers (wherein X is a number between 0 and 100, inclusive) are present.

[00116] The amide compounds of the present invention represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, may contain one or more tautomeric forms. Accordingly, compounds of this invention can exist as either individual tautomers or mixtures of tautomeric forms. A compound of the present invention will include both mixtures (*e.g.*, mixtures of tautomeric forms) and also individual respective tautomers that are substantially free from another possible tautomer.

[00117] The amide compounds of the present invention represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, may contain one or more geometric isomers. Accordingly, compounds of this invention can exist as either geometric isomers or mixtures of geometric isomers. A compound of the present invention will include both mixtures (*e.g.*, mixtures of geometric isomers) and also individual respective geometric isomers that are substantially free from another possible geometric isomer.

[00118] The term “haloalkyl” refers to an alkyl group having from 1 to 5 halogen substituents independently selected from -F, -Cl, -Br, and -I. For example, a haloalkyl may represent a -CF₃ group, a -CCl₃ group, a -CH₂CF₃ group, or a -CF₂CF₃ group.

[00119] The term “heteroaryl” refers to an aromatic ring system comprising at least one or more hetero- ring atoms, such as two, three, four, or five hetero- ring atoms, independently selected from N, O, and S. Suitable heteroaryl groups may include a single ring, for example, thienyl, pyridyl, thiazolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, oxazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, and furazanyl. Suitable heteroaryl groups may include a fused ring system, for example, a six-six fused ring system, a six-five fused ring system, or a five-six fused ring system, such as benzothienyl, quinolyl, benzofuranyl, benzothiazolyl,

benzothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, benzoxazolyl, isoquinolinyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, isoindolyl, purinyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, quinazolinyl, quinoxalinyl, naphthridinyl, and furopyridinyl.

[00120] Suitable “heterocycloalkyl” groups include those having at least one or more hetero- ring atoms, such as two or three hetero- ring atoms, independently selected from –O-, -S-, -S(O)₂-, -N(H)-, and –N(CH₂)_mR¹⁸-. Suitable heterocycloalkyl groups may include, for example, tetrahydrofurano, tetrahydropyrano, morpholino, pyrrolidino, piperidino, piperazino, azetidino, azetidinono, oxindolo, oxetano, dihydroimidazolo, and pyrrolidinono.

[00121] The pharmaceutically acceptable salt of the amide compounds represented by Formula (I), Formula (II), or Formula (III), according to the present invention may be acid addition salts with inorganic or organic acids. Specific examples of these salts include acid addition salts with, for instance, mineral acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid or phosphoric acid; organic acids, for example carboxylic acids or sulfonic acids, such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, benzoic acid, p-toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, isethionic acid, glucuronic acid, gluconic acid, methanesulfonic acid or ethanesulfonic acid; or acidic amino acids such as aspartic acid or glutamic acid.

[00122] In certain embodiments, a pharmaceutical composition may comprise an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[00123] In certain embodiments, the amide compounds represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, are suitable for use as medicaments for the treatment and/or prophylaxis of diseases in humans and/or animals.

[00124] In certain embodiments, the invention relates to a method comprising administering to a patient in need thereof an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[00125] In certain embodiments, the amide compounds represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, act as ligands, in particular as $\alpha 7$ -nAChR agonists.

[00126] In certain embodiments, a method of treating a patient in need thereof, comprising administering an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof. In certain embodiments, a method of treating a patient in need thereof, comprising administering a pharmaceutical composition comprising an amide

compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof. For example, the patient may suffer from a cognitive impairment or suffers from one or more symptoms associated with a cognitive impairment, such as Limited Cognitive Impairment (LCI), Mild Cognitive Impairment (MCI), Alzheimer's disease, dementia of an Alzheimer's-type, schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, positive symptoms of schizophrenia, negative symptoms of schizophrenia, or schizophrenia with dementia.

[00127] In certain embodiments, the amide compounds represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, can, because of their pharmacological properties, be employed alone or in combination with other active ingredients for the treatment and/or prevention of cognitive impairments, for example, Alzheimer's disease or schizophrenia. Because of their selective effect as $\alpha 7$ -nAChR agonists, the amide compounds represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, are particularly suitable for improving cognition, providing procognitive effects, improving perception, improving concentration, improving learning or memory, improving one or more aspects of cognition, e.g., one or more of: executive function, memory (e.g., working memory), social cognition, visual learning, verbal learning and speed of processing, especially after or associated with cognitive impairments like those occurring for example in situations/diseases/syndromes such as mild cognitive impairment, age-associated learning and memory impairments, age-associated memory loss, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post-stroke dementia), post-traumatic brain syndrome, general concentration impairments, concentration impairments in children with learning and memory problems, attention deficit hyperactivity disorder, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, dyskinesias associated with dopamine agonist therapy in Parkinson's Disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotrophic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jakob dementia, HIV dementia, schizophrenia (e.g., paranoid type, disorganized type, catatonic type, and undifferentiated type), schizophreniform disorder, schizoaffective disorder, delusional disorder, positive symptoms of schizophrenia, negative symptoms of schizophrenia, schizophrenia with dementia, Korsakoff's psychosis, depression, anxiety, mood and affective disorders, traumatic brain injury, withdrawal symptoms associated with smoking cessation and dependent drug cessation, Gilles de la Tourette's Syndrome, age-related macular degeneration, glaucoma, neurodegeneration associated with glaucoma, treatment (including amelioration, prevention or delay of progression) of sleep disorders (e.g., narcolepsy, excessive daytime sleepiness, nocturnal sleep disruption and/or cataplexy), treatment (including amelioration, prevention or delay) of progression of fatigue, or use for facilitation of emergence from general anesthesia.

[00128] In certain embodiments, the amide compounds represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, can be employed alone or in combination with other active ingredients for the prophylaxis and treatment of acute and/or chronic pain (for a classification, see “Classification of Chronic Pain, Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms”, 2nd edition, Meskey and Begduk, editors; IASP Press, Seattle, 1994), especially for the treatment of cancer-induced pain and chronic neuropathic pain like, for example, that associated with diabetic neuropathy, postherpetic neuralgia, peripheral nerve damage, central pain (for example as a consequence of cerebral ischaemia) and trigeminal neuralgia, and other chronic pain such as, for example, lumbago, backache (low back pain) or rheumatic pain. In addition, these active ingredients are also suitable for the therapy of primary acute pain of any origin and of secondary states of pain resulting therefrom, and for the therapy of states of pain which were formerly acute and have become chronic.

[00129] In certain embodiments, the invention relates to a method comprising administering to a patient in need thereof, such as a patient suffering from, or diagnosed as having, a cognitive impairment or having one or more symptoms associated with a cognitive impairment, an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent. For example, the method may treat and/or improve the one or more symptoms associated with a cognitive impairment and/or the cognitive impairment.

[00130] A certain embodiment of the present invention provides a method of improving one or more cognitive symptoms, improving one or more behavioral symptoms, or both, associated with a cognitive impairment, comprising: administering to a patient in need thereof an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising an effective dose of the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[00131] In a certain embodiment of the present invention, the method provides a pro-cognitive effect in a patient suffering from, or diagnosed as having, a cognitive disease or dementia, comprising: administering to a patient in need thereof an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising an effective dose of the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent; wherein the method provides at least one of the following: visual motor, learning, delayed memory, or

executive function; for example provides a pro-cognitive effect, exclusive of attention, in said patient; for example provides a pro-cognitive effect in at least one of the following: visual motor, learning, delayed memory, or executive function.

[00132] A certain embodiment of the present invention provides a method of treating a patient with a cognitive disease, comprising: administering to the patient a daily dose of a pharmaceutical composition comprising an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[00133] In a certain embodiment of the present invention, the method provides a pro-cognitive effect in a patient suffering from, or diagnosed as having, schizophrenia, for example, paranoid type schizophrenia, disorganized type schizophrenia, catatonic type schizophrenia, undifferentiated type schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, positive symptoms of schizophrenia, negative symptoms of schizophrenia, or schizophrenia with dementia, comprising: administering to a patient in need thereof an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to a patient in need thereof, a pharmaceutical composition comprising an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluents; wherein the method provides at least one of the following: visual motor, learning, delayed memory, or executive function; for example provides a pro-cognitive effect, exclusive of attention, in said patient; for example provides a pro-cognitive effect in at least one of the following: visual motor, learning, delayed memory, or executive function.

[00134] In an embodiment of the present invention, any one of the above-noted embodiments, includes wherein the daily dose is an initial daily dose.

[00135] In a certain embodiment of the present invention provides a method of improving cognition of a patient in need thereof, comprising: administering to the patient an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluents.

[00136] In a certain embodiment of the present invention provides a method of treating or improving one or more symptoms associated with a cognitive disease and/or a cognitive impairment in a patient in need thereof, comprising: administering to the patient an effective dose of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof; or administering to the patient a pharmaceutical composition comprising the amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

[00137] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes treating a symptom associated with a cognitive disease.

[00138] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes improving a symptom associated with a cognitive disease.

[00139] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes preventing progression of a cognitive disease.

[00140] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the patient has been diagnosed as having a cognitive disease.

[00141] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the patient has been diagnosed as having Alzheimer's disease.

[00142] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes treating a symptom associated with Alzheimer's disease.

[00143] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes improving a symptom associated with Alzheimer's disease.

[00144] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes preventing progression of Alzheimer's disease.

[00145] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the patient has been diagnosed as having mild-to-moderate Alzheimer's disease.

[00146] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes treating a symptom associated with schizophrenia.

[00147] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes improving a symptom associated with schizophrenia.

[00148] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes preventing progression of schizophrenia.

[00149] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the patient has been diagnosed as having schizophrenia.

[00150] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes treating a symptom associated with positive symptoms of schizophrenia.

[00151] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes improving a symptom associated with positive symptoms of schizophrenia.

[00152] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes preventing progression of positive symptoms of schizophrenia.

[00153] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes the patient has been diagnosed as having positive symptoms of schizophrenia.

[00154] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes treating a symptom associated with negative symptoms of schizophrenia.

[00155] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes improving a symptom associated with negative symptoms of schizophrenia.

[00156] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes preventing progression of negative symptoms of schizophrenia.

[00157] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes the patient has been diagnosed as having negative symptoms of schizophrenia.

[00158] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes treating a symptom associated with schizophrenia with dementia.

[00159] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes improving a symptom associated with schizophrenia with dementia.

[00160] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes preventing progression of schizophrenia with dementia.

[00161] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes the patient has been diagnosed as having schizophrenia with dementia.

[00162] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the method specifically includes the patient has been diagnosed as having a disease associated with chronic inflammation, including atherosclerosis, rheumatoid arthritis and inflammatory bowel diseases.

[00163] In an embodiment of the present invention, any one of the above-noted embodiments, wherein the pharmaceutical composition is in the form of a tablet.

[00164] Pharmaceutical Compositions

[00165] In certain embodiments, the invention also includes pharmaceutical preparations which, besides inert, nontoxic, pharmaceutically suitable excipients, adjuvants and carriers, contain one or more amide compounds represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, or consist of one or more amide compounds represented by

Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, and processes for producing these preparations.

[00166] An amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, may be formulated for administration in solid or liquid form. For example, an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, may be formulated for administration in a capsule, a tablet, or a powder form. For example, an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, may be formulated alone or as part of a pharmaceutical composition, suitable for oral administration, such as in a capsule or tablet, intravenous administration, parenteral administration, topical administration, or transdermal administration, such as in a patch, to a patient in need thereof.

[00167] An amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, may be administered as a pharmaceutical composition, for example, in the presence of carriers, adjuvants, excipients, diluents, fillers, buffers, stabilizers, preservatives, lubricants, and the like, for example, administered as a pharmaceutical composition (*e.g.*, formulation) comprising at least an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers, adjuvants, excipients, diluents, or other materials well known to those skilled in the art. As used herein, the term “pharmaceutically acceptable”, unless otherwise specified, includes the generally accepted meaning which encompasses combinations, compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for consumption by humans without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00168] Suitable pharmaceutically acceptable carriers, adjuvants, excipients, and diluents, can include, but are not limited to, lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum, acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propyl hydroxybenzoates, talc, magnesium stearate, and mineral oil. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[00169] The formulations can additionally include, but are not limited to, pharmaceutically acceptable lubricating agents, glidants, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, and/or flavoring agents. The pharmaceutical compositions of the present invention may be formulated so as to provide quick release, immediate release, sustained release, or delayed release of an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, after administration to the patient by employing procedures well-known in the art.

[00170] Another embodiment of the invention further comprises methods of making Pharmaceutical Composition, comprising admixing at least an amide compound represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilizers, or other materials.

[00171] In certain embodiments, the amide compounds represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, are to be present in these preparations in a concentration of from 0.1 to 99.5% by weight, preferably from 0.5 to 95% by weight, of the complete mixture. Besides the amide compounds represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, the pharmaceutical preparations may also contain other active pharmaceutical ingredients.

[00172] In certain embodiments, the novel active ingredients can be converted in a known manner into conventional formulations such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert, nontoxic, pharmaceutically suitable excipients or solvents. In these cases, the therapeutically active compound should in each case be present in a concentration of about 0.5 to 90% by weight of the entire mixture, i.e., in amounts which are sufficient to reach the stated dose range.

[00173] In certain embodiments, the formulations are produced, for example, by extending the active ingredients with solvents and/or excipients, where appropriate with use of emulsifiers and/or dispersants, it being possible for example when water is used as diluent where appropriate to use organic solvents as auxiliary solvents.

[00174] In certain embodiments, administration may take place in a conventional way, for example, orally, transdermally or parenterally, especially perlingually or intravenously. In certain embodiments, administration may also take place by inhalation through the mouth or nose, for example, with the aid of a spray, or topically via the skin.

[00175] In certain embodiments, the amide compounds represented by Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, may be administered in amounts of about 0.01 to 10 mg/kg, on oral administration, for example, about 0.05 to 5 mg/kg, of body weight to achieve effective results.

[00176] EXAMPLES**[00177]** Analytical instrument model:**Table 1**

LCMS	Shimadzu UFLC MS: LCMS-2020 Agilent Technologies 1200 series MS: Agilent Technologies 6110 Agilent Technologies 1200 series MS: LC/MSD VL
NMR	BRUKER AVANCE III/400
Prep-HPLC	Gilson GX-281 systems: instruments GX-A, GX-B, GX-C, GX-D, GX-E, GX-F, GX-G and GX-H
GCMS	SHIMADZU GCMS-QP2010 Ultra
Analytical cSFC	Agilent Technologies 1290 Infinity
Prep-cSFC	Waters SFC Prep 80

[00178] LCMS:

[00179] LCMS Conditions A (“LCMS (A)”): Instrument: Shimadzu LCMS 2020; Mobile phase A: 4L H₂O \ 1.5 mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 10-80AB_4MIN_2W; Flow Rate: 0.8 mL/min.; Gradient: 10%-80%; Column: Boston Green ODS 2.1*30 mm, 3 μm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00180] LCMS Conditions B (“LCMS (B)”): Instrument: Agilent 1200 Series; Mobile phase A: 4L H₂O \ 1.5 ml TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 5-95AB_R_2W; Flow Rate: 1.5 mL/min.; Gradient: 5%-95%; Column: Chromolith@Flash RP-18e 25-2 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00181] LCMS Conditions C (“LCMS (C)”): Instrument: Agilent 1200 Series; Mobile phase A: 4L H₂O \ 2 mL NH₃H₂O; Mobile phase B: Acetonitrile; Method name: 5-95CD_4.5MIN_2W; Flow Rate: 0.8 mL/min.; Gradient: 5%-95%; Column: Chromolith@Flash RP-18e 25-2 mm; Column temperature 50 °C; Wavelength: 220 nm & 254 nm.

[00182] LCMS Conditions D (“LCMS (D)”): Instrument: Agilent 1200 Series; Mobile phase A: 4L H₂O \ 1.5 mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 5-95AB_R_4MIN_2W; Flow Rate: 0.8 mL/min. ; Gradient: 5%-95%; Column: Chromolith@Flash RP-18e 25-2 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00183] LCMS Conditions E (“LCMS (E)”): Instrument: Agilent 1200 Series; Mobile phase A: 4L H₂O \ 1.5 ml TFA, Mobile phase B: 4L ACN\0.75 mL TFA; Method name: 5-95AB_R; Flow Rate: 1.5 mL/min. ; Gradient: 5%-95%; Column: Chromolith@Flash RP-18e 25-2 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00184] LCMS Conditions F (“LCMS (F)”): Instrument: Agilent 1200 Series; Mobile phase A: 4L H₂O \ 2 ml NH₃H₂O, Mobile phase B: Acetonitrile; Method name: 5-95CD_2MIN_2W; Flow Rate: 1.2 mL/min.; Gradient: 5%-95%; Column: XBrige Shield RP-18 2.1*50 mm, 5 μm; Column temperature: 30 °C; Wavelength: 220 nm & 254 nm.

[00185] LCMS Conditions G (“LCMS (G)”): Instrument: Agilent 1200 Series; Mobile phase A: 4L H₂O \ 2 mL NH₃H₂O, Mobile phase B: Acetonitrile; Method name: 10-80CD_4MIN_2W; Flow Rate: 0.8 mL/min.; Gradient: 10%-80%; Column: XBridge C-18 2.1*50 mm, 5μm; Column temperature: 40 °C; Wavelength: 220 nm & 254 nm.

[00186] LCMS Conditions H (“LCMS (H)”): Instrument: Agilent 1200 Series; Mobile phase A: 4L H₂O \ 1.5 mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 10-80AB_4MIN_2W; Flow Rate: 0.8 mL/min.; Gradient: 10%-80%; Column: Xtimate C-18, 2.1*30 mm, 3μm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00187] LCMS Conditions I (“LCMS (I)”): Instrument: Agilent 1200 Series; Mobile phase A: 4L H₂O \ 2 mL NH₃H₂O, Mobile phase B: Acetonitrile; Method name: 0-60CD_4.5MIN_2W; Flow Rate: 0.8 ml/min.; Gradient: 0%-60%; Column: XBrige Shield RP-18 2.1*50 mm, 5μm; Column temperature 50 °C; Wavelength: 220 nm & 254 nm.

[00188] LCMS Conditions J (“LCMS (J)”): Instrument: Agilent 1200 Series; Mobile phase A: 4L H₂O \ 2mL NH₃H₂O, Mobile phase B: Acetonitrile; Method name: 10-80CD_2MIN_POS_2W; Flow Rate: 1.2ml/min.; Gradient: 10%-80%; Column: Xbridge C-18 2.1*50 mm, 5μm; Column temperature: 40 °C; Wavelength: 220 nm & 254 nm.

[00189] LCMS Conditions K (“LCMS (K)”): Instrument: Shimadzu LCMS 2020; Mobile phase A: 4L H₂O \ 1.5mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 0-30AB_2MIN_2W; Flow Rate: 1.2 mL/min.; Gradient: 0%-30%; Column: Chromolith@Flash RP-18E 25-2 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00190] LCMS Conditions L (“LCMS (L)”): Instrument: Shimadzu LCMS 2020; Mobile phase A: 4L H₂O \ 1.5mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 0-30AB_4MIN_2W; Flow Rate: 0.8 mL/min.; Gradient: 0%-30%; Column: Chromolith@Flash RP-18E 25-2 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00191] LCMS Conditions M (“LCMS (M)”): Instrument: Shimadzu LCMS 2020; Mobile phase A: 4L H₂O \ 1.5mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 0-60AB_2MIN_2W; Flow Rate: 1.2 mL/min.; Gradient: 0%-60%; Column: Chromolith@Flash RP-18E 25-2 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00192] LCMS Conditions N (“LCMS (N)”): Instrument: Shimadzu LCMS 2020; Mobile phase A: 4L H₂O \ 1.5mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 0-60AB_4MIN_2W; Flow Rate: 0.8 mL/min.; Gradient: 0%-60%; Column: Chromolith@Flash RP-18E 25-2 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00193] LCMS Conditions O (“LCMS (O)”): Instrument: Agilent 1200 Series LCMS; Mobile phase A: 4L H₂O \ 2mL NH₃H₂O, Mobile phase B: CAN; Method name: 0-30CD_2MIN_POS_2W; Flow Rate: 1.0 mL/min.; Gradient: 0%-30%; Column: Xbridge C18 2.1*50 mm, 5μm; Column temperature: 40 °C; Wavelength: 220 nm & 254 nm.

[00194] LCMS Conditions P (“LCMS (P)”): Instrument: Agilent 1200 Series LCMS; Mobile phase A: 4L H₂O \ 2mL NH₃H₂O, Mobile phase B: CAN; Method name: 0-60CD_2MIN_POS_2W; Flow Rate: 1.0 mL/min.; Gradient: 0%-60%; Column: Xbridge C18 2.1*50 mm, 5μm; Column temperature: 40 °C; Wavelength: 220 nm & 254 nm.

[00195] LCMS Conditions Q (“LCMS (Q)”): Instrument: Agilent 1200 Series LCMS; Mobile phase A: 4L H₂O \ 2mL NH₃H₂O, Mobile phase B: CAN; Method name: 0-60CD_4MIN_2W; Flow Rate: 0.8 mL/min.; Gradient: 0%-60%; Column: Xbridge C18 2.1*50 mm, 5μm; Column temperature: 40 °C; Wavelength: 220 nm & 254 nm.

[00196] LCMS Conditions R (“LCMS (R)”): Instrument: Agilent 1200 Series LCMS; Mobile phase A: 4L H₂O \ 1.5mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 10-80AB_2MIN_2W; Flow Rate: 1.2 mL/min.; Gradient: 10%-80%; Column: Xtimate C18, 2.1*30mm, 3μm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00197] LCMS Conditions S (“LCMS (S)”): Instrument: Agilent 1200 Series LCMS; Mobile phase A: 4L H₂O \ 2mL NH₃H₂O, Mobile phase B: CAN; Method name: 30-90CD_4MIN_POS_2W; Flow Rate: 0.8 mL/min.; Gradient: 30%-90%; Column: Xbridge C18 2.1*50 mm, 5μm; Column temperature: 40 °C; Wavelength: 220 nm & 254 nm.

[00198] LCMS Conditions T (“LCMS (T)”): Instrument: Agilent 1200 Series LCMS; Mobile phase A: 4L H₂O \ 1.5mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 5-95AB_15MIN_YMC; Flow Rate: 1.0 mL/min.; Gradient: 5%-95%; Column: YMC-Pack ODS-A 5μm 150*4.6mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00199] LCMS Conditions U (“LCMS (U)”): Instrument: Agilent 1200 Series LCMS; Mobile phase A: 4L H₂O \ 1.5mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 0-30AB_2MIN_2W; Flow Rate: 1.2 mL/min.; Gradient: 0%-30%; Column: Chromolith@Flash RP-18E 25-2 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00200] LCMS Conditions V (“LCMS (V)”): Instrument: Agilent 1200 Series LCMS; Mobile phase A: 4L H₂O \ 1.5mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 0-30AB_4MIN_2W; Flow Rate: 0.8 mL/min.; Gradient: 0%-30%; Column: Chromolith@Flash RP-18E 25-2 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00201] LCMS Conditions W (“LCMS (W)”): Instrument: Agilent 1200 Series LCMS; Mobile phase A: 4L H₂O \ 1.5mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 0-60AB_2MIN_2W; Flow Rate: 1.2 mL/min.; Gradient: 0%-60%; Column: Chromolith@Flash RP-18E 25-2 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00202] LCMS Conditions X (“LCMS (X)”): Instrument: Agilent 1200 Series LCMS; Mobile phase A: 4L H₂O \ 1.5mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 0-60AB_4MIN_2W; Flow Rate: 0.8 mL/min.; Gradient: 0%-60%; Column: Chromolith@Flash RP-18E 25-2 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00203] LCMS Conditions Y (“LCMS (Y)”): Instrument: Shimadzu LCMS 2020; Mobile phase A: 4L H₂O \ 1.5 ml TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 5-95AB_R_2W; Flow Rate: 1.5 mL/min.; Gradient: 5%-95%; Column: Chromolith@Flash RP-18e 25-2 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00204] LCMS Conditions Z (“LCMS (Z)”): Instrument: Shimadzu LCMS 2020; Mobile phase A: 4L H₂O \ 1.5 mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 5-95AB_R_4MIN_2W; Flow Rate: 0.8 mL/min.; Gradient: 5%-95%; Column: Chromolith@Flash RP-18e 25-2 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00205] LCMS Conditions AA (“LCMS (AA)”): Instrument: Agilent 1200 Series LCMS; Mobile phase A: 4L H₂O \ 2mL NH₃/H₂O, Mobile phase B: ACN; Method name: 10-80CD_2MIN_NEG; Flow Rate: 1.2 mL/min.; Gradient: 10%-80%; Column: Xbridge C18 2.1*50 mm, 5μm; Column temperature: 40 °C; Wavelength: 220 nm & 254 nm.

[00206] LCMS Conditions BB (“LCMS (BB)”): Instrument: Agilent 1200 Series LCMS; Mobile phase A: 4L H₂O \ 1.5mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 0-60AB_R_2W; Flow Rate: 1.5 mL/min.; Gradient: 0%-60%; Column: Chromolith@Flash RP-18E 25-2 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00207] LCMS Conditions CC (“LCMS (CC)”): Instrument: Agilent 1200 Series LCMS; Mobile phase A: 4L H₂O \ 1.5mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 0-30AB_R_2W; Flow Rate: 1.5 mL/min.; Gradient: 0%-30%; Column: Chromolith@Flash RP-18E 25-2 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00208] LCMS Conditions DD (“LCMS (DD)”): Instrument: Agilent 1200 Series LCMS; Mobile phase A: 4L H₂O \ 1.5mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: 10-80AB_R_2W; Flow Rate: 1.5 mL/min.; Gradient: 10%-80%; Column: Chromolith@Flash RP-18E 25-2 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00209] LCMS Conditions EE (“LCMS (EE)”): Instrument: Agilent 1200 Series; Mobile phase A: 1L H₂O \ 0.375mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: WUXIAB00; Flow Rate: 0.6 -1.0mL/min; Gradient: 0%-80%-100%; Column: Agilent 5 TC-C18 50-2.1 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00210] LCMS Conditions FF (“LCMS (FF)”): Instrument: Agilent 1200 Series; Mobile phase A: 1L H₂O \ 0.375mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: WUXIAB01; Flow Rate: 0.8 -1.0mL/min; Gradient: 1%-90%-100%; Column: Agilent 5 TC-C18 50-2.1 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00211] LCMS Conditions GG (“LCMS (GG)”): Instrument: Agilent 1200 Series; Mobile phase A: 1L H₂O \ 0.375mL TFA, Mobile phase B: 4L ACN \ 0.75 mL TFA; Method name: WUXIAB10; Flow Rate: 0.8 -1.0mL/min; Gradient: 10%-100%; Column: Agilent 5 TC-C18 50-2.1 mm; Column temperature: 50 °C; Wavelength: 220 nm & 254 nm.

[00212] GCMS:

[00213] GCMS Conditions Instrument: SHIMADZU GCMS-QP2010 Ultra; Carrier gas: He; Column Flow: 1.5mL/min; Injector: 250 °C; Split Ratio:100:1; Column: HP-5MS 15m*0.25mm*0.25um; FILM From: 40 °C (holding 3min) to 250 °C (holding 3min) at the rate of 25°C/min.

[00214] cSFC Analytical:

[00215] cSFC Analytical Conditions: Flow rate: 3mL/min; Wavelength: 220 nm; and Column temperature: 35°C, were used for each of the specified conditions below:

[00216] cSFC Analytical Conditions A (“cSFC analytical (A)”): Column: Chiralpak OD-3 100×4.6mm I.D., 3um; Mobile phase: ethanol (0.05% diethylamine (“DEA”) in CO₂ from 5% to 40%.

[00217] cSFC Analytical Conditions B (“cSFC analytical (B)”): Column: Chiralpak OD-3 100×4.6mm I.D., 3um; Mobile phase: methanol (0.05% DEA) in CO₂ from 5% to 40%.

[00218] cSFC Analytical Conditions C (“cSFC analytical (C)”): Column: Chiralpak OD-3 100×4.6mm I.D., 3um; Mobile phase: 40% ethanol (0.05% DEA) in CO₂.

[00219] cSFC Analytical Conditions D (“cSFC analytical (D)”): Column: Chiralpak AY-3 100×4.6mm I.D., 3um; Mobile phase: ethanol (0.05% DEA) in CO₂ from 5% to 40%.

[00220] cSFC Analytical Conditions E (“cSFC analytical (E)”): Column: Chiralpak OJ-3 100×4.6mm I.D., 3um; Mobile phase: ethanol (0.05% DEA) in CO₂ from 5% to 40%.

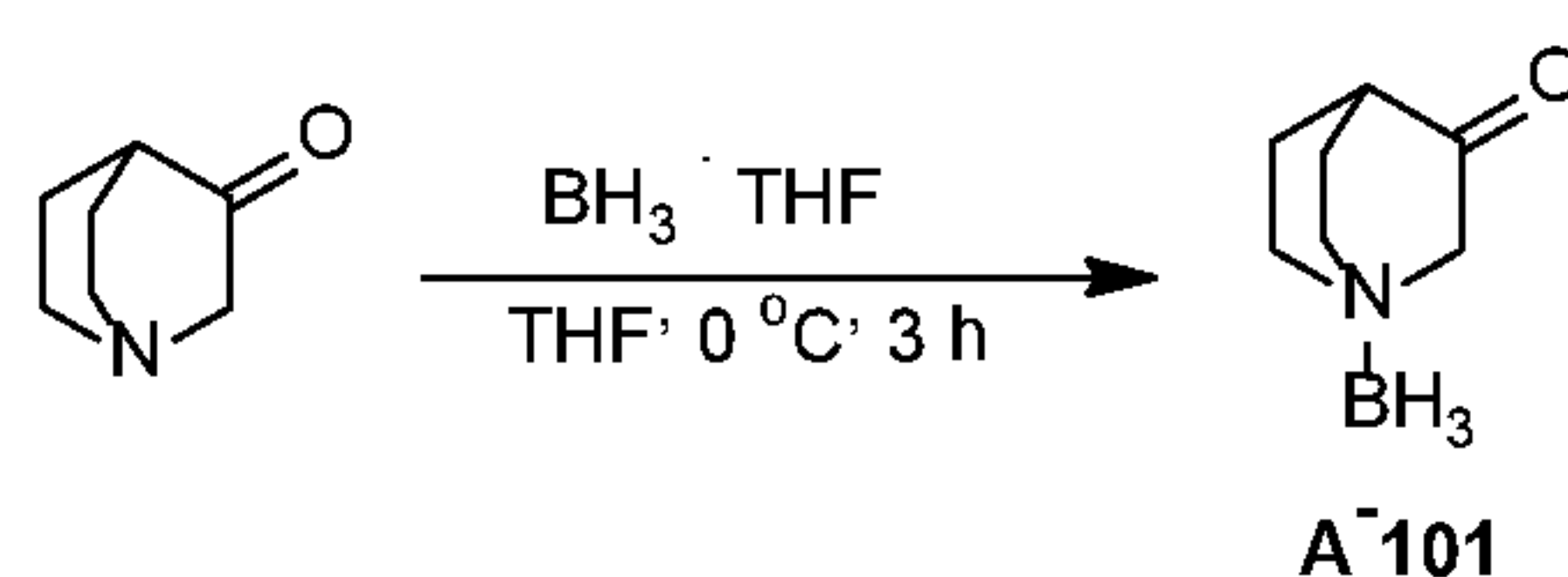
[00221] cSFC Analytical Conditions F (“cSFC analytical (F)”): Column: Chiralpak OJ-3 100×4.6mm I.D., 3um; Mobile phase: methanol (0.05% DEA) in CO₂ from 5% to 40%.

[00222] cSFC Analytical Conditions G (“cSFC analytical (G)”): Column: Chiralpak AD-3 100×4.6mm I.D., 3um; Mobile phase: ethanol (0.05% DEA) in CO₂ from 5% to 40%.

[00223] cSFC Analytical Conditions H (“cSFC analytical (H)”): Column: Chiralpak AD-3 100×4.6mm I.D., 3um; Mobile phase: methanol (0.05% DEA) in CO₂ from 5% to 40%.

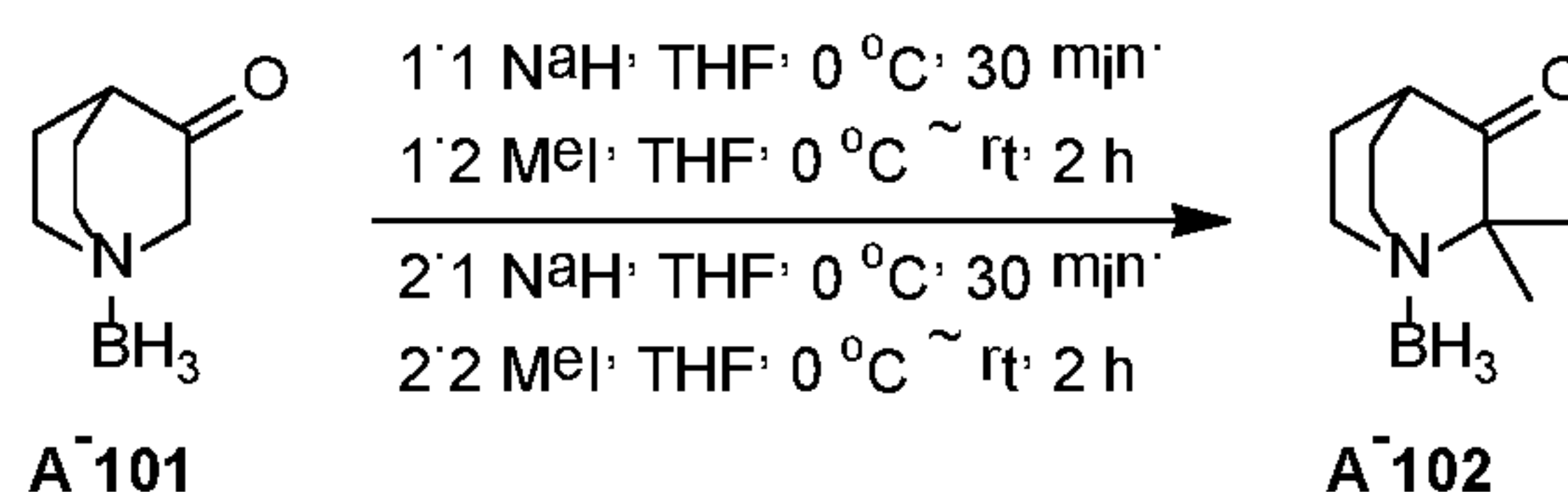
[00224] For each final compound prepared below that indicates the presence of a salt associated with the final compound (i.e., a salt complex), the specific molar equivalence of salt included in the final compound, unless specified, was not determined.

[00225] **Example 1A:** quinuclidin(*N*-borane)-3-one (A-101)



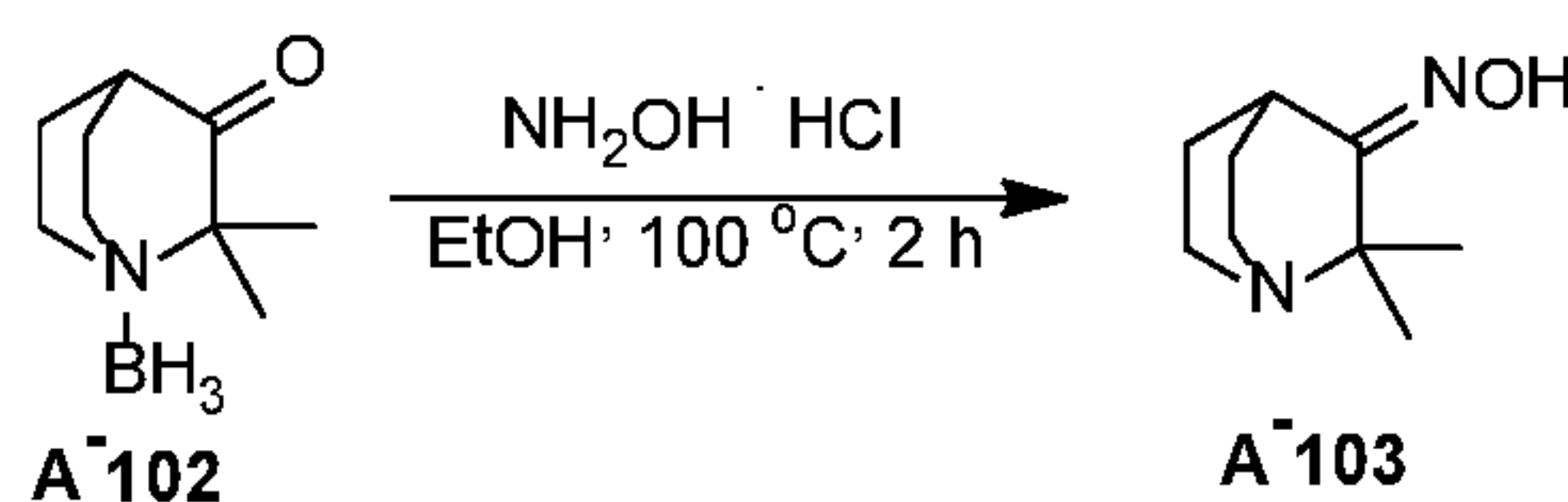
[00226] To a mixture of quinuclidin-3-one (0.20 kg, 1.6 mol) in tetrahydrofuran (1 L) at 0 °C was added dropwise 1 M borane in tetrahydrofuran (1.8 L, 1.8 mol). The mixture was stirred at 0 °C for 3 hours. On completion, the solution was quenched by methanol, evaporated and purified by silica gel chromatography (petroleum ether: ethyl acetate = 10:1) to give **compound A-101** (0.19 kg, 86% yield) as a white solid.

[00227] **Example 2A: 2,2-dimethylquinuclidin(*N*-borane)-3-one (A-102)**



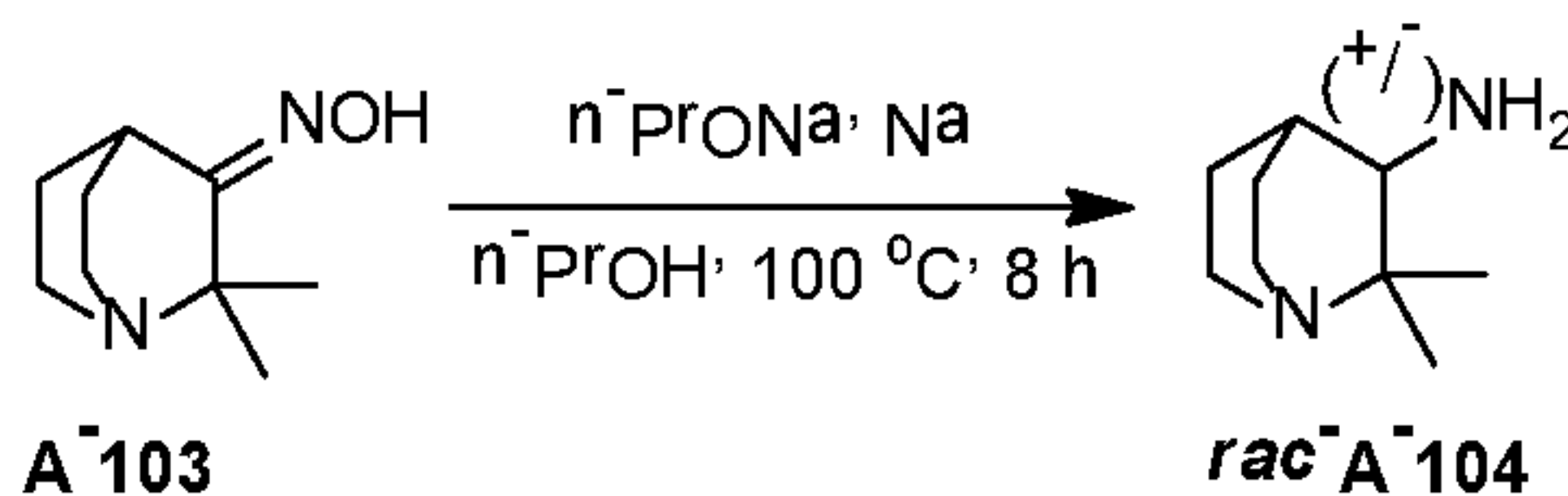
[00228] To a mixture of **compound A-101** (20 g, 0.14 mol) in tetrahydrofuran (200 mL) at 0 °C was added sodium hydride (8.6 g, 60%, 0.22 mol) in portions. The reaction was stirred for 30 minutes. Iodomethane (31 g, 0.22 mol) in tetrahydrofuran (30 mL) was added dropwise to the mixture at 0 °C, and the reaction was stirred at room temperature for 2 hours, and then cooled to 0 °C. Sodium hydride (8.6 g, 60%, 0.22 mol) was added in portions, and stirring was continued for 30 minutes. Iodomethane (31 g, 0.22 mol) in tetrahydrofuran (30 mL) was again added dropwise to the mixture at 0 °C, and the reaction was stirred at room temperature for another 2 hours. On completion, the reaction was quenched with saturated ammonium chloride aqueous solution and concentrated in vacuo. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate = 10:1) to give **compound A-102** (14 g, 58% yield) as a white solid.

[00229] **Example 3A: 2,2-dimethylquinuclidin-3-one oxime (A-103)**



[00230] To a mixture of **compound A-102** (0.50 g, 3.0 mmol) in anhydrous ethanol (2 mL) was added hydroxylamine hydrochloride (0.21 g, 3.0 mmol) at room temperature. The mixture was stirred at 100 °C for 2 hours. On completion, the solution was cooled to room temperature, resulting in formation of a precipitate. The precipitation was collected by filtration to give **compound A-103** (0.48 g, 96% yield) as a white solid. LCMS (K): tR=1.093 min., (ES⁺) m/z (M+H)⁺ = 169.1.

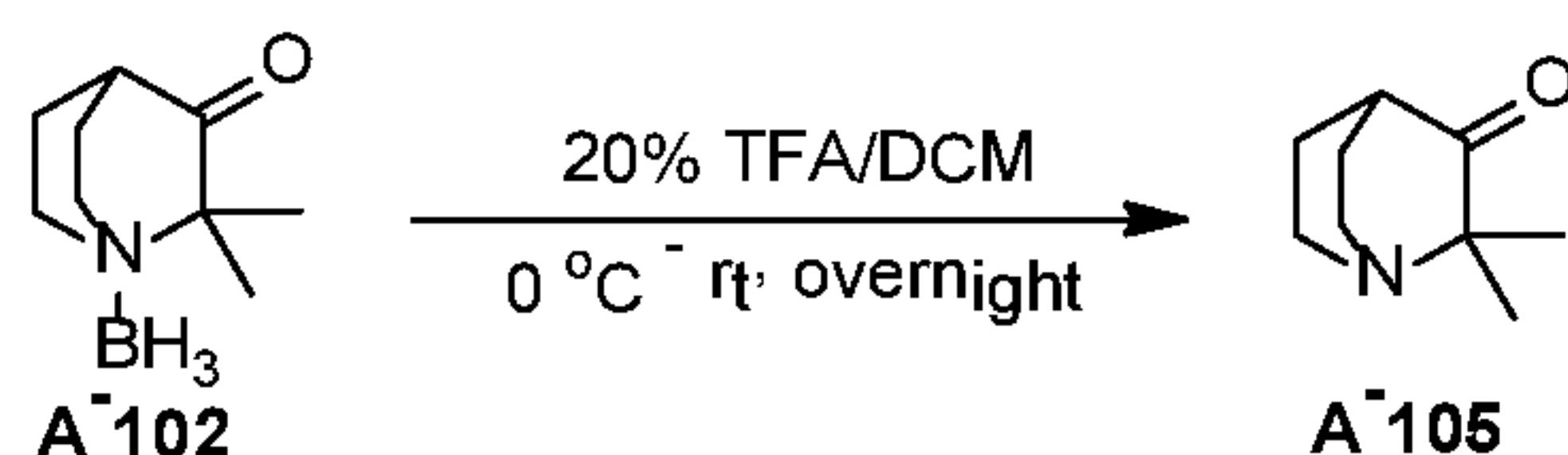
[00231] **Example 4A: (+/-)-2,2-dimethylquinuclidin-3-amine (rac-A-104)**



[00232] To a mixture of **compound A-103** (0.60 g, 2.9 mmol) in n-propyl alcohol (6 mL) was added sodium n-propoxide (67 mg, 2.9 mmol sodium in 1 mL n-propyl alcohol) at room temperature. The solution was heated to 100 °C, and sodium (0.67 g, 29 mmol) was added in portions. The mixture

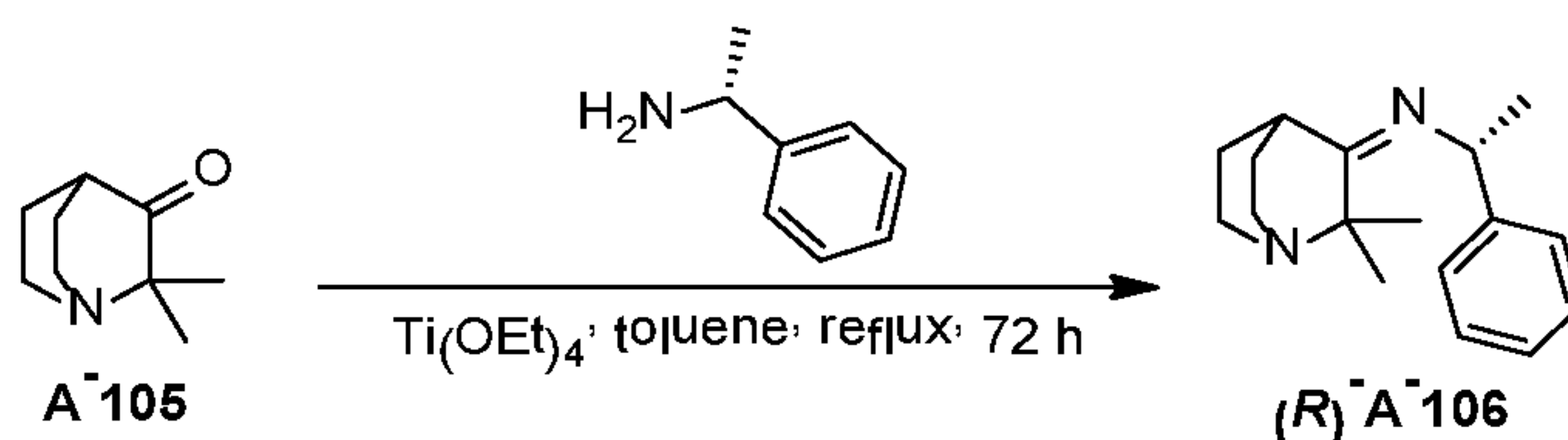
was stirred at this temperature for 8 hours. On completion, the mixture was poured into water (1 mL), concentrated in vacuo, diluted with dichloromethane and filtered. The resulting filtrate was concentrated in vacuo to give *rac*-**A-104** (0.40 g, 89% yield) as a yellow oil. LCMS (K): *t*R=0.988 min., (ES⁺) *m/z* (M+H)⁺ = 155.1.

[00233] **Example 5A: 2,2-dimethylquinuclidin-3-one (A-105)**



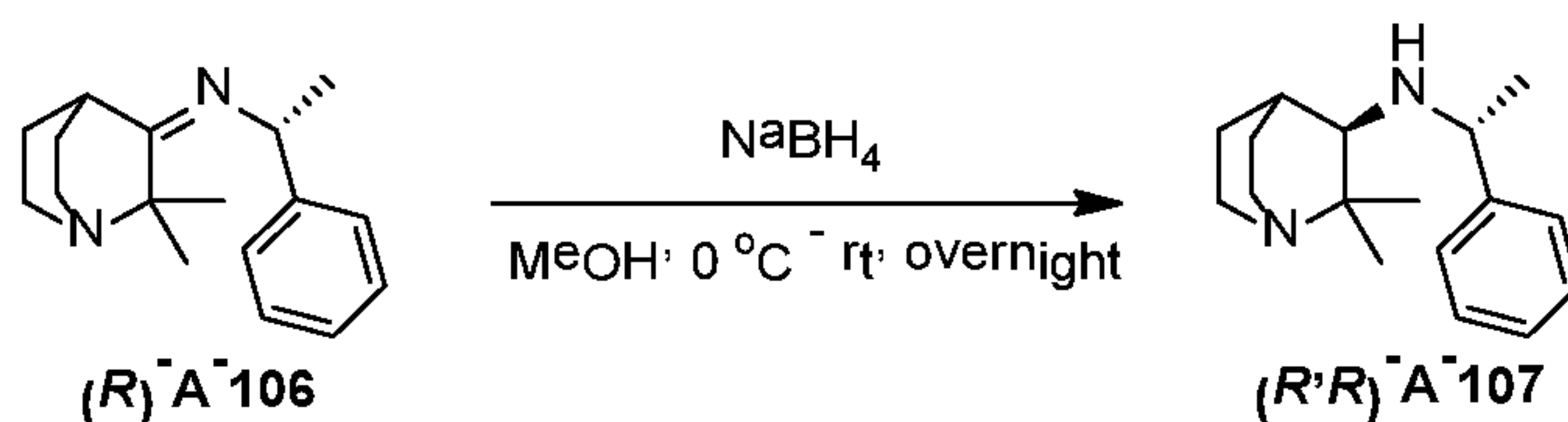
[00234] To a solution of 20% trifluoroacetic acid / dichloromethane (150 mL, v/v) at 0 °C was added portionwise **compound A-102** (45 g, 0.27 mol). The mixture was stirred at room temperature overnight. On completion, the pH was adjusted to 8 by addition of saturated aqueous potassium carbonate solution at 0 °C. The mixture was extracted with dichloromethane (2 × 200 mL). The combined organic layers were dried with sodium sulfate and concentrated in vacuo to give **compound A-105** (40 g, 98% yield) as a white solid. ¹H-NMR (CD₃OD, 400 MHz): 3.37-3.36 (m, 2H), 2.98-2.97 (m, 2H), 2.39-2.38 (m, 1H), 2.10-2.09 (m, 4H), 1.34 (s, 6H).

[00235] **Example 6A: (*R*)-N-(2,2-dimethylquinuclidin-3-ylidene)-1-phenylethanamine ((*R*)-A-106)**



[00236] To a solution of **compound A-105** (7.2 g, 47 mmol) and (*R*)-1-phenylethanamine (6.8 g, 56 mmol) in toluene (140 mL) was added titanium tetraethoxide (32 g, 0.14 mol), and the mixture was heated at reflux for 72 hours. On completion, the mixture was cooled to room temperature and poured into saturated aqueous potassium carbonate solution (500 mL). Ethyl acetate (500 mL) was added, and the mixture was stirred vigorously for 10 minutes and filtered over celite. The layers were separated, and the water layer was extracted with ethyl acetate (3 × 500 mL). The combined organic layers were dried with sodium sulfate and concentrated in vacuo to give **compound (R)-A-106** (13 g, crude, 52% purity by LCMS) as a yellow oil. The material was used for the next step without further purification. LCMS (J): *t*R=1.337, (ES⁺) *m/z* (M+H)⁺ = 257.1.

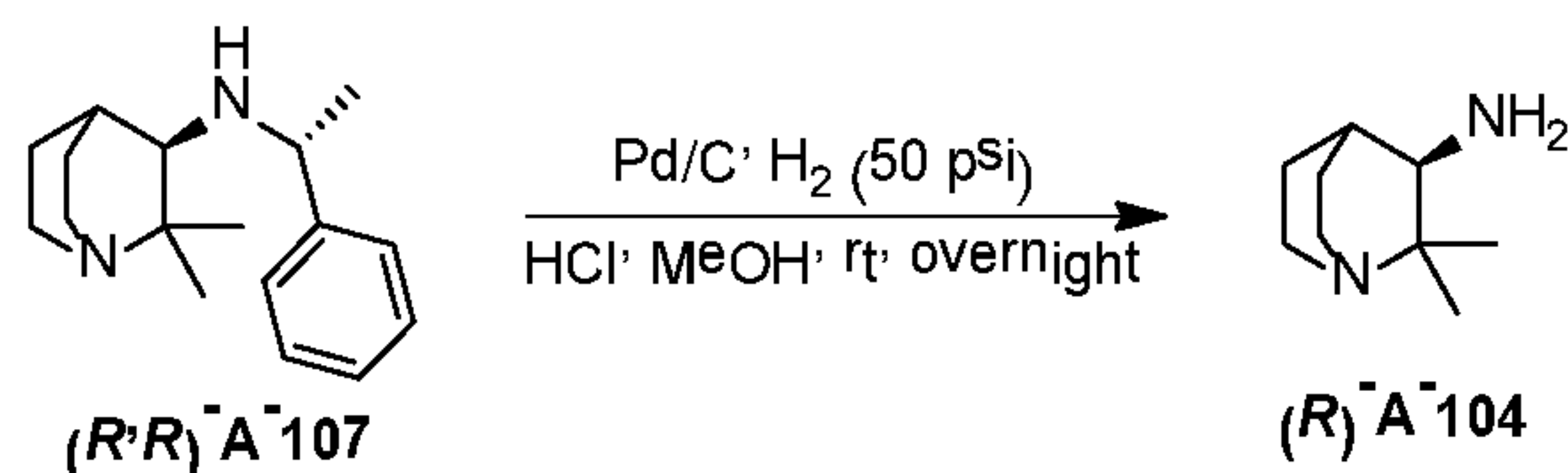
[00237] **Example 7A: (*R*)-2,2-dimethyl-N-((*R*)-1-phenylethyl)quinuclidin-3-amine ((*R,R*)-A-107)**



[00238] To a solution of **compound (R)-A-106** (13 g, 26 mmol, 52 % purity) in methanol (130 mL) at 0 °C was added sodium borohydride (5.0 g, 0.13 mol). The mixture was stirred for 30 minutes

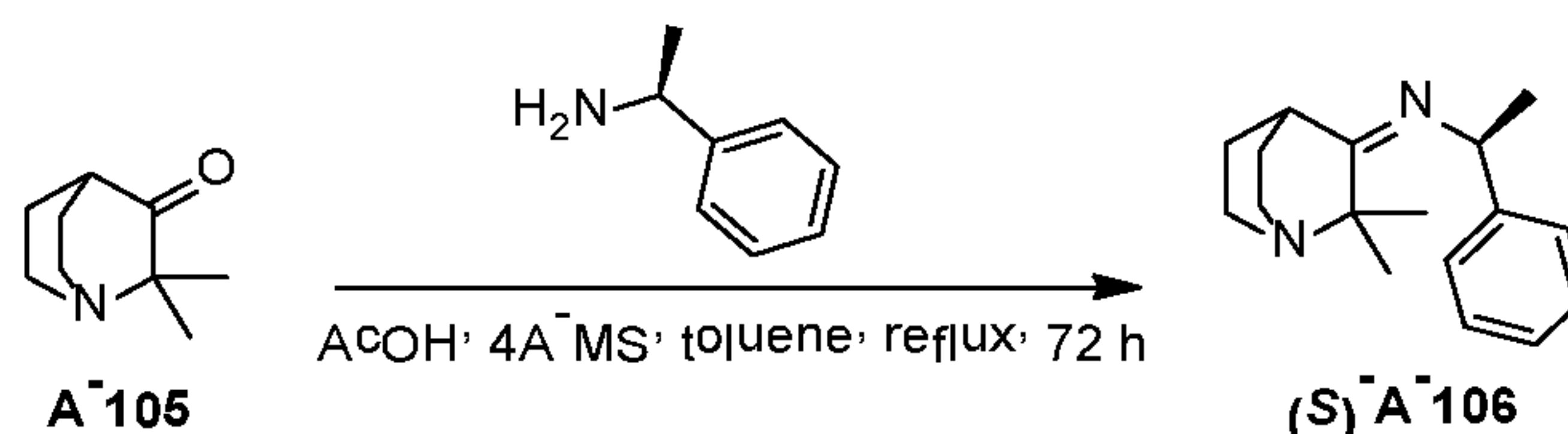
at 0 °C, then allowed to warm to room temperature and stirred overnight. On completion, the reaction was poured into saturated aqueous potassium carbonate (500 mL), and the mixture was extracted with ethyl acetate (2 × 500 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo to give 11 g of a clear oil. The crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate = 5:1) to give **compound (R,R)-A-107** (7.3 g, 58% yield for two steps) as a clear oil. ¹H-NMR (CD₃OD, 400 MHz): δ 7.34-7.26 (m, 4H), 7.22-7.18 (m, 1H), 3.78-3.73 (m, 1H), 3.35-3.18 (m, 1H), 3.06-3.01 (m, 1H), 2.61-2.53 (m, 2H), 2.32 (s, 1H), 1.81-1.78 (m, 1H), 1.63-1.54 (m, 2H), 1.44-1.42 (m, 1H), 1.41 (s, 3H), 1.31 (d, J=6.8 Hz, 3H), 1.30-1.26 (m, 1H), 1.21 (s, 3H).

[00239] **Example 8A: (R)-2,2-dimethylquinuclidin-3-amine ((R)-A-104)**



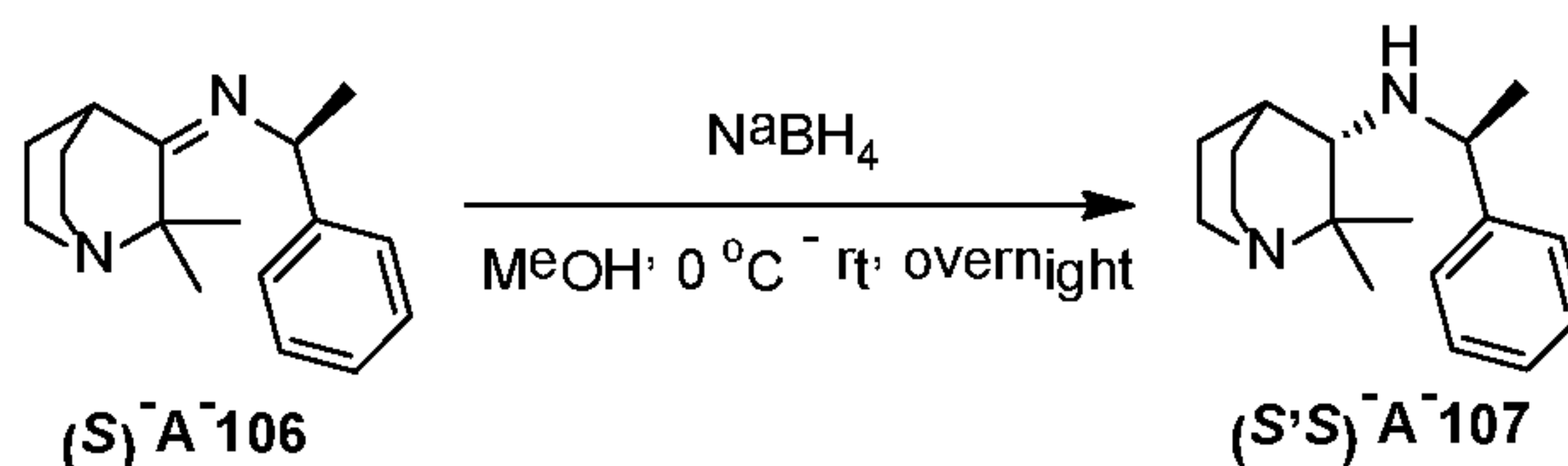
[00240] To a solution of **compound (R,R)-A-107** (5.3 g, 21 mmol) in methanol (100 mL) was added 10% palladium / carbon, 50% wet (1.5 g) under nitrogen. The suspension was degassed in vacuo and purged with hydrogen several times. The resulting mixture was stirred at room temperature overnight under hydrogen (50 psi). On completion, the reaction mixture was filtered, and the filtrate was concentrated in vacuo to give **compound (R)-A-104** (3.0 g, 93% yield) as a white semi-solid. ¹H-NMR (CD₃OD, 400 MHz): 3.28-3.24 (m, 2H), 2.79-2.73 (m, 3H), 1.92-1.90 (m, 1H), 1.76-1.73 (m, 3H), 1.45-1.44 (m, 1H), 1.31 (s, 3H), 1.29 (s, 3H).

[00241] **Example 9A: (S)-N-(2,2-dimethylquinuclidin-3-ylidene)-1-phenylethanamine ((S)-A-106)**



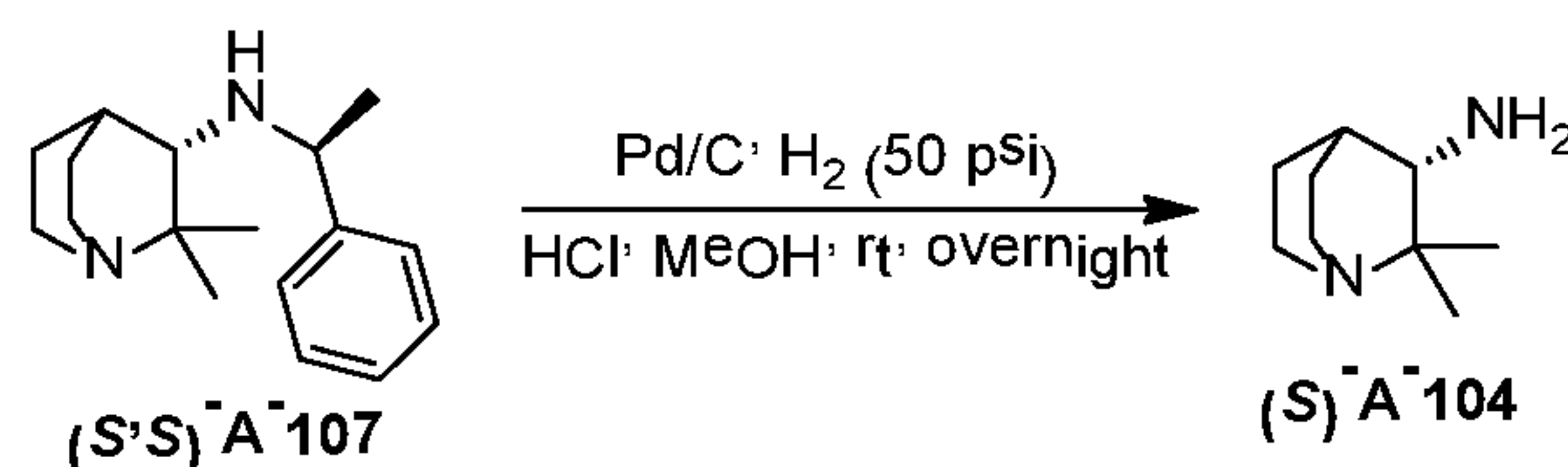
[00242] To a solution of **compound A-105** (4.1 g, 27 mmol) and (S)-1-phenylethanamine (3.9 g, 32 mmol) in toluene (40 mL) were added acetic acid (1.6 g, 27 mmol) and 4A-molecular sieve (1.0 g). The mixture was heated at reflux for 72 hours. On completion, the mixture was cooled to room temperature and concentrated in vacuo to give **compound (S)-A-106** (8.5 g, crude) as a yellow oil. LCMS showed 38% purity. This material was used for the next step directly without further purification. LCMS (J): tR=1.228, (ES⁺) m/z (M+H)⁺ = 257.2.

[00243] **Example 10A: (S)-2,2-dimethyl-N-((S)-1-phenylethyl)quinuclidin-3-amine ((S,S)-A-107)**



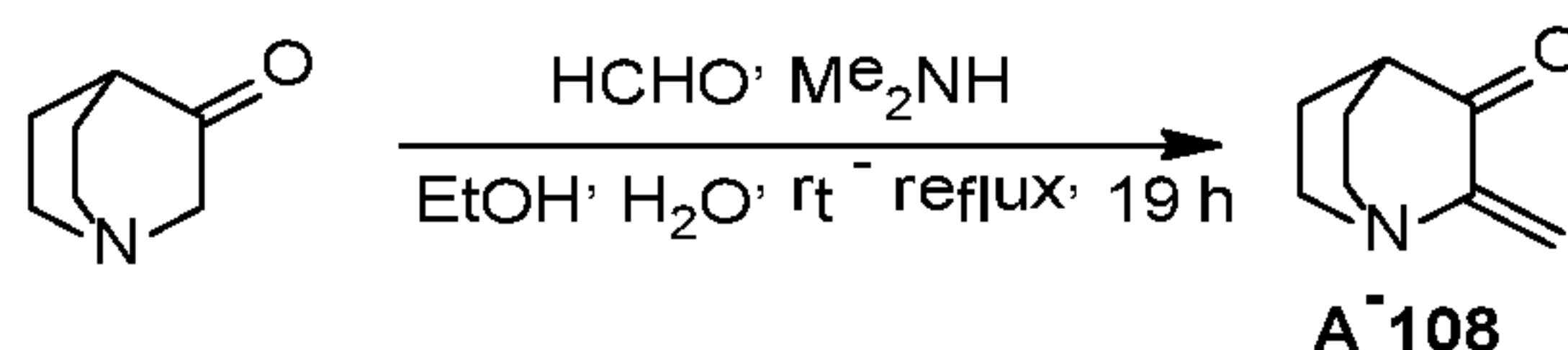
[00244] To a solution of **compound (S)-A-106** (8.5 g, 13 mmol, 38 % purity) in methanol (80 mL) at 0 °C was added sodium borohydride (2.4 g, 63 mmol). The reaction was stirred for 30 minutes at 0 °C, then allowed to warm to room temperature and stirred overnight. On completion, the mixture was poured into saturated aqueous potassium carbonate (100 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo to give 8.0 g of a clear oil. The crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate = 5:1) to give **compound (S,S)-A-107** (1.8 g, 26% yield for two steps) as a clear oil. ¹H-NMR (CD₃OD, 400 MHz): δ 7.34-7.28 (m, 4H), 7.22-7.19 (m, 1H), 3.78-3.73 (m, 1H), 3.27-3.21 (m, 1H), 3.08-3.04 (m, 1H), 2.65-2.58 (m, 2H), 2.34 (s, 1H), 1.84-1.82 (m, 1H), 1.65-1.56 (m, 2H), 1.45-1.43 (m, 1H), 1.36 (s, 3H), 1.31 (d, J=6.8 Hz, 3H), 1.23(s, 3H), 1.15-1.14 (m, 1H).

[00245] **Example 11A: (S)-2,2-dimethylquinuclidin-3-amine ((S)-A-104)**



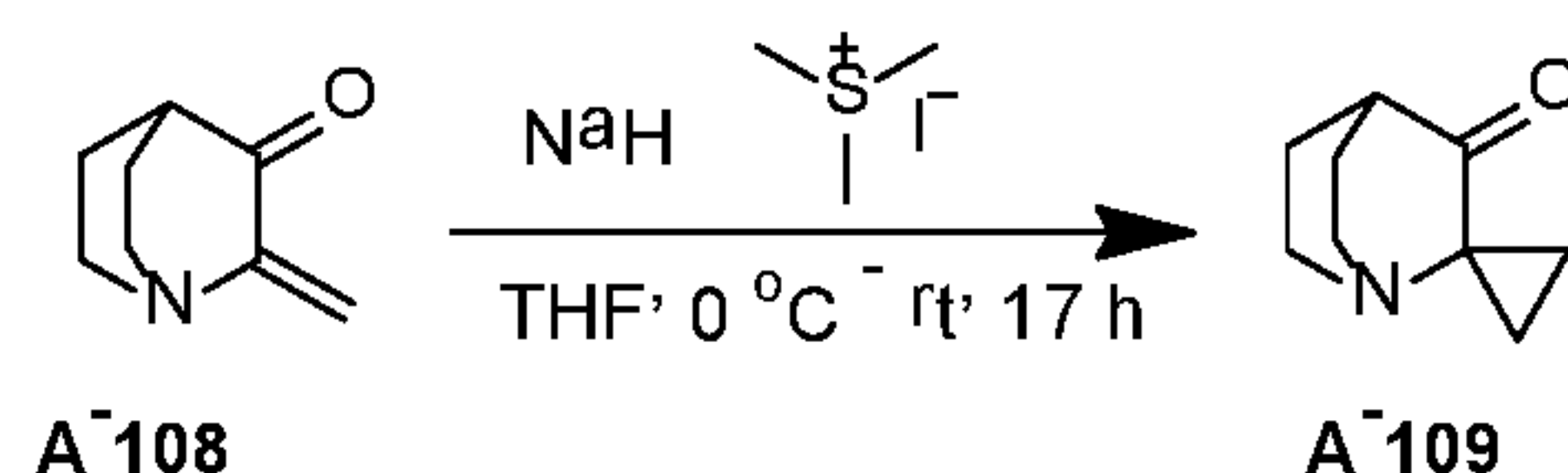
[00246] To a solution of **compound (S,S)-A-107** (1.8 g, 7.0 mmol) in methanol (40 mL) was added 10% palladium/ carbon, 50% wet (0.4 g) under nitrogen. The suspension was degassed in vacuo and purged with hydrogen several times. The resulting mixture was stirred under hydrogen (50 psi) at room temperature overnight. On completion, the reaction mixture was filtered, and the filtrate was concentrated in vacuo to give **compound (S)-A-104** (1.0 g, 93% yield) as a white semi-solid. ¹H-NMR (CD₃OD, 400 MHz): 3.44-3.36 (m, 2H), 3.03-2.93 (m, 2H), 2.90 (s, 1H), 2.07-2.02 (m, 1H), 1.92-1.85 (m, 3H), 1.65-1.58 (m, 1H), 1.43 (s, 3H), 1.39 (s, 3H).

[00247] **Example 12A: 2-methylenequinuclidin-3-one (A-108)**



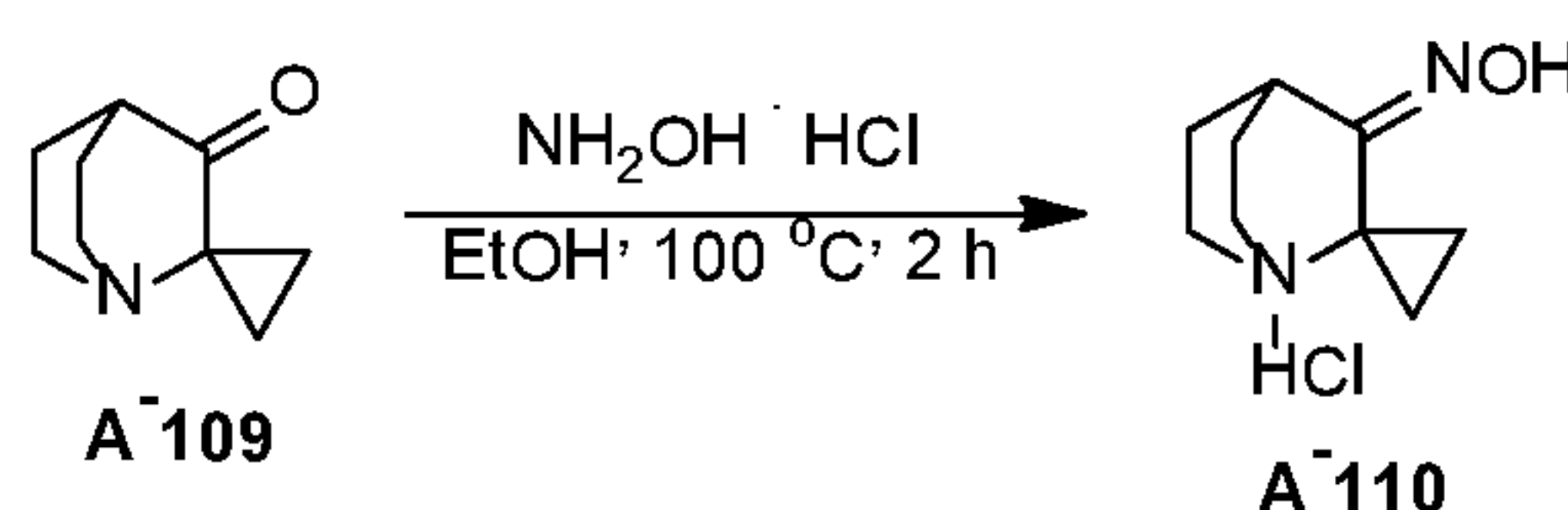
[00248] To a mixture of quinuclidin-3-one (30 g, 0.24 mol) in ethanol / water (0.65 L, 2.5: 1) was added dimethylamine (49 g, 0.36 mol) in one portion, followed by formaldehyde (28 g, 0.36 mol) in one portion at room temperature. After stirring at room temperature for 10 min, the reaction mixture was heated to reflux for 3 hours, and then stirred at 70 °C for 16 hours. TLC showed the starting material was consumed completely. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by distillation to give **compound A-108** (14 g, 43% yield) as yellow oil. GCMS: tR=5.629, (EI⁺) m/z (M) = 137.2.

[00249] **Example 13A:** 1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-one (**A-109**)



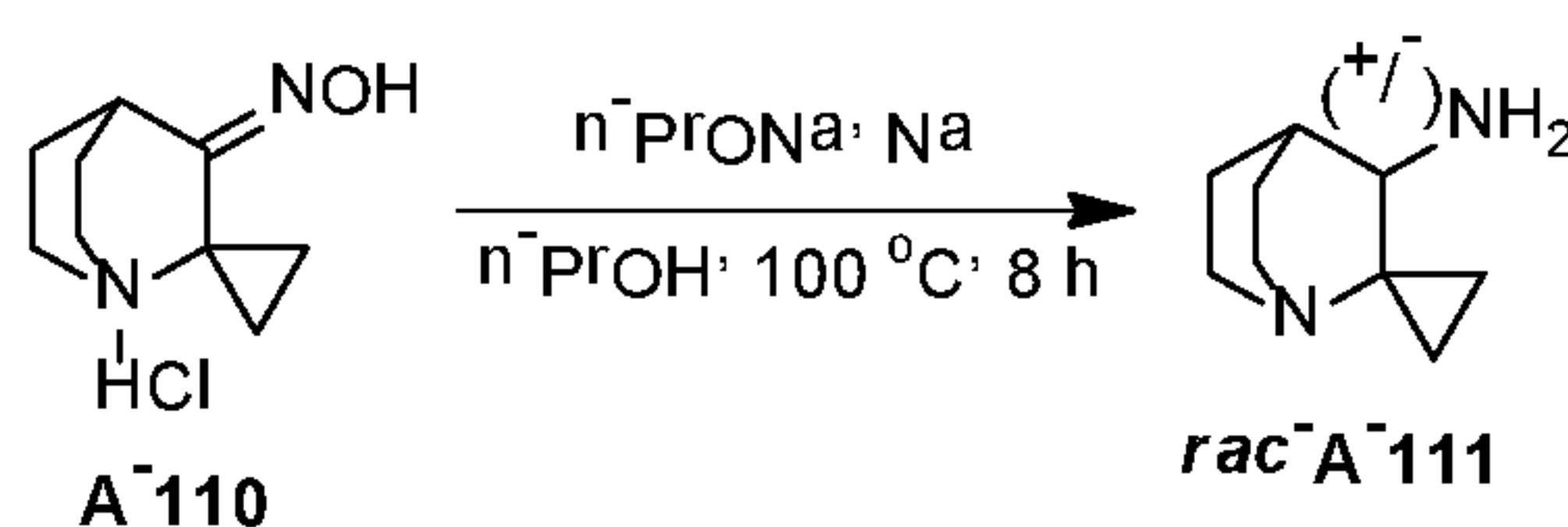
[00250] To a solution of trimethylsulfoxonium iodide (42 g, 0.19 mol) in anhydrous tetrahydrofuran (500 mL) at 0 °C was added sodium hydride (7.6 g, 0.19 mol). The reaction mixture was stirred at 0 °C for 1 hour, and **compound A-108** (20 g, 0.15 mol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 16 hours. GCMS showed the reaction was completed. The reaction was quenched with saturated aqueous ammonium chloride solution and filtered. The filtrate was concentrated in vacuo, diluted with dichloromethane (200 mL) and water (200 mL) and extracted with dichloromethane (3 × 600 mL). The combined organic layers were washed with brine (2 × 400 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by aluminum oxide column chromatography [petroleum ether : ethyl acetate = 5:1] to give **compound A-109** (4.8 g, 22% yield) as a white solid. GCMS: $t_R=7.253$, $(EI^+) m/z (M+H)^+ = 151.1$, $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 3.09-3.03 (m, 4H), 2.56-2.55 (m, 1H), 2.05-2.00 (m, 4H), 1.40-1.39 (m, 2H), 1.14-1.12 (m, 2H).

[00251] **Example 14A:** 1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-one oxime hydrochloride (**A-110**)



[00252] To a mixture of **compound A-109** (1.0 g, 6.6 mmol) in anhydrous ethanol (5 mL) was added hydroxylamine hydrochloride (0.48 g, 7.0 mmol) at room temperature. The mixture was stirred at 100 °C for 2 hours. On completion, the solution was cooled to room temperature, resulting in formation of a precipitate. The precipitation was collected by filtration to give **compound A-110** (0.80 g, 60% yield) as a white solid.

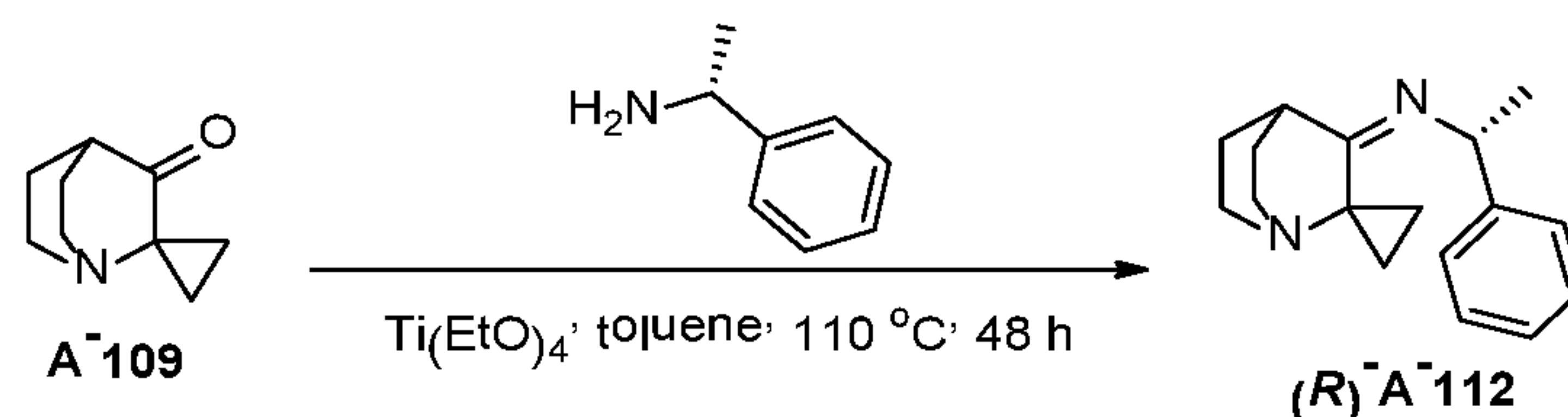
[00253] **Example 15A:** (+/-)-1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-amine (*rac*-**A-111**)



[00254] To a mixture of **compound A-110** (1.0 g, 4.9 mmol) in n-propyl alcohol (10 mL) was added sodium propoxide (0.40 g, 4.9 mmol sodium in 2 mL n-propyl alcohol) at room temperature. The solution was heated to 100 °C, and sodium (1.1 g, 49 mmol) was added in portions. The mixture was stirred at this temperature for 8 hours. On completion, the mixture was poured into water (2 mL),

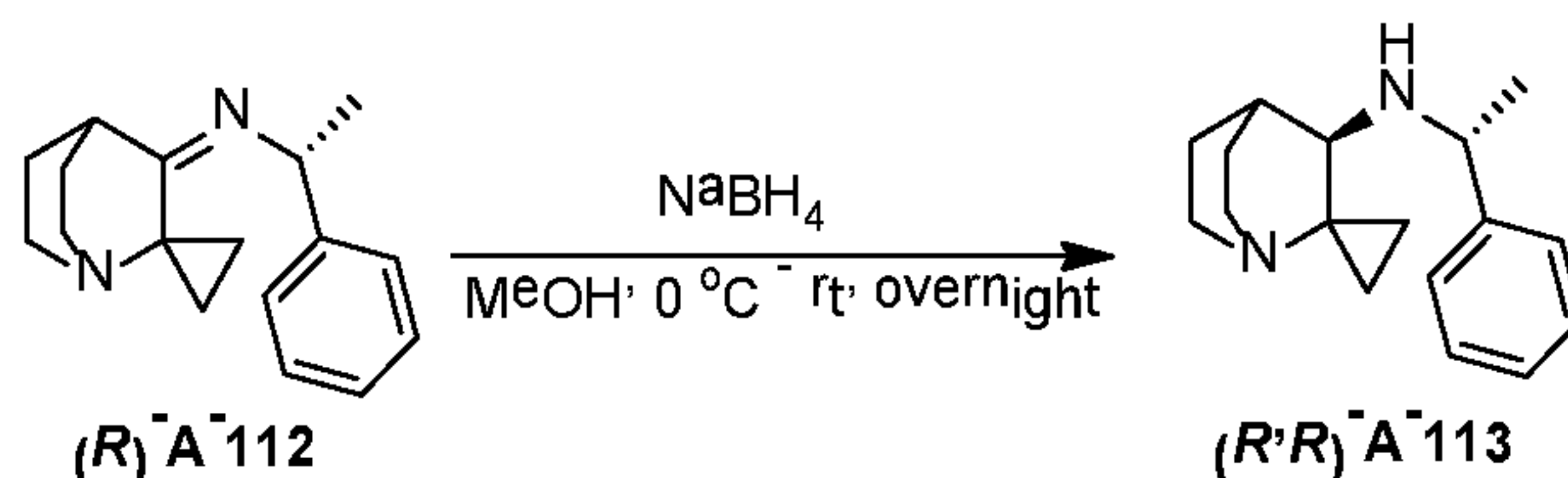
concentrated in vacuo, diluted with dichloromethane and filtered. The resulting filtrate was concentrated in vacuo to give *rac*-**A-111** (0.50 g, 67% yield) as a yellow oil.

[00255] Example 16A: (*R*)-1-phenyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-ylidene)ethanamine ((*R*)-A-112**)**



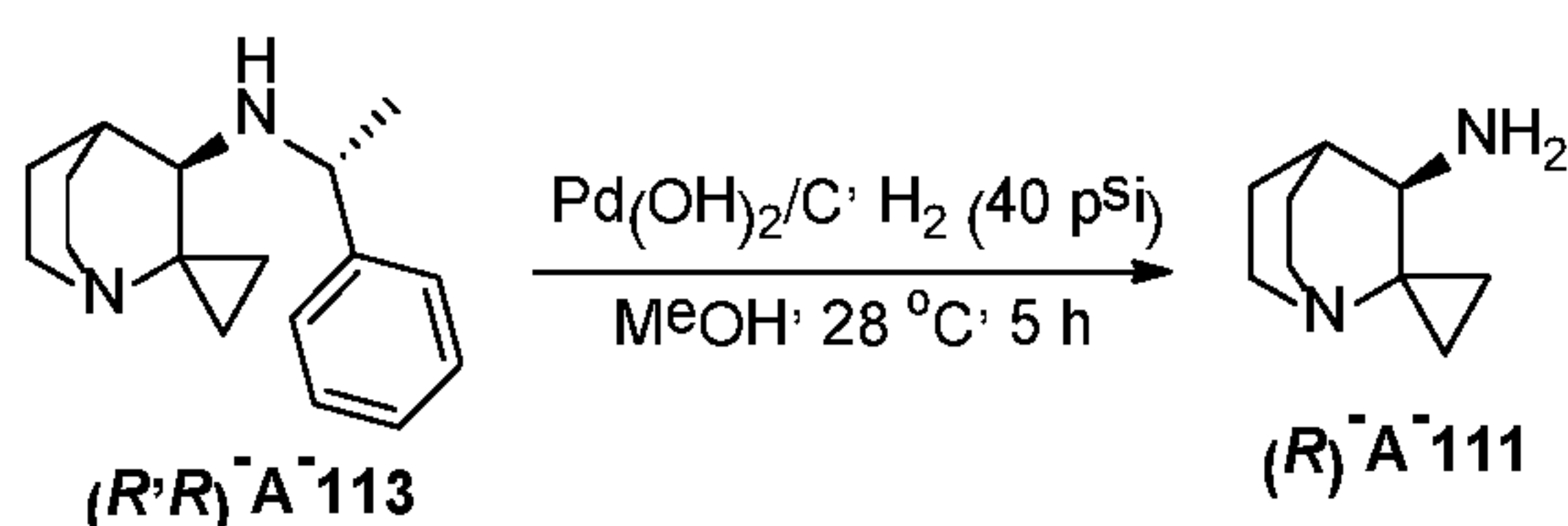
[00256] To a solution of **compound A-109** (2.0 g, 13 mmol) in anhydrous toluene (30 mL) was added (*R*)-1-phenylethanamine (1.6 g, 13 mmol) and ethyl titanate (9.1 g, 40 mmol). The resulting mixture was stirred at 110 °C for 48 hours. On completion, the reaction was quenched with saturated aqueous potassium carbonate (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo to give **compound (*R*)-A-112** (3.2 g, crude) as a yellow oil, which was used for next step without further purification. LCMS (J): *t*R=1.594, (ES⁺ *m/z* (M+H)⁺ = 255.1.

[00257] Example 17A: (*R*)-*N*-((*R*)-1-phenylethyl)-1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-amine ((*R,R*)-A-113**)**



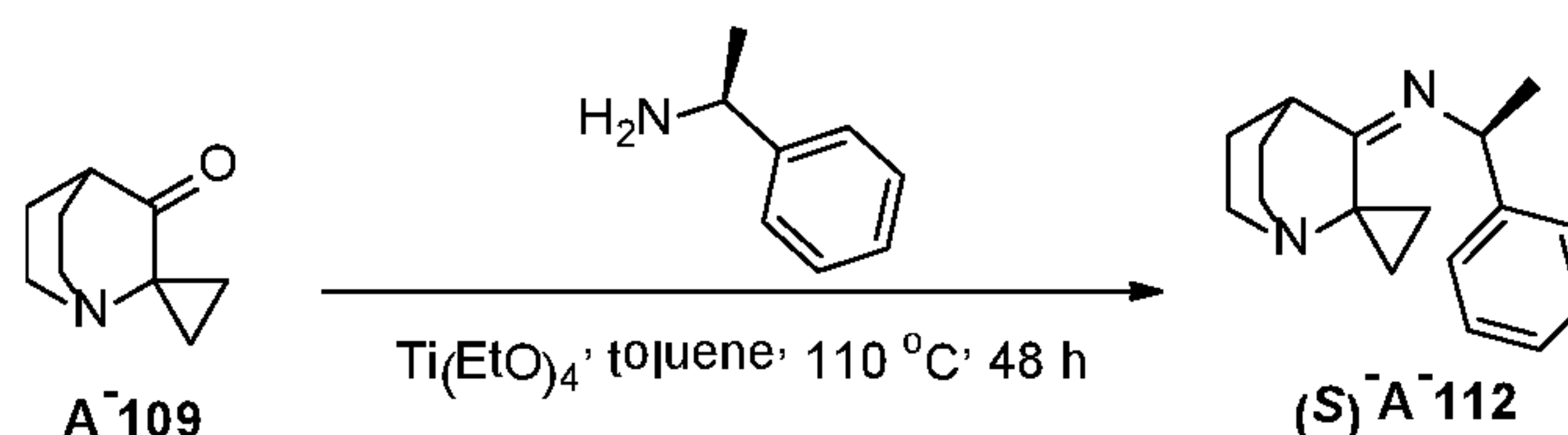
[00258] To a mixture of **compound (*R*)-A-112** (3.2 g, 13 mmol) in anhydrous methanol (30 mL) was added sodium borohydride (1.0 g, 25 mmol) slowly at 0 °C. The resulting mixture was stirred at room temperature overnight. On completion, the reaction was quenched with water (10 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried over sodium sulfate, concentrated in vacuo and purified by silica gel chromatography [dichloromethane: methanol = 5:1] to give **compound (*R,R*)-A-113** (1.1 g, 41% yield for two steps) as a yellow oil. ¹H-NMR (CD₃OD, 400 MHz): 7.34-7.28 (m, 4H), 7.24-7.22 (m, 1H), 3.66-3.63 (m, 1H), 3.01-2.89 (m, 1H), 2.74-2.73 (m, 1H), 2.72-2.65 (m, 3H), 1.90-1.79 (m, 2H), 1.70-1.65 (m, 1H), 1.55-1.51 (m, 1H), 1.37-1.35 (m, 1H), 1.29 (d, *J*=6.4 Hz, 3H), 1.12-1.07 (m, 1H), 0.85-0.80 (m, 1H), 0.59-0.47 (m, 2H).

[00259] Example 18A: (*R*)-1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-amine ((*R*)-A-111**)**



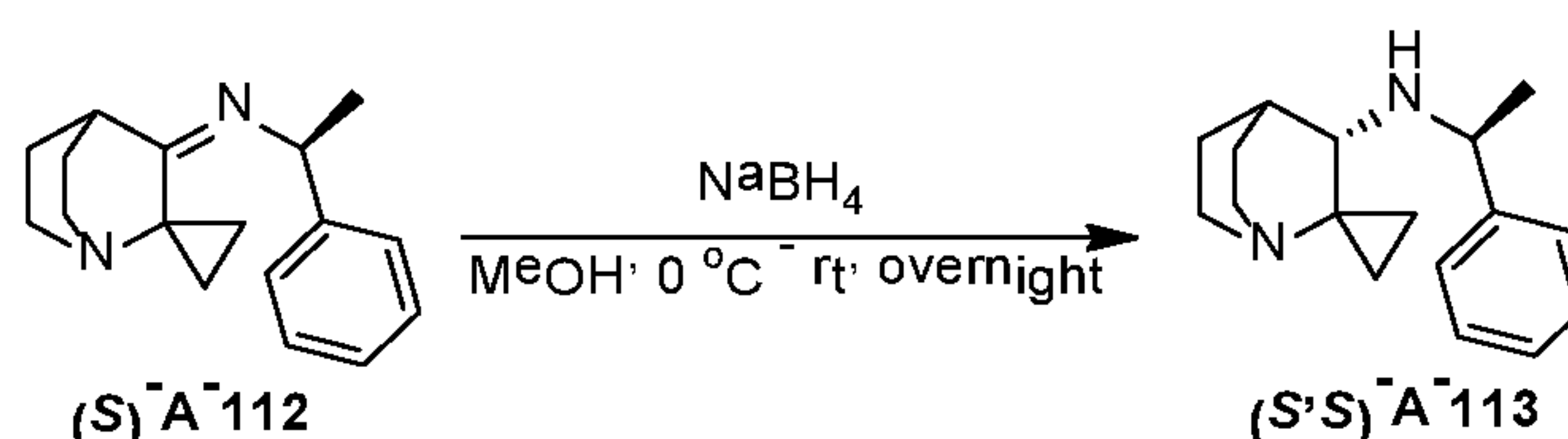
[00260] To a mixture of **compound (R,R)-A-113** (1.4 g, 5.5 mmol) in anhydrous methanol (15 mL) was added 10% palladium hydroxide/ carbon, 50% wet (600 mg) under nitrogen. The suspension was degassed in vacuo and purged with hydrogen several times. The resulting mixture was stirred under hydrogen (40 psi) at 28 °C for 5 hours. On completion, the reaction mixture was filtered, and the filtrate was concentrated in vacuo to give **compound (R)-A-111** (0.75 g, 90% yield) as a light yellow oil. ¹H-NMR (CD₃OD, 400 MHz): 3.04-2.94 (m, 2H), 2.82-2.76 (m, 3H), 1.92-1.84 (m, 2H), 1.79-1.70 (m, 2H), 1.46-1.43 (m, 1H), 1.00-0.95 (m, 1H), 0.82-0.77 (m, 1H), 0.58-0.49 (m, 2H).

[00261] **Example 19A: (S)-1-phenyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-ylidene)ethanamine ((S)-A-112)**



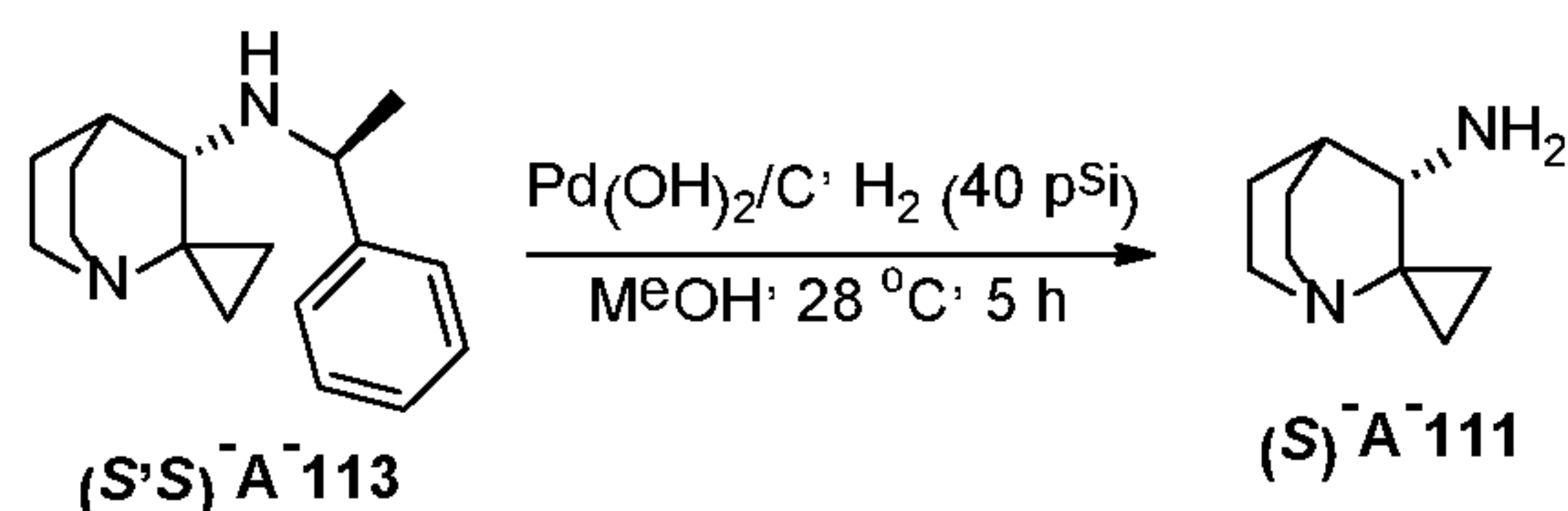
[00262] To a solution of **compound A-109** (2.0 g, 13 mmol) in anhydrous toluene (30 mL) was added (S)-1-phenylethanamine (1.6 g, 13 mmol) and ethyl titanate (9.1 g, 40 mmol). The resulting mixture was stirred at 110 °C for 48 hours. On completion, the reaction was quenched with saturated aqueous potassium carbonate (100 mL) and extracted with ethyl acetate (5 × 30 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo to give **compound (S)-A-112** (2.3 g, crude) as a yellow oil, which was used for the next step without further purification. LCMS (J): tR=1.295, (ES⁺ m/z (M+H)⁺ = 255.1.

[00263] **Example 20A: (S)-N-((S)-1-phenylethyl)-1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-amine ((S,S)-A-113)**



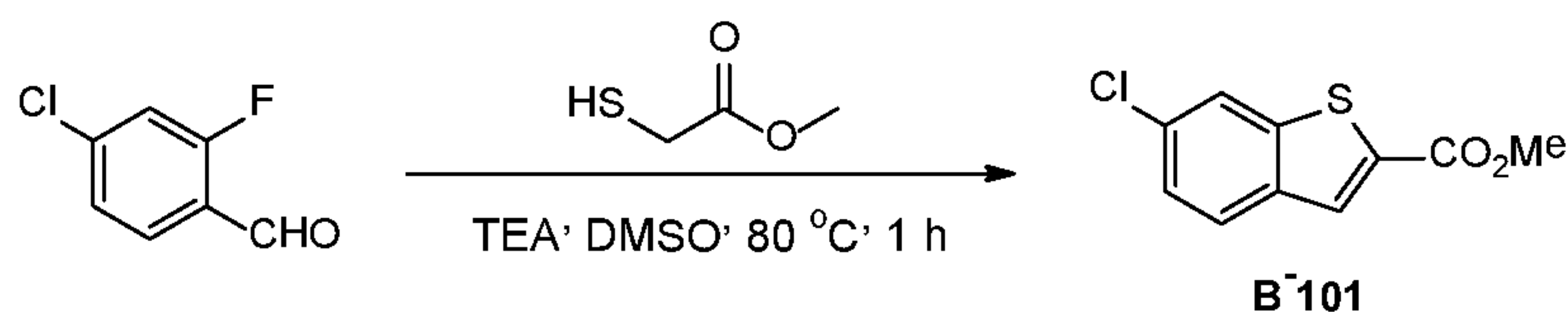
[00264] To a mixture of **compound (S)-A-112** (2.3 g, crude) in anhydrous methanol (25 mL) was added sodium borohydride (1.0 g, 25 mmol) slowly at 0 °C. The resulting mixture was stirred at room temperature overnight. On completion, the reaction was quenched by water (8 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were concentrated in vacuo and purified by silica gel chromatography [dichloromethane: methanol = 5:1] to give **compound (S,S)-A-113** (1.0 g, 37% yield for two steps) as a yellow oil. ¹H-NMR (CD₃OD, 400 MHz): 7.32-7.25 (m, 4H), 7.22-7.18 (m, 1H), 3.64-3.58 (m, 1H), 3.02-2.99 (m, 1H), 2.89-2.86 (m, 1H), 2.76-2.64 (m, 3H), 1.85-1.76 (m, 2H), 1.67-1.65 (m, 1H), 1.52-1.50 (m, 1H), 1.34-1.32 (m, 1H), 1.26 (d, J=6.4 Hz, 3H), 1.08-1.04 (m, 1H), 0.82-0.78 (m, 1H), 0.56-0.46 (m, 2H).

[00265] **Example 21A: (S)-1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-amine ((S)-A-111)**



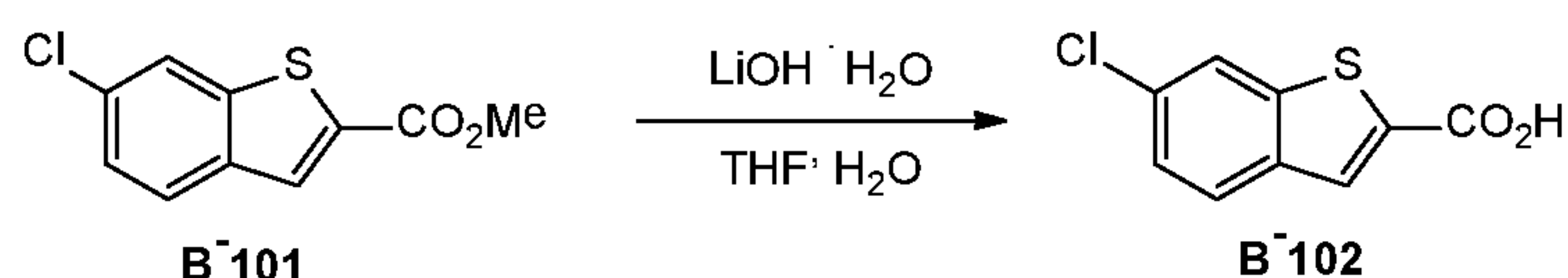
[00266] To a mixture of **compound (S,S)-A-113** (1.0 g, 3.9 mmol) in anhydrous methanol (10 mL) was added 10% palladium hydroxide/ carbon, 50% wet (400 mg) under nitrogen. The suspension was degassed in vacuo and purged with hydrogen several times. The mixture was stirred under hydrogen (40 psi) at 28 °C for 5 hours. On completion, the reaction mixture was filtered, and the filtrate was concentrated in vacuo to give **compound (S)-A-111** (0.55 g, 92% yield) as a light yellow oil. ¹H-NMR (CD₃OD, 400 MHz): 3.04-2.94 (m, 2H), 2.82-2.75 (m, 3H), 1.97-1.84 (m, 2H), 1.79-1.74 (m, 2H), 1.47-1.43 (m, 1H), 1.00-0.95 (m, 1H), 0.81-0.76 (m, 1H), 0.58-0.49 (m, 2H).

[00267] **Example 1B: methyl 6-chlorobenzo[b]thiophene-2-carboxylate (B-101)**

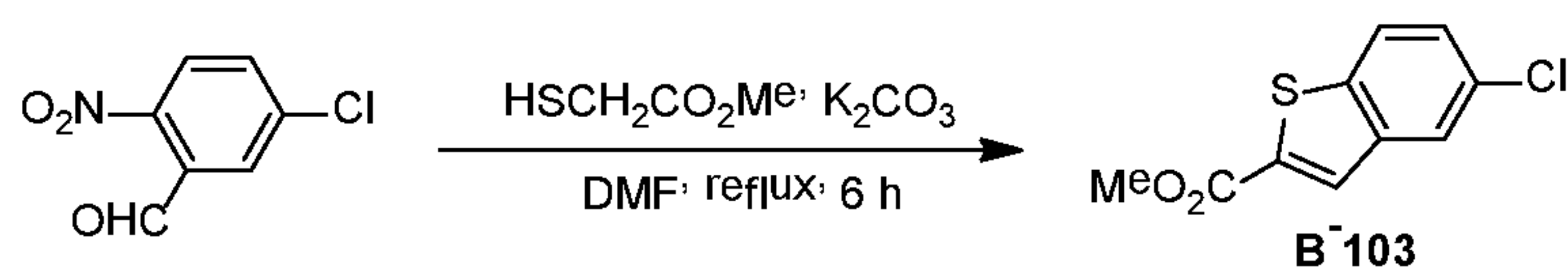


[00268] To a mixture of 4-chloro-2-fluorobenzaldehyde (50 g, 0.32 mol) and methyl 2-mercaptoacetate (40 g, 0.38 mol) in dimethylsulfoxide (500 mL) was added triethylamine (96 g, 0.95 mol) at room temperature. The mixture was stirred at 80 °C for 1 hour. On completion, the reaction mixture was cooled to room temperature and poured into ice water (4 L), resulting in formation of a solid. The mixture was stirred for half an hour, and the solid was collected by filtration, washed with water and dried in vacuo to give **compound B-101** (80 g, crude) as a yellow solid. LCMS: (ES⁺) m/z (M+H)⁺ = 227.0.

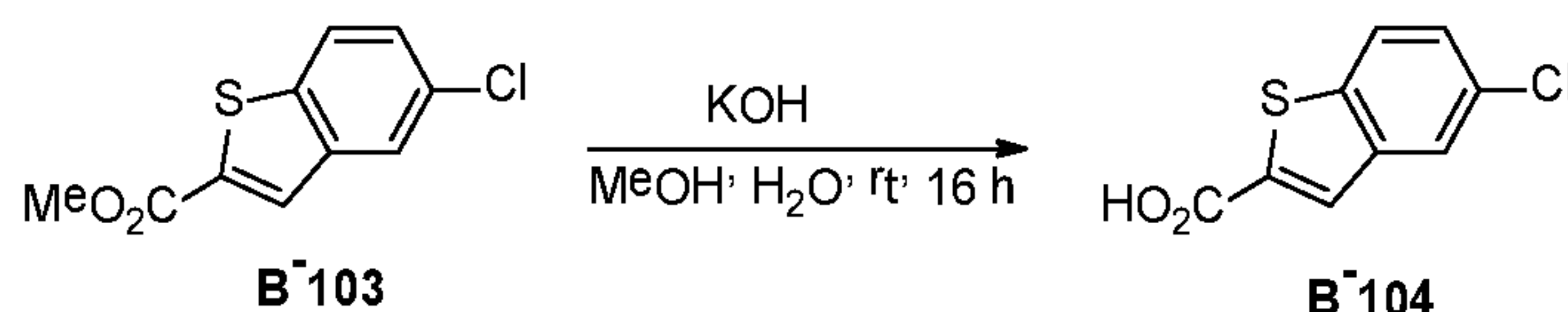
[00269] **Example 2B: 6-chlorobenzo[b]thiophene-2-carboxylic acid (B-102)**



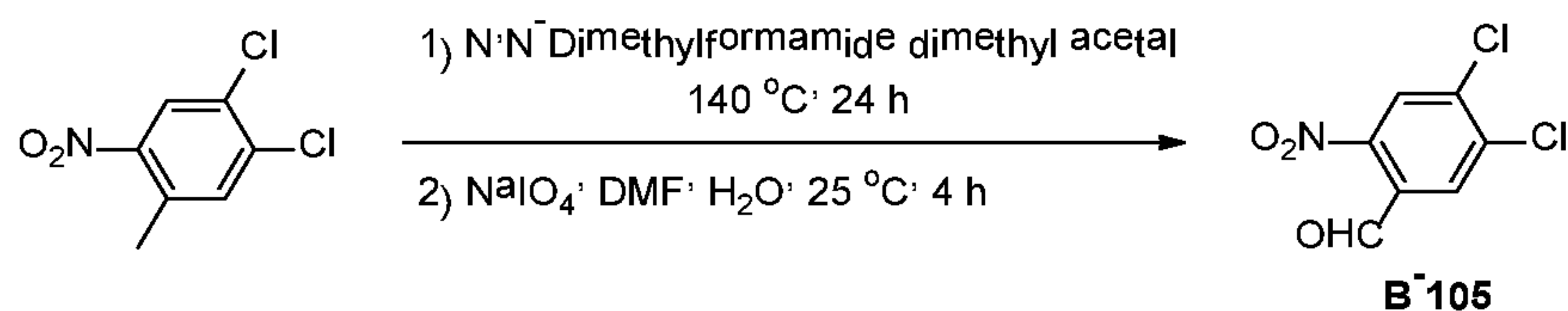
[00270] To a solution of **compound B-101** (10 g, 44 mmol) in tetrahydrofuran (200 mL) and water (10 mL) was added lithium hydroxide monohydrate (5.6 g, 0.13 mol). The reaction mixture was stirred at room temperature overnight. On completion, the reaction mixture was concentrated in vacuo to remove tetrahydrofuran and poured into water (400 mL). The pH was adjusted to 3 with 4M hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration, washed with water and dried in vacuo to give **compound B-102** (5.6 g, 60% yield) as a white solid. LCMS: (ES⁺) m/z (M+H)⁺ = 212.9.

[00271] **Example 3B: methyl 5-chlorobenzo[b]thiophene-2-carboxylate (B-103)**

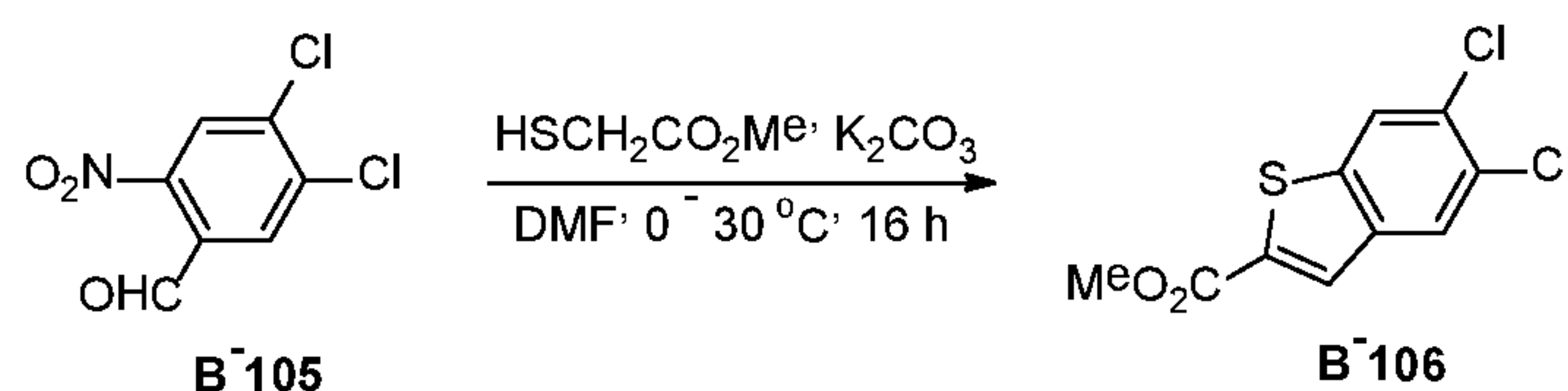
[00272] To a mixture of 5-chloro-2-nitrobenzaldehyde (10 g, 54 mmol) in anhydrous dimethyl formamide (100 mL) was added methyl 2-mercaptoacetate (5.7 g, 45 mmol) and K_2CO_3 (19 g, 135 mmol). The mixture was stirred at reflux for 6 hours. On completion, the reaction mixture was cooled to room temperature and poured into ice water (500 mL), resulting in formation of a solid. The mixture was stirred for 30 minutes, and the solid was collected by filtration, washed with water and dried in vacuo to give **compound B-103** (4 g, 31% yield) as a white solid. LCMS: (ES^+) m/z $(\text{M}+\text{H})^+ = 227.0$.

[00273] **Example 4B: 5-chlorobenzo[b]thiophene-2-carboxylic acid (B-104)**

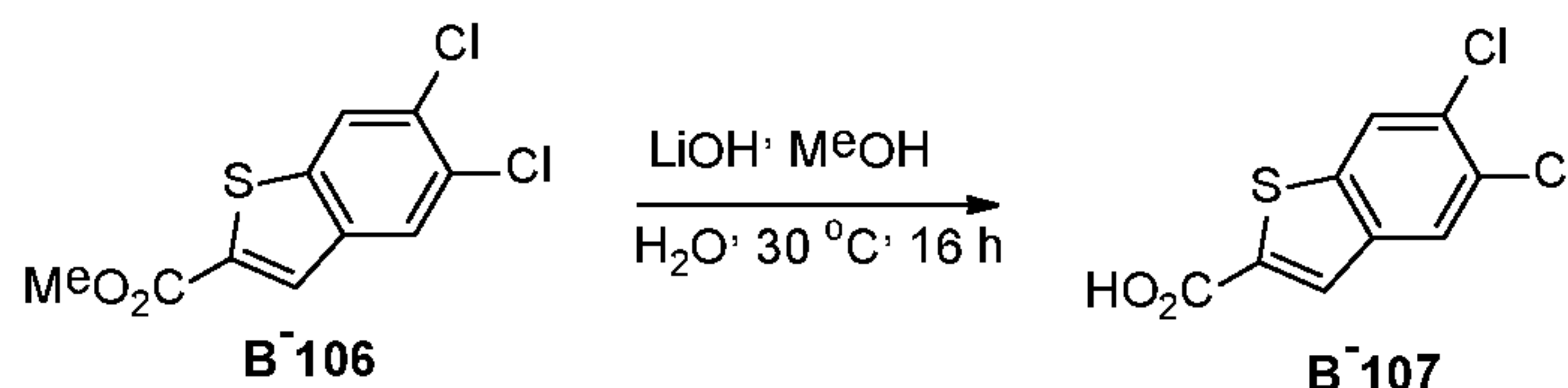
[00274] To a mixture of **compound B-103** (4.0 g, 18 mmol) in methanol (80 mL) and water (40 mL) was added potassium hydroxide (2.0 g, 2.9 mmol). The mixture was stirred at room temperature for 16 hours. On completion, the reaction mixture was concentrated in vacuo to remove methanol and poured into water (400 mL). The pH was adjusted to 3 with 4M hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration, washed with water and dried in vacuo to give **compound B-104** (3.5 g, 93% yield) as a white solid.

[00275] **Example 5B: 4,5-dichloro-2-nitrobenzaldehyde (B-105)**

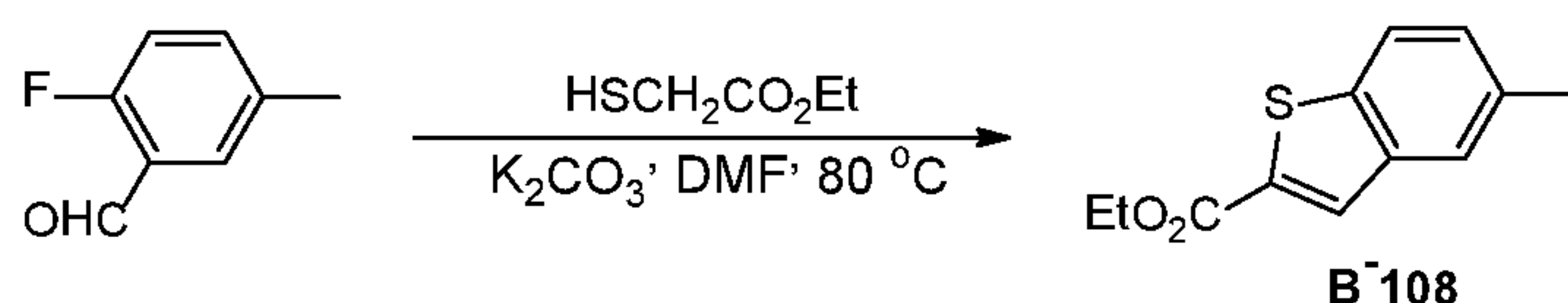
[00276] A solution of 4,5-dichloro-2-nitrotoluene (8.0 g, 39 mmol) in *N,N*-dimethylformamide dimethyl acetal (15 mL, 0.12 mol) was heated at reflux at 140 °C for 24 hours. The reaction mixture was then cooled to room temperature and added dropwise to a solution of sodium periodate (25 g, 0.12 mol) in *N,N*-dimethylformamide (50 mL) and water (75 mL). The reaction mixture was stirred at room temperature for 4 hours, and then filtered to remove solids. The filtrate was extracted with toluene (2 x 15 mL), and the combined organic layers were washed with water (2 x 30 mL) and brine (10 mL) and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-105** (1.8 g, 21% yield) as a white solid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 10.42 (s, 1H), 8.29 (s, 1H), 8.07 (s, 1H).

[00277] **Example 6B:** methyl 5,6-dichlorobenzo[b]thiophene-2-carboxylate (**B-106**)

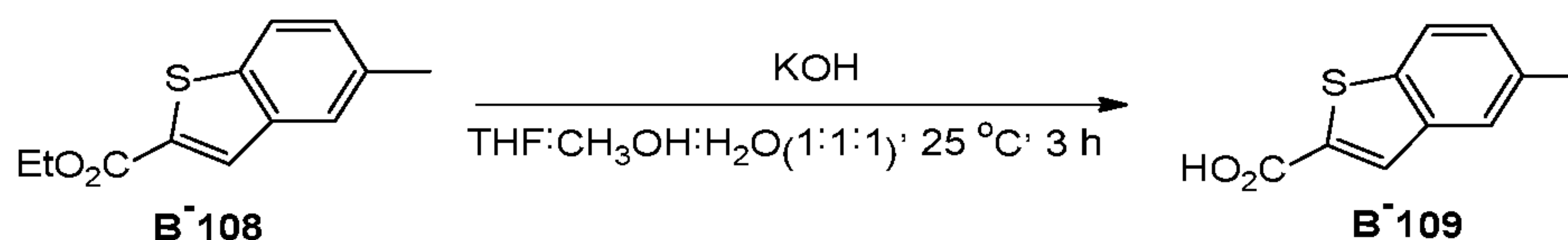
[00278] A solution of **compound B-105** (1.6 g, 7.1 mmol) and potassium carbonate (2.0 g, 14 mmol) in *N,N*-dimethylformamide (20 mL) was stirred at 0 °C for 30 min. Methyl 2-sulfanylacrylate (0.90 g, 8.5 mmol) was added slowly, and the reaction was stirred at 0 °C for 30 min and at 30 °C for 15 hours. On completion, the reaction was quenched with water (10 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 30:1] to give **compound B-106** (1.5 g, 81% yield) as a light yellow solid.

[00279] **Example 7B:** methyl 5,6-dichlorobenzo[b]thiophene-2-carboxylate (**B-107**)

[00280] To a solution of **compound B-106** (0.50 g, 1.9 mmol) in methanol (15 mL) and water (5 mL) was added lithium hydroxide (0.14 g, 5.7 mmol). The resulting mixture was stirred at 30 °C for 16 hours. On completion, the reaction solution was concentrated in vacuo to remove methanol. The pH was adjusted to 6 with concentrated hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-107** (0.40 g, 85% yield) as a white solid. LCMS: (ES⁺) *m/z* (M+H)⁺ = 200.9.

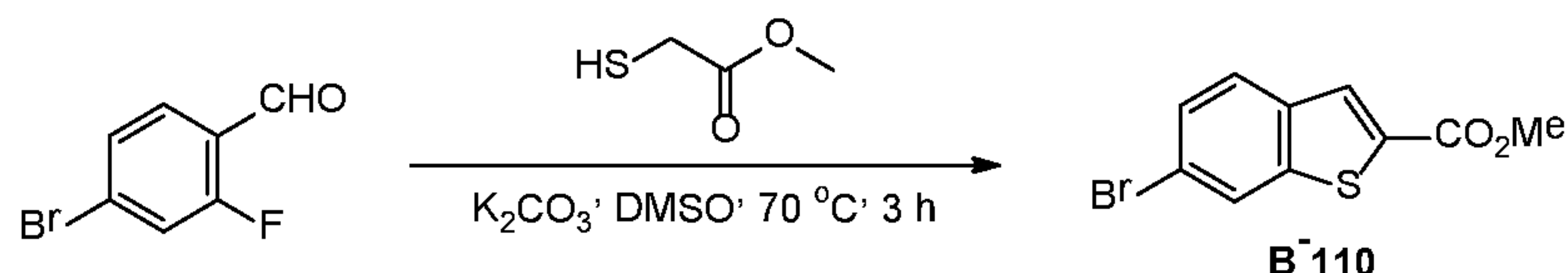
[00281] **Example 8B:** ethyl 5-methylbenzo[b]thiophene-2-carboxylate (**B-108**)

[00282] A mixture of 2-fluoro-5-methylbenzaldehyde (2.0 g, 14 mmol), ethyl 2-mercaptoacetate (1.8 g, 17 mmol) and potassium carbonate (4.0 g, 29 mmol) in *N,N*-dimethylformamide (30 mL) was stirred at 80 °C for 4 hours. On completion, the mixture was poured into ice-water, resulting in formation of a solid. The mixture was stirred for 30 min., and the solid was collected by filtration, washed with water and dried in vacuo to give **compound B-108** (2.2 g, 74% yield) as a yellow solid.

[00283] **Example 9B:** 5-methylbenzo[b]thiophene-2-carboxylic acid (**B-109**)

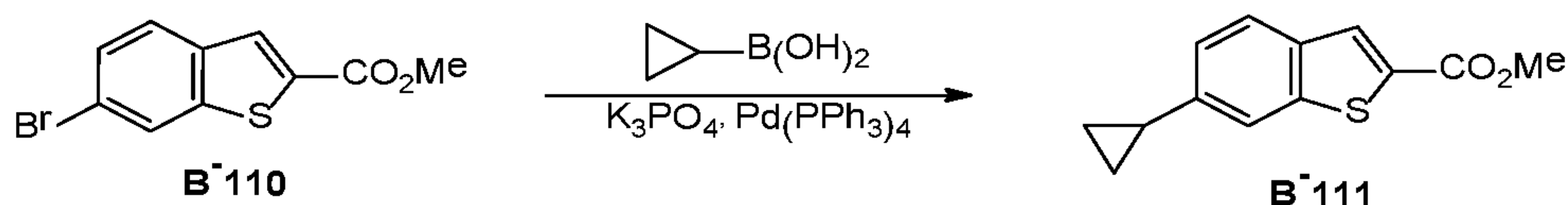
[00284] To a solution of **compound B-108** (0.20 g, 1.0 mmol) in tetrahydrofuran/methanol/water (1:1:1, 15 mL) was added lithium hydroxide hydrate (0.12 g, 2.9 mmol). The mixture was stirred at 25 °C for 3 hours. On completion, the reaction mixture was concentrated in vacuo to remove tetrahydrofuran and methanol and poured into water (10 mL). The pH was adjusted to 3 with 4M hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration, washed with water and dried in vacuo to give **compound B-109** (0.10 g, 54% yield) as a yellow solid. LCMS: (ES⁺) m/z (M+H)⁺ = 193.1.

[00285] **Example 10B: methyl 6-bromobenzo[b]thiophene-2-carboxylate (B-110)**



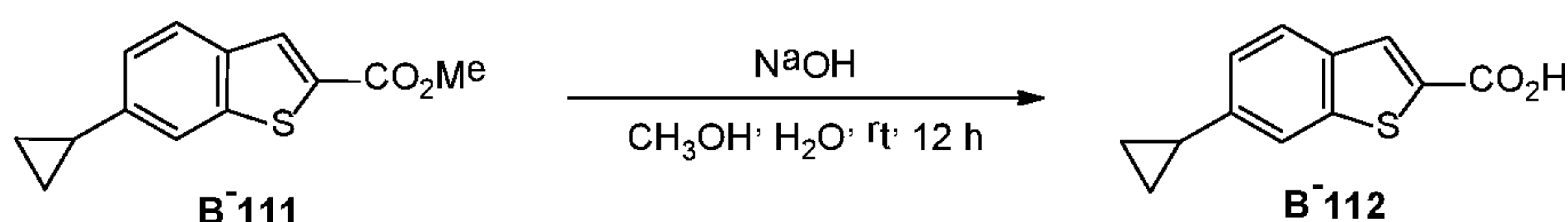
[00286] To a solution of 4-bromo-2-fluorobenzaldehyde (10 g, 49 mmol) and methyl 2-mercaptoacetate (7.8 g, 74 mmol) in dimethylsulfoxide (100 mL) was added potassium carbonate (13 g, 99 mmol) portionwise at room temperature. The resulting mixture was stirred at 70 °C for 3 hours. On completion, the mixture was poured into ice-water, resulting in formation of a solid. The mixture was stirred for 30 min., and the solid was collected by filtration, washed with water and dried in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 7:1] to give **compound B-110** (8.1 g, 61% yield) as a white solid.

[00287] **Example 11B: methyl 6-cyclopropylbenzo[b]thiophene-2-carboxylate (B-111)**



[00288] To a solution of **compound B-110** (2.7 g, 10 mmol) and cyclopropylboronic acid (0.73 g, 10 mmol) in anhydrous toluene (50 mL) under N₂ was added tetrakis(triphenylphosphine)palladium(0) (0.54 g, 0.47 mmol), followed by a solution of potassium phosphate (3.2 g, 15 mmol) in water (5 mL). The solution was stirred at room temperature for 0.5 hour before being heated to reflux for 7 hours. On completion, the mixture was cooled to room temperature and filtered. The filtrate was concentrated and purified by silica gel chromatography [petroleum ether: ethyl acetate = 60:1] to give **compound B-111** (1.8 g, 70% yield) as a white solid. LCMS: (ES⁺) m/z (M+H)⁺ = 233.0.

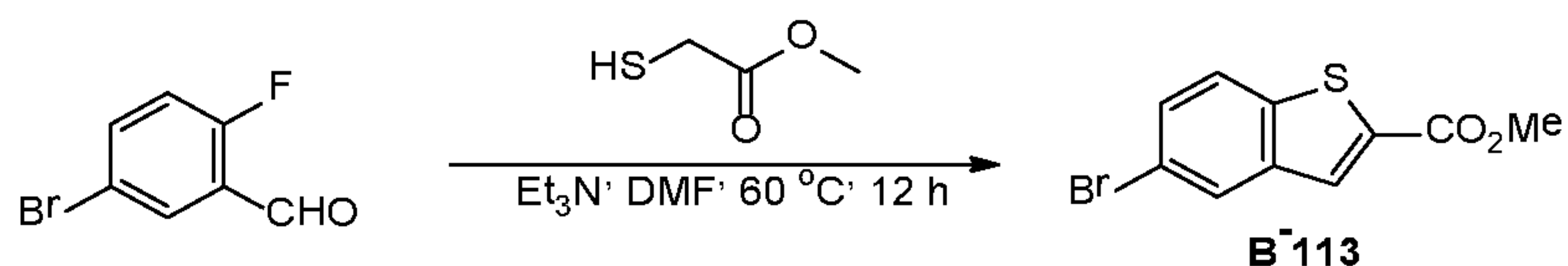
[00289] **Example 12B: 6-cyclopropylbenzo[b]thiophene-2-carboxylic acid (B-112)**



[00290] To a solution of **compound B-111** (0.52 g, 2.2 mmol) in methanol/water (1:1, 10 mL) was added sodium hydroxide (0.18 g, 4.4 mmol). The mixture was stirred at room temperature for 12

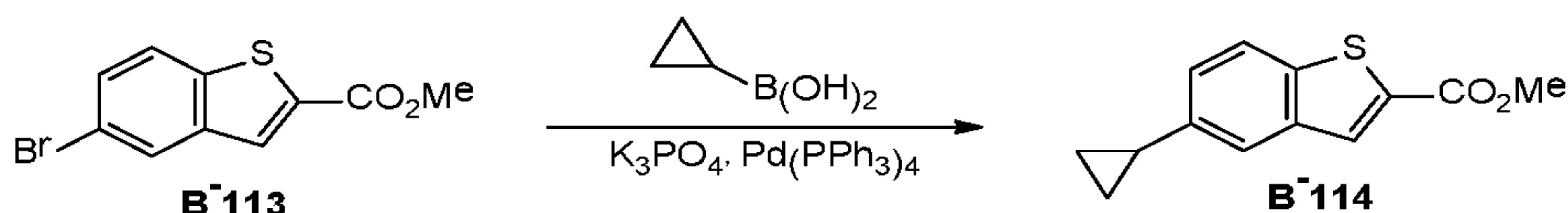
hours. On completion, the reaction mixture was concentrated in vacuo to remove tetrahydrofuran and poured into water (20 mL). The pH was adjusted to 3 with 4M hydrochloric acid, and the mixture was extracted with dichloromethane (20 mL×3). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-112** (0.38 g, 78% yield) as a white solid.

[00291] **Example 13B: methyl 5-bromobenzo[b]thiophene-2-carboxylate (B-113)**



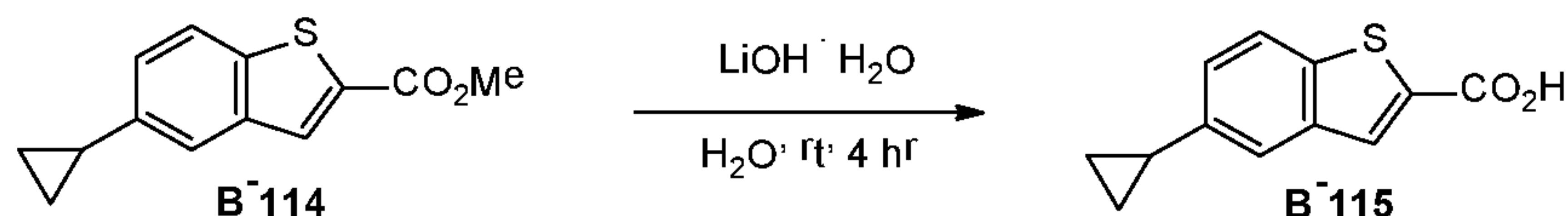
[00292] To a solution of 5-bromo-2-fluorobenzaldehyde (6.0 g, 30 mmol) and methyl 2-mercaptoacetate (3.8 g, 35 mmol) in *N,N*-dimethyl formamide (50 mL) was added triethylamine (8.97 g, 89 mmol) portionwise at room temperature. The resulting mixture was stirred at 60 °C for 12 hours. On completion, the mixture was poured into ice-water resulting in formation of a solid. The mixture was stirred for 30 min., and the solid was collected by filtration, washed with water and dried in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 7:1] to give **compound B-113** (5.5 g, 69% yield) as a white solid.

[00293] **Example 14B: methyl 5-cyclopropylbenzo[b]thiophene-2-carboxylate (B-114)**



[00294] To a solution of **compound B-113** (4.5 g, 17 mmol) and cyclopropylboronic acid (1.6 g, 18 mmol) in anhydrous toluene (30 mL) under N₂ was added tetrakis(triphenylphosphine)palladium(0) (0.98 g, 0.83 mmol), followed by a solution of potassium phosphate (5.3 g, 25 mmol) in water (10 mL). The resulting solution was stirred at room temperature for 0.5 hour before being heated to reflux for 12 hours. On completion, the mixture was cooled to room temperature and filtered. The resulting filtrate was concentrated and purified by silica gel chromatography [petroleum ether: ethyl acetate = 40:1~15:1] to give **compound B-114** (2.8 g, 73% yield) as a white solid. LCMS: (ES⁺) m/z (M+H)⁺ = 233.0.

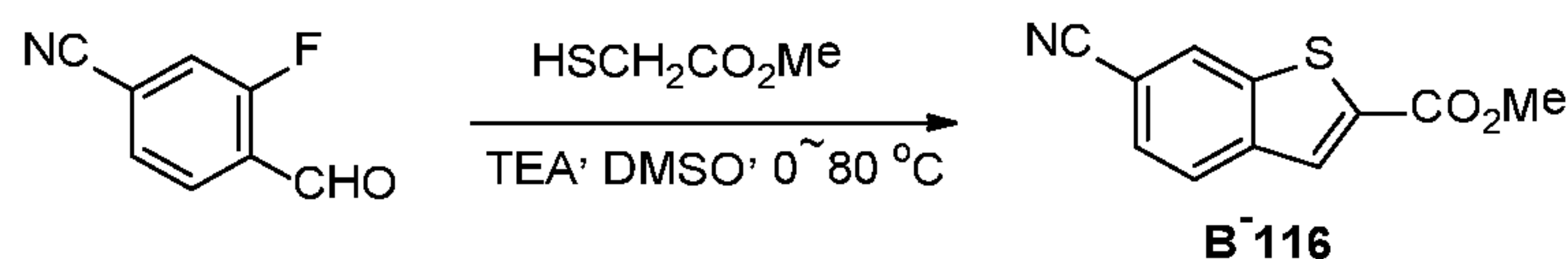
[00295] **Example 15B : 5-cyclopropylbenzo[b]thiophene-2-carboxylic acid (B-115)**



[00296] To a solution of **compound B-114** (0.80 g, 3.4 mmol) in water (20 mL) was added lithium hydroxide hydrate (0.43 g, 10 mmol), the result mixture was stirred at room temperature for 4 hours. On completion, the reaction mixture was concentrated in vacuo to remove tetrahydrofuran and was then poured into water (20 mL). The pH was adjusted to 3 with 4M hydrochloric acid, and the mixture was extracted with dichloromethane (60 mL×3). The combined organic layers were washed

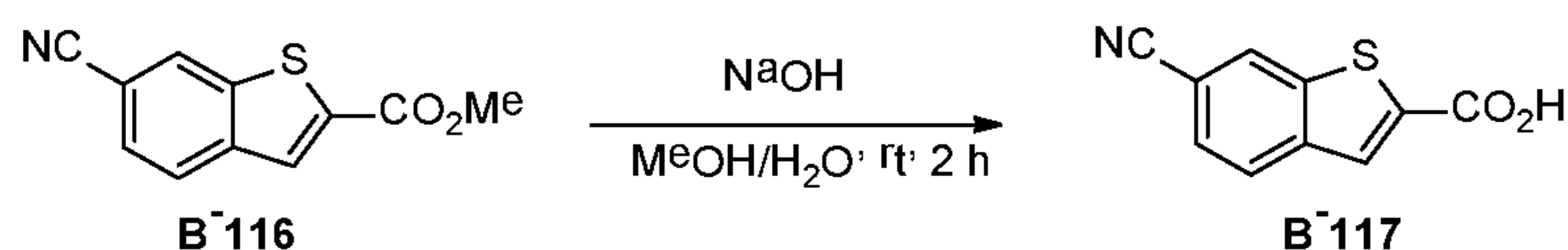
with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-115** (0.70 g, 92% yield) as a white solid.

[00297] **Example 16B: methyl 6-cyanobenzo[b]thiophene-2-carboxylate (B-116)**



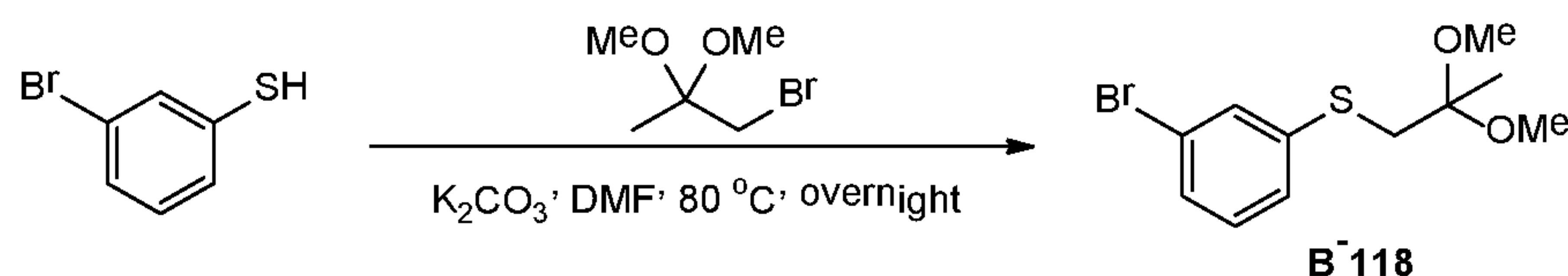
[00298] To a solution of 3-fluoro-4-formylbenzonitrile (3.6 g, 24 mmol) and triethylamine (4.8 g, 48 mmol) in dimethylsulfoxide (40 mL) was added methyl 2-mercaptoacetate (3.1 g, 29 mmol) at 0 °C. The reaction was stirred at 80 °C overnight. On completion, the solution was poured into ice water, and the resulting mixture was filtered. The filtrate was concentrated in vacuo to give **compound B-116** (4.0 g, 77% yield) as a yellow solid.

[00299] **Example 17B: 6-cyanobenzo[b]thiophene-2-carboxylic acid (B-117)**



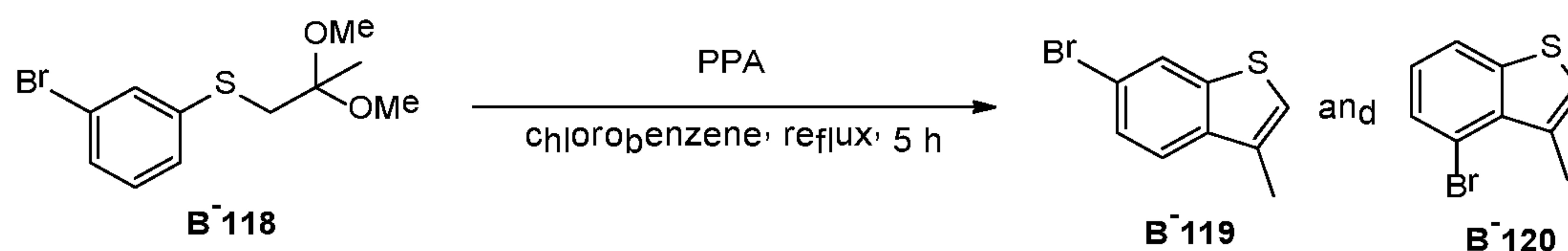
[00300] To a solution of **B-116** (4.0 g, 18 mmol) in methanol (20 mL) and water (20 mL) was added sodium hydroxide (1.5 g, 37 mmol) at room temperature. The mixture was stirred for 2 hours. On completion, the solution was concentrated to remove most of the methanol, and then the pH was adjusted to 4~5, resulting in formation of a solid. The solid was collected by filtration and dried to give **compound B-117** (3.4 g, 91% yield) as a brown solid.

[00301] **Example 18B: (3-bromophenyl)(2,2-dimethoxypropyl)sulfane (B-118)**



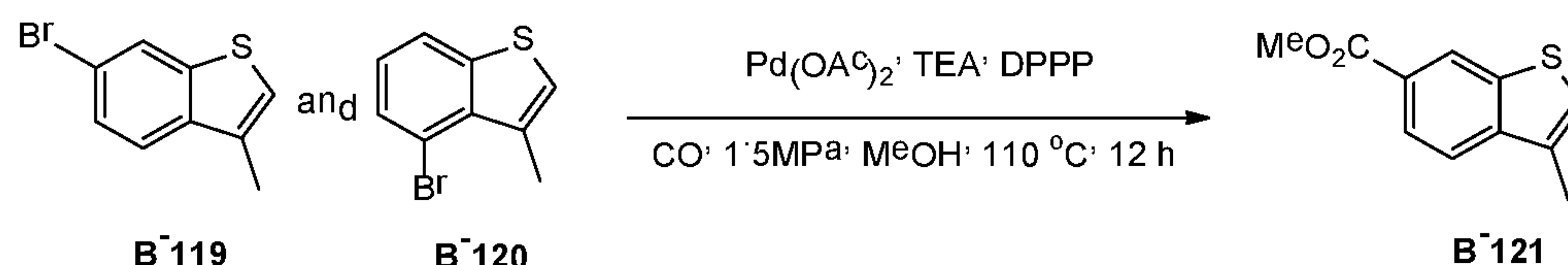
[00302] To a mixture of 3-bromobenzenethiol (8.7 g, 46 mmol) and 1-bromo-2,2-dimethoxypropane (8.4 g, 46 mmol) in *N,N*-dimethylformamide (50 mL) was added potassium carbonate (9.5 g, 69 mmol) at room temperature. The mixture was stirred at 80 °C overnight. On completion, the reaction mixture was quenched with water and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo to give crude **compound B-118** (13 g, 97% yield) as colorless oil.

[00303] **Example 19B: 6-bromo-3-methylbenzo[b]thiophene & 4-bromo-3-methylbenzo[b]thiophene (B-119 & B-120)**



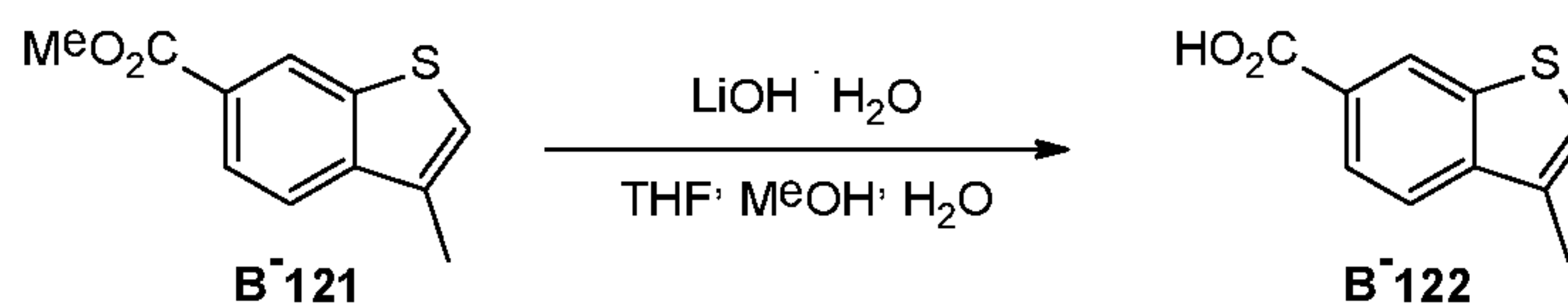
[00304] To a mixture of polyphosphoric acid (130 g) in chlorobenzene (100 mL) at reflux was added dropwise a solution of **B-118** (13 g, 45 mmol) in chlorobenzene (130 mL). The mixture was stirred at reflux for 5 hours. On completion, the reaction mixture was cooled to room temperature and quenched with water (200 mL). The resulting mixture was extracted with dichloromethane (3×200 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 1:0] to give **compound B-119 & B-120** (8.0 g, 79% yield) as a colorless oil.

[00305] **Example 20B:** methyl 3-methylbenzo[b]thiophene-6-carboxylate & methyl 3-methylbenzo[b] thiophene-4-carboxylate (**B-121**)



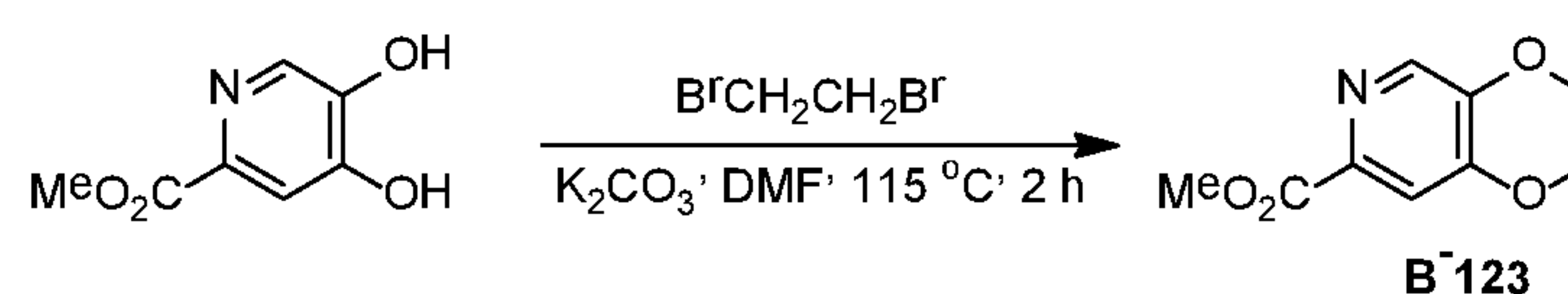
[00306] To a mixture of **compound B-119 & B-120** (0.50 g, 2.2 mmol), 1,3-bis(diphenylphosphino)propane (0.45 g, 1.1 mmol) and palladium acetate (0.12 g, 0.55 mmol) in methanol (10 mL) was added triethylamine (0.67 g, 6.6 mmol) at room temperature. The resulting mixture was stirred overnight in a 50 mL autoclave at 110 °C under carbon monoxide (1.5 MPa). On completion, the mixture was cooled to room temperature and filtered. The filtrate was poured into water and extracted with ethyl acetate (3×40 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 1:0] to give **compound B-121** (0.20 g, 44% yield) as a yellow solid. LCMS (B): tR=0.856., (ES⁺) m/z (M)⁺ = 207.1.

[00307] **Example 21B:** thieno[2,3-c]pyridine-5-carboxylic acid (**B-122**)



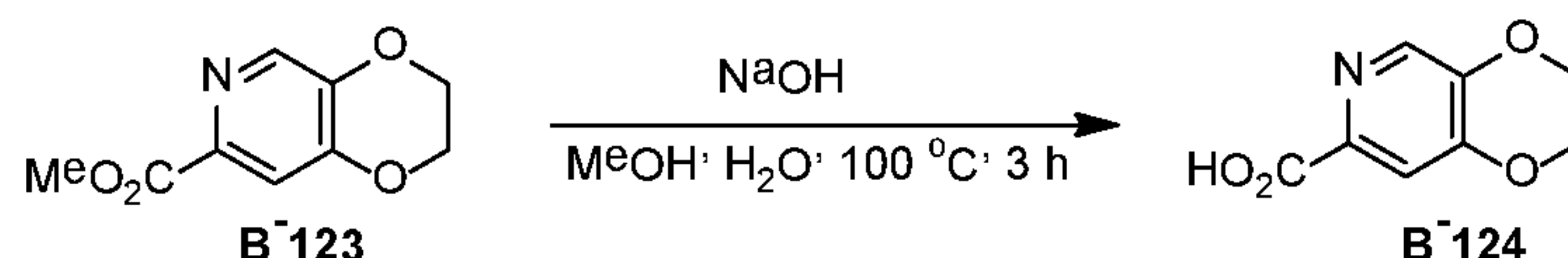
[00308] To a solution of **compound B-121** (0.18 g, 0.87 mmol) in tetrahydrofuran (5 mL), methanol (5 mL) and water (5 mL) was added lithium hydroxide monohydrate (73 mg, 1.8 mmol). The reaction mixture was stirred at room temperature overnight. On completion, the reaction mixture was concentrated in vacuo to remove tetrahydrofuran and poured into water (50 mL). The pH was adjusted to 3 with 4M hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration, washed with water and dried in vacuo to give **compound B-122** (0.16 g, 95% yield) as a white solid.

[00309] **Example 22B:** methyl 2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxylate (**B-123**)



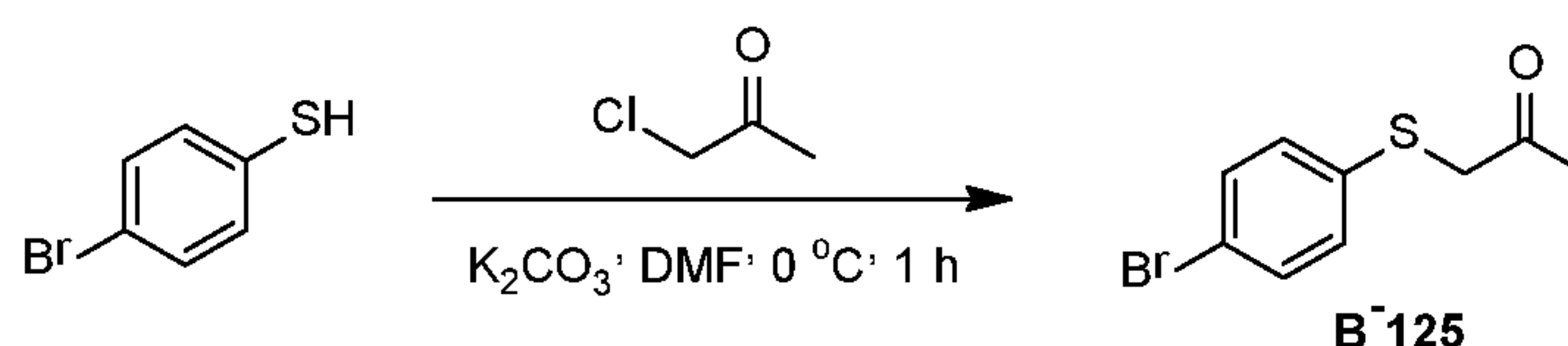
[00310] To a mixture of methyl 4,5-dihydroxypicolinate (1.0 g, 5.9 mmol) in *N,N*-dimethylformamide (70 mL) was added potassium carbonate (8.2 g, 59 mmol) and 1,2-dibromoethane (2.4 g, 13 mmol). The mixture was stirred at 115 °C for 2 hours. On completion, the mixture was diluted with ethyl acetate and washed with water three times. The organic layer was concentrated in vacuo to give **compound B-123** (0.80 g, 69% yield) as a yellow solid.

[00311] **Example 23B: 2,3-dihydro-[1,4]dioxino[2,3-*c*]pyridine-7-carboxylic acid (B-124)**



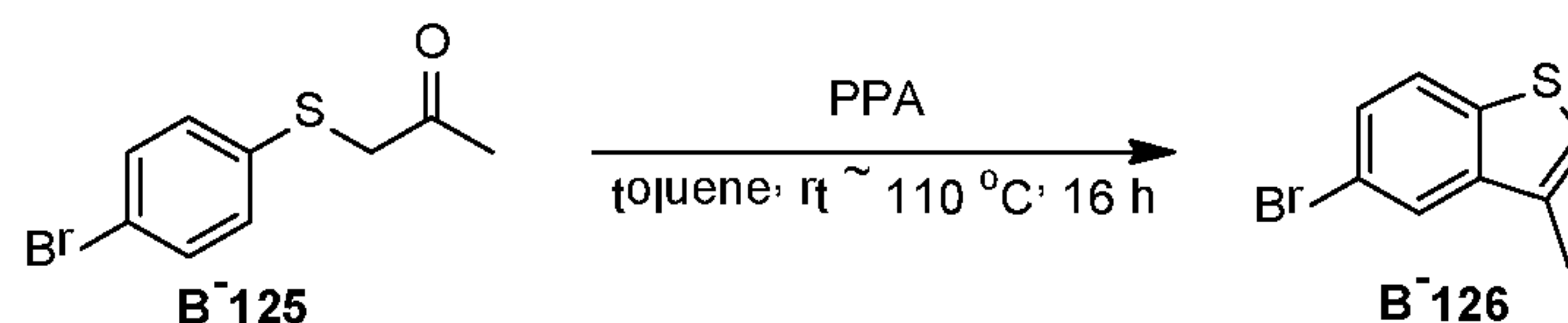
[00312] To a mixture of **compound B-123** (0.80 g, 4.1 mmol) in methanol (40 mL) and water (40 mL) was added sodium hydroxide (1.6 g, 41 mmol). The mixture was stirred at 100 °C for 3 hours. On completion, the mixture was adjusted to pH=5.0 with 1 M hydrochloric acid, evaporated to removed methanol and extracted with dichloromethane three times. The organic layer was concentrated in vacuo to give **compound B-124** (0.70 g, 94% yield) as a yellow solid: LCMS (A): tR=0.168 min., 182.0 m/z (M+1).

[00313] **Example 24B: 1-((4-bromophenyl)thio)propan-2-one (B-125)**

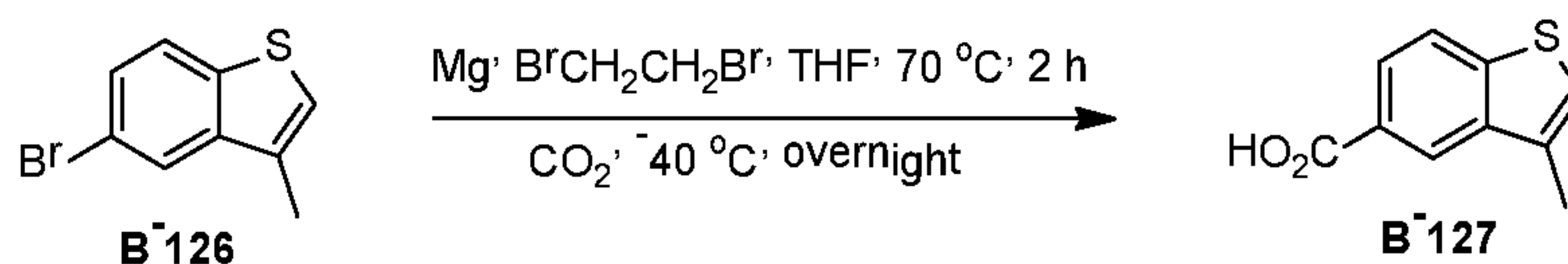


[00314] To a mixture of 4-bromobenzenethiol (20 g, 0.11 mol) in *N,N*-dimethylformamide (150 mL) was added 1-chloropropan-2-one (9.9 g, 0.11 mol) and potassium carbonate (29 g, 0.21 mol) at 0 °C. The mixture was stirred at this temperature for 1 hour. On completion, the reaction was diluted with ethyl acetate and washed four times with water. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-125** (25 g, crude) as a yellow oil which was used for the next step without another purification : LCMS (B): tR=0.828 min., 246.9 m/z (M+1).

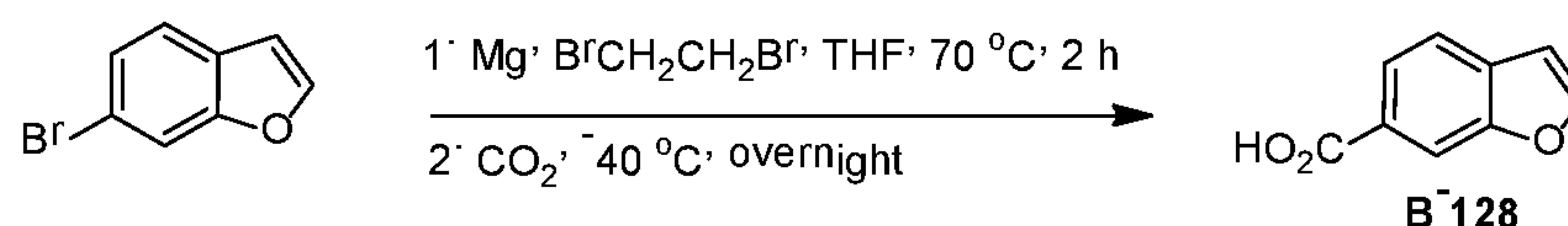
[00315] **Example 25B: 5-bromo-3-methylbenzo[*b*]thiophene (B-126)**



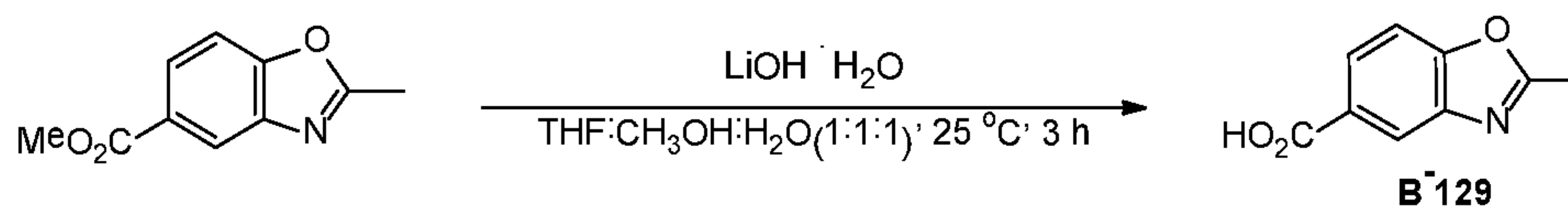
[00316] To a mixture of **compound B-125** (25 g, 0.10 mol) in toluene (400 mL) was added polyphosphoric acid (0.15 kg) at room temperature. The mixture was stirred at 110 °C for 16 hours. On completion, the reaction was poured into saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate = 10:1) to give **compound B-126** (16 g, 69% yield) as a yellow oil.

[00317] **Example 26B: 3-methylbenzo[b]thiophene-5-carboxylic acid (B-127)**

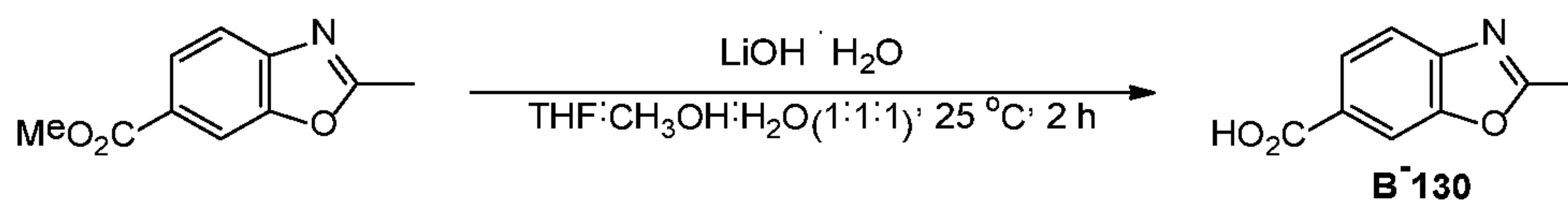
[00318] To a mixture of **compound B-126** (2.0 g, 8.8 mmol) in tetrahydrofuran (20 mL) was added magnesium (0.32 g, 13 mmol) and 1,2-dibromoethane (0.17 g, 0.88 mmol) at room temperature. The mixture was stirred at 70 °C for 2 hours, and then the reaction was stirred at -40 °C under carbon dioxide gas overnight. On completion, the reaction was poured into water and washed with ethyl acetate. The pH of the aqueous phase was adjusted to 5.0 with 1 M hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-127** (0.5 g, 30% yield) as a white solid: LCMS (B): tR=0.764 min., 193.1 m/z (M+1).

[00319] **Example 27B: benzofuran-6-carboxylic acid (B-128)**

[00320] To a mixture of 6-bromobenzofuran (1.0 g, 5.1 mmol) in tetrahydrofuran (15 mL) was added magnesium (0.19 g, 7.6 mmol) and 1,2-dibromoethane (95 mg, 0.51 mmol). The mixture was stirred at 70 °C for 2 hours, and then the reaction was stirred at -40 °C under carbon dioxide gas overnight. On completion, the mixture was poured into water and washed with ethyl acetate. The aqueous phase was adjusted to pH=5.0 with hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-128** (0.20 g, 24% yield) as a yellow solid.

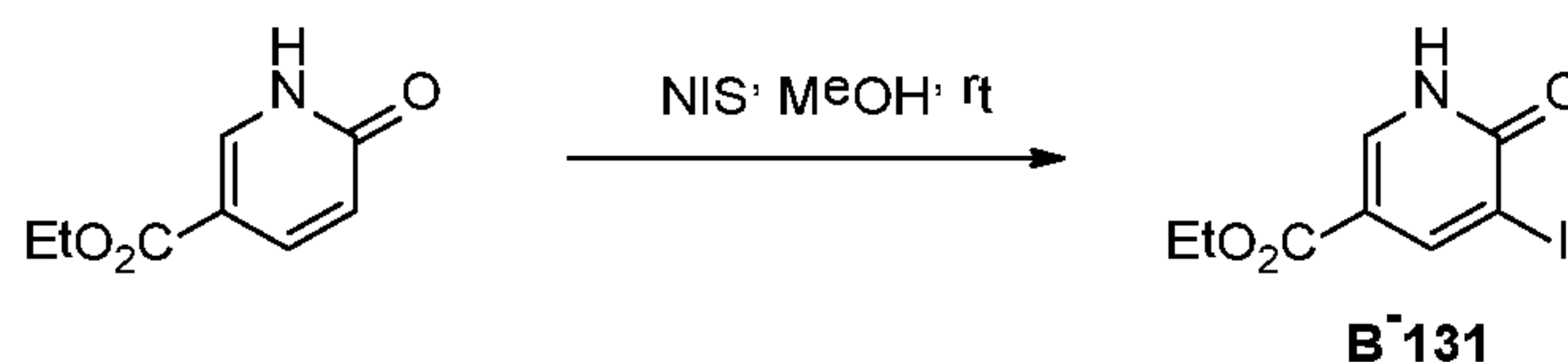
[00321] **Example 28B: 2-methylbenzo[d]oxazole-5-carboxylic acid (B-129)**

[00322] To a solution of methyl 2-methylbenzo[d]oxazole-5-carboxylate (0.50 g, 2.6 mmol) in tetrahydrofuran/methanol/water (1:1:1, 15 mL) was added lithium hydroxide hydrate (0.22 g, 5.2 mmol). The resulting mixture was stirred at 25 °C for 3 hours. On completion, the mixture was acidified by hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration, washed with water and dried in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 1:1] to give **compound B-129** (0.30 g, 65% yield) as a white solid.

[00323] **Example 29B: 2-methylbenzo[d]oxazole-6-carboxylic acid (B-130)**

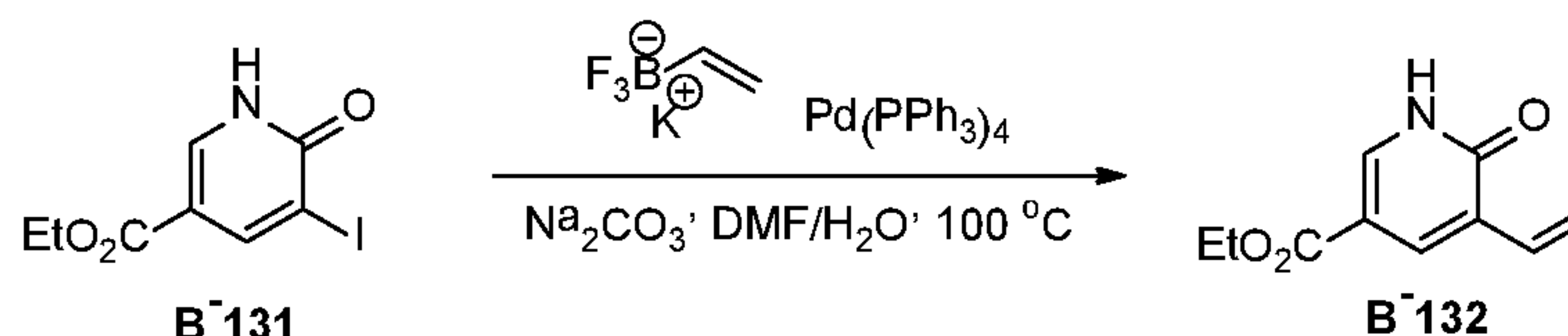
[00324] To a solution of methyl 2-methylbenzo[d]oxazole-6-carboxylate (2.0 g, 10 mmol) in tetrahydrofuran/methanol/water (1:1:1, 15 mL) was added lithium hydroxide hydrate (0.88 g, 21 mmol). The resulting mixture was stirred at 25 °C for 2 hours. On completion, the mixture was acidified with hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration, washed with water and dried in vacuo to give **compound B-130** (1.2 g, 65% yield) as a white solid.

[00325] **Example 30B: ethyl 5-iodo-6-oxo-1,6-dihydropyridine-3-carboxylate (B-131)**



[00326] To a solution of ethyl 6-oxo-1,6-dihydropyridine-3-carboxylate (2.0 g, 12 mmol) in methanol (20 mL) was added N-iodosuccinimide (4.1 g, 18 mmol). The reaction was stirred at room temperature overnight. On completion, the solution was concentrated, and the residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 15:1] to give **compound B-131** (3.0 g, 85% yield) as a brown solid.

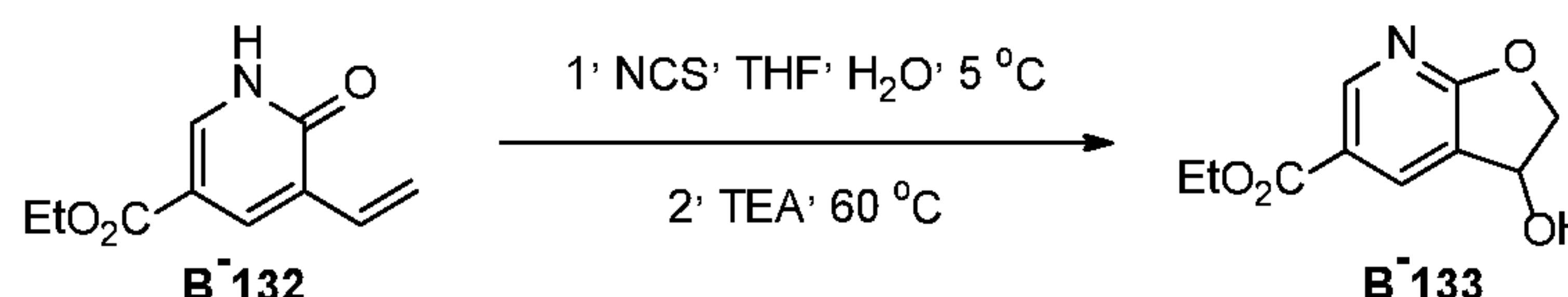
[00327] **Example 31B: ethyl 6-oxo-5-vinyl-1,6-dihydropyridine-3-carboxylate (B-132)**



To a mixture of **B-131** (2.8 g, 9.6 mmol), potassium trifluoro(vinyl)borate (1.3 g, 9.7 mmol), sodium carbonate (1.3 g, 12 mmol) in *N,N*-dimethyl formamide (30 mL) and water (6 mL) was added

[00328] tetrakis(triphenylphosphine) palladium (0) (1.1 g, 0.96 mmol) at room temperature. The suspension was degassed under vacuum and purged with nitrogen several times, then stirred at 100 °C for 16 hours. On completion, the mixture was diluted with water (30 mL) and extracted with ethyl acetate (3×40 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-132** (0.75 g, 41% yield) as a yellow oil.

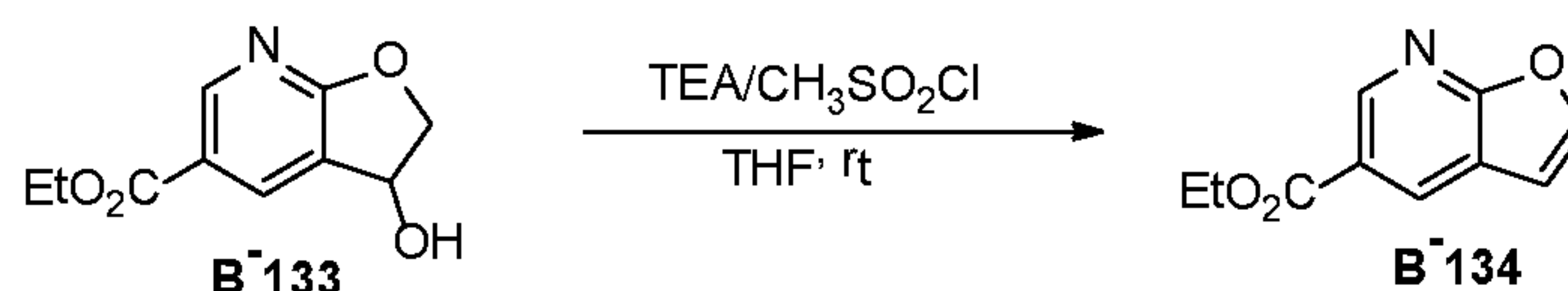
[00329] **Example 32B: ethyl 3-hydroxy-2,3-dihydrofuro[2,3-b]pyridine-5-carboxylate (B-133)**



[00330] A solution of **B-132** (0.45 g, 2.3 mmol) and N-chlorosuccinimide (0.31 g, 2.3 mmol) in tetrahydrofuran (4 mL) and water (4 mL) was stirred at 5 °C for 4 hours. Triethylamine (0.70 g, 6.9 mmol) was added to the mixture, and the reaction was stirred at 60 °C for another 4 hours. On

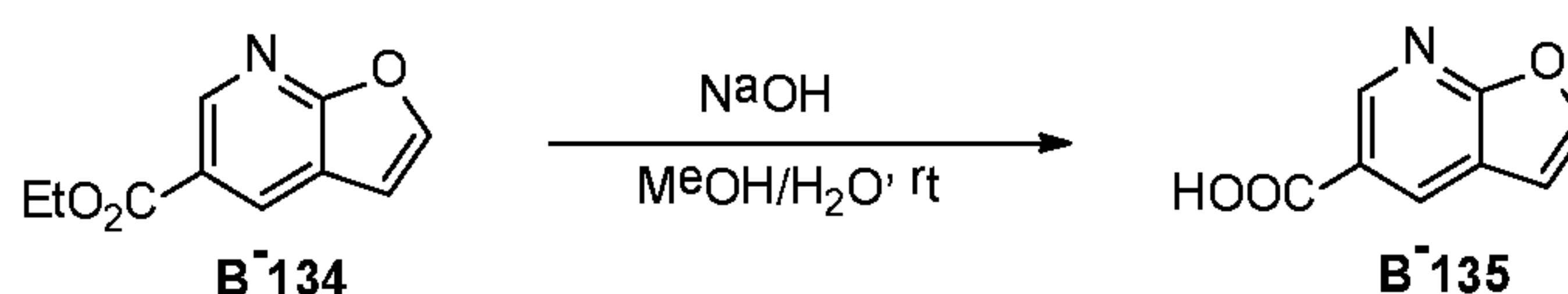
completion, the mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography [petroleum ether: ethyl acetate = 5:1] to give **compound B-133** (0.38 g, 78% yield) as a brown oil.

[00331] **Example 33B: ethyl furo[2,3-b]pyridine-5-carboxylate (B-134)**



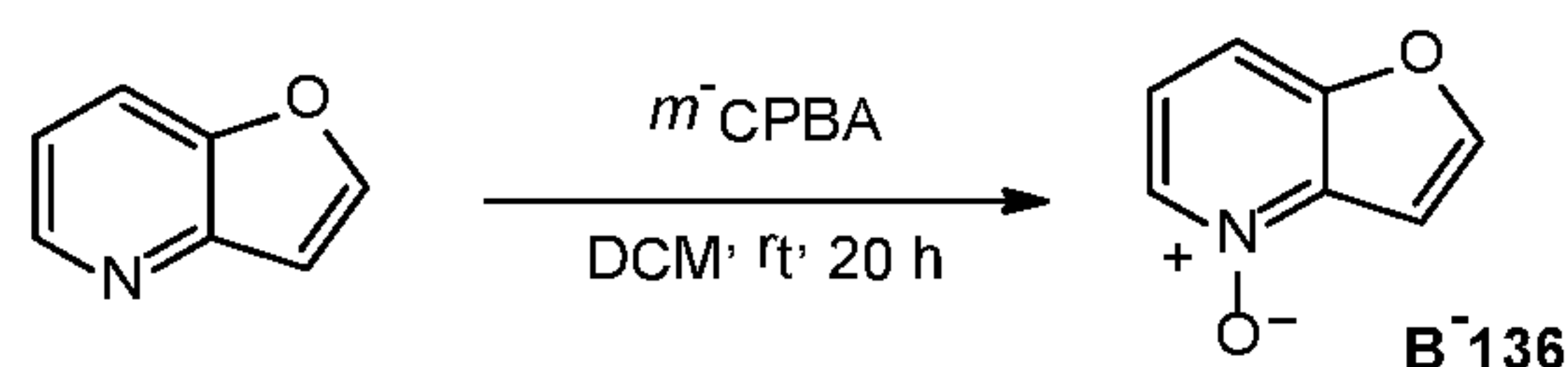
[00332] To a solution of **B-133** (0.38 g, 1.8 mmol) and triethylamine (0.27 g, 2.7 mmol) in tetrahydrofuran (5 mL) was added methanesulfonyl chloride (0.31 g, 2.7 mmol) at room temperature. The mixture was stirred at room temperature for 3 hours. On completion, the reaction was quenched with water (5 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-134** (0.22 g, 64% yield) as a white solid. LCMS (B): tR=0.693., (ES⁺) m/z (M+H)⁺ = 192.1.

[00333] **Example 34B: furo[2,3-b]pyridine-5-carboxylic acid (B-135)**

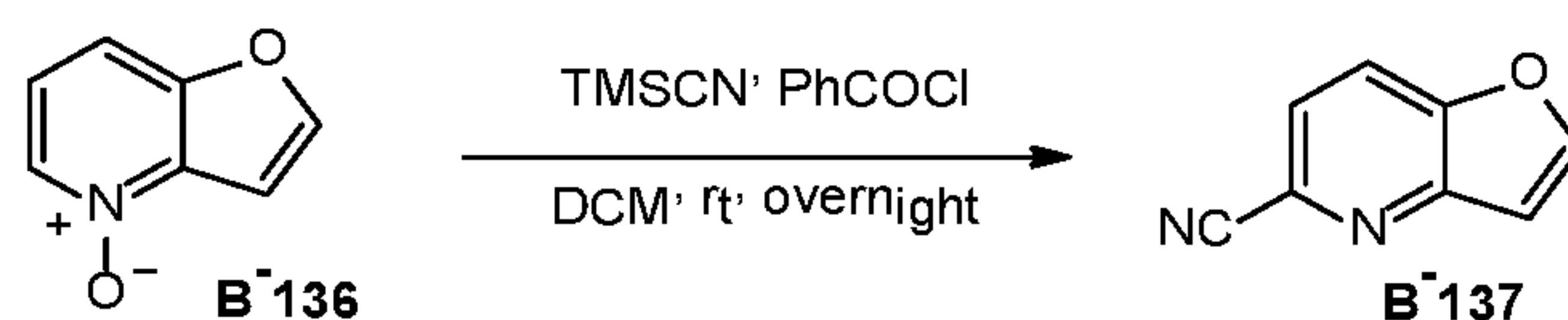


[00334] To a solution of **B-134** (0.22 g, 1.2 mmol) in methanol (3 mL) and water (3 mL) was added sodium hydroxide (96 mg, 2.4 mmol) at room temperature. The mixture was stirred at room temperature for 3 hours. On completion, the solution was concentrated to remove methanol, and the pH was adjusted to 4~5, resulting in formation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-135** (0.15 g, 77% yield) as a white solid.

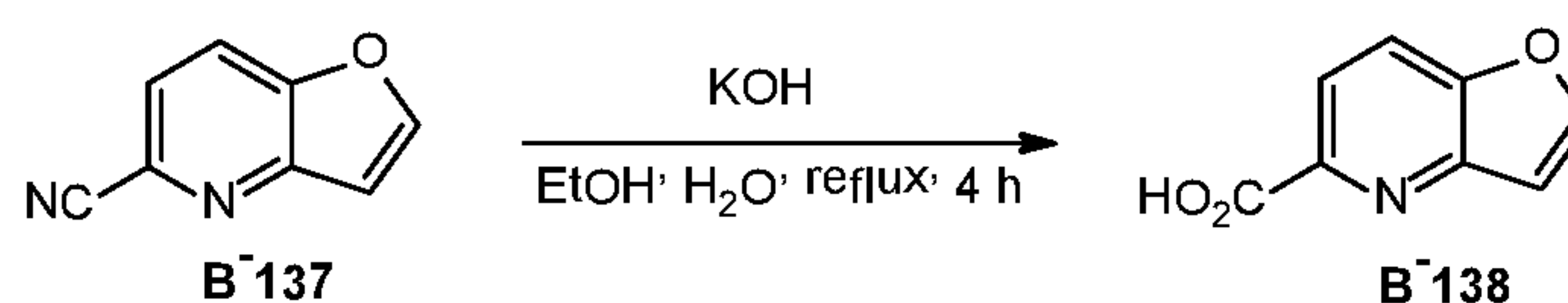
[00335] **Example 35B: 4-oxidofuro[3,2-b]pyridin-4-ium (B-136)**



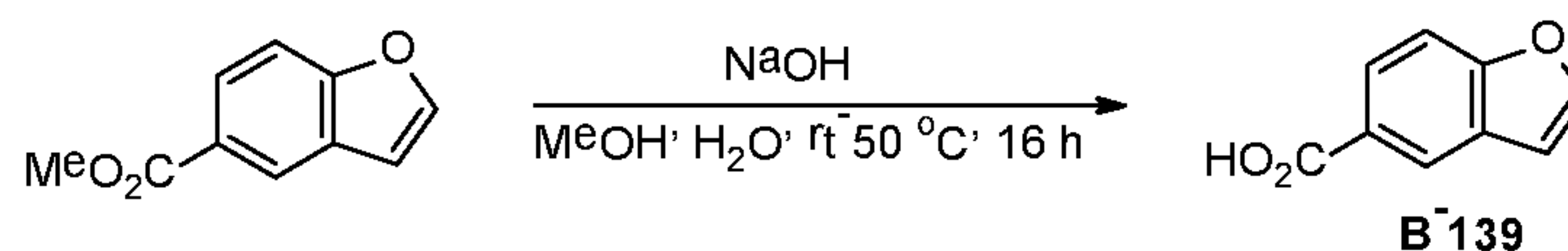
[00336] To a solution of furo[3,2-b]pyridine (1.0 g, 8.5 mmol) in dichloromethane (10 mL) was added metachloroperbenzoic acid (2.5 g, 14 mmol). The mixture was stirred at room temperature for 20 hours. On completion, the reaction mixture was quenched with 1 M aqueous potassium hydroxide (50 mL). The mixture was concentrated in vacuo, and the residue was poured into dichloromethane (10 mL). The mixture was filtered, and the filtrate was concentrated to give **compound B-136** (1.0 g, 87% yield) as yellow oil : LCMS (C): tR=1.070 min., (ES⁺) m/z (M+H)⁺ = 136.0.

[00337] **Example 36B: furo[3,2-b]pyridine-5-carbonitrile (B-137)**

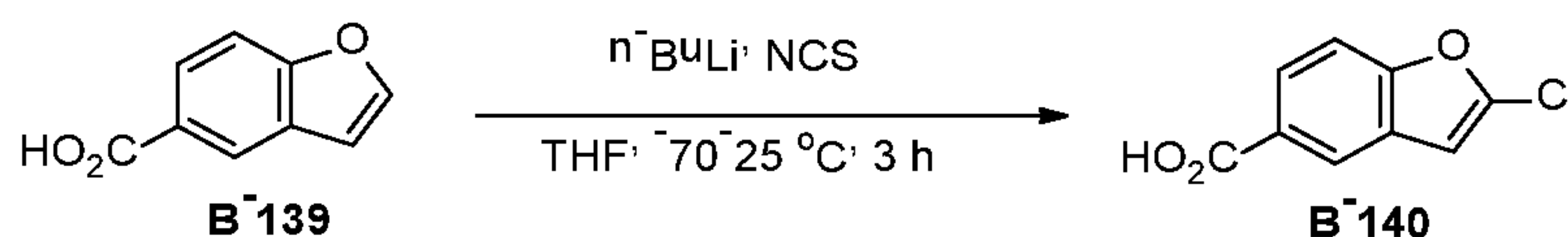
[00338] To a solution of **compound B-136** (1 g, 7.4 mmol) in dichloromethane (5 ml) was added a solution of trimethylsilyl cyanide (8 g, 81 mmol) in dichloromethane (35 ml). Then a solution of benzoyl chloride (11 g, 78 mmol) in dichloromethane (40 ml) was added dropwise. After vigorous stirring at room temperature overnight, the solvent was evaporation. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate = 2:1) to give **compound B-137** (730 mg, 68% yield) as light yellow solid: LCMS (A): $t_R=0.507$ min., $(ES^+) m/z (M+H)^+ = 145.0$.

[00339] **Example 37B: furo[3,2-b]pyridine-5-carboxylic acid (B-138)**

[00340] To a solution of **compound B-137** (450 mg, 3 mmol) in ethanol (10 mL) and water (2.5 mL) was added potassium hydroxide (1.2 g, 20 mmol). The mixture was heated at reflux for 4 hours. After evaporation to remove ethanol, the mixture was washed with ethyl acetate. The aqueous phase was adjusted to pH 5~6 with 1N hydrochloric acid and extracted with DCM (15 mL $\times$ 3). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo to give crude **compound B-138** (254 mg, 50% yield): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 8.22 (d, $J=4.4$ Hz, 1H), δ 8.17 (d, $J=8.4$ Hz, 1H), 8.07 (d, $J=8.4$ Hz, 2H), 7.12 (d, $J=1.6$ Hz, 1H).

[00341] **Example 38B: benzofuran-5-carboxylic acid (B-139)**

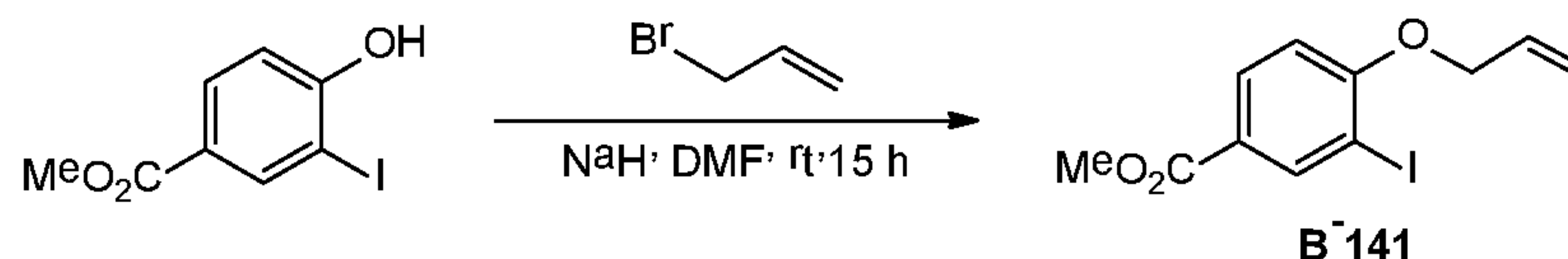
[00342] To a mixture of methyl benzofuran-5-carboxylate (1.0 g, 5.7 mmol) in methanol (10 mL) and water (1 mL) was added sodium hydroxide (0.45 g, 11 mmol). The mixture was stirred at room temperature for 16 hours. On completion, the mixture was adjusted to pH = 5~6 with 4 M hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-139** (0.61 g, 65% yield) as a white solid.

[00343] **Example 39B: 2-chlorobenzofuran-5-carboxylic acid (B-140)**

[00344] To a solution of **compound B-139** (0.70 g, 4.3 mmol) in tetrahydrofuran (10 mL) at -70 $^\circ\text{C}$ was added n-butyl lithium (4.3 ml, 11 mmol, 2.5M in n-hexane) portionwise over half an hour.

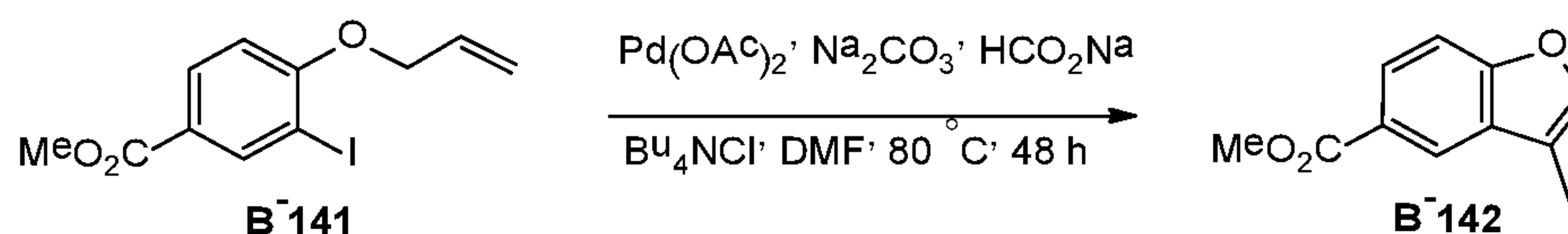
Then N-chlorosuccinimide (1.7 g, 13 mmol) was added portionwise, and the solution was stirred for another half an hour. The mixture was allowed to warm to room temperature and stirred for another 2 hours. The reaction was quenched with saturated aqueous ammonium chloride solution (3 mL) at 0 °C and concentrated to remove tetrahydrofuran. The pH was adjusted to 4 with 1 M hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration and dried in vacuo to give crude compound **B-140** (500 mg, crude) as a white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.21 (s, 1H), 7.94 (d, J=8.8 Hz, 1H), 7.65 (d, J=8.4 Hz, 1H), 7.14 (s, 1H).

[00345] **Example 40B: methyl 4-(allyloxy)-3-iodobenzoate (B-141)**



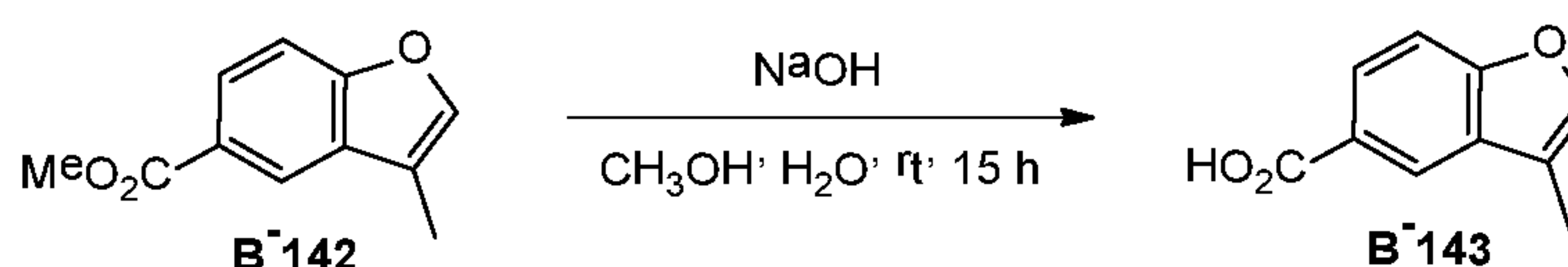
[00346] To a solution of methyl 4-hydroxy-3-iodobenzoate (21 g, 76 mmol) and 3-bromoprop-1-ene (14 g, 0.11 mol) in anhydrous *N,N*-dimethylformamide (200 mL) under nitrogen was added sodium hydride (4.5 g, 0.11 mol, 60%) portionwise. The resulting mixture was stirred at room temperature for 15 hours. On completion, the reaction was diluted with water (100 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-141** (25 g, 90% yield) as a tan solid. LCMS (B): tR=0.916., (ES⁺) m/z (M+H)⁺ = 319.0.

[00347] **Example 41B: methyl 3-methylbenzofuran-5-carboxylate (B-142)**



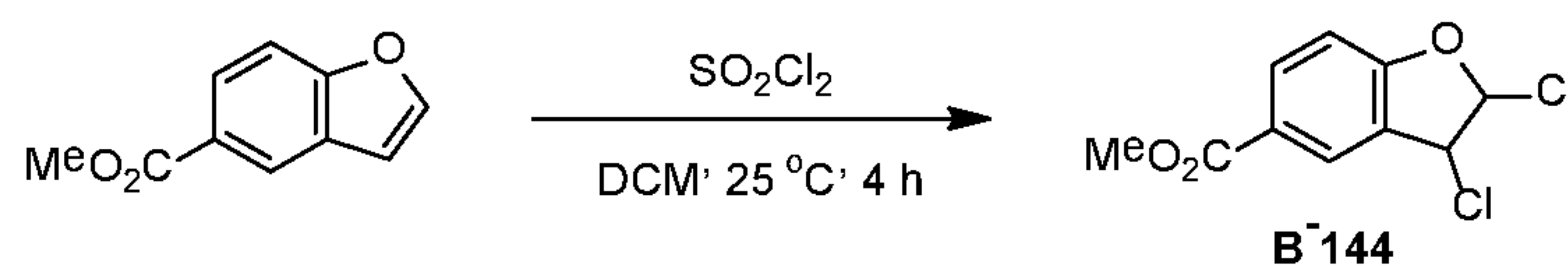
[00348] To a solution of **compound B-141** (2.0 g, 6.3 mmol) in anhydrous *N,N*-dimethylformamide (20 mL) under nitrogen was added palladium acetate (70 mg, 0.31 mmol), sodium carbonate (1.7 g, 16 mmol), sodium formate (0.43 g, 6.3 mmol) and tetrabutylammonium chloride (1.7 g, 6.3 mmol). The resulting mixture was stirred at 80 °C for 48 hours. On completion, the reaction mixture was filtered, and the filtrate was diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-142** (0.5 g, 45% yield) as a white solid. LCMS (B): tR=0.842., (ES⁺) m/z (M+H)⁺ = 191.1.

[00349] **Example 42B: 3-methylbenzofuran-5-carboxylic acid (B-143)**



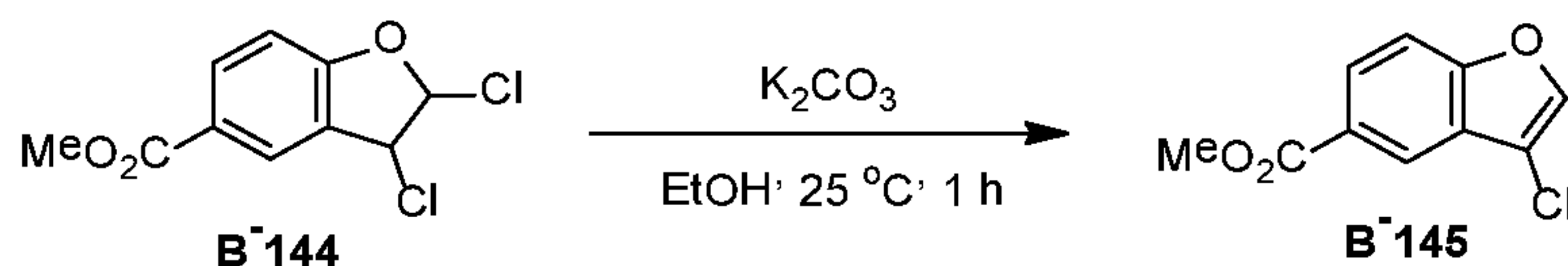
[00350] To a solution of **compound B-142** (0.55 g, 2.9 mmol) in methanol/water (10:1, 11 mL) was added sodium hydroxide (0.23 g, 5.8 mmol). The resulting mixture was stirred at room temperature for 15 hours. On completion, the volatiles were removed in vacuo. The residue was diluted with water (10 mL), and washed with ethyl acetate (10 mL). The aqueous solution was adjusted to pH 5 with 2 M hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-143** (0.47 g, 96% yield) as a white solid. LCMS (B): tR=0.708., (ES⁺) m/z (M+H)⁺ = 177.1. ¹H-NMR (CD₃Cl, 400 MHz): δ 8.38 (s, 1H), 8.12-8.10 (dd, J₁=8.8 Hz, J₂=4.0 Hz, 1H), 7.52 (t, J=8.0 Hz, 2H), 2.31 (s, 3H).

[00351] **Example 43B: methyl 2,3-dichloro-2,3-dihydrobenzofuran-5-carboxylate (B-144)**



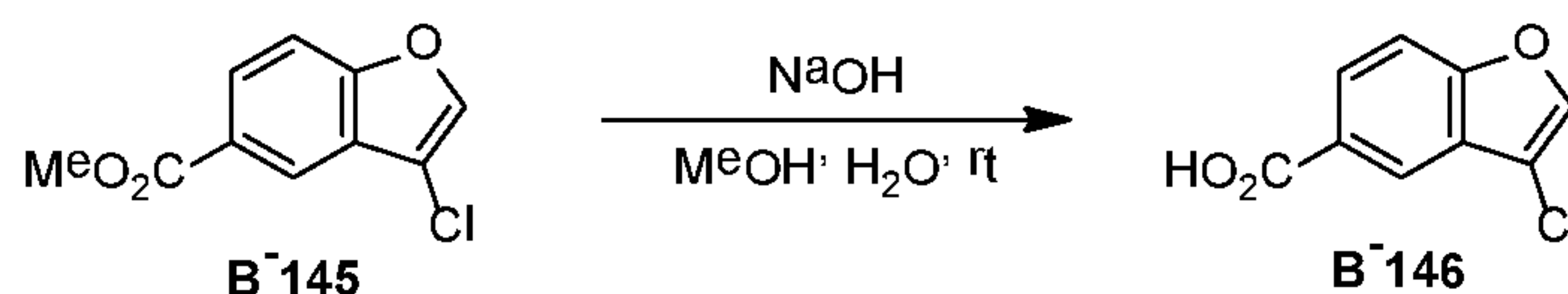
[00352] A mixture of methyl benzofuran-5-carboxylate (1.0 g, 5.7 mmol) and SO₂Cl₂ (3.0 g, 22.7 mmol) in dichloromethane (10 mL) was stirred at 25 °C for 4 hours. TLC showed a new spot formed. On completion, the reaction was concentrated, and the residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-144** (0.42 g, 30% yield) as an oil.

[00353] **Example 44B: methyl 3-chlorobenzofuran-5-carboxylate (B-145)**



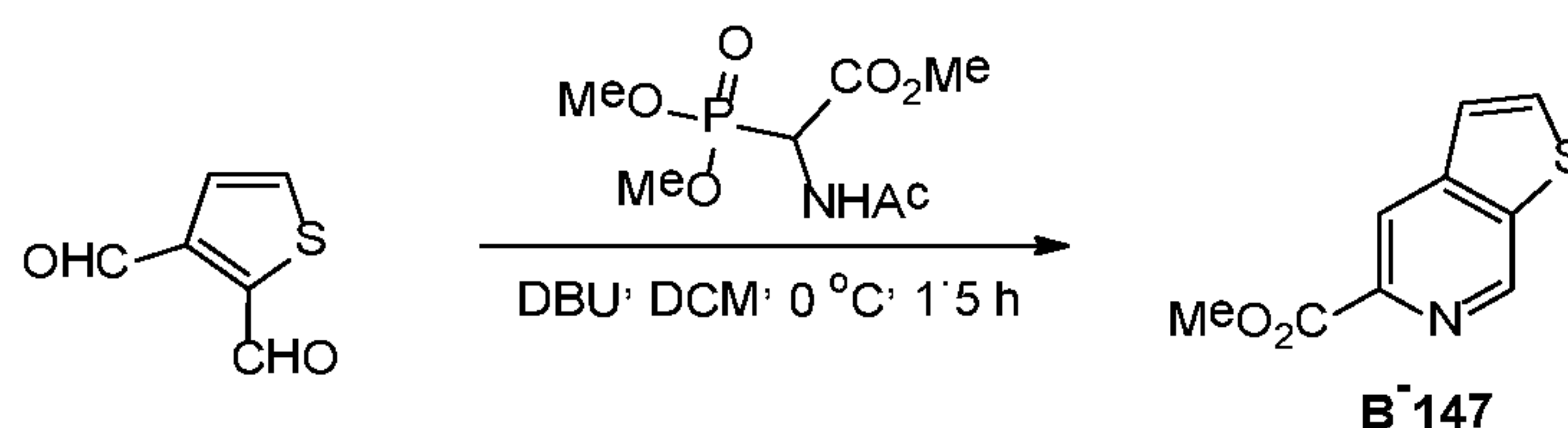
[00354] A mixture of **compound B-144** (0.42 g, 1.7 mmol) and potassium carbonate (0.71 g, 5.1 mmol) in ethanol (40 mL) was stirred at 25 °C for 1 hour. On completion, the mixture was filtered, and the filtrate was concentrated to give the crude **compound B-145** (0.35 g, 97% yield) as a white solid.

[00355] **Example 45B: 3-chlorobenzofuran-5-carboxylic acid (B-146)**



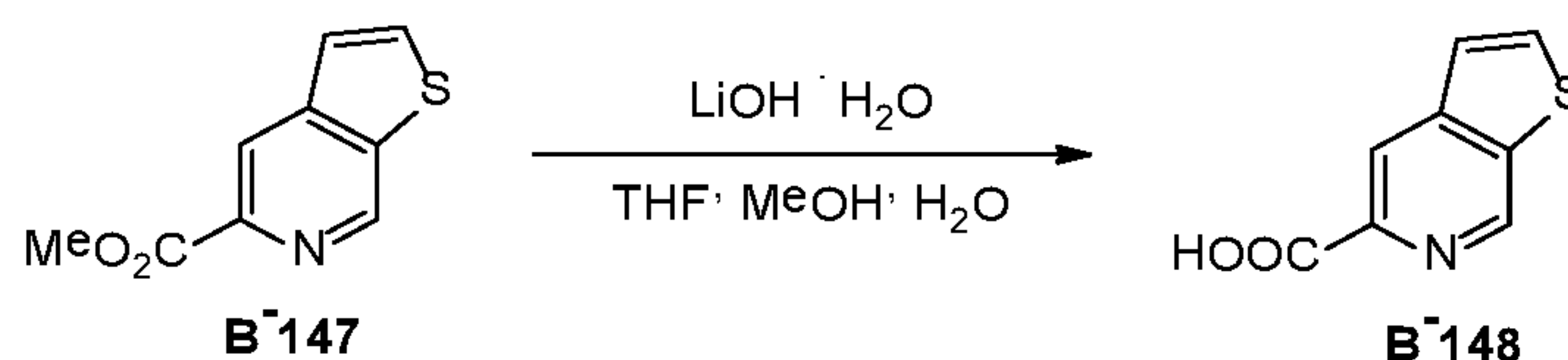
[00356] A mixture of **compound B-145** (0.35 g, 1.7 mmol) and sodium hydroxide (0.14 g, 3.4 mmol) in methanol (10 mL) and water (5 mL) was stirred at room temperature for 12 hours. On completion, the reaction mixture was concentrated in vacuo to remove methanol. The residue was poured into water, and the pH was adjusted to 3, resulting in formation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-146** (0.26 g, 80% yield).

[00357] **Example 46B:** methyl thieno[2,3-c]pyridine-5-carboxylate (**B-147**)



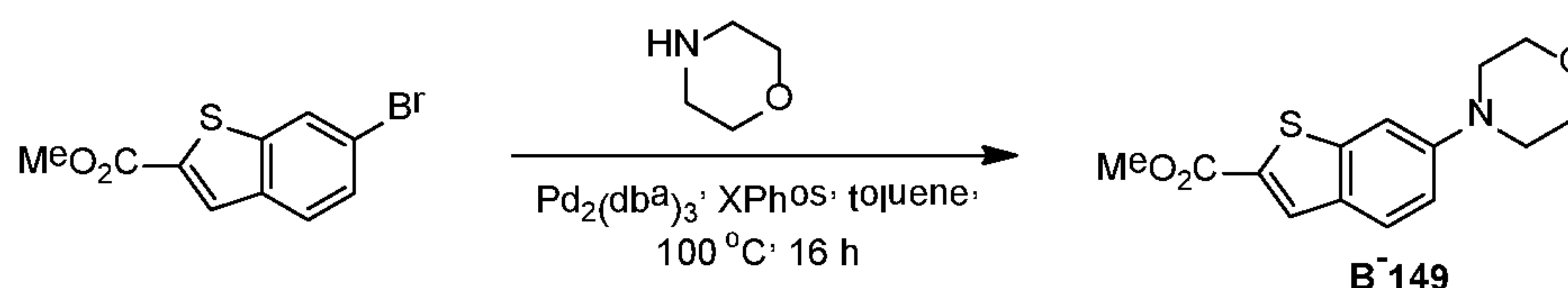
[00358] To a mixture of thiophene-2,3-dicarbaldehyde (2.0 g, 14 mmol) and methyl 2-acetamido-2-(dimethoxyphosphoryl)acetate (3.4 g, 14 mmol) in dichloromethane (20 mL) at 0 °C was added dropwise 1,8-diazabicyclo[5.4.0]undec-7-ene (2.4 g, 16 mmol). The mixture was stirred at 0 °C for 1.5 hours. On completion, the reaction mixture was quenched with water and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-147** (1.5 g, 54% yield) as a white solid.

[00359] **Example 47B:** thieno[2,3-c]pyridine-5-carboxylic acid (**B-148**)



[00360] To a solution of **compound B-147** (0.50 g, 2.6 mmol) in tetrahydrofuran (5 mL), methanol (5 mL) and water (5 mL) was added lithium hydroxide monohydrate (0.22 g, 5.2 mmol). The reaction mixture was stirred at room temperature overnight. On completion, the reaction mixture was concentrated in vacuo to remove tetrahydrofuran and poured into water (400 mL). The pH was adjusted to 5 with 4M hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration, washed with water and dried in vacuo to give **compound B-148** (0.50 g, crude) as a yellow solid.

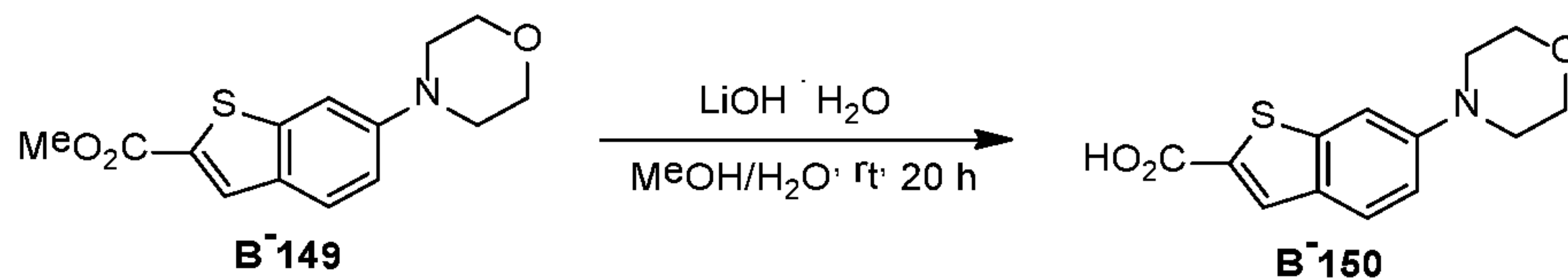
[00361] **Example 48B:** methyl 6-morpholinobenzo[*b*]thiophene-2-carboxylate (**B-149**)



[00362] Methyl 6-bromobenzo[2,3-b]thiophene-2-carboxylate (1.4 g, 5.0 mmol), morpholine (0.65 g, 7.5 mmol), cesium carbonate (3.3 g, 10 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.46 g, 0.50 mmol) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (0.24 g, 0.50 mmol) in toluene (30 mL) was de-gassed and then heated to 100 °C for 16 hours under nitrogen. On completion, the reaction mixture was poured into water (40 mL) and extracted with ethyl acetate (30 mL x 3). The organic phase was washed with brine (30 mL), dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography [petroleum ether: ethyl

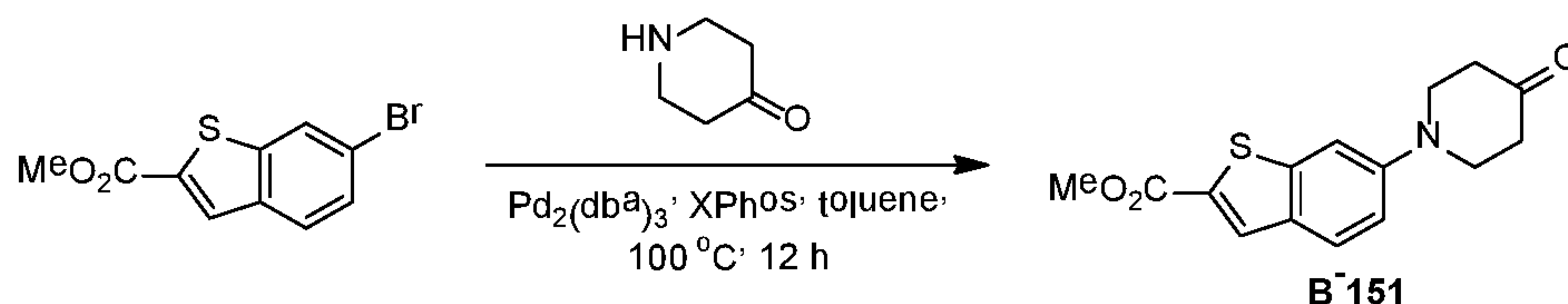
acetate = 5:1] to afford the **compound B-149** (0.95 g, crude) as a yellow solid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): 7.95 (s, 1H), 7.74 (d, $J=8.8$ Hz, 1H), 7.24 (d, $J=2.0$ Hz, 1H), 7.08 (d, $J=8.8$, 2.4 Hz, 1H), 3.93 (s, 3H), 3.90 (t, $J=4.8$ Hz, 4H), 3.27 (t, $J=4.8$ Hz, 4H).

[00363] **Example 49B: 6-morpholinobenzo[*b*]thiophene-2-carboxylic acid (B-150)**



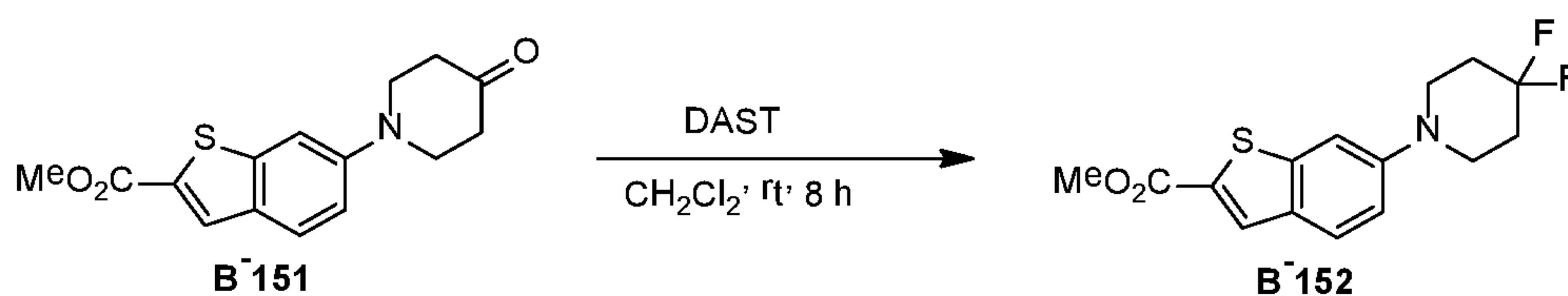
[00364] A mixture of **compound B-149** (0.50 g, 1.8 mmol) and lithium hydroxide (0.42 g, 10 mmol) in methanol (10 mL) and water (5 mL) was stirred at 25 °C for 20 hours. On completion, the mixture was concentrated in vacuo and poured into water (20 mL). The aqueous phase was washed with ethyl acetate (20 mL $\times$ 2), acidified and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic phases were washed with brine (40 mL $\times$ 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo to give **compound B-150** (0.36 g, 75% yield) as faint yellow solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): 8.06-8.00 (m, 3H), 7.54 (d, $J=9.2$, 2.0 Hz, 1H), 4.04 (t, $J=4.4$ Hz, 4H), 3.27 (t, $J=4.4$ Hz, 4H).

[00365] **Example 50B: methyl 6-(4-oxopiperidin-1-yl)benzo[*b*]thiophene-2-carboxylate (B-151)**



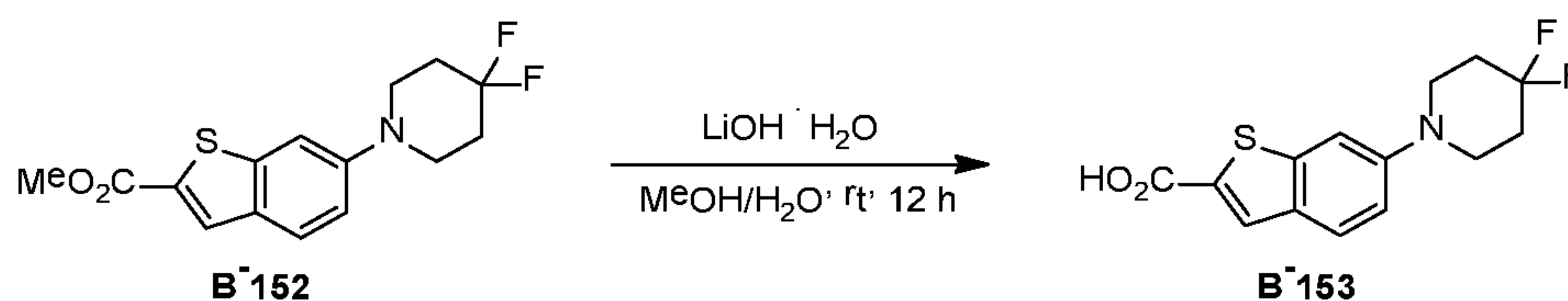
[00366] A mixture of methyl 6-bromobenzo[1,2-b:4,5-b']dithiophene-2-carboxylate (1.4 g, 5.0 mmol), piperidin-4-one (0.75 g, 7.5 mmol), cesium carbonate (3.3 g, 10 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.46 g, 0.50 mmol) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (0.24 g, 0.50 mmol) in toluene (30 mL) was de-gassed and then heated to 100 °C for 12 hours under nitrogen. On completion, the reaction mixture was poured into water (40 mL) and extracted with ethyl acetate (30 mL $\times$ 3). The combined organic phase was washed with brine (30 mL), dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography [petroleum ether: ethyl acetate = 5:1] to afford **compound B-151** (0.46 g, crude) as a yellow solid. LCMS (A): $t_R=0.845$ min., $(\text{ES}^+) m/z (\text{M}+\text{H})^+ = 289.9$.

[00367] **Example 51B: methyl 6-(4,4-difluoropiperidin-1-yl)benzo[*b*]thiophene-2-carboxylate (B-152)**



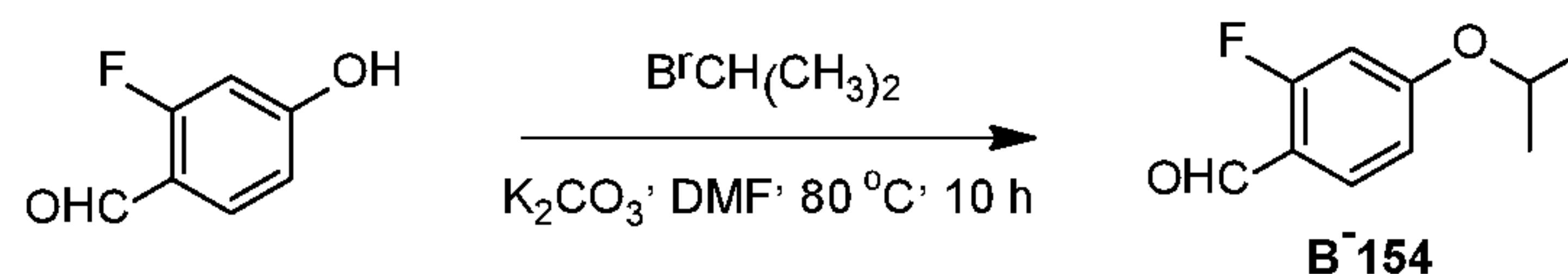
[00368] A mixture of **compound B-151** (0.30 g, 1.0 mmol) and diethylaminosulfur trifluoride (0.50 g, 3.1 mmol) in dichloromethane (10 mL) was stirred at room temperature for 8 hours. On completion, the mixture was added into saturated sodium bicarbonate solution (10 mL) at 0 °C. The aqueous phase was extracted with dichloromethane (20 mL $\times$ 3). The organic phases were combined and washed with brine (20 mL $\times$ 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by prep-HPLC [Instrument: GX-B; Column: YMC-pack ODS-AQ C18 150 $\times$ 30 mm, particle size: 5 μ m; Mobile phase: 50-80% acetonitrile in H₂O (add 0.5% TFA, v/v)] to give **compound B-152** (0.16 g, 49% yield) as a yellow solid. ¹H-NMR (CD₃OD, 400 MHz): 7.95 (s, 1H), 7.78 (d, J=8.8 Hz, 1H), 7.43 (d, J=1.6 Hz, 1H), 7.21 (d, J=8.8, 2.0 Hz, 1H), 3.90 (s, 3H), 3.49 (t, J=5.6 Hz, 4H), 2.16-2.06 (m, 4H).

[00369] **Example 52B:** 6-(4,4-difluoropiperidin-1-yl)benzo[*b*]thiophene-2-carboxylic acid (**B-153**)

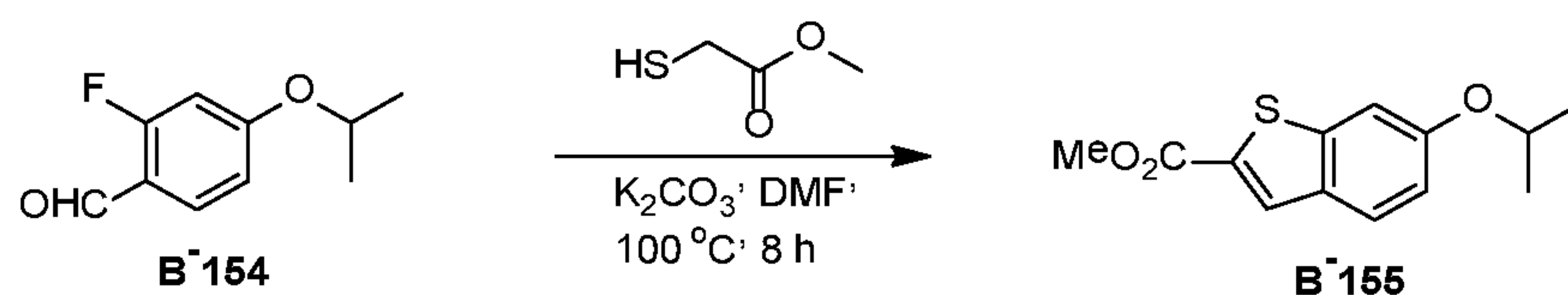


[00370] A mixture of **compound B-152** (0.16 g, 0.51 mmol) and lithium hydroxide (0.11 g, 2.6 mmol) in methanol (1 mL) and water (0.5 mL) was stirred at room temperature for 12 hours. On completion, the mixture was concentrated in vacuo and poured into water (10 mL). The aqueous phase was washed with ethyl acetate (10 mL $\times$ 2), acidified and extracted with ethyl acetate (10 mL $\times$ 3). The combined organic phase was washed with brine (20 mL $\times$ 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo to give **compound B-153** (0.11 g, 74% yield) as a yellow solid. ¹H-NMR (CD₃OD, 400 MHz): 7.90 (s, 1H), 7.77 (d, J=8.8 Hz, 1H), 7.43 (s, 1H), 7.20 (d, J=9.2, 2.0 Hz, 1H), 3.48 (t, J=5.6 Hz, 4H), 2.16-2.06 (m, 4H).

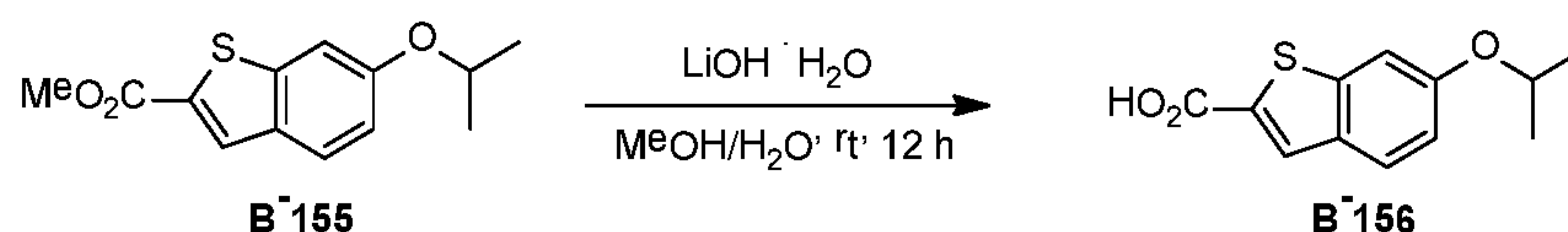
[00371] **Example 53B:** 2-fluoro-4-isopropoxybenzaldehyde (**B-154**)



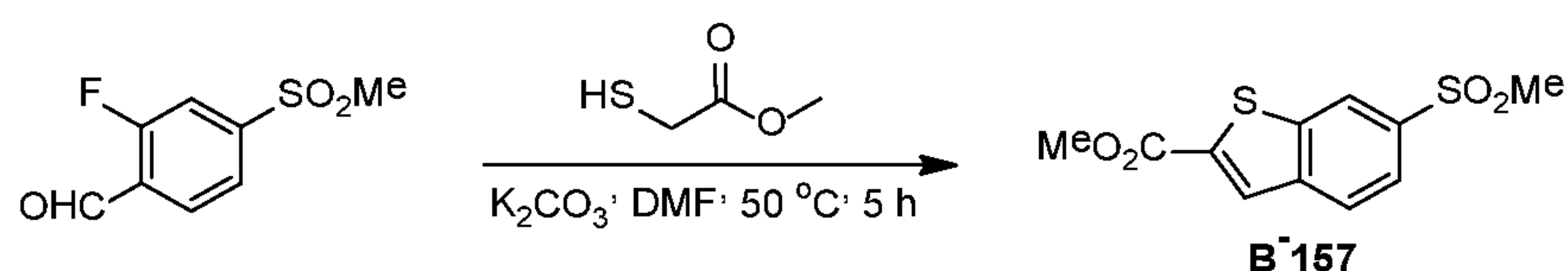
[00372] To a mixture of 2-fluoro-4-hydroxy-benzaldehyde (2.0 g, 14 mmol) and potassium carbonate (3.9 g, 29 mmol) in *N,N*-dimethylformamide (20 mL) at 25 °C under nitrogen was added 2-bromopropane (2.0 g, 16 mmol). The mixture was heated to 80 °C for 10 hours. On completion, the mixture was concentrated in vacuo, poured into water (20 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic phases were washed with brine (10 mL $\times$ 5), dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography [petroleum ether: ethyl acetate = 10:1] to afford **compound B-154** (1.6 g, crude) as a colorless liquid. ¹H-NMR (CD₃OD, 400 MHz): 10.11 (s, 1H), 7.86-7.77 (m, 1H), 6.88-6.64 (m, 2H), 4.79-4.64 (m, 1H), 1.37 (d, J=6.0 Hz, 4H).

[00373] **Example 54B:** methyl 6-isopropoxybenzo[*b*]thiophene-2-carboxylate (**B-155**)

[00374] To a solution of **compound B-154** (1.0 g, 5.5 mmol) in *N,N*-dimethylformamide (10 mL) was added potassium carbonate (2.3 g, 16 mmol) and methyl 2-mercaptoacetate (1.2 g, 11 mmol). The mixture was stirred at 100 °C for 8 hours. On completion, the mixture was diluted with water (60 mL) and extracted with ethyl acetate 270 mL (90 mL $\times$ 3). The combined organic layers were washed with brine 120 mL (20 mL $\times$ 6), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo to give **compound B-155** (1.9 g, crude) as black brown liquid, which was used directly without further purification. LCMS (B): *t*R=0.946 min., (ES⁺) *m/z* (M+H)⁺ = 251.0.

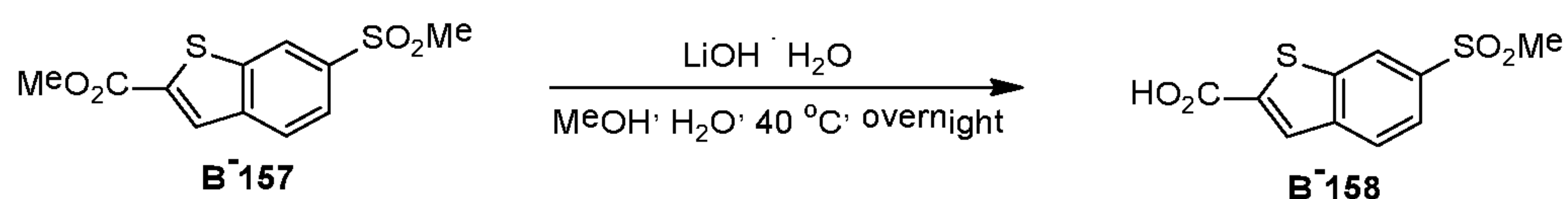
[00375] **Example 55B:** 6-isopropoxybenzo[*b*]thiophene-2-carboxylic acid (**B-156**)

[00376] A mixture of **compound B-155** (1.96 g, 7.8 mmol) and lithium hydroxide (1.6 g, 39 mmol) in methanol (10 mL) and water (5 mL) was stirred at 80 °C for 2.5 hours under nitrogen. On completion, the mixture was concentrated and poured into water (60 mL). The aqueous phase was washed with ethyl acetate (20 mL $\times$ 3), acidified and extracted with ethyl acetate (70 mL $\times$ 3). The combined organic phases were washed with brine (50 mL $\times$ 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo to give **compound B-156** (1.0 g, 54% yield) as a red solid. ¹H-NMR (CD₃OD, 400 MHz): 7.94 (s, 1H), 7.80-7.76 (m, 1H), 7.41-7.39 (m, 1H), 7.00-6.98 (m, 1H), 4.74-4.67 (m, 1H), 1.35 (d, *J*=4.4Hz, 4H).

[00377] **Example 56B:** methyl 6-(methylsulfonyl)benzo[*b*]thiophene-2-carboxylate (**B-157**)

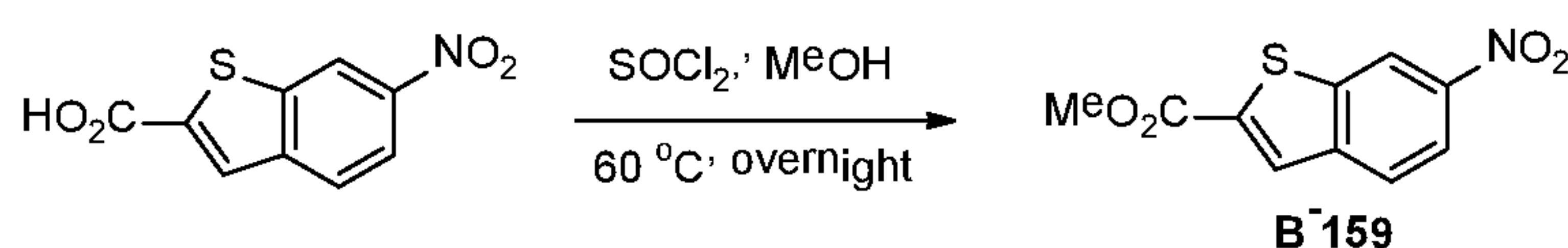
[00378] To a mixture of 2-fluoro-4-(methylsulfonyl)benzaldehyde (0.50 g, 2.5 mmol) in *N,N*-dimethylformamide (10 mL) was added methyl 2-mercaptoacetate (0.26 g, 2.5 mmol) and potassium carbonate (0.41 g, 3.0 mmol). The mixture was stirred at 50 °C for 5 hours. On completion, the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-157** (0.62 g, 93% yield) as a yellow solid. LCMS (A): *t*R=0.709 min., (ES⁺) *m/z* (M+H)⁺ = 271.0.

[00379] **Example 57B:** 6-(methylsulfonyl)benzo[b]thiophene-2-carboxylic acid (**B-158**)



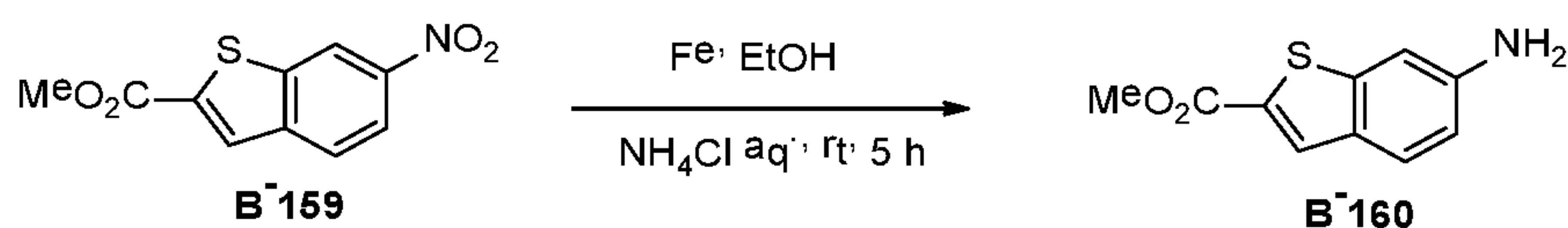
[00380] To a mixture of **compound B-157** (0.62 g, 2.3 mmol) in methanol (4 mL) and water (2 mL) was added lithium hydroxide monohydrate (0.19 g, 4.6 mmol). The mixture was stirred at 40 °C overnight. On completion, the mixture was concentrated to remove methanol, diluted with water and adjusted to pH to 3.0 with 1 M hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-158** (0.52 g, 89% yield) as a yellow solid.

[00381] **Example 58B:** methyl 6-nitrobenzothiophene-2-carboxylate (**B-159**)



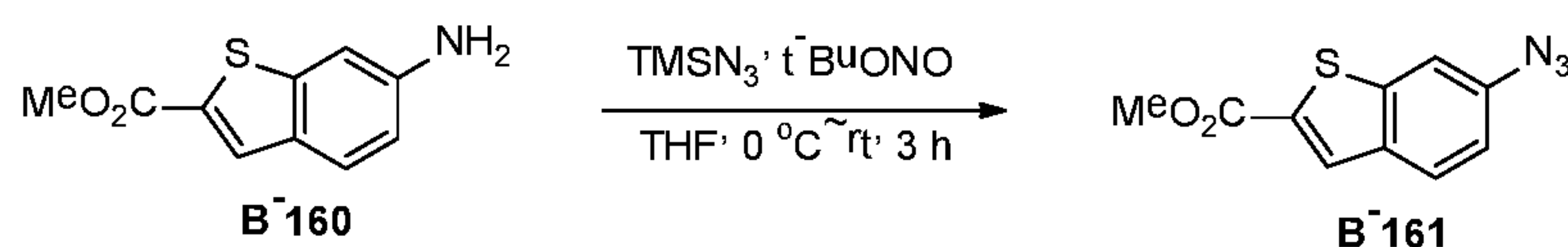
[00382] To a solution of 6-nitrobenzo[b]thiophene-2-carboxylic acid (0.98 g, 4.4 mmol) in methanol (10 mL) at 0 °C was added thionyl chloride (0.78 g, 6.6 mmol). The mixture was stirred at 60 °C overnight. On completion, the reaction mixture was evaporated to give **compound B-159** (1.1 g, 97% yield) as a yellow solid, which was used for next step without further purification.

[00383] **Example 59B:** methyl 6-aminobenzo[b]thiophene-2-carboxylate (**B-160**)



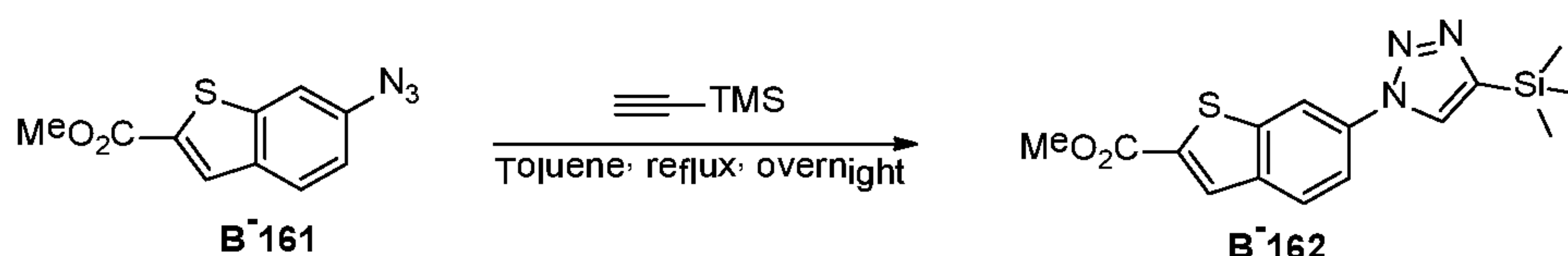
[00384] To a solution of **compound B-159** (1.1 g, 4.6 mmol) in ethanol (4 mL) and saturated NH_4Cl aqueous (2 mL) under nitrogen was added iron powder (1.3 g, 23 mmol). The reaction was stirred at room temperature for 5 hours. On completion, the mixture was concentrated, and the product was purified by silica gel chromatography [petroleum ether: ethyl acetate = 6:1] to give **compound B-160** (0.65 g, 87% yield) as a pale yellow solid.

[00385] **Example 60B:** methyl 6-azidobenzo[b]thiophene-2-carboxylate (**B-161**)



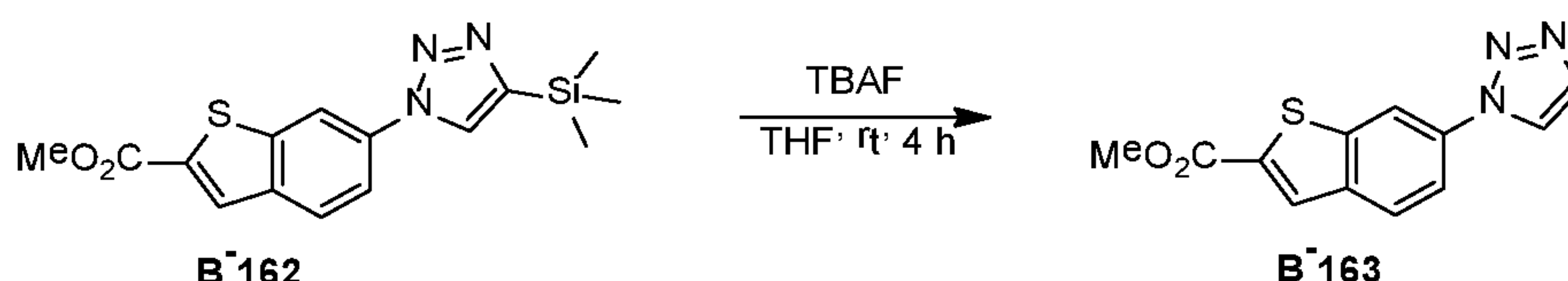
[00386] To a solution of **compound B-160** (0.65 g, 3 mmol) in tetrahydrofuran (2 mL) at 0 °C was added dropwise tert-butyl nitrite (1.8 g, 17 mmol). The mixture was stirred for 5 minutes. Azidotrimethylsilane (0.82 g, 7.1 mmol) was then added dropwise. The mixture stirred at 0 °C for 30 minutes and at room temperature for 2.5 hours. On completion, the reaction mixture was concentrated, and the product was purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-161** (0.45 g, 62% yield) as a pale yellow solid.

[00387] **Example 61B:** methyl 6-(4-trimethylsilyl-1H-1,2,3-triazol-1-yl)benzothiophene-2-carboxylate (**B-162**)



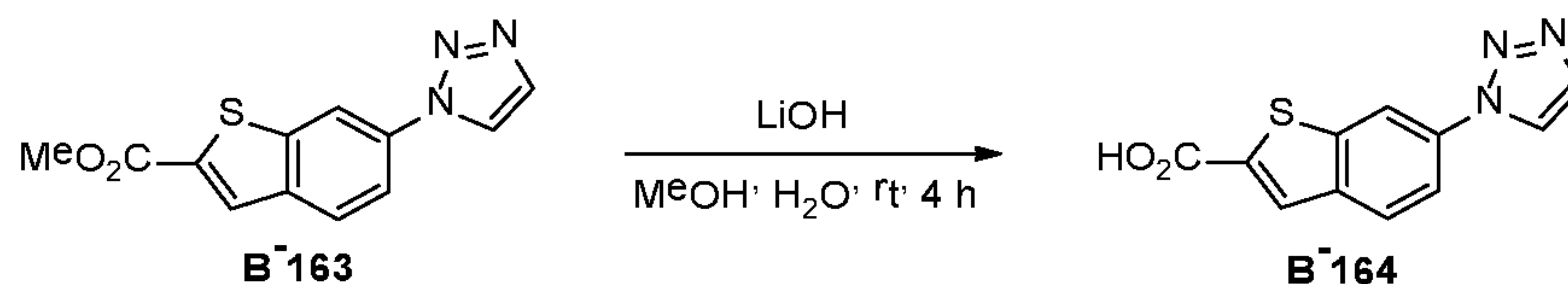
[00388] To a solution of **compound B-161** (0.38 g, 1.6 mmol) in toluene (10 mL) under nitrogen was added ethynyltrimethylsilane (0.18 g, 1.8 mmol). The reaction mixture was stirred at reflux overnight. On completion, the mixture was concentrated, and the residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 5:1] to give **compound B-162** (0.25 g, 45% yield) as light yellow solid.

[00389] **Example 62B:** methyl 6-(1H-1,2,3-triazol-1-yl)benzothiophene-2-carboxylate (**B-163**)



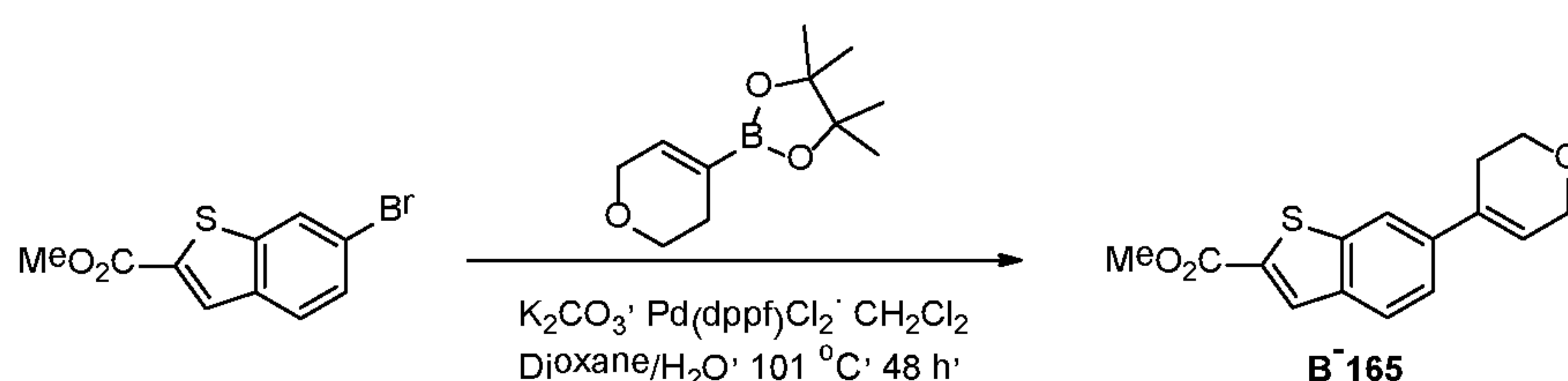
[00390] To a solution of **compound B-162** (0.25 g, 0.74 mmol) in tetrahydrofuran (2 mL) was added tetrabutylammonium fluoride (0.29 g, 1.1 mmol). The reaction mixture was stirred at room temperature for 4 hours. On completion, the reaction mixture was concentrated, and the residue was purified by recrystallization from ethanol to give **compound B-163** (0.19 g, 97 % yield) as a yellow solid.

[00391] **Example 63B:** 6-(1H-1,2,3-triazol-1-yl)benzothiophene-2-carboxylic acid (**B-164**)



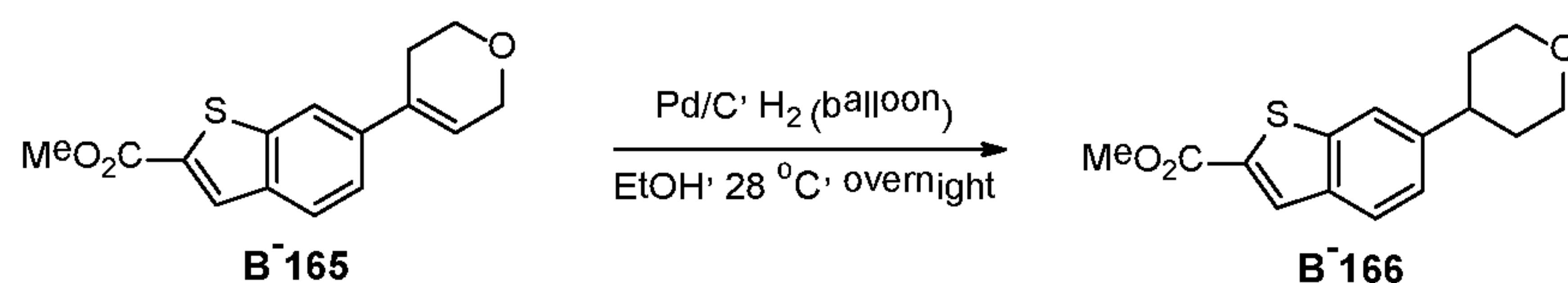
[00392] To a solution of **compound B-163** (0.19 g, 0.72 mmol) in methanol (5 mL) and water (2 mL) was added LiOH · H₂O (37 mg, 0.89 mmol). The mixture was stirred at room temperature for 4 hours. After evaporation of methanol, the aqueous phase was adjusted to pH 5~6 with 1N hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-164** (0.17 g, 97% yield) as a white solid: LCMS (E): t_R=1.003 min., (ES⁺) m/z (M+H)⁺ = 246.0.

[00393] **Example 64B:** methyl 6-(3,6-dihydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxylate (**B-165**)



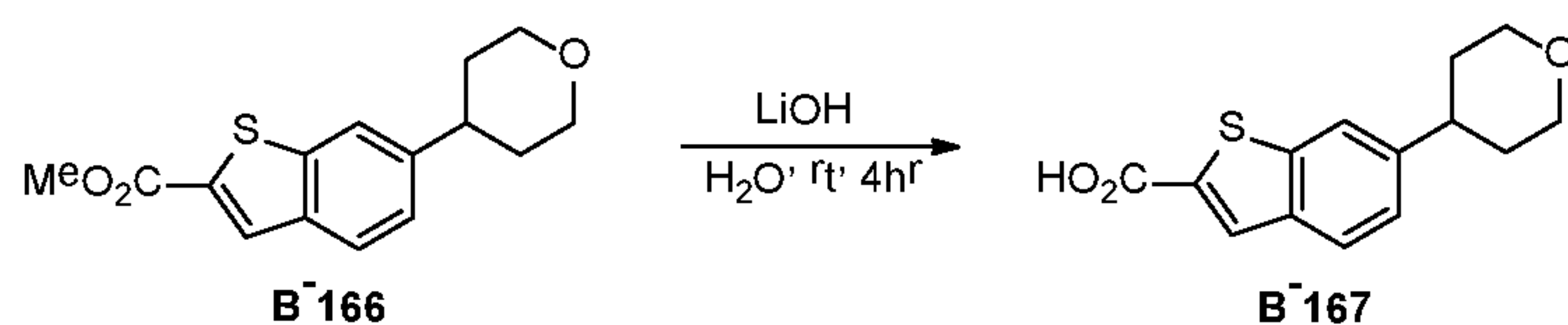
[00394] To a solution of methyl 6-bromobenzothiophene-2-carboxylate (1.0 g, 3.7 mmol) in dioxane (30 mL) and H₂O (6 mL) under nitrogen was added K₂CO₃ (1.5 g, 11 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (301 mg, 0.37 mmol) and 2-(3,6-dihydro-2*H*-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (930 mg, 4.4 mmol). The mixture was stirred at 101 °C for 48 hours. On completion, the reaction mixture was evaporated and purified by silica gel chromatography (petroleum ether: ethyl acetate = 16 : 1) to give compound **B-165** (300 mg, 60% yield) as a white solid. ¹H-NMR (CDCl₃, 400 MHz): δ 8.04 (s, 1H), 7.83 (d, J=8.4 Hz, 2H), 7.51-7.48 (m, 1H), 6.28 (d, J=1.6 Hz, 1H), 4.38-4.36 (m, 2H), 3.99-3.96 (m, 2H), 3.95 (s, 3H), 2.62-2.59 (m, 2H).

[00395] **Example 65B:** methyl 6-(tetrahydro-2*H*-pyran-4-yl)benzo[b]thiophene-2-carboxylate (**B-166**)

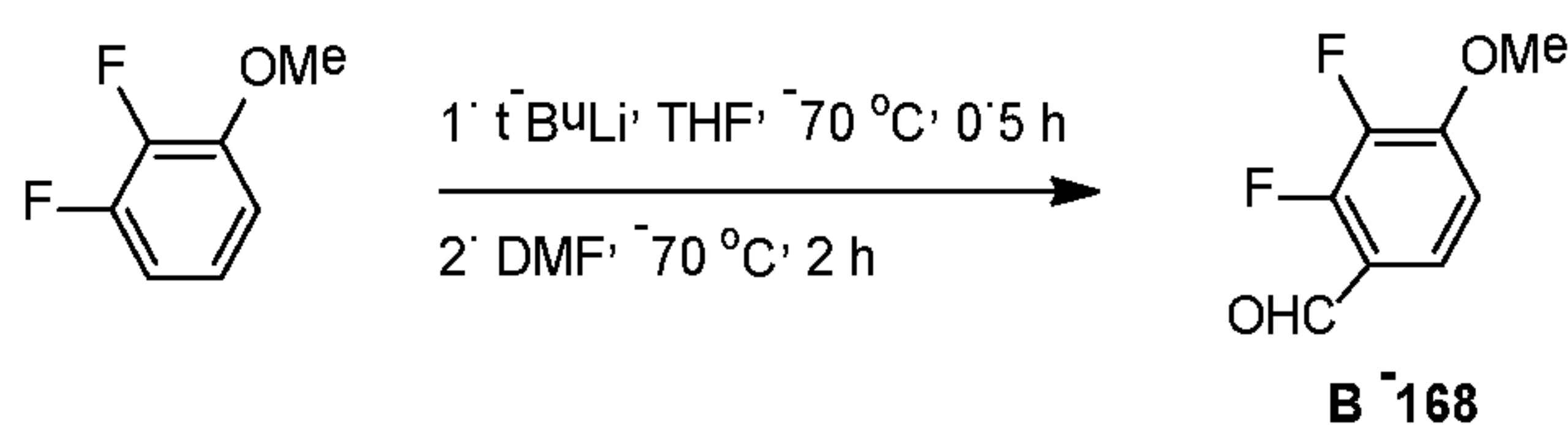


[00396] To a solution of **compound B-165** (300 mg, 1.1 mmol) in ethanol (8 mL) under nitrogen was added palladium/carbon (5%, 100 mg). The suspension was degassed in vacuo and purged with hydrogen several times. The mixture was stirred under hydrogen (balloon) at 28 °C overnight. On completion, the reaction mixture was filtered, and the filtrate was concentrated to give **compound B-166** (300 mg, 99% yield) as a white solid. ¹H-NMR (CDCl₃, 400 MHz): δ 8.03 (s, 1H), 7.82 (d, J=8 Hz, 2H), 7.71 (s, 1H), 7.29 (m, 1H), 4.14-4.10 (m, 2H), 3.95 (s, 3H), 3.60-3.54 (m, 2H), 2.90 (s, 1H), 2.91-2.85 (m, 4H).

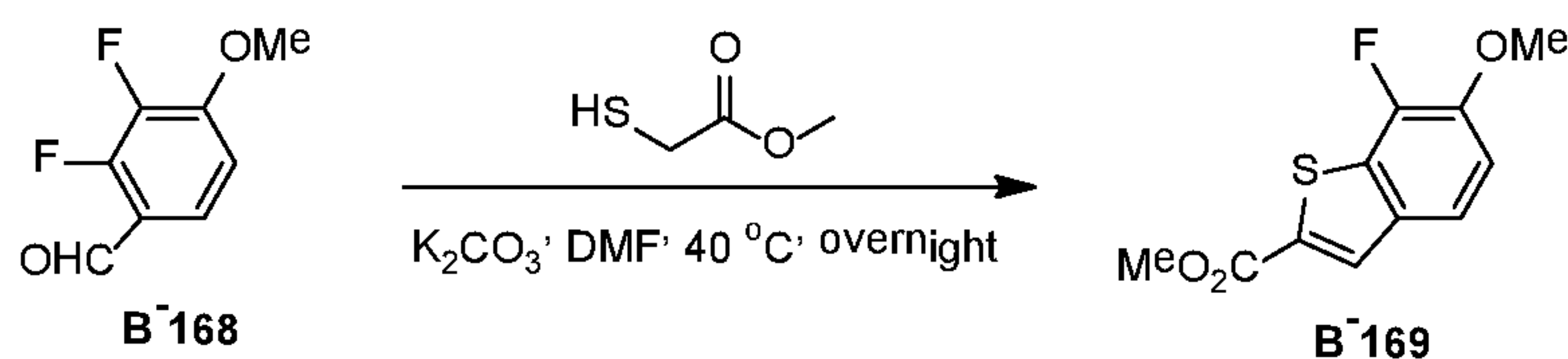
[00397] **Example 66B:** 6-(tetrahydro-2*H*-pyran-4-yl)benzo[b]thiophene-2-carboxylic acid (**B-167**)



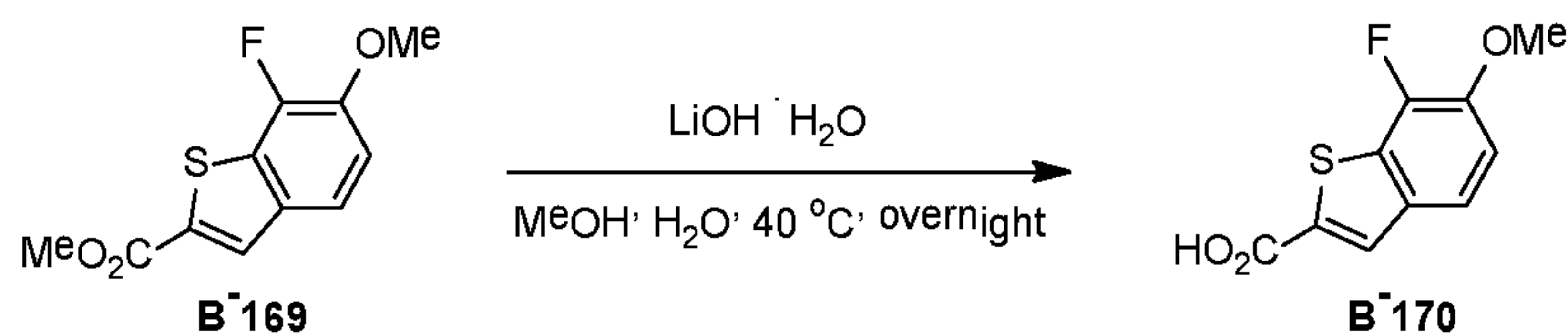
[00398] To compound **B-166** (0.3 g, 1.1 mmol) in methanol (8 mL) and water (4 mL) was added lithium hydroxide hydrate (78 mg, 1.87 mmol). The reaction was stirred at room temperature for 4 hours. On completion, the reaction mixture was adjusted to pH 5~6 with 4 N hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-167** (260 mg, 92%) as a white solid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.99 (s, 1H), 7.86 (d, J=8.4 Hz, 2H), 7.79 (s, 1H), 7.36-7.33 (m, 1H), 4.08-4.04 (m, 2H), 3.71-3.54 (m, 2H), 3.00-2.70 (m, 1H), 1.81-1.82 (m, 4H).

[00399] **Example 67B:** 2,3-difluoro-4-methoxybenzaldehyde (**B-168**)

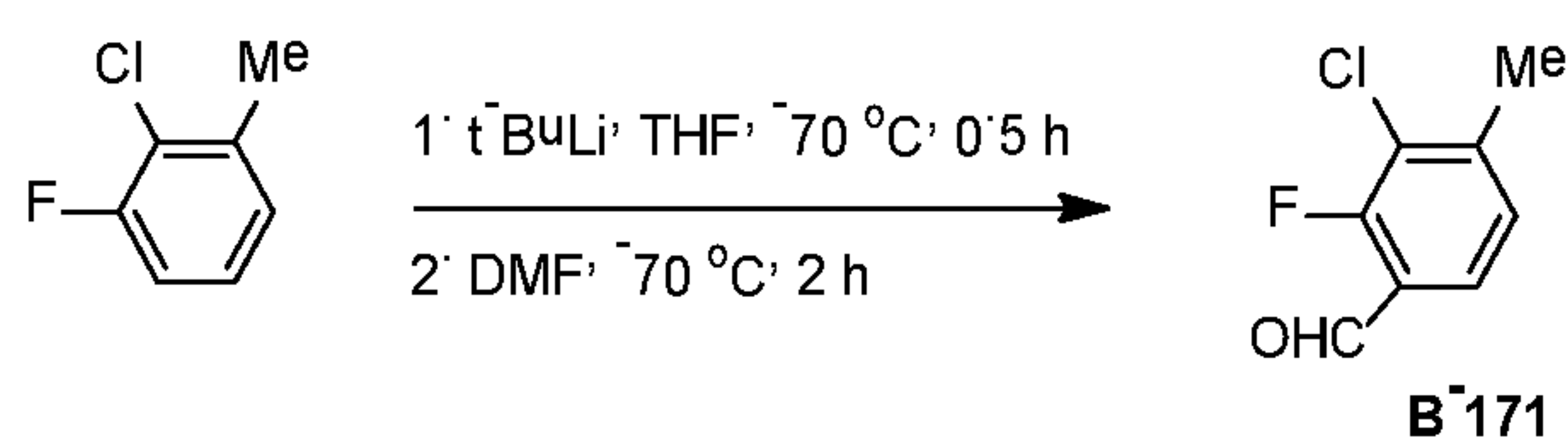
[00400] To a mixture of 1,2-difluoro-3-methoxybenzene (3.0 g, 21 mmol) in anhydrous tetrahydrofuran (40 mL) at -70 °C under nitrogen was added dropwise tert-butyllithium (19 mL, 25 mmol, 1.3 M in n-pentane). The mixture was stirred at this temperature for 30 minutes, then *N,N*-dimethylformamide (6.1 g, 83 mmol) was added dropwise at -70 °C. The reaction was stirred at -70 °C for another 2 hours. On completion, the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-168** (4.0 g, crude) as a yellow solid. LCMS (B): tR=0.661 min., (ES⁺) m/z (M+H)⁺ = 173.1.

[00401] **Example 68B:** methyl 7-fluoro-6-methoxybenzo[b]thiophene-2-carboxylate (**B-169**)

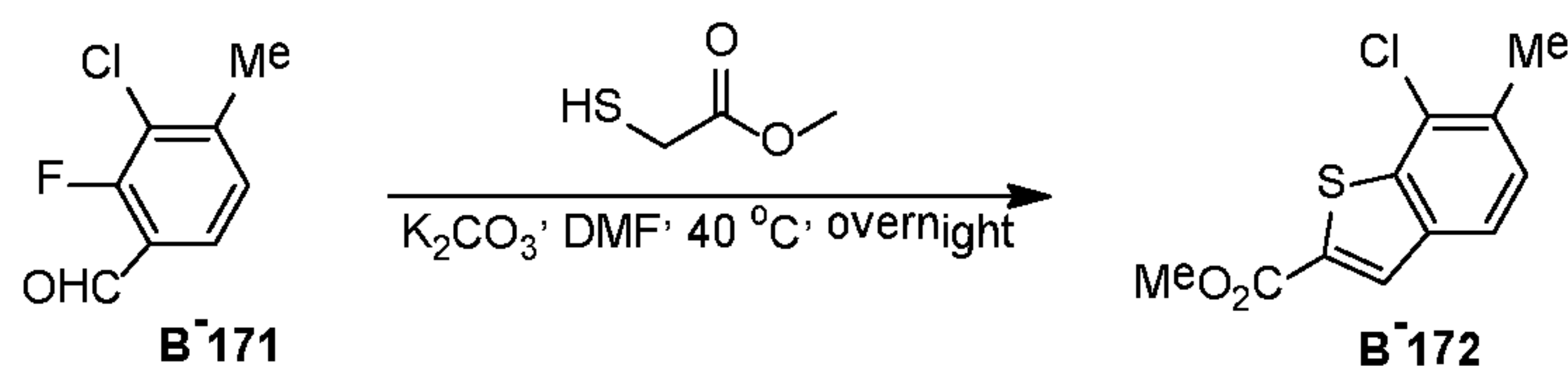
[00402] To a mixture of **compound B-168** (4.0 g, 23 mmol) in *N,N*-dimethylformamide (60 mL) was added methyl 2-mercaptoacetate (2.5 g, 23 mmol) and potassium carbonate (3.9 g, 28 mmol). The mixture was stirred at 40 °C overnight. On completion, the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-169** (4.0 g, 72% yield) as a white solid. LCMS (B): tR=0.869 min., (ES⁺) m/z (M+H)⁺ = 241.0.

[00403] **Example 69B:** 7-fluoro-6-methoxybenzo[b]thiophene-2-carboxylic acid (**B-170**)

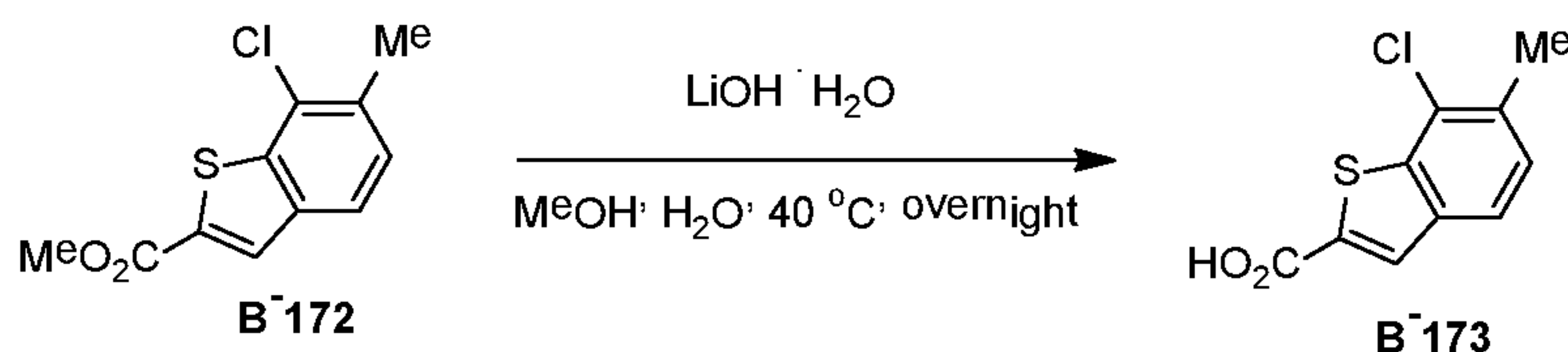
[00404] To a mixture of **compound B-169** (2.5 g, 10 mmol) in methanol (14 mL) and water (7 mL) was added lithium hydroxide monohydrate (0.87 g, 21 mmol). The mixture was stirred at 40 °C overnight. On completion, the mixture was concentrated to remove methanol, diluted with water and adjusted to pH 3 with 1 M hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-170** (2.0 g, 85% yield) as a white solid. LCMS (B): tR=0.739 min., (ES⁺) m/z (M+H)⁺ = 227.1.

[00405] Example 70B: 3-chloro-2-fluoro-4-methylbenzaldehyde (B-171)

[00406] To a mixture of 2-chloro-1-fluoro-3-methylbenzene (1.0 g, 6.9 mmol) in anhydrous tetrahydrofuran (15 mL) at $-70\text{ }^\circ\text{C}$ under nitrogen was added dropwise tert-butyllithium (6.4 mL, 8.3 mmol, 1.3 M in n-pentane). The mixture was stirred at this temperature for 30 minutes, and then *N,N*-dimethylformamide (2.0 g, 28 mmol) was added dropwise at $-70\text{ }^\circ\text{C}$. The reaction was stirred at $-70\text{ }^\circ\text{C}$ for another 2 hours. On completion, the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-171** (1.5 g, crude) as a yellow solid. LCMS (B): $t_R=0.797\text{ min.}$, $(\text{ES}^+) m/z (\text{M}+\text{H})^+ = 173.1$.

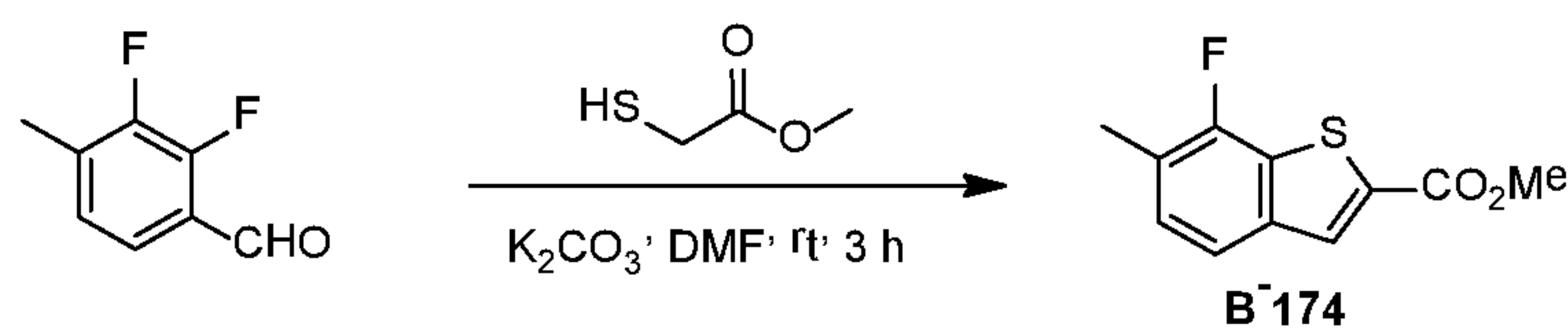
[00407] Example 71B: methyl 7-chloro-6-methylbenzo[b]thiophene-2-carboxylate (B-172)

[00408] To a solution of **compound B-171** (1.5 g, 8.7 mmol) in *N,N*-dimethylformamide (15 mL) was added methyl 2-mercaptoacetate (0.92 g, 8.7 mmol) and potassium carbonate (1.4 g, 10 mmol). The mixture was stirred at $40\text{ }^\circ\text{C}$ overnight. On completion, the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-172** (1.2 g, 57% yield) as a white solid. LCMS (B): $t_R=0.953\text{ min.}$, $(\text{ES}^+) m/z (\text{M}+\text{H})^+ = 241.0$.

[00409] Example 72B: 7-chloro-6-methylbenzo[b]thiophene-2-carboxylic acid (B-173)

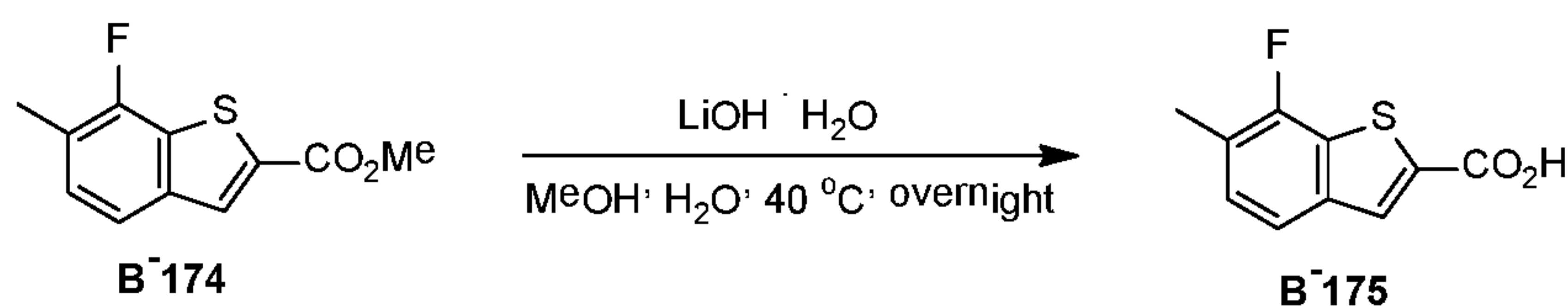
[00410] To a mixture of **compound B-172** (0.6 g, 2.5 mmol) in methanol (14 mL) and water (7 mL) was added lithium hydroxide monohydrate (0.21 g, 5.0 mmol). The mixture was stirred at $40\text{ }^\circ\text{C}$ overnight. On completion, the mixture was concentrated to remove methanol, diluted with water and adjusted to $\text{pH} = 3$ with 1 M hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-173** (0.50 g, 89% yield) as a white solid. LCMS (A): $t_R=0.842\text{ min.}$, $(\text{ES}^+) m/z (\text{M}+\text{H})^+ = 227.0$.

[00411] **Example 73B:** methyl 7-fluoro-6-methylbenzo[b]thiophene-2-carboxylate (**B-174**)



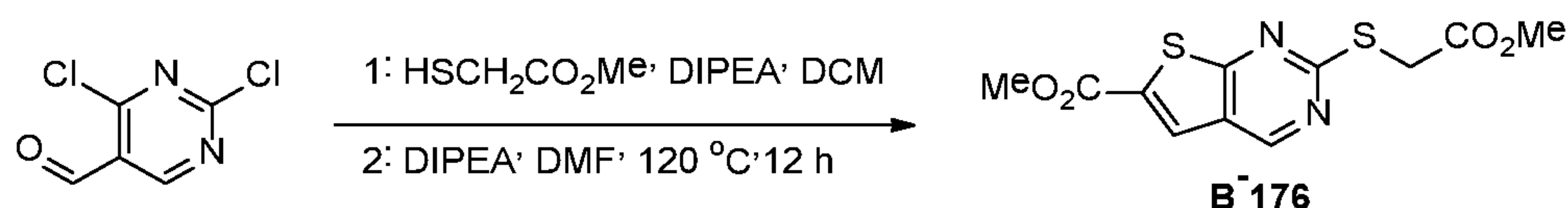
[00412] To a mixture of 2,3-difluoro-4-methylbenzaldehyde (1 g, 6.4 mmol) in *N,N*-dimethylformamide (40 mL) was added methyl 2-mercaptoacetate (0.68 g, 6.4 mmol) and potassium carbonate (1.06 g, 7.68 mmol). The mixture was stirred at room temperature for 3 hours. On completion, the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-174** (0.85 g, 59% yield) as a white solid. LCMS (B): *t*R=0.918 min., (ES⁺) *m/z* (M+H)⁺ = 225.1.

[00413] **Example 74B:** 7-fluoro-6-methylbenzo[b]thiophene-2-carboxylic acid (**B-175**)



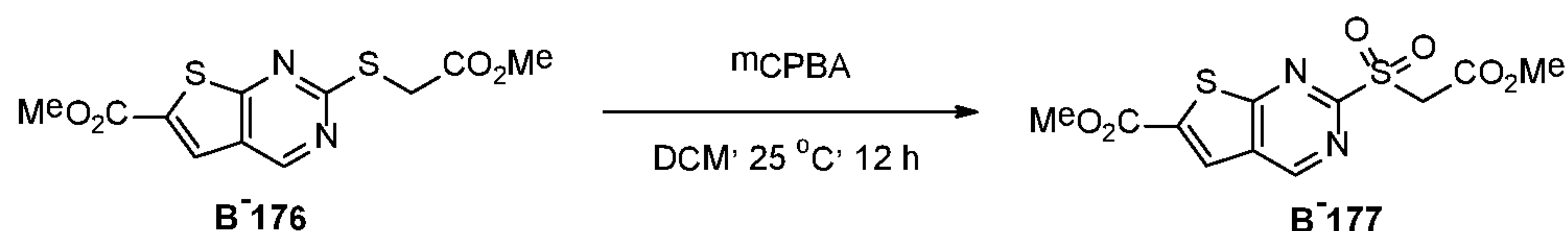
[00414] To a mixture of **compound B-174** (0.45 g, 2.0 mmol) in methanol (8 mL) and water (4 mL) was added lithium hydroxide monohydrate (0.13 g, 3.0 mmol). The mixture was stirred at 40 °C overnight. On completion, the mixture was concentrated to remove methanol, diluted with water, and adjusted to pH = 3 with 1 M hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-175** (0.35 g, 83% yield) as a white solid.

[00415] **Example 75B:** methyl 2-((2-methoxy-2-oxoethyl)thio)thieno[2,3-d]pyrimidine-6-carboxylate (**B-176**)



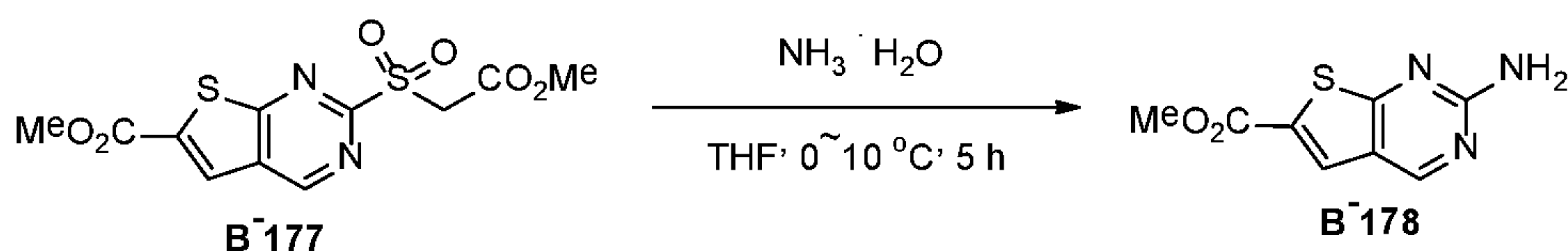
[00416] To a solution of 2,4-dichloropyrimidine-5-carbaldehyde (0.22 g, 1.2 mmol) in dichloromethane (30 mL) under nitrogen was added diisopropylethylamine (0.16 g, 1.2 mmol). Then a solution of methyl 2-sulfanylacetate (0.26 g, 2.5 mmol) in dichloromethane (15 mL) was added dropwise over 10 min. The resulting solution was stirred at room temperature for 2 hours. On completion, the mixture was diluted with water (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was dissolved in *N,N*-dimethylformamide (40 mL), and diisopropylethylamine (0.16 g, 1.2 mmol) was added. The resulting solution was heated to 120 °C for 1.5 hours. On completion, the mixture was concentrated, and the residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 5:1] to give **compound B-176** (0.12 g, 32% yield) as a white solid.

[00417] **Example 76B:** methyl 2-((2-methoxy-2-oxoethyl)sulfonyl)thieno[2,3-d]pyrimidine-6-carboxylate (**B-177**)



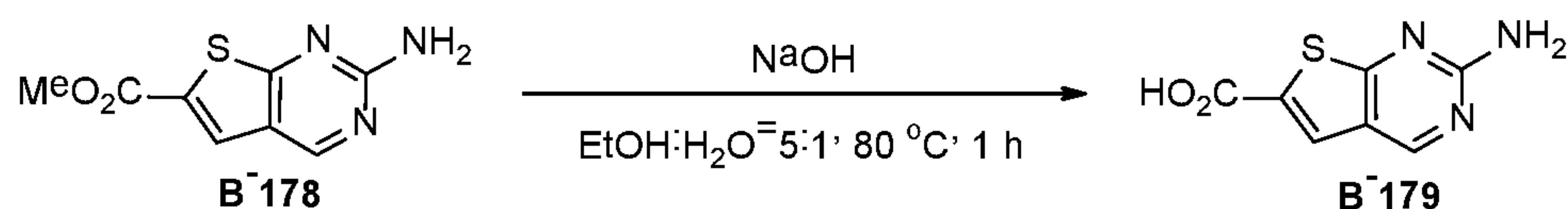
[00418] To a solution of **compound B-176** (0.60 g, 2.0 mmol) in dichloromethane (40 mL) was added m-chloroperoxybenzoic acid (1.0 g, 6.0 mmol). The resulting mixture was stirred at 25 °C for 12 hours. On completion, the mixture was quenched with sodium thiosulfate, washed with water and concentrated. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 2:1] to give **compound B-177** (0.36 g, 54% yield) as a white solid.

[00419] **Example 77B:** methyl 2-aminothieno[2,3-d]pyrimidine-6-carboxylate (**B-178**)



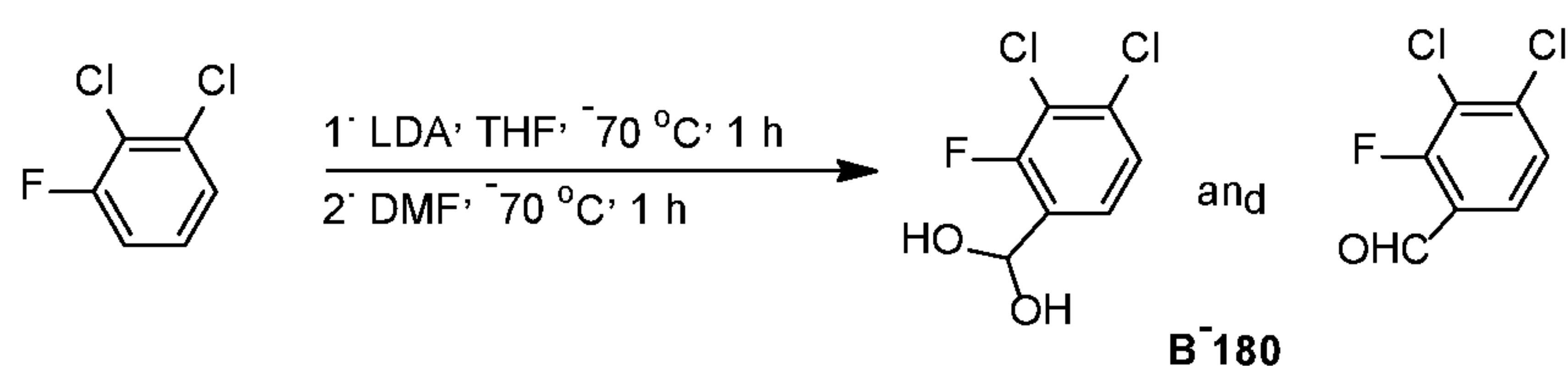
[00420] To a solution of **compound B-177** (0.30 g, 0.91 mmol) in tetrahydrofuran (20 mL) at 0 °C was added aqueous ammonia (9.1 g, 0.26 mol) dropwise. The mixture was stirred at 10 °C for 5 hours, then diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 0:1] to give **compound B-178** (0.12 g, 63% yield) as a yellow solid.

[00421] **Example 78B:** 2-aminothieno[2,3-d]pyrimidine-6-carboxylic acid (**B-179**)



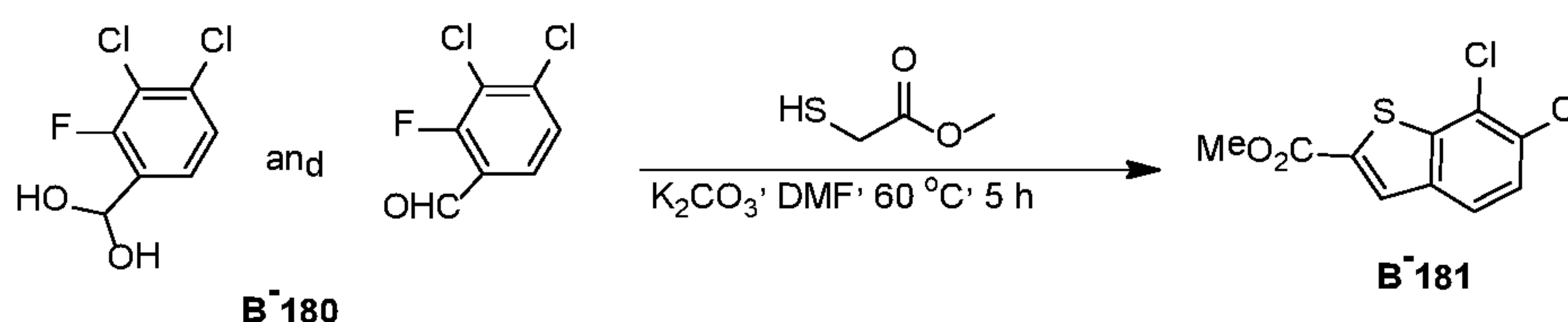
[00422] To a solution of **compound B-178** (60 mg, 0.29 mmol) in ethanol (5 mL) and water (1 mL) was added sodium hydroxide (57 mg, 1.4 mmol). The mixture was stirred at 80 °C for 1 h, then concentrated to remove ethanol, diluted with water, acidified to pH 1 with hydrochloric acid and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-179** (60 mg, crude) as a yellow solid.

[00423] **Example 79B:** (3, 4-dichloro-2-fluorophenyl)methanediol and 3,4-dichloro-2-fluorobenzaldehyde (**B-180**)



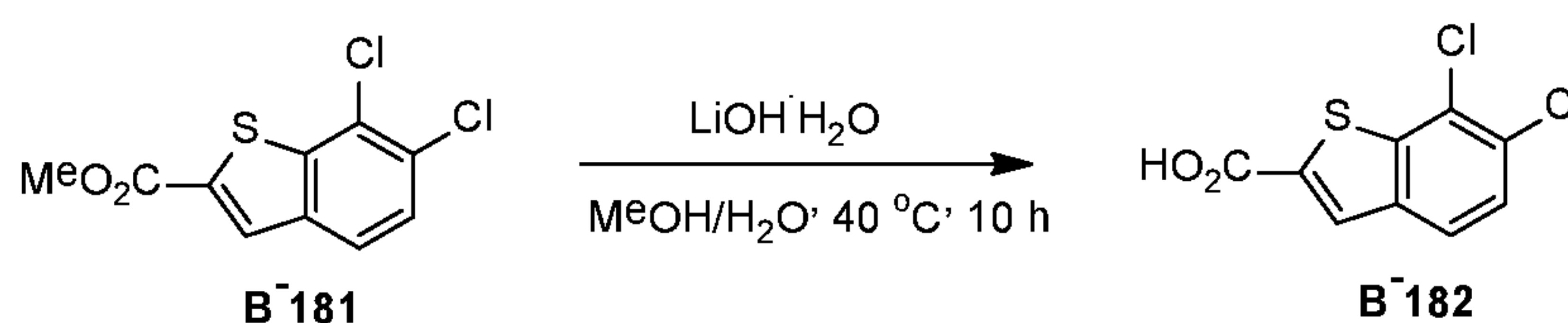
[00424] To a mixture of 1,2-dichloro-3-fluorobenzene (0.5 g, 3.0 mmol) in anhydrous tetrahydrofuran (10 mL) at -70 °C under nitrogen was added dropwise 2 M lithium diisopropylamide (2.0 M in tetrahydrofuran/n-heptane solution, 2.3 mL, 4.6 mmol). The mixture was stirred at -70 °C for 1 hour, and *N,N*-dimethylformamide (0.3 g, 3.6 mmol) was added dropwise. The reaction was stirred at -70 °C for another 1 hour. On completion, then quenched with saturated ammonium chloride solution (70 mL) at 0 °C and extracted with ethyl acetate (3 × 70 mL). The combined organic layers were washed with brine (6 × 15 mL), dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound mixture B-180** (335 mg, 5:1 ratio of hydrate to aldehyde by NMR) as a yellow solid. ¹H-NMR (CD₃OD, 400 MHz): δ 10.23 (s, 1H), 7.76-7.77 (m, 1H), 7.53 (t, J=8.0 Hz, 6H), 7.36 (d, J=8.4 Hz, 5H), 5.73 (s, 5H).

[00425] **Example 80B: methyl 6, 7-dichlorobenzo[*b*]thiophene-2-carboxylate (B-181)**

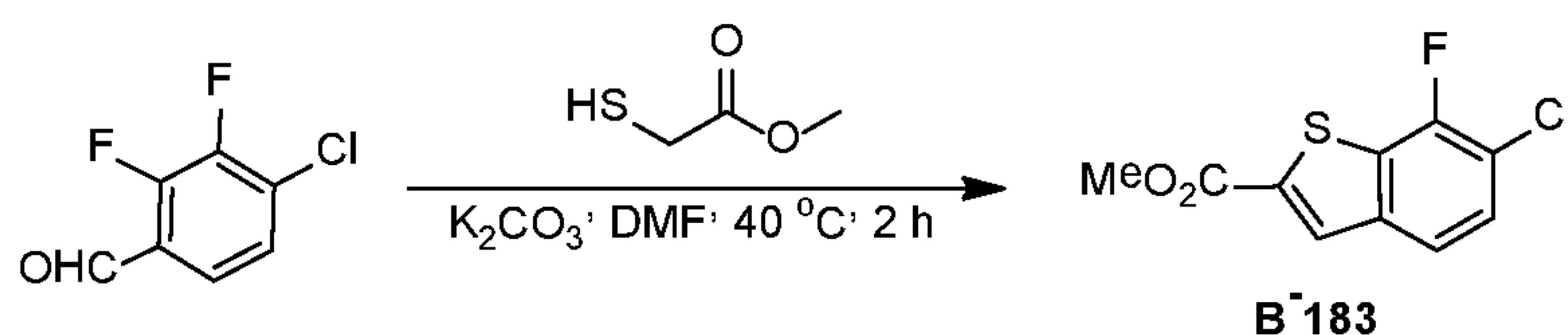


[00426] To a solution of **compound mixture B-180** (0.3 g, 1.4 mmol) in *N,N*-dimethylformamide (3 mL) was added potassium carbonate (0.4 g, 4.3 mmol) and methyl 2-mercaptoacetate (0.3 g, 2.8 mmol). The mixture was stirred at 60 °C for 5 hours, then diluted with water (40 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with saturated brine (6 × 5 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-181** (0.3 g, crude) as a white solid. ¹H-NMR (CD₃OD, 400 MHz): δ 8.13 (s, 1H), 7.88 (d, J=8.4 Hz, 1H), 7.59 (d, J=8.8 Hz, 1H), 3.95 (s, 3H).

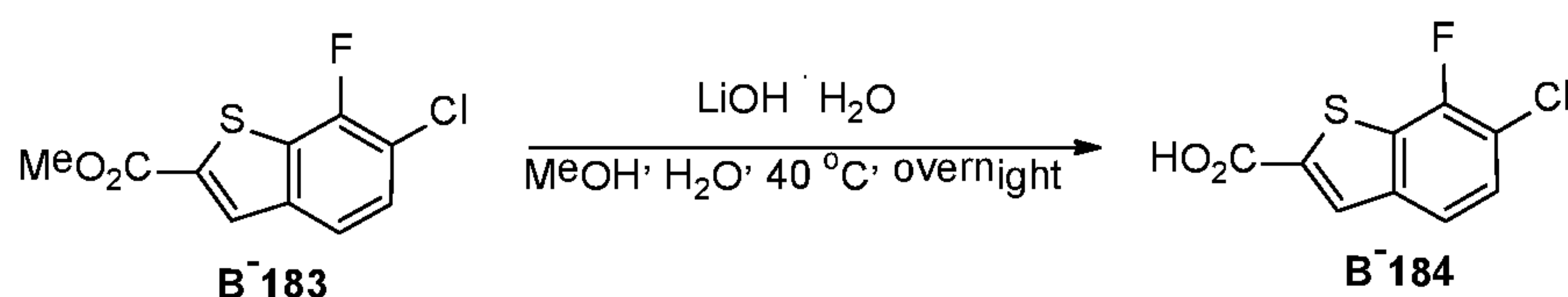
[00427] **Example 81B: 6, 7-dichlorobenzo[*b*]thiophene-2-carboxylic acid (B-182)**



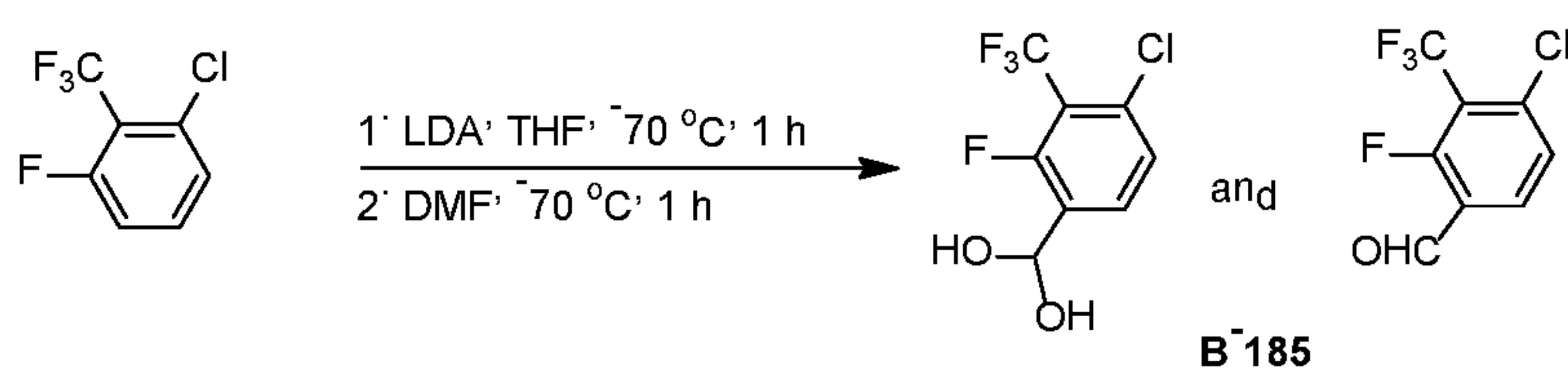
[00428] A mixture of **compound B-181** (0.3 g, 1.1 mmol) and lithium hydroxide monohydrate (0.24 g, 2.8 mmol) in methanol (5 mL) and water (2.5 mL) was stirred at 40 °C for 10 hours. The mixture was concentrated in vacuo, and the residue was added into water (50 mL). The aqueous phase was washed with ethyl acetate (2 × 10 mL), acidified to pH 2 with concentrated hydrochloric acid and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (3 × 10 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was washed with the *n*-hexane (3 × 2 mL) to give **compound B-182** (0.23 g, 81% yield) as a white solid. ¹H-NMR (CD₃OD, 400 MHz): 8.09 (s, 1H), 7.87 (d, J=7.6 Hz, 1H), 7.58 (d, J=7.2 Hz, 1H).

[00429] **Example 82B:** methyl 6-chloro-7-fluorobenzo[b]thiophene-2-carboxylate (**B-183**)

[00430] To a mixture of 4-chloro-2,3-difluorobenzaldehyde (1.0 g, 5.7 mmol) in *N,N*-dimethylformamide (15 mL) was added methyl 2-mercaptoacetate (0.60 g, 5.7 mmol) and potassium carbonate (1.6 g, 11 mmol). The mixture was stirred at 40 °C for 2 hours. On completion, the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, concentrated in vacuo and purified by silica gel chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-183** (1.2 g, 87% yield) as a white solid. LCMS (B): $t_R=0.930$ min., (ES⁺) m/z (M+H)⁺ = 245.0.

[00431] **Example 83B:** 6-chloro-7-fluorobenzo[b]thiophene-2-carboxylic acid (**B-184**)

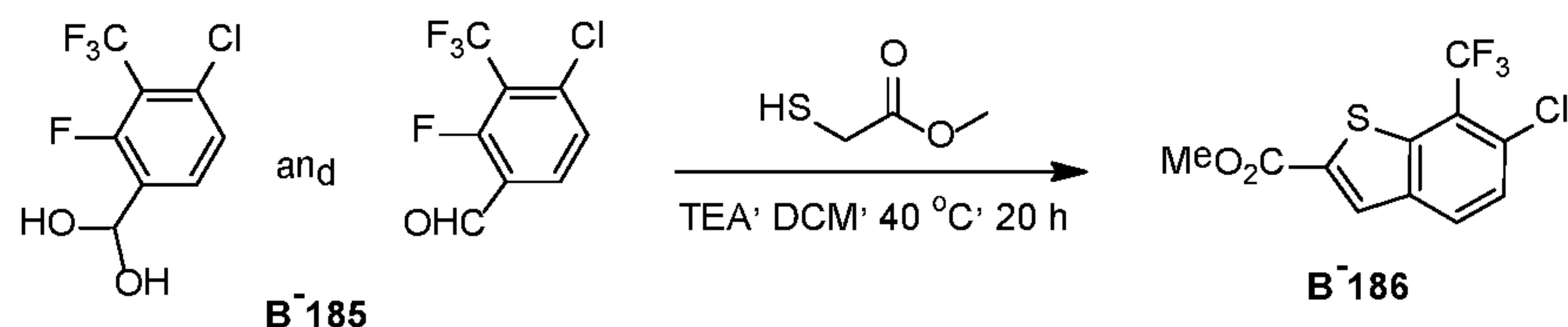
[00432] To a mixture of **compound B-183** (1.2 g, 4.9 mmol) in methanol (16 mL) and water (8 mL) was added lithium hydroxide monohydrate (0.41 g, 9.8 mmol). The mixture was stirred at 40 °C overnight. On completion, the mixture was concentrated to remove methanol, diluted with water and acidified to pH 3 with 1 M hydrochloric acid, resulting in formation of a solid. The white solid was collected by filtration and dried in vacuo to give **compound B-184** (0.70 g, 62% yield). LCMS (B): $t_R=0.829$ min., (ES⁺) m/z (M+H)⁺ = 231.0.

[00433] **Example 84B:** (4-chloro-2-fluoro-3-(trifluoromethyl)phenyl)methanediol and 4-chloro-2-fluoro-3-(trifluoromethyl)benzaldehyde (**B-185**)

[00434] To a mixture of 1-chloro-3-fluoro-2-(trifluoromethyl)benzene (2 g, 10 mmol) in anhydrous tetrahydrofuran (40 mL) at -70 °C under nitrogen was added dropwise 2 M lithium diisopropylamide (2.0 M in tetrahydrofuran/*n*-heptane, 7.6 mL, 15 mmol). The mixture was stirred for 1 hour, and then *N,N*-dimethylformamide (0.9 g, 12 mmol) was added dropwise at -70 °C. The reaction was stirred at -70 °C for another 1 hour, then quenched by addition of water (20 mL), acidified to pH 2 with concentrated hydrochloric acid at 0 °C, and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated brine (3 × 10 mL), dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give **compound**

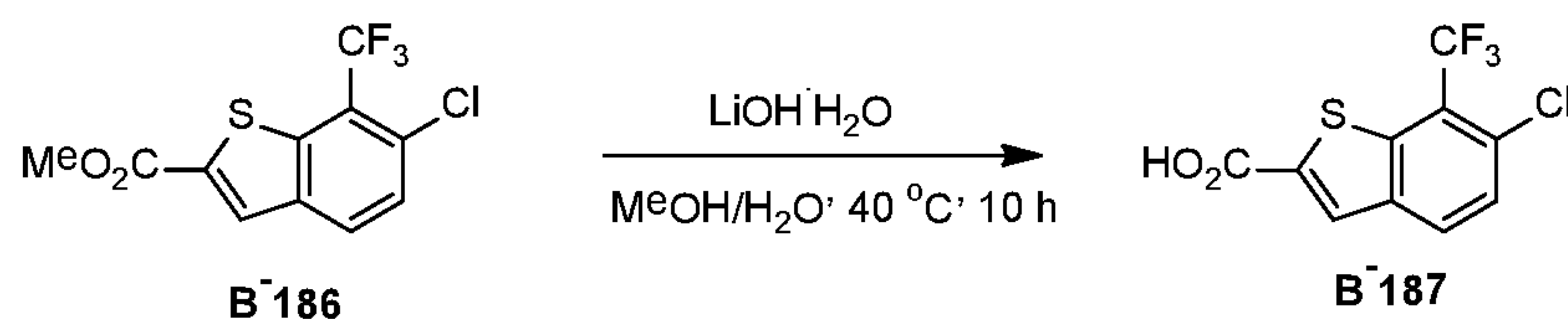
mixture B-185 (1.7 g, 11:1 ratio of hydrate:aldehyde) as a yellow solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 10.27 (s, 1H), 8.09-8.03 (m, 1H), 7.81 (t, $J=8.0$ Hz, 1H), 7.60 (d, $J=8.0$ Hz, 1H), 7.43 (d, $J=8.8$ Hz, 1H), 5.75 (s, 1H).

[00435] **Example 85B: methyl 6-chloro-7-(trifluoromethyl)benzo[*b*]thiophene-2-carboxylate (B-186)**



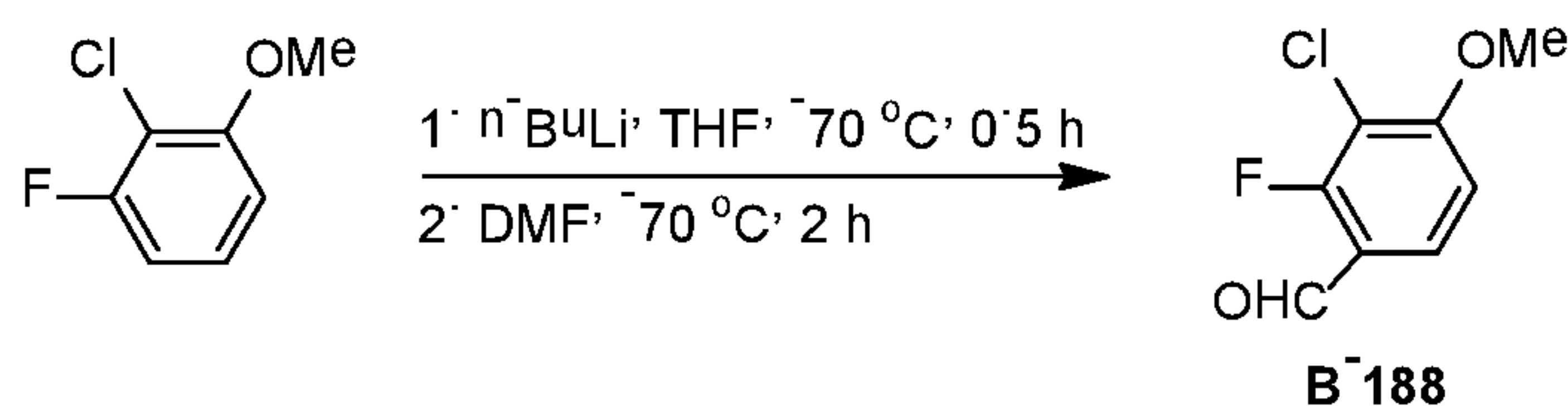
[00436] To a solution of **compound mixture B-185** (0.5 g, 2 mmol) in dichloromethane (5 mL) was added triethylamine (0.3 g, 3 mmol) and methyl 2-sulfanylacrylate (0.3 g, 3 mmol). The mixture was stirred at 40 °C for 20 hours, then diluted with water (40 mL) and extracted with ethyl acetate (3×40 mL). The combined organic layers were washed with brine (3×10 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-186** (0.4 g, 70% yield) as a white solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 8.14 (d, $J=6.4$ Hz, 2H), 7.65 (d, $J=8.4$ Hz, 1H), 3.96 (s, 3H).

[00437] **Example 86B: 6-chloro-7-(trifluoromethyl)benzo[*b*]thiophene-2-carboxylic acid (B-187)**



[00438] A mixture of **compound B-186** (0.40 g, 1.4 mmol) and lithium hydroxide monohydrate (0.40 g, 9.5 mmol) in methanol (8 mL) and water (4 mL) was stirred at 40 °C for 10 hours. The mixture was concentrated in vacuo, diluted with water (50 mL), acidified to pH 2 with concentrated hydrochloric acid, and extracted with ethyl acetate (3×50 mL). The combined organic phase was washed with brine (3×10 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo to give **compound B-187** (0.3 g, 81% yield) as a yellow solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): 8.16-8.11 (m, 2H), 7.66-7.63 (m, 1H).

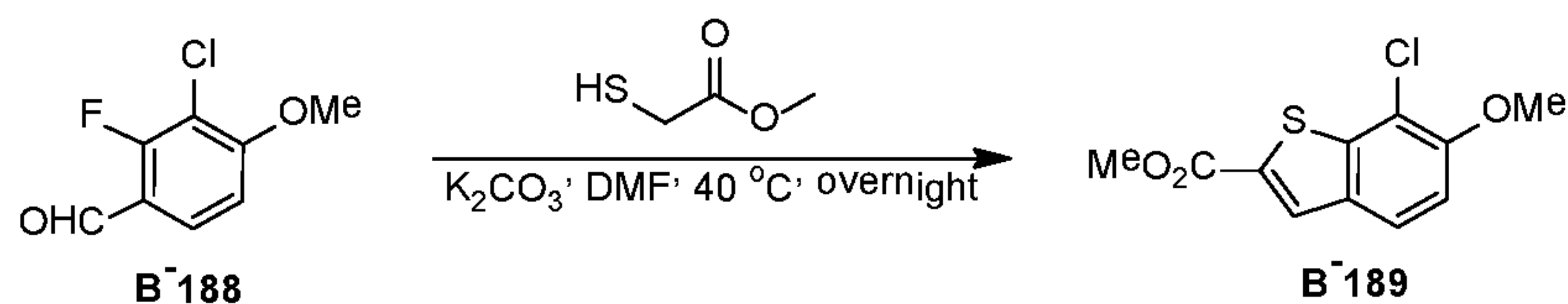
[00439] **Example 87B: 3-chloro-2-fluoro-4-methoxybenzaldehyde (B-188)**



[00440] To a mixture of 2-chloro-1-fluoro-3-methoxybenzene (1.0 g, 6.2 mmol) in anhydrous tetrahydrofuran (15 mL) at -70 °C under nitrogen was added dropwise *n*-butyllithium (2.5 M in *n*-hexane, 3.7 mL, 9.3 mmol). The mixture was stirred for 30 minutes, and *N,N*-dimethylformamide

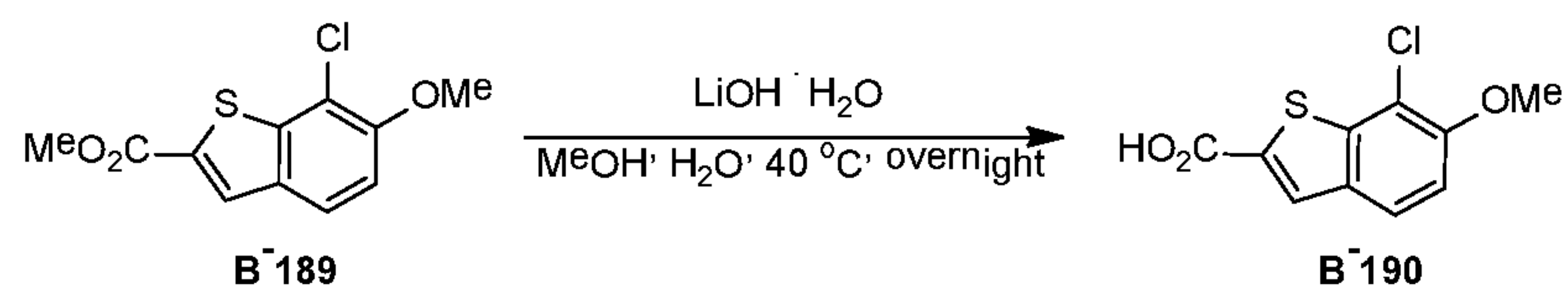
(0.91 g, 12 mmol) was added dropwise at -70 °C. The reaction was stirred at -70 °C for another 2 hours, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-188** (1.0 g, crude) as a white solid.

[00441] **Example 88B: methyl 7-chloro-6-methoxybenzo[b]thiophene-2-carboxylate (B-189)**



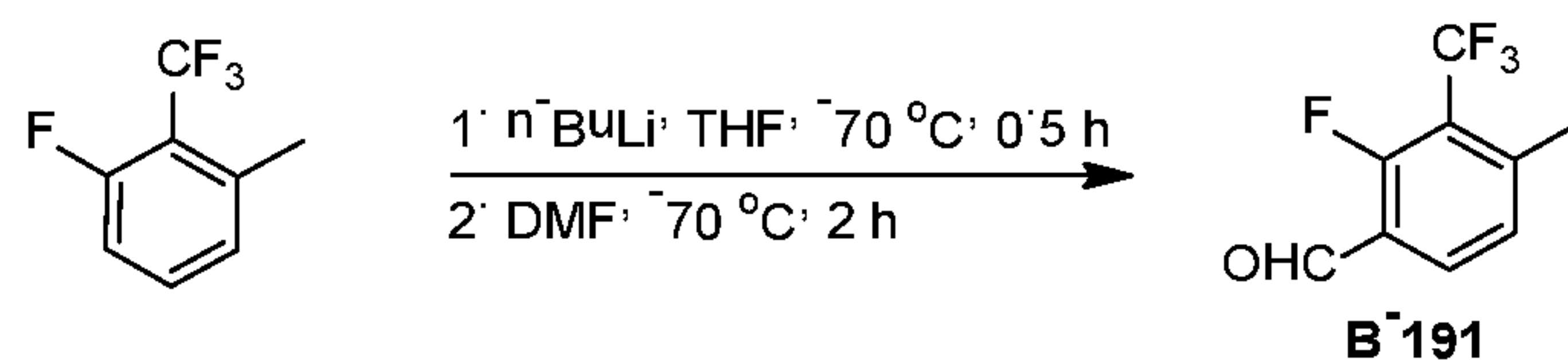
[00442] To a mixture of **compound B-188** (1.0 g, 5.3 mmol) in *N,N*-dimethylformamide (15 mL) was added methyl 2-mercaptoacetate (0.56 g, 5.3 mmol) and potassium carbonate (1.5 g, 11 mmol). The mixture was stirred at 40 °C overnight, then poured into ice water, resulting in formation of a solid. The white solid was collected by filtration and dried in vacuo to give **compound B-189** (1.1 g, 81% yield). LCMS (R): tR=1.121 min., (ES⁺) m/z (M+H)⁺ = 257.0.

[00443] **Example 89B: 7-chloro-6-methoxybenzo[b]thiophene-2-carboxylic acid (B-190)**



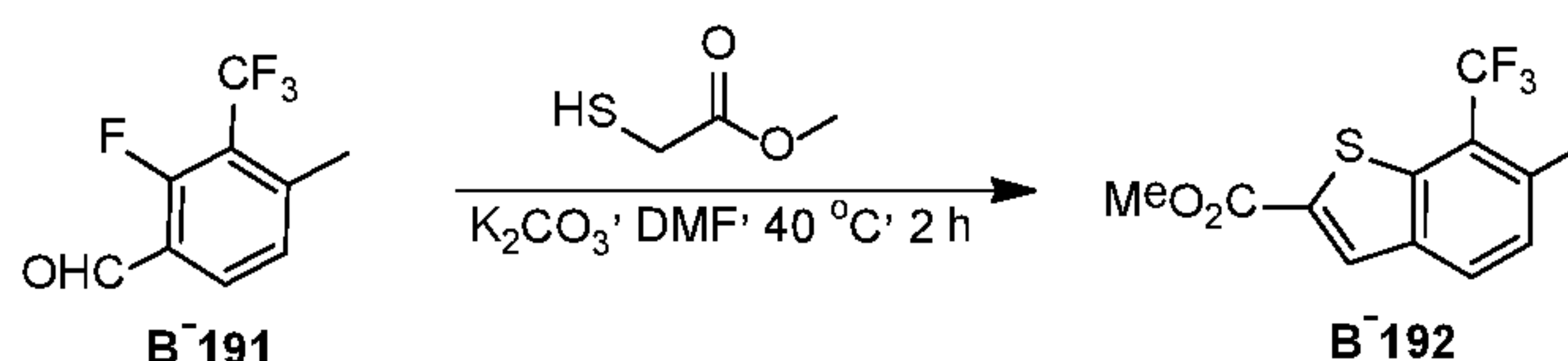
[00444] To a mixture of **compound B-189** (0.60 g, 2.3 mmol) in methanol (10 mL) and water (5 mL) was added lithium hydroxide monohydrate (0.20 g, 4.7 mmol). The mixture was stirred at 40 °C overnight, then concentrated to remove methanol, diluted with water and acidified to pH 3 with 1 M hydrochloric acid, resulting in formation of a solid. The white solid was collected by filtration and dried in vacuo to give **compound B-190** (0.50 g, 88% yield). LCMS (B): tR=0.765 min., (ES⁺) m/z (M+H)⁺ = 243.0.

[00445] **Example 90B: 2-fluoro-4-methyl-3-(trifluoromethyl)benzaldehyde (B-191)**



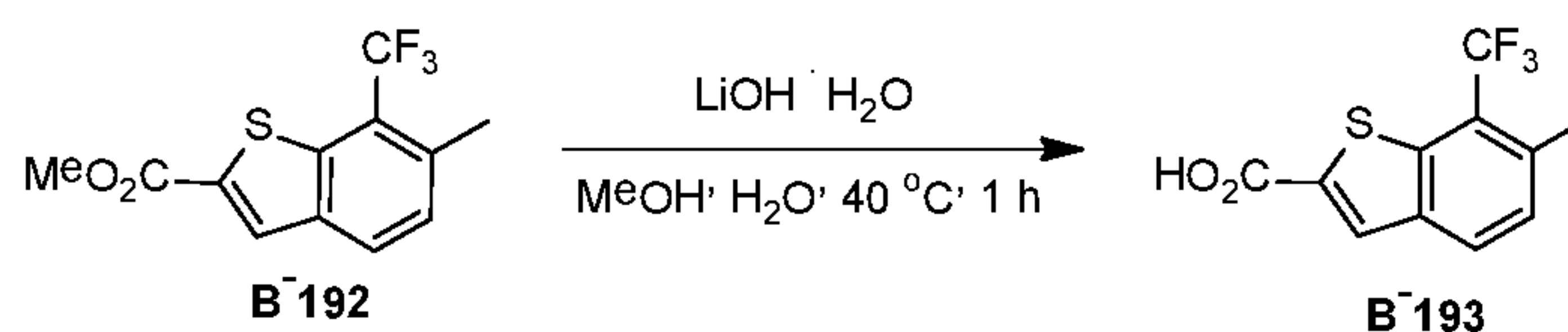
[00446] To a mixture of 1-fluoro-3-methyl-2-(trifluoromethyl)benzene (0.40 g, 2.3 mmol) in anhydrous tetrahydrofuran (5 mL) at -70 °C under nitrogen was added dropwise *n*-butyllithium (2.5 M in cyclohexane, 1.4 mL, 3.4 mmol). The mixture was stirred at this temperature for half an hour, and *N,N*-dimethylformamide (0.49 g, 6.8 mmol) was added dropwise. The reaction was stirred at -70 °C for another 2 hours, then acidified to pH 5.0 with 6 N HCl and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-191** (0.40 g, 86% yield) as yellow oil. LCMS (DD): tR=0.983 min., (ES⁺) m/z (M+H)⁺ = 207.0.

[00447] **Example 91B:** methyl 6-methyl-7-(trifluoromethyl)benzo[b]thiophene-2-carboxylate (**B-192**)



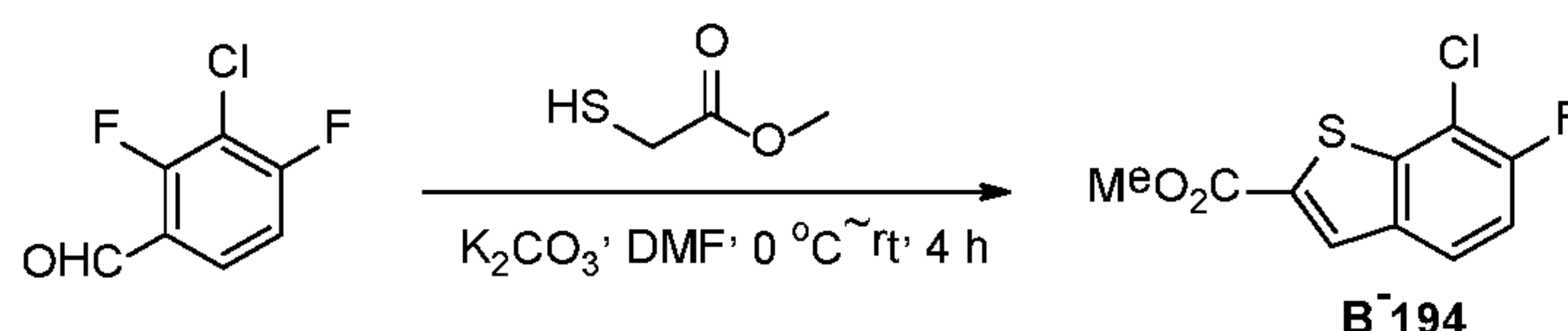
[00448] To a mixture of **compound B-191** (0.38 g, 1.8 mmol) in *N,N*-dimethylformamide (5 mL) was added methyl 2-mercaptoacetate (0.23 g, 2.2 mmol) and potassium carbonate (0.51 g, 3.7 mmol). The mixture was stirred at 40 °C for 2 hours, then poured into water (5 mL) and extracted with ethyl acetate (2 × 20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-192** (0.50 g, 95% yield) as a yellow solid. LCMS (DD): *t*R=1.157 min., (ES⁺) *m/z* (M+H)⁺=275.0.

[00449] **Example 92B:** 6-methyl-7-(trifluoromethyl)benzo[b]thiophene-2-carboxylic acid (**B-193**)



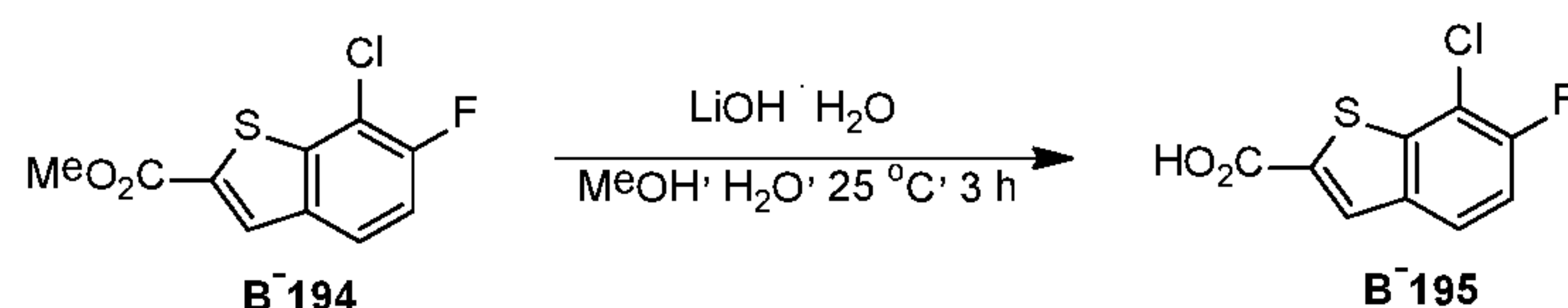
[00450] To a mixture of **compound B-192** (0.48 g, 1.8 mmol) in methanol (6 mL) and water (3 mL) was added lithium hydroxide monohydrate (0.15 g, 3.5 mmol). The mixture was stirred at 40 °C for 1 hour, then concentrated to remove methanol, diluted with water and acidified to pH 3 with 1 M hydrochloric acid, resulting in formation of a solid. The white solid was collected by filtration and dried in vacuo to give **compound B-193** (0.40 g, 88% yield). LCMS (DD): *t*R=1.009 min., (ES⁺) *m/z* (M+H)⁺=261.0.

[00451] **Example 93B:** methyl 7-chloro-6-fluorobenzo[b]thiophene-2-carboxylate (**B-194**)



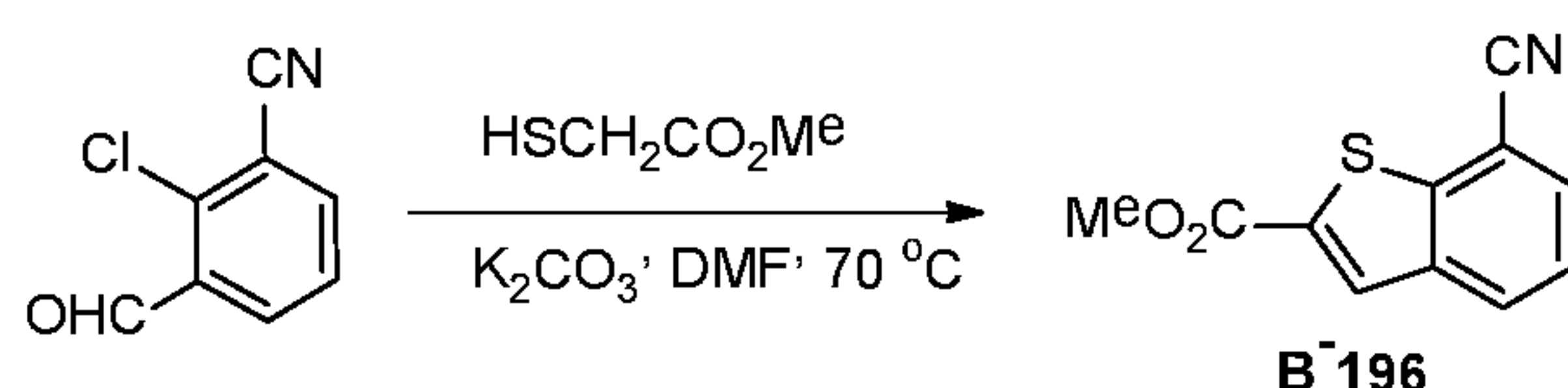
[00452] To a solution of 3-chloro-2,4-difluorobenzaldehyde (2.0 g, 11 mmol) and potassium carbonate (2.4 g, 17 mmol) in *N,N*-dimethylformamide (20 mL) at 0 °C was added dropwise methyl 2-mercaptoacetate (1.4 g, 14 mmol). The mixture was stirred at room temperature for 4 hours, then diluted with water (30 mL) and extracted with ethyl acetate (2 × 50 mL). The organic layer was concentrated in vacuo, and the residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-194** (1.6 g, 58% yield) as a yellow solid. LCMS (B): *t*R=0.912 min., (ES⁺) *m/z* (M+H)⁺=245.0.

[00453] **Example 94B: 7-chloro-6-fluorobenzo[b]thiophene-2-carboxylic acid (B-195)**



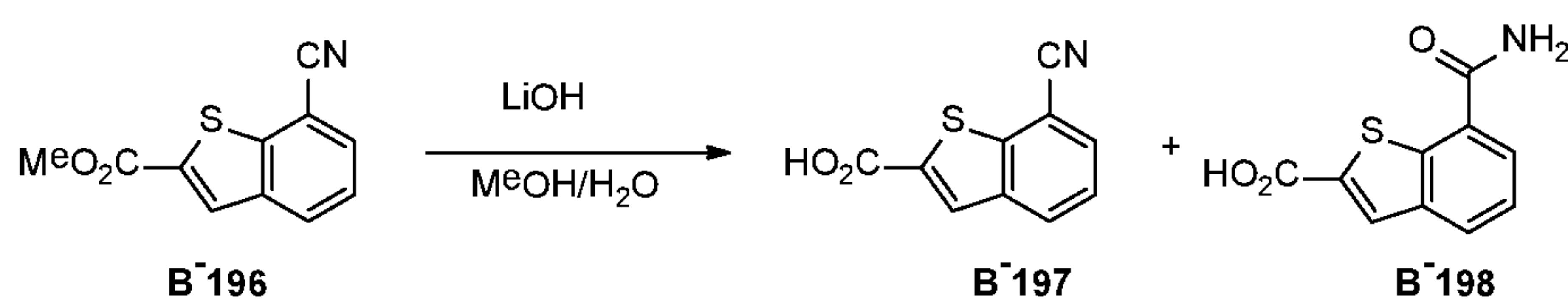
[00454] To a mixture of **compound B-194** (2.5 g, 10 mmol) in methanol (10 mL) and water (10 mL) was added lithium hydroxide monohydrate (0.82 g, 20 mmol). The mixture was stirred at 25 °C for 3 hours, then concentrated to remove methanol, diluted with water and acidified to pH 3 with 1 M hydrochloric acid, resulting in formation of a solid. The yellow solid was collected by filtration and dried in vacuo to give **compound B-195** (1.5 g, 64% yield).

[00455] **Example 95B: methyl 7-cyanobenzo[b]thiophene-2-carboxylate (B-196)**



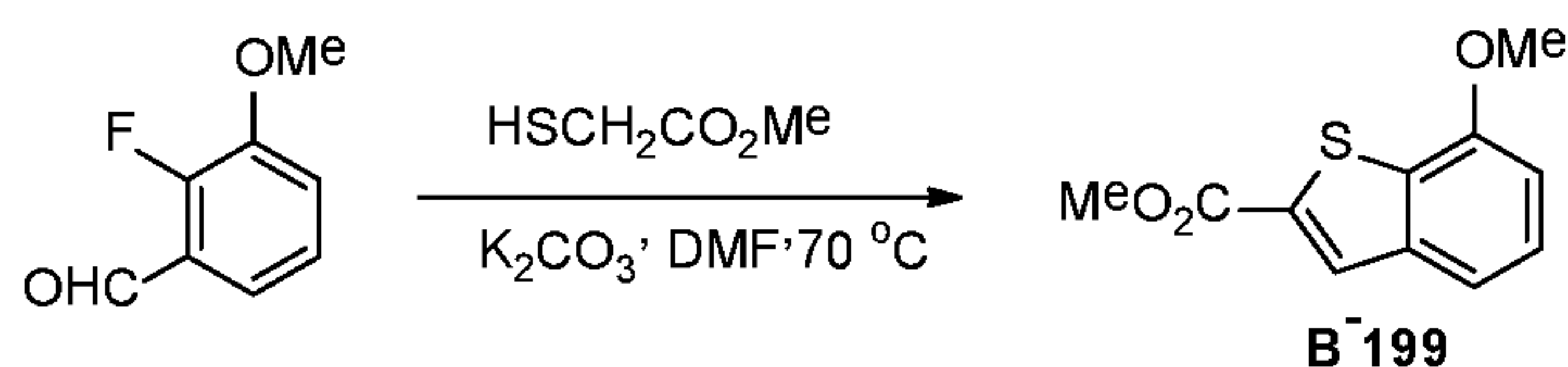
[00456] To a solution of 2-chloro-3-formylbenzonitrile (1.2 g, 7.3 mmol) and potassium carbonate (2.0 g, 15 mmol) in *N,N*-dimethylformamide (15 mL) at 28 °C was added methyl 2-mercaptoacetate (1.5 g, 15 mmol). The mixture was stirred overnight at 70 °C, then diluted with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-196** (0.98 g, 62% yield) as a yellow solid.

[00457] **Example 96B: 7-cyanobenzo[b]thiophene-2-carboxylic acid (B-197)**



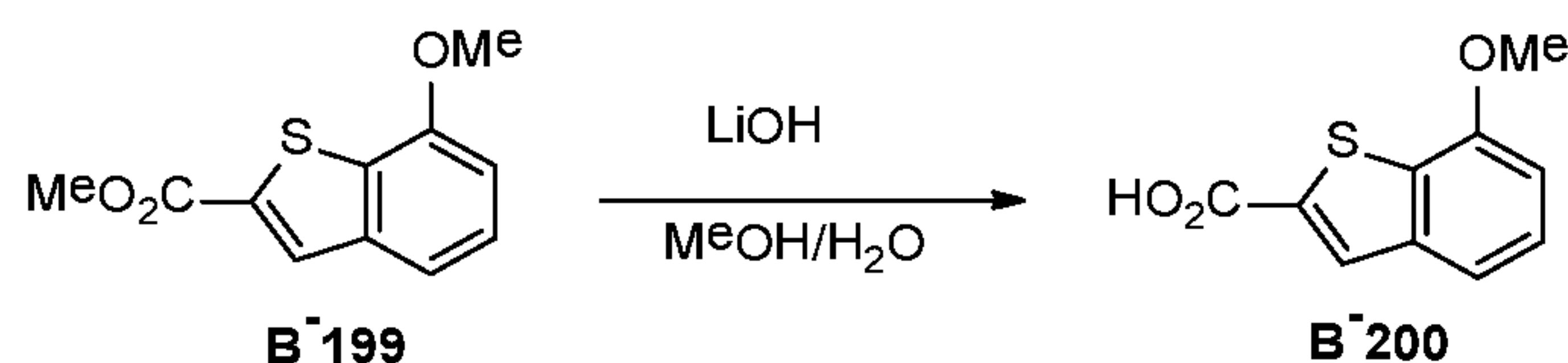
[00458] To a solution of **B-196** (0.98 g, 4.5 mmol) in methanol (10 mL) and water (2 mL) was added lithium hydroxide (0.38 g, 9.0 mmol) at room temperature. The mixture was stirred for 1 hour until TLC showed the reaction was complete. The solution was concentrated to remove most of methanol and acidified to pH 4~5, resulting in formation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-197** as a mixture with **compound B-198** (0.75 g) as a white solid.

[00459] **Example 97B: methyl 7-methoxybenzo[b]thiophene-2-carboxylate (B-199)**



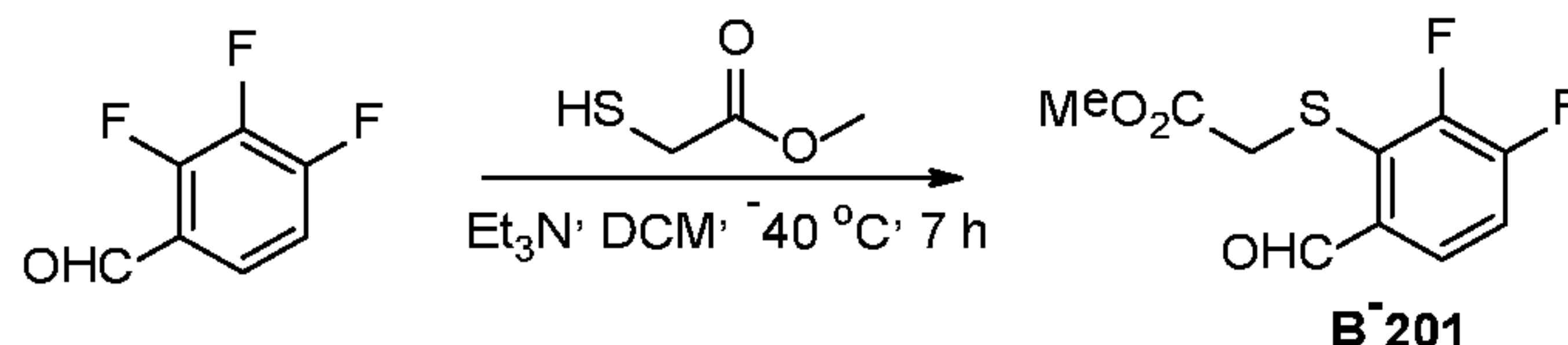
[00460] To a solution of 2-fluoro-3-methoxybenzaldehyde (2.0 g, 13 mmol) and potassium carbonate (3.6 g, 26 mmol) in *N,N*-dimethylformamide (20 mL) at 28 °C was added methyl 2-mercaptoacetate (1.7 g, 11 mmol). The mixture was stirred at 70 °C overnight, then diluted with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was then purified by silica gel column chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-199** (2.5 g, 89% yield) as a white solid.

[00461] **Example 98B: 7-methoxybenzo[b]thiophene-2-carboxylic acid (B-200)**



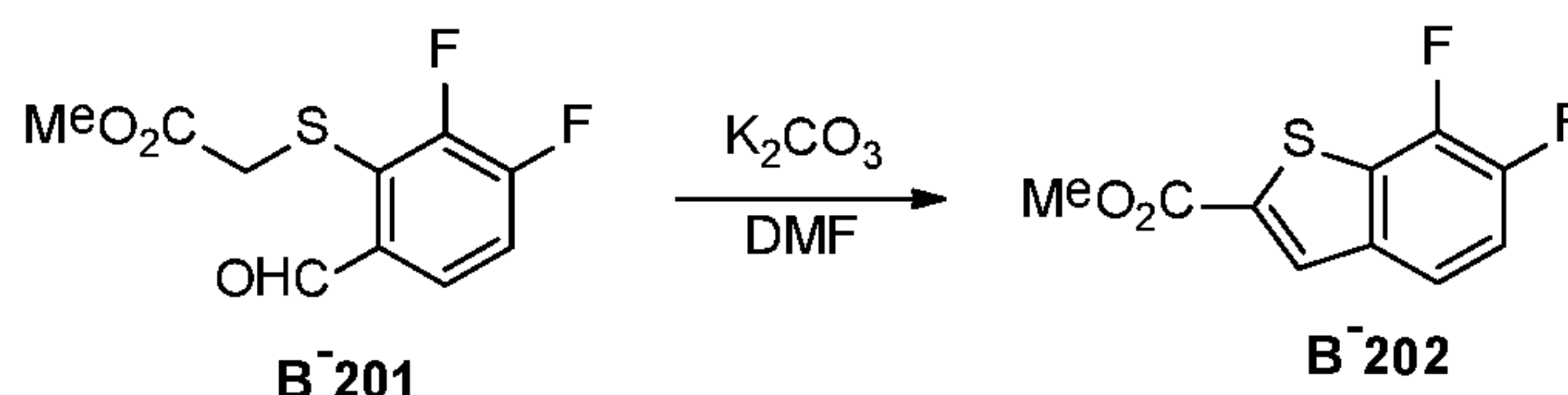
[00462] To a solution of **B-199** (1.0 g, 4.5 mmol) in methanol (10 mL) and water (2 mL) at room temperature was added lithium hydroxide (0.38 g, 9.0 mmol). The mixture was stirred for 2 hours, then concentrated to remove most of methanol and acidified to pH 4~5, resulting in formation of a solid. The white solid was collected by filtration and dried in vacuo to give **compound B-200** (0.85 g, 91% yield). ¹H-NMR (CD₃OD, 400 MHz): δ 8.04 (s, 1H), 7.53 (d, J=8.0 Hz, 1H), 7.40 (t, J=8.0 Hz, 1H), 7.01 (d, J=8.0 Hz, 1H), 4.03 (s, 3H).

[00463] **Example 99B: methyl 2-((2,3-difluoro-6-formylphenyl)thio)acetate (B-201)**



[00464] To a solution of 2,3,4-trifluorobenzaldehyde (1.00 g, 6.25 mmol) and methyl 2-sulfanylacetate (663 mg, 6.25 mmol) in dichloromethane (15 mL) at -40°C was added triethylamine (632 mg, 6.25 mmol). The reaction was stirred at this temperature for 7 hours, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-201** (0.25 g, 17% yield) as white as a white solid. LCMS (B): tR=0.735 min., (ES⁺) m/z (M+H)⁺=246.0.

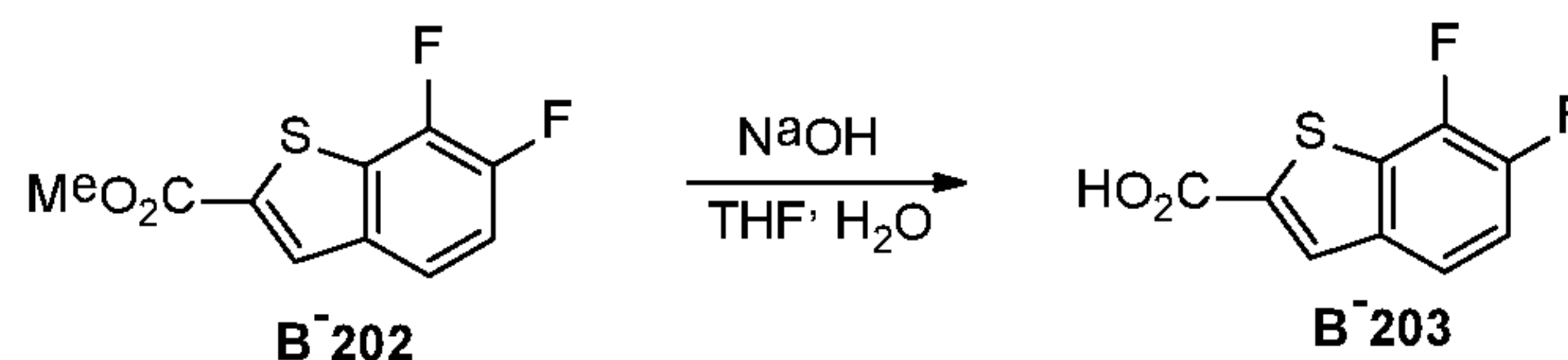
[00465] **Example 100B: methyl 6,7-difluorobenzo[b]thiophene-2-carboxylate (B-202)**



[00466] A mixture of **compound B-201** (100 mg, 0.41mmol) and potassium carbonate (56 mg, 0.41 mmol) in *N,N*-dimethylformamide (5.0 mL) was stirred at 50 °C for 16 hrs. On completion, the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over

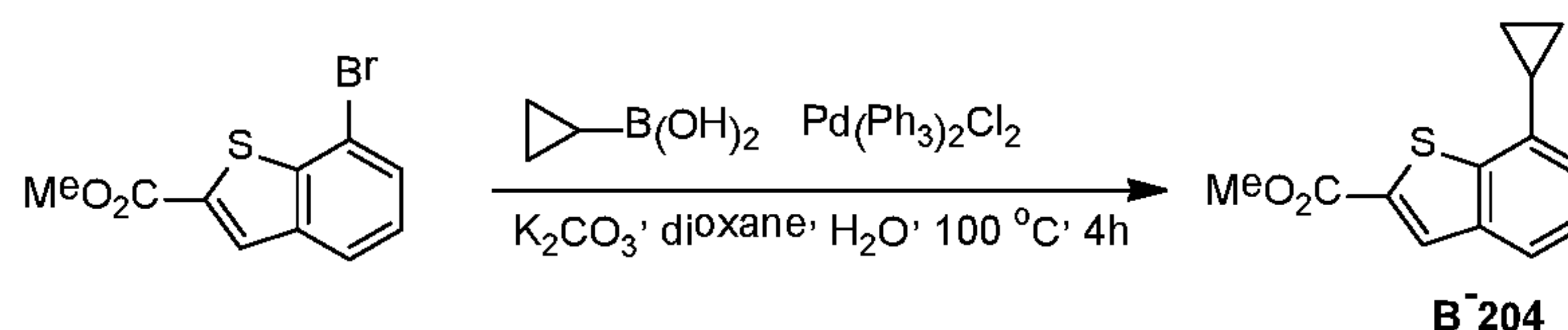
anhydrous sodium sulfate concentrated in vacuo and purified by column chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-202** (88 mg, 95% yield) as a white solid. LCMS (B): tR=0.871 min., (ES+) m/z (M+H)⁺ =228.0.

[00467] **Example 101B: 6,7-difluorobenzo[b]thiophene-2-carboxylic acid (B-203)**



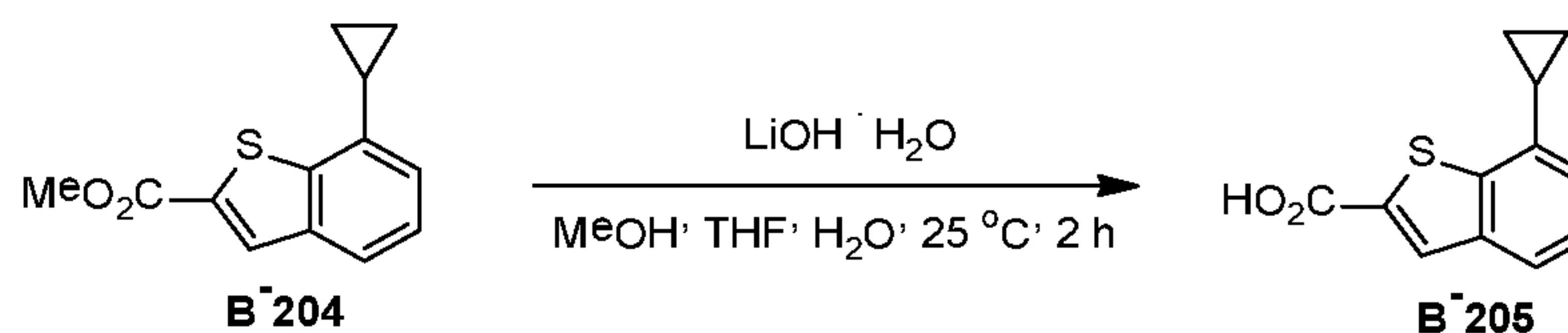
[00468] To a solution of **compound B-202** (88 mg, 0.39 mmol) in tetrahydrofuran (15 mL) at 25 °C was added sodium hydroxide (23 mg, 0.57 mmol) and water (6.0 mL). The mixture was stirred at room temperature for 4 hrs, then concentrated to remove tetrahydrofuran and acidified to pH 3 with 0.2 N hydrochloric acid, resulting in formation of a solid. The white solid was collected by filtration and dried in vacuo to give **compound B-203** (76 mg, 92% yield). ¹H-NMR (CD₃OD, 400 MHz): δ8.10 (d, J=4, 1H), 7.80-7.77 (dd, J₁=4, J₂=8.8, 1H), 7.45-7.38 (m, 1H).

[00469] **Example 102B: methyl 7-cyclopropylbenzo[b]thiophene-2-carboxylate (B-204)**



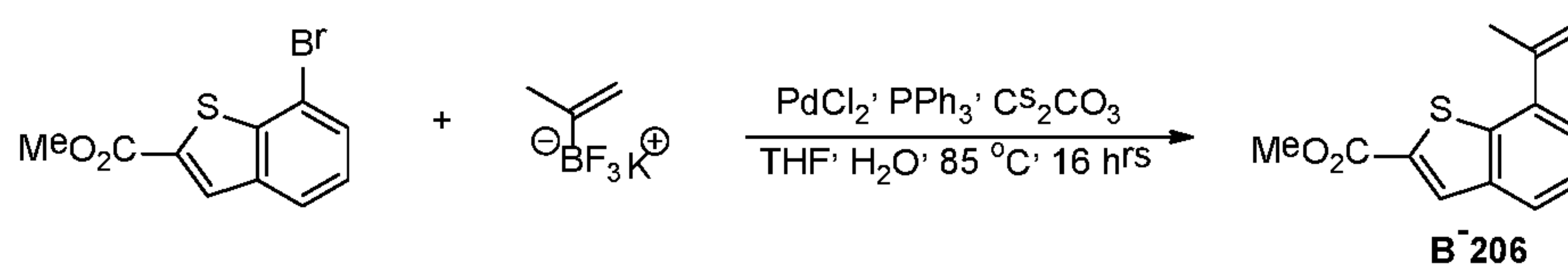
[00470] A mixture of methyl 7-bromobenzo[b]thiophene-2-carboxylate (1.0 g, 3.7 mmol), cyclopropylboronic acid (0.38 g, 4.4 mmol), bis(triphenylphosphine)palladium(II) dichloride (0.26 g, 0.37 mmol) and potassium carbonate (1.5 g, 11 mmol) in dioxane (15 mL) and water (3 mL) was stirred at 100 °C under nitrogen for 4 hours. On completion, the solution was diluted with water (20 mL) and extracted with ethyl acetate (2 × 40 mL). The combined organic layers were concentrated in vacuo to give **compound B-204** (0.70 g, crude) as a yellow solid, used for the next step without further purification.

[00471] **Example 103B: 7-cyclopropylbenzo[b]thiophene-2-carboxylic acid (B-205)**



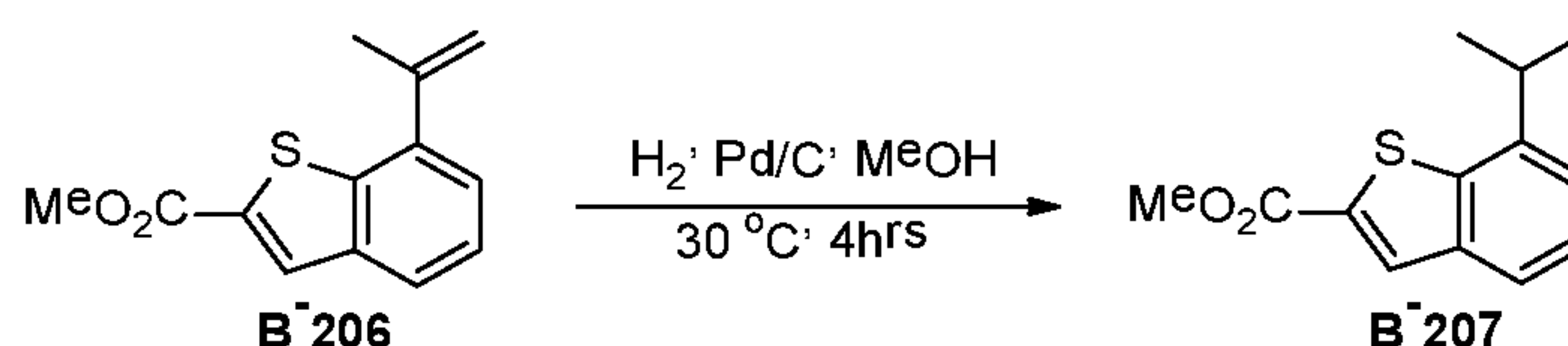
[00472] To a mixture of **compound B-204** (1.0 g, 4.3 mmol) in methanol (5 mL), tetrahydrofuran (5 mL) and water (5 mL) was added lithium hydroxide monohydrate (0.55 g, 13 mmol). The mixture was stirred at 25 °C for 2 h, then concentrated to remove methanol, diluted with water and acidified to pH 3 with 1 M hydrochloric acid, resulting in formation of a solid. The yellow solid was collected by filtration and dried in vacuo to give **compound B-205** (0.70 g, 75% yield). LCMS (B): tR=0.817 min., (ES⁺) m/z (M+H)⁺ =219.1.

[00473] **Example 104B:** methyl 7-(prop-1-en-2-yl)benzo[b]thiophene-2-carboxylate (**B-206**)



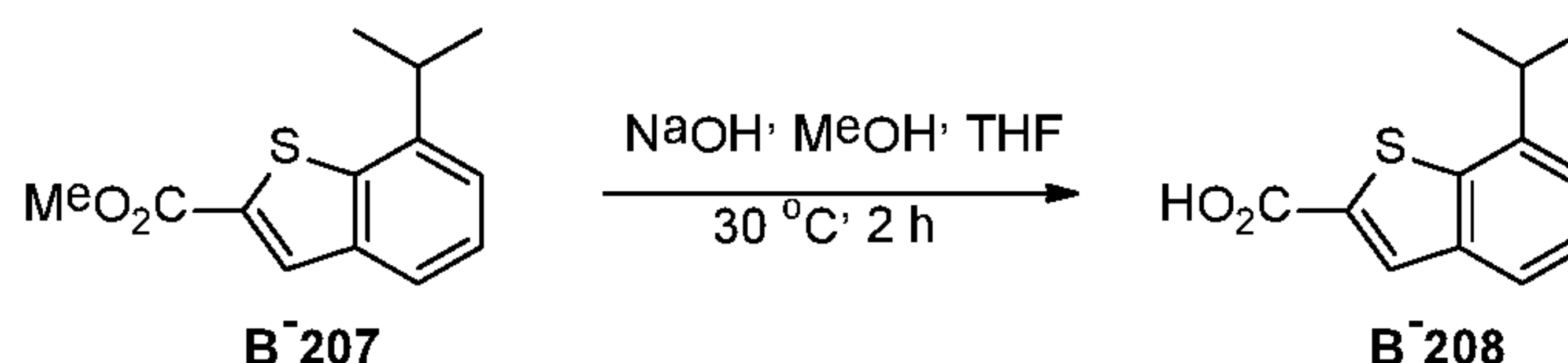
[00474] A solution of potassium vinyltrifluoroborate (0.33 g, 2.2 mmol), palladium chloride (6.5 mg, 37 μ mol), triphenylphosphine (29 mg, 0.11 mmol), cesium carbonate (1.8 g, 5.5 mmol) and methyl 7-bromobenzo[b]thiophene-2-carboxylate (0.50 g, 1.8 mmol) in tetrahydrofuran (9 mL) and water (1 mL) was stirred under nitrogen at 85 °C for 16 hours. On completion, the mixture was cooled to room temperature, diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL) and concentrated in vacuo. The residue was purified by silica gel column chromatography [petroleum ether: ethyl acetate = 100:1] to give **compound B-206** (0.30 g, 70% yield) as an oil. LCMS (B): (ES⁺) m/z (M+H)⁺ = 233.0, tR=0.997.

[00475] **Example 105B:** methyl 7-(prop-1-en-2-yl)benzo[b]thiophene-2-carboxylate (**B-207**)



[00476] To a solution of **compound B-206** (0.30 g, 1.3 mmol) in methanol (10 mL) under nitrogen was added wet 10% palladium/carbon (30 mg). The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under balloon hydrogen at 30 °C for 4 hours until TLC showed the starting material was consumed completely. The reaction mixture was filtered, and the filtrate was concentrated in vacuo and purified by prep-HPLC-HCl [Instrument: GX-E; Column: Phenomenex Synergi C18 250*21.2 mm, particle size: 4 μ m; Mobile phase: 58-88% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give **compound B-207** (0.25 g, 83% yield) as a yellow solid. ¹H-NMR (CD₃OD, 400 MHz): δ 8.12 (s, 1H), 7.81-7.78 (m, 1H), 7.46-7.40 (m, 2H), 3.29-3.19 (m, 1H), 1.43-1.42 (d, J = 7.2 Hz, 6 H).

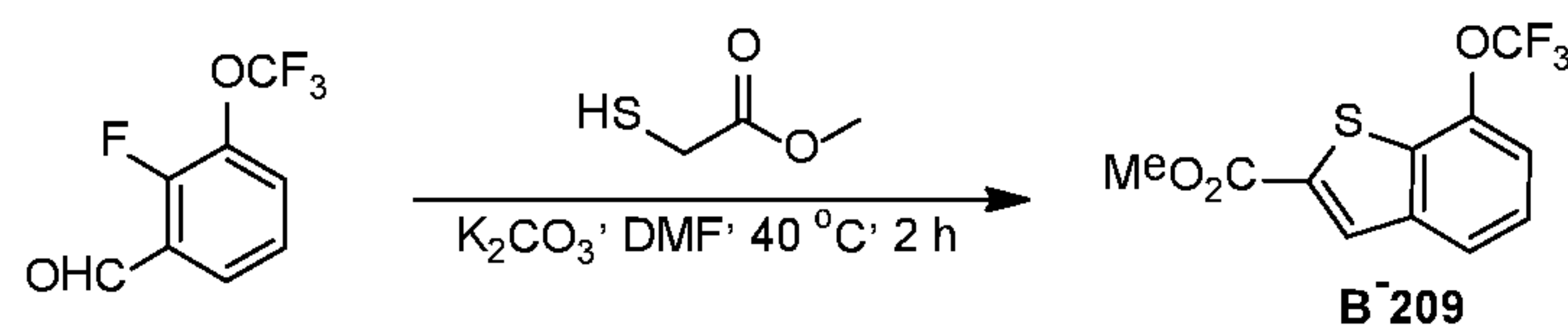
[00477] **Example 106B:** 7-isopropylbenzo[b]thiophene-2-carboxylic acid (**B-208**)



[00478] To a solution of **compound B-207** (0.25 g, 1.1 mmol) in methanol (2 mL) and tetrahydrofuran (12 mL) was added aqueous sodium hydroxide (1 M, 1.6 mL, 1.6 mmol). The resulting mixture was stirred at 30 °C for 2 hours, then partially concentrated and acidified to pH~6 with concentrated hydrochloric acid, resulting in formation of a solid. The white solid was collected

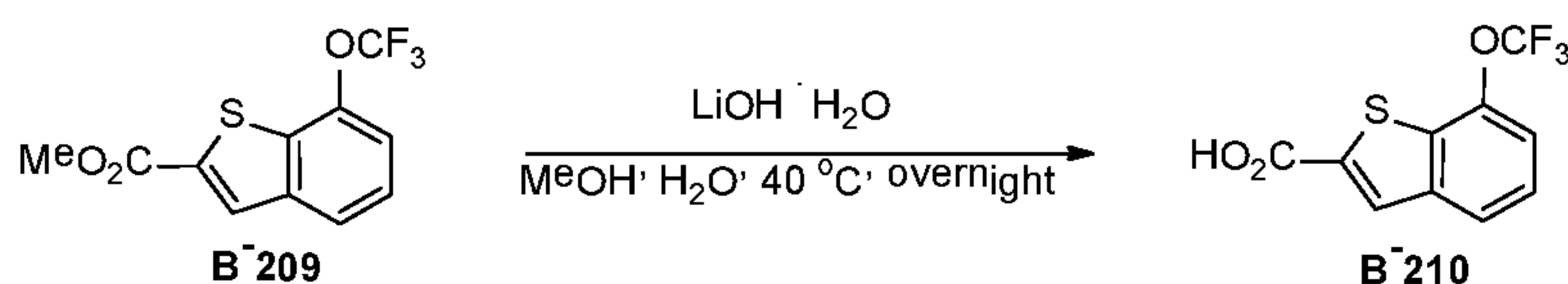
by filtration and dried in vacuo to give **compound B-208** (0.20 g, 85% yield). LCMS (AA): (ES⁺) m/z (M+H)⁺ = 219.1, tR=0.21.

[00479] **Example 107B:** methyl 7-(trifluoromethoxy)benzo[b]thiophene-2-carboxylate (**B-209**)



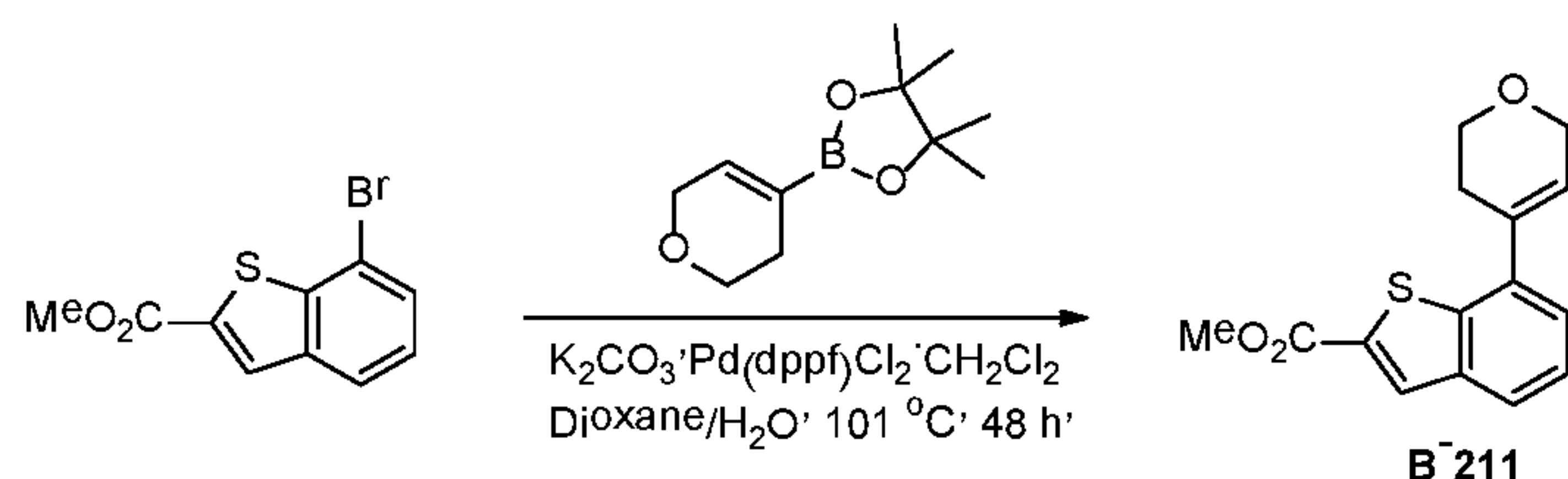
[00480] To a mixture of 2-fluoro-3-(trifluoromethoxy)benzaldehyde (0.5 g, 2.4 mmol) in *N,N*-dimethylformamide (5 mL) was added methyl 2-mercaptoacetate (0.28 g, 2.6 mmol) and potassium carbonate (0.66 g, 4.8 mmol). The mixture was stirred at 40 °C for 2 hours, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-209** (0.6 g, 90% yield) as a white solid. ¹H-NMR (CD₃OD, 400 MHz): δ 8.17 (s, 1H), 7.95 (d, J=8.0 Hz, 1H), 7.53 (t, J=8.0 Hz, 1H), 7.46 (d, J=7.6 Hz, 1H), 3.96 (s, 3H).

[00481] **Example 108B:** 7-(trifluoromethoxy)benzo[b]thiophene-2-carboxylic acid (**B-210**)



[00482] To a mixture of **compound B-209** (0.6 g, 2.3 mmol) in methanol (8 mL) and water (4 mL) was added lithium hydroxide monohydrate (0.14 g, 3.4 mmol). The mixture was stirred at 40 °C overnight, then concentrated to remove methanol, diluted with water and acidified to pH to 2 with 1 M hydrochloric acid, resulting in formation of a solid. The white solid was collected by filtration and dried in vacuo to give **compound B-210** (0.48 g, 84% yield) as a white solid. ¹H-NMR (CD₃OD, 400 MHz): δ 8.13 (s, 1H), 7.95 (d, J=10.4 Hz, 1H), 7.53 (t, J=10.4 Hz, 1H), 7.45 (d, J=10.8 Hz, 1H).

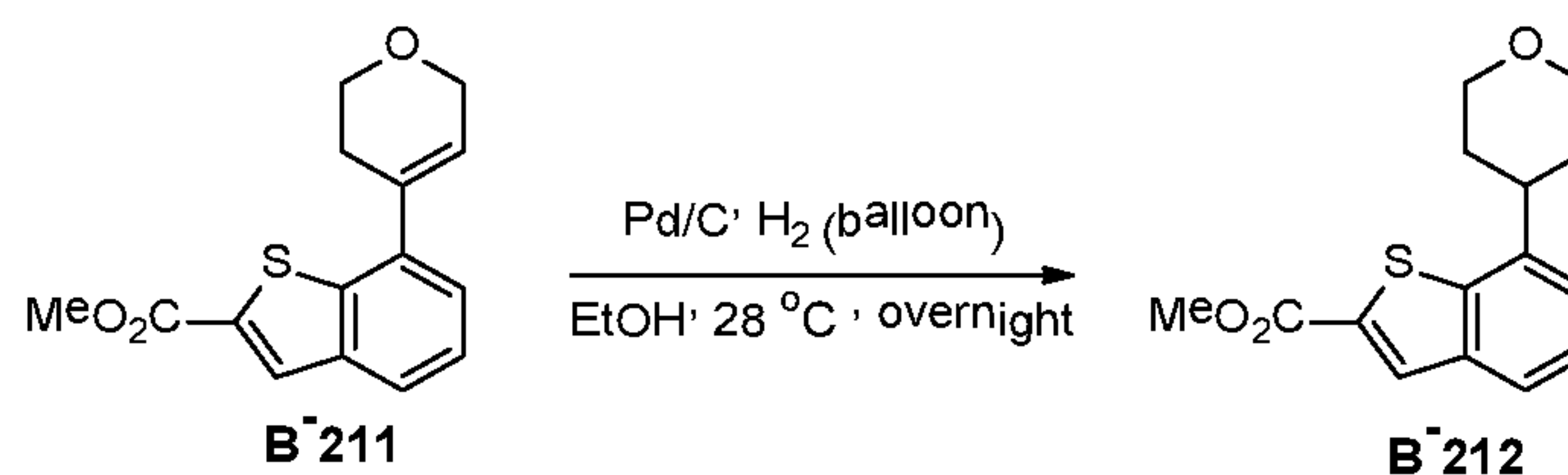
[00483] **Example 109B:** methyl 7-(3,6-dihydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxylate (**B-211**)



[00484] To a solution of methyl 7-(3,6-dihydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxylate (1.0 g, 3.7 mmol) in dioxane (30 mL) and water (6 mL) under nitrogen was added K₂CO₃ (1.5 g, 11 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (301 mg, 0.37 mmol) and 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (930 mg, 4.4 mmol). The mixture was stirred at 101 °C for 48 hours. On completion, the reaction mixture was concentrated and purified by silica gel chromatography [petroleum ether: ethyl acetate = 16 : 1] to give **compound B-211** (300 mg, 60% yield) as a white

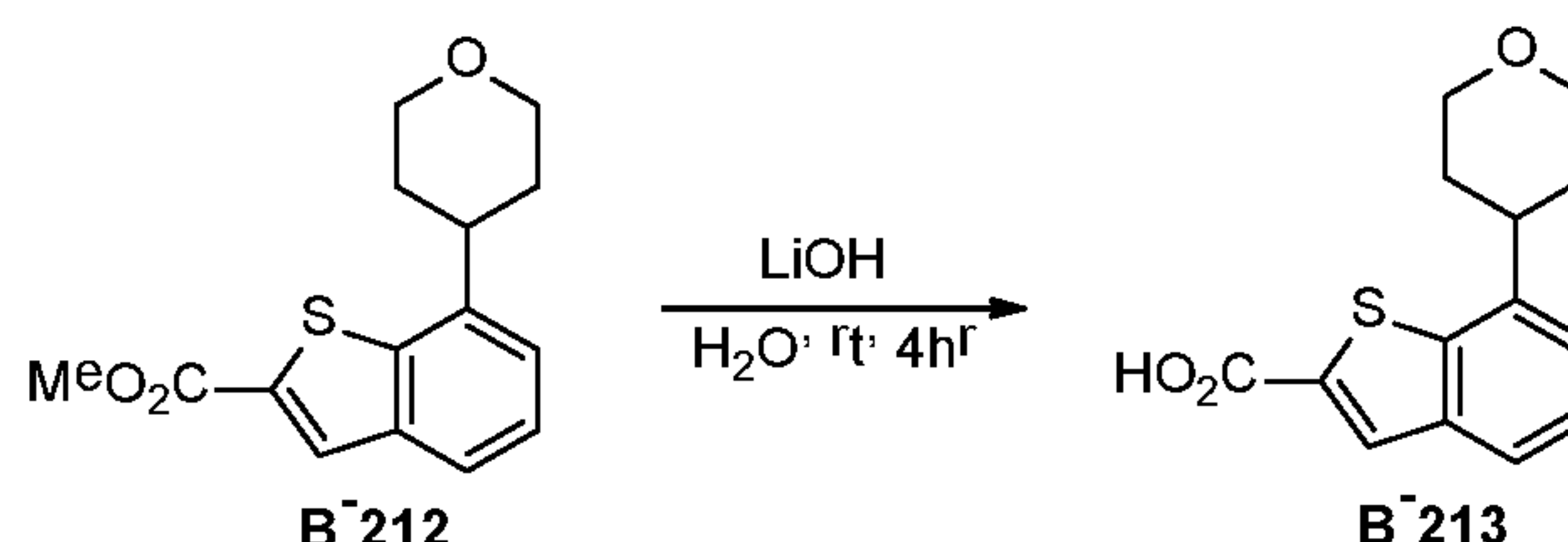
solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 8.12 (s, 1H), 7.86 (dd, $J_1=8.0$ Hz, $J_2=1.6$ Hz 1H), 7.48-7.42 (m, 2H), 6.35-6.34 (m, 1H), 4.39-4.36 (m, 2H), 4.00-3.97 (m, 2H), 3.93 (s, 3H), 2.62-2.59 (m, 2H).

[00485] **Example 110B:** methyl 7-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxylate (**B-212**)



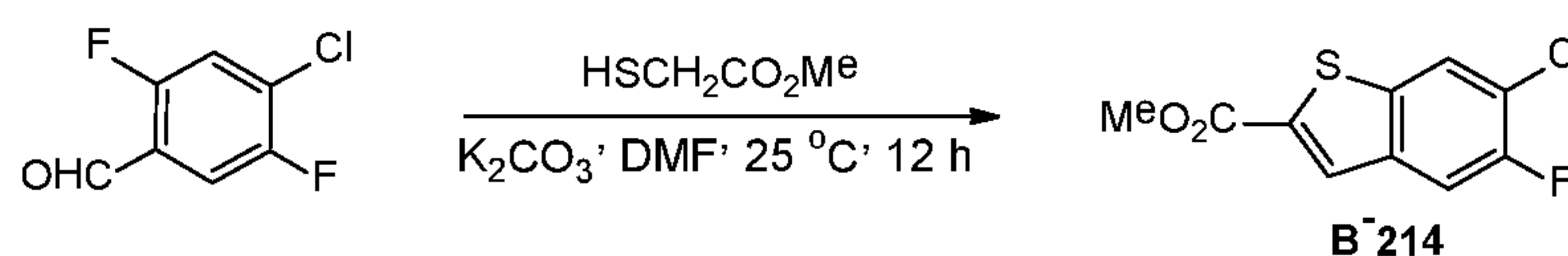
[00486] To a solution of **compound B-211** (300 mg, 1.1 mmol) in ethanol (8 mL) under nitrogen was added Pd/C (10%, 100 mg). The suspension was degassed under vacuo and purged with hydrogen several times. The mixture was stirred under balloon hydrogen at 28 °C overnight. On completion, the reaction mixture was filtered, and the filtrate was concentrated to give **compound B-212** (300 mg, 99% yield) as a white solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 8.12 (s, 1H), 7.80 (dd, $J_1=8.0$ Hz, $J_2=1.2$ Hz, 1H), 7.47-7.40 (m, 2H), 4.12-4.08 (m, 2H), 3.94 (s, 3H), 3.72-3.63 (m, 2H), 3.15-3.10 (m, 1H), 1.99-1.91 (m, 4H).

[00487] **Example 111B:** 7-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxylic acid (**B-213**)



[00488] To compound **B-212** (300 mg, 1.1 mmol) in methanol (8 mL) and water (4 mL) was added lithium hydroxide monohydrate (78 mg, 1.87 mmol). The mixture was stirred at room temperature for 4 hours, then acidified to pH 5~6, resulting in formation of a solid. The white solid was collected by filtration and dried in vacuo to give **compound B-213** (260 mg, 92%). $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 8.08 (s, 1H), 7.80 (dd, $J_1=8.0$ Hz, $J_2=1.2$ Hz, 1H), 7.48-7.39 (m, 2H), 4.11 (d, $J=12$ Hz, 2H), 3.70-3.63 (m, 2H), 3.17-3.10 (m, 1H), 2.03-1.95 (m, 4H).

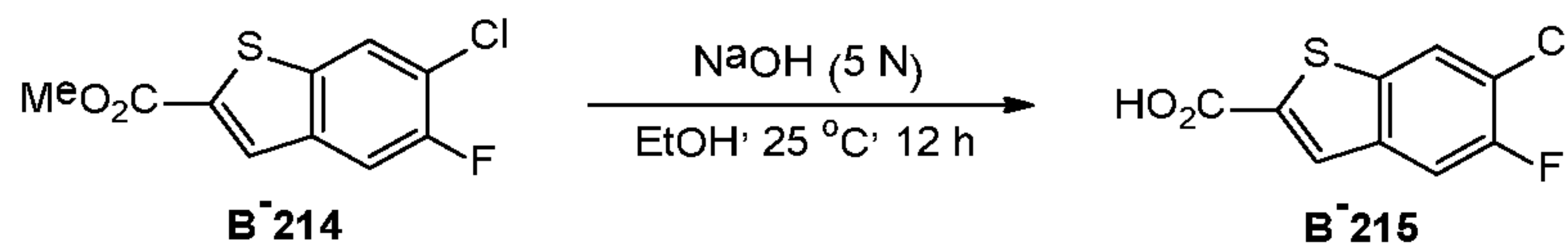
[00489] **Example 112B:** methyl 6-chloro-5-fluorobenzo[b]thiophene-2-carboxylate (**B-214**)



[00490] A mixture of 4-chloro-2,5-difluorobenzaldehyde (1.0 g, 5.7 mmol), ethyl 2-mercaptoacetate (0.7 g, 6.8 mmol) and potassium carbonate (1.6 g, 11 mmol) in *N,N*-dimethylformamide (20 mL) was stirred at 25 °C for 24 hours. On completion, the mixture was diluted with water (50 mL) and extracted with EtOAc (3 $\times$ 30 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated to dryness. The

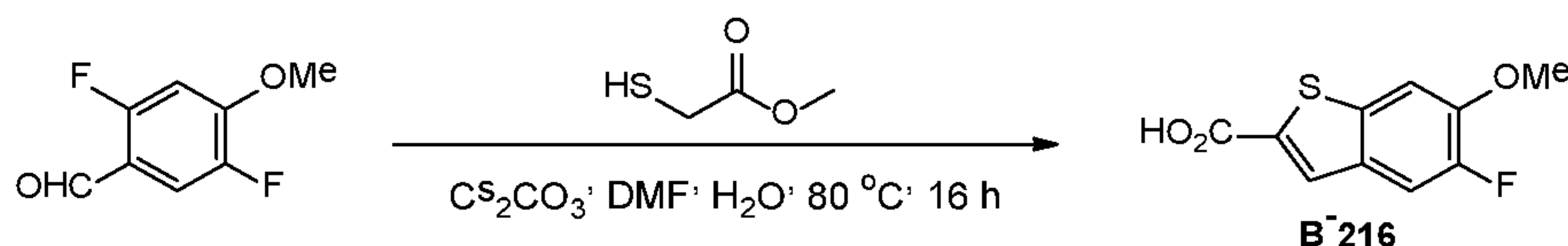
residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 3:1] to give **compound B-214** (0.7 g, 50% yield) as a white solid. LCMS (C): t_R =1.072 min., 244.9 m/z (M+1); ^1H -NMR ($CDCl_3$, 400 MHz): δ 7.97 (s, 1H), δ 7.91-7.90 (d, J =6.4 Hz, 1H), 7.63-7.61 (d, J =8.8 Hz, 1H), 3.96 (s, 3H).

[00491] **Example 113B: 6-chloro-5-fluorobenzo[b]thiophene-2-carboxylic acid (B-215)**



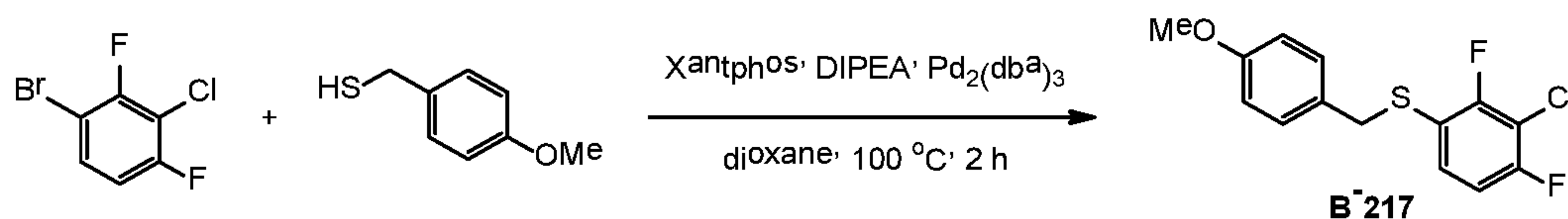
[00492] To a solution of **compound B-214** (0.7 g, 3.0 mmol) in ethanol (15 mL) was added an aqueous solution of sodium hydroxide (5 N, 1.8 mL, 9 mmol). The reaction was stirred at 25 °C for 12 hours. On completion, the volatiles were removed in vacuo. The residue was dissolved in water, washed with ethyl acetate (2 × 20 mL) and acidified to pH 3 with 6 N hydrochloric acid (6 N), resulting in formation of a solid. The white solid was collected by filtration and dried in vacuo to give **compound B-215** (0.6 g, 91% yield) as a white solid. LCMS (C): t_R =1.211 min., 228.9 m/z (M-1); ^1H -NMR ($DMSO-d_6$, 400 MHz): δ 8.42-8.41 (d, J =6.8 Hz, 1H), 8.07 (s, 1H), 8.05-8.03 (d, J =10 Hz, 1H).

[00493] **Example 114B: 5-fluoro-6-methoxybenzo[b]thiophene-2-carboxylic acid (B-216)**



[00494] To a mixture of 2,5-difluoro-4-methoxybenzaldehyde (0.20 g, 1.2 mmol) and methyl 2-mercaptoacetate (0.15 g, 1.4 mmol) in *N,N*-dimethylformamide (10 mL) was added cesium carbonate (1.1 g, 3.5 mmol). The mixture was stirred at 80 °C for 16 hours. On completion, water (1.0 mL) was added to the reaction mixture, and stirring was continued at 80 °C for half an hour. The solution was cooled to room temperature and poured into ice water (10 mL), resulting in formation of a solid. After stirring for half an hour, the white solid was collected by filtration, washed with water and dried in vacuo to give **compound B-216** (231 mg, 89% yield). LCMS (B): (ES^+) m/z (M+H) $^+$ = 227.1, t_R =0.719.

[00495] **Example 115B: (3-chloro-2,4-difluorophenyl)(4-methoxybenzyl)sulfane (B-217)**



[00496] To a mixture of 1-bromo-3-chloro-2,4-difluorobenzene (8.0 g, 35 mmol), (4-methoxyphenyl) methanethiol (5.4 g, 35 mmol) and *N,N*-diisopropylethylamine (9.1 g, 70 mmol) in dioxane (100 mL) at room temperature under nitrogen were added 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (1.0 g, 1.8 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.97 g, 1.1 mmol).

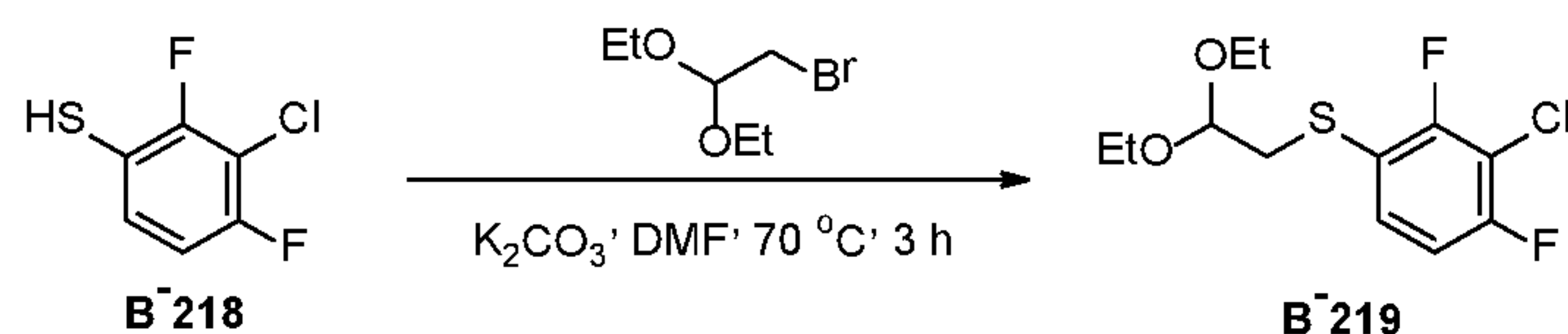
The reaction mixture was stirred at 100 °C for 2 hours, then filtered, concentrated in vacuo and purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-217** (9.0 g, 85% yield) as a white solid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.17-7.13 (m, 3H), 6.89-6.87 (m, 1H), 6.83-6.81 (d, J = 8.4 Hz, 2H), 4.03 (s, 2H), 3.80 (s, 3H).

[00497] **Example 116B: 3-chloro-2,4-difluorobenzenethiol (B-218)**



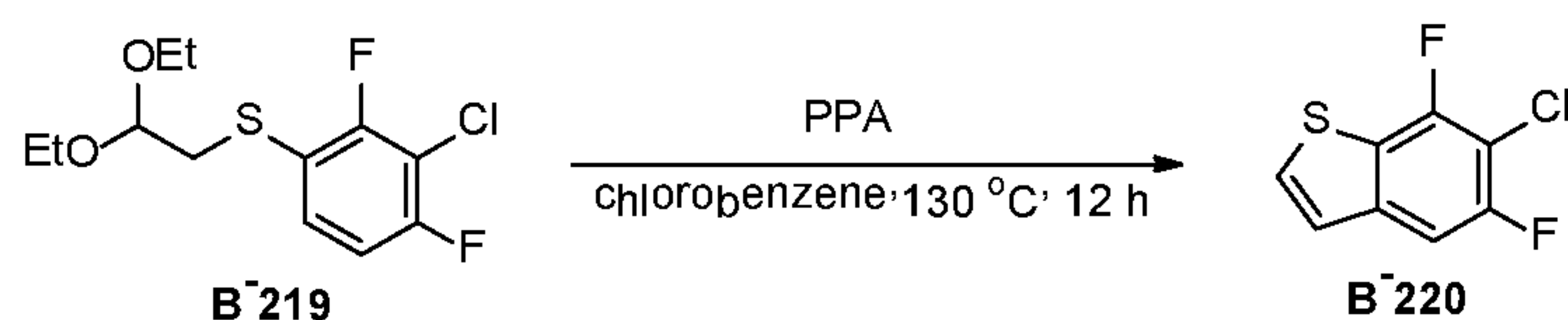
[00498] A solution of **compound B-217** (3.0 g, 10 mmol) in trifluoroacetic acid (10 mL) was stirred at 70 °C for 16 hours. On completion, the reaction mixture was quenched with aqueous sodium bicarbonate to pH 7-8 and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-218** (2.0 g, crude) as a yellow oil. TLC [petroleum ether:ethyl acetate = 10:1]: R_f = 0.57.

[00499] **Example 117B: (3-chloro-2,4-difluorophenyl)(2,2-dimethoxyethyl)sulfane (B-219)**



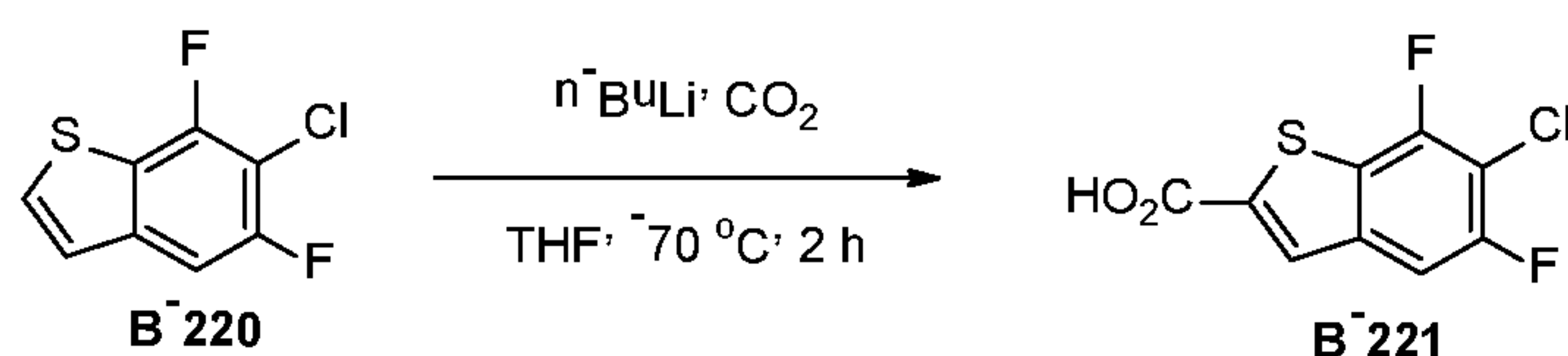
[00500] A mixture of **compound B-218** (1.5 g, 8.31 mmol), 2-bromo-1,1-diethoxyethane (1.8 g, 9.14 mmol) and potassium carbonate (1.7 g, 12 mmol) in *N,N*-dimethylformamide (15 mL) was stirred at 70 °C for 3 hours. On completion, the mixture was poured into water (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated in vacuo to give **compound B-219** (2.0 g, crude) as a yellow oil. [petroleum ether:ethyl acetate = 8:1]: R_f = 0.70.

[00501] **Example 118B: 6-chloro-5,7-difluorobenzo[b]thiophene (B-220)**



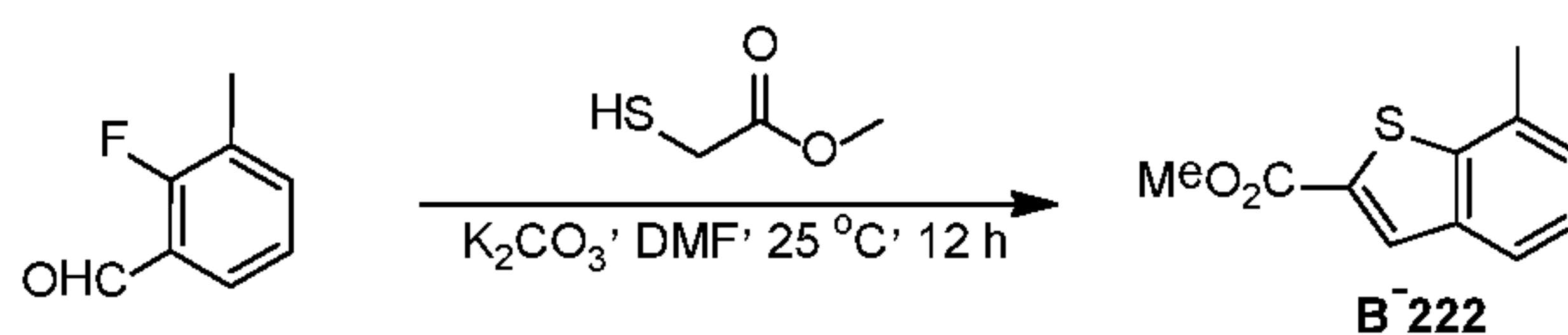
[00502] A solution of **compound B-219** (1.5 g, 5.6 mmol) and polyphosphoric acid (10 g, 74 mmol) in chlorobenzene (50 mL) was stirred at 130°C for 12 hours. On completion, the mixture was poured into water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford **compound B-220** (0.20 g, 18% yield) as a yellow oil. ¹H-NMR (CDCl₃, 400 MHz): δ 7.59-7.57 (d, J = 7.2 Hz, 1H), 7.45-7.42 (m, 1H), 7.34-7.31 (m, 1H).

[00503] **Example 119B: 6-chloro-5,7-difluorobenzo[b]thiophene-2-carboxylic acid (B-221)**



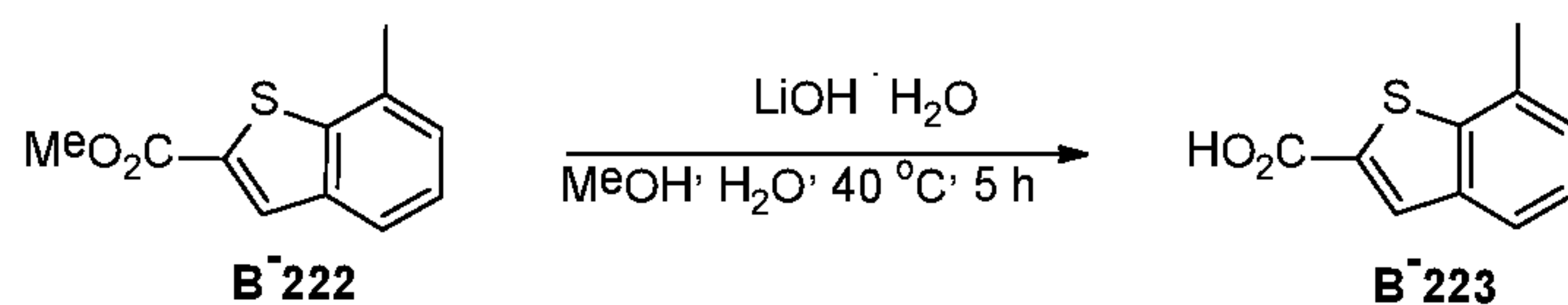
[00504] To a solution of **compound B-220** (0.15 g, 0.73 mmol) in anhydrous tetrahydrofuran (20 mL) at -70°C was added dropwise n-butyllithium (0.35 mL, 2.5 N in hexane, 0.88 mmol). The reaction was stirred at -70°C for 1 hour and then under carbon dioxide at -70°C for 1 hour. On completion, the mixture was quenched with saturated ammonium chloride solution (20 mL) at 0°C and extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm ; Mobile phase: 19-49% acetonitrile in H_2O (add 0.05% TFA, v/v)] to give **compound B-221** (80 mg, 44% yield) as a yellow solid. LCMS (M): $t_R=1.165$ min., $(\text{ES}^+) m/z (M+H)^+ = 249.0$.

[00505] **Example 120B: methyl 7-methylbenzo[b]thiophene-2-carboxylate (B-222)**



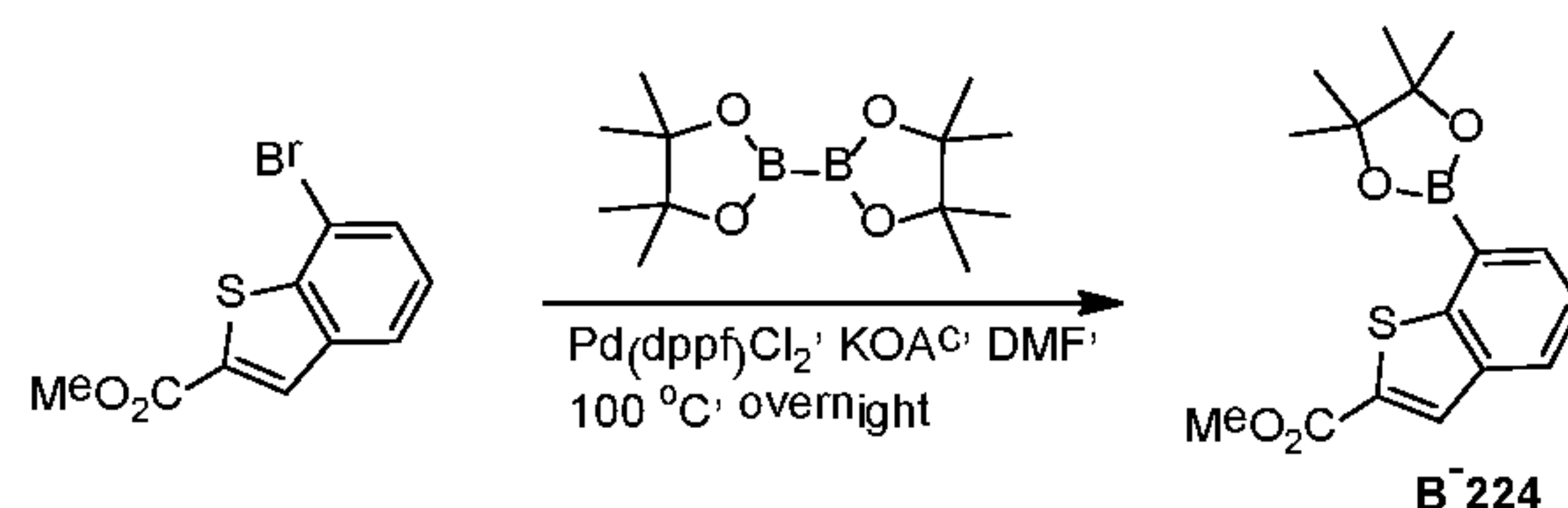
[00506] To a mixture of 2-fluoro-3-methylbenzaldehyde (1.0 g, 7.2 mmol) in *N,N*-dimethylformamide (10 mL) was added methyl 2-mercaptoacetate (1.5 g, 14.5 mmol) and potassium carbonate (2.0 g, 14.5 mmol). The mixture was stirred at 25°C for 12 hours. On completion, the mixture was poured into water and extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated in vacuo and purified by silica gel chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-222** (180 mg, 11% yield) as a white solid. LCMS (B): $t_R=0.872$ min., $(\text{ES}^+) m/z (M+H)^+ = 207.1$.

[00507] **Example 121B: 7-methylbenzo[b]thiophene-2-carboxylic acid (B-223)**



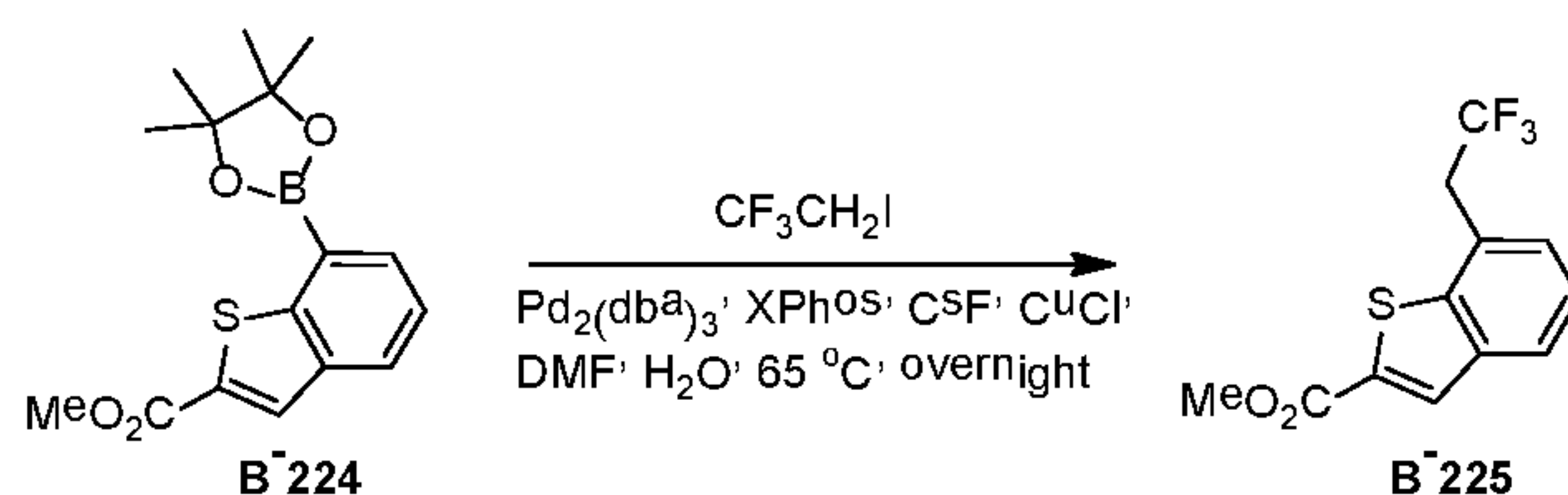
[00508] To a mixture of **compound B-222** (150 mg, 4.9 mmol) in methanol (6 mL) and water (3 mL) was added lithium hydroxide monohydrate (46 mg, 1.1 mmol). The mixture was stirred at 40°C for 5, then concentrated to remove methanol, diluted with water and acidified to pH 3 with 1 M hydrochloric acid, resulting in formation of a solid. The white solid was collected by filtration and dried in vacuo to give **compound B-223** (125 mg, 87% yield). $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 8.15 (s, 1H), 7.86 (d, $J=7.6$ Hz, 1H), 7.43-7.35 (m, 2H), 2.53 (s, 3H).

[00509] **Example 122B:** methyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophene-2-carboxylate (**B-224**)



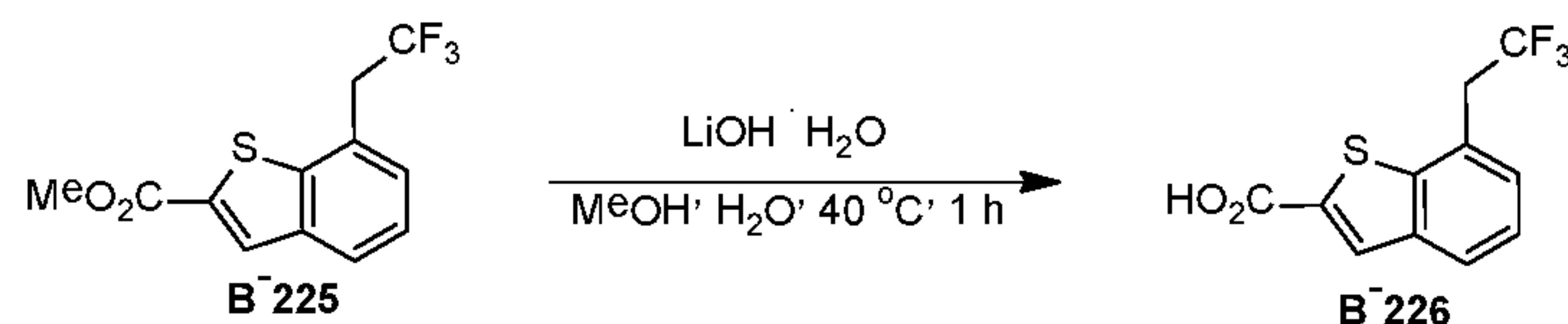
[00510] To a mixture of methyl 7-bromobenzo[b]thiophene-2-carboxylate (1.0 g, 3.7 mmol) in *N,N*-dimethylformamide (10 mL) under nitrogen was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.9 g, 7.4 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.27 g, 0.37 mmol) and potassium acetate (1.1 g, 11 mmol). The mixture was stirred at 100 °C overnight. On completion, the mixture was poured into water (20 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-224** (1.0 g, 55% yield) as a white solid. LCMS (DD): tR=1.182 min., (ES⁺) m/z (M+H)⁺ =319.1.

[00511] **Example 123B:** methyl 7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxylate (**B-225**)



[00512] To a mixture of **compound B-224** (1.0 g, 3.1 mmol) and 1,1,1-trifluoro-2-iodoethane (1.3 g, 6.3 mmol) in *N,N*-dimethylformamide (10 mL) and water (1 mL) under nitrogen was added tris(dibenzylideneacetone)dipalladium (86 mg, 94 μmol), 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl (0.15 g, 0.31 mmol), cesium fluoride (1.4 g, 9.4 mmol) and cuprous chloride (0.31 g, 3.1 mmol). The mixture was stirred at 65 °C overnight. On completion, the mixture was poured into water (10 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-225** (0.22 g, 26% yield) as a white solid.

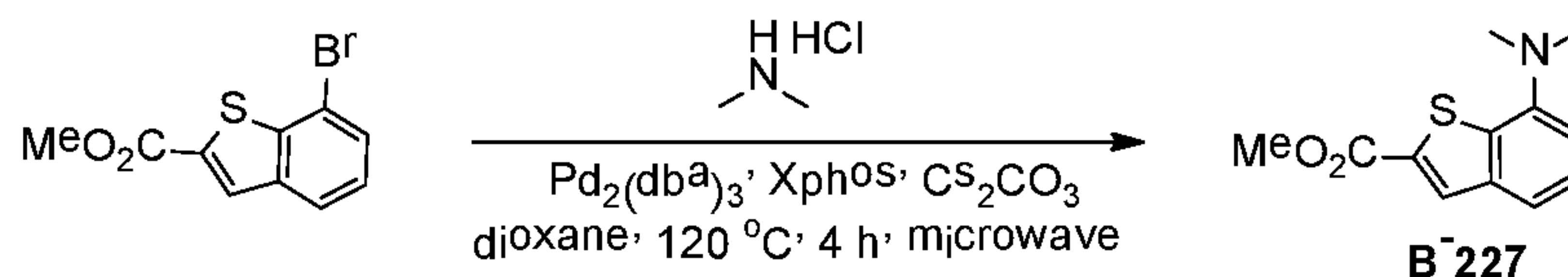
[00513] **Example 124B:** 7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxylic acid (**B-226**)



[00514] To a mixture of **compound B-225** (0.22 g, 0.80 mmol) in methanol (3 mL) and water (1.5 mL) was added lithium hydroxide monohydrate (67 mg, 1.6 mmol). The mixture was stirred at 40 °C for 1 hour, then concentrated to remove methanol, diluted with water and acidified to pH 3 with 1 M

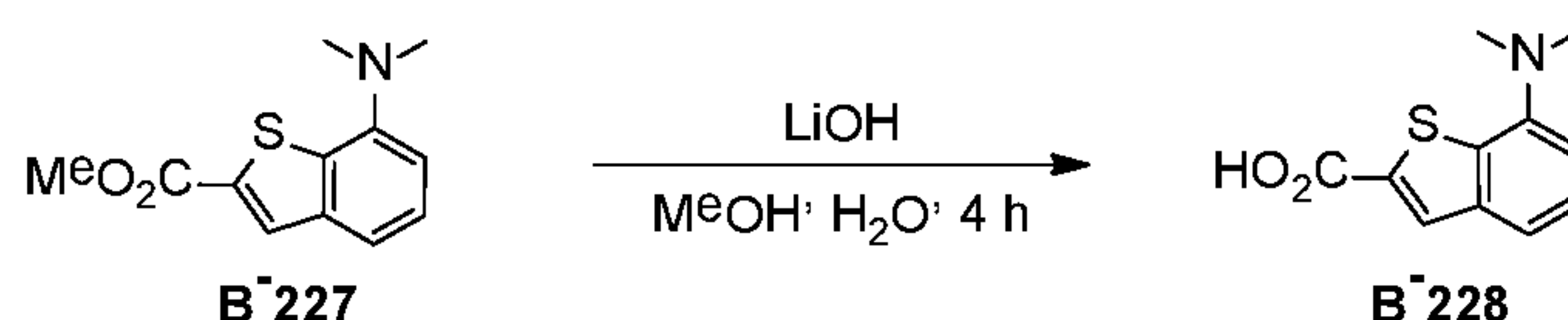
hydrochloric acid, resulting in formation of a solid. The yellow solid was collected by filtration and dried in vacuo to give **compound B-226** (0.15 g, 72% yield). LCMS (DD): $t_R=0.912$ min., (ES^+) m/z $(M+H)^+ = 261.0$.

[00515] **Example 125B: methyl 7-(dimethylamino)benzo[b]thiophene-2-carboxylate (B-227)**



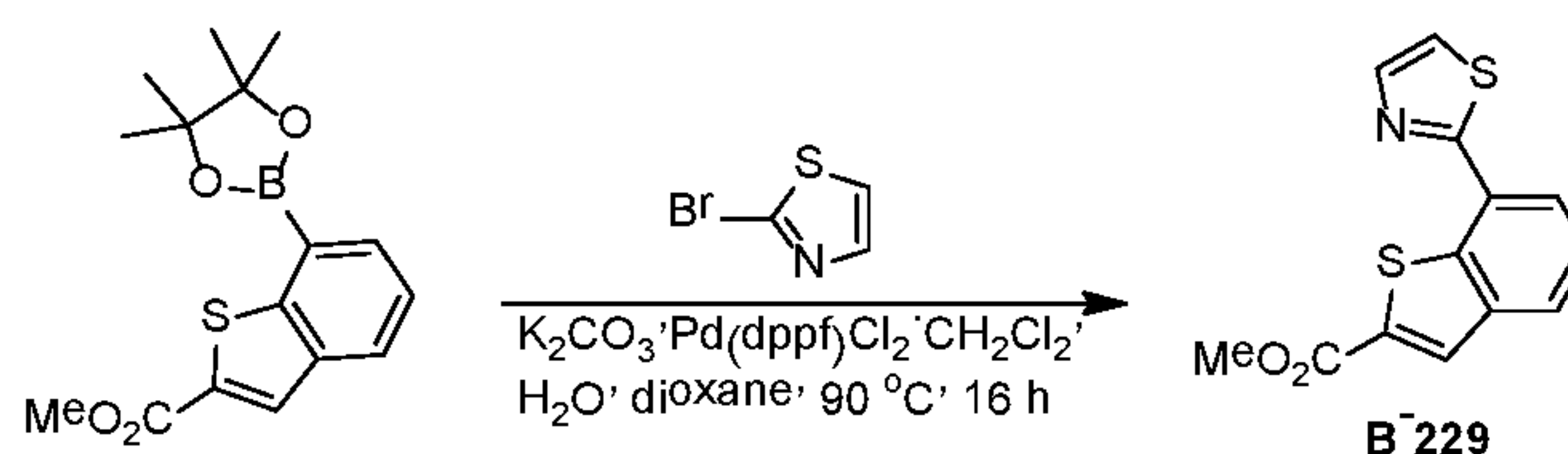
[00516] Methyl 7-bromobenzo[b]thiophene-2-carboxylate (600 mg, 2.2 mmol), cesium carbonate (2.2 g, 6.6 mmol), tris(dibenzylideneacetone)dipalladium(0) (405 mg, 0.44 mmol), 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl (421 mg, 0.88 mmol), and *N*-methylethanamine hydrochloride (1.1 g, 13 mmol) in dioxane (10 mL) were placed in a microwave reaction vessel. The mixture was degassed by bubbling nitrogen through it for 6 min. The reaction was heated by microwave irradiation at 120 °C for 4 hours. On completion, the solvent was evaporated. The residue was purified by silica gel column chromatography [petroleum ether] to give **compound B-227** (1.0 g, crude) as a green solid.

[00517] **Example 126B: 7-(dimethylamino)benzo[b]thiophene-2-carboxylic acid (B-228)**



[00518] To **compound B-227** (900 mg, crude) in methanol (8 mL) and water (4 mL) was added lithium hydroxide monohydrate (160 mg, 3.8 mmol). The reaction was stirred at room temperature for 4 hours, then acidified to pH 5~6, resulting in formation of a solid. The green solid was collected by filtration and dried to give **compound B-228** (400 mg, 67%), which was used for the next step without further purification. LCMS (N): $t_R=1.909$ min., (ES^+) m/z $(M+H)^+ = 222.0$.

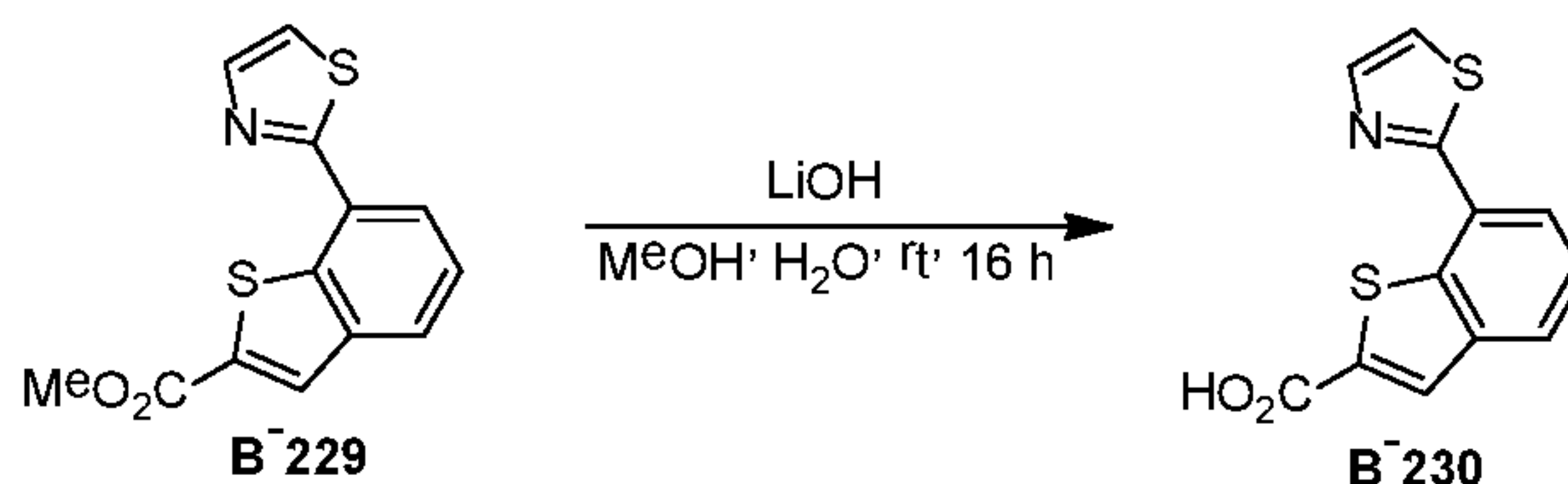
[00519] **Example 127B: methyl 7-(thiazol-2-yl)benzo[b]thiophene-2-carboxylate (B-229)**



[00520] To a solution of methyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophene-2-carboxylate (500 mg, 1.6 mmol) in water (4.5 mL) and dioxane (45.00 mL) was added 2-bromothiazole (387 mg, 2.4 mmol), potassium carbonate (1.2 g, 8.6 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(ii) (257 mg, 0.31 mmol). The vessel was flushed with argon and stirred at 90 °C for 16 h. On completion, the reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography [petroleum ether: ethyl acetate =

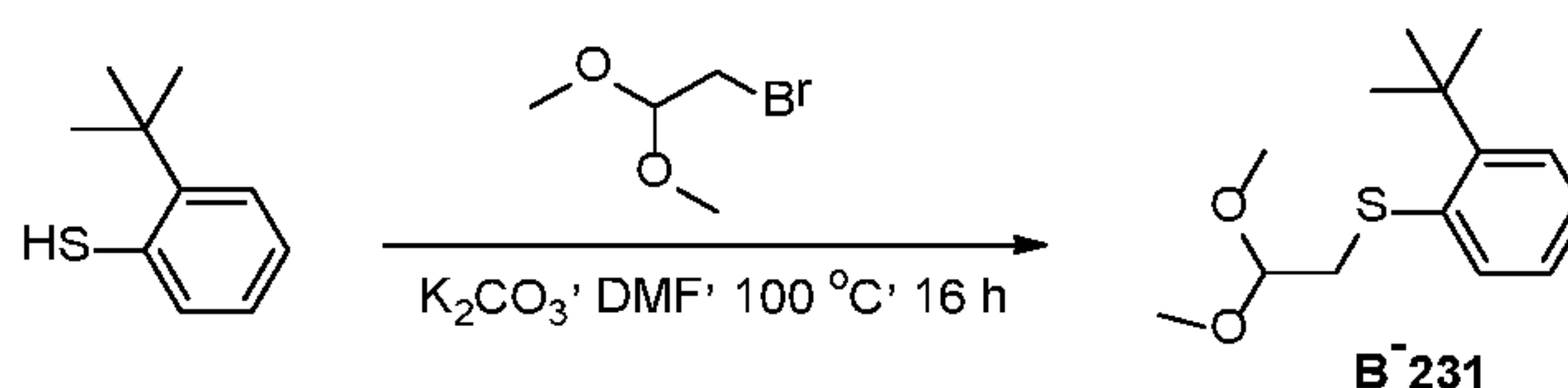
20 : 1] to give **compound B-229** (280 mg, 65%) as a white solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): 8.17 (s, 1H), 8.09-8.03 (m, 3H), 7.67 (d, $J=3.2$ Hz, 1H), 7.59-7.57 (m, 1H), 3.96 (s, 3H).

[00521] **Example 128B: 7-(thiazol-2-yl)benzo[b]thiophene-2-carboxylic acid (B-230)**



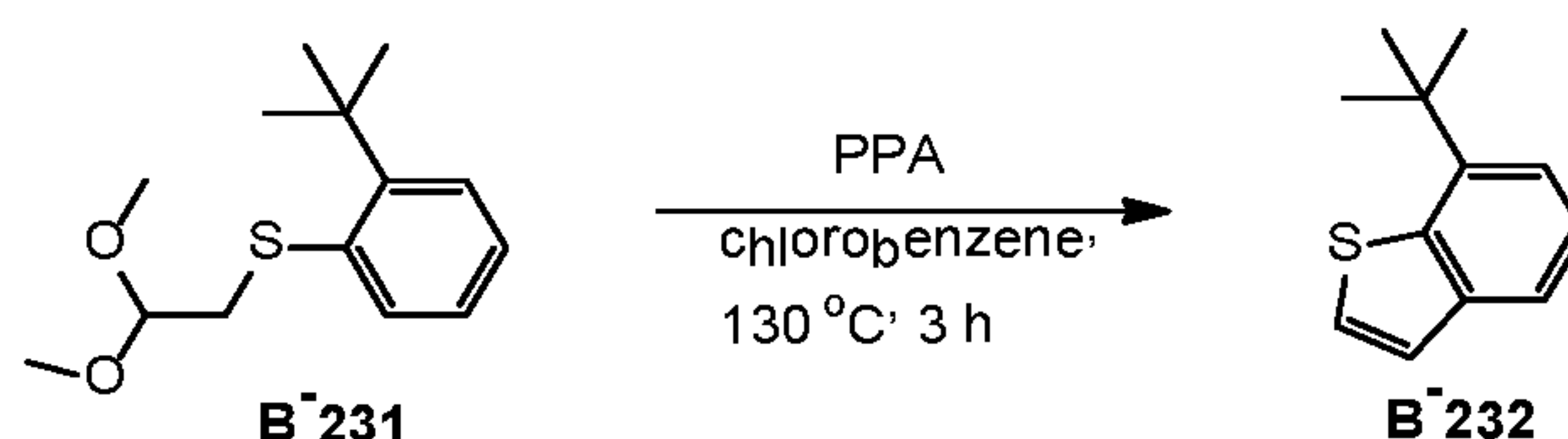
[00522] To a solution of **compound B-229** (290 mg, 1.1 mmol) in methanol (8 mL) and H_2O (4 mL) was added lithium hydroxide monohydrate (44 mg, 1.1 mmol). The reaction was stirred at room temperature for 16 hours, then concentrated to remove methanol and acidified to pH 5~6, resulting in formation of a solid. The white solid was collected by filtration and dried to give **compound B-230** (230 mg, 83%). $^1\text{H-NMR}$ (CD_3OD , 400 MHz): 8.14 (s, 1H), 8.09-8.04 (m, 3H), 7.67 (d, $J=4$ Hz, 1H), 7.59-7.55 (m, 1H).

[00523] **Example 129B: (2-(tert-butyl)phenyl)(2,2-dimethoxyethyl)sulfane (B-231)**

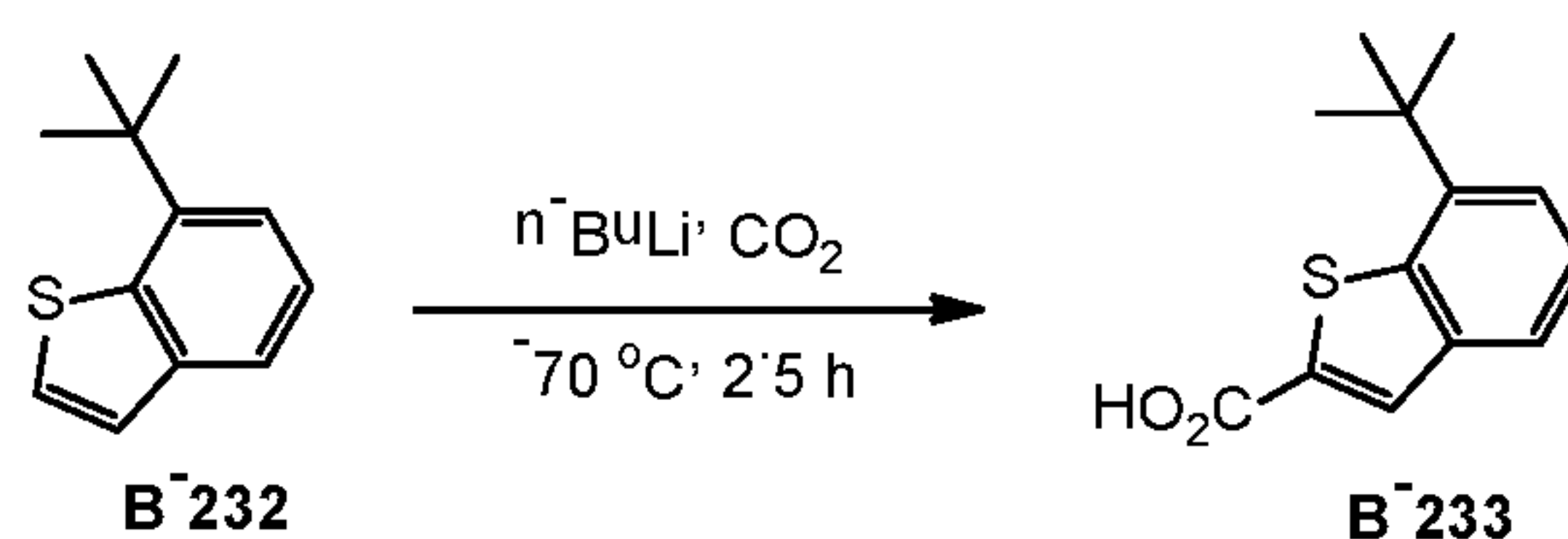


[00524] To a solution of 2-(tert-butyl)benzenethiol (1.5 g, 9.0 mmol) and 2-bromo-1,1-dimethoxyethane (1.7 g, 9.9 mmol) in *N,N*-dimethylformamide (8.0 mL) was added potassium carbonate (1.9 g, 14 mmol). The mixture was heated to 100 °C for 16 hours, then diluted with water (30 mL) and extracted with tert-butyl methyl ether (3×40 mL). The combined organic phases were washed with brine (2×25 mL), dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-231** (2.2 g, crude) as a yellow oil. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.50-7.47 (m, 1H), 7.42-7.39 (m, 1H), 7.20-7.14 (m, 1H), 3.39 (s, 1H), 3.18-3.19 (m, 2H), 1.55 (s, 9H).

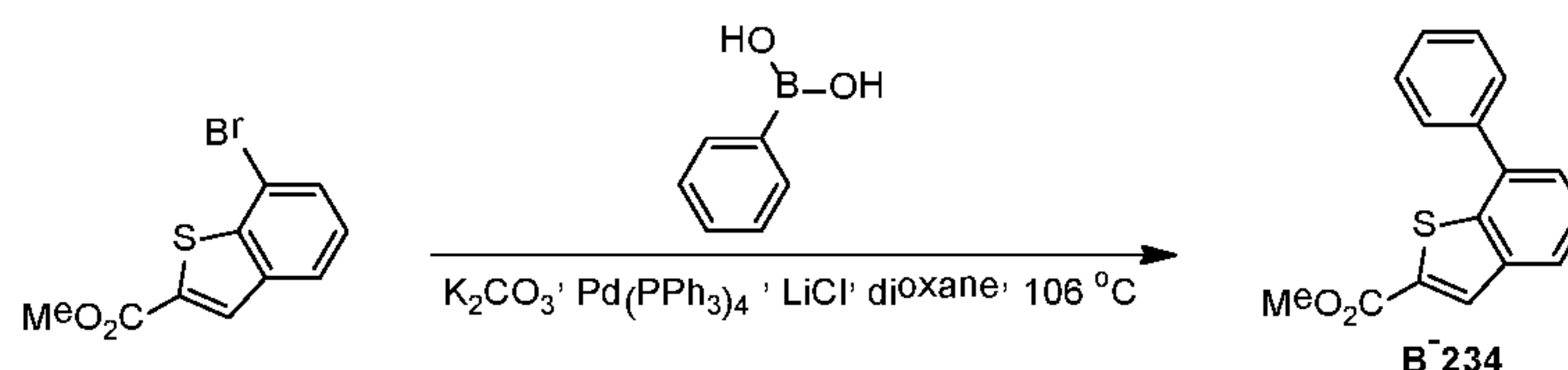
[00525] **Example 130B: 7-(tert-butyl)benzo[b]thiophene (B-232)**



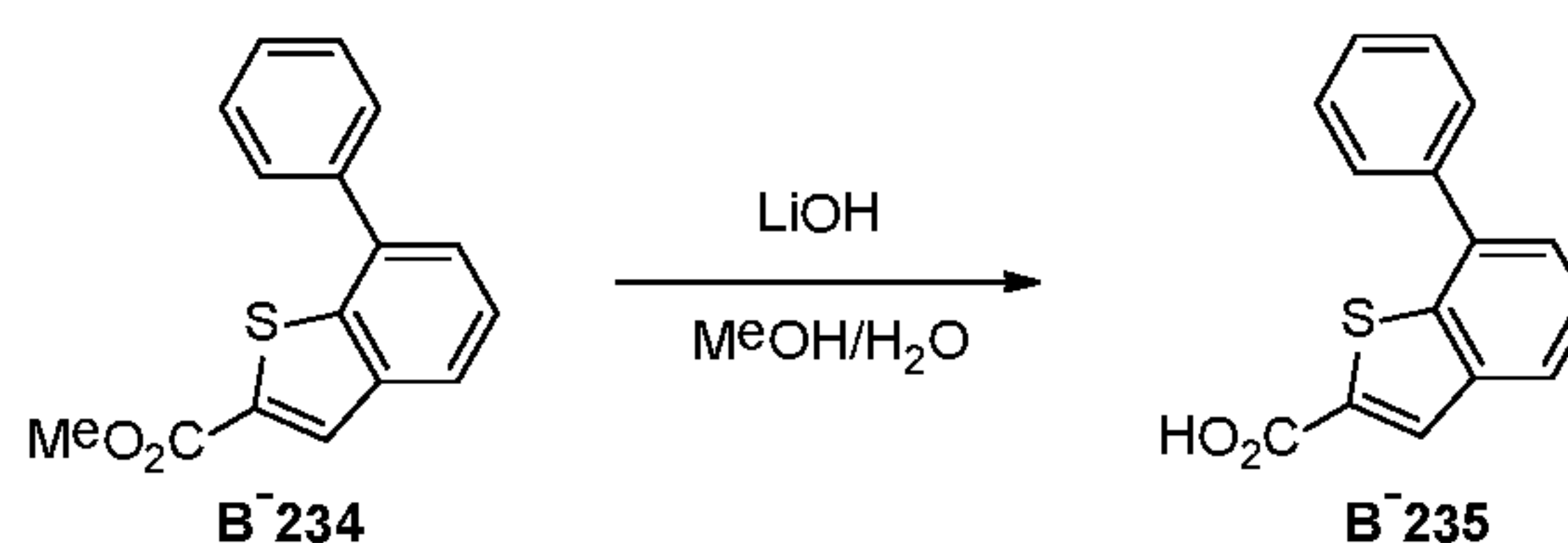
[00526] To a solution of polyphosphoric acid (16 g, 63 mmol, 8.0 eq) in chlorobenzene (15 mL) at 100 °C was added **compound B-231** (2.0 g, 7.9 mmol). The reaction was heated at 130 °C for 3 hours, then concentrated under vacuum, diluted with water (30 mL), and extracted with tert-butyl methyl ether (3×40 mL). The combined organic phases were washed with brine (2×25 mL) and concentrated to give **compound B-232** (0.5 g, crude) as a yellow oil. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.78-7.74 (m, 2H), 7.48 (d, $J=5.6$ Hz, 1H), 7.37-7.30 (m, 2H).

[00527] **Example 131B: 7-(tert-butyl)benzo[b]thiophene-2-carboxylic acid (B-233)**

[00528] To a solution of **compound B-232** (0.50 g, 2.6 mmol) in anhydrous tetrahydrofuran (2.0 mL) at -70 °C was added n-butyllithium (2.5 M in cyclohexane, 1.6 mL). The reaction was stirred for 0.5 h at -70 °C. Then carbon dioxide was bubbled through the reaction for about 0.5 hour, and stirring was continued at -70 °C for another 1.5 h until TLC analysis showed the reaction was complete. The reaction was quenched slowly with 0.02 N hydrochloric acid (10 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic phases were concentrated to give **compound B-233** (0.3 g, crude) as a gray solid.

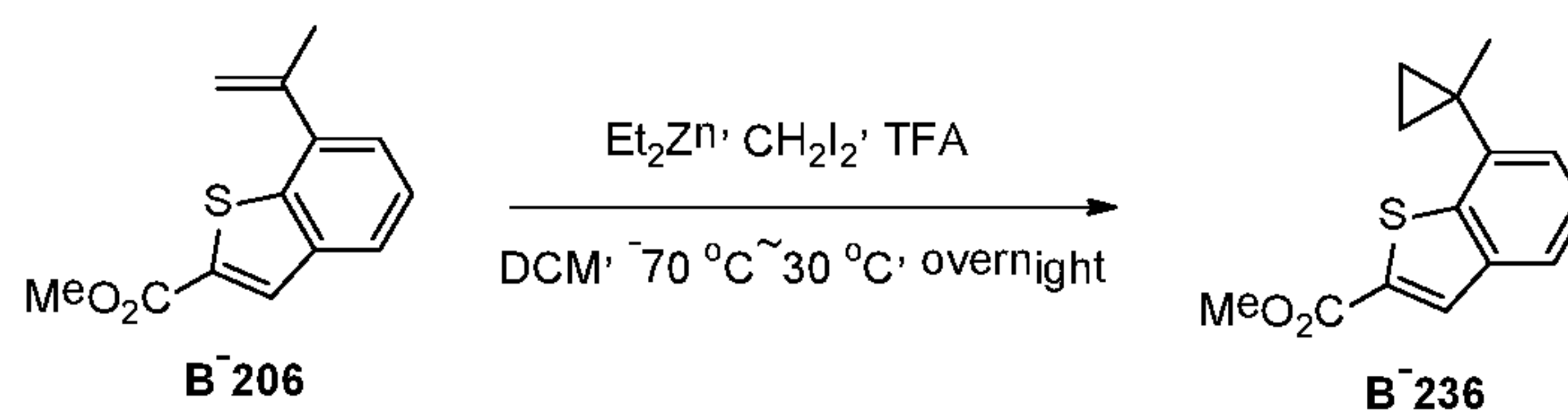
[00529] **Example 132B: methyl 7-phenylbenzo[b]thiophene-2-carboxylate (B-234)**

[00530] To a solution of methyl 7-bromobenzo[b]thiophene-2-carboxylate (1.2 g, 4.4 mmol) in dioxane (15 mL) at room temperature under nitrogen was added potassium carbonate (1.2 g, 8.8 mmol), phenylboronic acid (0.64 g, 5.3 mmol), tetrakis(triphenylphosphine)palladium(0) (0.50 g, 0.44 mmol) and lithium chloride (0.53 g, 8.8 mmol). The mixture was stirred at 106 °C for 7 hours, then diluted with water (30 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography [petroleum ether: ethyl acetate = 40:1] to give **compound B-234** (0.48 g, 40% yield) as a yellow solid.

[00531] **Example 133B: 7-phenylbenzo[b]thiophene-2-carboxylic acid (B-235)**

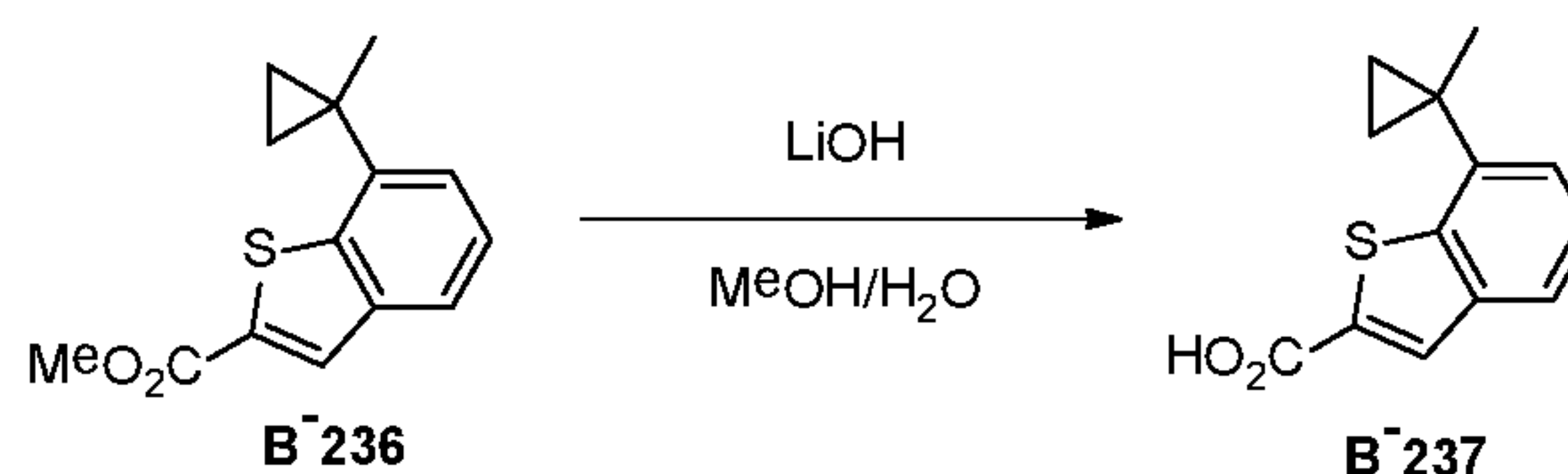
[00532] To a solution of **compound B-234** (0.48 g, 1.8 mmol) in methanol (10 mL) and water (5 mL) was added lithium hydroxide monohydrate (0.15 g, 3.6 mmol). The mixture was stirred at room temperature for 1 hour, then concentrated to remove most of the methanol and acidified to pH 4~5, resulting in the formation of a solid. The white solid was collected by filtration and dried in vacuo to give **compound B-235** (0.36 g, 79% yield). ¹H-NMR (CD₃OD, 400 MHz): δ 8.10 (s, 1H), 7.93 (d, J=7.2 Hz, 1H), 7.73 (d, J=7.2 Hz, 2H), 7.56-7.44 (m, 5H).

[00533] Example 134B: methyl 7-(1-methylcyclopropyl)benzo[b]thiophene-2-carboxylate (B-236)



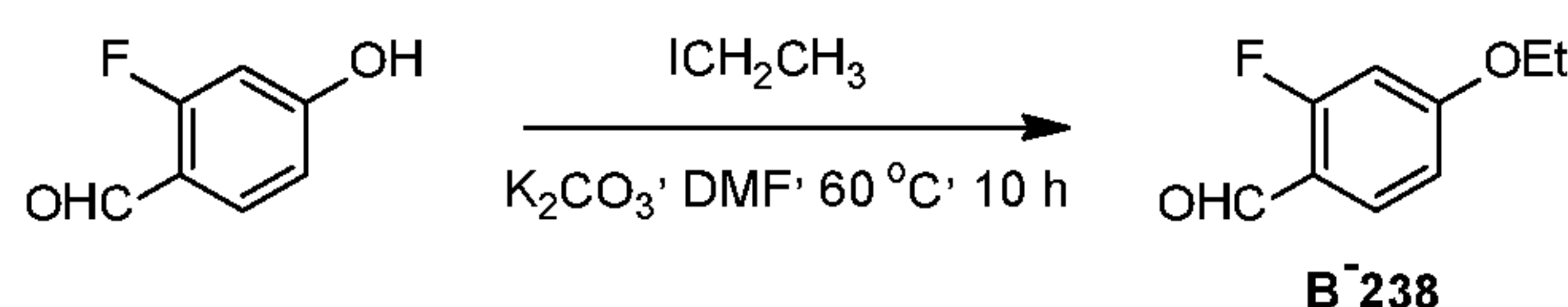
[00534] To a solution of diethylzinc (40 mL, 1.0 mol/L in toluene, 40 mmol) in anhydrous dichloromethane (20 mL) at $-70\text{ }^\circ\text{C}$ under nitrogen was added dropwise a solution of diiodomethane (11 g, 40 mmol), maintaining the temperature below $-70\text{ }^\circ\text{C}$ for the duration of the addition. The reaction mixture was warmed to $-15\text{ }^\circ\text{C}$ and stirred for 30 min. Then trifluoroacetic acid (4.5 g, 40 mmol) was added dropwise to the mixture, and stirring was continued at $-15\text{ }^\circ\text{C}$ for another 0.5 hour. Then **compound B-206** (0.77 g, 3.3 mmol) was added. The reaction mixture was stirred at $30\text{ }^\circ\text{C}$ for 7 hours, then quenched dropwise at $0\text{ }^\circ\text{C}$ with saturate aqueous ammonium chloride (40 mL) and extracted with ethyl acetate ($3 \times 50\text{ mL}$). The combined organic layers were washed with brine ($2 \times 50\text{ mL}$), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography [petroleum ether: ethyl acetate = 40:1] to give **compound B-236** (0.42 g, 51% yield) as a yellow oil. GCMS: $t_R=8.328\text{ min.}$, 246.1 m/z (M) .

[00535] Example 135B: 7-(1-methylcyclopropyl)benzo[b]thiophene-2-carboxylic acid (B-237)



[00536] To a solution of **B-236** (0.42 g, 1.8 mmol) in methanol (10 mL) and water (5 mL) was added lithium hydroxide monohydrate (0.15 g, 3.6 mmol). The mixture was stirred at $25\text{ }^\circ\text{C}$ for 1 hour, then concentrated to remove methanol, diluted with water and acidified to pH 4-5 with 1 M hydrochloric acid, resulting in precipitation of a solid. The solid was collected by filtration and dried in vacuo to give compound **B-237** (0.32 g, 81% yield) as a white solid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 8.22 (s, 1H), 7.79 (d, $J=7.6\text{ Hz}$, 1H), 7.47 (d, $J=7.2\text{ Hz}$, 1H), 7.39 (t, $J=8.0\text{ Hz}$, 1H), 1.50 (s, 3H), 0.99-0.98 (m, 2H), 0.88-0.86 (m, 2H).

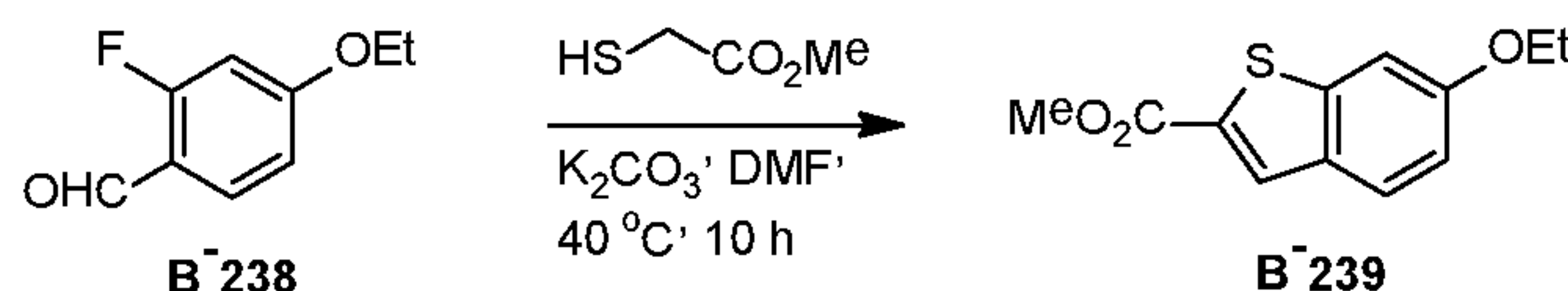
[00537] Example 136B: 4-ethoxy-2-fluorobenzaldehyde (B-238)



[00538] To a mixture of 2-fluoro-4-hydroxy-benzaldehyde (1.0 g, 7.1 mmol) and potassium carbonate (2.0 g, 14 mmol) in *N,N*-dimethylformamide (10 mL) at $25\text{ }^\circ\text{C}$ under nitrogen was added iodoethane (1.1 g, 7.1 mmol). The mixture was stirred at $60\text{ }^\circ\text{C}$ for 10 hours, concentrated in vacuo, diluted with ethyl acetate (200 mL), washed with saturated sodium bicarbonate solution ($3 \times 50\text{ mL}$) and brine ($3 \times 50\text{ mL}$), dried with anhydrous sodium sulfate and concentrated in vacuo to give

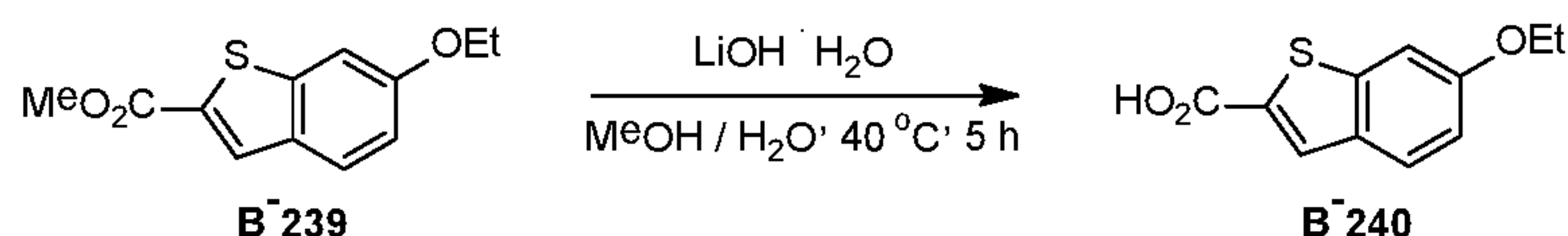
compound B-238 (1.0 g, 83% yield) as a red solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): 10.09 (s, 1H), 7.76-7.67 (m, 1H), 6.83-6.74 (m, 2H), 4.11 (t, $J=6.8$ Hz, 2H), 1.40 (t, $J=7.0$ Hz, 3H).

[00539] **Example 137B: methyl 6-ethoxybenzo[*b*]thiophene-2-carboxylate (B-239)**



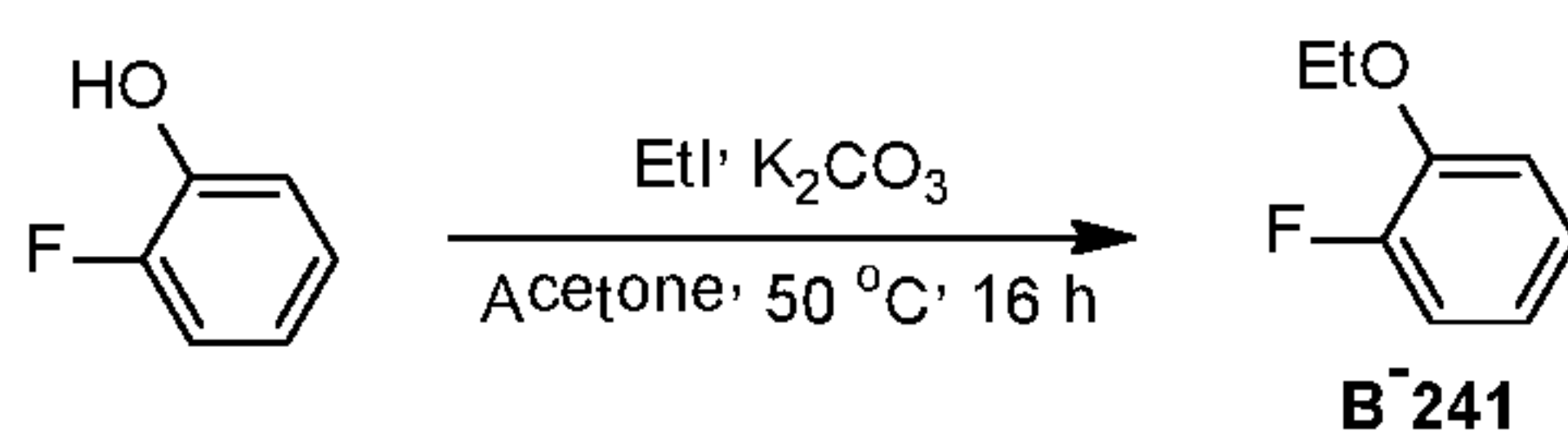
[00540] To a solution of **compound B-238** (0.5 g, 3 mmol) in *N,N*-dimethylformamide (5 mL) was added potassium carbonate (0.8 g, 6 mmol) and methyl 2-mercaptoacetate (0.6 g, 6 mmol). The mixture was stirred at $40\text{ }^\circ\text{C}$ for 10 hours, then diluted with ethyl acetate (250 mL), washed with brine 120 (4×30 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo to give **compound B-239** (0.58 g, 83% yield) as a yellow solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): 7.97 (s, 1H), 7.77 (d, $J=8.4$ Hz, 1H), 7.40 (s, 1H), 7.02 (d, $J=8.8$ Hz, 1H), 4.10 (q, $J=2.8$ Hz, 2H), 3.89 (s, 3H), 1.14 (t, $J=6.8$ Hz, 3H).

[00541] **Example 138B: 6-ethoxybenzo[*b*]thiophene-2-carboxylic acid (B-240)**



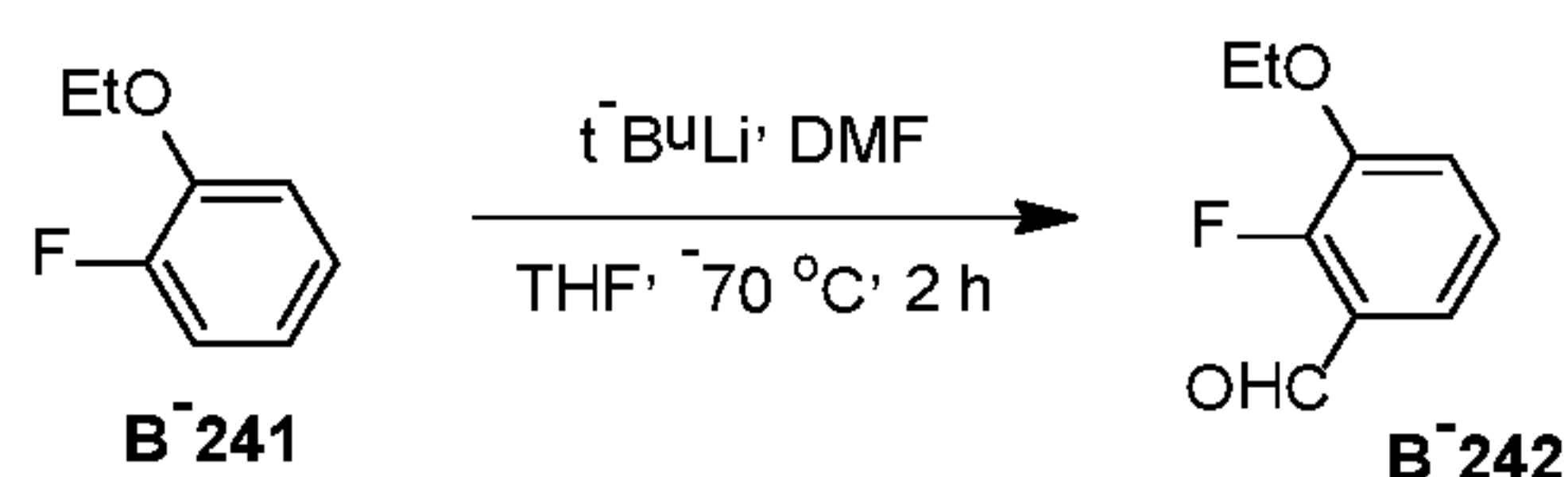
[00542] A mixture of **compound B-239** (0.5 g, 2.1 mmol) and lithium hydroxide monohydrate (0.62 g, 15 mmol) in methanol (5 mL) and water (2.5 mL) was stirred at $40\text{ }^\circ\text{C}$ for 5 hours. The mixture was concentrated in vacuo, added to water (50 mL), washed with ethyl acetate (3×10 mL), acidified and extracted with ethyl acetate (3×50 mL). The combined organic phases were washed with brine (3×10 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo to give **compound B-240** (0.36 g, 76% yield) as a yellow solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): 7.92 (s, 1H), 7.75 (d, $J=8.8$ Hz, 1H), 7.38 (d, $J=2.0$ Hz, 1H), 6.99 (dd, $J=8.8, 2.0$ Hz, 1H), 4.10 (q, $J=7.2$ Hz, 2H), 1.40 (t, $J=7.0$ Hz, 3H).

[00543] **Example 139B: 1-ethoxy-2-fluorobenzene (B-241)**



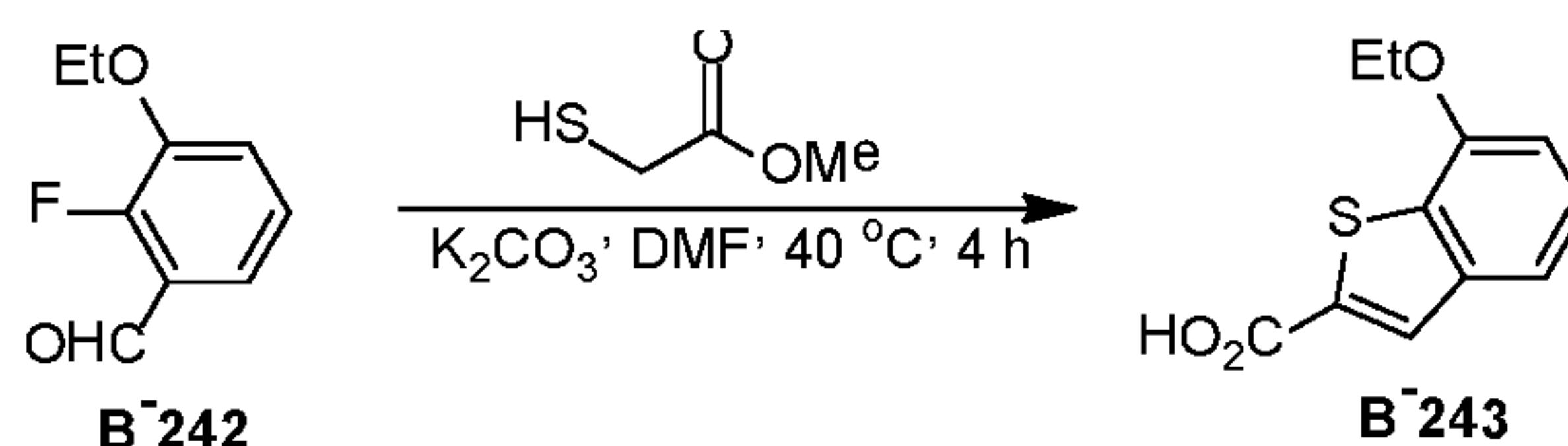
[00544] A mixture of 2-fluorophenol (5.0 g, 45 mmol), iodoethane (11 g, 71 mmol) and finely powdered potassium carbonate (12 g, 89 mmol) was stirred in acetone (5.0 mL) at $50\text{ }^\circ\text{C}$ for 16 h. On completion, the mixture was filtered over a pad of silica gel, washing with methyl tert-butyl ether. The solution was carefully concentrated (due to volatility of product) to give **compound B-241** (6.0 g, 96%) as a colorless liquid.

[00545] Example 140B: 3-ethoxy-2-fluorobenzaldehyde (B-242)



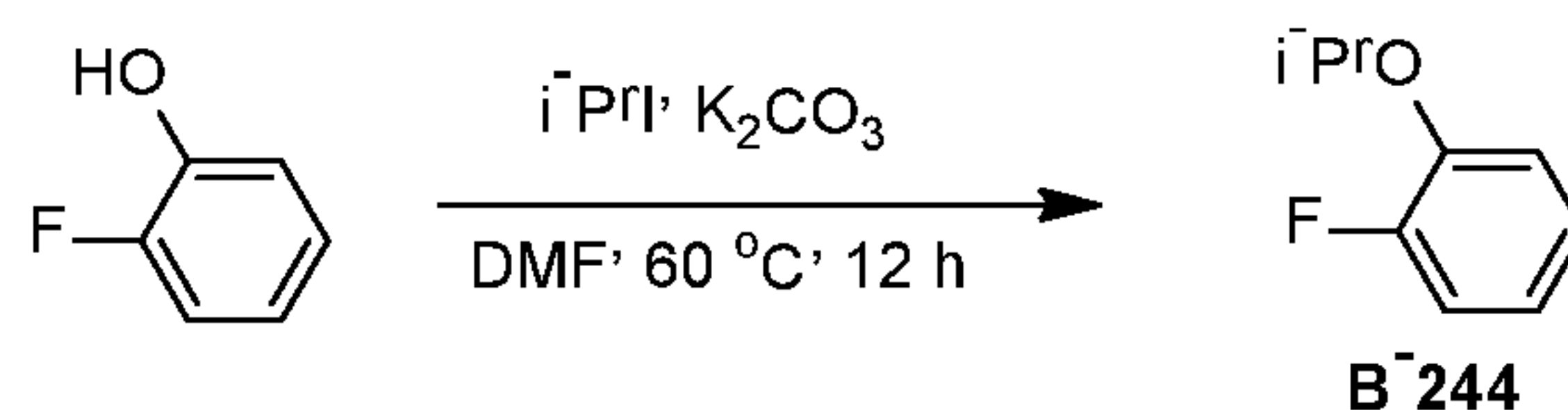
[00546] To a solution of **compound B-241** (6.0 g, 44 mmol) in tetrahydrofuran (30 mL) at $-70\text{ }^{\circ}\text{C}$ was added dropwise tert-butyllithium (41 mL, 1.3 M). The mixture was stirred for 30 min, and then *N,N*-dimethyl formamide (6.8 g, 88 mmol) was added, and stirring was continued for an additional 30 min. The cold bath was removed, and the reaction mixture was stirred at $15\text{ }^{\circ}\text{C}$ for 1 hour. On completion, the reaction was quenched with water (20 mL) and extracted with ethyl acetate ($3 \times 20\text{ mL}$). The combined organic phases were dried over sodium sulfate, filtered and concentrated in vacuo to give **compound B-242** (7.0 g, 94%) as colorless liquid. LCMS (Y): $t_R=0.770\text{ min.}$, $(\text{ES}^+) m/z (M+H)^+ = 169.1$.

[00547] Example 141B: 7-ethoxybenzo[b]thiophene-2-carboxylic acid (B-243)

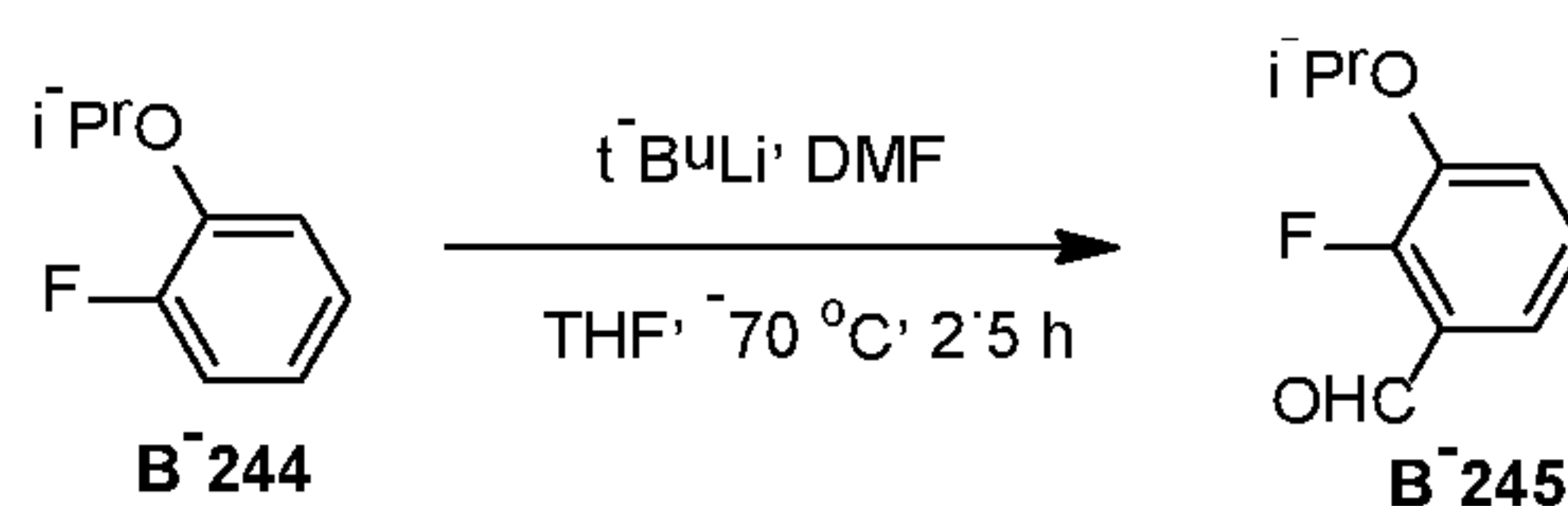


[00548] To a solution of **compound B-242** (7.0 g, 43 mmol) in dimethyl formamide (70 mL) was added methyl 2-mercaptoacetate (5.5 g, 51 mmol) and potassium carbonate (12 g, 86 mmol). The reaction mixture was stirred at $40\text{ }^{\circ}\text{C}$ for 4 hours, then quenched with water (15 mL), washed with ethyl acetate ($3 \times 10\text{ mL}$), acidified with 4 N HCl and extracted with ethyl acetate ($3 \times 10\text{ mL}$). The combined organic phases were dried over sodium sulfate, filtered and concentrated in vacuo to give **compound B-243** (9.0 g, 95% yield) as a light yellow solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 8.01 (s, 1H), 7.49 (d, $J=8.0\text{ Hz}$, 1H), 7.37-7.33 (m, 1H), 6.96 (d, $J=8.0\text{ Hz}$, 1H), 4.25 (dd, $J_1=8.4\text{ Hz}$, $J_2=2.0\text{ Hz}$, 2H), 1.50-1.17 (m, 3H).

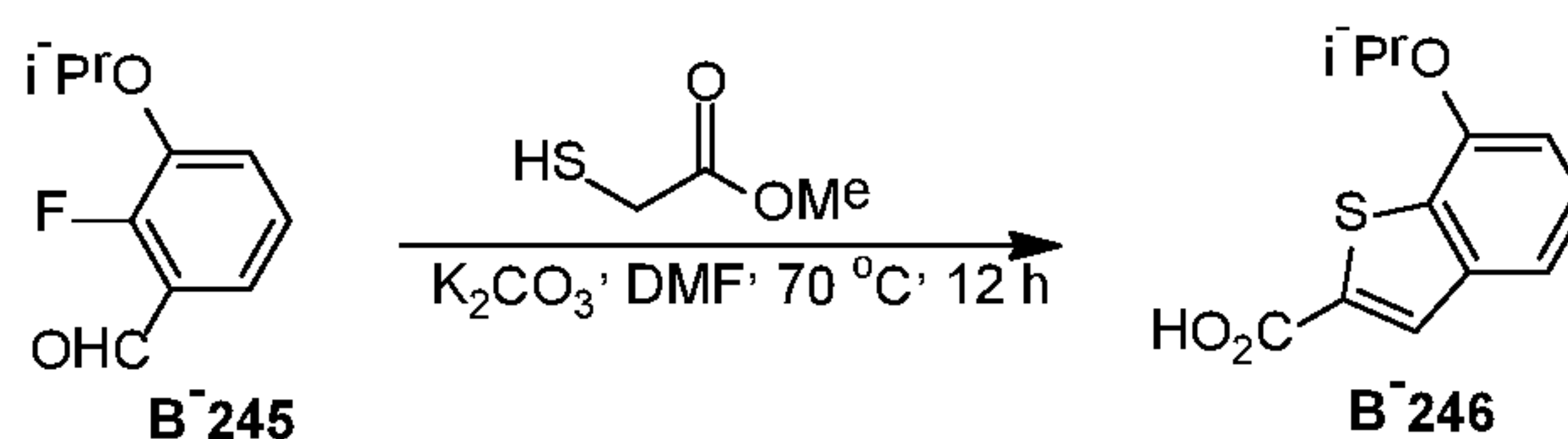
[00549] Example 142B: 1-fluoro-2-isopropoxybenzene (B-244)



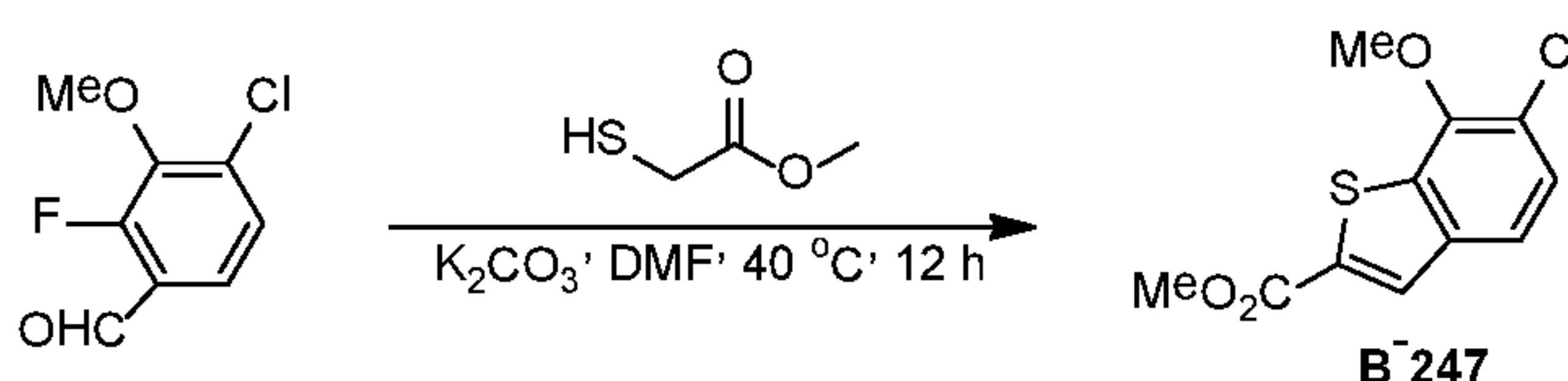
[00550] A mixture of 2-fluorophenol (1.0 g, 8.9 mmol), 2-iodopropane (3.0 g, 17.8 mmol) and finely powdered potassium carbonate (4.9 g, 35.7 mmol) was stirred in *N,N*-dimethylformamide (10.0 mL) at $60\text{ }^{\circ}\text{C}$ for 12 h. On completion, the mixture was filtered over a pad of silica gel, washing with methyl tert-butyl ether. The solution was carefully concentrated (due to volatility of product) to give **compound B-244** (1.4 g, 58%) as a yellow oil. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.29-7.01 (m, 3H), 6.92-6.91 (m, 1H), 4.59-4.53 (m, 1H), 1.40-1.33 (m, 6H).

[00551] Example 143B: 2-fluoro-3-isopropoxybenzaldehyde (B-245)

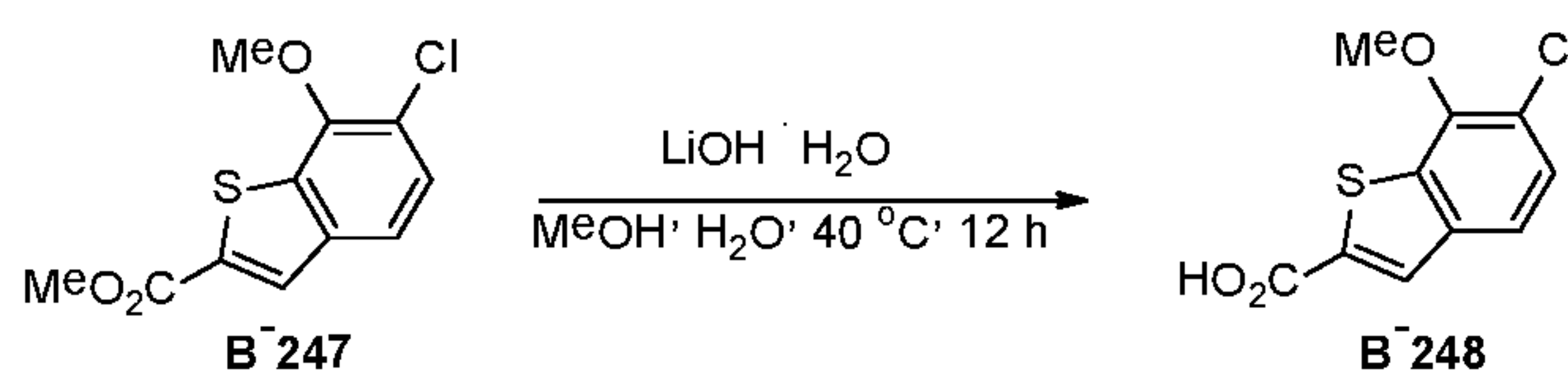
[00552] To a solution of **compound B-244** (2.0 g, 13 mmol) in tetrahydrofuran (20 mL) at $-70\text{ }^{\circ}\text{C}$ was added dropwise tert-butyllithium (20.0 mL, 1.3 M). The reaction was stirred for 30 mins., and then *N,N*-dimethylformamide (1.9 g, 25.9 mmol) was added, and stirring was continued for an additional 2 h. On completion, the reaction was quenched with water (5 ml) and extracted with ethyl acetate ($3 \times 30\text{ mL}$). The combined organic phases were dried over sodium sulfate and concentrated to give **compound B-245** (2.4 g, 50%) as a yellow oil. LCMS (B): $t_R=0.700\text{ min.}$, $(\text{ES}^+) m/z (\text{M}+\text{H})^+ = 183.2$.

[00553] Example 144B: 7-isopropoxybenzo[b]thiophene-2-carboxylic acid (B-246)

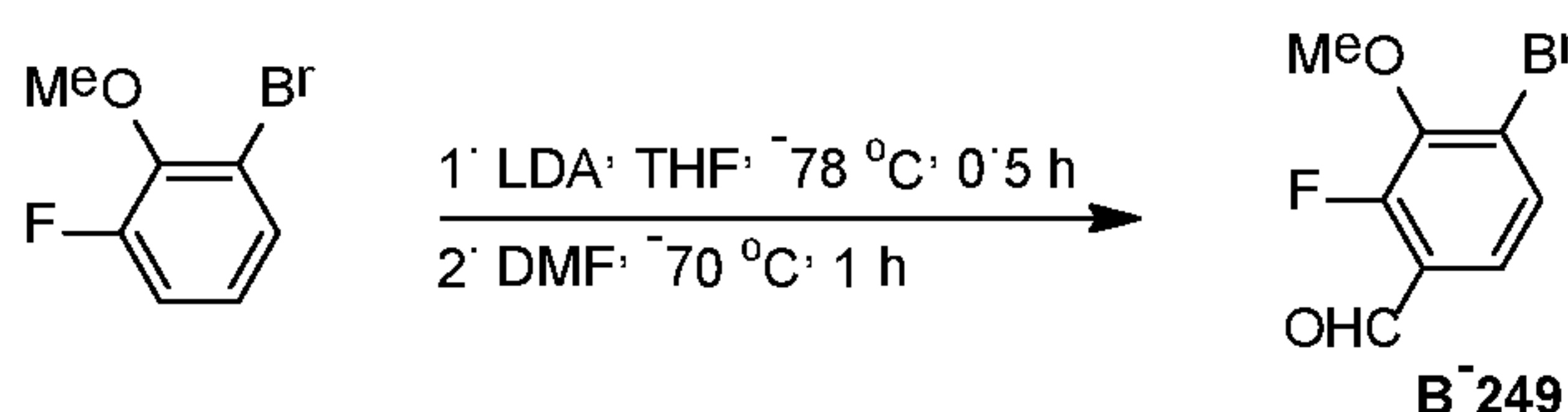
[00554] To a solution of **compound B-245** (2.5 g, 13.7 mmol) in *N,N*-dimethylformamide (25 mL) was added methyl 2-mercaptoacetate (2.9 g, 27.4 mmol) and potassium carbonate (3.8 g, 27.4 mmol). The reaction mixture was stirred at $70\text{ }^{\circ}\text{C}$ for 12 hours, then quenched with water (20 mL), washed with ethyl acetate ($3 \times 20\text{ mL}$) and acidified to pH 3 with 1 M hydrochloric acid, resulting in formation of a solid. The white solid was collected by filtration and dried in vacuo to give **compound B-246** (700 mg, 21% yield). $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 8.17 (s, 1H), 7.52 (d, $J=8.0\text{ Hz}$, 1H), 7.38 (t, $J=8.0\text{ Hz}$, 1H), 6.93 (d, $J=7.6\text{ Hz}$, 1H), 4.80-4.77 (m, 1H), 1.48-1.46 (m, 6H).

[00555] Example 145B: methyl 6-chloro-7-methoxybenzo[b]thiophene-2-carboxylate (B-247)

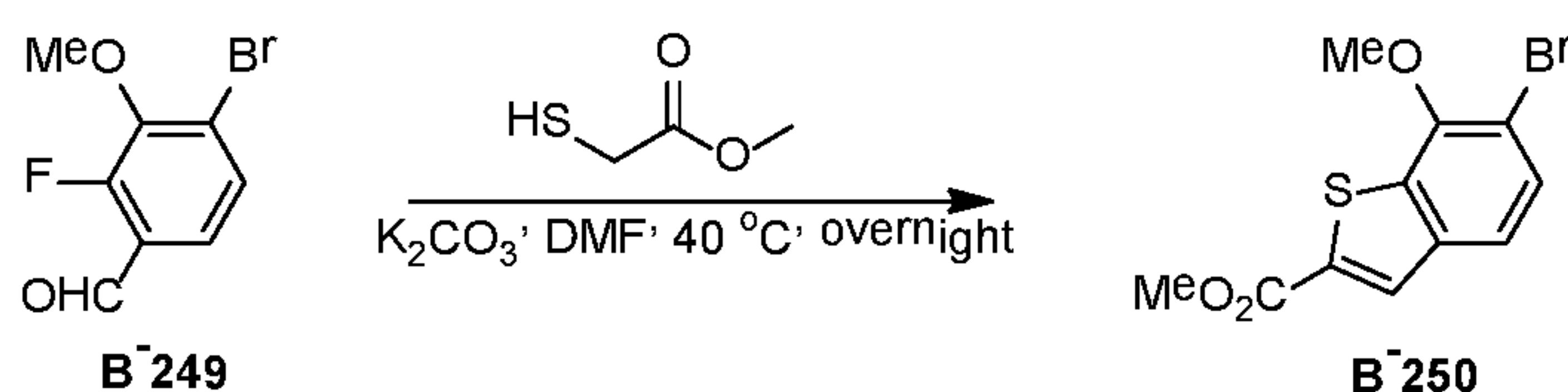
[00556] To a mixture of 4-chloro-2-fluoro-3-methoxybenzaldehyde (0.5 g, 2.65 mmol) in *N,N*-dimethylformamide (5.0 mL) was added methyl 2-mercaptoacetate (0.56 g, 5.30 mmol) and potassium carbonate (0.73 g, 5.30 mmol). The mixture was stirred at $40\text{ }^{\circ}\text{C}$ for 12 hours. On completion, the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-247** (230 mg, 33% yield) as a white solid. LCMS (B): $t_R=0.820\text{ min.}$, $(\text{ES}^+) m/z (\text{M}+\text{H})^+ = 257.1$.

[00557] Example 146B: 6-chloro-7-methoxybenzo[b]thiophene-2-carboxylic acid (B-248)

[00558] To a mixture of **compound B-247** (230 mg, 0.90 mmol) in methanol (6 mL) and water (3 mL) was added lithium hydroxide monohydrate (56 mg, 1.3 mmol). The mixture was stirred at 40 °C for 12 hours, then concentrated to remove methanol, diluted with water and acidified to pH 3 with 1 M hydrochloric acid, resulting in formation of a solid. The white solid was collected by filtration and dried in vacuo to give **compound B-248** (200 mg, 91% yield). ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 13.71 (s, 1H), 8.16 (s, 1H), 7.80 (d, J=8.4 Hz, 1H), 7.57 (d, J=8.8 Hz, 1H), 4.00 (s, 3H).

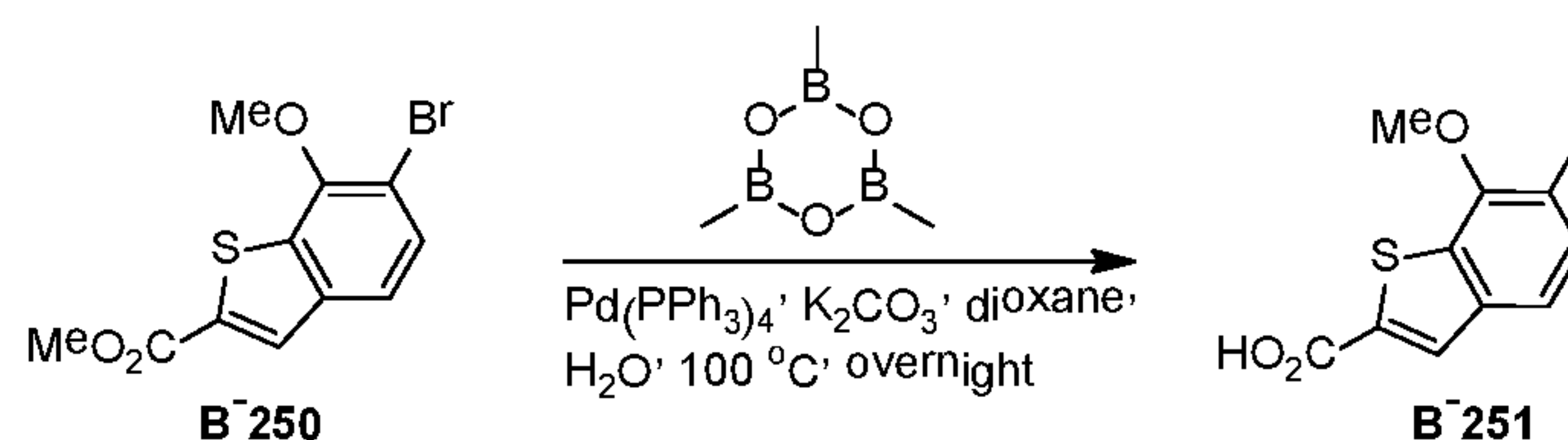
[00559] Example 147B: 4-bromo-2-fluoro-3-methoxybenzaldehyde (B-249)

[00560] To a mixture of 1-bromo-3-fluoro-2-methoxybenzene (5.0 g, 25 mmol) in anhydrous tetrahydrofuran (50 mL) at -78 °C under nitrogen was added dropwise lithium diisopropylamide (2.0 M in *n*-heptane, 18 mL, 37 mmol). The mixture was stirred at this temperature for half an hour, then *N,N*-dimethylformamide (5.4 g, 73 mmol) was added dropwise, and stirring was continued at -78 °C for another 1 hour. On completion, the mixture was poured into water (50 mL) and extracted with ethyl acetate (2 × 80 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-249** (5.5 g, crude) as yellow oil.

[00561] Example 148B: methyl 6-bromo-7-methoxybenzo[b]thiophene-2-carboxylate (B-250)

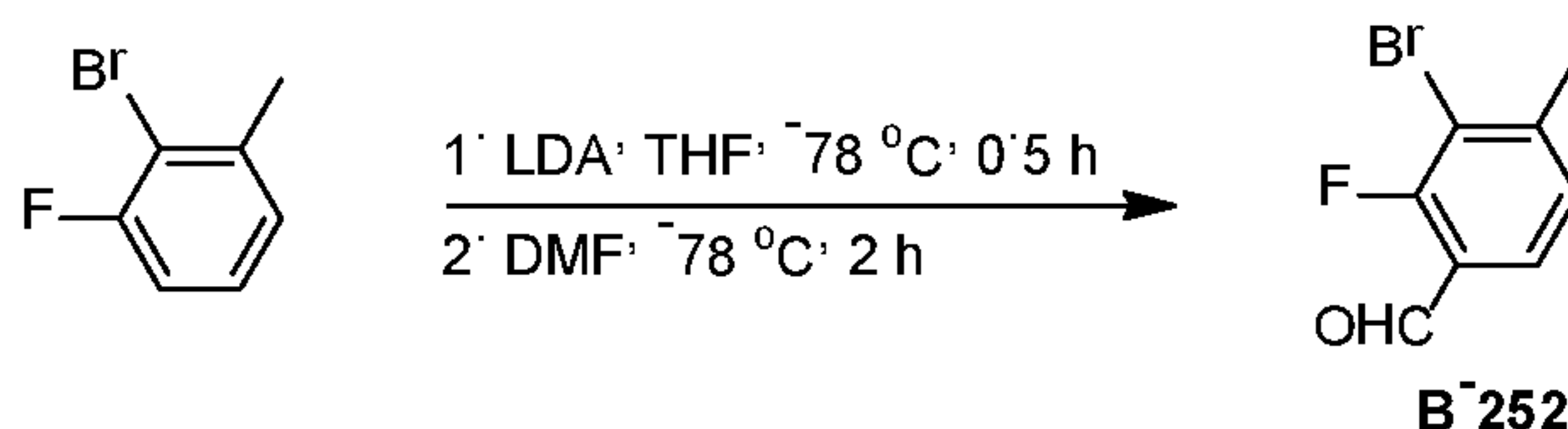
[00562] To a mixture of **compound B-249** (5.5 g, crude) in *N,N*-dimethylformamide (55 mL) was added methyl 2-mercaptoacetate (3.0 g, 28 mmol) and potassium carbonate (6.5 g, 47 mmol). The mixture was stirred at 40 °C overnight, then poured into water (20 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-250** (3.2 g, 45% yield) as a white solid. LCMS (R): tR=0.900 min., (ES⁺) m/z (M+H)⁺=302.9.

[00563] **Example 149B: 7-methoxy-6-methylbenzo[b]thiophene-2-carboxylic acid (B-251)**



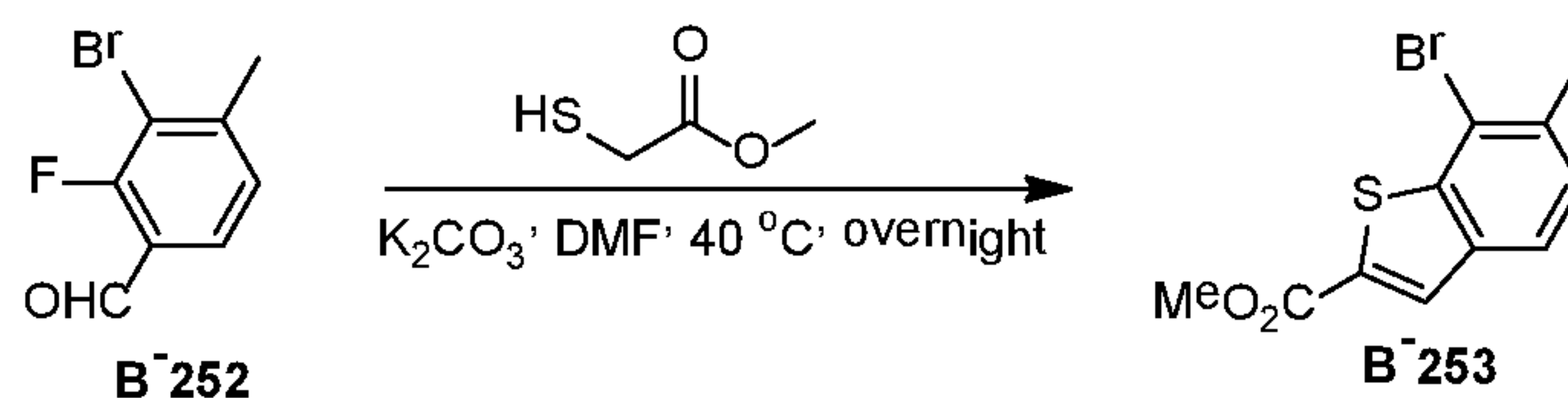
[00564] To a mixture of methyl **compound B-250** (1.0 g, 3.3 mmol) in dioxane (20 mL) and water (4 mL) under nitrogen was added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (1.3 g, 10 mmol), tetrakis(triphenylphosphine)palladium (0.38 g, 0.33 mmol) and potassium carbonate (0.92 g, 6.6 mmol). The mixture was stirred at 100 °C overnight, then concentrated in vacuo to remove dioxane, poured into water (20 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 33-63% acetonitrile in H₂O (add 0.05% HCl, v/v)] to give **compound B-251** (0.20 g, 27% yield) as a white solid. LCMS (B): tR=0.764 min., (ES⁺) m/z (M+H)⁺=223.1.

[00565] **Example 150B: 3-bromo-2-fluoro-4-methylbenzaldehyde (B-252)**



[00566] To a mixture of 2-bromo-1-fluoro-3-methylbenzene (3.0 g, 16 mmol) in anhydrous tetrahydrofuran (30 mL) at -78 °C under nitrogen was added dropwise lithium diisopropylamide (2.0 M in n-heptane solution, 12 mL, 24 mmol). The mixture was stirred at this temperature for 0.5 hour, then *N,N*-dimethylformamide (3.5 g, 48 mmol) was added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for another 2 hours. On completion, the mixture was poured into water (20 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-252** (2.1 g, 62% yield) as a white solid. TLC [Petroleum ether: Ethyl acetate = 10:1]: R_f = 0.4.

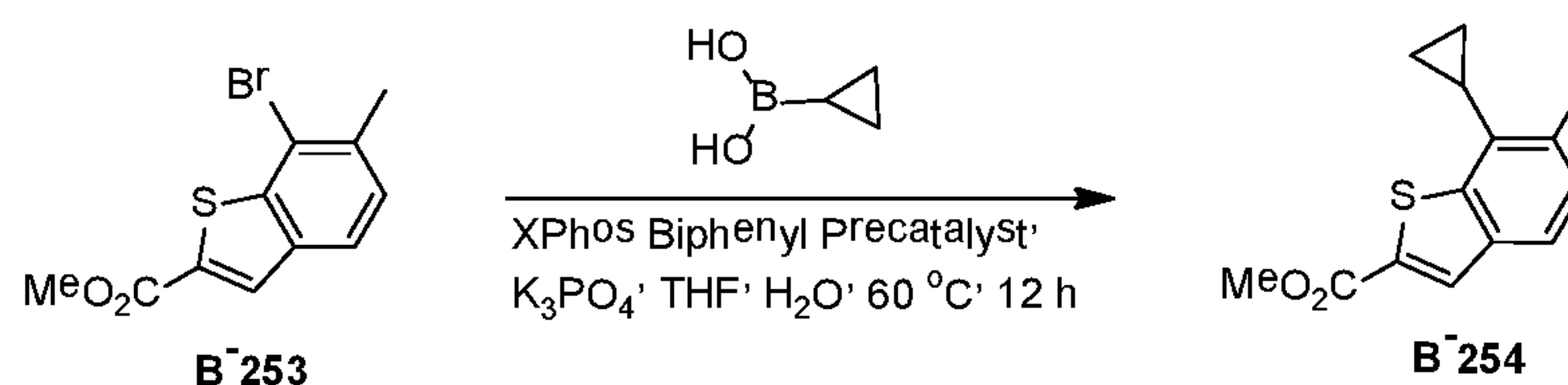
[00567] **Example 151B: methyl 7-bromo-6-methylbenzo[b]thiophene-2-carboxylate (B-253)**



[00568] To a mixture of **compound B-252** (2.1 g, 9.8 mmol) in *N,N*-dimethylformamide (30 mL) was added methyl 2-mercaptoacetate (1.4 g, 13 mmol) and potassium carbonate (2.7 g, 20 mmol). The mixture was stirred at 40 °C overnight. On completion, the mixture was poured into water (20 mL), extracted with ethyl acetate (2 × 40 mL). The combined organic layers were dried over anhydrous

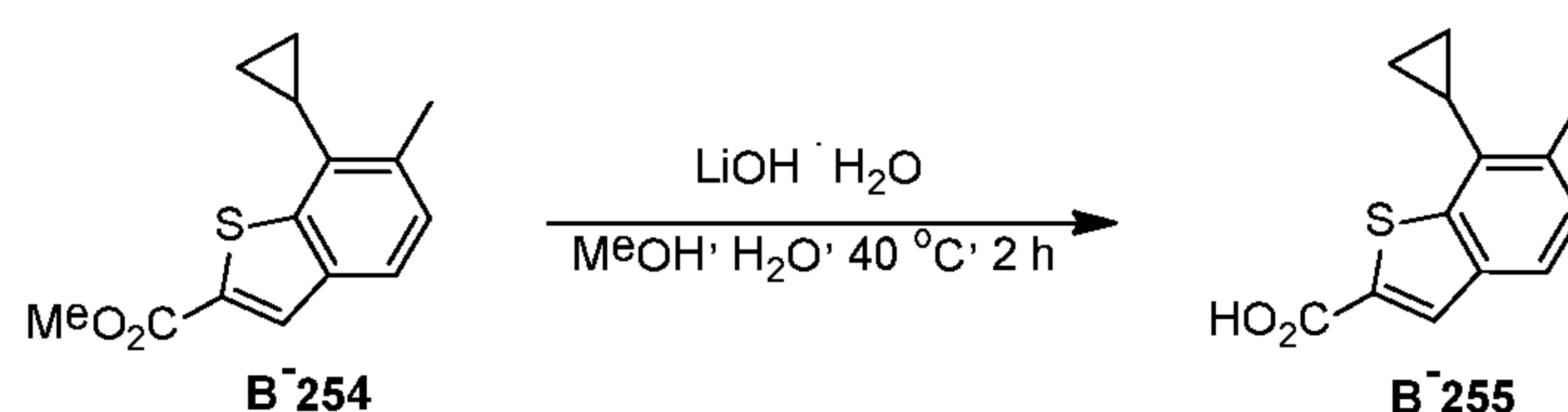
sodium sulfate and concentrated in vacuo to give **compound B-253** (2.4 g, 92% purity, 79% yield) as a white solid. LCMS (B): tR=1.052 min., (ES⁺) m/z (M+H)⁺=287.0.

[00569] **Example 152B:** methyl 7-cyclopropyl-6-methylbenzo[*b*]thiophene-2-carboxylate (**B-254**)



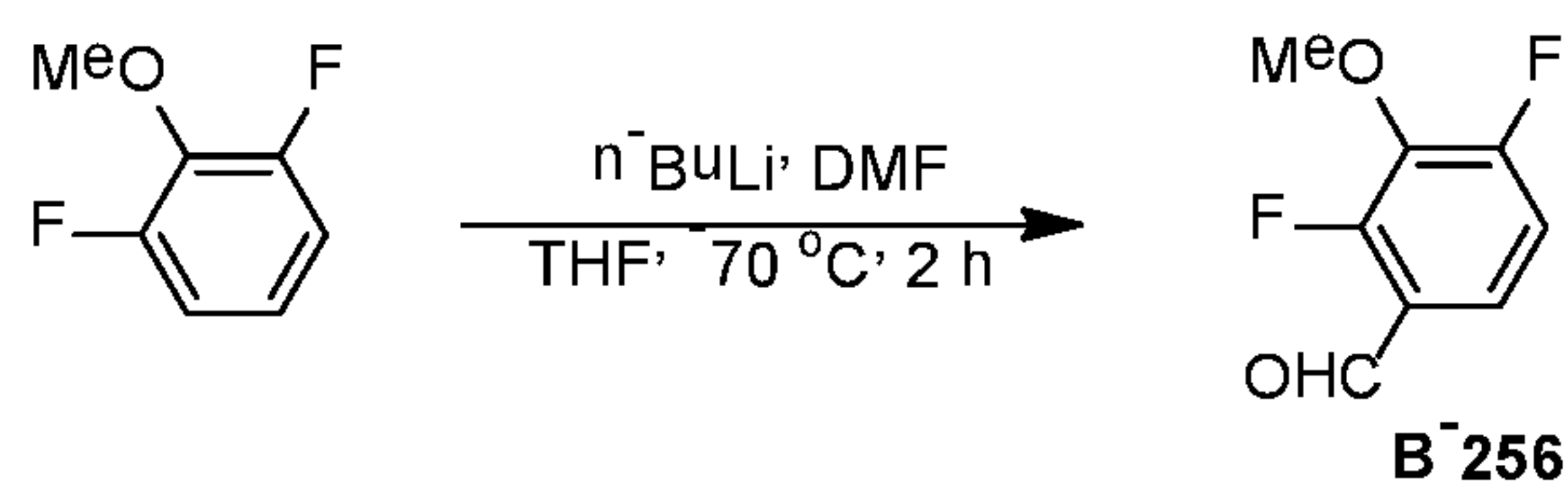
[00570] To a mixture of **compound B-253** (0.60 g, 2.1 mmol) in tetrahydrofuran (15 mL) and water (5 mL) under nitrogen was added cyclopropylboronic acid (0.90 g, 11 mmol), potassium phosphate (0.89 g, 4.2 mmol) and [2-(2-aminophenyl)phenyl]-chloro-palladium;dicyclohexyl-[3-(2,4,6-triisopropylphenyl)phenyl]phosphane (83 mg, 0.11 mmol). The mixture was stirred at 60 °C for 12 hours, then diluted with water (15 mL) and extracted with ethyl acetate (2 × 30 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 50:1] to give **compound B-254** (0.43 g, 83% purity, 69% yield) as a yellow solid. LCMS (B): tR=0.935 min., (ES⁺) m/z (M+H)⁺=247.1.

[00571] **Example 153B:** 7-cyclopropyl-6-methylbenzo[*b*]thiophene-2-carboxylic acid (**B-255**)



[00572] To a mixture of **compound B-254** (0.43 g, 1.8 mmol) in methanol (8 mL) and water (4 mL) was added lithium hydroxide monohydrate (0.15 g, 3.5 mmol). The mixture was stirred at 40 °C for 2 hours, then concentrated to remove methanol, diluted with water, acidified to pH 3 with 6 M hydrochloric acid and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-255** (0.39 g, 81% purity, 78% yield) as a white solid. LCMS (B): tR=0.815 min., (ES⁺) m/z (M+H)⁺=233.1.

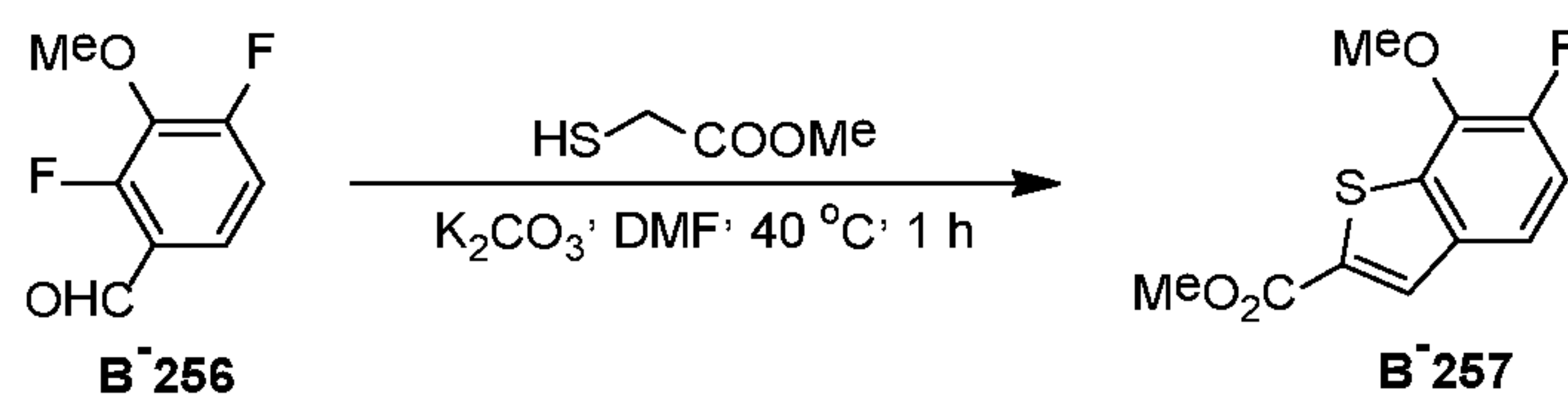
[00573] **Example 154B:** 1,3-difluoro-2-methoxy-benzene (**B-256**)



[00574] To a solution of 1,3-difluoro-2-methoxybenzene (3.0 g, 20.8 mmol) in tetrahydrofuran (30 mL) at -70 °C was added dropwise n-butyl lithium (1.6 g, 25.0 mmol). The reaction was stirred for 30 mins. Then *N,N*-dimethylformamide (4.6 g, 63 mmol) was added, and stirring was continued for another 30 minute. The cold bath was removed, and the reaction mixture was stirred at 15 °C for 1 hour. On completion, the mixture was extracted with ethyl acetate (2 × 15 mL). The aqueous phase was acidified with 4 M hydrochloric acid and extracted with ethyl acetate (3 × 10 mL). The organic

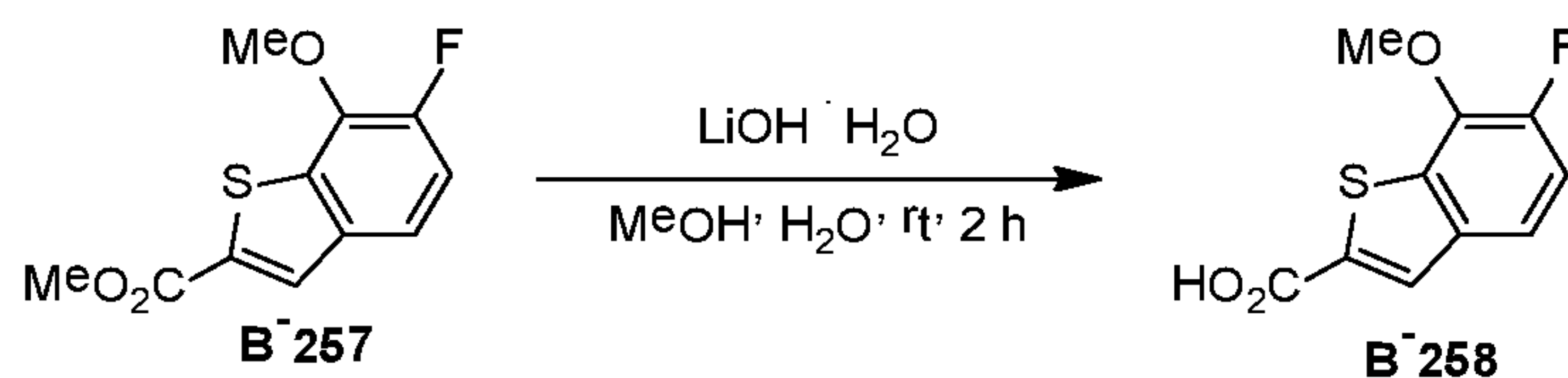
phases were combined, dried over sodium sulfate and evaporated in vacuo to give **compound B-256** (3.0 g, 84% yield) as a light yellow liquid. LCMS (B): tR=0.624 min., 173.1 m/z (M+1).

[00575] **Example 155B:** methyl 6-fluoro-7-methoxybenzo[b]thiophene-2-carboxylate (**B-257**)



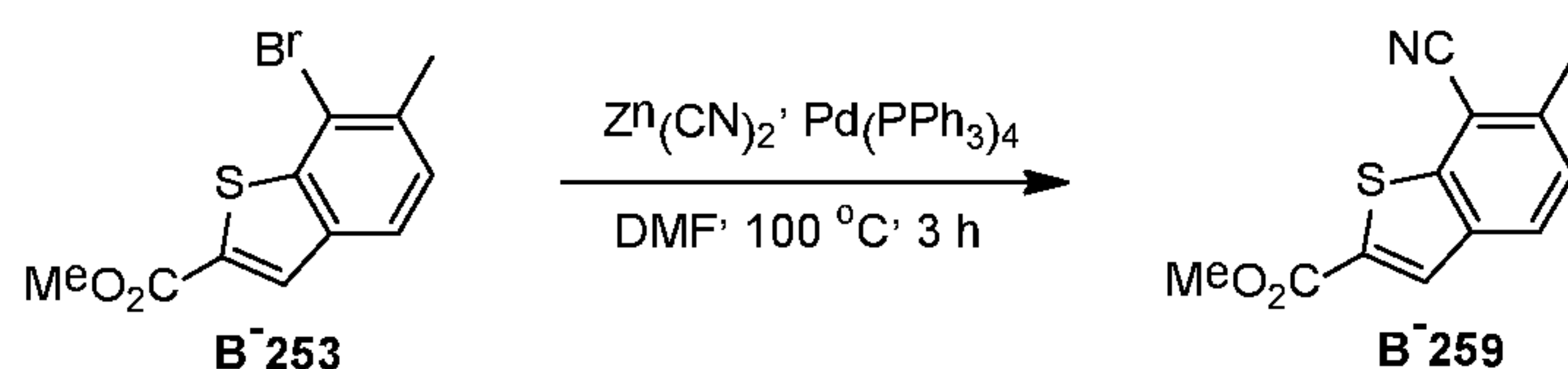
[00576] To a solution of **compound B-256** (3.0 g, 17.4 mmol) in *N,N*-dimethylformamide (30 mL) was added methyl 2-mercaptoacetate (1.8 g, 17.4 mmol) and potassium carbonate (4.8 g, 34.9 mmol). The mixture was stirred at $15\text{ }^\circ\text{C}$ for 2 hours, then poured in to water (30 mL) and extracted with ethyl acetate ($3 \times 10\text{ mL}$). The combined organic phases were washed with brine ($2 \times 10\text{ mL}$), dried over sodium sulfate and concentrated in vacuo to give **compound B-257** (2.1 g, 50% yield) as a light yellow solid. LCMS (B): tR=0.882 min., 241.0 m/z (M+1).

[00577] **Example 156B:** 6-fluoro-7-methoxybenzo[b]thiophene-2-carboxylic acid (**B-258**)



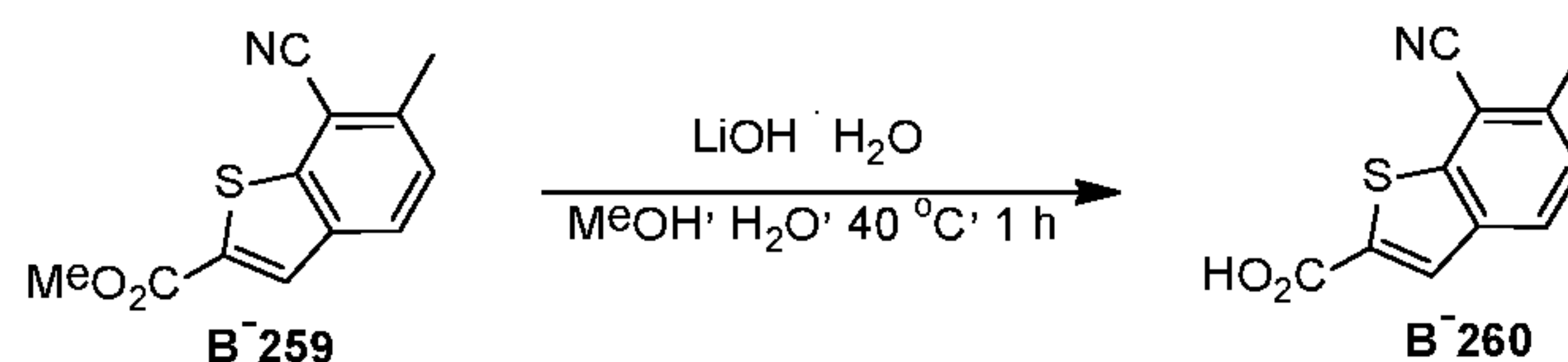
[00578] To a solution of **B-257** (2.1 g, 8.7 mmol) in methanol (20 mL) and water (10 mL) was added lithium hydroxide hydrate (367 mg, 8.7 mmol). The mixture was stirred at $25\text{ }^\circ\text{C}$ for 2 hours, then concentrated to remove methanol, diluted with water, and acidified to pH 3 with 1 M hydrochloric acid and extracted with ethyl acetate ($2 \times 10\text{ mL}$). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo to give **B-258** (900 mg, 46% yield) as a white solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 8.01 (s, 1H), 7.54 (dd, $J_1=8.4\text{ Hz}$, $J_2=4.0\text{ Hz}$, 1H), 7.26 (dd, $J_1=12\text{ Hz}$, $J_2=8.4\text{ Hz}$, 1H), 4.12 (d, $J=2.4\text{ Hz}$, 3H).

[00579] **Example 157B:** methyl 7-cyano-6-methylbenzo[b]thiophene-2-carboxylate (**B-259**)



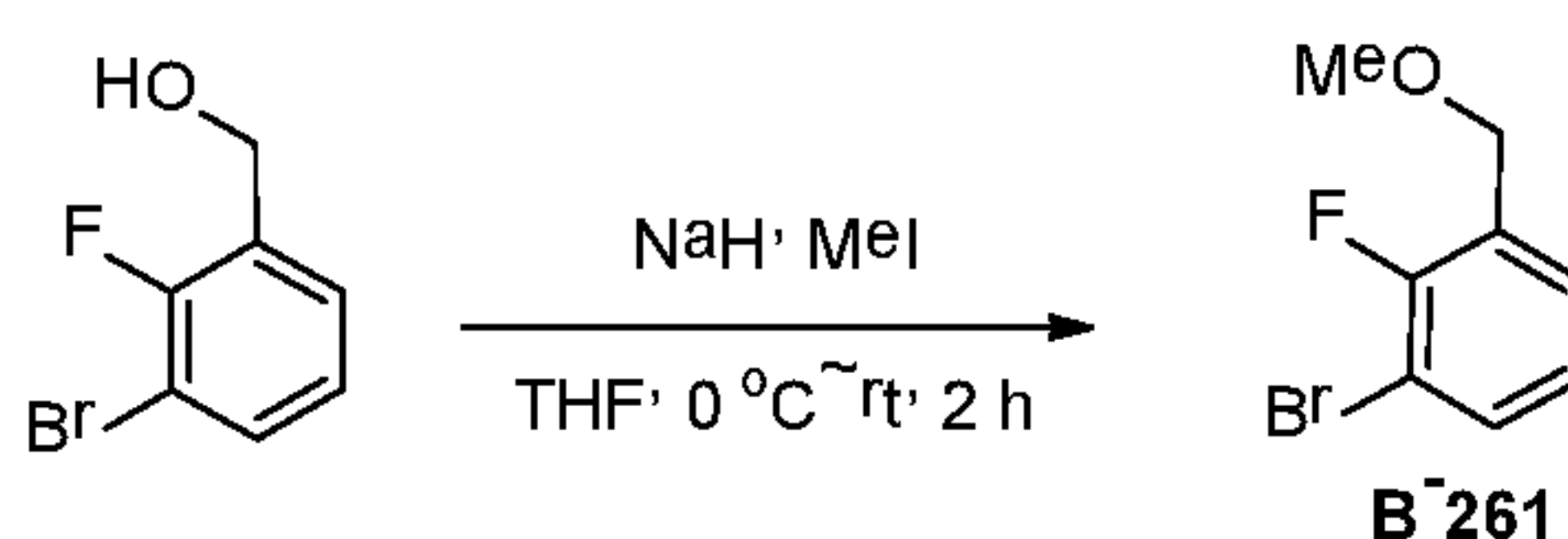
[00580] To a mixture of **compound B-253** (0.50 g, 1.8 mmol) in *N,N*-dimethylformamide (20 mL) under nitrogen was added zinc cyanide (0.41 g, 3.5 mmol) and tetrakis(triphenylphosphine)palladium (0.20 g, 0.18 mmol). The mixture was stirred at $100\text{ }^\circ\text{C}$ for 3 hours, then diluted with water (20 mL) and extracted with ethyl acetate ($2 \times 30\text{ mL}$). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-259** (0.15 g, 96% purity, 36% yield) as a white solid. LCMS (B): tR=0.846 min., (ES^+) m/z ($\text{M}+\text{H}$) $^+$ =232.0.

[00581] **Example 158B: 7-cyano-6-methylbenzo[*b*]thiophene-2-carboxylic acid (B-260)**



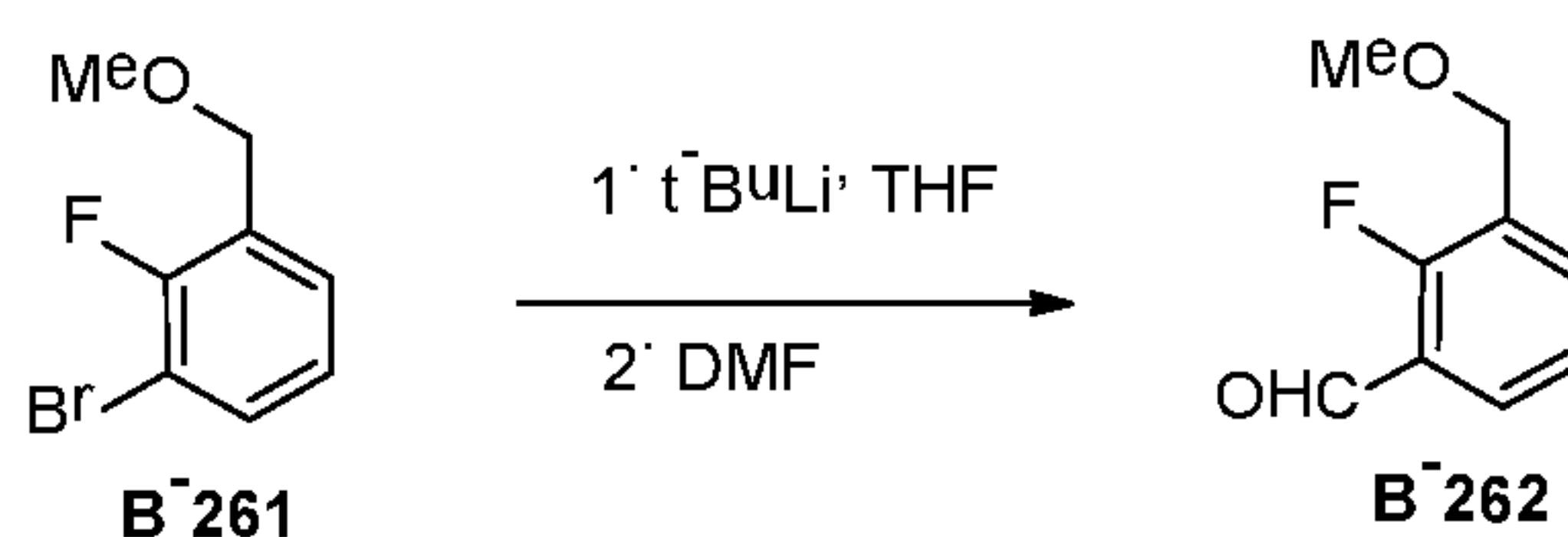
[00582] To a mixture of **compound B-259** (0.15 g, 0.65 mmol) in methanol (2 mL) and water (1 mL) was added lithium hydroxide monohydrate (54 g, 1.3 mmol). The mixture was stirred at 40 °C for 1 hour, then concentrated to remove methanol, diluted with water, acidified to pH 3 with 6 M hydrochloric acid and extracted with ethyl acetate (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-260** (0.14 g, 98% purity, 93% yield) as a white solid. LCMS (B): tR=0.724 min., (ES⁺) m/z (M+H)⁺=218.0.

[00583] **Example 159B: 1-bromo-2-fluoro-3-(methoxymethyl)benzene (B-261)**

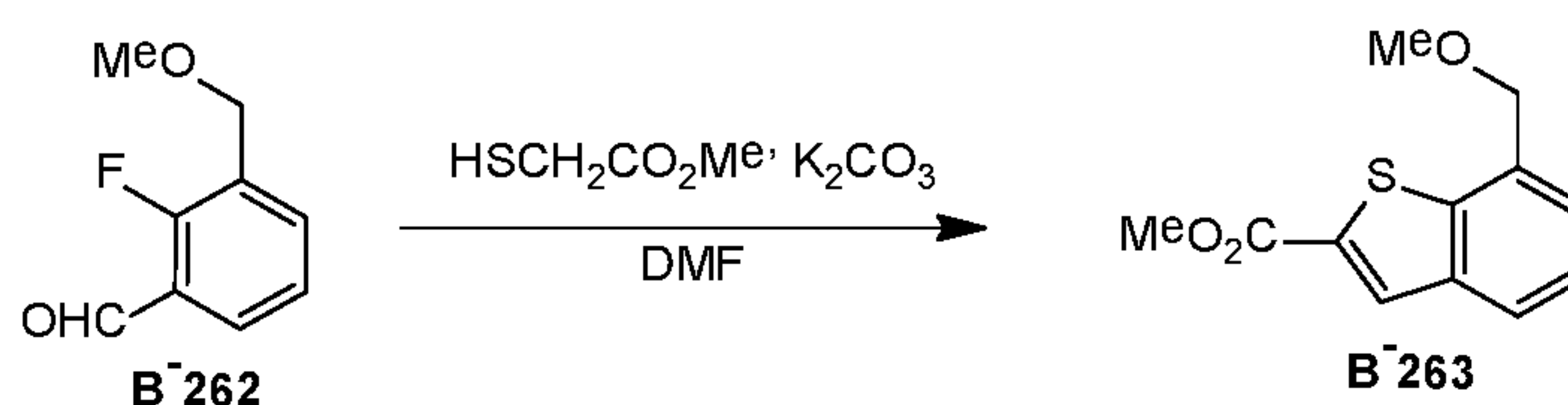


[00584] To a solution of (3-bromo-2-fluorophenyl)methanol (5.0 g, 24 mmol) in tetrahydrofuran (50 mL) at 0 °C under nitrogen was added sodium hydride (1.9 g, 49 mmol, 60 % w/w) in portions. The mixture was stirred at 0 °C for 30 minutes, and iodomethane (17 g, 72 mmol) was added to the mixture. The reaction mixture was stirred at room temperature for 1.5 h, then quenched with ice-water (50 mL), stirred for 30 min. and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over anhydrous sodium sulfate, concentrated in vacuo and purified by silica gel column chromatography [petroleum ether: ethyl acetate = 15:1] to give **compound B-261** (5.2 g, 94% yield) as a yellow oil.

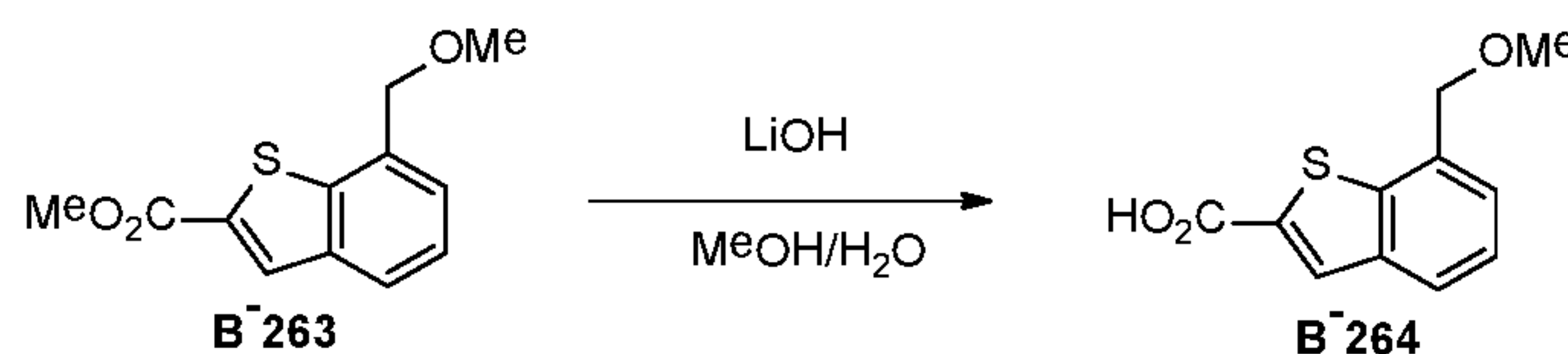
[00585] **Example 160B: 2-fluoro-3-(methoxymethyl)benzaldehyde (B-262)**



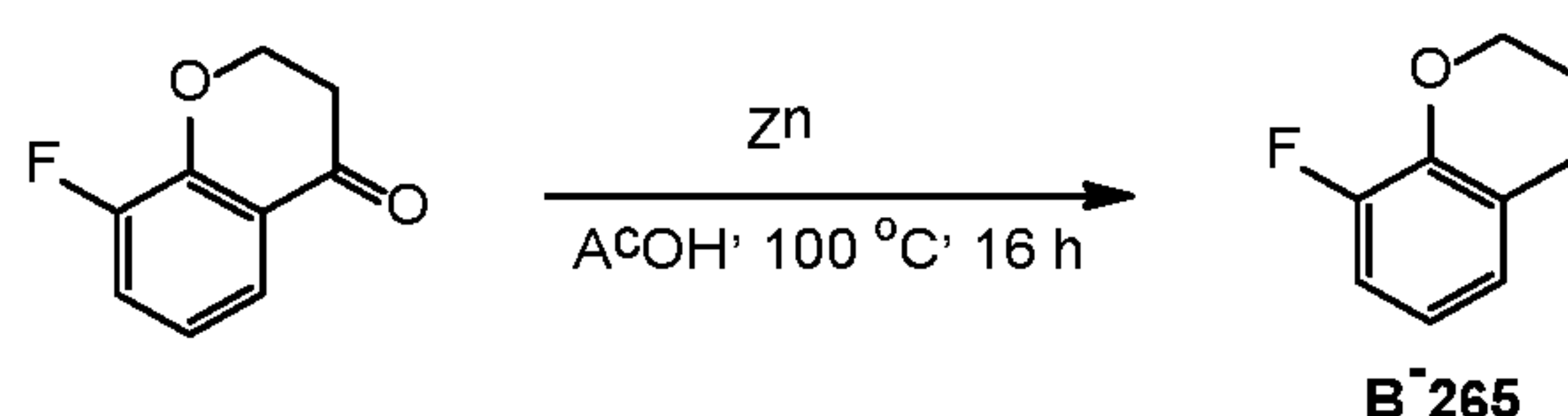
[00586] To a solution of **compound B-261** (3.0 g, 14 mmol) in tetrahydrofuran (30 mL) at -78 °C was added n-butyllithium (2.5 mol/L, 3.8 mL, 15 mmol). The reaction mixture was stirred at this temperature for 30 min., and *N,N*-dimethylformamide (2.0 g, 28 mmol) was added. The reaction was allowed to warm from -78 °C to 0 °C over 1 hour, then quenched with saturated aqueous ammonium chloride (30 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were concentrated, and the residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-262** (1.6 g, 69% yield) as a yellow oil. ¹H-NMR (CDCl₃, 400 MHz): δ 7.50 (t, J=7.2 Hz, 1H), 7.38 (t, J=6.8 Hz, 1H), 7.05 (t, J=7.6 Hz, 1H).

[00587] **Example 161B: methyl 7-(methoxymethyl)benzo[b]thiophene-2-carboxylate (B-263)**

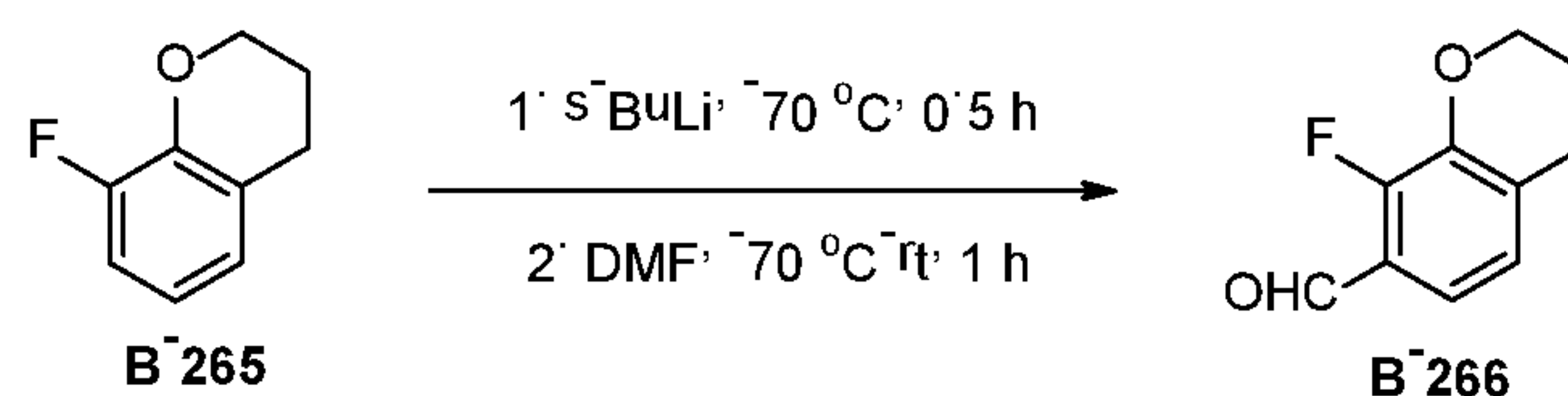
[00588] To a solution of **compound B-262** (1.6 g, 9.5 mmol) in *N,N*-dimethylformamide (20 mL) under nitrogen was added potassium carbonate (2.6 g, 19 mmol) and methyl 2-mercaptoacetate (1.5 g, 14 mmol). The resulting mixture was stirred at 50 °C for 5 hours. On completion, the mixture was diluted with water (20 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 30:1] to give **compound B-263** (1.8 g, 80% yield) as a yellow oil. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 8.02 (s, 1H), 7.79-7.74 (m, 1H), 7.34-7.32 (m, 2H), 4.67 (s, 2H), 3.88 (s, 3H), 3.38 (s, 3H).

[00589] **Example 162B: 7-(methoxymethyl)benzo[b]thiophene-2-carboxylic acid (B-264)**

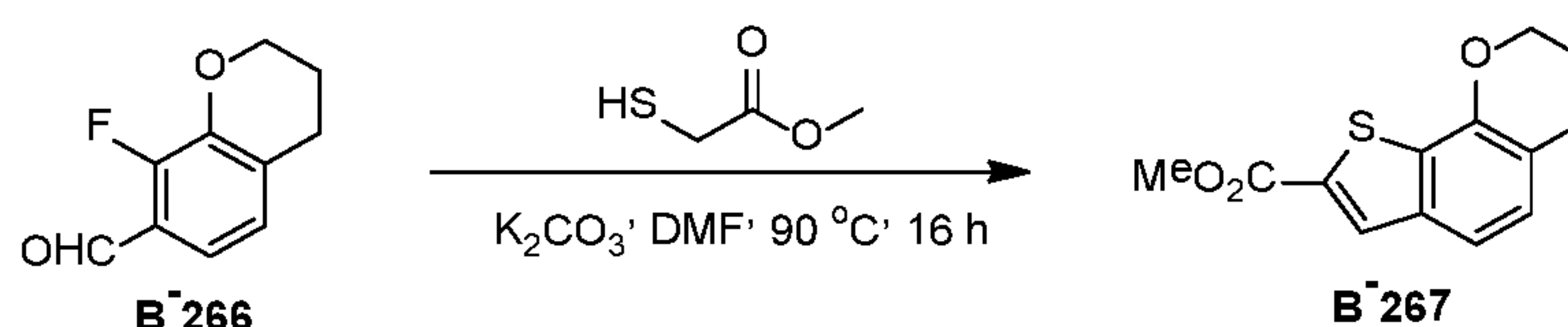
[00590] To a solution of **B-263** (1.8 g, 7.6 mmol) in methanol (10 mL) and water (5 mL) was added lithium hydroxide monohydrate (0.36 g, 15 mmol). The mixture was stirred at 25 °C for 1 hour, then concentrated to remove methanol, diluted with water, and acidified to pH 4-5 with 1 M hydrochloric acid, resulting in precipitation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-264** (1.7 g, 71% yield) as a white solid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.50 (s, 1H), 7.89-7.87 (dd, $J_1=7.2$ Hz, $J_2=2.0$ Hz, 1H), 7.47-7.42 (m, 2H), 4.78 (s, 2H), 3.49 (s, 3H).

[00591] **Example 163B: 8-fluorochroman (B-265)**

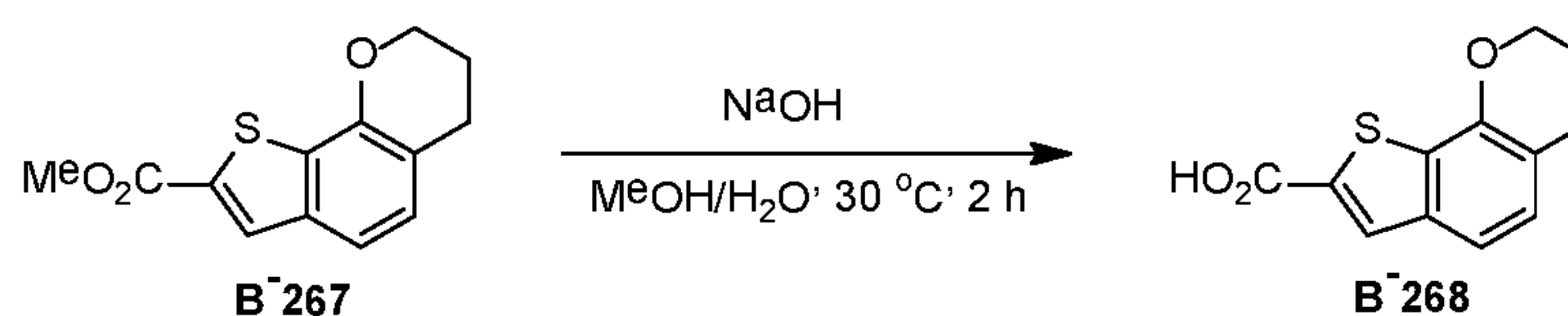
[00592] To a mixture of zinc powder (30 g, 0.45 mol) in acetic acid (10 mL) at room temperature was added slowly a solution of 8-fluorochroman-4-one (3.0 g, 18 mmol) in acetic acid (10 mL). The reaction mixture was stirred at 100 °C for 16 hours, then diluted with ethyl acetate (100 mL) and filtered. The filtrate was concentrated in vacuo and purified by silica gel chromatography [petroleum ether: ethyl acetate = 50:1] to give **compound B-265** (2.1 g, 67% yield) as a yellow oil. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 6.94-6.89 (m, 1H), 6.84-6.82 (m, 1H), 6.79-6.76 (m, 1H), 4.30-4.27 (t, $J = 5.2$ Hz, 2H), 2.85-2.81 (t, $J = 6.4$ Hz, 2H), 2.12-2.04 (m, 2H).

[00593] **Example 164B: 8-fluorochroman-7-carbaldehyde (B-266)**

[00594] To a mixture of **compound B-265** (1.0 g, 6.6 mmol) in anhydrous tetrahydrofuran (50 mL) at $-70\text{ }^{\circ}\text{C}$ under nitrogen was added dropwise sec-butyllithium (1.3 M in n-hexane solution, 10 mL, 13 mmol). The mixture was stirred at $-70\text{ }^{\circ}\text{C}$ for 0.5 hour, and then *N,N*-dimethylformamide (2.4 g, 33 mmol) was added dropwise. The reaction was allowed to warm from $-70\text{ }^{\circ}\text{C}$ to room temperature over 1 hour, then quenched at $0\text{ }^{\circ}\text{C}$ with saturated ammonium chloride solution (150 mL) and extracted with ethyl acetate ($3 \times 150\text{ mL}$). The combined organic layers were washed with brine (100 mL), dried with anhydrous sodium sulfate, filtered and concentrated under in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-266** (701 mg, 59% yield) as a yellow oil. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 10.33 (s, 1H), 7.32-7.28 (m, 1H), 6.94-6.92 (d, $J = 8.0\text{ Hz}$, 1H), 4.33-4.26 (m, 2H), 2.89-2.86 (t, $J = 6.4\text{ Hz}$, 2H), 2.11-2.06 (m, 2H).

[00595] **Example 165B: methyl 3,4-dihydro-2H-thieno[3,2-h]chromene-8-carboxylate (B-267)**

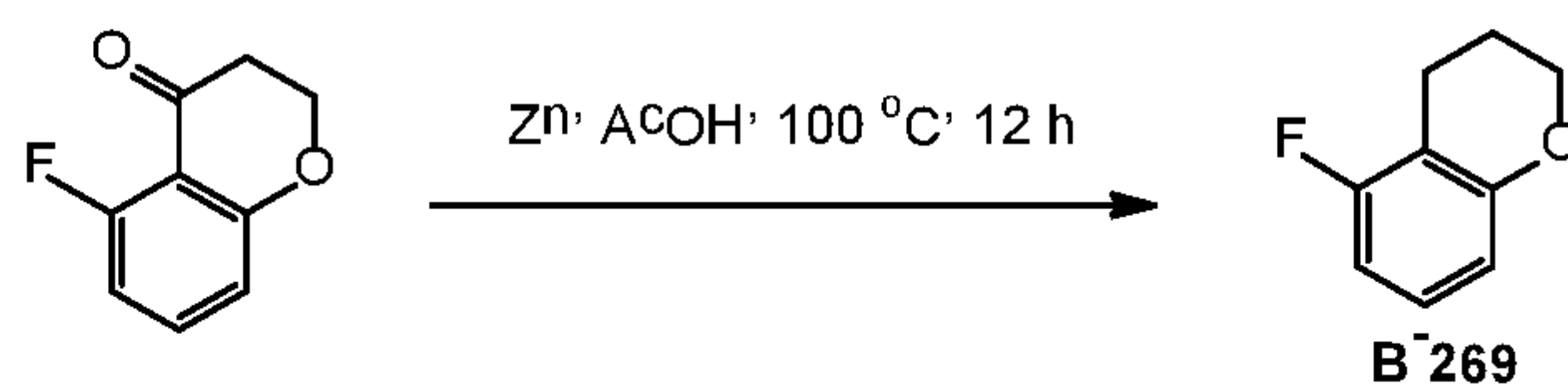
[00596] To a solution of **compound B-266** (0.60 g, 3.3 mmol) in *N,N*-dimethylformamide (20 mL) was added potassium carbonate (0.92 g, 6.7 mmol) and methyl 2-mercaptoacetate (0.42 g, 4.0 mmol). The mixture was stirred at $90\text{ }^{\circ}\text{C}$ for 16 hours, then quenched with water (100 mL) and extracted with ethyl acetate ($3 \times 100\text{ mL}$). The combined organic layers were washed with brine (100 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo to give **compound B-267** (0.70 g, crude) as a yellow solid. LCMS (M): $t_R = 1.132\text{ min.}$, $(\text{ES}^+) m/z (M+H)^+ = 248.9$.

[00597] **Example 166B: 3,4-dihydro-2H-thieno[3,2-h]chromene-8-carboxylic acid (B-268)**

[00598] To a mixture of **compound B-267** (0.60 g, 2.4 mmol) in methanol (20 mL) and water (4 mL) was added sodium hydroxide (0.20 g, 4.8 mmol). The mixture was stirred at $30\text{ }^{\circ}\text{C}$ for 2 hours, then concentrated to remove methanol, diluted with water, and acidified to pH 2 with 1 M hydrochloric acid, resulting in precipitation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-268** (0.50 g, 88% yield) as a yellow solid. $^1\text{H-NMR}$ (CD_3OD , 400

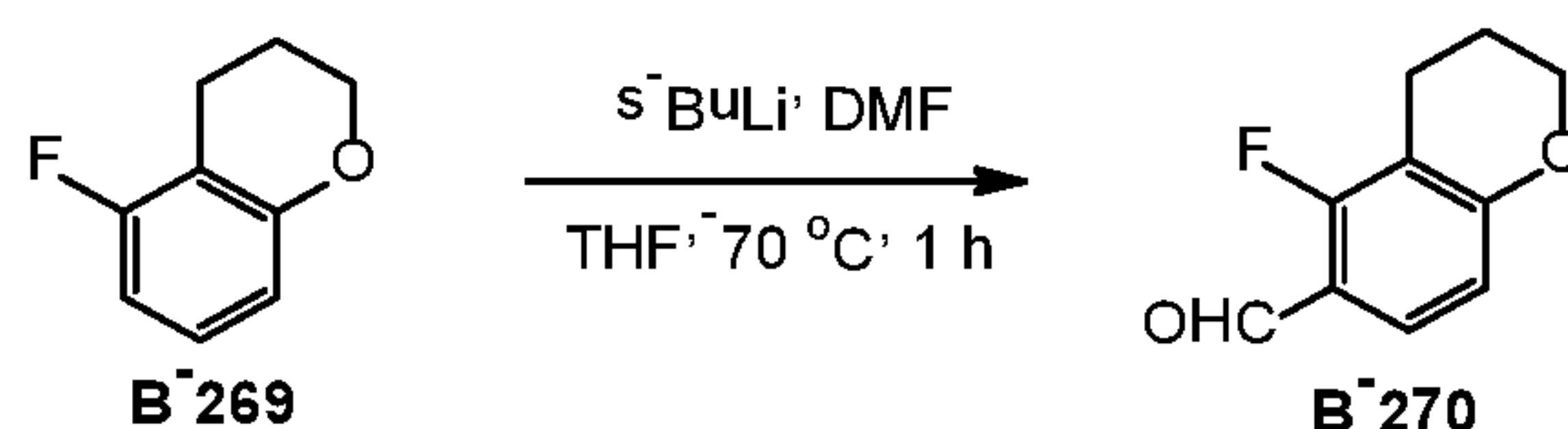
MHz): δ 7.97 (s, 1H), 7.41-7.39 (d, J = 8.0 Hz, 1H), 7.17-7.13 (d, J = 8.0 Hz, 1H), 4.38-4.36 (t, J = 5.2 Hz, 2H), 2.93-2.90 (t, J = 6.4 Hz, 2H), 2.15-2.09 (m, 2H).

[00599] **Example 167B: 5-fluorochroman (B-269)**



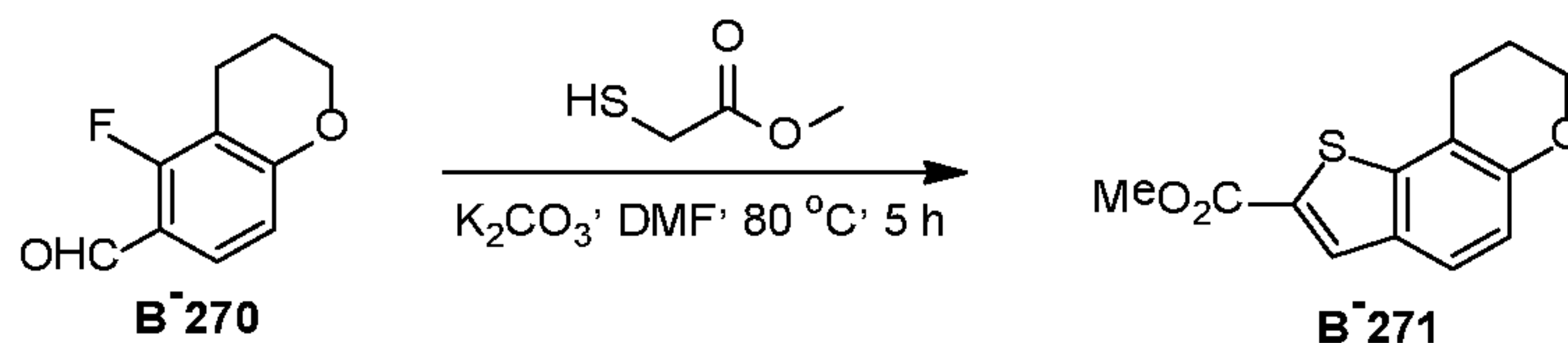
[00600] To a mixture of zinc (9.8 g, 0.15 mol) in acetic acid (20 mL) was added a solution of 5-fluorochroman-4-one (1.0 g, 6.0 mmol) in acetic acid (20 mL). The mixture was stirred at 100 °C for 12 hours, then filtered (washing with ethyl acetate) and concentrated in vacuo. The residue was purified by silica gel column chromatography [petroleum ether: ethyl acetate = 1:0] to give **compound B-269** (0.50 g, 55% yield) as a yellow solid. GCMS: t_R =6.634 min., (ES⁺) m/z (M)⁺ =152.1.

[00601] **Example 168B: 5-fluorochroman-6-carbaldehyde (B-270)**



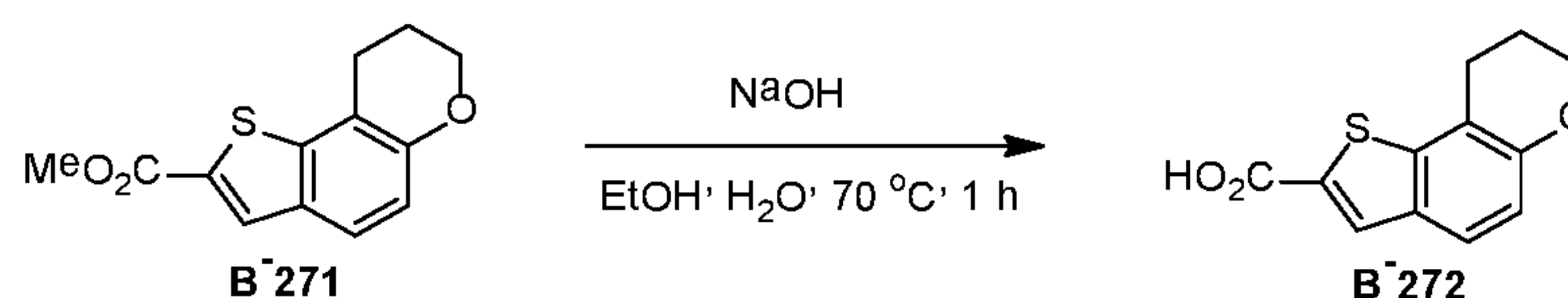
[00602] To a solution of **compound B-269** (0.20 g, 1.3 mmol) in anhydrous tetrahydrofuran (15 mL) at -70 °C was added dropwise sec-butyllithium (1.3 N in n-hexane, 2.0 mL, 2.6 mmol). The reaction was stirred at -70 °C for 0.5 hour, and then *N,N*-dimethylformamide (0.38 g, 5.2 mmol) was added dropwise. The reaction was stirred at -70 °C for 0.5 hour, then quenched with saturated aqueous ammonium chloride (20 ml) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate and concentrated in vacuo to give **compound B-270** (0.20 g, crude) as a yellow solid. LCMS (B): t_R =0.699 min., (ES⁺) m/z (M+H)⁺ =181.2.

[00603] **Example 169B: methyl 8,9-dihydro-7H-thieno[2,3-f]chromene-2-carboxylate (B-271)**



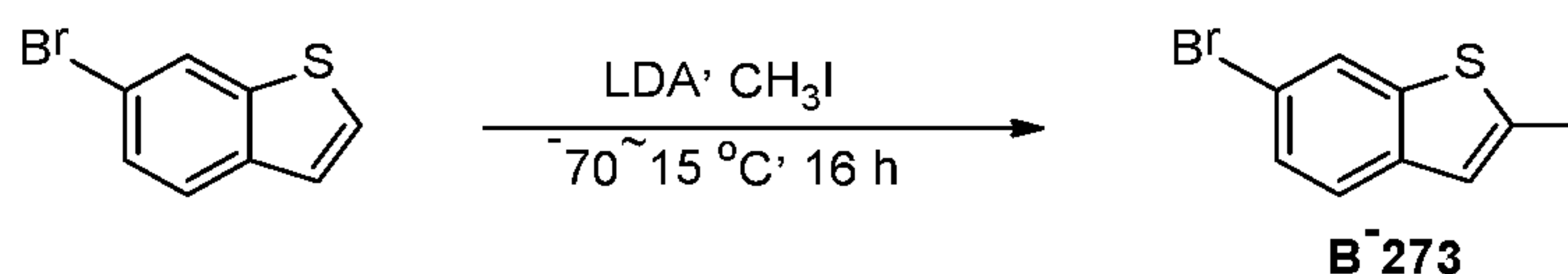
[00604] A mixture of **compound B-270** (0.30 g, 1.7 mmol), potassium carbonate (0.46 g, 3.3 mmol) and methyl 2-mercaptoacetate (0.21 g, 2.0 mmol) in *N,N*-dimethylformamide (15 mL) was stirred at 80 °C for 5 hours. On completion, the mixture was poured into water (20 ml) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate and concentrated in vacuo to give **compound B-271** (0.25 g, crude) as a yellow solid. LCMS (B): t_R =0.759 min., (ES⁺) m/z (M+H)⁺ =249.1.

[00605] **Example 170B: 8,9-dihydro-7H-thieno[2,3-f]chromene-2-carboxylic acid (B-272)**



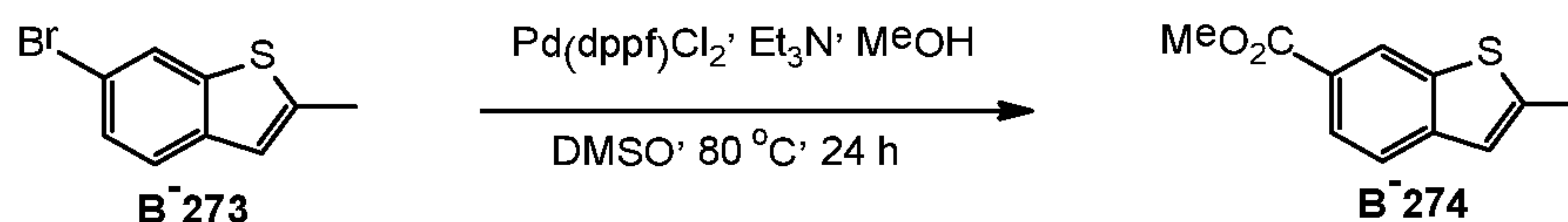
[00606] To a mixture of **compound B-271** (0.12 g, 0.48 mmol) in ethanol (5.0 mL) and water (1.0 mL) was added sodium hydroxide (97 mg, 2.4 mmol). The mixture was stirred at 70 °C for 1 hour, then concentrated to remove methanol, diluted with water, and acidified to pH 1 with 1 M hydrochloric acid, resulting in precipitation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-272** (0.10 g, crude). TLC [dichloromethane : methanol = 10:1]: R_f = 0.04.

[00607] **Example 171B: 6-bromo-2-methylbenzo[b]thiophene (B-273)**

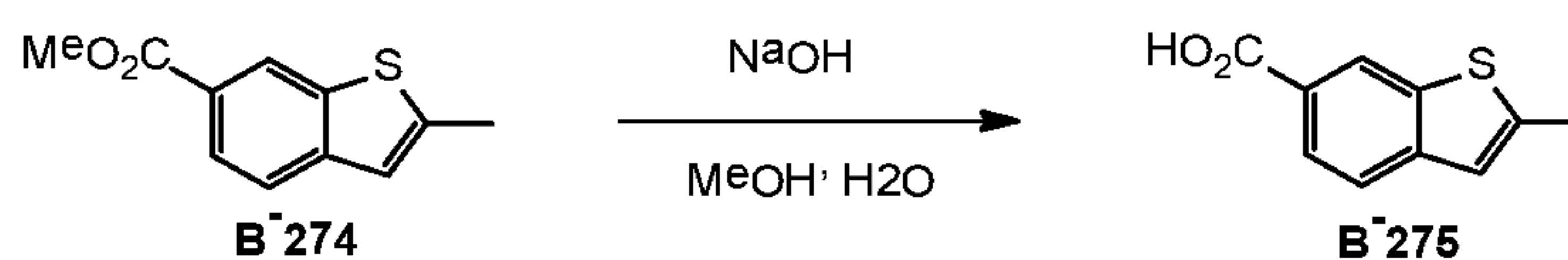


[00608] To a solution of 6-bromobenzo[b]thiophene (3.0 g, 14 mmol) in THF (10 mL) was added lithium diisopropylamide (2 M in tetrahydrofuran/n-heptane, 8.4 mL, 17 mmol). The mixture was stirred at -70 °C for 30 min, and then iodomethane (17.98 g, 126.71 mmol) was added dropwise. The mixture was stirred at 15 °C for 15.5 hours, then quenched at -70 °C with saturated aqueous ammonium chloride (2 mL), diluted with water (10 mL) and extracted with ethyl acetate (3 × 80 mL). The combined organic phases were concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 1:0] to give **compound B-273** (1.60 g, 50% yield). ¹H-NMR (CD₃OD, 400 MHz): δ 7.94 (s, 1H), 7.42-7.39 (m, 1H), 7.20-7.14 (m, 1H), 3.39 (s, 1H), 3.18-3.19 (m, 2H), 1.55 (s, 9H).

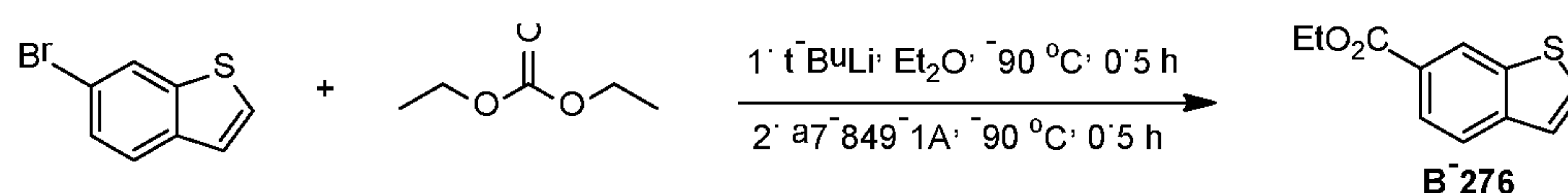
[00609] **Example 172B: methyl 2-methylbenzo[b]thiophene-6-carboxylate (B-274)**



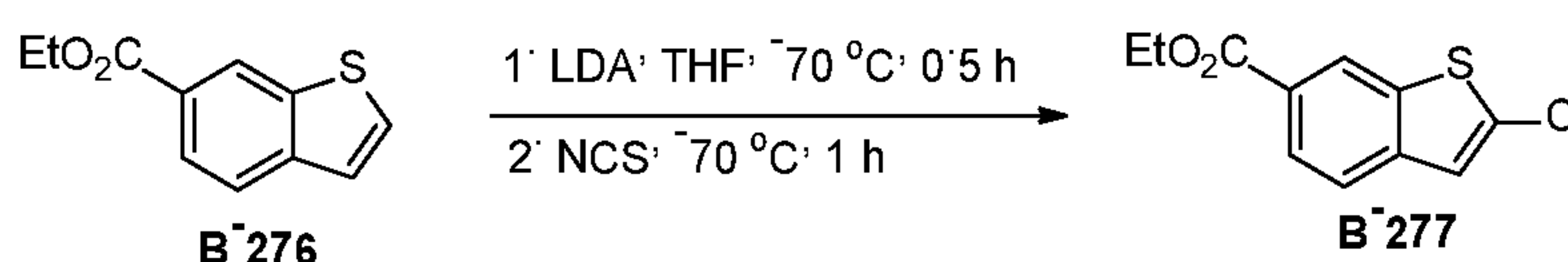
[00610] To a solution of **compound B-273** (600 mg, 2.6 mmol) in dimethylsulfoxide (10 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (193 mg, 0.26 mmol), triethylamine (801 mg, 7.9 mmol) and methanol (254 mg, 7.9 mmol). The mixture was stirred at 80 °C under CO atmosphere (100 psi) for 24 hours until TLC analysis showed the reaction was complete. The mixture was added to water (30 mL) and extracted with methyl tert-butyl ether (3 × 40 mL). The combined organic phases were washed with water (2 × 40 mL), dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-274** (0.30 g, 55% yield) as a white solid. TLC [petroleum ether: ethyl acetate = 20:1]: R_f = 0.4; ¹H-NMR (CD₃OD, 400 MHz): δ 8.33 (s, 1H), 7.82 (d, J=8.4 Hz, 1H), 7.61 (d, J=8.4 Hz, 1H), 7.01 (s, 1H), 4.77 (s, 2H), 3.82 (s, 3H), 2.52 (s, 3H).

[00611] **Example 173B: 2-methylbenzo[b]thiophene-6-carboxylic acid (B-275)**

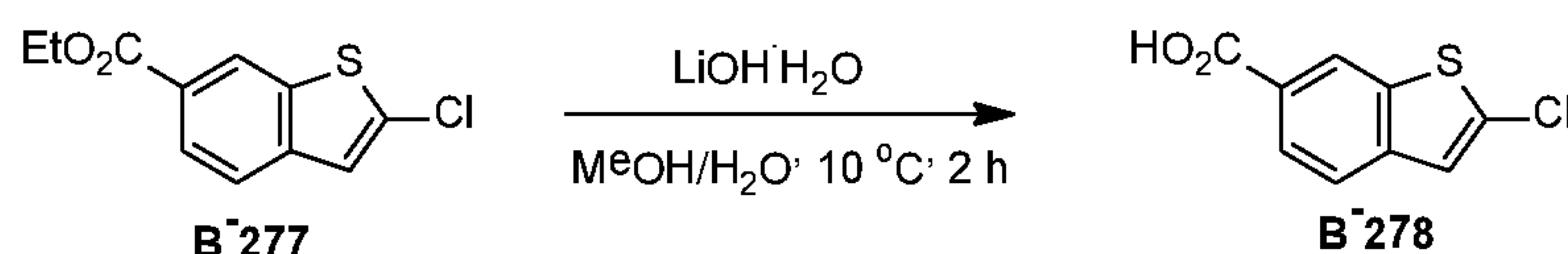
[00612] To a solution of **compound B-274** (200 mg, 0.91 mmol) in methanol (10 mL) and water (1.0 mL) was added sodium hydroxide (91 mg, 2.3 mmol). The mixture was stirred at 15 °C for 1 hour, then concentrated to remove methanol, diluted with water, acidified to pH 3 with 5 M hydrochloric acid and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (3 × 30 mL) and concentrated to give **compound B-275** (0.15 g, 86% yield) as a white solid. TLC [petroleum ether: ethyl acetate = 1:1]: R_f = 0.4.

[00613] **Example 174B: ethyl benzo[b]thiophene-6-carboxylate (B-276)**

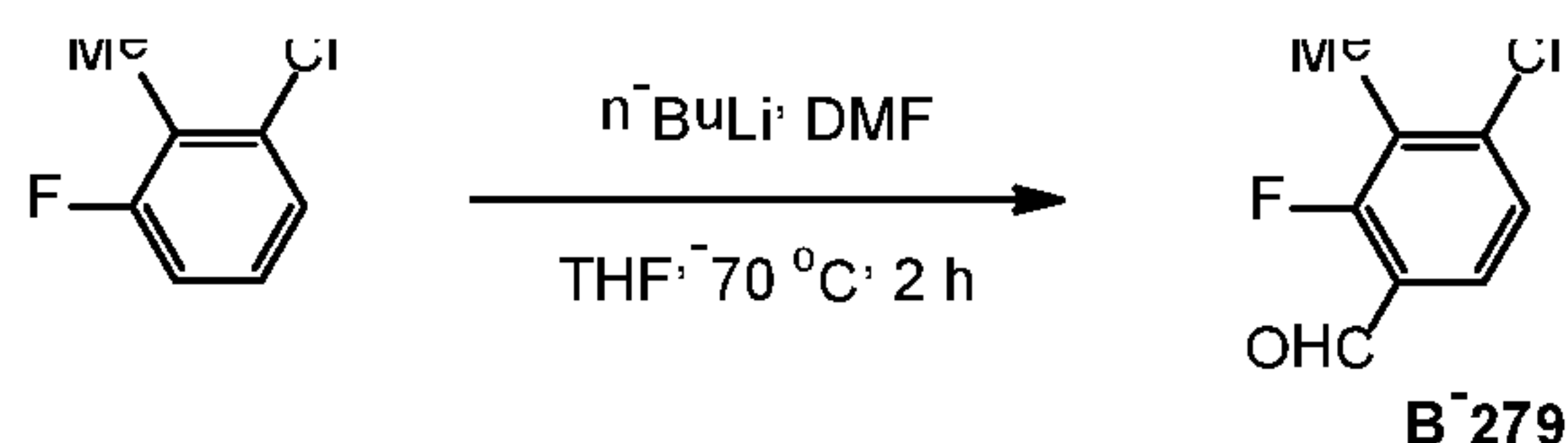
[00614] To a mixture of 6-bromobenzo[b]thiophene (5.0 g, 23 mmol) in diethyl ether (50 mL) at -90 °C under nitrogen was added dropwise tert-butyllithium (1.3 M in pentane solution, 27 mL, 35 mmol). The mixture was stirred at -90 °C for 0.5 hour, and diethyl carbonate (4.1 g, 35 mmol) was added dropwise. The reaction was stirred at -90 °C for another 0.5 hour, then quenched at 0 °C with saturated aqueous ammonium chloride (20 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (3 × 20 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 50:1] to give **compound B-276** (1.0 g) as a yellow oil. LCMS (B): t_R=0.863 min., (ES⁺) m/z (M+H)⁺ = 207.1.

[00615] **Example 175B: ethyl 2-chlorobenzo[b]thiophene-6-carboxylate (B-277)**

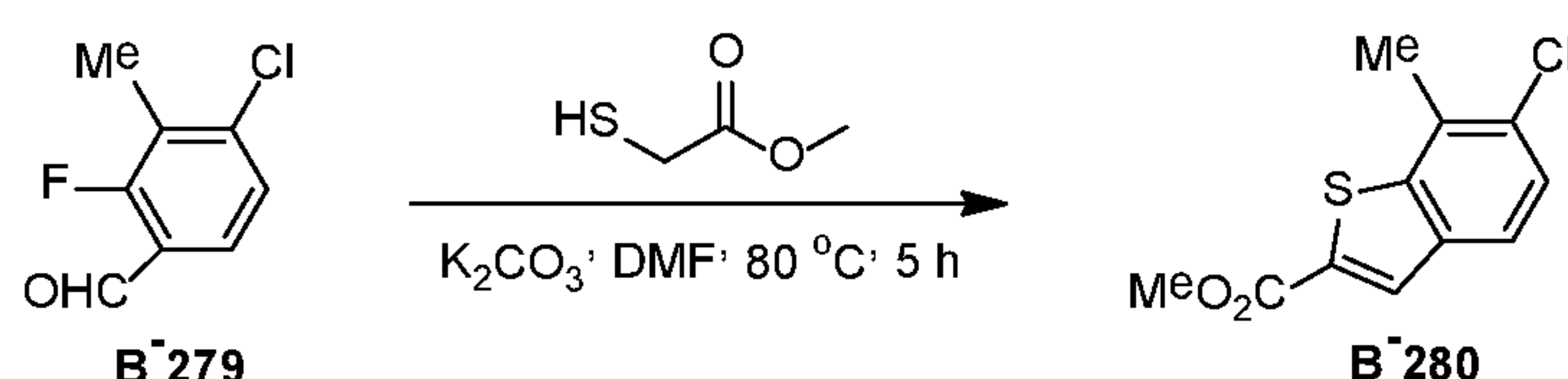
[00616] To a mixture of **compound B-276** (0.40 g, 1.93 mmol) in anhydrous tetrahydrofuran (10 mL) at -70 °C under nitrogen was added dropwise lithium diisopropylamide (2.0 M in tetrahydrofuran/n-heptane, 1.2 mL, 2.4 mmol). The mixture was stirred for 0.5 hour, and then 1-chloropyrrolidine-2,5-dione (0.31 g, 2.3 mmol) was added dropwise at -70 °C. The reaction was stirred at -70 °C for another 1 hour, then quenched with water (10 mL), acidified to pH 4 with 2 N hydrochloric acid at 0 °C, and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (3 × 10 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo to give a 1:1 mixture (350 mg) of starting material **compound B-276** and product **compound B-277** as a white solid. LCMS (B): t_R=0.864 min., (ES⁺) m/z (M+H)⁺ = 207.0; t_R=0.950 min., (ES⁺) m/z (M+H)⁺ = 241.0.

[00617] **Example 176B: 2-chlorobenzo[b]thiophene-6-carboxylic acid (B-278)**

[00618] To a mixture of **compound B-277** (0.35 g, 0.64 mmol, 45% purity) in methanol (5 mL) and water (5 mL) was added sodium hydroxide (80 mg, 1.9 mmol). The mixture was stirred at 10 °C for 2 hour, then concentrated to remove methanol, diluted with water, acidified to pH 2 with 1 M hydrochloric acid, and extracted with ethyl acetate (2 × 20 mL). The combined organic phase was washed with brine (3 × 10 mL), dried with anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 40-65% acetonitrile in H₂O (add 0.05% HCl, v/v)] to give **compound B-278** (70 mg, 51% yield) as a white solid. ¹H-NMR (DMSO, 400 MHz): 8.59 (s, 1H), 7.95 (d, J=8.4 Hz, 1H), 7.88 (d, J=8.4 Hz, 1H), 7.65 (s, 1H).

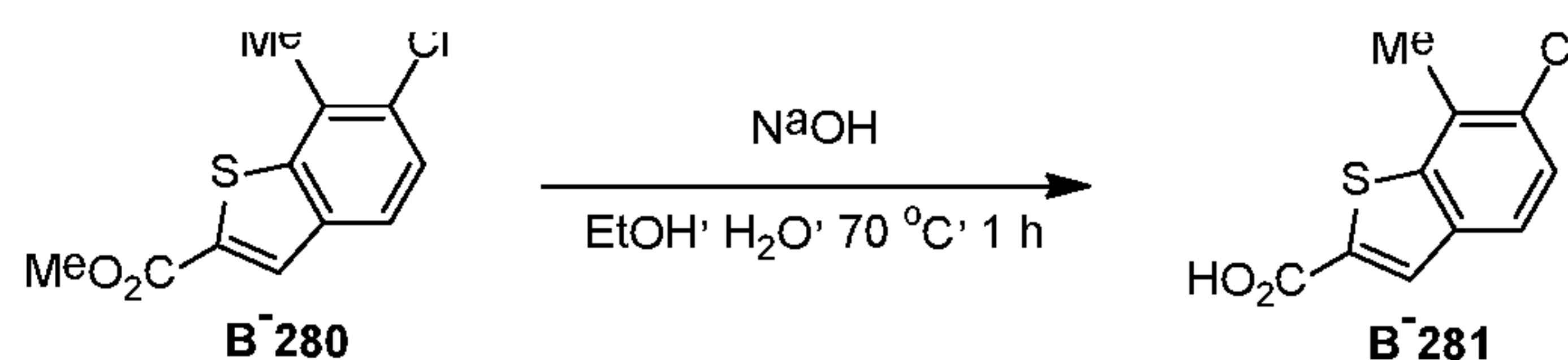
[00619] **Example 177B: 4-chloro-2-fluoro-3-methylbenzaldehyde (B-279)**

[00620] To a solution of 1-chloro-3-fluoro-2-methylbenzene (3.5 g, 24 mmol) in anhydrous tetrahydrofuran (50 mL) at -70 °C was added dropwise n-butyllithium (2.5 M in n-hexane, 19 mL, 48 mmol). The reaction was stirred at -70 °C for 0.5 hour, and then *N,N*-dimethylformamide (7.1 g, 97 mmol) was added dropwise. The reaction was stirred at -70 °C for 0.5 hour, then quenched with saturated aqueous ammonium chloride (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-279** (0.40 g, 10% yield) as a yellow solid. TLC [petroleum ether: ethyl acetate = 10:1]: R_f = 0.19.

[00621] **Example 178B: methyl 6-chloro-7-methylbenzo[b]thiophene-2-carboxylate (B-280)**

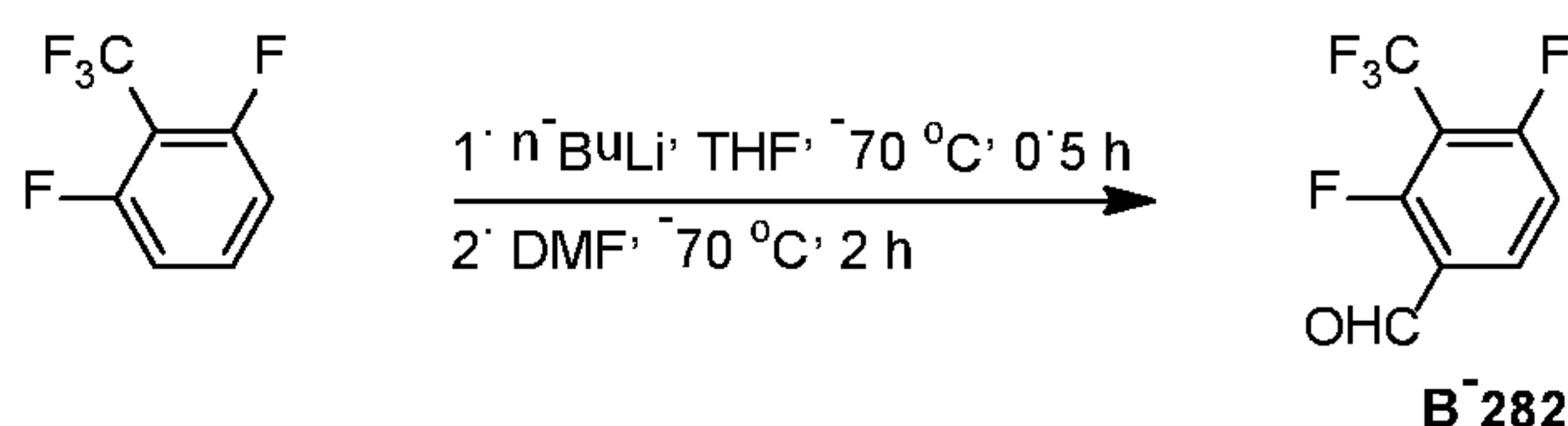
[00622] A mixture of **compound B-279** (0.36 g, 2.1 mmol), potassium carbonate (0.58 g, 4.2 mmol) and methyl 2-mercaptoacetate (0.27 g, 2.5 mmol) in *N,N*-dimethylformamide (15 mL) was stirred at 80 °C for 5 hours. On completion, the mixture was poured into water (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate and concentrated in vacuo to give **compound B-280** (0.40 g, crude) as a yellow solid. LCMS (B): t_R=0.944 min., (ES⁺) m/z (M+H)⁺ = 241.0.

[00623] **Example 179B:** 6-chloro-7-methylbenzo[b]thiophene-2-carboxylic acid (**B-281**)



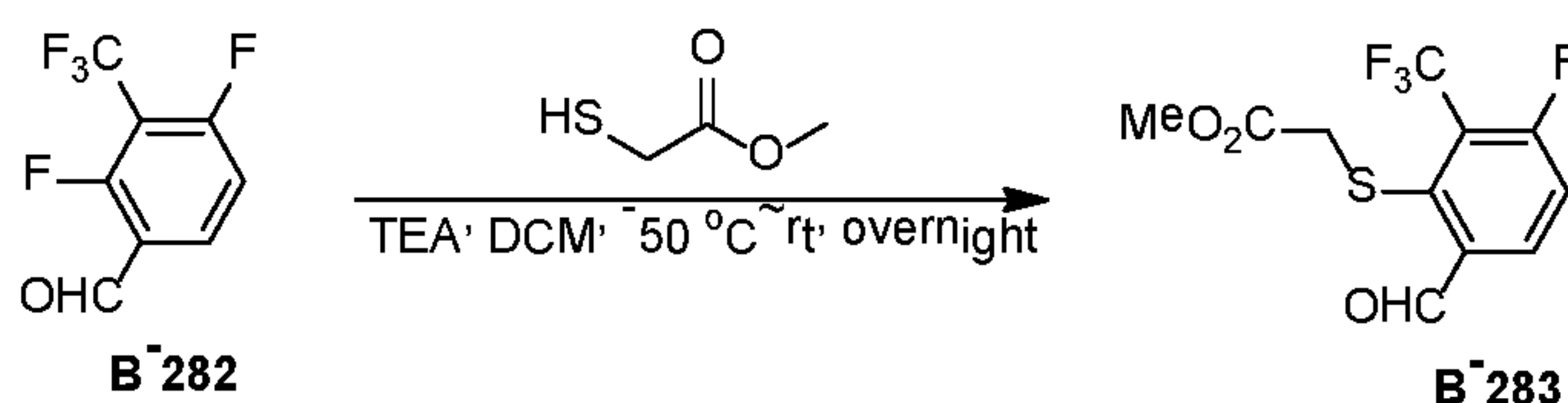
[00624] To a mixture of **compound B-280** (0.40 g, 1.7 mmol) in ethanol (10 mL) and water (2.0 mL) was added sodium hydroxide (0.33 g, 8.3 mmol). The mixture was stirred at 80 °C for 1 hour, then concentrated to remove methanol, diluted with water, and acidified to pH 1 with 1 M hydrochloric acid, resulting in precipitation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-281** (0.35 g, 93% yield) as a white solid. TLC [petroleum ether: ethyl acetate = 10:1]: R_f = 0.04.

[00625] **Example 180B:** 2,4-difluoro-3-(trifluoromethyl)benzaldehyde (**B-282**)



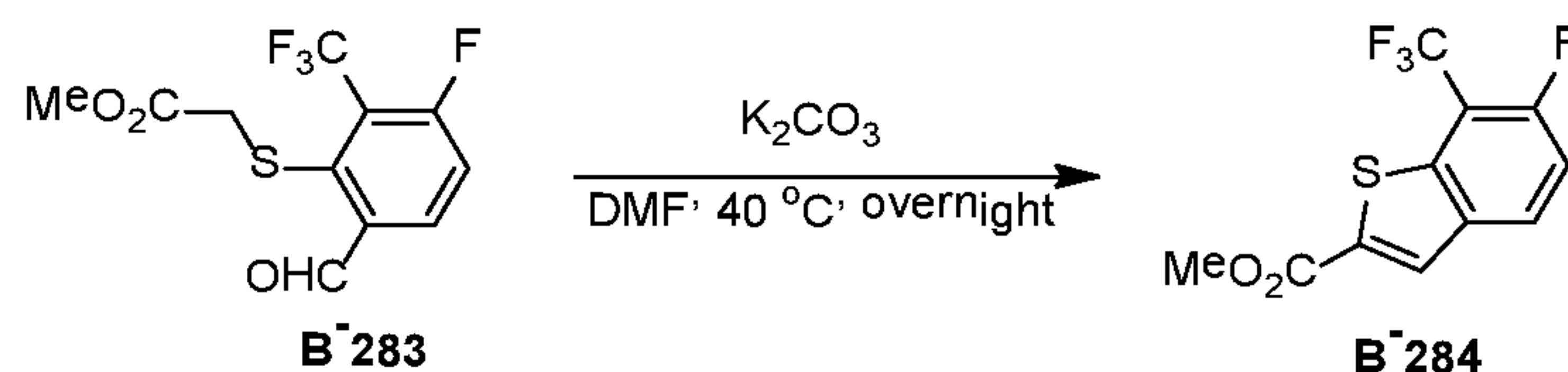
[00626] To a mixture of 1,3-difluoro-2-(trifluoromethyl)benzene (2.0 g, 11 mmol) in anhydrous tetrahydrofuran (30 mL) at -70 °C under nitrogen was added dropwise n-butyllithium (2.5 M in cyclohexane, 5.3 mL, 13 mmol). The mixture was stirred for 30 minutes, and *N,N*-dimethylformamide (1.6 g, 22 mmol) was added dropwise at -70 °C. The reaction was stirred at -70 °C for another 2 hours, then acidified pH to 5.0 with 6 N hydrochloric acid, then diluted with water (10 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-282** (1.5 g, 65% yield) as a yellow oil.

[00627] **Example 181B:** methyl 2-((3-fluoro-6-formyl-2-(trifluoromethyl)phenyl)thio)acetate (**B-283**)



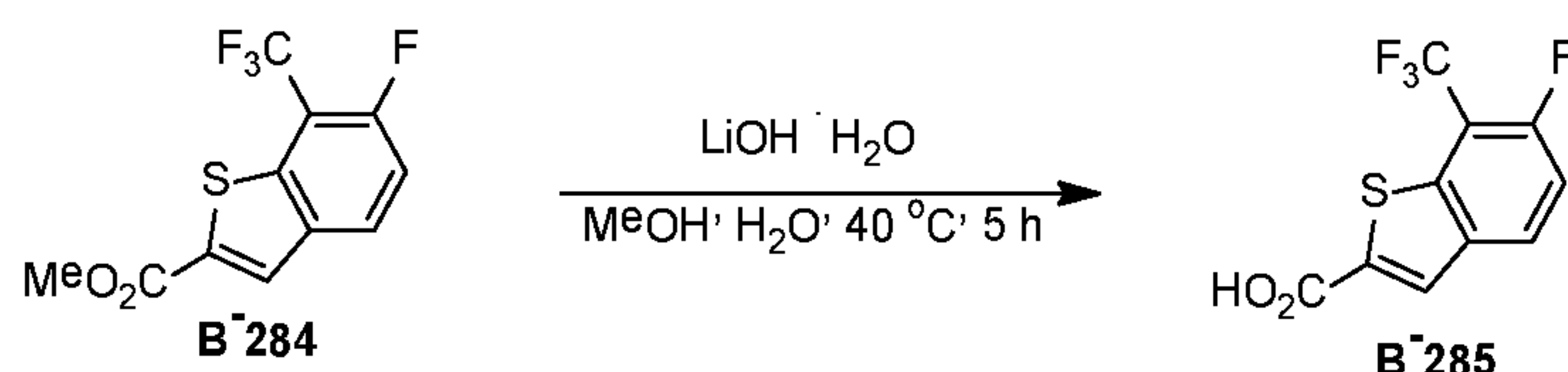
[00628] To a mixture of **compound B-282** (1.0 g, 4.8 mmol) and triethylamine (0.48 g, 4.8 mmol) in dichloromethane (15 mL) at -50 °C was added dropwise methyl 2-mercaptoacetate (0.51 g, 4.8 mmol). The mixture was stirred at room temperature overnight. On completion, the mixture was concentrated in vacuo to give **compound B-283** (1.0 g, crude) as a yellow solid, which was used in the next step without further purification.

[00629] **Example 182B:** methyl 6-fluoro-7-(trifluoromethyl)benzo[b]thiophene-2-carboxylate (**B-284**)



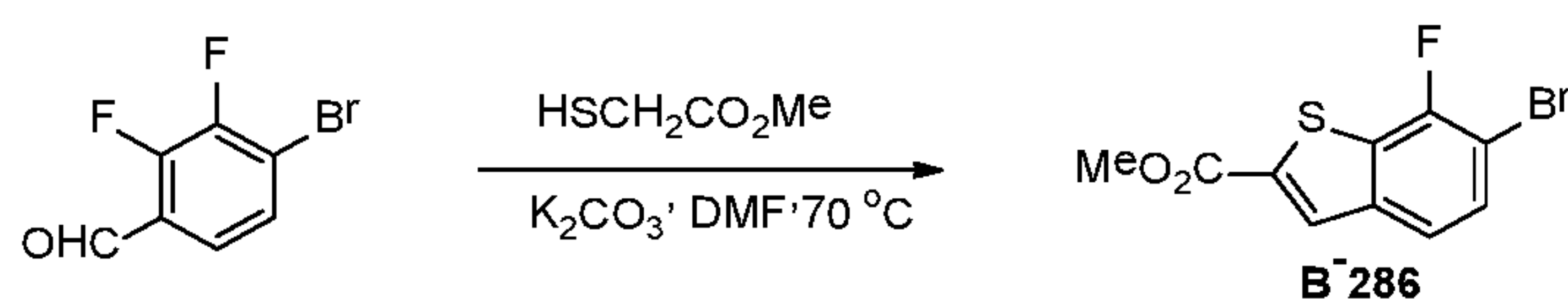
[00630] To a mixture of **compound B-283** (2.0 g, 6.8 mmol) in *N,N*-dimethylformamide (20 mL) was added potassium carbonate (1.9 g, 14 mmol). The mixture was stirred at 40 °C overnight. On completion, the mixture was poured into water (20 mL) and extracted with ethyl acetate (2 × 40 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-284** (0.5 g, 25% yield) as a yellow solid. LCMS (R): tR=1.172 min., (ES⁺) m/z (M+H)⁺=279.0.

[00631] **Example 183B:** 6-fluoro-7-(trifluoromethyl)benzo[b]thiophene-2-carboxylic acid (**B-285**)



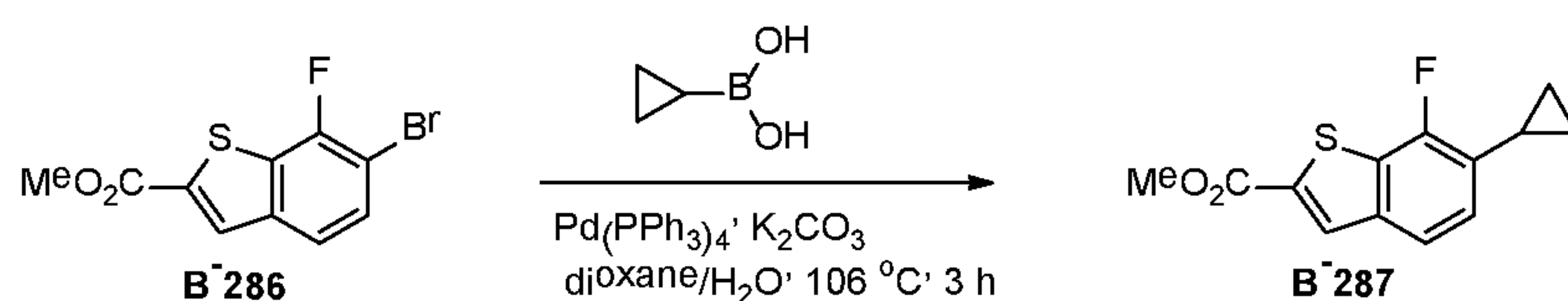
[00632] To a mixture of **compound B-284** (0.40 g, 1.4 mmol) in methanol (4 mL) and water (2 mL) was added lithium hydroxide monohydrate (0.12 g, 2.9 mmol). The mixture was stirred at 40 °C for 5 hours, then concentrated to remove methanol, diluted with water and acidified to pH 3 with 1 M hydrochloric acid, resulting in formation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-285** (0.25 g, 66% yield) as a yellow solid. LCMS (R): tR=1.044 min., (ES⁺) m/z (M+H)⁺=265.0.

[00633] **Example 184B:** methyl 6-bromo-7-fluorobenzo[b]thiophene-2-carboxylate (**B-286**)



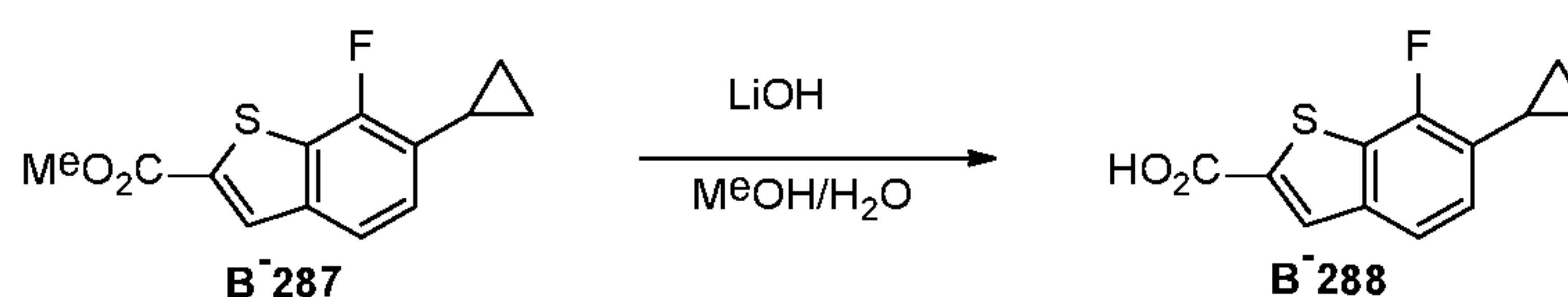
[00634] To a solution of 4-bromo-2,3-difluorobenzaldehyde (2.0 g, 9.1 mmol) and potassium carbonate (2.5 g, 18 mmol) in *N,N*-dimethylformamide (20 mL) at 28 °C was added methyl 2-mercaptoacetate (1.2 g, 11 mmol). The mixture was stirred at 70 °C overnight, then diluted with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-286** (2.2 g, 85% yield) as a white solid.

[00635] **Example 185B: methyl 6-cyclopropyl-7-fluorobenzo[b]thiophene-2-carboxylate (B-287)**



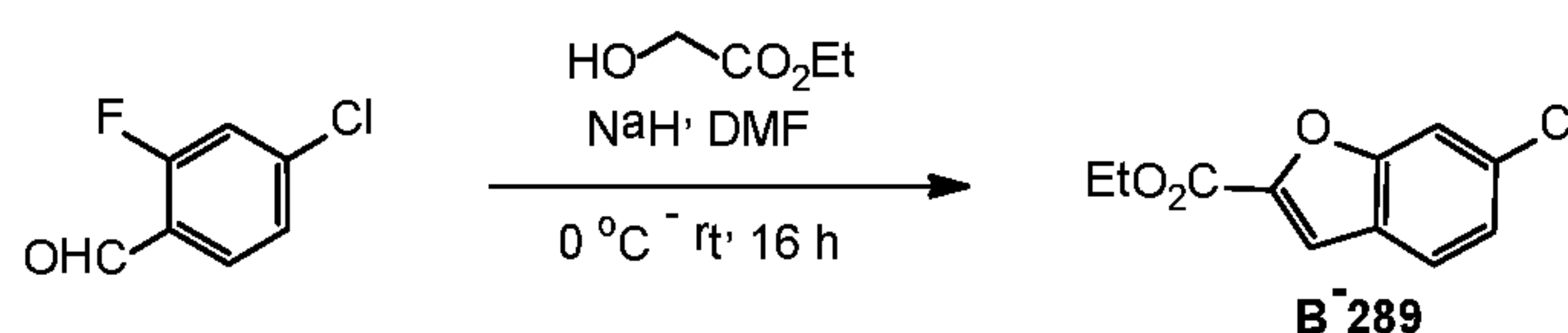
[00636] To a solution of **B-286** (1.2 g, 4.2 mmol) in dioxane (10 mL) and water (2 mL) under nitrogen at room temperature was added potassium carbonate (1.2 g, 8.4 mmol), cyclopropylboronic acid (0.72 g, 8.4 mmol) and $\text{Pd(PPh}_3)_4$ (0.23 g, 0.21 mmol). The mixture was stirred at $106\text{ }^\circ\text{C}$ for 3 hours, then diluted with water (5 mL) and extracted with ethyl acetate ($3 \times 20\text{ mL}$). The combined organic layers were washed with brine ($2 \times 20\text{ mL}$), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-287** (0.80 g, 76% yield) as a white solid.

[00637] **Example 186B: 6-cyclopropyl-7-fluorobenzo[b]thiophene-2-carboxylic acid (B-288)**



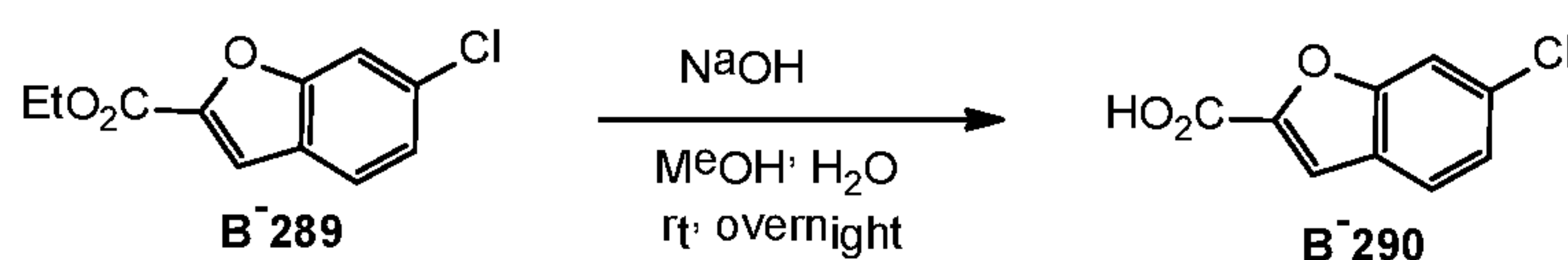
[00638] To a solution of **B-287** (0.80 g, 3.2 mmol) in methanol (10 mL) and water (2 mL) was added lithium hydroxide (0.27 g, 6.4 mmol) at room temperature. The mixture was stirred for 2 hours, then concentrated to remove most of the methanol, and acidified to pH 4~5, resulting in formation of a solid. The solid was collected by filtration dried to give **compound B-288** (0.65 g, 86% yield) as a brown solid.

[00639] **Example 187B: ethyl 6-chlorobenzofuran-2-carboxylate (B-289)**



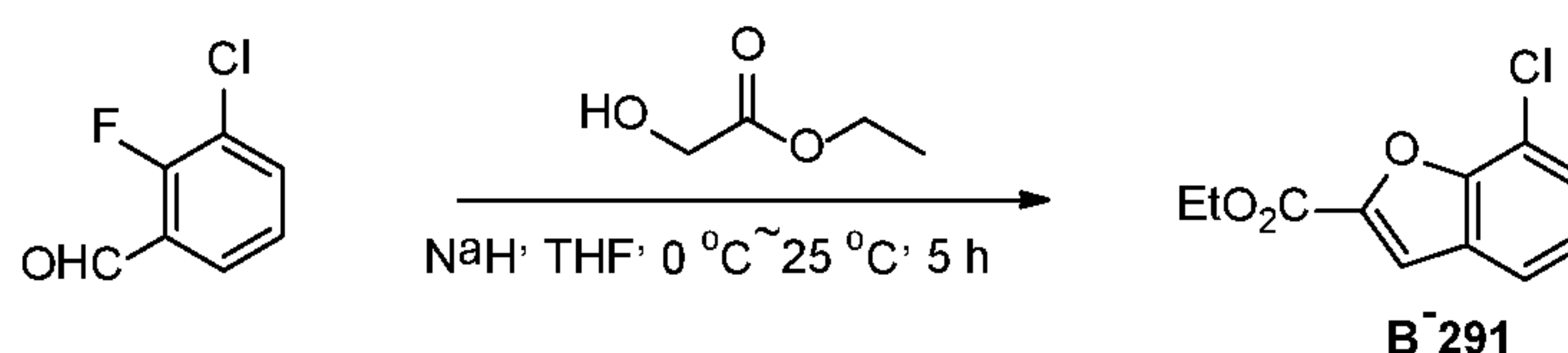
[00640] To a mixture of ethyl 2-hydroxyacetate (0.66 g, 6.3 mmol) in *N,N*-dimethylformamide (10 mL) at $0\text{ }^\circ\text{C}$ was added sodium hydride (0.30 g, 7.6 mmol) in portions, followed by 4-chloro-2-fluoro-benzaldehyde (1.0 g, 6.3 mmol) in portions. The resulting mixture was stirred at $0\text{ }^\circ\text{C}$ for 2hr, then allowed to warm to $25\text{ }^\circ\text{C}$ and stirred for 14hr. On completion, the mixture was quenched at $0\text{ }^\circ\text{C}$ dropwise with saturated aqueous ammonium chloride (15 ml) and extracted with ethyl acetate ($2 \times 40\text{ mL}$). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography [petroleum ether] to give **compound B-289** as a mixture with **compound B-290** (0.30 g, crude) as a yellow solid

[00641] **Example 188B: 6-chlorobenzofuran-2-carboxylic acid (B-290)**



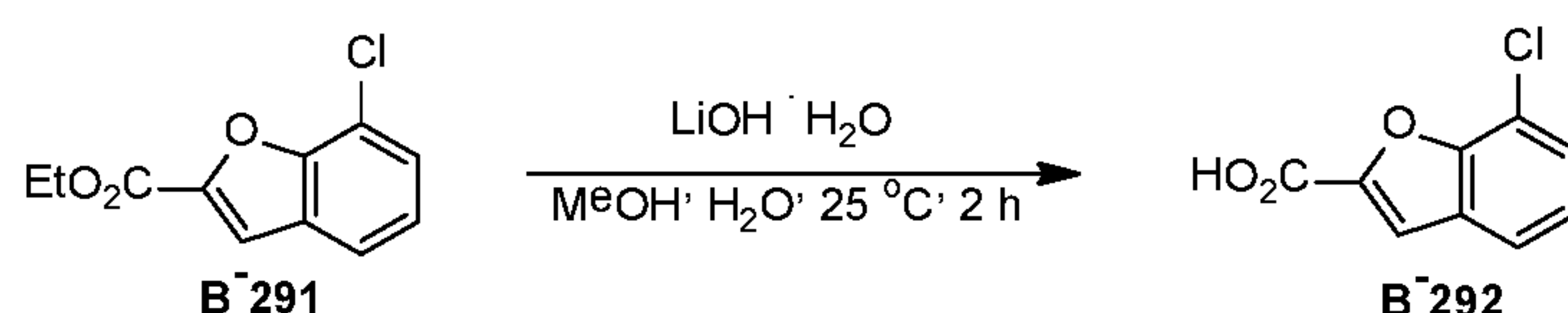
[00642] To a mixture of **compound B-289** and **compound B-290** (0.40 g, 1.8 mmol) in methanol (10 mL) and water (1 mL) was added sodium hydroxide (143 mg, 3.7 mmol). The mixture was stirred at 25 °C overnight, then concentrated to remove methanol, diluted with water, and acidified to pH 3 with 1 M hydrochloric acid, resulting in formation of a solid. The white solid was collected by filtration and dried in vacuo to give **compound B-290** (0.15 g, 43% yield). ¹H-NMR (CD₃OD, 400 MHz): δ 7.93 (s, 1H), 7.81 (d, J = 8.5 Hz, 1H), 7.67 (s, 1H), 7.41 (dd, J₁ = 8.3 Hz, J₂ = 1.8 Hz, 1H).

[00643] **Example 189B: ethyl 7-chlorobenzofuran-2-carboxylate (B-291)**



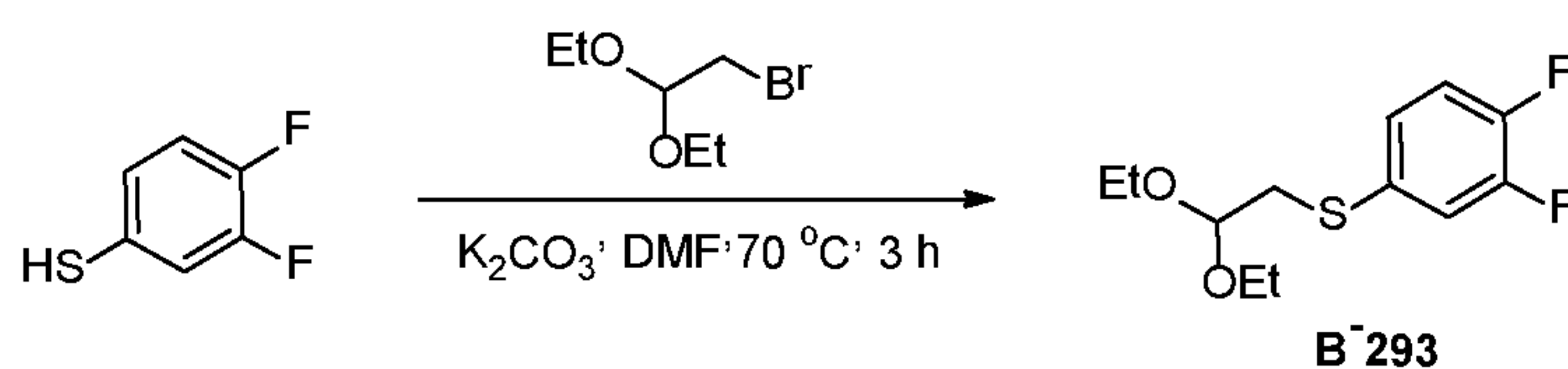
[00644] To a solution of ethyl 2-hydroxyacetate (1.6 g, 15 mmol) in tetrahydrofuran (25 mL) at 0 °C was added sodium hydride (0.61 g, 15 mmol). The reaction was stirred for 0.5 hour, and 3-chloro-2-fluorobenzaldehyde (2.0 g, 13 mmol) was added. The mixture was stirred at 25 °C for 4.5 hours, then quenched with water (5 mL) and extracted with ethyl acetate (2 × 40 mL). The combined organic layers were concentrated in vacuo and purified by silica gel chromatography [petroleum ether: ethyl acetate = 15:1] to give **compound B-291** (0.80 g, 28% yield) as a yellow solid. LCMS (J): t_R=1.551 min., (ES⁺) m/z (M+H)⁺=225.0.

[00645] **Example 190B: 7-chlorobenzofuran-2-carboxylic acid (B-292)**



[00646] To a mixture of **compound B-291** (1.24 g, 5.5 mmol) in methanol (7 mL) and water (7 mL) was added lithium hydroxide monohydrate (0.46 g, 11 mmol). The mixture was stirred at 25 °C for 2 h, then concentrated to remove methanol, diluted with water and acidified to pH 3 with 1 M hydrochloric acid, resulting in formation of a solid. The white solid was collected by filtration and dried in vacuo to give **compound B-292** (0.50 g, 46% yield). ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 7.79-7.77 (m, 2H), 7.62 (d, J=7.6 Hz, 1H), 7.37 (t, J=7.6 Hz, 1H).

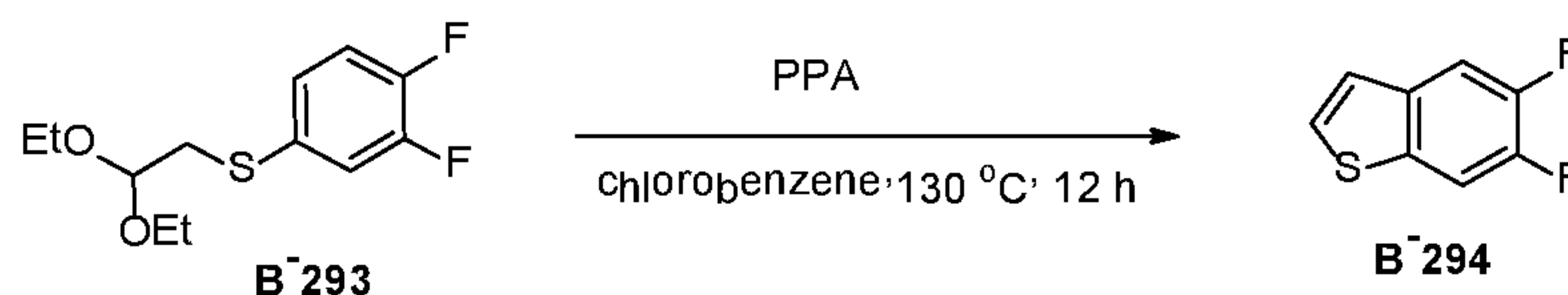
[00647] **Example 191B: (2,2-diethoxyethyl)(3,4-difluorophenyl)sulfane (B-293)**



[00648] A solution of 3,4-difluorobenzenethiol (3.0 g, 21 mmol), 2-bromo-1,1-diethoxyethane (4.5 g, 23 mmol) and potassium carbonate (4.3 g, 31 mmol) in *N,N*-dimethylformamide (50 mL) was stirred at 70 °C for 3 hours. On completion, the mixture was poured into water (40 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with water and brine, dried

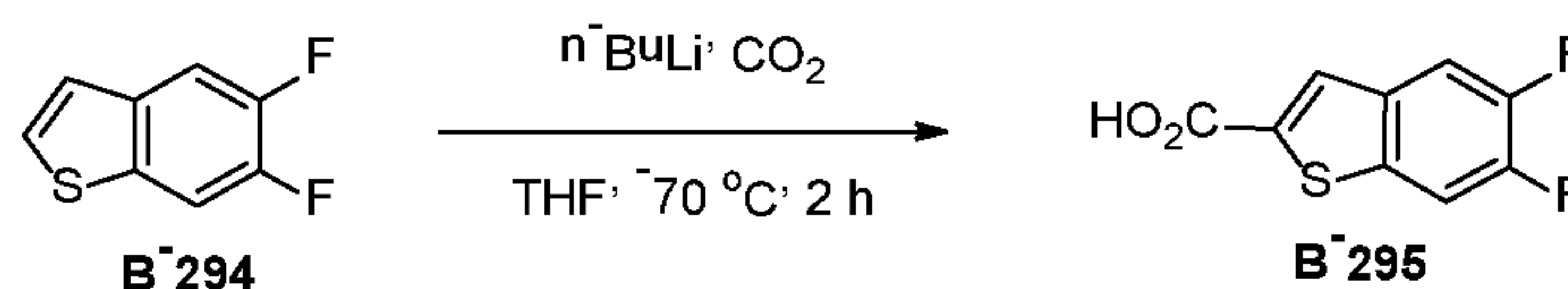
over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-293** (5.0 g, crude) as a yellow solid.

[00649] Example 192B: 5,6-difluorobenzo[b]thiophene (B-294)



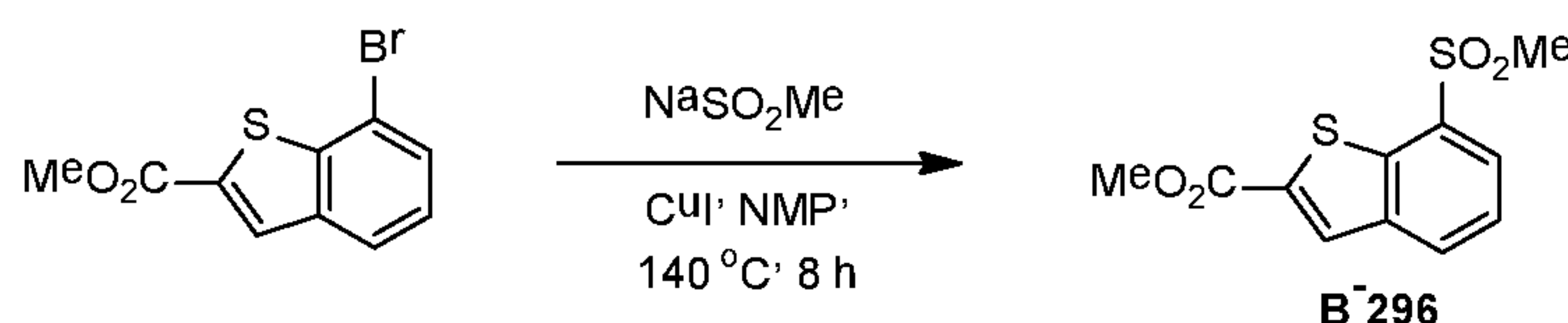
[00650] A solution of **compound B-293** (7.0 g, 28 mmol) and polyphosphoric acid (15 g) in chlorobenzene (100 mL) was stirred at 130 °C for 12 hours. On completion, the mixture was poured into water (40 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 1:0] to give **compound B-294** (2.6 g, 57% yield) as a yellow solid.

[00651] Example 193B: 5,6-difluorobenzo[b]thiophene-2-carboxylic acid (B-295)



[00652] To a solution of **compound B-294** (1.0 g, 5.9 mmol) in anhydrous tetrahydrofuran (30 mL) was added n-butyllithium (2.6 mL, 2.5 N in hexane, 6.5 mmol) dropwise at -70 °C. The reaction was stirred at -70 °C for 1 hour. The atmosphere was replaced with carbon dioxide, and the reaction was stirred for an additional 1 hour at -70 °C. On completion, the mixture was quenched with saturated ammonium chloride solution (2.6 mL) at 0 °C and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 µm; Mobile phase: 19-49% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give **compound B-295** (0.24 g, 19% yield) as a white solid.

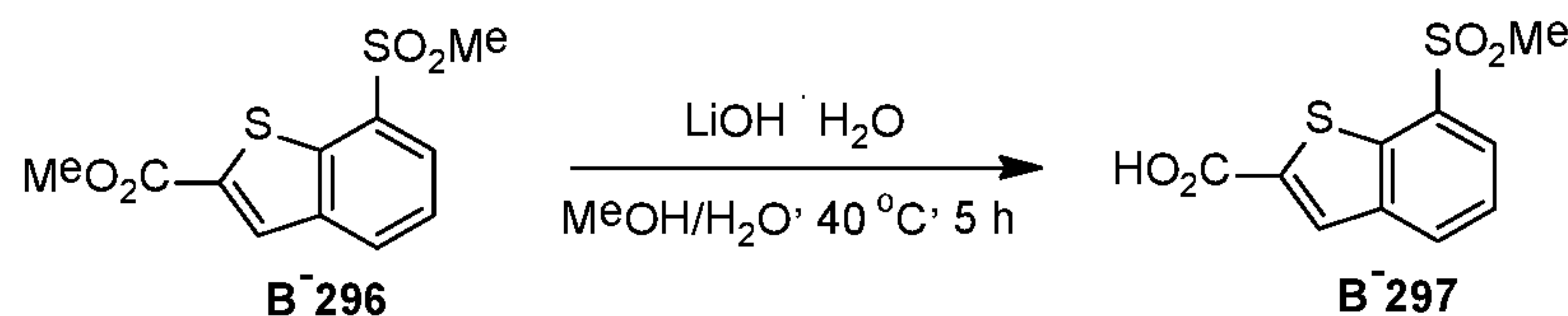
[00653] Example 194B: methyl 7-(methylsulfonyl)benzo[b]thiophene-2-carboxylate (B-296)



[00654] A mixture of methyl 7-bromobenzo[b]thiophene-2-carboxylate (1.0 g, 3.7 mmol), sodium methanesulfinate (1.7 g, 17 mmol) and copper iodide (3.2 g, 17 mmol) in *N*-methyl-2-pyrrolidone (25 mL) was de-gassed and then heated to 140 °C for 8 hours under nitrogen. The mixture was diluted with ethyl acetate (500 mL), filtered, washed with brine (6 × 50 mL), dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography [petroleum ether: ethyl acetate = 5:1 to 10:1] to afford **compound B-296** (0.42 g, 42% yield) as a yellow solid.

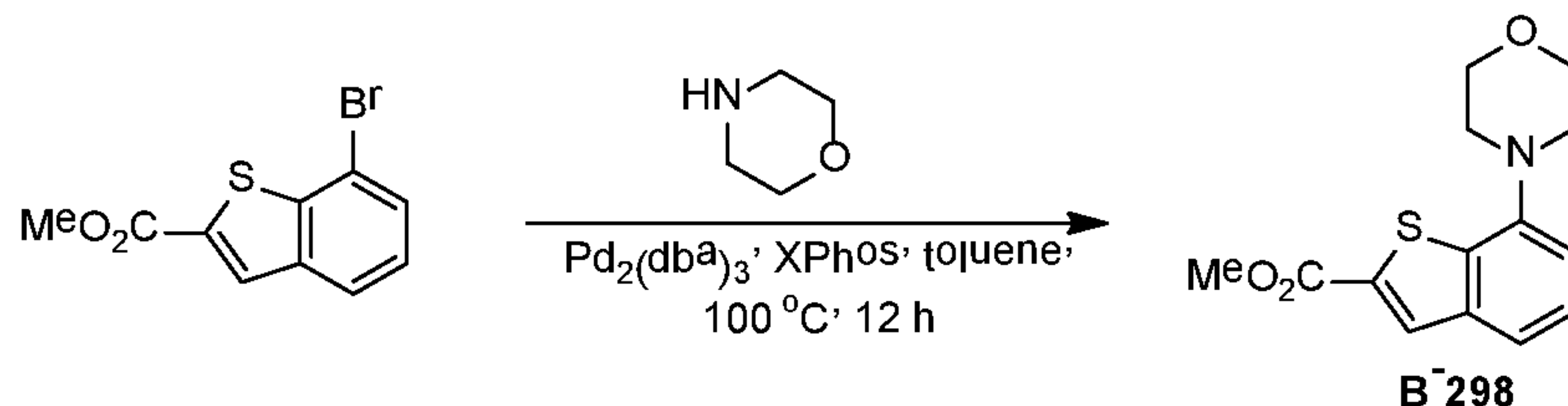
$^1\text{H-NMR}$ (CD_3OD , 400 MHz): 8.28 (d, $J=8.0$ Hz, 1H), 8.24 (s, 1H), 8.10 (d, $J=8.0$ Hz, 1H), 7.69 (t, $J=8.0$ Hz, 1H), 3.95 (s, 3H), 3.20 (s, 3H).

[00655] Example 195B: 7-(methylsulfonyl)benzo[*b*]thiophene-2-carboxylic acid (B-297)



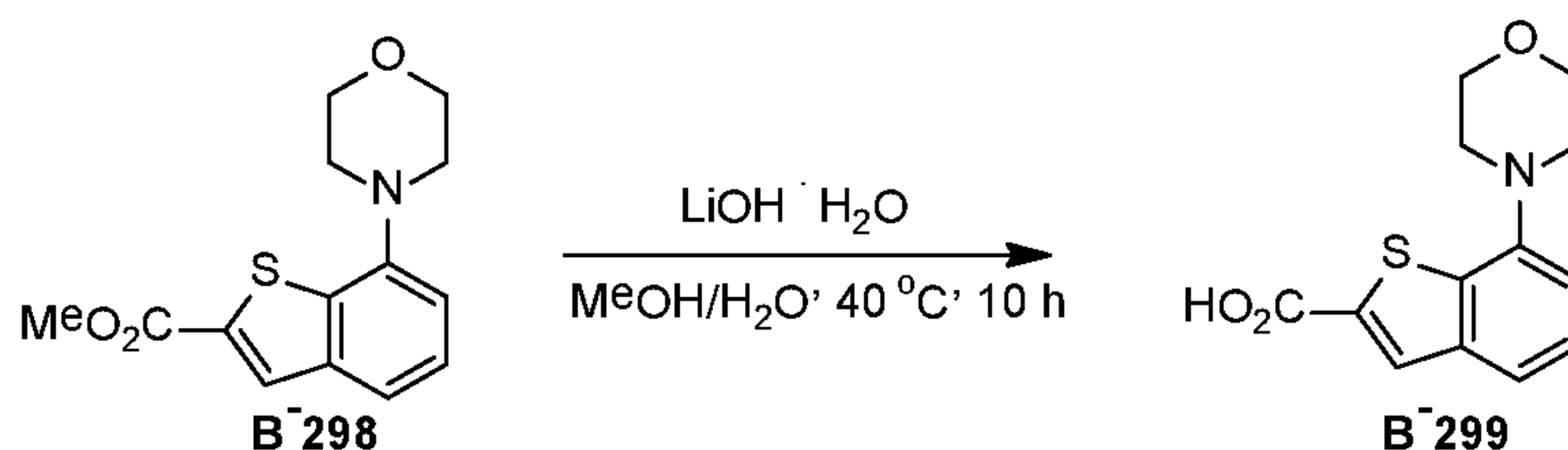
[00656] A mixture of **compound B-296** (0.40 g, 1.5 mmol) and lithium hydroxide monohydrate (0.43 g, 10 mmol) in methanol (4 mL) and water (2 mL) was stirred at 40 °C for 5 hours. On completion, the mixture was concentrated in vacuo, added to water (50 mL), washed with ethyl acetate (3×10 mL), acidified and extracted with ethyl acetate (3×50 mL). The combined organic phases were washed with brine (3×10 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo to give **compound B-297** (0.34 g, 90% yield) as a yellow solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): 8.27 (d, $J=8.0$ Hz, 1H), 8.20 (s, 1H), 8.09 (d, $J=7.2$ Hz, 1H), 7.68 (t, $J=8.0$ Hz, 1H), 3.19 (s, 3H).

[00657] Example 196B: methyl 7-morpholinobenzo[*b*]thiophene-2-carboxylate (B-298)



[00658] Methyl 7-bromobenzo[*b*]thiophene-2-carboxylate (1.0 g, 3.7 mmol), morpholine (0.32 g, 3.7 mmol), cesium carbonate (2.4 g, 7.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.34 g, 0.37 mmol) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (0.18 g, 0.37 mmol) in toluene (50 mL) was de-gassed and heated to 100 °C for 12 hours under nitrogen. The reaction mixture was poured into water (40 mL) and extracted with ethyl acetate (120 mL). The organic phase was washed with brine (3×20 mL), dried with anhydrous sodium sulfate, concentrated in vacuo and purified by column chromatography [petroleum ether: ethyl acetate = 10:1] to afford the **compound B-298** (0.95 g, crude) as a yellow gum. LCMS (B): $t_R=0.838$ min., $(\text{ES}^+) m/z (M+H)^+ = 278.1$

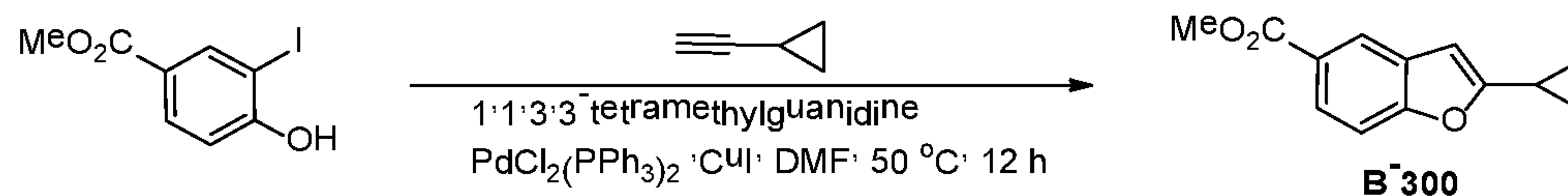
[00659] Example 197B: 7-morpholinobenzo[*b*]thiophene-2-carboxylic acid (B-299)



[00660] A mixture of **compound B-298** (0.95 g, 2.8 mmol) and lithium hydroxide monohydrate (0.81 g, 19 mmol) in methanol (10 mL) and water (5 mL) was stirred at 40 °C for 10 hours. The mixture was concentrated in vacuo, added into water (50 mL), washed with ethyl acetate (3×10 mL),

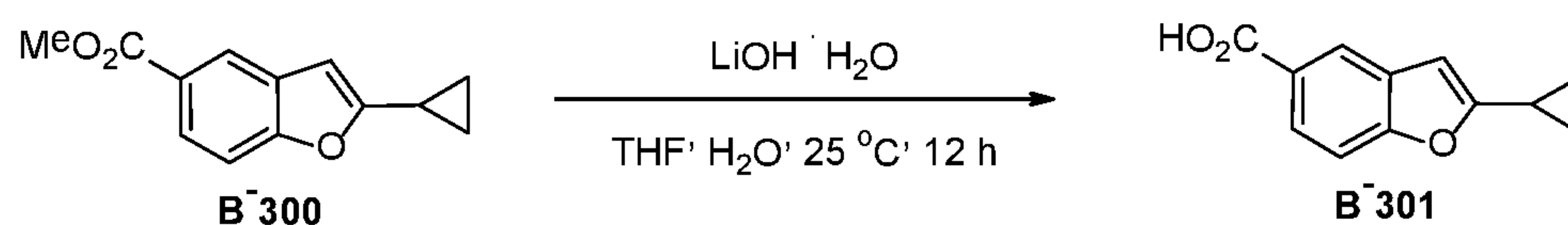
acidified and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (3×15 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo to give **compound B-299** (0.63 g, 86% yield) as a yellow solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): 8.02 (s, 1H), 7.60 (d, $J=8.4$ Hz, 1H), 7.37 (t, $J=8.0$ Hz, 1H), 7.10 (d, $J=8.0$ Hz, 1H), 3.89 (t, $J=4.8$ Hz, 4H), 3.17 (t, $J=4.8$ Hz, 4H).

[00661] **Example 198B: methyl 2-cyclopropylbenzofuran-5-carboxylate (B-300)**



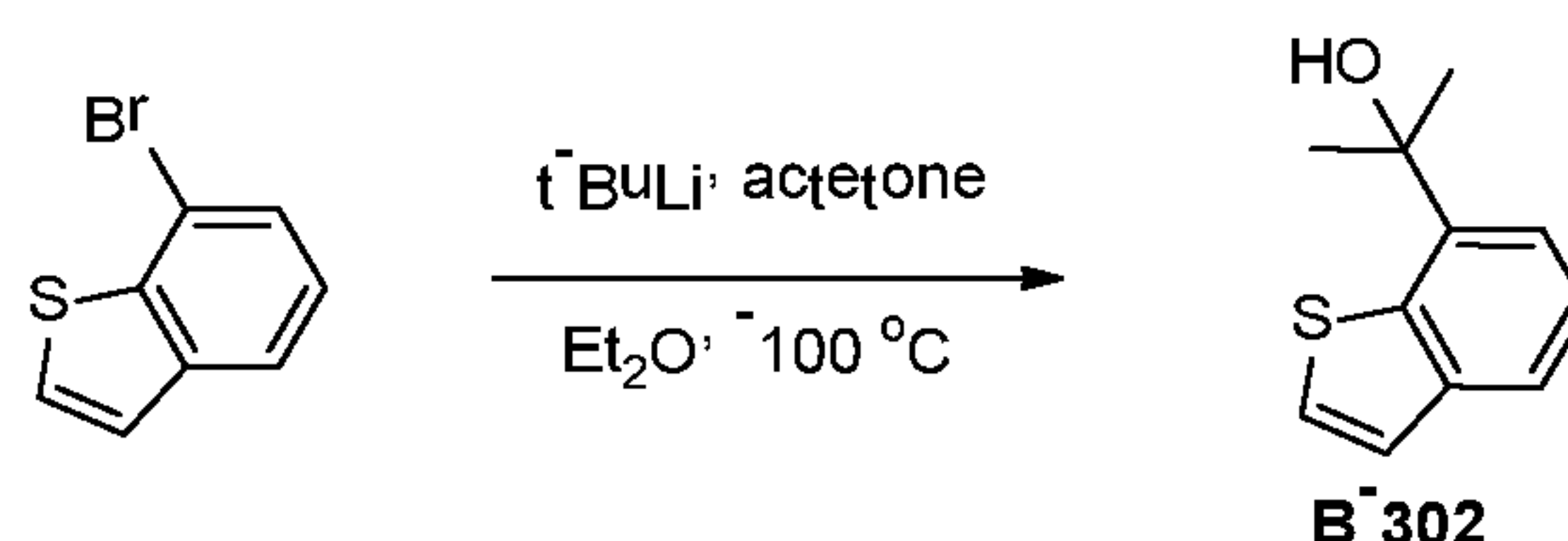
[00662] A solution of methyl 4-hydroxy-3-iodobenzoate (4.2 g, 15 mmol), ethynylcyclopropane (1.0 g, 15 mmol), 1,1,3,3-tetramethylguanidine (17 g, 0.15 mol), bis(triphenylphosphine)palladium(II) chloride (1.05 g, 1.5 mmol) and copper iodide (0.29 g, 1.5 mmol) in *N,N*-dimethylformamide (40 mL) was stirred at 50 °C for 12 hours. On completion, the reaction mixture was quenched with 50 mL of water and extracted with dichloromethane (3×50 mL). The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, concentrated in vacuo and purified by silica gel chromatography [petroleum ether: ethyl acetate = 8:1] to give **compound B-300** (2.0 g, 61% yield) as a yellow solid.

[00663] **Example 199B: 2-cyclopropylbenzofuran-5-carboxylic acid (B-301)**



[00664] To a solution of **compound B-300** (0.50 g, 2.3 mmol) in THF (15 mL) was added lithium hydroxide monohydrate (0.29 g, 6.9 mmol) in water (5.0 mL). The resulting solution was stirred at room temperature for 12 hours, then acidified with 2.0 M aqueous hydrochloric acid and extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-301** (0.16 g, 34% yield) as a yellow solid.

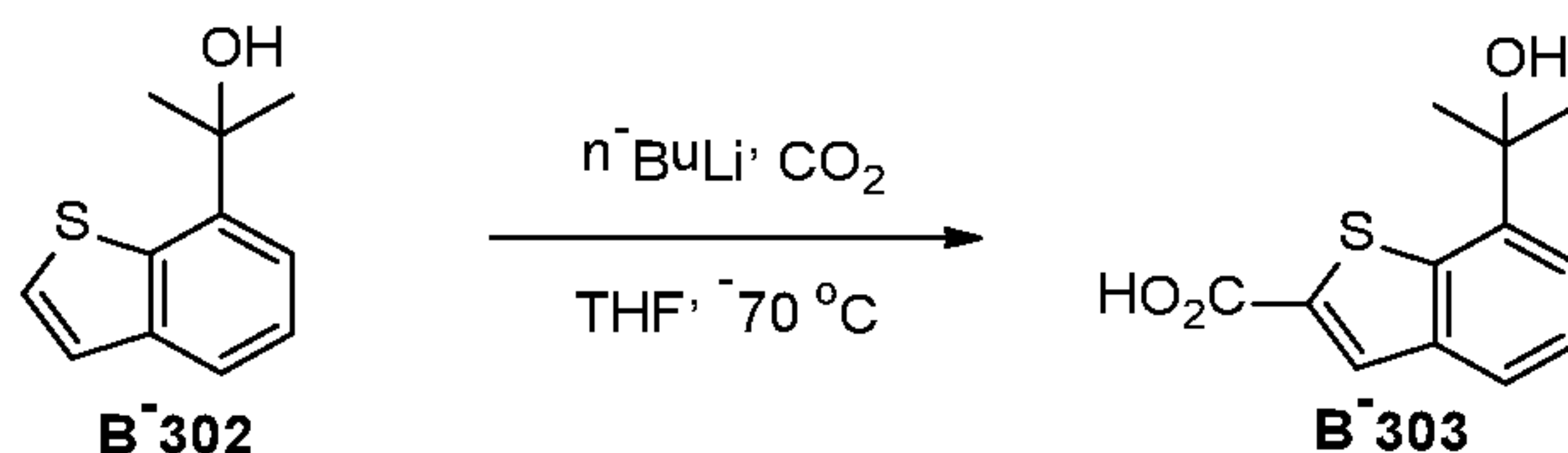
[00665] **Example 200B: 2-(benzo[b]thiophen-7-yl)propan-2-ol (B-302)**



[00666] To a solution of 7-bromobenzo[b]thiophene (5.0 g, 24 mmol) in diethyl ether (50 mL) at -100 °C under nitrogen was added dropwise *t*-BuLi (1.3 mol/L, 55 mL). The mixture was stirred at -100 °C for 15 min, and dry acetone (3.6 g, 48 mmol) was added dropwise at -100 °C. The mixture was stirred at -100 °C for 2 hours. TLC showed the reaction was complete and the formation of two

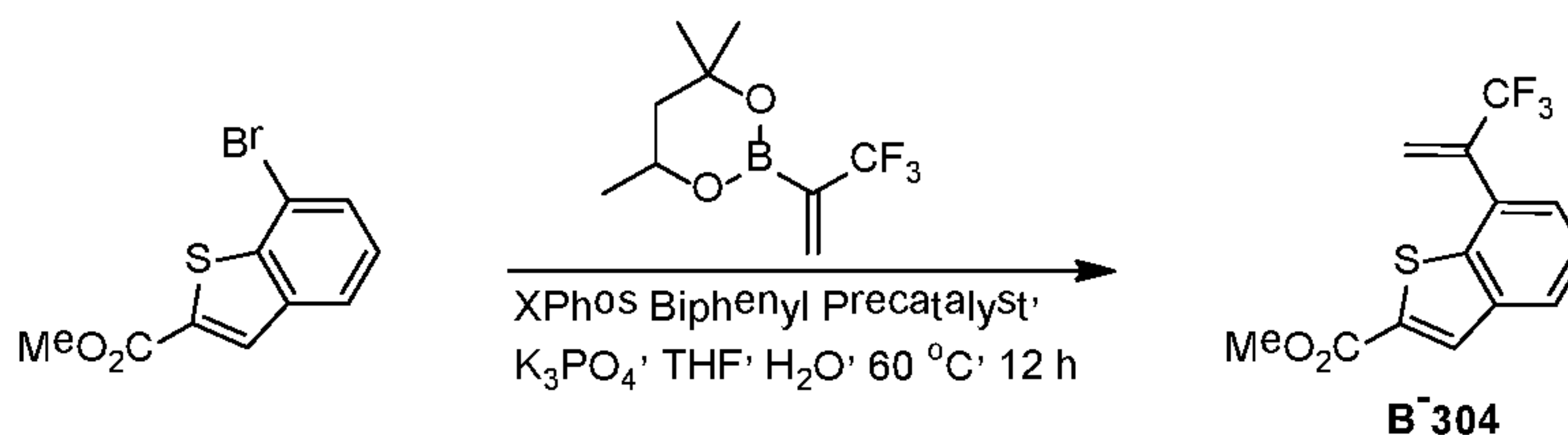
products (about 1:1). The reaction mixture was quenched with saturated aqueous ammonium chloride (20 mL) dropwise at 0 °C, and then extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over anhydrous sodium sulfate, concentrated in vacuo and purified by silica gel column chromatography [petroleum ether: ethyl acetate = 40:1] to give **compound B-302** (0.80 g, 34% yield, the lower spot on TLC) as a yellow oil.

[00667] **Example 201B: 7-(2-hydroxypropan-2-yl)benzo[*b*]thiophene-2-carboxylic acid (B-303)**



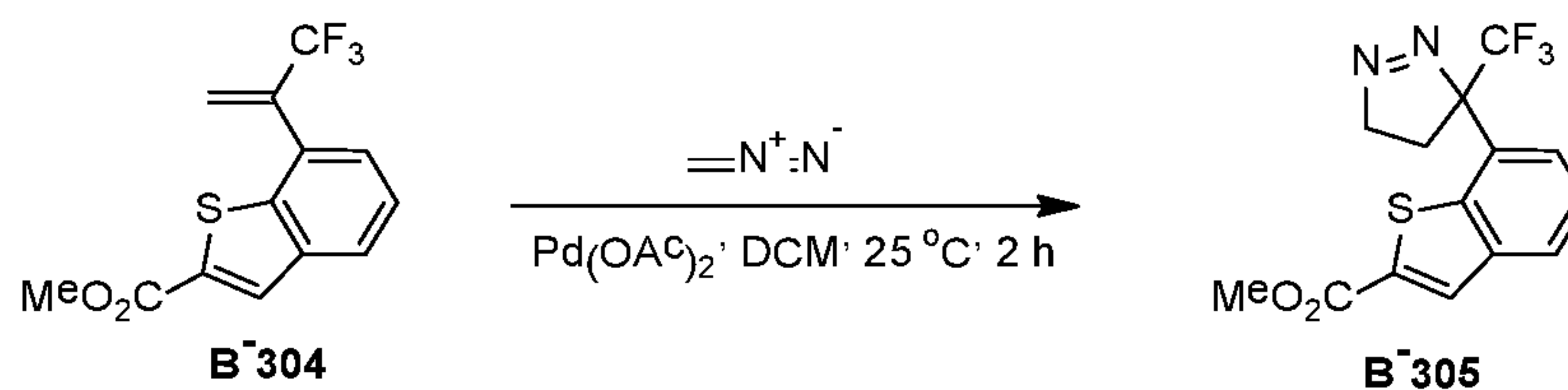
[00668] To a solution of **B-302** (0.80 g, 4.2 mmol) in tetrahydrofuran (10 mL) at -70 °C under nitrogen was added n-BuLi (2.5 mol/L, 4 mL, 10 mmol) dropwise. The mixture was stirred at -70 °C for 0.5 hour. Carbon dioxide was bubbled into the mixture for 0.5 hour. On completion, the reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL) dropwise at 0 °C, and washed with ethyl acetate (2 × 20 mL). The aqueous phase was acidified to pH 4~5 with HCl (aq), then extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-303** (0.85 g, 36% yield) as a white solid. ¹H-NMR (CDCl₃, 400 MHz): δ 8.20 (s, 1H), 7.85-7.83 (m, 1H), 7.44 (m, 2H), 1.79 (s, 3H).

[00669] **Example 202B: methyl 7-(3,3,3-trifluoroprop-1-en-2-yl)benzo[*b*]thiophene-2-carboxylate (B-304)**



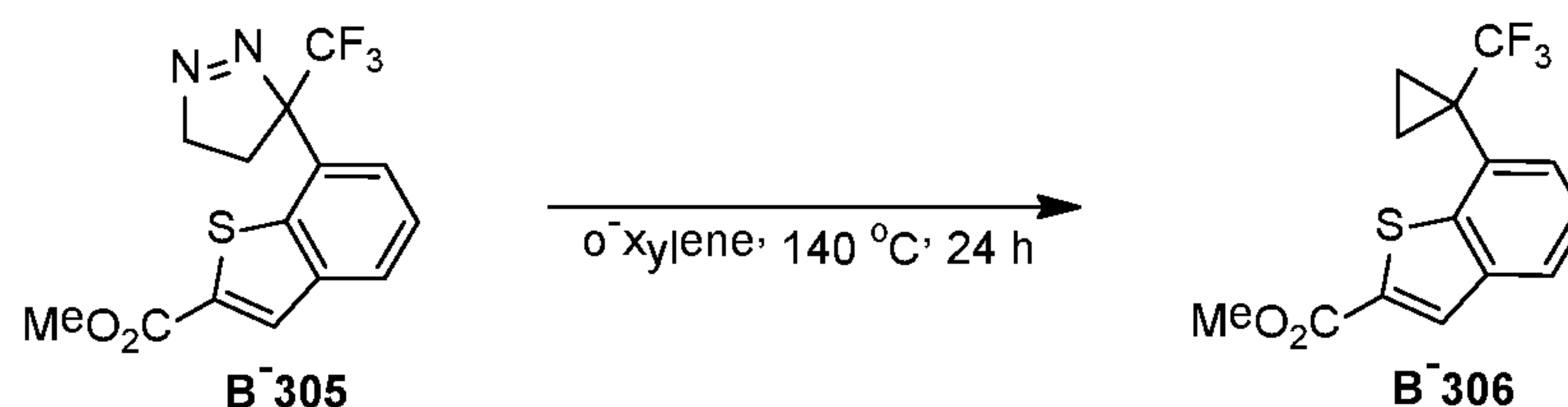
[00670] To a mixture of methyl 7-bromobenzo[*b*]thiophene-2-carboxylate (0.60 g, 2.2 mmol) in tetrahydrofuran (20 mL) and water (6 mL) under nitrogen was added 4,4,6-trimethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborinane (0.59 g, 2.7 mmol), potassium phosphate (0.94 g, 4.4 mmol) and [2-(2-aminophenyl)phenyl]-chloro-palladium;dicyclohexyl-[3-(2,4,6-triisopropylphenyl)phenyl]phosphane (87 mg, 0.11 mmol). The mixture was stirred at 60 °C for 12 hours, then added into water (10 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-304** (0.60 g, 95% purity, 90% yield) as a yellow solid. LCMS (B): tR=0.906 min., (ES⁺) m/z (M+H)⁺ =287.1.

[00671] **Example 203B:** methyl 7-(3-(trifluoromethyl)-4,5-dihydro-3H-pyrazol-3-yl)benzo[*b*]thiophene-2-carboxylate (**B-305**)



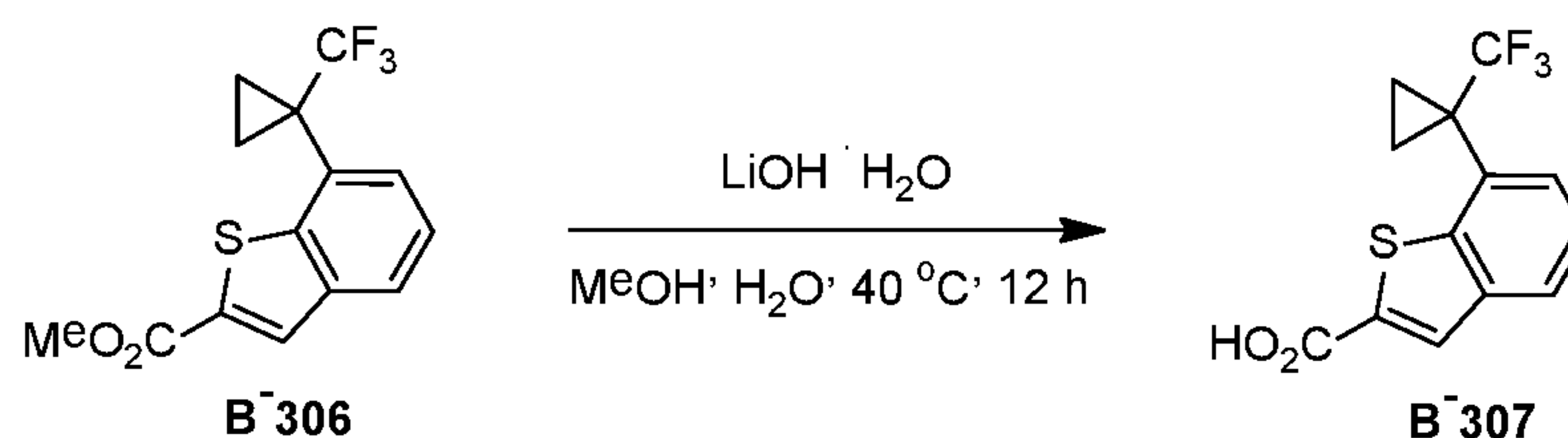
[00672] To a mixture of **compound B-304** (0.60 g, 2.1 mmol) in dichloromethane (18 mL) under nitrogen was added diazomethane (0.46 M in diethyl ether, 0.14 L) and palladium acetate (47 mg, 0.21 mmol). The mixture was stirred at 25 °C for 2 hours. On completion, the mixture was added into acetic acid (3.8 g, 63 mmol), concentrated in vacuo to remove diethyl ether, diluted with water (15 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-305** (0.70 g, 82% purity, 83% yield) as a yellow solid. LCMS (B): tR=0.856 min., (ES⁺) m/z (M+H)⁺=329.1.

[00673] **Example 204B:** methyl 7-(1-(trifluoromethyl)cyclopropyl)benzo[*b*]thiophene-2-carboxylate (**B-306**)

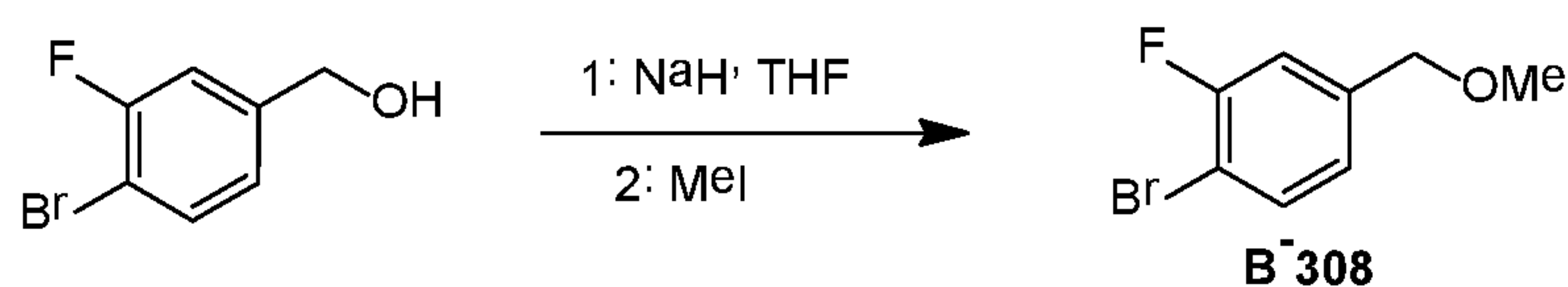


[00674] A mixture of **compound B-305** (0.70 g, 2.1 mmol) in o-xylene (50 mL) was stirred at 140 °C for 24 hours. On completion, the mixture was concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-306** (0.24 g, 85% purity, 32% yield) as a white solid. LCMS (B): tR=0.920 min., (ES⁺) m/z (M+H)⁺=301.1.

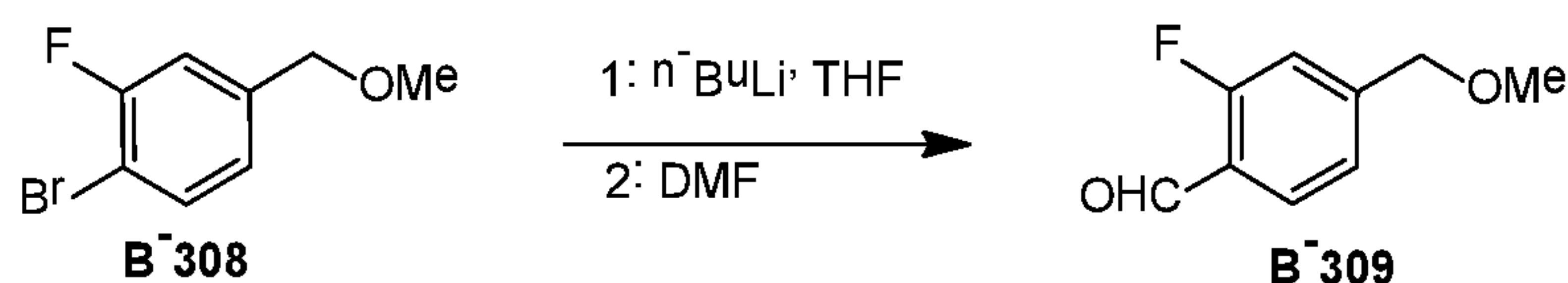
[00675] **Example 205B:** 7-(1-(trifluoromethyl)cyclopropyl)benzo[*b*]thiophene-2-carboxylic acid (**B-307**)



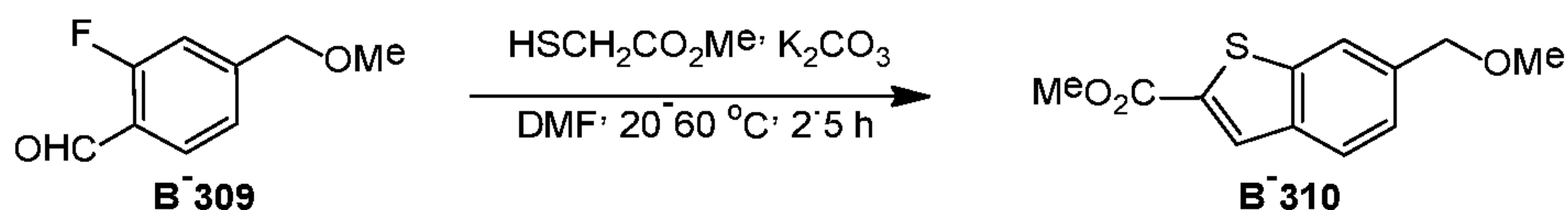
[00676] To a mixture of **compound B-306** (0.40 g, 1.3 mmol) in methanol (5 mL) and water (2 mL) was added lithium hydroxide monohydrate (0.11 g, 2.7 mmol). The mixture was stirred at 40 °C for 12 hours, then concentrated to remove methanol, diluted with water, acidified to pH 3 with 6 M hydrochloric acid and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give **compound B-307** (0.38 g, 90% purity, 90% yield) as a white solid. LCMS (B): tR=0.831 min., (ES⁺) m/z (M+H)⁺=287.1.

[00677] **Example 206B:** 1-bromo-2-fluoro-4-(methoxymethyl)benzene (**B-308**)

[00678] To a solution of (4-bromo-3-fluorophenyl)methanol (5.0 g, 24 mmol) in tetrahydrofuran (150 mL) at 0 °C was added sodium hydride (1.4 g, 34 mmol). The reaction was stirred at this temperature for 10 min, and then methyl iodide (4.1 g, 29 mmol) was added. The reaction was allowed to warm from 0 °C to 20 °C over 3 hours, then quenched with saturated aqueous ammonium chloride (50 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography [petroleum ether: ethyl acetate = 30:1] to give **compound B-308** (4.8 g, 90% yield) as an orange oil. TLC [petroleum ether: ethyl acetate = 10:1]: R_f =0.5; ^1H -NMR (CDCl_3 , 400 MHz): δ 7.53 (t, J =8.0 Hz, 1H), 7.14 (d, J =9.2 Hz, 1H), 7.01 (d, J =8.0 Hz, 1H), 4.43 (s, 2H), 3.42 (s, 3H).

[00679] **Example 207B:** 2-fluoro-4-(methoxymethyl)benzaldehyde (**B-309**)

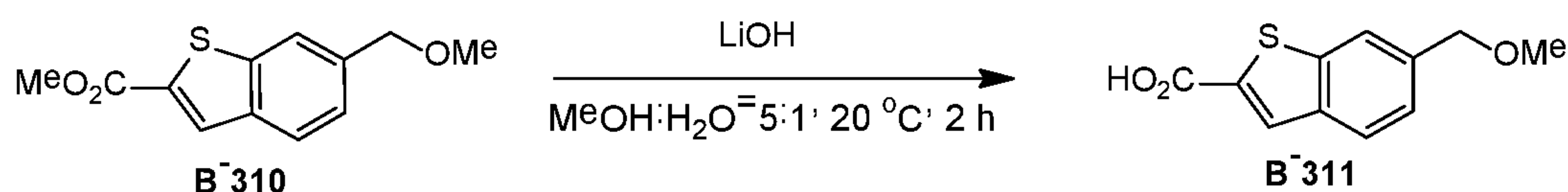
[00680] To a solution of **compound B-308** (4.0 g, 18 mmol) in tetrahydrofuran (50 mL) at -78 °C was added *n*-butyllithium (20 mmol, 8.0 mL). The reaction was stirred at this temperature for 30 min, and then *N,N*-dimethylformamide (6.7 g, 91 mmol) was added. The reaction was allowed to warm from -78 °C to 0 °C over 1 hour, then quenched with saturated aqueous ammonium chloride (30 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phase was concentrated and purified by silica gel chromatography [petroleum ether: ethyl acetate = 20:1] to give **compound B-309** (2.1 g, 68% yield) as a yellow oil. TLC [petroleum ether: ethyl acetate = 10:1]: R_f = 0.4; ^1H -NMR (CDCl_3 , 400 MHz): δ 10.22 (s, 1H), δ 7.72 (t, J =8.0 Hz, 1H), 7.09-7.04 (m, 2H), 4.39 (s, 2H), 3.32 (s, 3H).

[00681] **Example 208B:** methyl 2-aminothieno[2,3-d]pyrimidine-6-carboxylate (**B-310**)

[00682] To a solution of **compound B-309** (2.0 g, 12 mmol) in *N,N*-dimethylformamide (20 mL) under nitrogen was added potassium carbonate (3.3 g, 24 mmol) and methyl 2-mercaptoacetate (1.9 g, 18 mmol). The mixture was stirred at 60 °C for 2.5 hours, then diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel

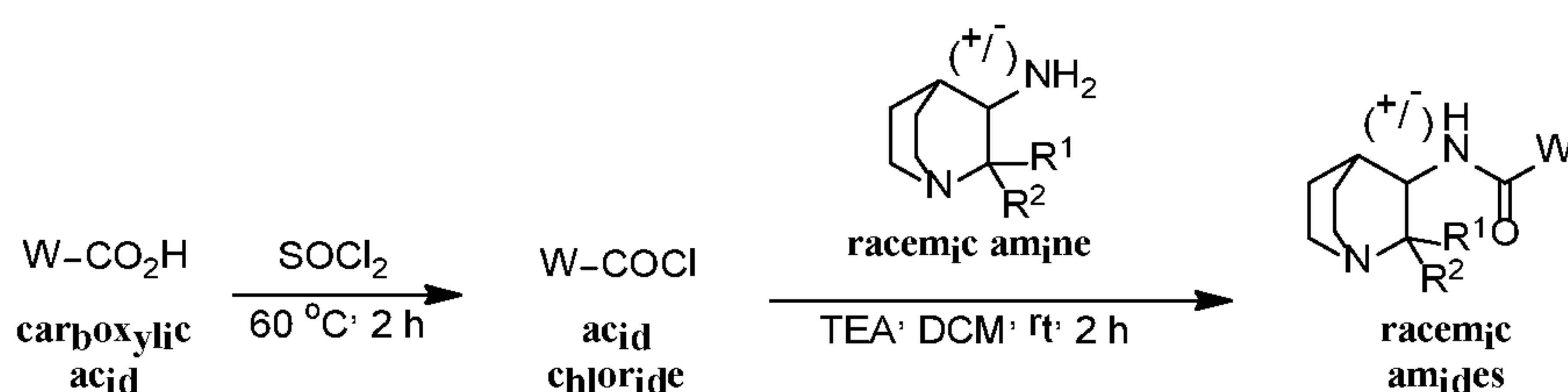
chromatography [petroleum ether: ethyl acetate = 10:1] to give **compound B-310** (1.5 g, 53% yield) as a yellow oil. LCMS (B): tR=0.792 min., (ES+) m/z (M+1)⁺=237.0.

[00683] **Example 209B: 6-(methoxymethyl)benzo[b]thiophene-2-carboxylic acid (B-311)**



[00684] To a solution of **compound B-310** (1.5 g, 6.4 mmol) in methanol (15 mL) and water (3 mL) was added lithium hydroxide (0.30 g, 13 mmol). The mixture was stirred at 25 °C for 2 hours, then concentrated to remove methanol, diluted with water, and acidified to pH 3 with 1 M hydrochloric acid, resulting in precipitation of a solid. The solid was collected by filtration and dried in vacuo to give **compound B-311** (0.70 g, 50% yield) as a white solid. TLC [dichloromethane : methanol = 10:1] : R_f = 0.4. ¹H-NMR (CDCl₃, 400 MHz): δ 8.18 (s, 1H), δ 7.92-7.90 (m, 2H), 7.42 (d, J=8 Hz, 1H), 4.64 (s, 2H), 3.47 (s, 3H).

[00685] **General Procedure A: Synthesis and chiral separation of amides**

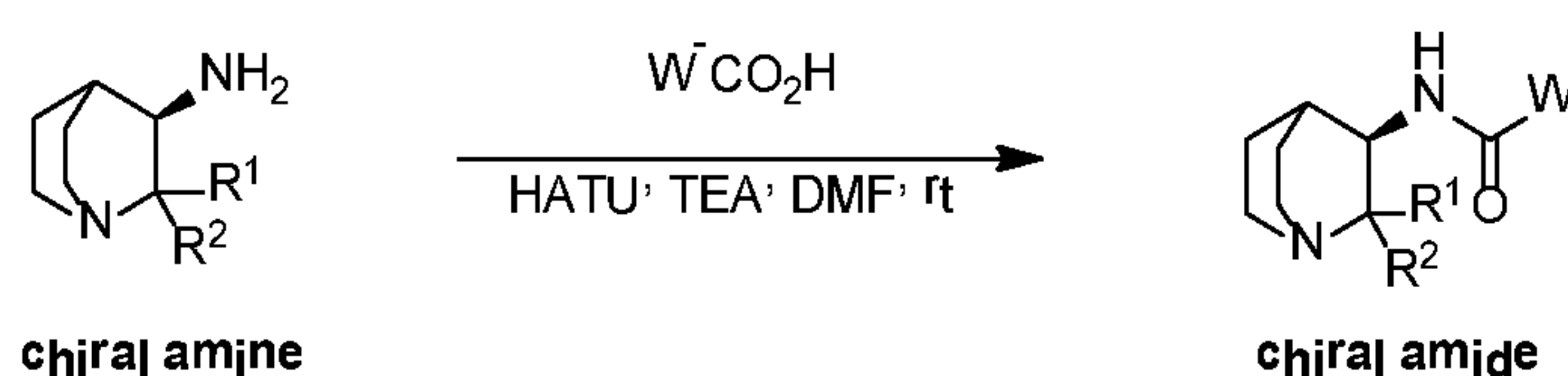


[00686] A mixture of carboxylic acid in thionyl chloride (5 mL/mmol carboxylic acid) was stirred at 60 °C for 2 hours. On completion, the solution was concentrated in vacuo to give the acid chloride, which was used directly without further purification. This material (1.1 eq) was added to a mixture of **racemic amine** (1 eq.) and triethylamine (2 eq.) in dichloromethane (3-5 mL/mmol racemic amine) at room temperature. The mixture was stirred at this temperature for 2 hours. On completion, the reaction was filtered, and the resulting filtrate was concentrated and purified by prep-HPLC to give racemic amide product.

[00687] Chiral Separation:

[00688] A solution of racemic amide product in 3-5 mL of methanol or ethanol was separated by cSFC (Waters SFC Prep 80, Column temperature: 35 °C, back pressure: 100 bar, and wavelength: 220 nm). Each set of collected fractions was concentrated at room temperature and lyophilized. The resulting solids were dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give each enantiomer of the amide product.

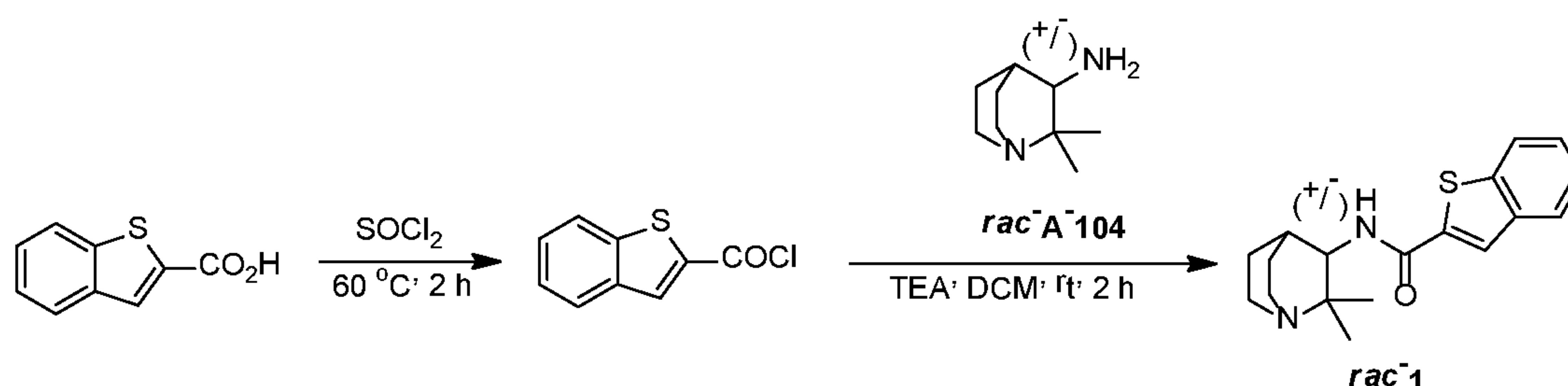
[00689] **General Procedure B: Synthesis of chiral amide products from chiral amines**



[00690] To a mixture of carboxylic acid (1 eq.) in *N,N*-dimethylformamide (2 mL/mmol carboxylic acid) was added 2-(3H-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate (1.2 eq.), followed by chiral amine (1 eq.) and triethylamine (2 eq.). The mixture was stirred at room temperature for 2-12 hours. On completion, the reaction was diluted with ethyl acetate and washed 4 times with water. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by prep-HPLC and lyophilized to give the target compound.

[00691] **Example 1:**

[00692] Preparation of (+/-)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide (*rac*-1)



[00693] Following general procedure A, *rac*-1 was prepared from benzo[*b*]thiophene-2-carboxylic acid and *rac*-A-104 (0.10 g, 0.65 mmol). The product was purified by prep-HPLC [Instrument: GX-C; Column: Phenomenex Gemini C18 150×30 mm, particle size: 5 μm; Mobile phase: 35-65% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give *rac*-1 (0.15 g, 73% yield) as a white solid. LCMS: (ES⁺) *m/z* (M+H)⁺ = 315.1.

[00694] Chiral Separation:

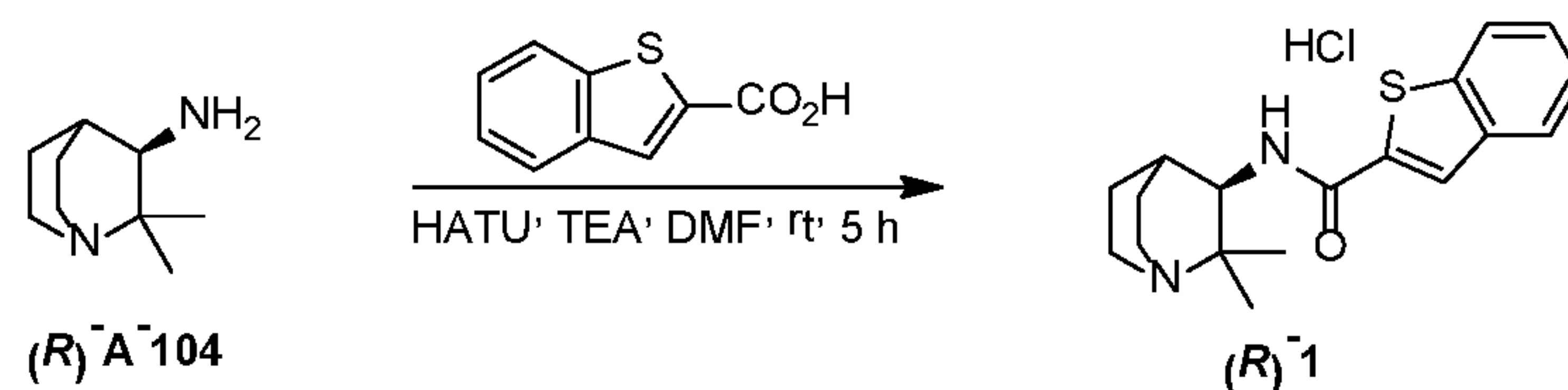
[00695] *rac*-1 (0.20 g, 0.64 mmol) in 3 mL of methanol was separated by SFC (Instrument: SFC 80; Column: Chiralpak AD-H 250×30 mm I.D., 10 μm; Mobile phase: 50% methanol (0.01% NH₃·H₂O) in CO₂) according to general procedure A to give:

N-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide-enantiomer1 hydrochloride (**compound 1a**) (0.08 g, 40% yield) as a white solid: cSFC analytical (A) *t*R=2.80 min., purity: 100%; LCMS (Z): *t*R=1.459 min., (ES⁺) *m/z* (M+H)⁺ = 315.0; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 10.50 (s, 1H), 8.61 (d, *J*=8.0 Hz, 1H), 8.39 (s, 1H), 8.04-8.02 (m, 1H), 7.98-7.95 (m, 1H), 7.50-7.45 (m, 2H), 4.11 (d, *J*=7.6 Hz, 1H), 3.50 (m, 2H), 3.22-3.11 (m, 2H), 2.43-2.42 (m, 1H), 2.10-2.02 (m, 2H), 1.92-1.87 (m, 1H), 1.73-1.67 (m, 1H), 1.62 (s, 3H), 1.40 (s, 3H); and

N-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide-enantiomer2 hydrochloride (**compound 1b**) (0.08 g, 40% yield) as a white solid : cSFC analytical (A) *t*R=3.43 min., purity: 99.72%; LCMS (Z): *t*R=1.439 min., (ES⁺) *m/z* (M+H)⁺ = 315.0; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 10.43 (s, 1H), 8.61 (d, *J*=7.6 Hz, 1H), 8.38 (s, 1H), 8.04-8.02 (m, 1H), 7.98-7.96 (m, 1H),

7.50-7.45 (m, 2H), 4.11 (d, J=7.6 Hz, 1H), 3.50 (m, 2H), 3.22-3.12 (m, 2H), 2.43-2.42 (m, 1H), 2.11-2.02 (m, 2H), 1.93-1.87 (m, 1H), 1.73-1.67 (m, 1H), 1.62 (s, 3H), 1.40 (s, 3H).

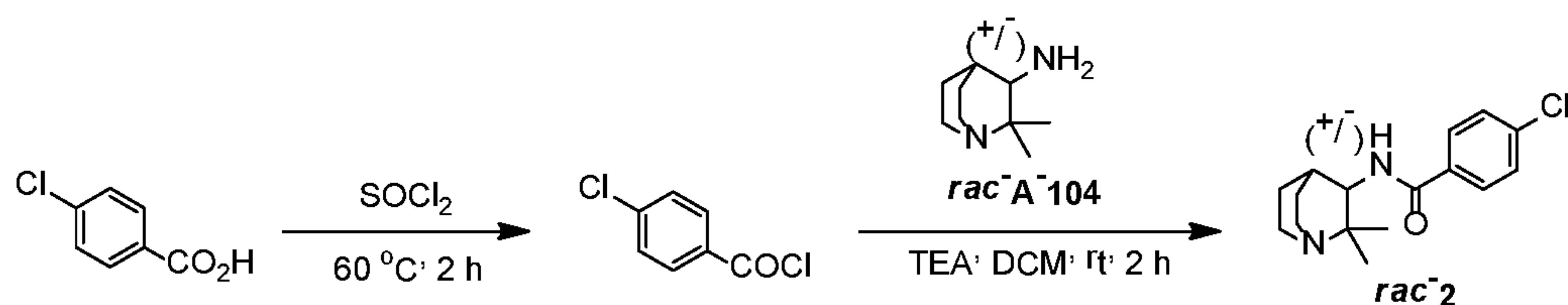
[00696] Preparation of (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**(*R*)-1**)



[00697] Following general procedure B, **compound (R)-1** was prepared from benzo[b]thiophene-2-carboxylic acid (0.35 g, 1.9 mmol) and **compound (R)-A-104** (0.30 g, 1.9 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-1**) (0.22 g, 36% yield) as a white solid : cSFC analytical (A) t_R=2.78 min., purity: 98.60%; LCMS (Z): t_R=1.496 min., 315.0 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.16 (s, 1H), 7.94-7.92 (m, 2H), 7.49-7.42 (m, 2H), 4.26 (s, 1H), 3.76-3.67 (m, 2H), 3.38-3.33 (m, 2H), 2.43-2.41 (m, 1H), 2.29-2.27 (m, 1H), 2.18-2.10 (m, 2H), 1.97-1.94 (m, 1H), 1.75 (s, 3H), 1.50 (s, 3H).

[00698] **Example 2: (+/-)-4-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzamide (*rac*-2)**



[00699] Following general procedure A, ***rac*-2** was prepared from 4-chlorobenzoic acid and ***rac*-A-104** (0.31 g, 1.76 mmol). The product was purified by prep-HPLC [Instrument: GX-D; Column: Boston Symmetrix C18 ODS-R 150*30mm, particle size: 5 μm; Mobile phase: 6-36% acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)] to give ***rac*-2** (0.5 g, 37% yield) as a yellow solid. LCMS: (ES⁺) m/z (M+H)⁺ = 293.2.

[00700] Chiral Separation:

[00701] ***rac*-2** (0.15 g, 0.51 mmol) in 3 mL of methanol was separated by SFC (Instrument: SFC 80; Column: Chiralpak AD-H 250×25 mm I.D., 10 μm; Mobile phase: 30% methanol (0.01% NH₃ · H₂O) in CO₂) according to general procedure A to give:

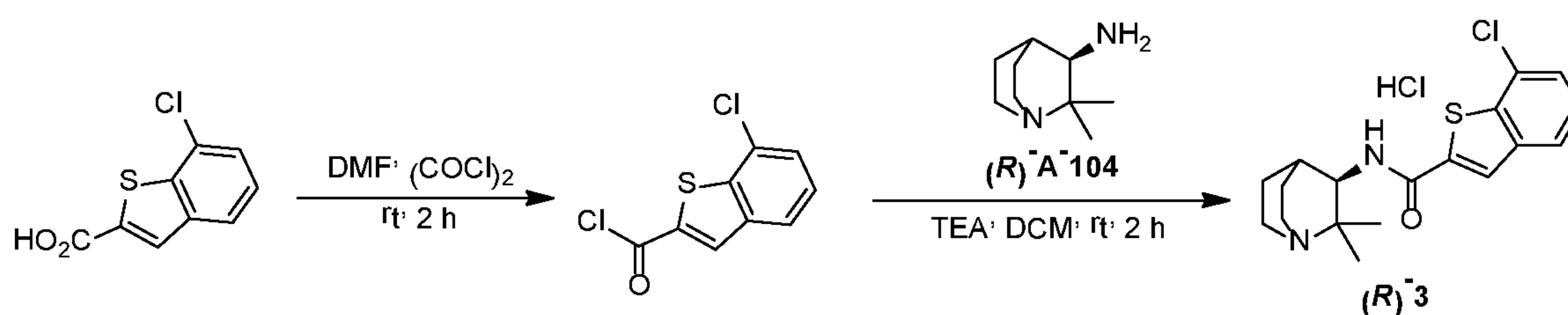
4-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzamide-enantiomer1 hydrochloride (**compound 2a**) (0.05 g, 33% yield) as yellow solid: cSFC analytical (B) t_R: 2.02 min., purity: 99.83%; LCMS (Y): t_R: 0.603 min., (ES⁺) m/z (M+H)⁺ = 293.0; ¹H-NMR (CD₃OD, 400 MHz): δ 7.84 (d, J=8.4 Hz, 2H), 7.51 (d, J=8.4 Hz, 2H), 4.23 (s, 1H), 3.75-3.63 (m, 2H), 3.36-3.34 (m, 1H), 3.28-3.26 (m, 1H),

2.35-2.24 (m, 1H), 2.23-2.21 (m, 1H), 2.16-2.06 (m, 2H), 1.94-1.88 (m, 1H), 1.75 (s, 3H), 1.46 (s, 3H); and

4-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzamide-enantiomer2 hydrochloride (**compound 2b**) (0.051 g, 33% yield) as yellow solid: cSFC analytical (B) tR: 2.40 min., purity: 99.84%; LCMS (Y): tR: 0.592 min., (ES⁺) m/z (M+H)⁺ = 293.0; ¹H-NMR (CD₃OD, 400 MHz): δ 7.84 (d, J=8.4 Hz, 2H), 7.51 (d, J=8.4 Hz, 2H), 4.23 (s, 1H), 3.72-3.67 (m, 2H), 3.36-3.34 (m, 1H), 3.28-3.26 (m, 1H), 2.38-2.33 (m, 1H), 2.24-2.23 (m, 1H), 2.19-2.09 (m, 2H), 1.94-1.88 (m, 1H), 1.75 (s, 3H), 1.46 (s, 3H).

[00702] Example 3:

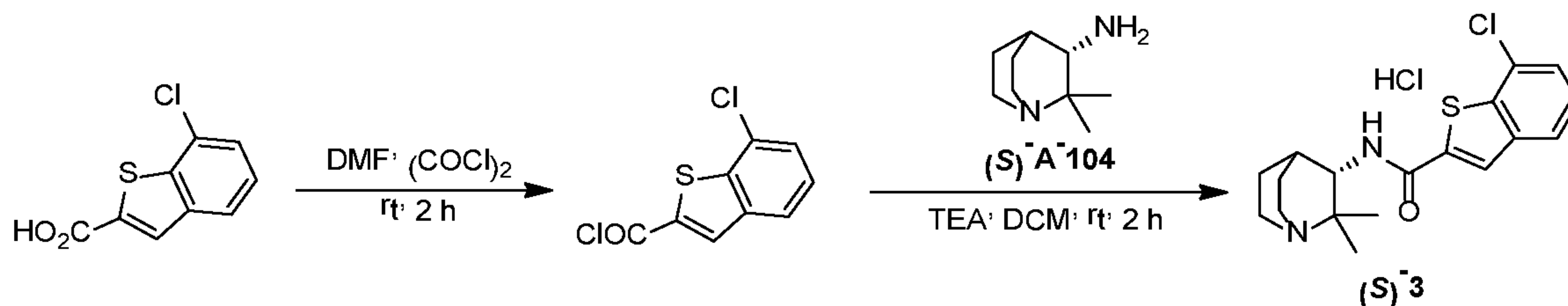
[00703] Preparation of (*R*)-7-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-3)



[00704] To a mixture of 7-chlorobenzo[b]thiophene-2-carboxylic acid (70 mg, 0.33 mmol) in oxalyl chloride (2 mL) was added *N,N*-dimethylformamide (2 drops). The mixture was stirred at room temperature for 2 hours. On completion, the solution was concentrated in vacuo to give the acid chloride, which was used directly without further purification. This material (1.0 eq.) was added to a mixture of **compound (R)-A-104** (50 mg, 0.32 mmol) and triethylamine (66 mg, 0.65 mmol) in dichloromethane (2 mL) at room temperature. The mixture was stirred at this temperature for 2 hours. On completion, the reaction was filtered, and the resulting filtrate was concentrated and purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 19-49% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-7-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-3**) (53.9 mg, 43% yield) as white solid: cSFC analytical (A) tR=3.04 min., purity: 98.99%; LCMS (A): tR=1.642 min., (ES⁺) m/z (M+H)⁺ = 349.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.22 (s, 1H), 7.89 (d, J=8.0 Hz, 1H), 7.52-7.44 (m, 2H), 4.26 (s, 1H), 3.73-3.69 (m, 2H), 3.38-3.31 (m, 2H), 2.45-2.37 (m, 1H), 2.28-2.27 (m, 1H), 2.18-2.06 (m, 2H), 1.97-1.91 (m, 1H), 1.75 (m, 3H), 1.49 (m, 3H);

[00705] Preparation of (*S*)-7-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride ((*S*)-3)

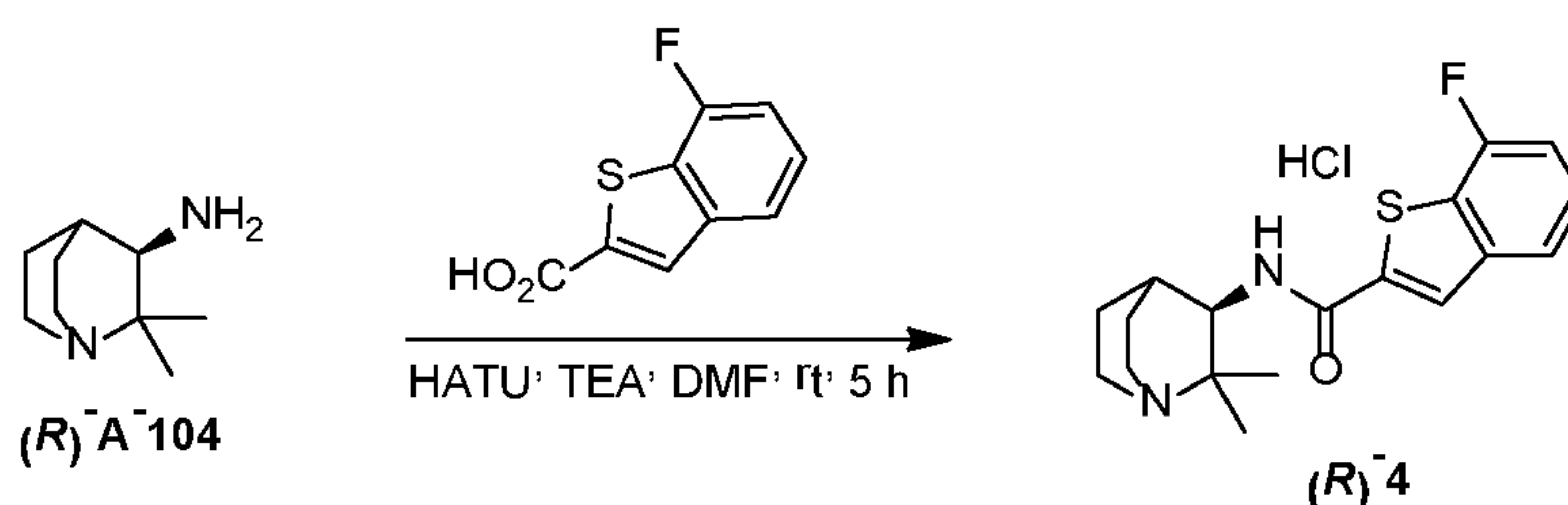


[00706] To a mixture of 7-chlorobenzo[b]thiophene-2-carboxylic acid (70 mg, 0.33 mmol) in oxalyl chloride (2 mL) was added *N,N*-dimethylformamide (2 drops). The mixture was stirred at room temperature for 2 hours. On completion, the solution was concentrated in vacuo to give the acid chloride, which was used directly without further purification. This material (1.0 eq.) was added to a mixture of **compound (S)-A-104** (50 mg, 0.32 mmol) and triethylamine (66 mg, 0.65 mmol) in dichloromethane (2 mL) at room temperature. The mixture was stirred at this temperature for 2 hours. On completion, the reaction was filtered, and the resulting filtrate was concentrated and purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm ; Mobile phase: 19-49% acetonitrile in H_2O (add 0.5% HCl , v/v)] to give:

(*S*)-7-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (S)-3**) (35 mg, 31% yield) as white solid: cSFC analytical (A) t_R =4.40 min., purity: 97.85%; LCMS (B): t_R =0.699 min., (ES^+) m/z ($\text{M}+\text{H}$) $^+$ = 349.1; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 8.24 (s, 1H), 7.89 (d, J =8.0 Hz, 1H), 7.52-7.44 (m, 2H), 4.26 (s, 1H), 3.76-3.66 (m, 2H), 3.38-3.33 (m, 2H), 2.46-2.43 (m, 1H), 2.28-2.27 (m, 1H), 2.17-2.10 (m, 2H), 1.97-1.91 (m, 1H), 1.76 (m, 3H), 1.51 (m, 3H);

[00707] **Example 4:**

[00708] Preparation of (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-benzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-4)

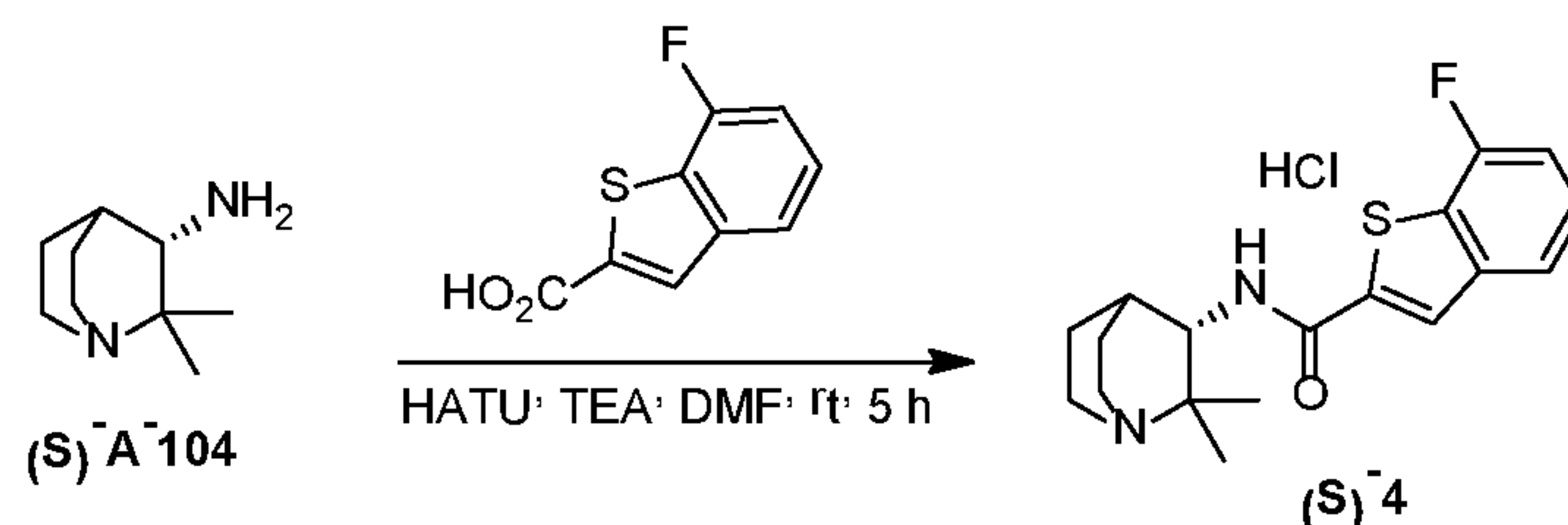


[00709] Following general procedure B, **Compound (R)-4** was prepared from 7-fluorobenzo[b]thiophene-2-carboxylic acid (76 mg, 0.39 mmol) and **compound (R)-A-104** (0.30 g, 1.9 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm ; Mobile phase: 16-46% acetonitrile in H_2O (add 0.5% HCl , v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-4**) (37 mg, 31% yield) as a white solid : cSFC analytical (A) t_R =2.71 min., purity: 100%; LCMS (A): t_R =1.509 min., (ES^+) m/z ($\text{M}+\text{H}$) $^+$ = 333.1; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 8.20 (d, J =3.6 Hz, 1H), 7.76 (d, J =8.0 Hz, 1H), 7.26-7.20 (m, 2H), 4.26 (s, 1H), 3.76-3.65

(m, 2H), 3.38-3.32 (m, 2H), 2.45-2.40 (m, 1H), 2.29-2.27 (m, 1H), 2.18-2.10 (m, 2H), 1.98-1.91 (m, 1H), 1.75 (s, 3H), 1.50 (s, 3H).

[00710] Preparation of (*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-benzo[*b*]thiophene-2-carboxamide hydrochloride ((*S*)-4)

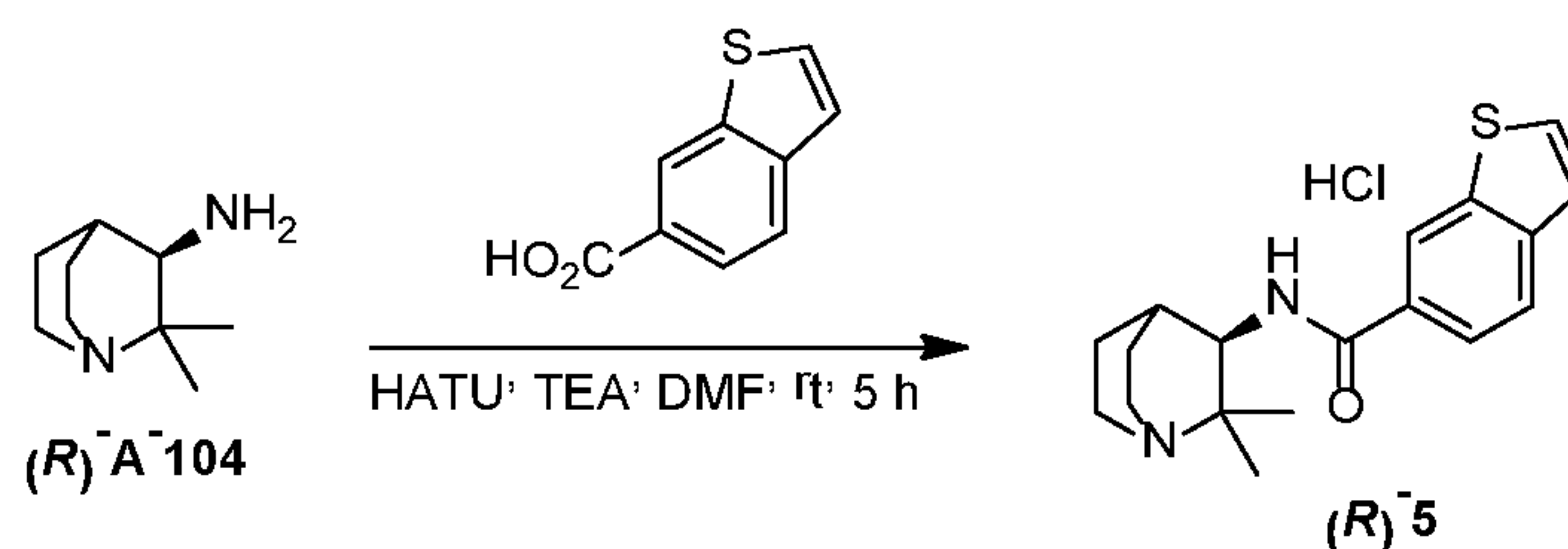


[00711] Following general procedure B, **Compound (S)-4** was prepared from 7-fluorobenzo[*b*]thiophene-2-carboxylic acid (76 mg, 0.39 mmol) and **compound (S)-A-104** (0.50 g, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 16-46% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (S)-4**) (31 mg, 29% yield) as a white solid: cSFC analytical (A) t_R=3.54 min., purity: 100%; LCMS (B): t_R=0.694 min., (ES⁺) m/z (M+H)⁺ = 333.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.22 (d, J=3.2 Hz, 1H), 7.77 (d, J=7.6 Hz, 1H), 7.49-7.44 (m, 2H), 4.26 (s, 1H), 3.76-3.67 (m, 2H), 3.38-3.35 (m, 2H), 2.43-2.42 (m, 1H), 2.29-2.28 (m, 1H), 2.18-2.10 (m, 2H), 1.98-1.91 (m, 1H), 1.75 (s, 3H), 1.50 (s, 3H).

[00712] **Example 5:**

[00713] Preparation of (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-6-carboxamide hydrochloride ((*R*)-5)

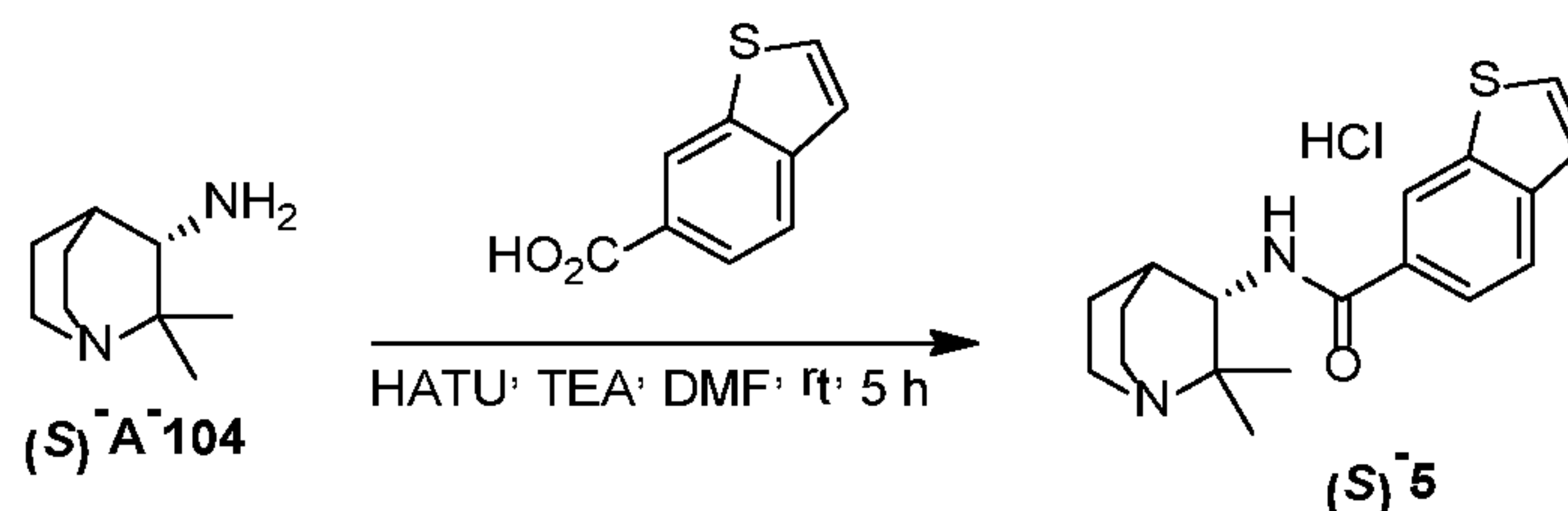


[00714] Following general procedure B, **Compound (R)-5** was prepared from benzo[*b*]thiophene-6-carboxylic acid (57 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 19-49% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-6-carboxamide hydrochloride (**compound (R)-5**) (53 mg, 46% yield) as a white solid : cSFC analytical (A) t_R=2.96 min., purity: 95.55%; LCMS (A): t_R=1.153 min., 315.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.46 (s, 1H), 7.95 (d, J=8.4 Hz, 1H), 7.85 (dd, J₁=8.4 Hz, J₂=1.6 Hz, 1H), 7.80 (d, J=5.6 Hz, 1H), 7.47 (d, J=6 Hz,

1H), 4.29 (s, 1H), 3.76-3.65 (m, 2H), 3.37-3.33 (m, 2H), 2.43-2.38 (m, 1H), 2.28-2.26 (m, 1H), 2.19-2.09 (m, 2H), 1.95-1.89 (m, 1H), 1.77 (s, 3H), 1.49 (s, 3H).

[00715] Preparation of (*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide hydrochloride ((*S*)-**5**)

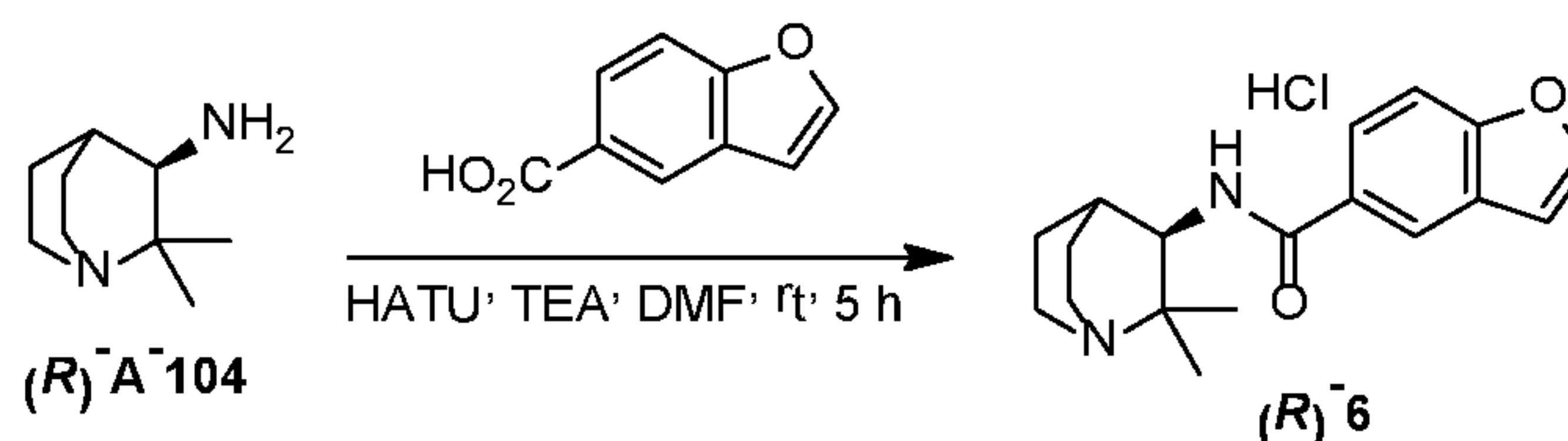


[00716] Following general procedure B, **Compound (S)-5** was prepared from benzo[b]thiophene-6-carboxylic acid (57 mg, 0.32 mmol) and **compound (S)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 µm; Mobile phase: 19-49% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide hydrochloride (**compound (S)-5**) (32 mg, 31% yield) as a white solid : cSFC analytical (A) t_R=3.92 min., purity: 97.22%; LCMS (B): t_R=0.569 min., 315.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.46 (s, 1H), 7.95 (d, J= 8.8 Hz, 1H), 7.84 (dd, J₁= 8.0 Hz, J₂= 1.2 Hz, 1H), 7.80 (d, J= 5.6 Hz, 1H), 7.47 (d, J= 5.6 Hz, 1H), 4.29 (s, 1H), 3.76-3.65 (m, 2H), 3.37-3.35 (m, 2H), 2.42-2.39 (m, 1H), 2.28-2.27 (m, 1H), 2.19-2.10 (m, 2H), 1.96-1.89 (m, 1H), 1.78 (s, 3H), 1.50 (s, 3H).

[00717] **Example 6:**

[00718] Preparation of (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide hydrochloride ((*R*)-**6**)

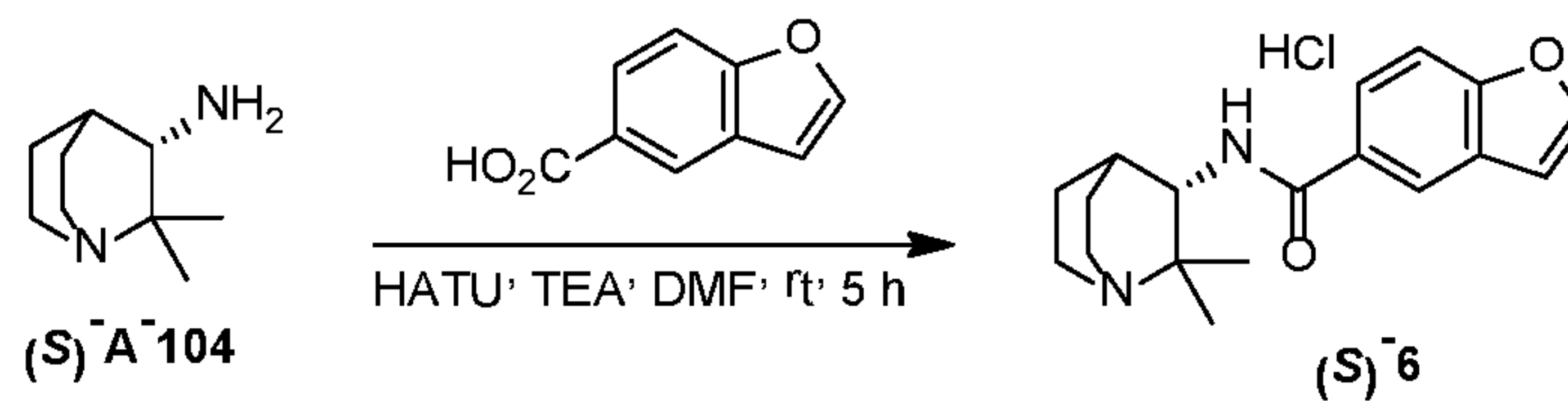


[00719] Following general procedure B, **Compound (R)-6** was prepared from benzofuran-5-carboxylic acid (52 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 µm; Mobile phase: 21-51% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide hydrochloride (**compound (R)-6**) (57 mg, 52% yield) as a white solid : cSFC analytical (A) t_R=2.45 min., purity: 98.53%; LCMS (A): t_R=0.566 min., 299.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.17 (d, J=1.2 Hz, 1H), 7.87 (d, J=2.0 Hz, 1H), 7.82 (dd, J₁=8.8 Hz, J₂=1.0 Hz, 1H), 7.60 (d, J=8.4 Hz, 1H), 6.96 (d,

$J=1.6$ Hz, 1H), 4.27 (s, 1H), 3.76-3.65 (m, 2H), 3.37-3.34 (m, 2H), 2.41-2.39 (m, 1H), 2.38-2.36 (m, 1H), 2.26-2.09 (m, 2H), 1.96-1.89 (m, 1H), 1.77 (s, 3H), 1.49 (s, 3H).

[00720] Preparation of (*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide hydrochloride ((*S*)-**6**)

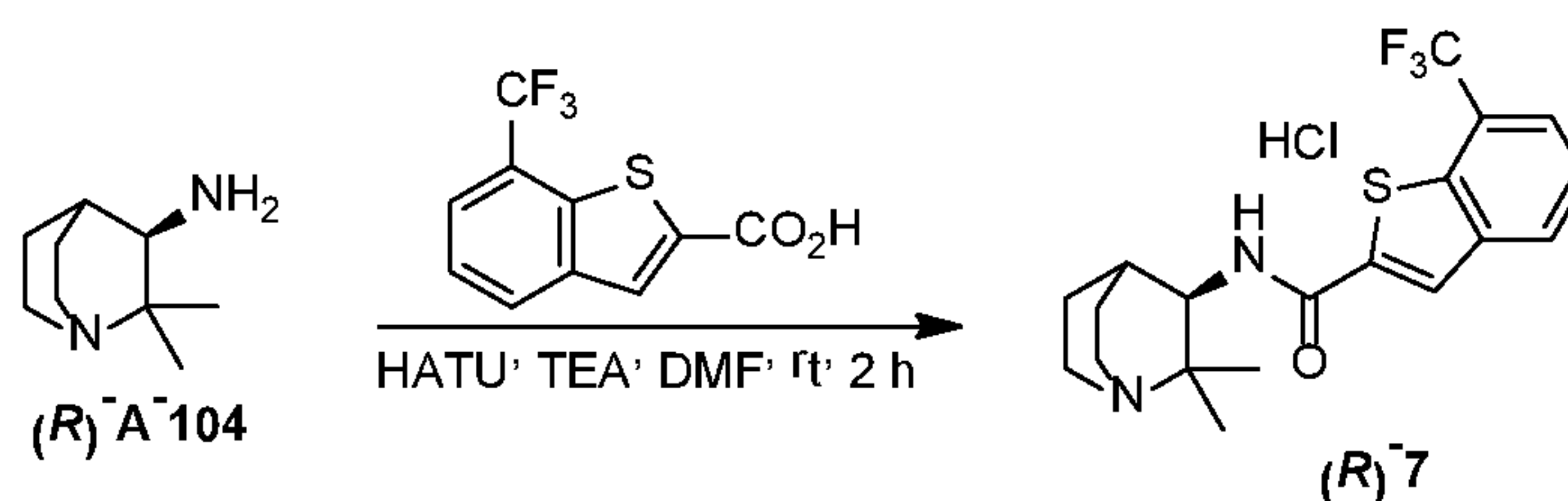


[00721] Following general procedure B, **Compound (S)-6** was prepared from benzofuran-5-carboxylic acid (52 mg, 0.32 mmol) and **compound (S)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μ m; Mobile phase: 21-51% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide hydrochloride (**compound (S)-6**) (35 mg, 36% yield) as a white solid : cSFC analytical (A) $t_R=2.97$ min., purity: 98.28%; LCMS (B): $t_R=0.156$ min., 299.2 m/z ($M+1$); ¹H-NMR (CD₃OD, 400 MHz): δ 8.18 (d, $J=1.6$ Hz, 1H), 7.88 (d, $J=2.4$ Hz, 1H), 7.82 (dd, $J_1=8.8$ Hz, $J_2=2.0$ Hz, 1H), 7.61 (d, $J=8.4$ Hz, 1H), 6.97 (d, $J=1.6$ Hz, 1H), 4.28 (s, 1H), 3.76-3.67 (m, 2H), 3.38-3.33 (m, 2H), 2.41-2.39 (m, 1H), 2.28-2.26 (m, 1H), 2.19-2.10 (m, 2H), 1.96-1.89 (m, 1H), 1.77 (s, 3H), 1.50 (s, 3H).

[00722] **Example 7:**

[00723] Preparation of (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide ((*R*)-**7**)

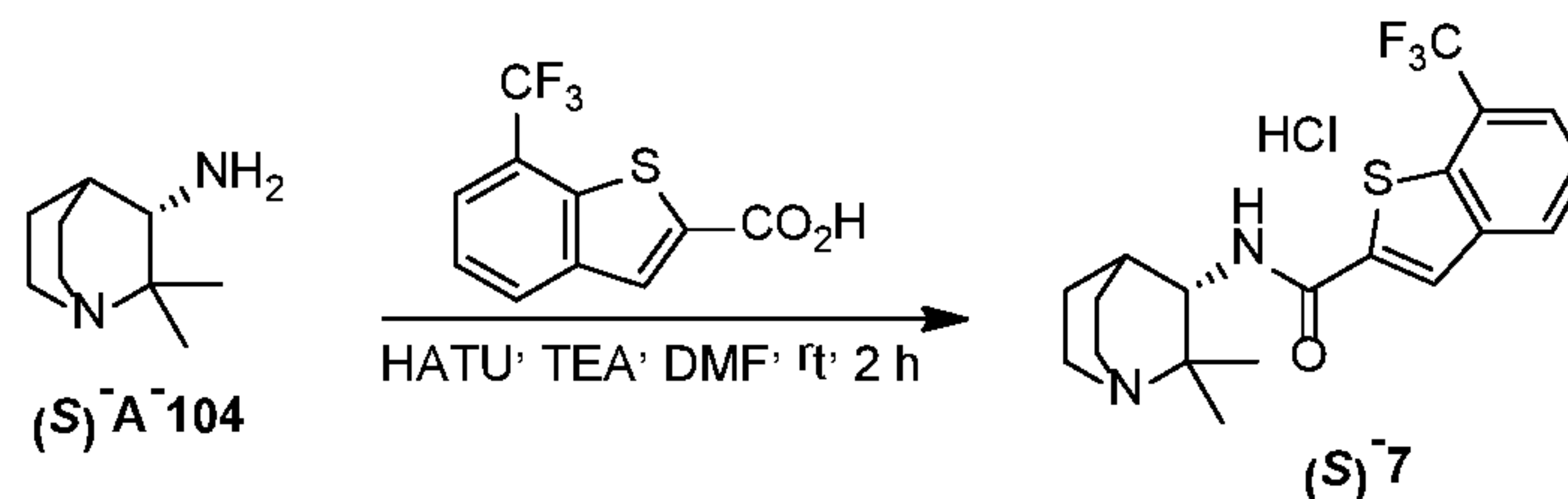


[00724] Following general procedure B, **Compound (R)-7** was prepared from 7-(trifluoromethyl)benzo[b]thiophene-2-carboxylic acid (80 mg, 1.9 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μ m; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-7**) (39 mg, 31% yield) as a white solid : cSFC analytical (A) $t_R=2.49$ min., purity: 98.99%; LCMS (T): $t_R=2.323$ min., 383.1 m/z ($M+1$); ¹H-NMR (CD₃OD, 400 MHz): 8.30 (s, 1H), 8.22 (d, $J=8.4$ Hz, 1H), 7.85 (d, $J=7.6$ Hz, 1H), 7.67-7.63 (t, $J=7.2$ Hz, 1H), 4.30 (s, 1H),

3.75-3.69 (m, 2H), 3.40-3.36 (m, 2H), 2.45 (m, 1H), 2.31 (m, 1H), 2.20-2.13 (m, 2H), 2.00-1.94 (m, 1H), 1.78 (s, 3H), 1.53 (s, 3H).

[00725] Preparation of (*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[*b*]thiophene-2-carboxamide ((*S*)-7)

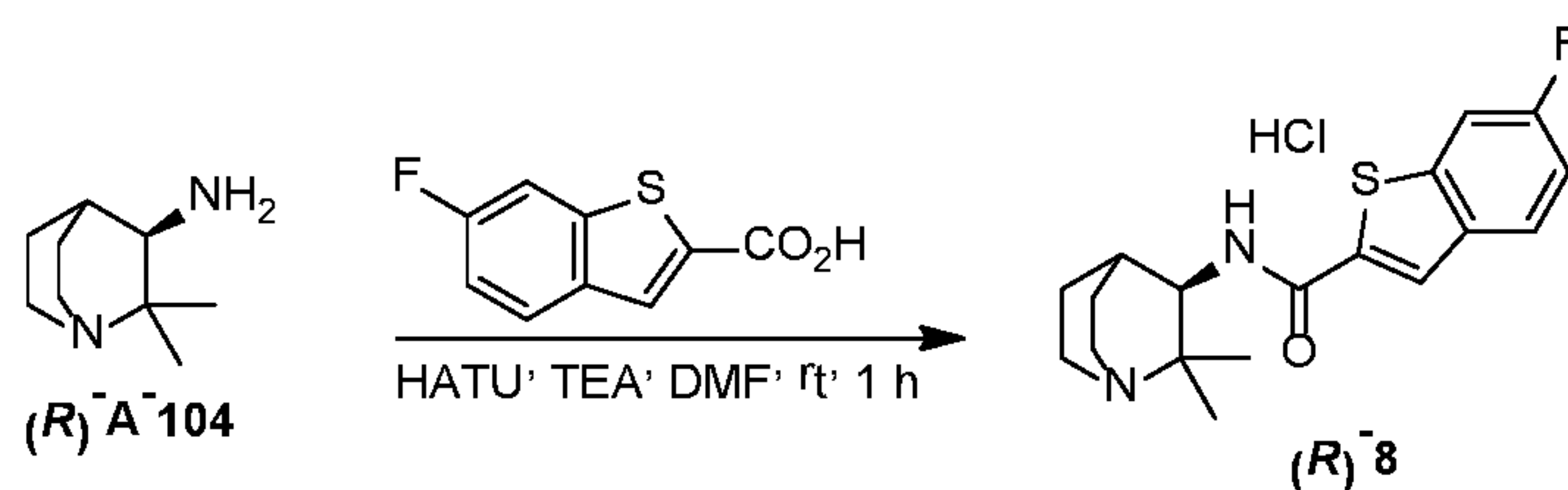


[00726] Following general procedure B, **Compound (S)-7** was prepared from 7-(trifluoromethyl)benzo[*b*]thiophene-2-carboxylic acid (80 mg, 1.9 mmol) and **compound (S)-A-104** (50 mg, 0.32 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (S)-7**) (46 mg, 37% yield) as a white solid : cSFC analytical (A) t_R=3.31 min., purity: 98.39%; LCMS (G): t_R=2.772 min., 383.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.28 (s, 1H), 8.21 (d, J=8.4 Hz, 1H), 7.86 (d, J=7.6 Hz, 1H), 7.67-7.63 (t, J=8.0 Hz, 1H), 4.29 (s, 1H), 3.79-3.69 (m, 2H), 3.40-3.37 (m, 2H), 2.47-2.43 (m, 1H), 2.32-2.31 (m, 1H), 2.21-1.94 (m, 3H), 1.78 (s, 3H), 1.52 (s, 3H).

[00727] **Example 8:**

[00728] Preparation of (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-8)

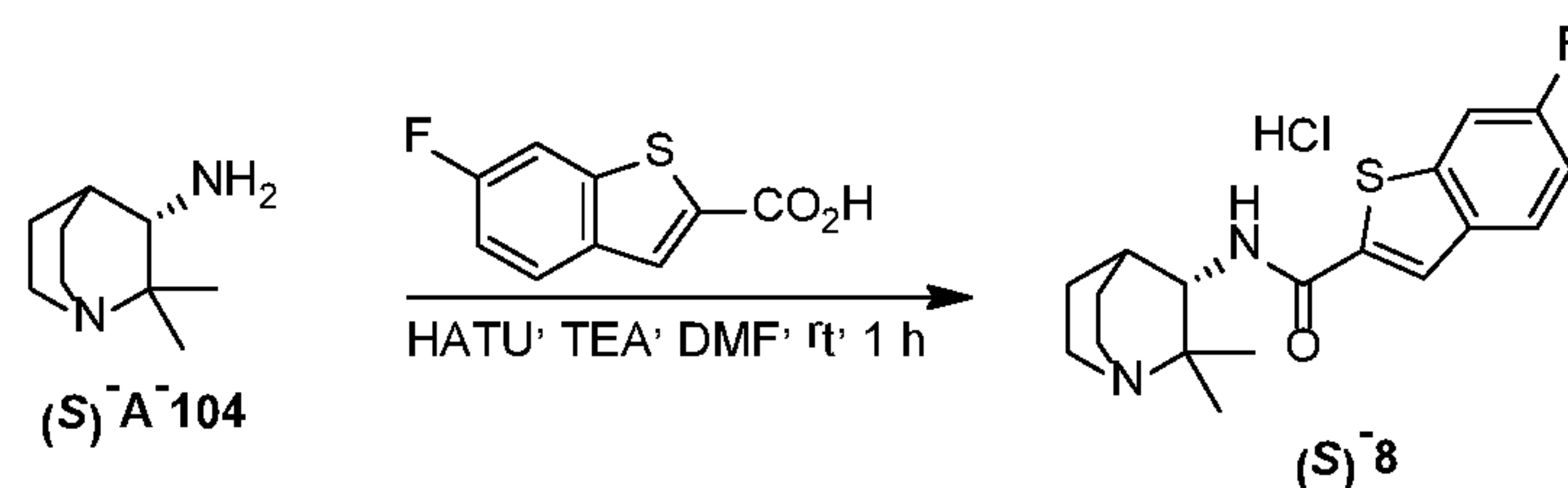


[00729] Following general procedure B, **Compound (R)-8** was prepared from 6-fluorobenzo[*b*]thiophene-2-carboxylic acid (76 mg, 0.39 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 1 hour. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 18-48% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-8**) (30 mg, 25% yield) as a white solid : cSFC analytical (A) t_R=2.66 min., purity: 98.54%; LCMS (B): t_R=0.648 min., 333.2 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.15 (s, 1H), 7.95 (dd, J=8.8 Hz, 1H), 7.73 (dd, J=8.8 Hz, 1H), 7.26 (td, J=9.2 Hz, 1H), 4.27 (s, 1H),

3.78-3.68 (m, 2H), 3.39-3.30 (m, 2H), 2.46-2.43 (m, 1H), 2.30-2.29 (m, 1H), 2.20-2.12 (m, 2H), 1.99-1.93 (m, 1H), 1.76 (s, 3H), 1.50 (s, 3H).

[00730] Preparation of (*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide hydrochloride ((*S*)-**8**)

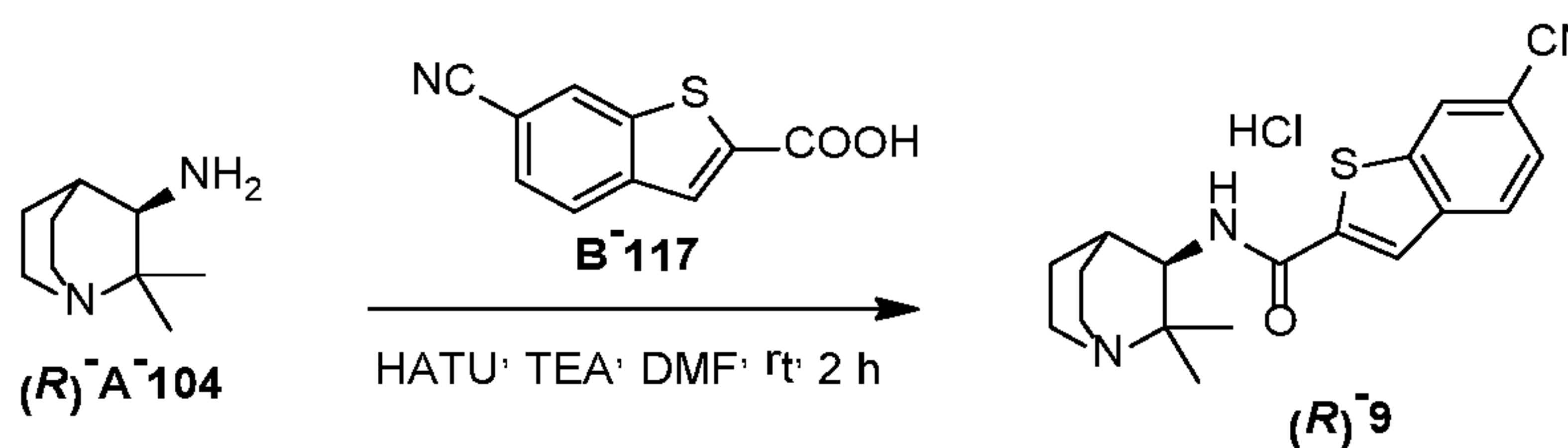


[00731] Following general procedure B, **Compound (S)-8** was prepared from 6-fluorobenzo[b]thiophene-2-carboxylic acid (76 mg, 0.39 mmol) and **compound (S)-A-104** (50 mg, 0.32 mmol), with a reaction time of 1 hour. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 µm; Mobile phase: 26-56% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide hydrochloride (**compound (S)-8**) (60 mg, 50% yield) as a white solid : cSFC analytical (A) t_R=3.38 min., purity: 98.22%; LCMS (A): t_R=1.422 min., 333.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.14 (s, 1H), 7.95 (dd, J=8.8 Hz, 1H), 7.73 (dd, J=8.8 Hz, 1H), 7.27 (td, J=9.2 Hz, 1H), 4.27 (s, 1H), 3.77-3.68 (m, 2H), 3.39-3.33 (m, 2H), 2.43-2.42 (m, 1H), 2.30-2.29 (m, 1H), 2.20-2.12 (m, 2H), 1.99-1.93 (m, 1H), 1.76 (s, 3H), 1.50 (s, 3H).

[00732] Example 9:

[00733] Preparation of (*R*)-6-cyano-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-**9**)

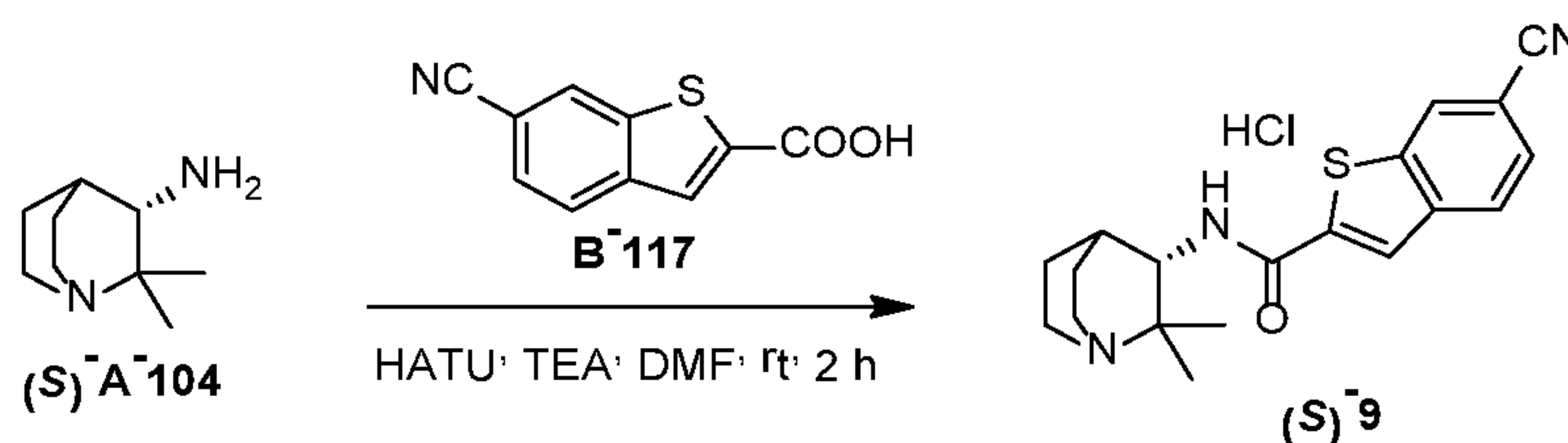


[00734] Following general procedure B, **Compound (R)-9** was prepared from **compound B-117** (66 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 µm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-6-cyano-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-9**) (31 mg, 28% yield) as a yellow solid : cSFC analytical (A) t_R=3.07 min., purity: 98.89%; LCMS (T): t_R=1.977 min., 340.5 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.45 (s, 1H), 8.27 (s, 1H), 8.10 (d, J=8.4 Hz, 2H), 7.73 (d, J=8.0 Hz, 1H), 4.28 (s, 1H), 3.78-3.69 (m,

2H), 3.40-3.37 (m, 2H), 2.48-2.43 (m, 1H), 2.31-2.20 (m, 1H), 2.19-2.13 (m, 2H), 2.08-1.94 (m, 1H), 1.77 (s, 3H), 1.52 (s, 3H).

[00735] Preparation of (*S*)-6-cyano-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride ((*S*)-9)

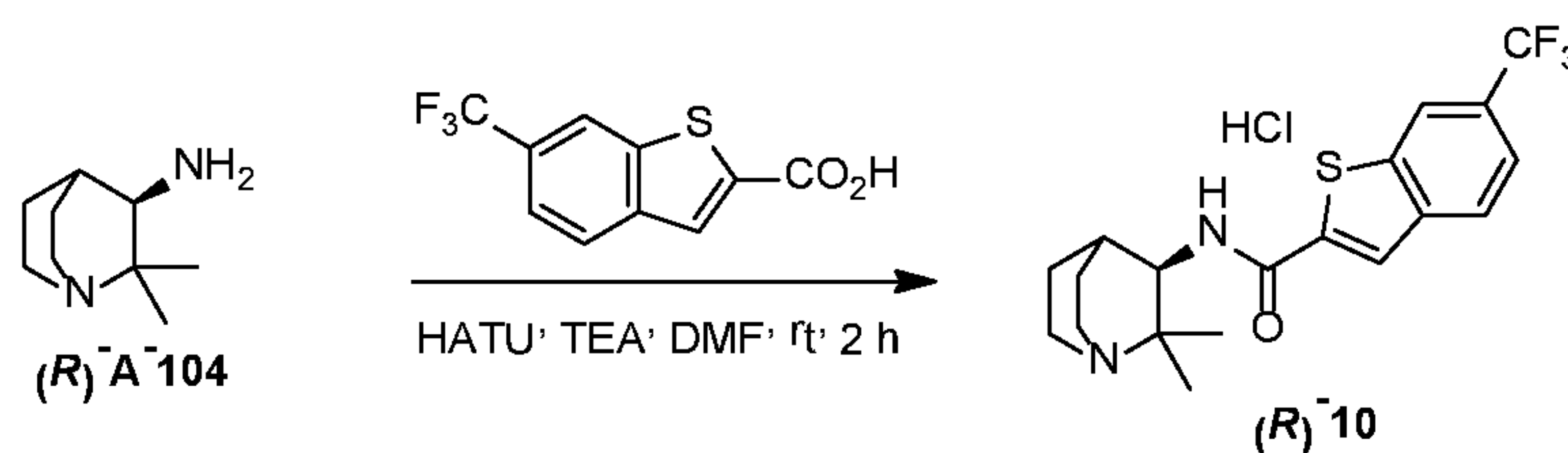


[00736] Following general procedure B, **Compound (S)-9** was prepared from **compound B-117** (66 mg, 0.32 mmol) and **compound (S)-A-104** (50 mg, 0.32 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-6-cyano-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (S)-9**) (20 mg, 18% yield) as a yellow solid : cSFC analytical (A) t_R=4.30 min., purity: 97.74%; LCMS (R): t_R=0.781 min., 340.5 m/z (M+1); ¹H-NMR (DMSO-d₆, 400 MHz): δ 10.49 (s, 1H), 8.82 (d, J=7.6 Hz, 1H), 8.68 (s, 1H), 8.53 (s, 2H), 8.16 (d, J=8.0 Hz, 1H), 7.83 (d, J=8.0 Hz, 1H), 4.12 (d, J=7.2 Hz, 1H), 3.18 (m, 3H), 2.34 (m, 2H), 2.11-2.02 (m, 2H), 1.91 (m, 1H), 1.71 (m, 1H), 1.62 (s, 3H), 1.41 (s, 3H).

[00737] **Example 10:**

[00738] Preparation of (*R*)-N-(2,2-dimethylquinuclidin-3-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide ((*R*)-10)

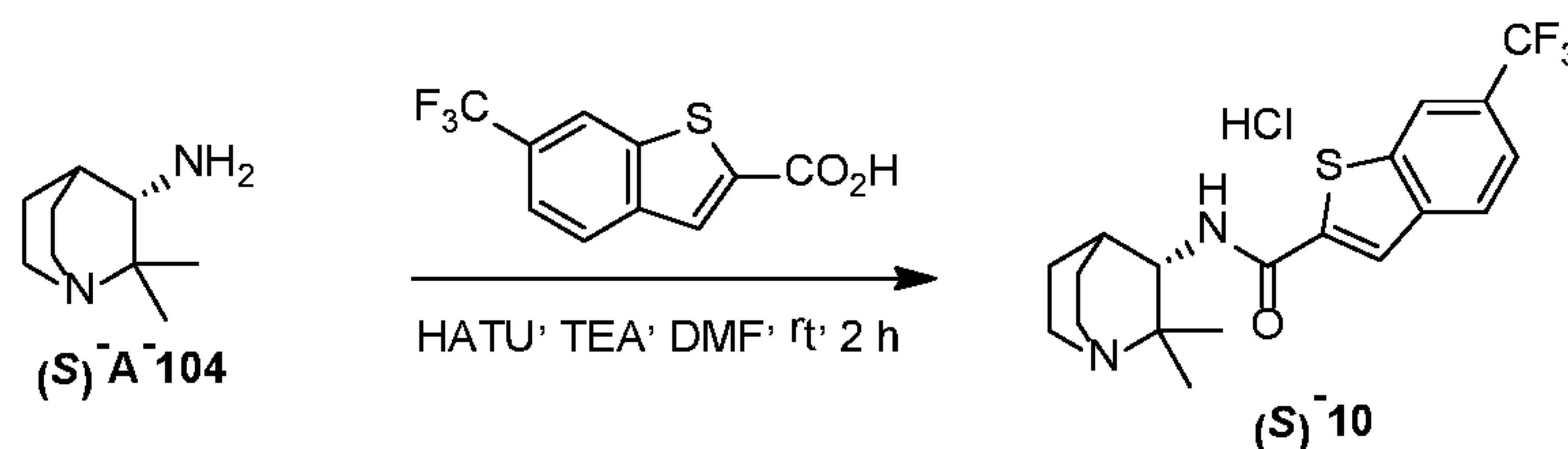


[00739] Following general procedure B, **Compound (R)-10** was prepared from 6-(trifluoromethyl)benzo[b]thiophene-2-carboxylic acid (80 mg, 1.9 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-10**) (32 mg, 26% yield) as a white solid : cSFC analytical (A) t_R=2.44 min., purity: 98.49%; LCMS (T): t_R=2.345 min., 383.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): 8.37 (s, 1H), 8.26 (s, 1H), 8.13 (d, J=8.8 Hz, 1H), 7.72 (d, J=8.4 Hz, 1H), 4.29 (s, 1H), 3.79-3.68 (m,

2H), 3.40-3.36 (m, 2H), 2.47-2.44 (m, 1H), 2.31-2.21 (m, 1H), 2.20-2.13 (m, 2H), 2.12-1.94 (m, 1H), 1.76 (s, 3H), 1.52 (s, 3H).

[00740] Preparation of (*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(trifluoromethyl)benzo[*b*]thiophene-2-carboxamide ((*S*)-10)

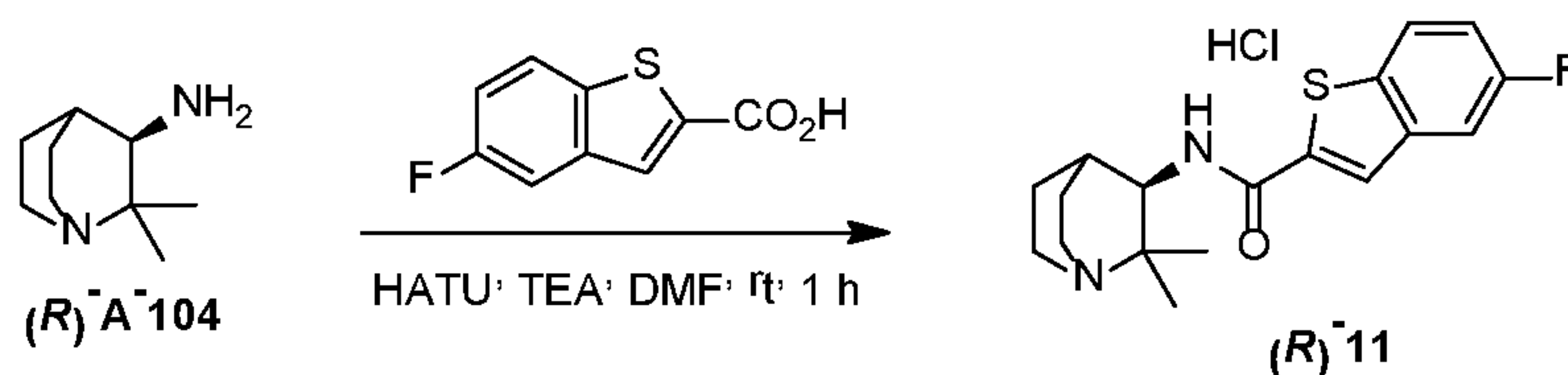


[00741] Following general procedure B, **Compound (S)-10** was prepared from 6-(trifluoromethyl)benzo[*b*]thiophene-2-carboxylic acid (80 mg, 1.9 mmol) and **compound (S)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(trifluoromethyl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (S)-10**) (41 mg, 33% yield) as a white solid : cSFC analytical (A) t_R=3.52 min., purity: 97.90%; LCMS (G): t_R=2.850 min., 383.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): 8.37 (s, 1H), 8.27 (s, 1H), 8.13 (d, J=8.4 Hz, 1H), 7.72 (d, J=8.4 Hz, 1H), 4.29 (s, 1H), 3.78-3.69 (m, 2H), 3.40-3.36 (m, 2H), 2.48-2.44 (m, 1H), 2.31-2.21 (m, 1H), 2.20-2.13 (m, 2H), 2.12-1.94 (m, 1H), 1.77 (s, 3H), 1.52 (s, 3H).

[00742] **Example 11:**

[00743] Preparation of (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-11)

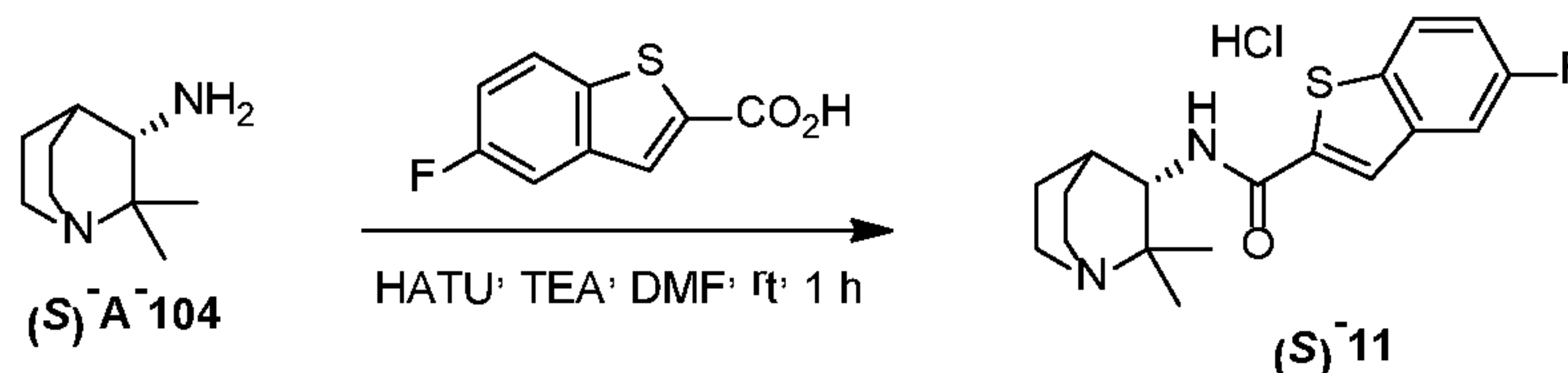


[00744] Following general procedure B, **Compound (R)-11** was prepared from 5-fluorobenzo[*b*]thiophene-2-carboxylic acid (76 mg, 0.39 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 1 hour. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 18-48% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-11**) (60 mg, 50% yield) as a white solid: cSFC analytical (A) t_R=2.62 min., purity: 98.90%; LCMS (B): t_R=0.644 min., 333.2 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.47 (d, 1H), 8.12 (s, 1H), 7.96 (dd, J=8.8 Hz, 1H), 7.65 (dd, J=9.2 Hz, 1H), 7.30 (td, J=9.2 Hz, 1H),

4.27 (s, 1H), 3.75-3.68 (m, 2H), 3.38-3.30 (m, 2H), 2.44-2.42 (m, 1H), 2.30-2.29 (m, 1H), 2.20-2.12 (m, 2H), 1.99-1.93 (m, 1H), 1.77 (s, 3H), 1.51 (s, 3H).

[00745] Preparation of (*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[*b*]thiophene-2-carboxamide hydrochloride ((*S*)-11)

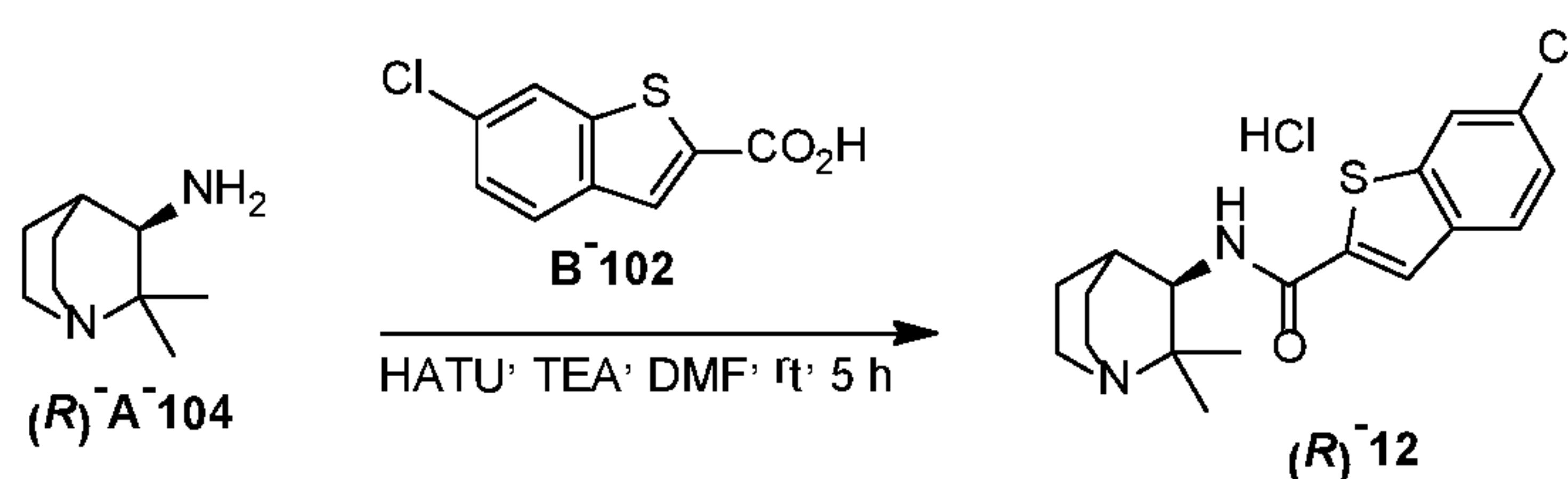


[00746] Following general procedure B, **Compound (S)-11** was prepared from 5-fluorobenzo[b]thiophene-2-carboxylic acid (76 mg, 0.39 mmol) and **compound (S)-A-104** (50 mg, 0.32 mmol), with a reaction time of 1 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 µm; Mobile phase: 26-56% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (S)-11**) (70 mg, 58% yield) as a white solid: cSFC analytical (A) tR=3.08 min., purity: 97.88%; LCMS (B): tR=0.695 min., 333.2 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.48 (d, 1H), 8.12 (s, 1H), 7.96 (dd, J=8.8 Hz, 1H), 7.65 (dd, J=9.2 Hz, 1H), 7.30 (td, J=8.8 Hz, 1H), 4.27 (s, 1H), 3.78-3.68 (m, 2H), 3.40-3.32 (m, 2H), 2.44-2.42 (m, 1H), 2.30-2.29 (m, 1H), 2.20-2.12 (m, 2H), 1.99-1.93 (m, 1H), 1.77 (s, 3H), 1.51 (s, 3H).

[00747] Example 12:

[00748] Preparation of (*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-12)

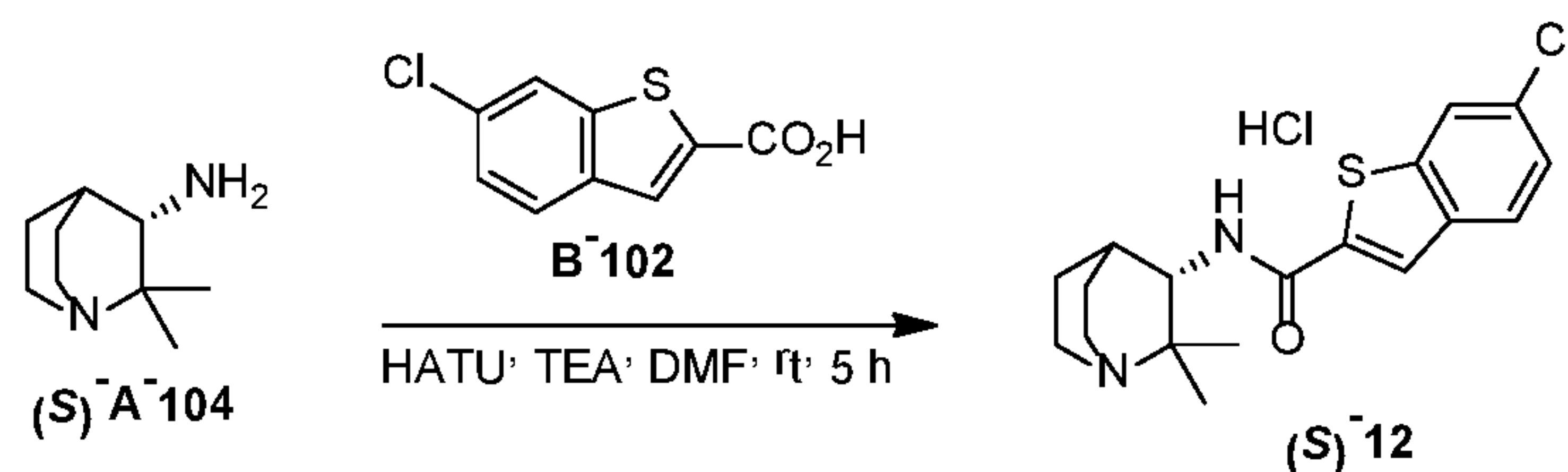


[00749] Following general procedure B, **Compound (R)-12** was prepared from **compound B-102** (66 mg, 0.31 mmol) and **compound (R)-A-104** (40 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 µm; Mobile phase: 25-55% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (*R*)-12**) (45 mg, 45% yield) as a white solid: cSFC analytical (A) t_R=3.01 min., purity: 99.84%; LCMS (B): t_R=0.705 min., 349.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.13 (s, 1H), δ 8.01 (d, J=4 Hz, 1H), 7.90 (d, J=8 Hz, 1H), 7.45 (dd, J₁=8 Hz, J₂=4 Hz, 1H), 4.25 (s,

1H), 3.72-3.69 (m, 2H), 3.37-3.35 (m, 2H), 2.41-2.40 (m, 1H), 2.28-2.26 (m, 1H), 2.17-2.10 (m, 2H), 1.97-1.94 (m, 1H), 1.74 (s, 3H), 1.48 (s, 3H).

[00750] Preparation of (*S*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*S*)-12)

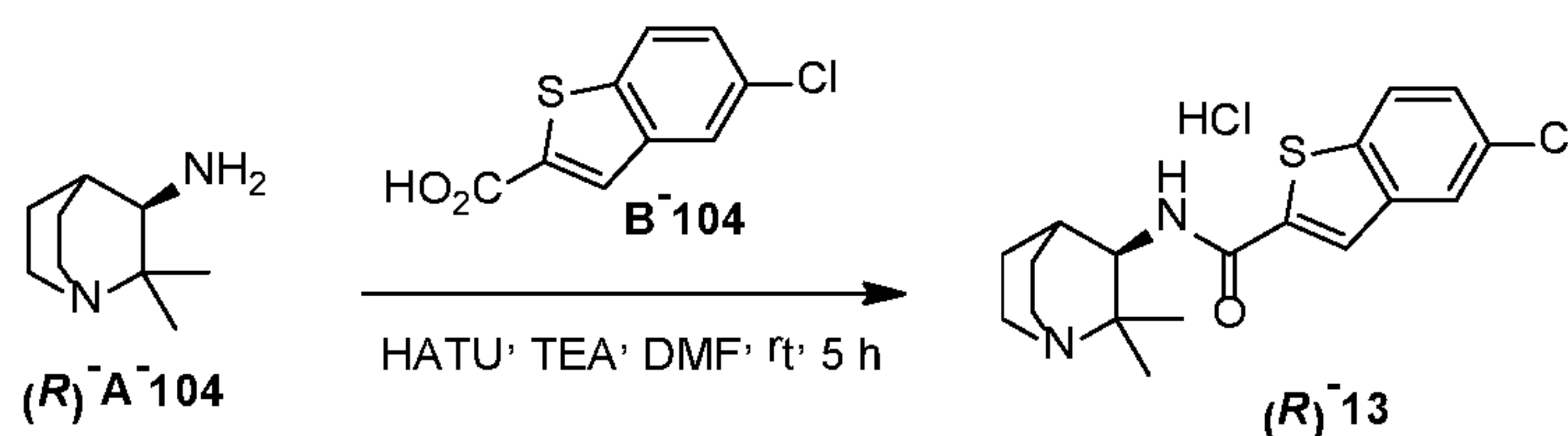


[00751] Following general procedure B, **Compound (S)-12** was prepared from **compound B-102** (66 mg, 0.31 mmol) and **compound (S)-A-104** (40 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 µm; Mobile phase: 29-59% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (S)-12**) (46 mg, 46% yield) as a white solid: cSFC analytical (A) t_R=3.78 min., purity: 98.88%; LCMS (R): t_R=0.890 min., 348.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.15 (s, 1H), 8.00 (s, 1H), 7.90 (d, J=8 Hz, 1H), 7.44 (dd, J=4 Hz, J=8 Hz, 1H), 4.25 (s, 1H), 3.75-3.66 (m, 2H), 3.34-3.31 (m, 2H), 2.42-2.41 (m, 1H), 2.28-2.27 (m, 1H), 2.17-2.10 (m, 2H), 1.97-1.94 (m, 1H), 1.74 (s, 3H), 1.49 (s, 3H).

[00752] **Example 13:**

[00753] Preparation of (*R*)-5-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-13)

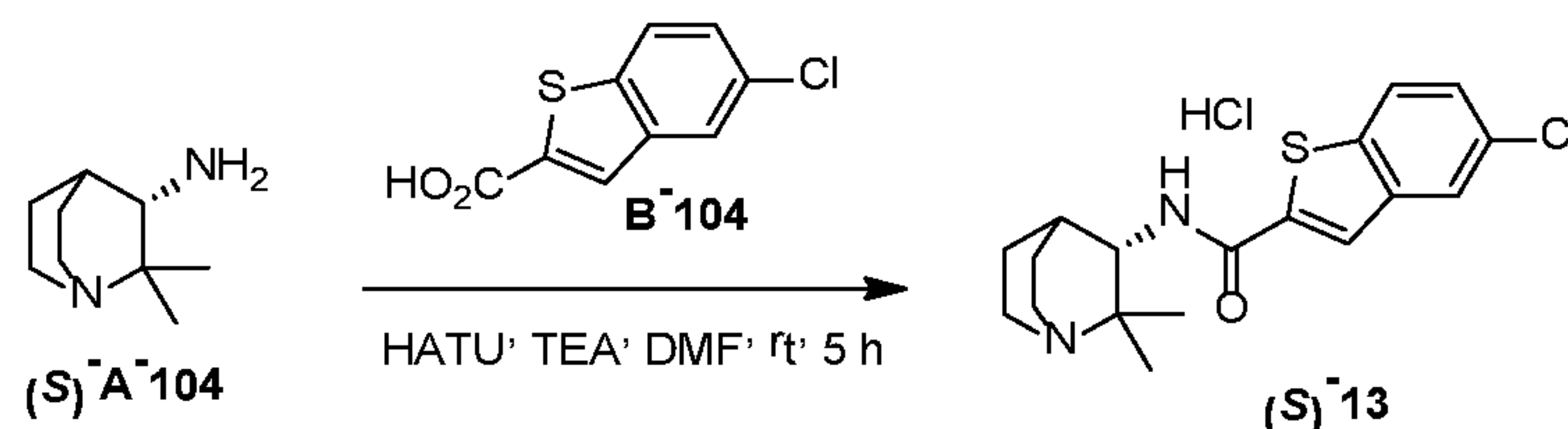


[00754] Following general procedure B, **Compound (R)-13** was prepared from **compound B-104** (68 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 µm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-5-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-13**) (59 mg, 47% yield) as a white solid: cSFC analytical (A) t_R=2.98 min., purity: 97.23%; LCMS (A): t_R=1.629 min., 349.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.09 (s, 1H), 7.95-7.91 (m, 2H), 7.45 (dd, J₁=8.8 Hz, J₂=1.2 Hz, 1H), 4.25 (s, 1H), 3.75-3.66 (m, 2H),

3.37-3.32 (m, 2H), 2.44-2.41 (m, 1H), 2.28-2.26 (m, 1H), 2.17-2.10 (m, 2H), 1.97-1.91 (m, 1H), 1.74 (s, 3H), 1.49 (s, 3H).

[00755] Preparation of (*S*)-5-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*S*)-13)

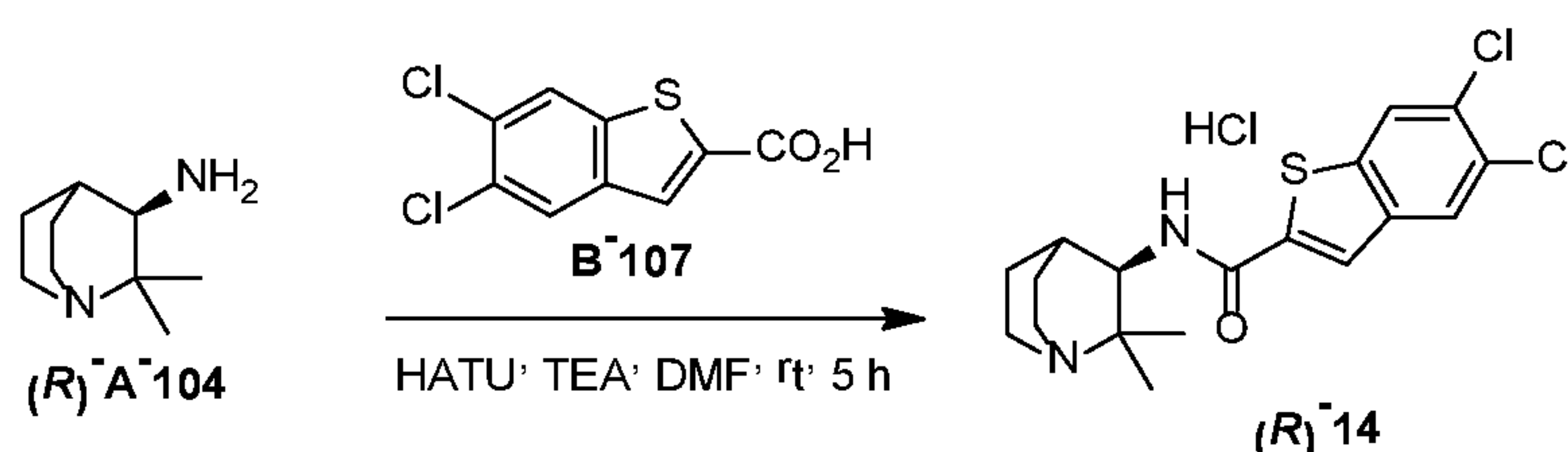


[00756] Following general procedure B, **Compound (S)-13** was prepared from **compound B-104** (68 mg, 0.32 mmol) and **compound (S)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-5-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (S)-13**) (33 mg, 29% yield) as a white solid: cSFC analytical (A) *t*_R=3.59 min., purity: 98.95%; LCMS (B): *t*_R=0.720 min., 349.1 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.12 (s, 1H), 7.95-7.91 (m, 2H), 7.45 (dd, *J*₁=8.8 Hz, *J*₂=2.0 Hz, 1H), 4.25 (s, 1H), 3.75-3.67 (m, 2H), 3.37-3.34 (m, 2H), 2.46-2.42 (m, 1H), 2.28-2.27 (m, 1H), 2.18-2.08 (m, 2H), 1.97-1.91 (m, 1H), 1.75 (s, 3H), 1.50 (s, 3H).

[00757] **Example 14:**

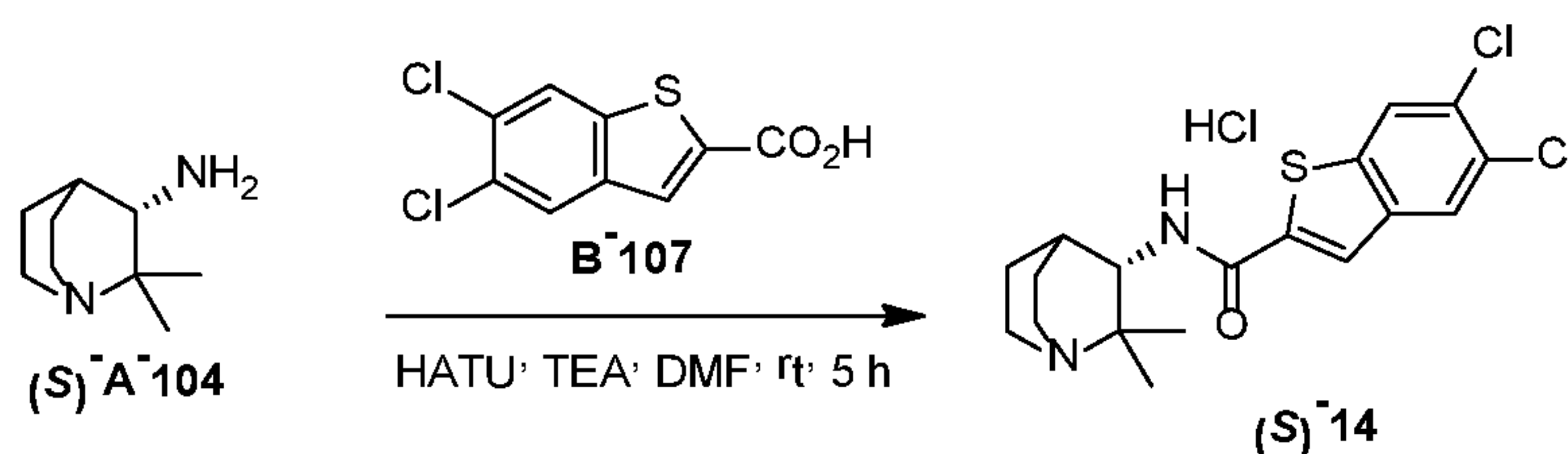
[00758] Preparation of (*R*)-5,6-dichloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-14)



[00759] Following general procedure B, **Compound (R)-14** was prepared from **compound B-107** (77 mg, 0.31 mmol) and **compound (R)-A-104** (40 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 25-55% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-5,6-dichloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-14**) (47 mg, 43% yield) as a white solid: cSFC analytical (A) *t*_R=3.30 min., purity: 99.85%; LCMS (B): *t*_R=0.749 min., 382.1 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.19 (s, 1H), δ 8.11 (s, 1H), 8.10 (s, 1H), 4.25 (s, 1H), 3.73-3.66 (m, 2H), 3.38-3.33 (m, 2H), 2.41-2.40 (m, 1H), 2.28-2.26 (m, 1H), 2.17-2.10 (m, 2H), 1.97-1.95 (m, 1H), 1.74 (s, 3H), 1.48 (s, 3H).

[00760] Preparation of (*S*)-5,6-dichloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*S*)-14)

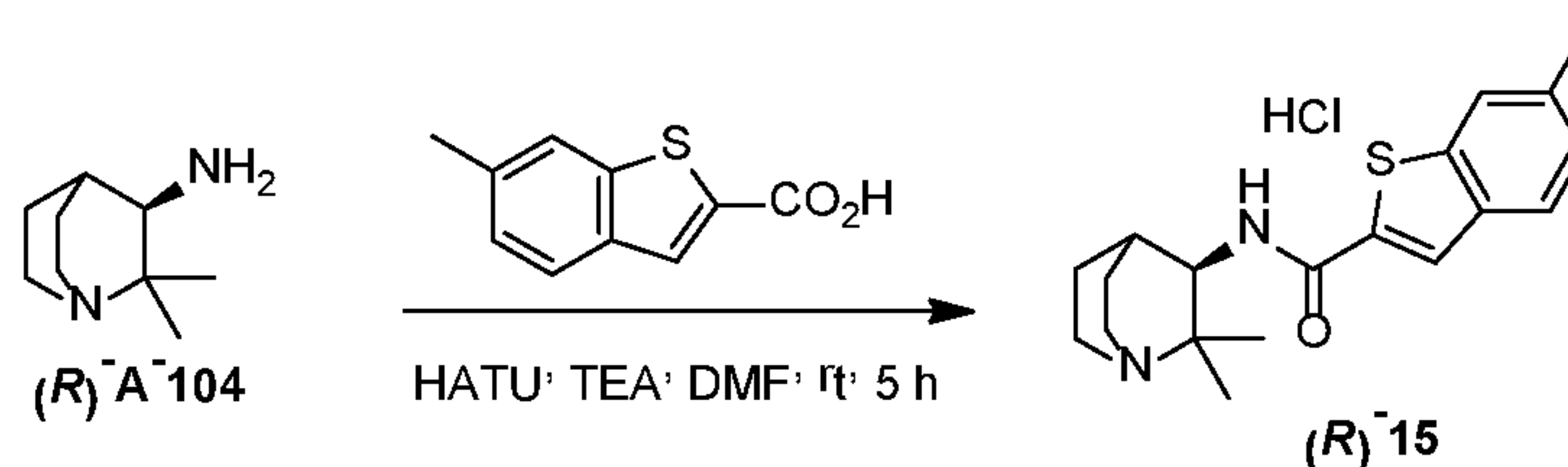


[00761] Following general procedure B, **Compound (S)-14** was prepared from **compound B-107** (77 mg, 0.31 mmol) and **compound (S)-A-104** (40 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 24-54% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-5,6-dichloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (S)-14**) (40 mg, 38% yield) as a white solid: cSFC analytical (A) t_R=3.86 min., purity: 98.88%; LCMS (R): t_R=0.956 min., 382.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.20 (s, 1H), 8.13 (s, 1H), 8.12 (s, 1H), 4.25 (s, 1H), 3.73-3.70 (m, 2H), 3.37-3.34 (m, 2H), 2.45-2.44 (m, 1H), 2.30-2.29 (m, 1H), 2.19-2.12 (m, 2H), 1.99-1.97 (m, 1H), 1.76 (s, 3H), 1.51 (s, 3H).

[00762] **Example 15:**

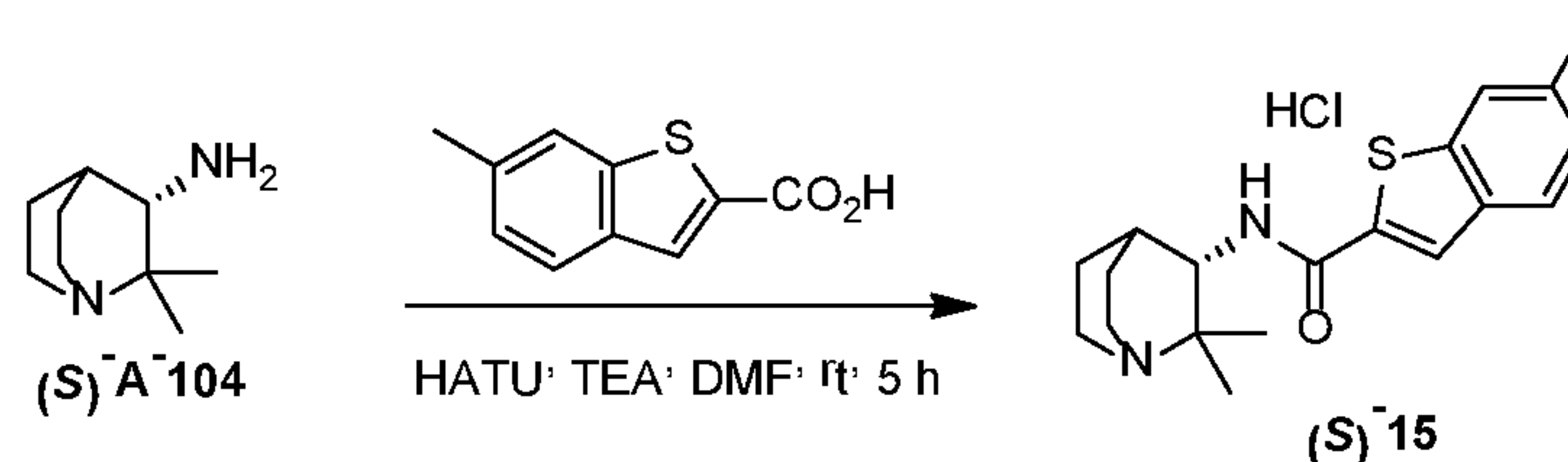
[00763] Preparation of (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-15)



[00764] Following general procedure B, **Compound (R)-15** was prepared from 6-methylbenzo[*b*]thiophene-2-carboxylic acid (60 mg, 0.31 mmol) and **compound (R)-A-104** (40 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 26-56% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-15**) (43 mg, 45% yield) as a white solid: cSFC analytical (A) t_R=2.98 min., purity: 99.54%; LCMS (B): t_R=0.688 min., 328.2 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.08 (s, 1H), δ 7.80 (d, J=8 Hz, 1H), 7.73 (s, 1H), 7.28 (d, J=8 Hz, 1H), 4.25 (s, 1H), 3.76-3.66 (m, 2H), 3.37-3.34 (m, 2H), 2.49 (s, 3H), 2.41-2.40 (m, 1H), 2.27-2.26 (m, 1H), 2.17-2.10 (m, 2H), 1.97-1.94 (m, 1H), 1.74 (s, 3H), 1.48 (s, 3H).

[00765] Preparation of (*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride ((*S*)-15)

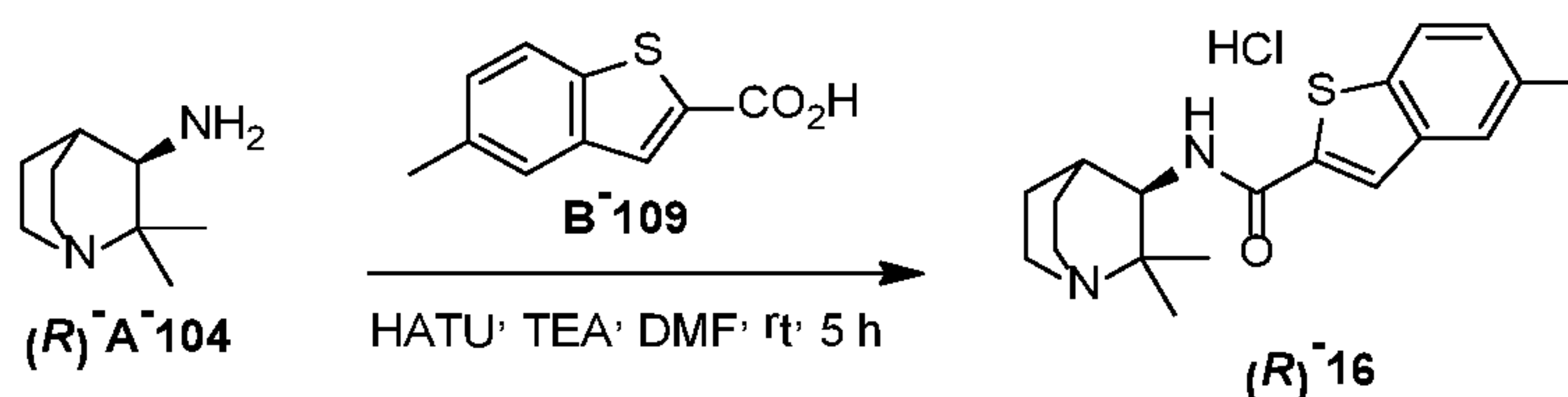


[00766] Following general procedure B, **Compound (S)-15** was prepared from 6-chlorobenzo[*b*]thiophene-2-carboxylic acid (60 mg, 0.31 mmol) and **compound (S)-A-104** (40 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 24-54% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (S)-15**) (40 mg, 42% yield) as a white solid: cSFC analytical (A) *t*_R=3.45 min., purity: 99.45%; LCMS (R): *t*_R=0.861 min., 328.2 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.09 (s, 1H), 7.80 (d, *J*=8 Hz, 1H), 7.73 (s, 1H), 7.28 (d, *J*=8 Hz, 1H), 4.25 (s, 1H), 3.73-3.69 (m, 2H), 3.37-3.34 (m, 2H), 2.49 (s, 3H), 2.41-2.40 (m, 1H), 2.27-2.26 (m, 1H), 2.17-2.10 (m, 2H), 1.97-1.90 (m, 1H), 1.74 (s, 3H), 1.49 (s, 3H).

[00767] **Example 16:**

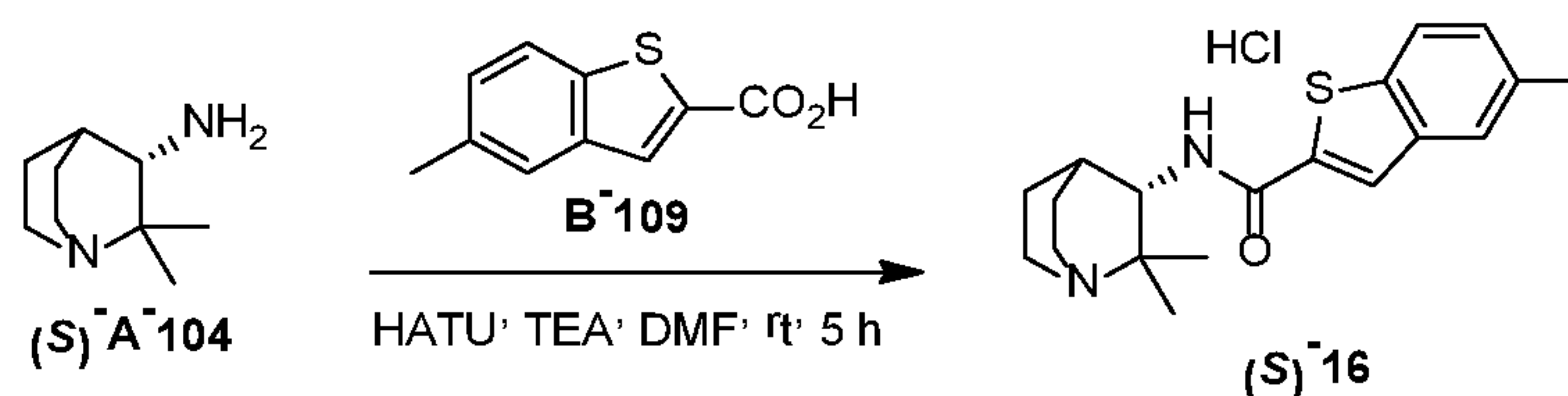
[00768] Preparation of (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-16)



[00769] Following general procedure B, **Compound (R)-16** was prepared from **compound B-109** (60 mg, 0.31 mmol) and **compound (R)-A-104** (40 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 18-48% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-16**) (35 mg, 37% yield) as a white solid: cSFC analytical (A) *t*_R=2.99 min., purity: 99.11%; LCMS (B): *t*_R=0.687 min., 328.2 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.07 (s, 1H), 7.80 (d, *J*=8 Hz, 1H), 7.72 (s, 1H), 7.32 (d, *J*=8 Hz, 1H), 4.25 (s, 1H), 3.72-3.66 (m, 2H), 3.38-3.34 (m, 2H), 2.48 (s, 3H), 2.28-2.27 (m, 1H), 2.17-2.10 (m, 2H), 1.97-1.94 (m, 1H), 1.75 (s, 3H), 1.49 (s, 3H).

[00770] Preparation of (*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride ((*S*)-16)

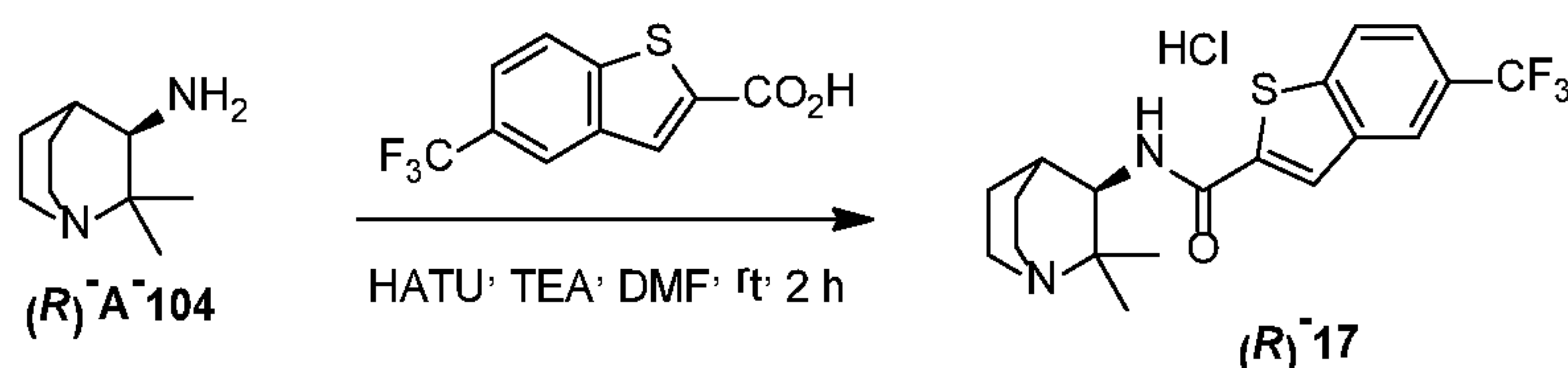


[00771] Following general procedure B, **Compound (S)-16** was prepared from **compound B-109** (60 mg, 0.31 mmol) and **compound (S)-A-104** (40 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (S)-16**) (31 mg, 33% yield) as a white solid: cSFC analytical (A) t_R=3.68 min., purity: 99.80%; LCMS (R): t_R=0.866 min., 328.2 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.06 (s, 1H), 7.80 (d, J=8 Hz, 1H), 7.72 (s, 1H), 7.32 (d, J=8 Hz, 1H), 4.25 (s, 1H), 3.73-3.69 (m, 2H), 3.38-3.34 (m, 2H), 2.48 (s, 3H), 2.28-2.27 (m, 1H), 2.17-2.10 (m, 2H), 1.97-1.94 (m, 1H), 1.75 (s, 3H), 1.49 (s, 3H).

[00772] **Example 17:**

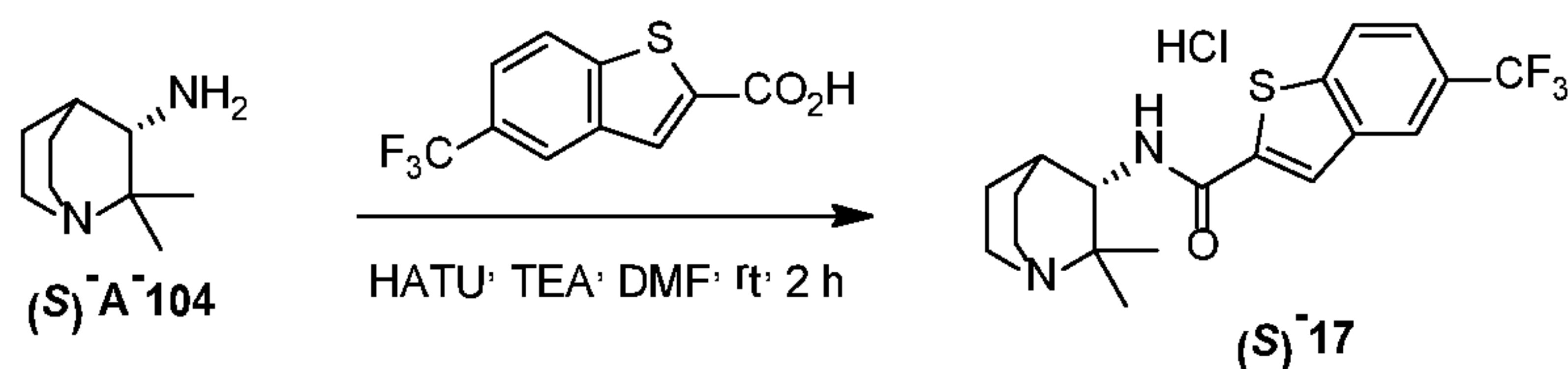
[00773] Preparation of (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-(trifluoromethyl)benzo[*b*]thiophene-2-carboxamide ((*R*)-17)



[00774] Following general procedure B, **Compound (R)-17** was prepared from 5-(trifluoromethyl)benzo[*b*]thiophene-2-carboxylic acid (80 mg, 1.9 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-(trifluoromethyl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-17**) (58 mg, 46% yield) as a yellow solid: cSFC analytical (A) t_R=2.17 min., purity: 98.14%; LCMS (T): t_R=0.741 min., 383.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.28 (s, 2H), 8.18 (d, J=8.8 Hz, 1H), 7.74 (d, J=8.0 Hz, 1H), 4.29 (s, 1H), 3.78-3.69 (m, 2H), 3.40-3.36 (m, 2H), 3.45-3.44 (m, 1H), 2.31 (m, 1H), 2.21-2.11 (m, 2H), 2.01-1.94 (m, 1H), 1.77 (s, 3H), 1.52 (s, 3H).

[00775] Preparation of *(S)*-*N*-(2,2-dimethylquinuclidin-3-yl)-5-(trifluoromethyl)benzo[*b*]thiophene-2-carboxamide (**(S)**-17)

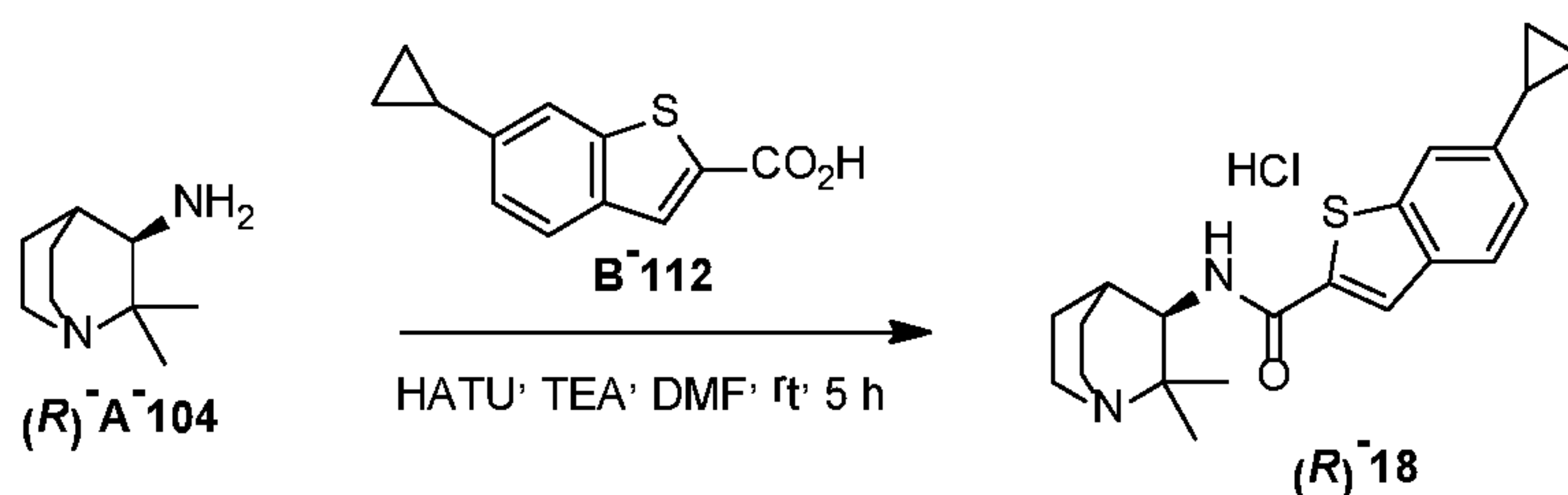


[00776] Following general procedure B, **Compound (S)**-17 was prepared from 5-(trifluoromethyl)benzo[*b*]thiophene-2-carboxylic acid (80 mg, 1.9 mmol) and **compound (S)**-A-104 (50 mg, 0.32 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(S)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-(trifluoromethyl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (S)**-17) (32 mg, 26% yield) as a yellow solid: cSFC analytical (A) *t*_R=2.49 min., purity: 97.08%; LCMS (B): *t*_R=0.724 min., 383.1 *m/z* (*M*+1); ¹H-NMR (CD₃OD, 400 MHz): 8.28 (s, 2H), 8.18 (d, *J*=8.4 Hz, 1H), 7.74 (d, *J*=8.8 Hz, 1H), 4.29 (s, 1H), 3.79-3.69 (m, 2H), 3.40-3.36 (m, 2H), 3.48-3.45 (m, 1H), 2.43 (m, 1H), 2.31-2.13 (m, 2H), 2.00-1.94 (m, 1H), 1.78 (s, 3H), 1.52 (s, 3H).

[00777] **Example 18:**

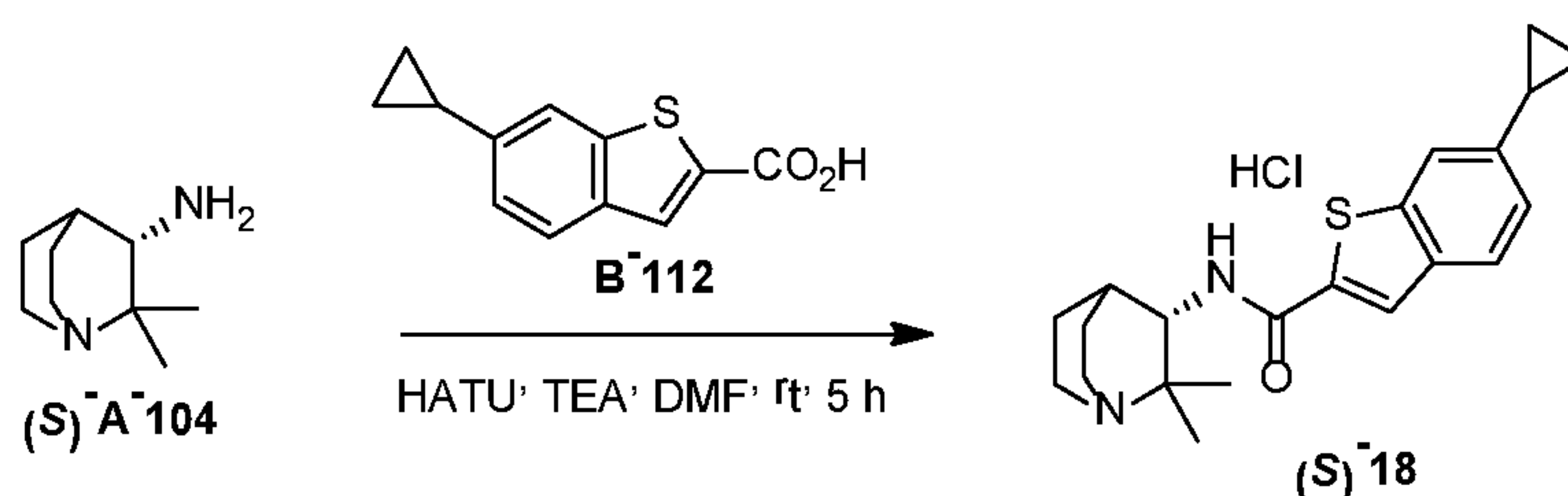
[00778] Preparation of *(R)*-6-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**(R)**-18)



[00779] Following general procedure B, **Compound (R)**-18 was prepared from **compound B**-112 (68 mg, 0.31 mmol) and **compound (R)**-A-104 (40 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 26-56% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(R)-6-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)**-18) (36 mg, 36% yield) as a white solid: cSFC analytical (A) *t*_R=3.19 min., purity: 99.84%; LCMS (B): *t*_R=0.726 min., 354.2 *m/z* (*M*+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.07 (s, 1H), δ 7.78 (d, *J*=8 Hz, 1H), 7.63 (s, 1H), 7.17 (d, *J*=8 Hz, 1H), 4.24 (s, 1H), 3.73-3.66 (m, 2H), 3.37-3.34 (m, 2H), 2.41 (m, 1H), 2.27-2.26 (m, 1H), 2.16-2.06 (m, 3H), 2.05-1.94 (m, 1H), 1.74 (s, 3H), 1.48 (s, 3H), 1.07-1.03 (m, 2H), 0.81-0.78 (m, 2H).

[00780] Preparation of (*S*)-6-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*S*)-18)

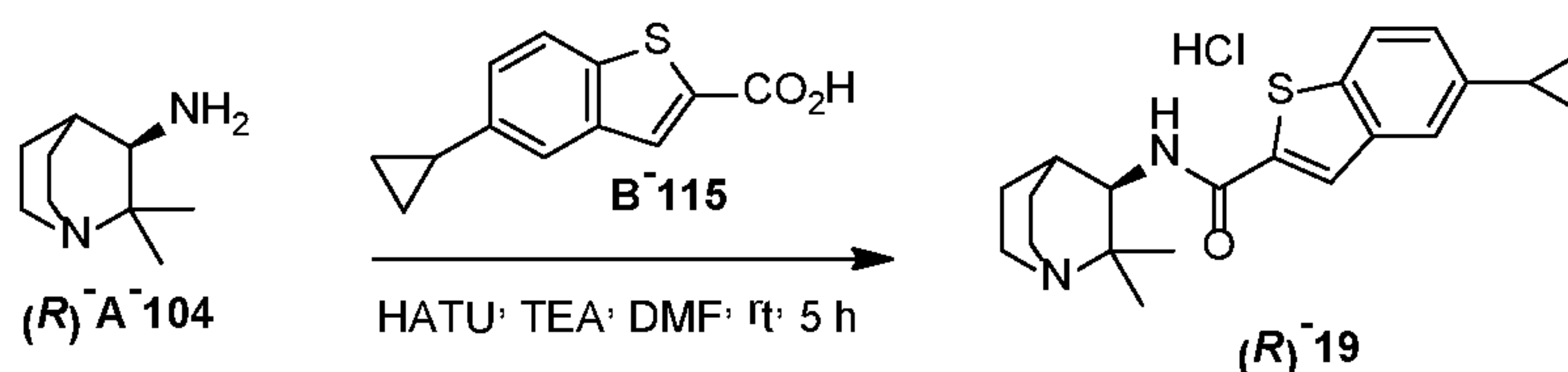


[00781] Following general procedure B, **Compound (S)-18** was prepared from **compound B-112** (68 mg, 0.31 mmol) and **compound (S)-A-104** (40 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 25-55% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-6-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (S)-18**) (34 mg, 34% yield) as a white solid: cSFC analytical (A) t_R=3.74 min., purity: 99.91%; LCMS (R): t_R=0.920 min., 354.2 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.07 (s, 1H), δ 7.78 (d, J=8 Hz, 1H), 7.63 (s, 1H), 7.17 (dd, J₁=4 Hz, J₂=8 Hz, 1H), 4.24 (s, 1H), 3.75-3.66 (m, 2H), 3.37-3.34 (m, 2H), 2.41 (m, 1H), 2.27-2.26 (m, 1H), 2.14-2.05 (m, 3H), 2.04-1.94 (m, 1H), 1.74 (s, 3H), 1.48 (s, 3H), 1.07-1.03 (m, 2H), 0.81-0.78 (m, 2H).

[00782] **Example 19:**

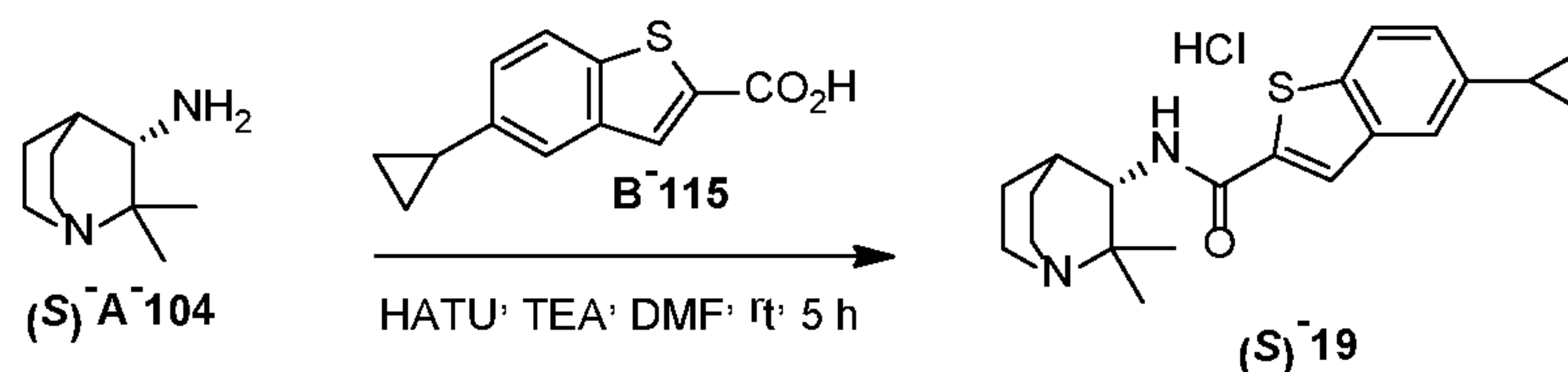
[00783] Preparation of (*R*)-5-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-19)



[00784] Following general procedure B, **Compound (R)-19** was prepared from **compound B-115** (68 mg, 0.31 mmol) and **compound (R)-A-104** (40 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-5-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-19**) (46 mg, 45% yield) as a white solid: cSFC analytical (A) t_R=3.25 min., purity: 100%; LCMS (B): t_R=0.728 min., 354.2 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.05 (s, 1H), δ 7.89 (d, J=8 Hz, 1H), 7.63 (s, 1H), 7.21 (d, J₁=8 Hz, J₂=1.6 Hz, 1H), 4.25 (s, 1H), 3.70-3.69 (m, 2H), 3.35 (m, 2H), 2.41 (m, 1H), 2.28-2.27 (m, 1H), 2.14-2.06 (m, 3H), 2.05-1.94 (m, 1H), 1.74 (s, 3H), 1.49 (s, 3H), 1.04-1.01 (m, 2H), 0.77-0.74 (m, 2H).

[00785] Preparation of (*S*)-5-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*S*)-19)

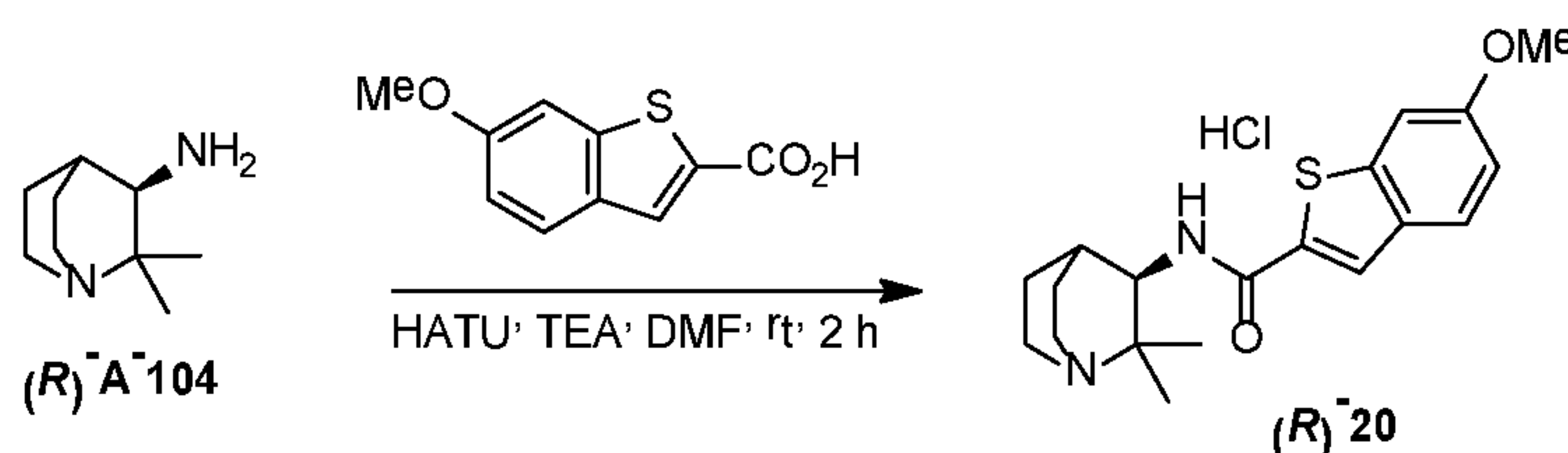


[00786] Following general procedure B, **Compound (S)-19** was prepared from **compound B-115** (68 mg, 0.31 mmol) and **compound (S)-A-104** (40 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 18-48% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-5-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (S)-19**) (44 mg, 43% yield) as a white solid: cSFC analytical (A) *t*_R=3.80 min., purity: 99.95%; LCMS (R): *t*_R=0.922 min., 354.2 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.04 (s, 1H), δ 7.89 (d, *J*=8 Hz, 1H), 7.63 (s, 1H), 7.21 (d, *J*₁=8 Hz, *J*₂=1.6 Hz, 1H), 4.25 (s, 1H), 3.73-3.66 (m, 2H), 3.73-3.34 (m, 2H), 2.41-2.39 (m, 1H), 2.28-2.27 (m, 1H), 2.14-2.06 (m, 3H), 2.05-1.94 (m, 1H), 1.74 (s, 3H), 1.49 (s, 3H), 1.04-1.00 (m, 2H), 0.77-0.74 (m, 2H).

[00787] **Example 20:**

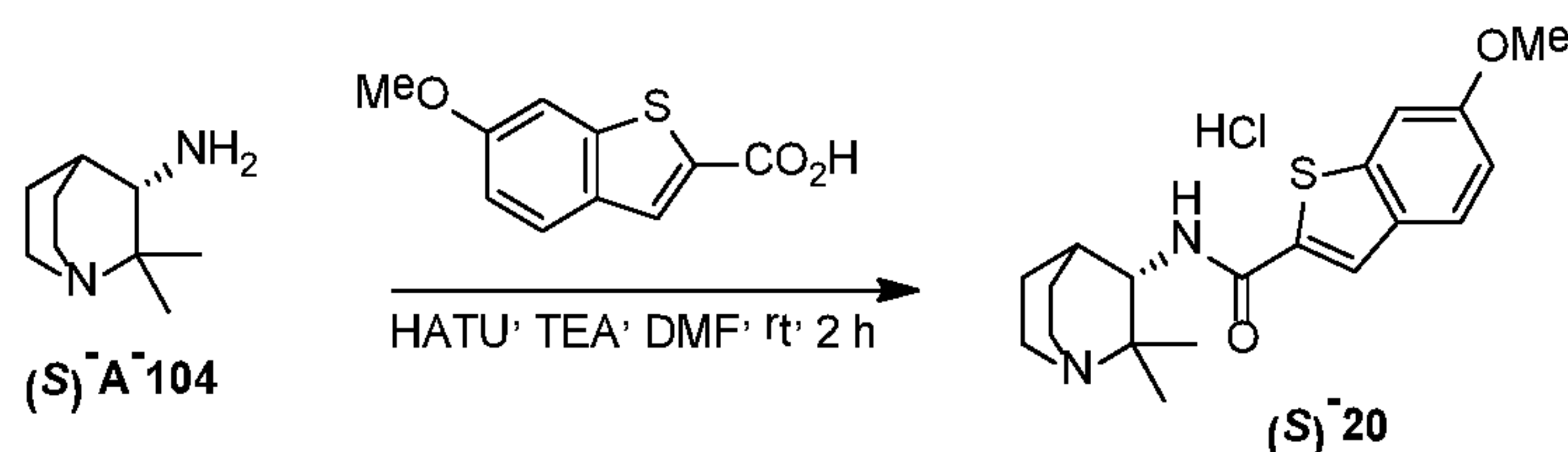
[00788] Preparation of (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[*b*]thiophene-2-carboxamide ((*R*)-20)



[00789] Following general procedure B, **Compound (R)-20** was prepared from 6-methoxybenzo[*b*]thiophene-2-carboxylic acid (67 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-20**) (45 mg, 41% yield) as a white solid: cSFC analytical (A) *t*_R=2.95 min., purity: 98.73%; LCMS (T): *t*_R=2.050 min., 345.1 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.32 (d, *J*=7.6 Hz, 1H), 8.09 (s, 1H), 7.80 (d, *J*=8.8 Hz, 1H), 7.47 (s, 1H), 7.09-7.06 (dd, *J*₁=2.4 Hz, *J*₂=8.8 Hz, 1H), 4.26 (s, 1H), 3.93 (s, 3H), 3.77-3.68 (m, 2H), 3.39-3.29 (m, 2H), 2.46-2.43 (m, 1H), 2.28 (m, 1H), 2.18-2.12 (m, 2H), 1.99-1.92 (m, 1H), 1.76 (s, 3H), 1.50 (s, 3H).

[00790] Preparation of *(S)*-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide (**(S)**-20)

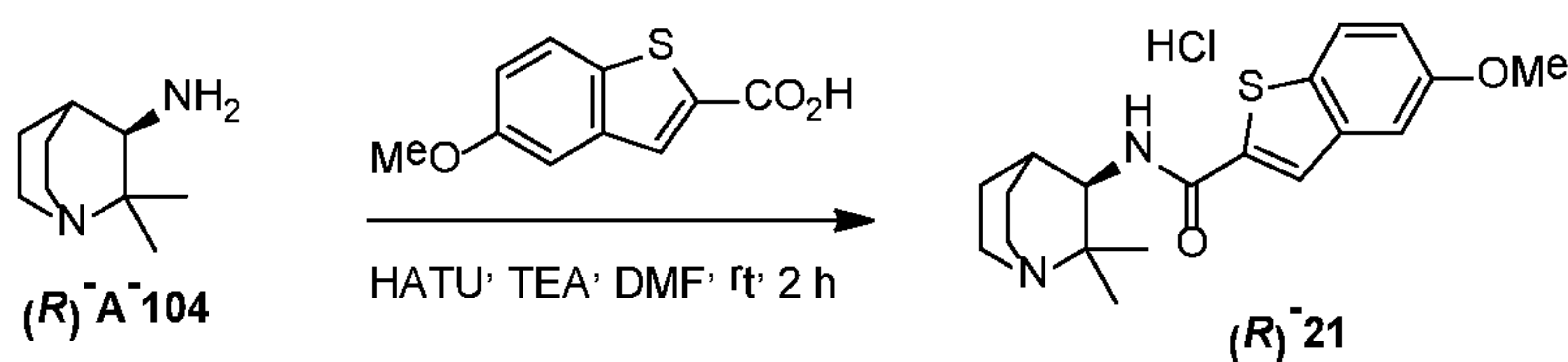


[00791] Following general procedure B, **Compound (S)-20** was prepared from 6-methoxybenzo[b]thiophene-2-carboxylic acid (67 mg, 0.32 mmol) and **compound (S)-A-104** (50 mg, 0.32 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(S)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide hydrochloride (**compound (S)-20**) (25 mg, 23% yield) as a white solid: cSFC analytical (A) t_R=3.34 min., purity: 97.60%; LCMS (B): t_R=0.634 min., 345.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): 8.31 (d, J=7.2 Hz, 1H), 8.08 (s, 1H), 7.80 (d, J=9.2 Hz, 1H), 7.47 (s, 1H), 7.08 (dd, J₁=8.8 Hz, J₂=2.4 Hz, 1H), 4.25 (s, 1H), 3.90 (s, 3H), 3.78-3.68 (m, 2H), 3.39-3.34 (m, 2H), 2.46-2.41 (m, 1H), 2.28 (m, 1H), 2.19-2.12 (m, 2H), 1.99-1.92 (m, 1H), 1.76 (s, 3H), 1.50 (s, 3H).

[00792] **Example 21:**

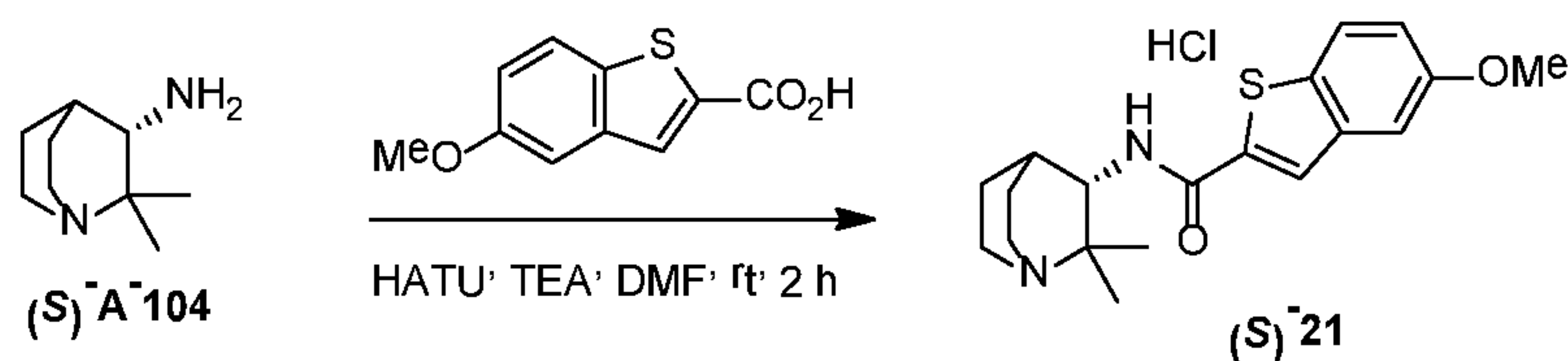
[00793] Preparation of *(R)*-*N*-(2,2-dimethylquinuclidin-3-yl)-5-methoxybenzo[b]thiophene-2-carboxamide (**(R)**-21)



[00794] Following general procedure B, **Compound (R)-21** was prepared from 5-methoxybenzo[b]thiophene-2-carboxylic acid (67 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(R)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-methoxybenzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-21**) (22 mg, 20% yield) as a white solid: cSFC analytical (A) t_R=2.98 min., purity: 94.47%; LCMS (B): t_R=0.664 min., 345.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): 8.42 (d, J=7.6 Hz, 1H), 8.10-8.06 (m, 1H), 7.81 (d, J=8.8 Hz, 1H), 7.42 (s, 1H), 7.16-7.13 (dd, J₁=8.8 Hz, J₂=2.0 Hz, 1H), 4.27 (s, 1H), 3.90 (s, 3H), 3.75-3.69 (m, 2H), 3.39-3.36 (m, 2H), 2.43 (m, 1H), 2.30-2.19 (m, 1H), 2.16-2.08 (m, 2H), 1.99-1.93 (m, 1H), 1.77 (s, 3H), 1.51 (s, 3H).

[00795] Preparation of (*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-methoxybenzo[*b*]thiophene-2-carboxamide ((*S*)-21)

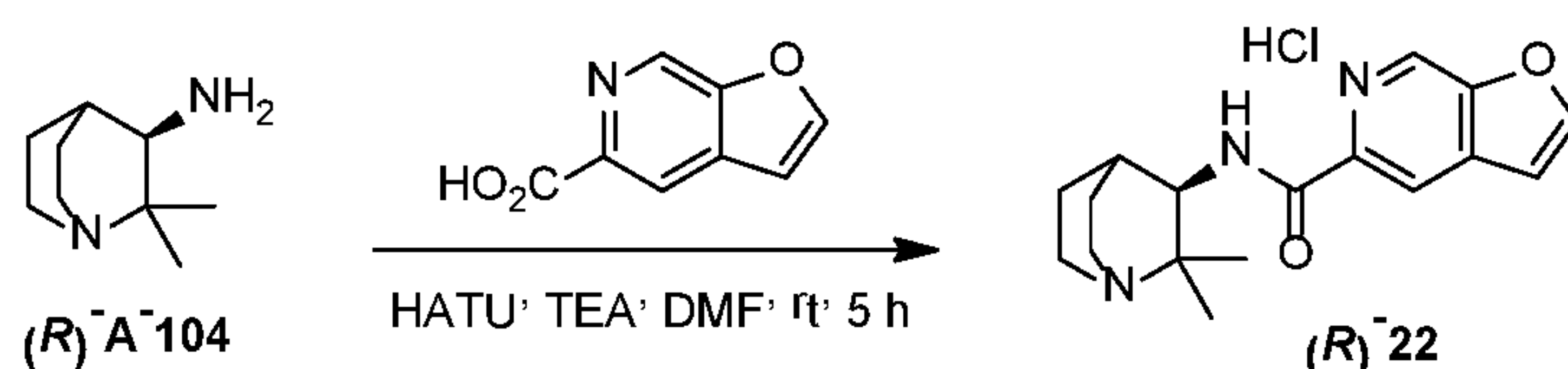


[00796] Following general procedure B, **Compound (S)-21** was prepared from 5-methoxybenzo[*b*]thiophene-2-carboxylic acid (67 mg, 0.32 mmol) and **compound (S)-A-104** (50 mg, 0.32 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-methoxybenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (S)-21**) (19 mg, 17% yield) as a white solid: cSFC analytical (A) t_R=3.40 min., purity: 97.93%; LCMS (B): t_R=0.664 min., 345.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): 8.42 (d, J=7.2 Hz, 1H), 8.10 (s, 1H), 7.80 (d, J=9.2 Hz, 1H), 7.42 (s, 1H), 7.14 (dd, J₁=8.8 Hz, J₂=2.4 Hz, 1H), 4.27 (d, J=6.8 Hz, 1H), 3.89 (s, 3H), 3.75-3.70 (m, 2H), 3.39-3.37 (m, 2H), 2.45 (m, 1H), 2.30-2.18 (m, 1H), 2.18-2.09 (m, 2H), 2.08-1.93 (m, 1H), 1.77 (s, 3H), 1.52 (s, 3H).

[00797] **Example 22:**

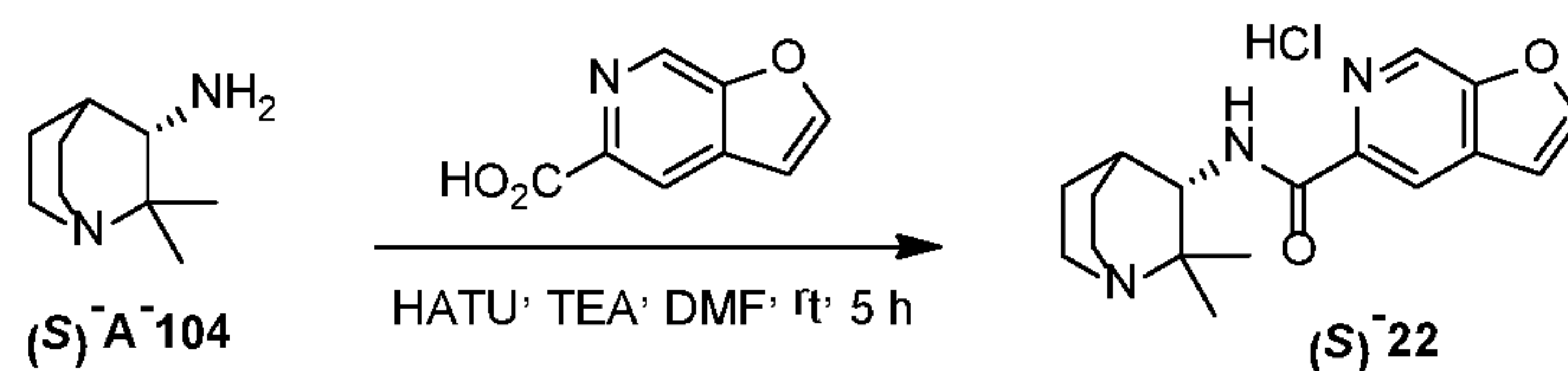
[00798] Preparation of (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)furo[2,3-*c*]pyridine-5-carboxamide hydrochloride ((*R*)-22)



[00799] Following general procedure B, **Compound (R)-22** was prepared from furo[2,3-*c*]pyridine-5-carboxylic acid (53 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 5-35% acetonitrile in H₂O (add 0.5% TFA, v/v)], treated with 0.2 M hydrochloric acid and lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)furo[2,3-*c*]pyridine-5-carboxamide hydrochloride (**compound (R)-22**) (40 mg, 41% yield) as a yellow solid: cSFC analytical (H) t_R=2.49 min., purity: 100%; LCMS (L): t_R=2.148 min., 300.0 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 9.24 (s, 1H), 8.90 (s, 1H), 8.51 (d, J=2.0 Hz, 1H), 7.40 (d, J=1.6 Hz, 1H), 4.33 (s, 1H), 3.77-3.71 (m, 2H), 3.40-3.34 (m, 2H), 2.49-2.45 (m, 1H), 2.33-2.32 (m, 1H), 2.19-2.12 (m, 2H), 2.01-1.95 (m, 1H), 1.78 (s, 3H), 1.54 (s, 3H).

[00800] Preparation of (*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)furo[2,3-*c*]pyridine-5-carboxamide hydrochloride ((*S*)-22)

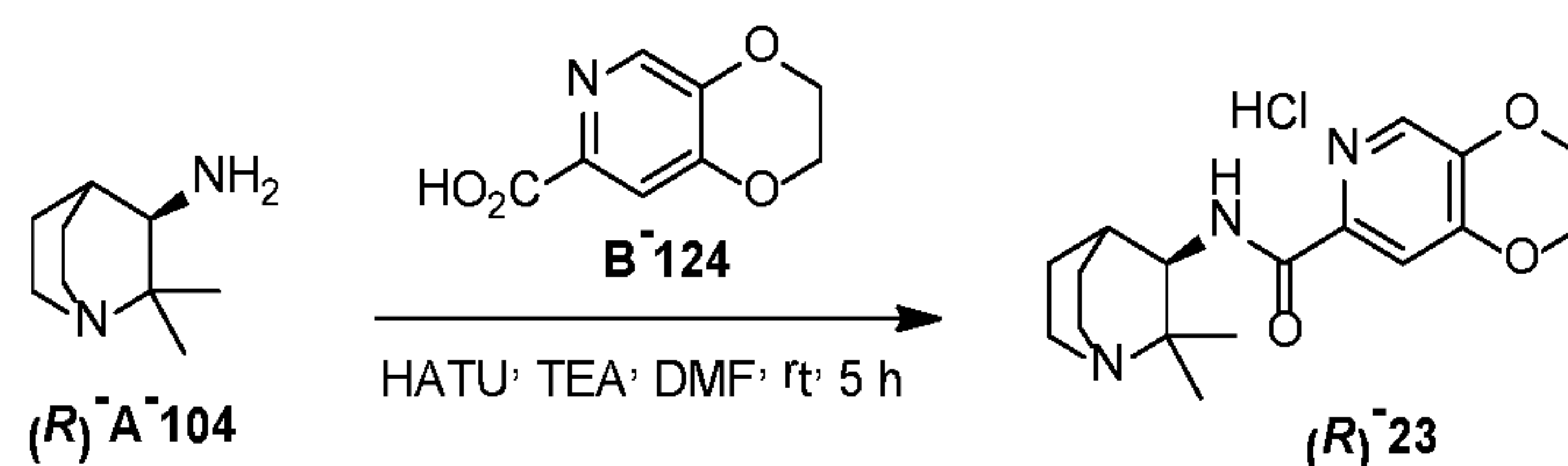


[00801] Following general procedure B, **Compound (S)-22** was prepared from furo[2,3-c]pyridine-5-carboxylic acid (53 mg, 0.32 mmol) and **compound (S)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 5-35% acetonitrile in H₂O (add 0.5% TFA, v/v)], treated with 0.2 M hydrochloric acid and lyophilized to give:

(S)-N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-c]pyridine-5-carboxamide hydrochloride (**compound (S)-22**) (30 mg, 33% yield) as a yellow solid: cSFC analytical (H) t_R=3.40 min., purity: 97.76%; LCMS (L): t_R=2.116 min., 300.0 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 9.10 (s, 1H), 8.70 (s, 1H), 8.35 (d, J=2.0 Hz, 1H), 7.28 (d, J=1.6 Hz, 1H), 4.31 (s, 1H), 3.77-3.71 (m, 2H), 3.40-3.34 (m, 2H), 2.40-2.39 (m, 1H), 2.31-2.30 (m, 1H), 2.21-2.09 (m, 2H), 2.02-1.95 (m, 1H), 1.77 (s, 3H), 1.51 (s, 3H).

[00802] **Example 23:**

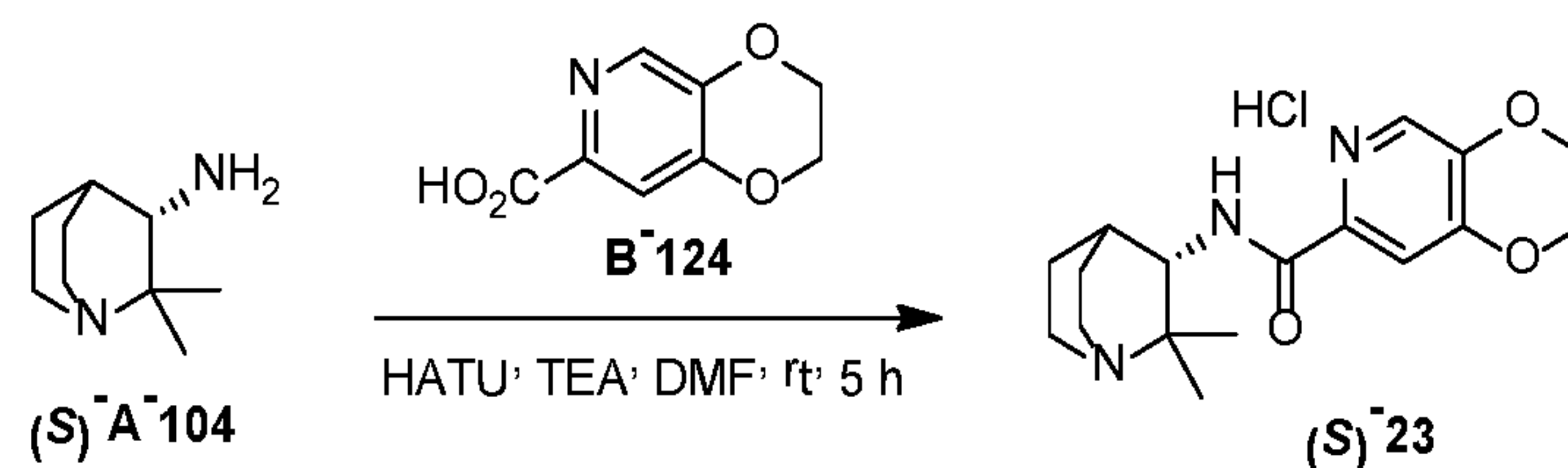
[00803] Preparation of (R)-N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxamide hydrochloride ((R)-23)



[00804] Following general procedure B, **Compound (R)-23** was prepared from **compound B-124** (59 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 10 μm; Mobile phase: 5-40% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(R)-N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxamide hydrochloride (**compound (R)-23**) (55 mg, 53% yield) as a yellow solid: cSFC analytical (H) t_R=3.36 min., purity: 95.72%; LCMS (M): t_R=0.929 min., 318.0 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.45 (s, 1H), 8.18 (s, 1H), 4.67-4.65 (m, 2H), 4.57-4.55 (m, 2H), 4.29 (s, 1H), 3.76-3.69 (m, 2H), 3.40-3.36 (m, 2H), 2.47-2.44 (m, 1H), 2.30 (m, 1H), 2.19-2.12 (m, 2H), 1.99-1.93 (m, 1H), 1.77 (s, 3H), 1.51 (s, 3H).

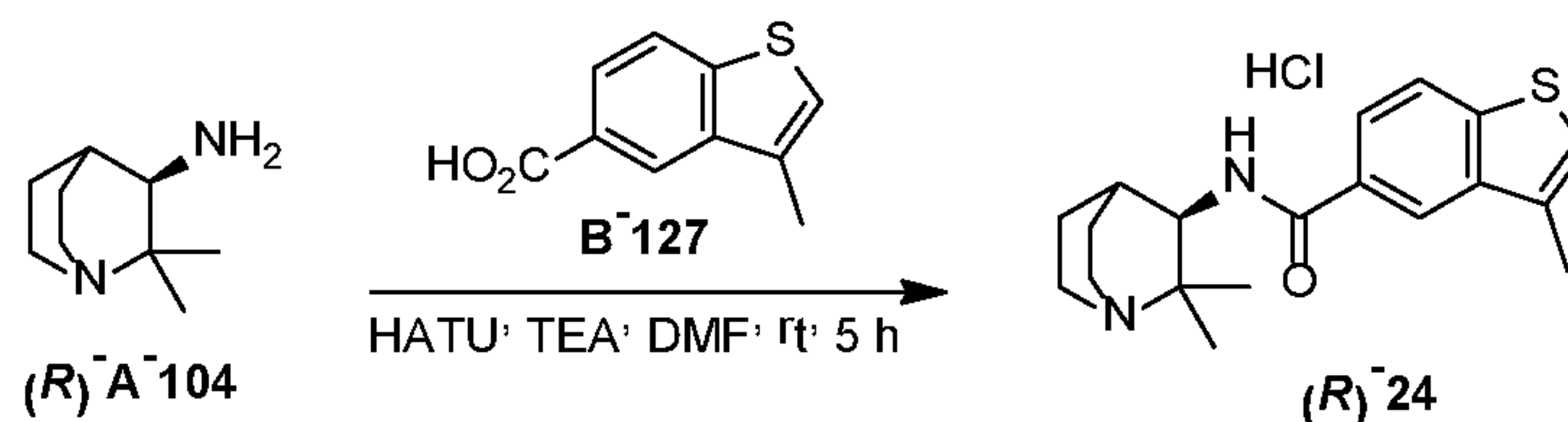
[00805] Preparation of (S)-N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxamide hydrochloride ((S)-23)



[00806] Following general procedure B, **Compound (S)-23** was prepared from **compound B-124** (47 mg, 0.26 mmol) and **compound (S)-A-104** (40 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 10 μm; Mobile phase: 5-40% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(S)-N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxamide hydrochloride (**compound (S)-23**) (50 mg, 61% yield) as a yellow solid: cSFC analytical (H) t_R=3.67 min., purity: 98.64%; LCMS (M): t_R=0.916 min., 318.0 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.45 (s, 1H), 8.17 (s, 1H), 4.65-4.63 (m, 2H), 4.54-4.52 (m, 2H), 4.27 (s, 1H), 3.74-3.67 (m, 2H), 3.38-3.34 (m, 2H), 2.45-2.40 (m, 1H), 2.28-2.27 (m, 1H), 2.17-2.11 (m, 2H), 1.97-1.91 (m, 1H), 1.75 (s, 3H), 1.49 (s, 3H).

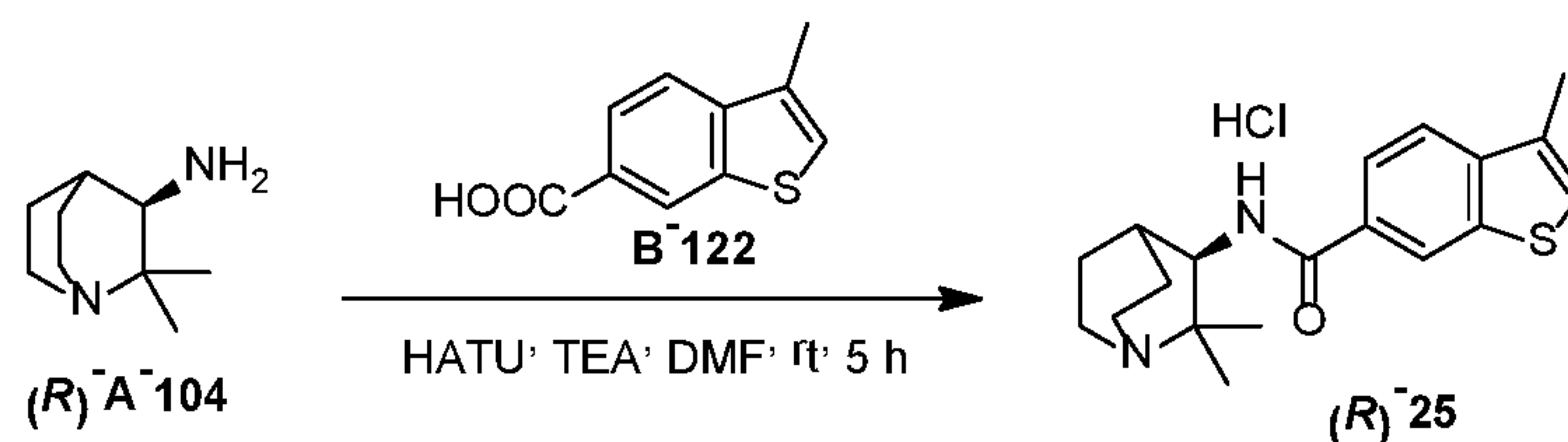
[00807] **Example 24:** (R)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzo[b]thiophene-5-carboxamide hydrochloride ((R)-24)



[00808] Following general procedure B, **Compound (R)-24** was prepared from **compound B-127** (62 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 10 μm; Mobile phase: 20-50% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(R)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzo[b]thiophene-5-carboxamide hydrochloride (**compound (R)-24**) (65 mg, 61% yield) as a white solid: cSFC analytical (B) t_R=2.87 min., purity: 98.24%; LCMS (B): t_R=0.658 min., 329.2 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.28 (d, J=1.2 Hz, 1H), 7.98 (d, J=8.4 Hz, 1H), 7.83 (d, J₁=8.4 Hz, J₂=1.2 Hz, 1H), 7.33 (s, 1H), 4.30 (s, 1H), 3.77-3.67 (m, 2H), 3.38-3.34 (m, 2H), 2.52 (s, 3H), 2.52-2.41 (m, 1H), 2.40-2.29 (m, 1H), 2.19-2.11 (m, 2H), 1.97-1.90 (m, 1H), 1.79 (s, 3H), 1.51 (s, 3H).

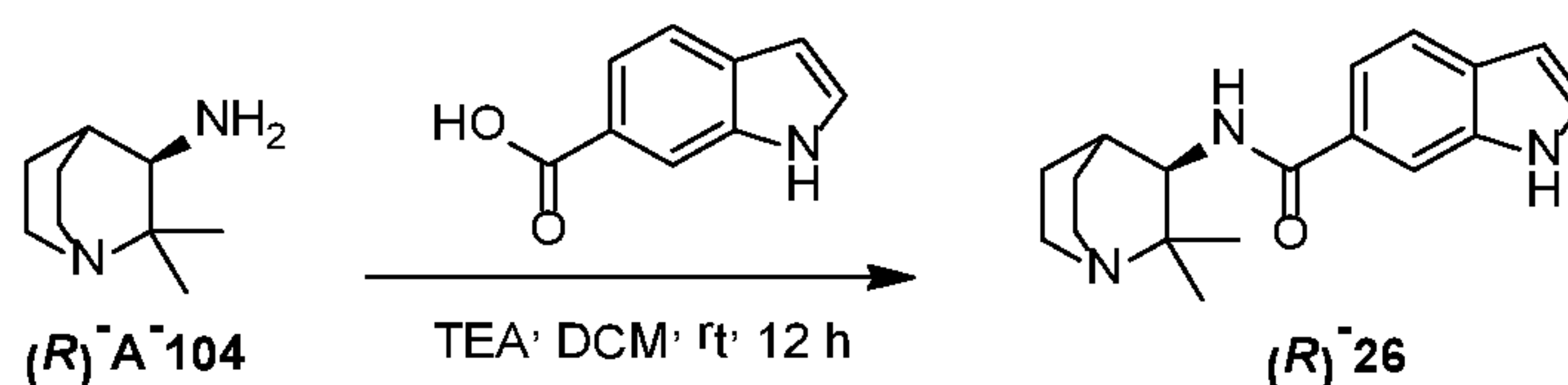
[00809] **Example 25:** (R)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzo[b]thiophene-6-carboxamide ((R)-25)



[00810] Following general procedure B, **Compound (R)-25** was prepared from **compound B-122** (69 mg, 0.36 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex SynergiC18 150×30mm, particle size: 10 μm; Mobile phase: 14-44% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(R)-*N*-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzo[b]thiophene-6-carboxamide hydrochloride (**compound (R)-25**) (30 mg, 25% yield) as a white solid: cSFC analytical (A) t_R=2.96 min., purity: 97.81%; LCMS (B): t_R=0.663 min., 329.1 m/z (M+1); ¹H-NMR (DMSO, 400 MHz): δ 10.40 (s, 1H), 8.53 (s, 1H), 8.41 (d, J=8.0Hz, 1H), 7.91-7.85 (m, 2H), 7.61 (s, 1H), 4.14 (d, J=7.2Hz, 1H), 3.52-3.49 (m, 2H), 3.23-3.11 (m, 2H), 2.44 (s, 3H), 2.42-2.34 (m, 1H), 2.12-2.03 (m, 2H), 1.94-1.88 (m, 1H), 1.76-1.69 (m, 1H), 1.65 (s, 3H), 1.41 (s, 3H).

[00811] **Example 26:** *(R)*-*N*-(2,2-dimethylquinuclidin-3-yl)-1H-indole-6-carboxamide ((**R**)-26)

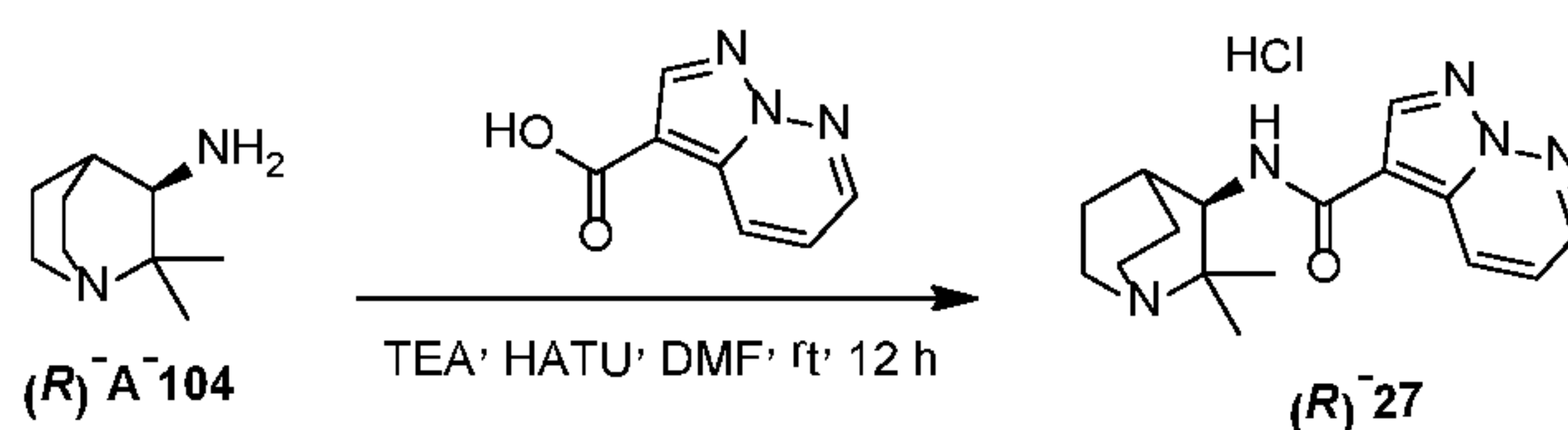


[00812] Following general procedure B, **Compound (R)-26** was prepared from 1H-indole-6-carboxylic acid and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 150×25 mm, particle size: 10 μm; Mobile phase: 28-58% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(R)-*N*-(2,2-dimethylquinuclidin-3-yl)-1H-indole-6-carboxamide hydrochloride (**compound (R)-26**) (20 mg, 21% yield) as a white solid: cSFC analytical (A) t_R: 3.17 min., purity: 96%; LCMS (P): t_R=1.672 min., 298.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 7.93 (s, 1H), 7.64 (d, J=8.4 Hz, 1H), 7.51-7.49 (m, 1H), 7.42 (d, J=2.8 Hz, 1H), 6.54 (d, J=3.2Hz, 1H), 4.07 (s, 1H), 3.39-3.35 (m, 2H), 2.84-2.82 (m, 2H), 2.07-2.05 (m, 1H), 1.96 (s, 1H), 1.88-1.83 (m, 2H), 1.58-1.56 (m, 1H), 1.50 (s, 3H), 1.33 (s, 3H).

[00813] **Example 27:**

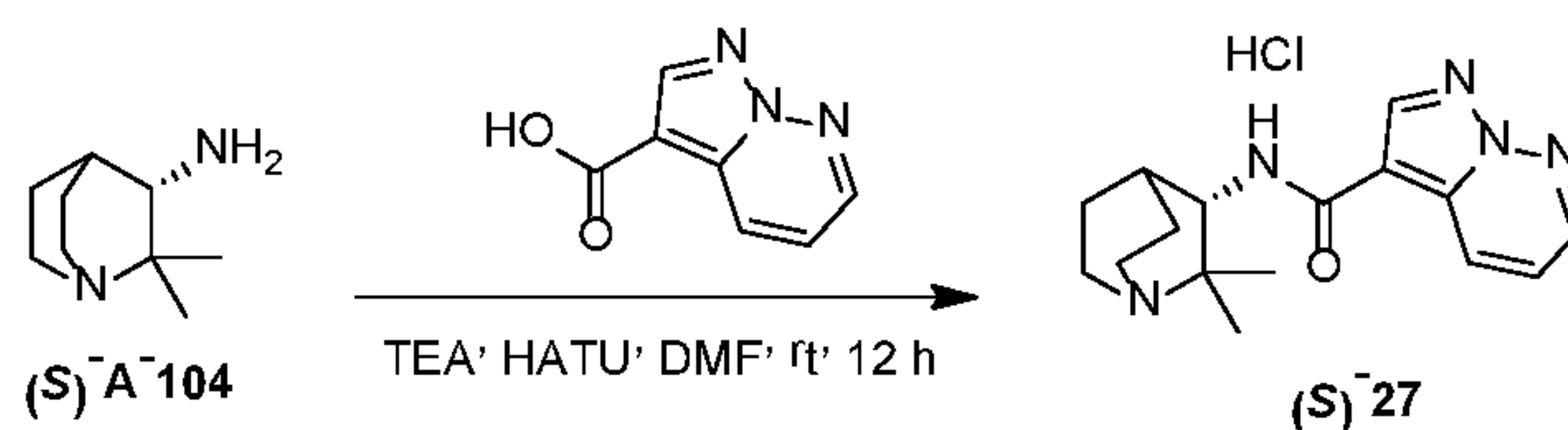
[00814] Preparation of *(R)*-*N*-(2,2-dimethylquinuclidin-3-yl)pyrazolo[1,5-b]pyridazine-3-carboxamide hydrochloride ((**R**)-27)



[00815] Following general procedure B, **Compound (R)-27** was prepared from pyrazolo[1,5-b]pyridazine-3-carboxylic acid (50 mg, 0.31 mmol) and **compound (R)-A-104** (47 mg, 0.31 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 16-46% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)pyrazolo[1,5-b]pyridazine-3-carboxamide hydrochloride (**compound (R)-27**) (30 mg, 33% yield) as a white solid: cSFC analytical (B) t_R = 3.40 min., purity: 99.40%; LCMS (N): t_R=1.485 min., (ES⁺) m/z (M+H)⁺ = 300.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.71 (s, 1H), 8.66 (dd, J₁=8.8 Hz, J₂=1.6 Hz, 1H), 8.53 (dd, J₁=4.4 Hz, J₂=2.0 Hz, 1H), 7.43-7.40 (m, 1H), 4.29 (s, 1H), 3.74-3.67 (m, 2H), 3.37-3.31 (m, 2H), 2.45-2.42 (m, 1H), 2.27-2.25 (m, 1H), 2.17-2.14 (m, 2H), 1.97-1.90 (m, 1H), 1.76 (m, 3H), 1.49 (m, 3H).

[00816] Preparation of (*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)pyrazolo[1,5-b]pyridazine-3-carboxamide hydrochloride (**(S)-27**)

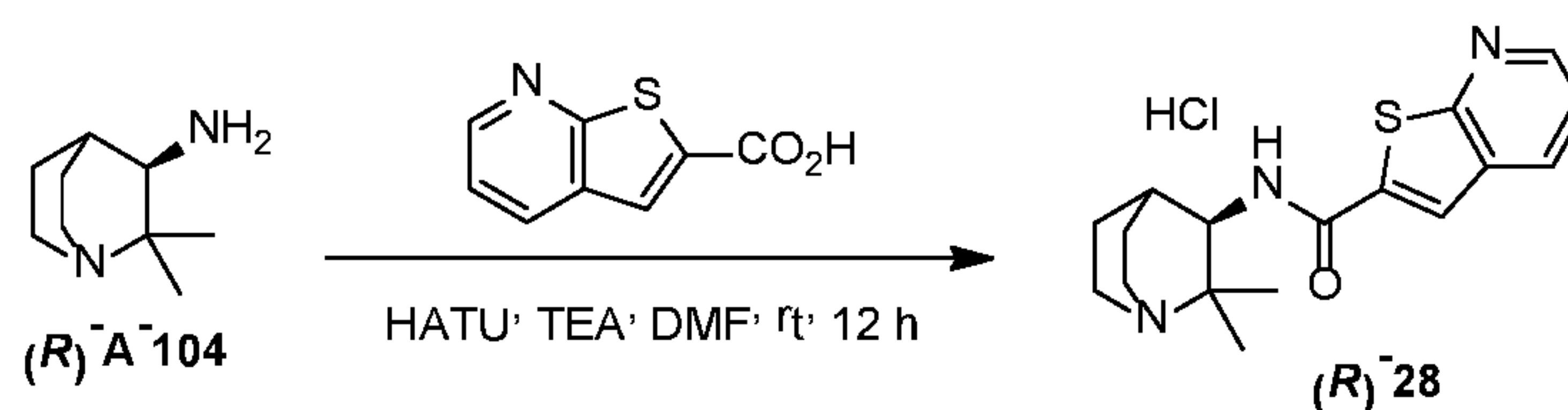


[00817] Following general procedure B, **Compound (S)-27** was prepared from pyrazolo[1,5-b]pyridazine-3-carboxylic acid (50 mg, 0.31 mmol) and **compound (S)-A-104** (47 mg, 0.20 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 16-46% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)pyrazolo[1,5-b]pyridazine-3-carboxamide hydrochloride (**compound (S)-27**) (44 mg, 48% yield) as a white solid: cSFC analytical (B) t_R = 3.14 min., purity: 99.11%; LCMS (N): t_R=1.579 min., (ES⁺) m/z (M+H)⁺ = 300.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.69 (s, 1H), 8.66 (dd, J₁=9.2 Hz, J₂=1.6 Hz, 1H), 8.53-8.52 (dd, J₁=4.4 Hz, J₂=1.6 Hz, 1H), 7.43-7.40 (m, 1H), 4.28 (s, 1H), 3.75-3.66 (m, 2H), 3.37-3.31 (m, 2H), 2.45-2.40 (m, 1H), 2.27-2.24 (m, 1H), 2.17-2.06 (m, 2H), 1.96-1.90 (m, 1H), 1.76 (m, 3H), 1.48 (m, 3H).

[00818] **Example 28:**

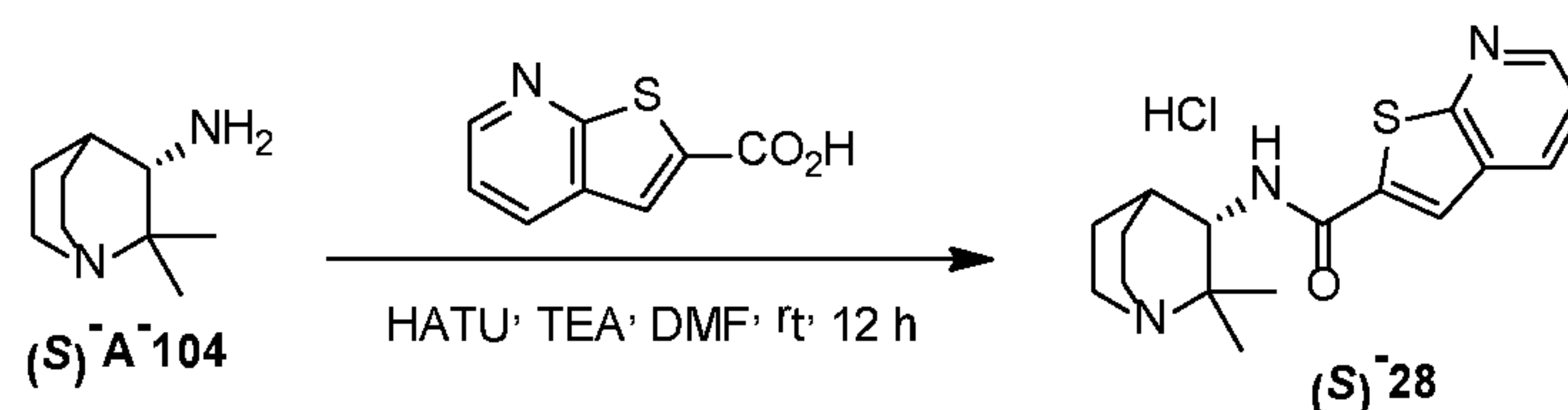
[00819] Preparation of (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-b]pyridine-2-carboxamide hydrochloride (**(R)-28**)



[00820] Following general procedure B, **Compound (R)-28** was prepared from thieno[2,3-b]pyridine-2-carboxylic acid (58 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 4-34% acetonitrile in H₂O (add 0.5% TFA, v/v)], treated with 0.2 M hydrochloric acid solution and lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-b]pyridine-2-carboxamide hydrochloride (**compound (R)-28**) (45 mg, 39% yield) as a yellow solid: cSFC analytical (A) *t*_R=3.006 min., purity: 98.57%; LCMS (X): *t*_R=1.517 min., (ES⁺) *m/z* (M+H)⁺ = 316.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.79 (d, *J*=5.2 Hz, 1H), 8.60 (d, *J*=8.0 Hz, 1H), 8.30 (s, 1H), 7.69 (t, *d*=8.4 Hz, 1H), 4.30 (s, 1H), 3.78-3.71 (m, 2H), 3.40-3.36 (m, 2H), 2.50-2.45 (m, 1H), 2.32-2.31 (m, 1H), 2.21-2.10 (m, 2H), 2.00-1.94 (m, 1H), 1.78 (s, 3H), 1.53 (s, 3H).

[00821] Preparation of (*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-b]pyridine-2-carboxamide hydrochloride (**(S)-28**)

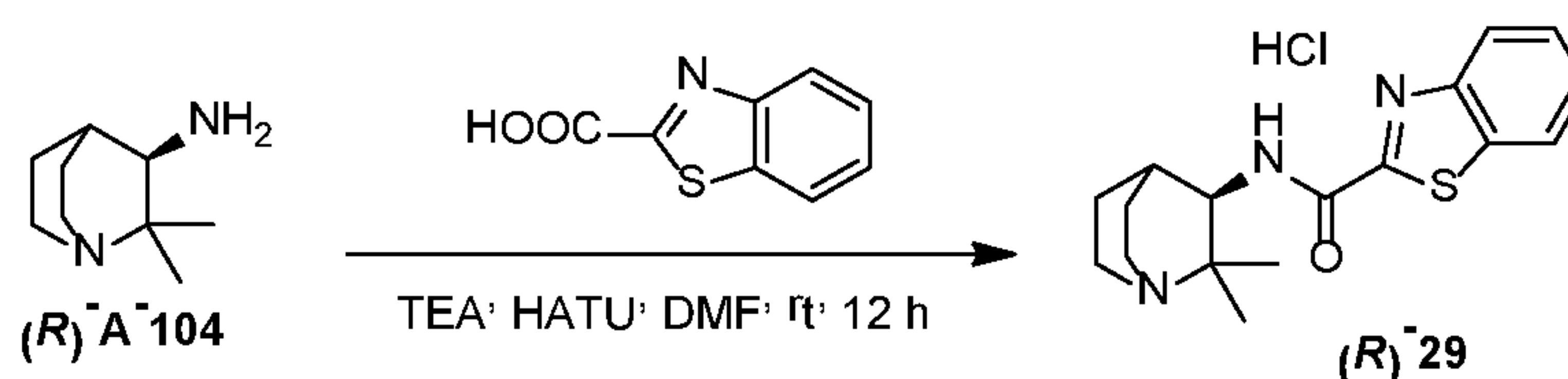


[00822] Following general procedure B, **Compound (S)-28** was prepared from thieno[2,3-b]pyridine-2-carboxylic acid (58 mg, 0.32 mmol) and **compound (S)-A-104** (50 mg, 0.32 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 4-34% acetonitrile in H₂O (add 0.5% TFA, v/v)], treated with 0.2 M hydrochloric acid solution and lyophilized to give:

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-b]pyridine-2-carboxamide hydrochloride (**compound (S)-28**) (36 mg, 32% yield) as a yellow solid: cSFC analytical (A) *t*_R=3.684 min., purity: 98.05%; LCMS (X): *t*_R=1.523 min., (ES⁺) *m/z* (M+H)⁺ = 316.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.78 (d, *J*=4.8 Hz, 1H), 8.58 (d, *J*=8.0 Hz, 1H), 8.29 (s, 1H), 7.68 (t, *d*=8.4 Hz, 1H), 4.30 (s, 1H), 3.78-3.70 (m, 2H), 3.40-3.36 (m, 2H), 2.50-2.45 (m, 1H), 2.32-2.31 (m, 1H), 2.21-2.10 (m, 2H), 2.00-1.94 (m, 1H), 1.78 (s, 3H), 1.53 (s, 3H).

[00823] **Example 29:**

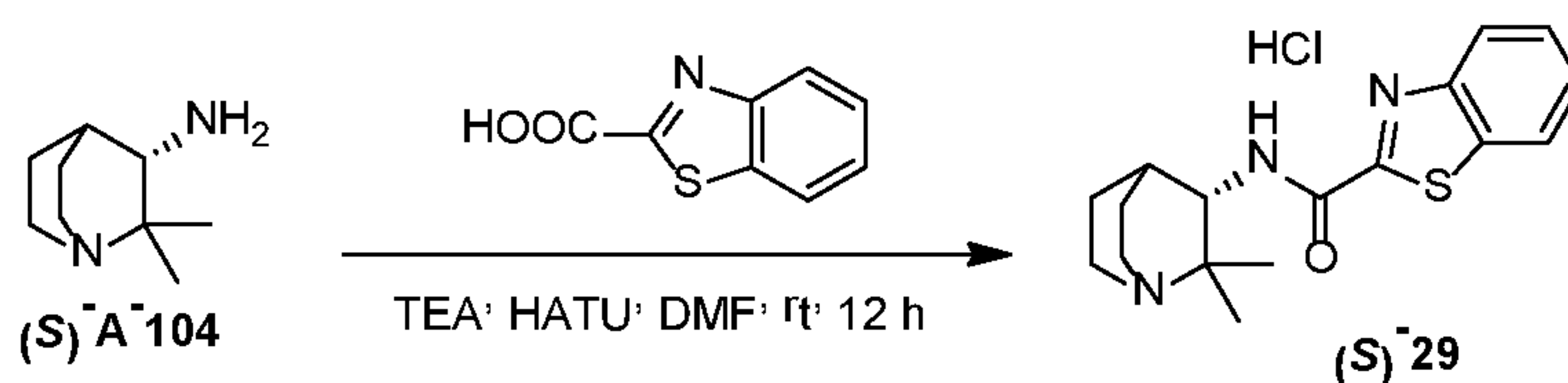
[00824] Preparation of (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[d]thiazole-2-carboxamide hydrochloride (**(R)-29**)



[00825] Following general procedure B, **Compound (R)-29** was prepared from benzo[d]thiazole-2-carboxylic acid (58 mg, 0.33 mmol) and **(R)-A-104** (50 mg, 0.33 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 16-46% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(R)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]thiazole-2-carboxamide hydrochloride (compound (R)-29) (40 mg, 39% yield) as a white solid: cSFC analytical (D) tR = 2.93 min., purity: 99.32%; LCMS (X): tR=1.793 min., (ES⁺) m/z (M+H)⁺ = 316.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.17-8.10 (m, 2H), 7.65-7.56 (m, 2H), 4.30 (m, 1H), 3.72-3.69 (m, 2H), 3.39-3.33 (m, 2H), 2.40-2.39 (m, 1H), 2.31-2.20 (m, 1H), 2.18-2.08 (m, 2H), 2.00-1.94 (m, 1H), 1.76 (m, 3H), 1.52 (m, 3H).

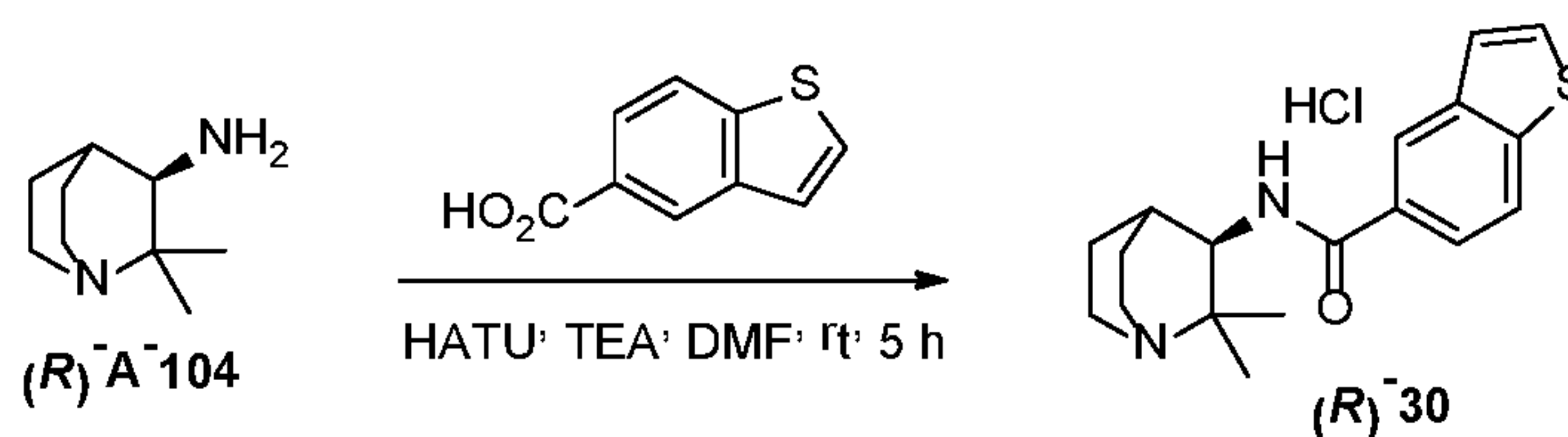
[00826] Preparation of **(S)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]thiazole-2-carboxamide hydrochloride ((S)-29)**



[00827] Following general procedure B, **Compound (S)-29** was prepared from benzo[d]thiazole-2-carboxylic acid (50 mg, 0.31 mmol) and **compound (S)-A-104** (47 mg, 0.20 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 16-46% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(S)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]thiazole-2-carboxamide hydrochloride (compound (S)-29) (44 mg, 48% yield) as a white solid: cSFC analytical (D) tR = 3.38 min., purity: 98.29%; LCMS (X): tR=1.781 min., (ES⁺) m/z (M+H)⁺ = 316.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.17-8.11 (m, 2H), 7.66-7.56 (m, 2H), 4.30 (m, 1H), 3.76-3.70 (m, 2H), 3.37-3.34 (m, 2H), 2.40-2.39 (m, 1H), 2.31-2.21 (m, 1H), 2.20-2.11 (m, 2H), 2.00-1.94 (m, 1H), 1.75 (m, 3H), 1.52 (m, 3H).

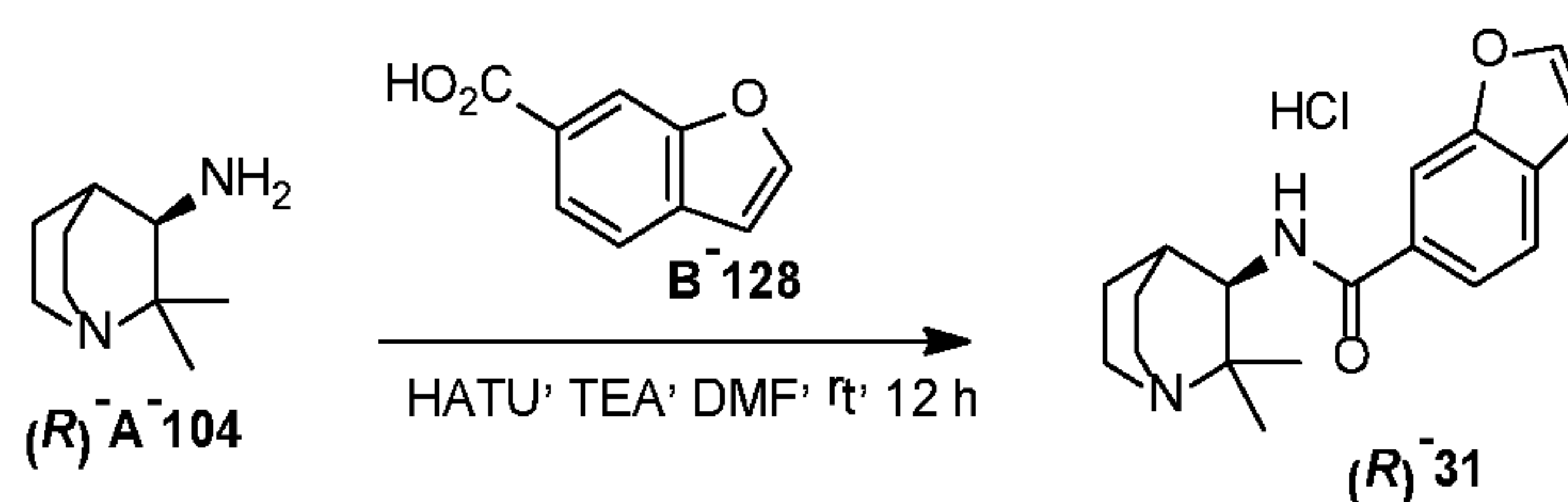
[00828] **Example 30: (R)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-5-carboxamide hydrochloride ((R)-30)**



[00829] Following general procedure B, **Compound (R)-30** was prepared from benzo[b]thiophene-5-carboxylic acid (60 mg, 0.34 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30mm, particle size: 4 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-5-carboxamide hydrochloride (**compound (R)-30**) (30 mg, 28% yield) as a white solid: cSFC analytical (A) t_R=2.998 min., purity: 96.86%; LCMS (J): t_R=1.355 min., 315.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.39 (s, 1H), 8.05 (d, J=8.8 Hz, 1H), 7.83 (d, J=8.4 Hz, 1H), 7.73 (d, J=5.2 Hz, 1H), 7.52 (d, J=5.6 Hz, 1H), 4.61 (s, 1H), 4.30 (s, 1H), 3.75-3.60 (m, 2H), 3.28-3.25 (m, 1H), 2.39 (m, 1H), 2.28 (m, 1H), 2.18-2.12 (m, 2H), 1.93 (m, 1H), 1.78 (s, 3H), 1.51 (s, 3H).

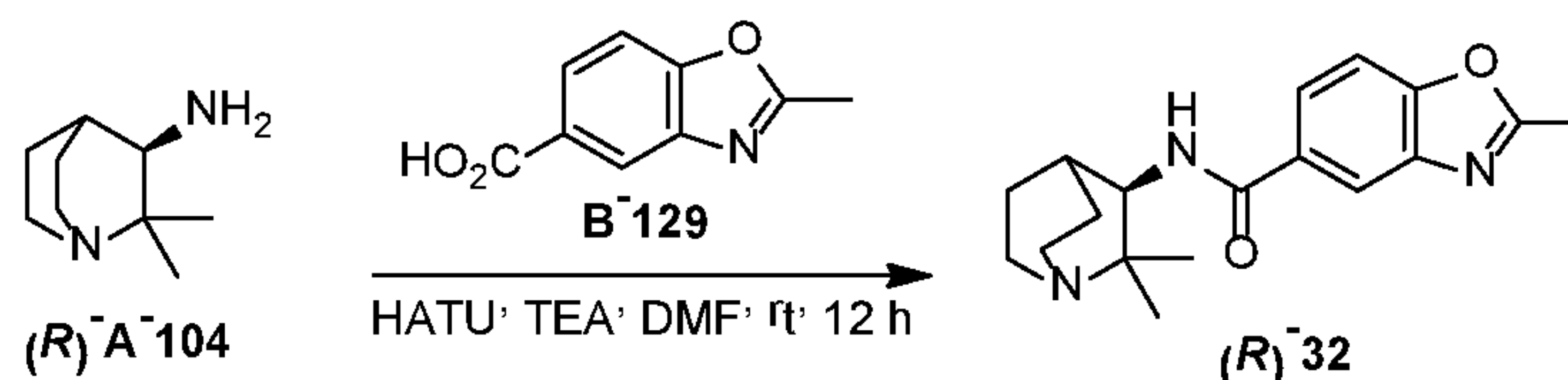
[00830] **Example 31: (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)benzofuran-6-carboxamide hydrochloride ((*R*)-31)**



[00831] Following general procedure B, **Compound (R)-31** was prepared from **compound B-128** (53 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30mm, particle size: 10 μm; Mobile phase: 12-42% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)benzofuran-6-carboxamide hydrochloride (**compound (R)-31**) (46 mg, 42% yield) as a white solid: cSFC analytical (A) t_R=2.52 min., purity: 97.64%; LCMS (B): t_R=0.115 min., (ES⁺) m/z (M+H)⁺=299.2; ¹H-NMR (CD₃OD, 400 MHz): δ 8.05 (s, 1H), 7.93 (d, J=2.0 Hz, 1H), 7.78-7.72 (m, 2H), 6.94 (d, J=1.2 Hz, 1H), 4.28 (s, 1H), 3.75-3.66 (m, 2H), 3.37-3.31 (m, 2H), 2.39-2.38 (m, 1H), 2.27-2.26 (m, 1H), 2.18-2.10 (m, 2H), 1.96-1.89 (m, 1H), 1.77 (s, 3H), 1.49 (s, 3H).

[00832] **Example 32: (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]oxazole-5-carboxamide ((*R*)-32)**

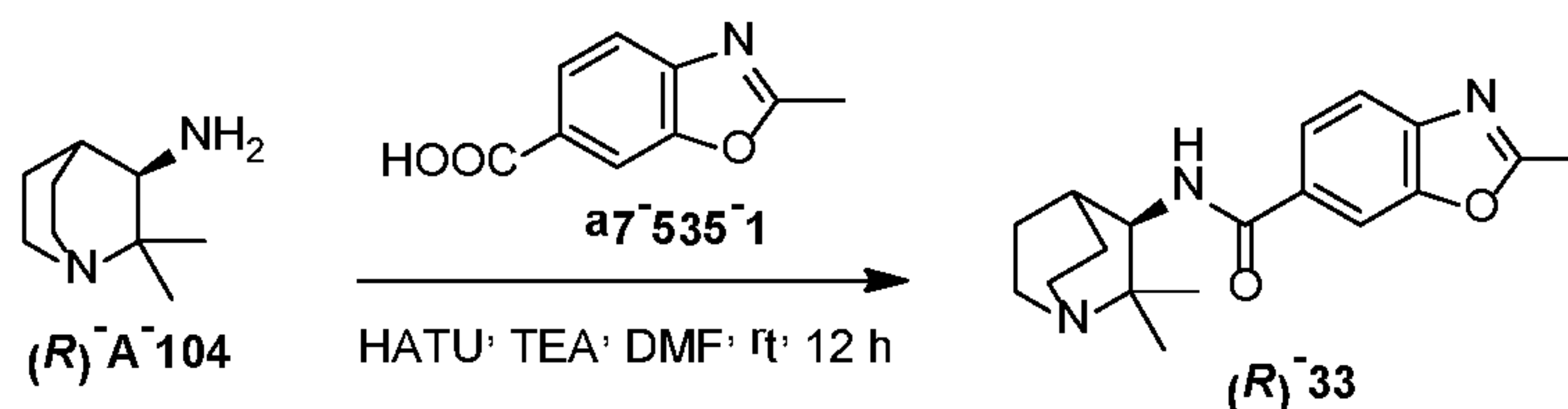


[00833] Following general procedure B, **Compound (R)-32** was prepared from **compound B-129** (69 mg, 0.39 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 12 hours.

The product was purified by prep-HPLC [Instrument: GX-C; Column: Phenomenex Gemini C18 150×30 mm, particle size: 5 µm; Mobile phase: 35-65% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]oxazole-5-carboxamide (**compound (R)-32**) (30 mg, 30% yield) as a white solid: cSFC analytical (A) t_R=2.44 min., purity: 96.08%; LCMS (J): t_R=0.995 min., 314.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.10 (s, 1H), 7.87-7.85 (m, 1H), 7.67 (d, J=8.8 Hz, 1H), 4.07 (s, 1H), 3.33-3.33 (m, 2H), 2.85-2.85 (m, 2H), 2.69 (s, 3H), 2.09-2.09 (m, 1H), 1.97-1.86 (m, 3H), 1.67-1.64 (m, 1H), 1.51 (s, 3H), 1.32 (s, 3H).

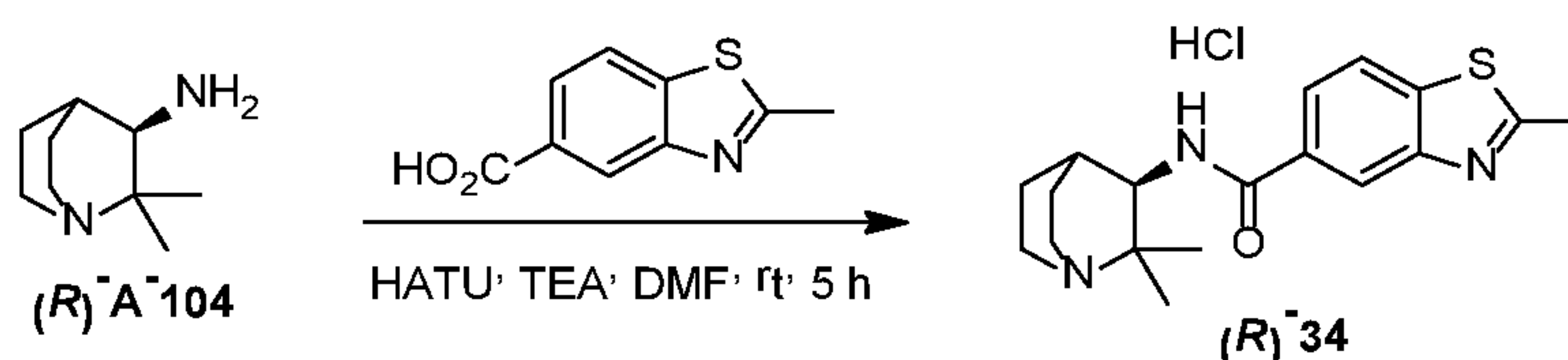
[00834] **Example 33:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]oxazole-6-carboxamide ((*R*)-33)



[00835] Following general procedure B, **Compound (R)-33** was prepared from **compound B-130** (60 mg, 0.34 mmol) and **compound (R)-A-104** (52 mg, 0.34 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-C; Column: Phenomenex Gemini C18 150×30 mm, particle size: 5 µm; Mobile phase: 35-65% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]oxazole-6-carboxamide (**compound (R)-33**) (40 mg, 38% yield) as a white solid: cSFC analytical (A) t_R=2.42 min., purity: 97.31%; LCMS (J): t_R=0.986 min., 314.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.05 (s, 1H), 7.86-7.84 (m, 1H), 7.70 (d, J=8.4 Hz, 1H), 4.03 (s, 1H), 3.33-3.33 (m, 2H), 2.81-2.75 (m, 2H), 2.70 (s, 3H), 2.02-2.02 (m, 1H), 1.91-1.91 (m, 1H), 1.82-1.80 (m, 2H), 1.53-1.50 (m, 1H), 1.46 (s, 3H), 1.29 (s, 3H).

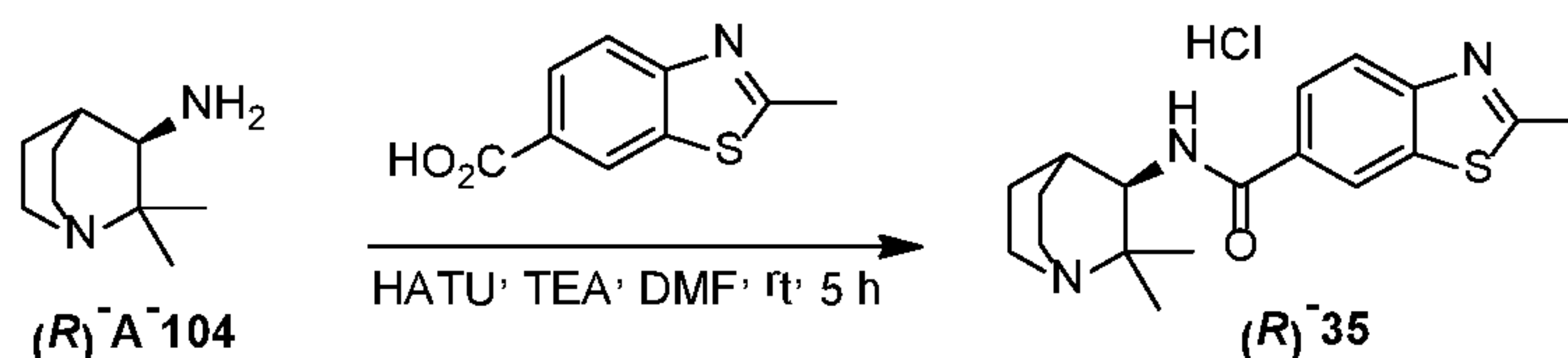
[00836] **Example 34:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]thiazole-5-carboxamide hydrochloride ((*R*)-34)



[00837] Following general procedure B, **Compound (R)-34** was prepared from 2-methylbenzo[d]thiazole-5-carboxylic acid (63 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 µm; Mobile phase: 16-46% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]thiazole-5-carboxamide hydrochloride (**compound (R)-34**) (35 mg, 33% yield) as a white solid: cSFC analytical (A) t_R =2.85 min., purity: 94.01%; LCMS (K): t_R =1.217 min., (ES⁺) m/z (M+H)⁺ = 330.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.39 (s, 1H), 8.08 (d, J =8.4 Hz, 1H), 7.88 (d, J =8.4 Hz, 1H), 4.29 (s, 1H), 3.78-3.68 (m, 2H), 3.38-3.31 (m, 2H), 2.88 (s, 3H), 2.39-2.38 (m, 1H), 2.28-2.27 (m, 1H), 2.18-2.07 (m, 2H), 1.99-1.90 (m, 1H), 1.78 (s, 3H), 1.51 (s, 3H).

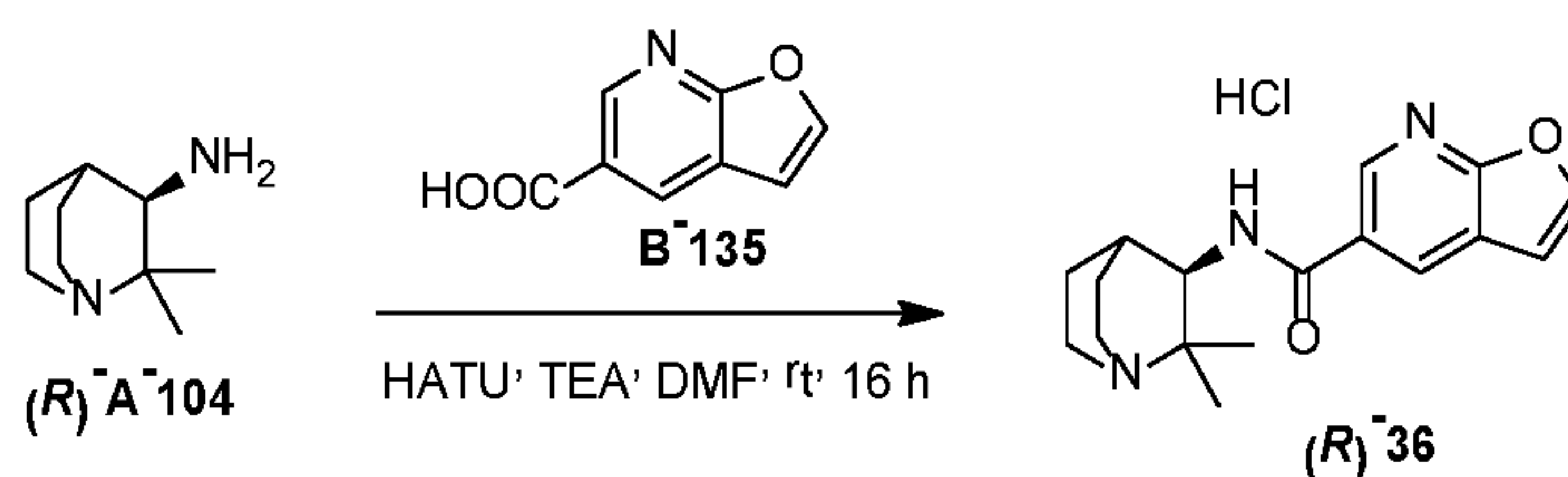
[00838] **Example 35:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]thiazole-6-carboxamide hydrochloride (**(R)-35**)



[00839] Following general procedure B, **Compound (R)-35** was prepared from 2-methylbenzo[d]thiazole-6-carboxylic acid (62 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μ m; Mobile phase: 8-38% acetonitrile in H₂O (add 0.5% TFA, v/v)], treated with HCl and then lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]thiazole-6-carboxamide hydrochloride (**compound (R)-35**) (70 mg, 59% yield) as a white solid: cSFC analytical (A) t_R =2.81 min., purity: 97.50%; LCMS (K): t_R =1.192 min., (ES⁺) m/z (M+H)⁺ = 330.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.49 (s, 1H), 7.98 (m, 2H), 4.28 (s, 1H), 3.74-3.69 (m, 2H), 3.35-3.31 (m, 2H), 2.90 (s, 3H), 2.42-2.38 (m, 1H), 2.26-2.27 (m, 1H), 2.09-2.19 (m, 2H), 1.89-1.96 (m, 1H), 1.77 (s, 3H), 1.50 (s, 3H).

[00840] **Example 36:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)furo[2,3-b]pyridine-5-carboxamide (**(R)-36**)

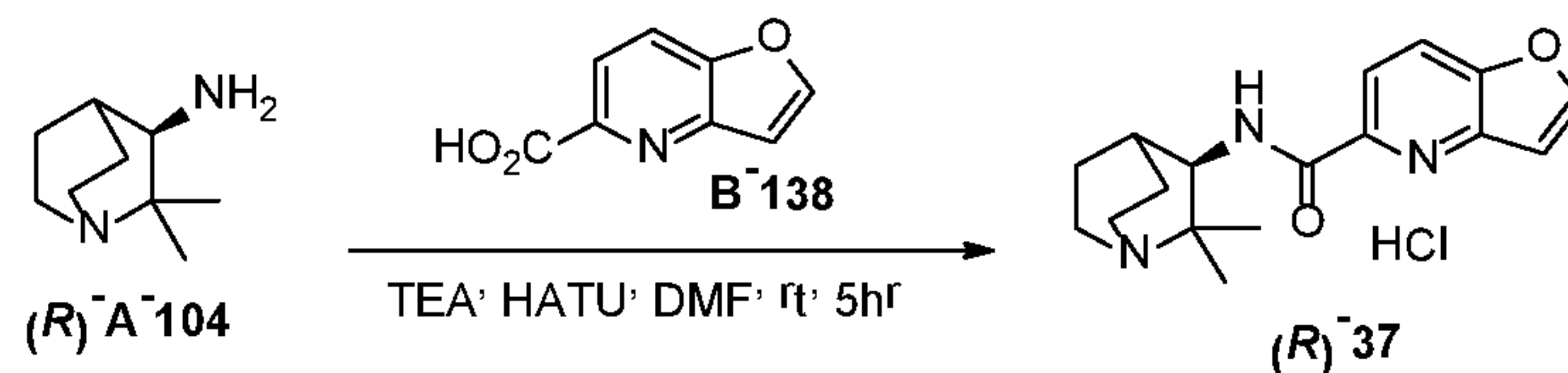


[00841] Following general procedure B, **Compound (R)-36** was prepared from **compound B-135** (53 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 16 hours. The product was purified by prep-HPLC [Instrument: GX-H; Column: welch Xtimate C18 150×30 mm, particle size: 5 μ m; Mobile phase: 20-50% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)furo[2,3-b]pyridine-5-carboxamide hydrochloride (**compound (R)-36**) (20 mg, 19% yield) as a white solid: cSFC analytical (A) t_R =2.95 min., purity: 100%; LCMS (J): t_R =1.17 min., 300.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.73 (d, J =2 Hz, 1H), 8.52 (d, J =2 Hz, 1H), 8.02 (d, J =2.4 Hz, 1H), 7.05 (d, J =2.4 Hz, 1H), 4.08 (s, 1H), 3.40-3.34 (m,

2H), 2.88-2.78 (m, 2H), 2.06-1.97 (m, 1H), 1.96-1.91 (m, 1H), 1.88-1.83 (m, 2H), 1.58-1.50 (m, 4H), 1.32 (s, 3H).

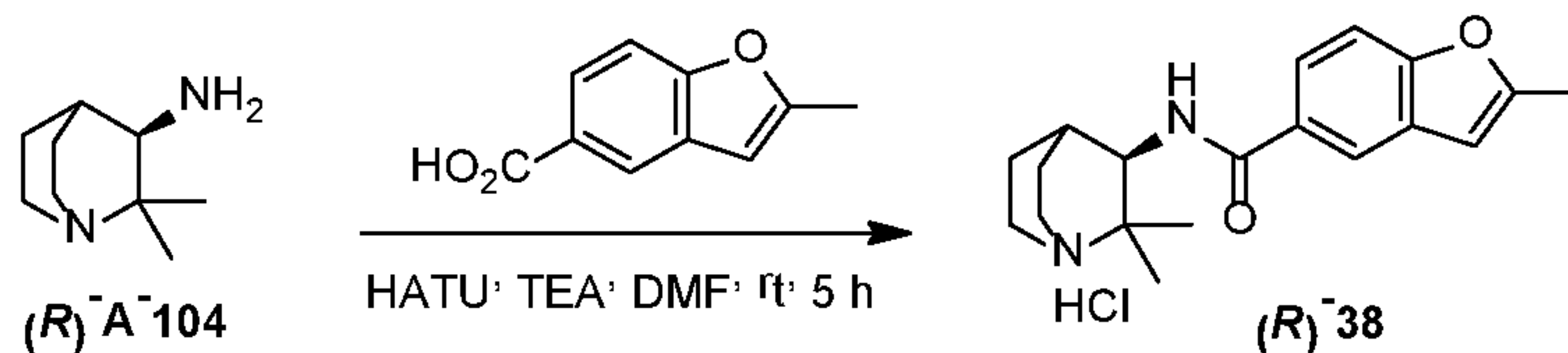
[00842] Example 37: (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)furo[3,2-*b*]pyridine-5-carboxamide hydrochloride ((*R*)-37)



[00843] Following general procedure B, **Compound (*R*)-37** was prepared from **compound B-138** (53 mg, 0.33 mmol) and **compound (*R*)-A-104** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 16-46% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)furo[3,2-*b*]pyridine-5-carboxamide hydrochloride (**compound (*R*)-37**) (45 mg, 46% yield) as a white solid: cSFC analytical (A) *t*_R=2.30 min., purity: 97.55%; LCMS (M): *t*_R=0.918 min., (ES⁺) *m/z* (M+H)⁺ = 300.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.34 (d, *J*=2.4 Hz, 1H), 8.25 (s, 2H), 7.20 (d, *J*=2.4 Hz, 1H), 4.29 (s, 1H), 3.74-3.73 (m, 2H), 3.38-3.31 (m, 2H), 2.38-2.31 (m, 1H), 2.30-2.29 (m, 1H), 2.19-2.12 (m, 2H), 2.02-1.99 (m, 1H), 1.77 (s, 3H), 1.51 (s, 3H).

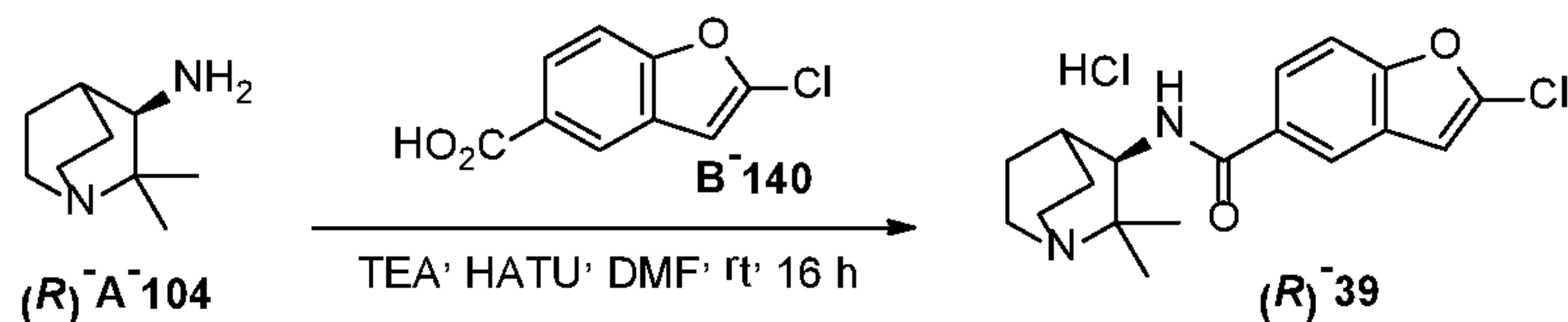
[00844] Example 38: (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzofuran-5-carboxamide hydrochloride ((*R*)-38)



[00845] Following general procedure B, **Compound (*R*)-38** was prepared from 2-methylbenzofuran-5-carboxylic acid (60 mg, 0.34 mmol) and **compound (*R*)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-pack ODS-AQ 150×30 mm, particle size: 5 μm; Mobile phase: 25-55% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzofuran-5-carboxamide hydrochloride (**compound (*R*)-38**) (20 mg, 17% yield) as a white solid: cSFC analytical (A) *t*_R=2.46 min., purity: 98.28%; LCMS (B): *t*_R=0.601 min., 313.2 *m/z* (M+1); ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 10.70 (s, 1H), 8.35 (d, *J*=8.0, 1H), 8.08 (s, 1H), 7.74 (q, 1H), 7.57 (d, *J*=8.8, 1H), 6.69 (s, 1H), 4.12 (d, *J*=7.2, 1H), 3.50-3.43 (m, 2H), 3.19-3.08 (m, 2H), 2.48 (s, 3H), 2.39-2.38 (m, 1H), 2.08-2.01 (m, 2H), 1.93-1.87 (m, 1H), 1.70-1.64 (m, 4H), 1.40 (s, 3H).

[00846] **Example 39:** (*R*)-2-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide hydrochloride ((*R*)-39)

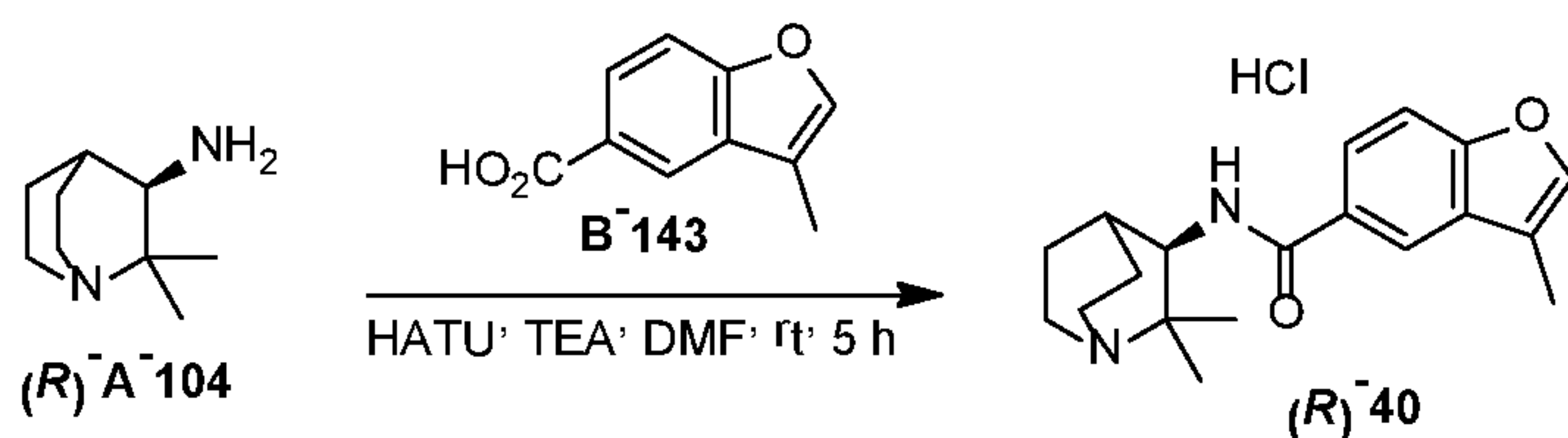


[00847] Following general procedure B, **Compound (*R*)-39** was prepared from **compound B-140** (0.11 g, 0.57 mmol) and **compound (*R*)-A-104** (80 mg, 0.52 mmol), with a reaction time of 16 hours.

[00848] The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 10 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-2-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide hydrochloride (**compound (*R*)-39**) (18 mg, 10% yield) as a white solid: cSFC analytical (A) t_R=2.51 min., purity: 98.66%; LCMS (S): t_R=1.24 min., (ES⁺) m/z (M+H)⁺ = 333.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.11 (s, 1H), 7.85 (dd, J₁=8.4 Hz, J₁=1.2 Hz 1H), 7.60 (d, J₁=8.8 Hz, 1H), 6.91 (s, 1H), 4.28 (s, 1H), 3.77-3.70 (m, 2H), 3.39-3.36 (m, 1H), 3.35-3.29 (m, 1H), 2.43-2.38 (m, 1H), 2.28-2.27 (m, 1H), 2.20-2.12 (m, 2H), 1.97-1.91 (m, 1H), 1.79 (s, 3H), 1.51 (s, 3H).

[00849] **Example 40:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzofuran-5-carboxamide hydrochloride ((*R*)-40)

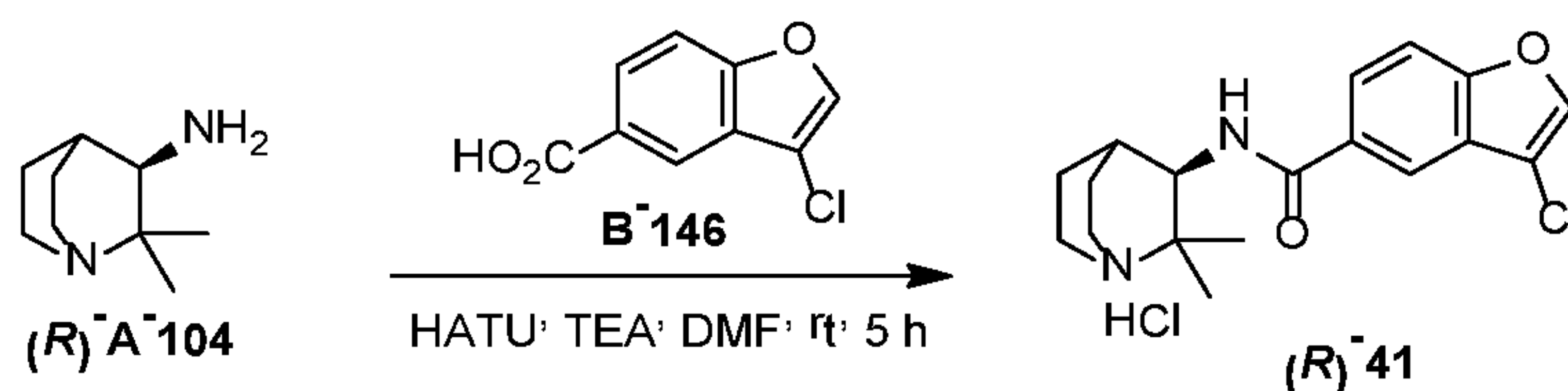


[00850] Following general procedure B, **Compound (*R*)-40** was prepared from **compound B-143** (69 mg, 0.39 mmol) and **compound (*R*)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours.

The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 10 μm; Mobile phase: 10-40% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzofuran-5-carboxamide hydrochloride (**compound (*R*)-40**) (61 mg, 54% yield) as a yellow solid: cSFC analytical (A) t_R=2.51 min., purity: 99.57%; LCMS (B): t_R=0.609 min., 313.2 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.14 (d, J=4 Hz, 1H), δ 7.83 (d, J₁=8 Hz, J₂=4 Hz, 1H), 7.65 (d, J=4 Hz, 1H), 7.54 (d, J=8 Hz, 1H), 4.28 (s, 1H), 3.73-3.70 (m, 2H), 3.35-3.34 (m, 2H), 2.41-2.40 (m, 1H), 2.32 (s, 3H), 2.31-2.28 (m, 1H), 2.18-2.11 (m, 2H), 1.97-1.90 (m, 1H), 1.78 (s, 3H), 1.50 (s, 3H).

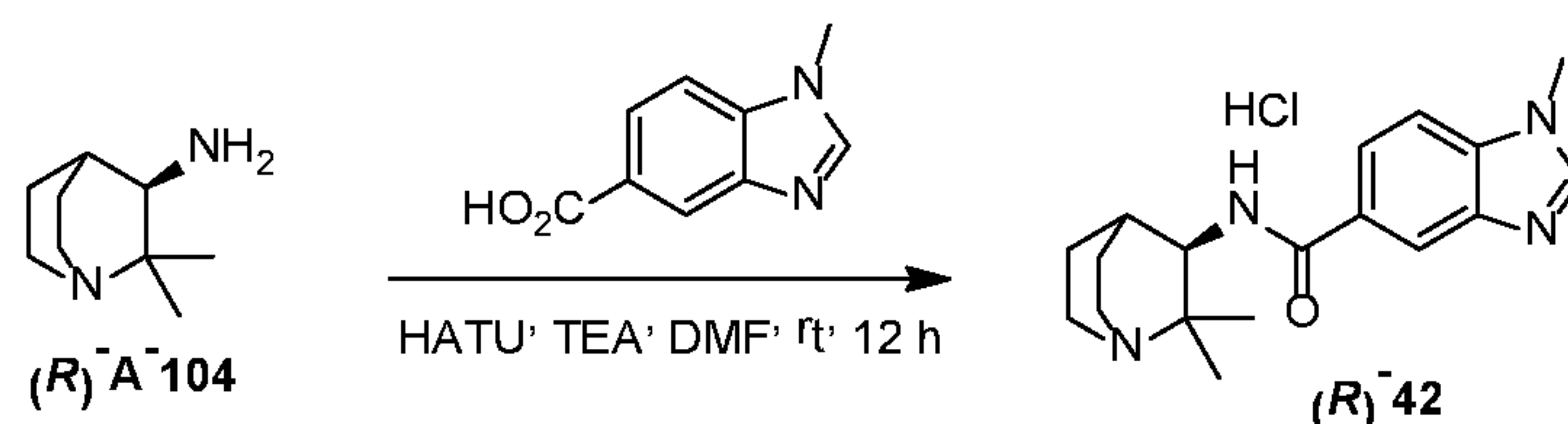
[00851] **Example 41:** (*R*)-3-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide hydrochloride ((*R*)-41)



[00852] Following general procedure B, **Compound (R)-41** was prepared from **compound B-146** (66 mg, 0.34 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μ m; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-3-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide hydrochloride (**compound (R)-41**) (20 mg, 17% yield) as a white solid: cSFC analytical (A) *t*_R=2.48 min., purity: 97.53%; LCMS (B): *t*_R=0.622 min., 333.1 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.18 (s, 1H), 8.06 (s, 1H), 7.95 (d, *J*=8.8, 1H), 7.67 (d, *J*=8.8, 1H), 4.30 (s, 1H), 3.75-3.68 (m, 2H), 3.40-3.35 (m, 2H), 2.42 (m, 1H), 2.30 (m, 1H), 2.29-2.10 (m, 2H), 1.98-1.92 (m, 1H), 1.80 (s, 3H), 1.53 (s, 3H).

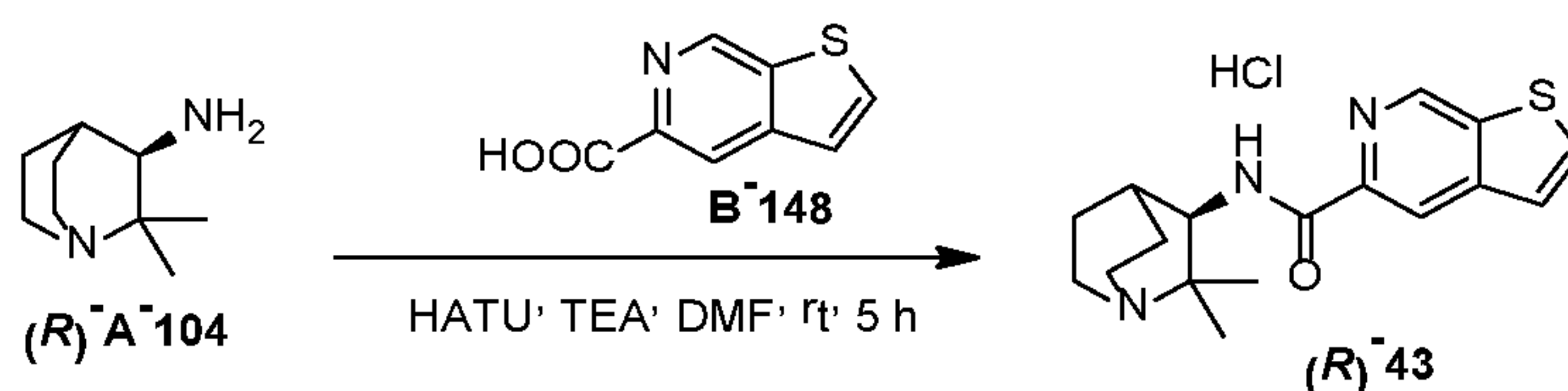
[00853] **Example 42: (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxamide hydrochloride ((*R*)-42)**



[00854] Following general procedure B, **Compound (R)-42** was prepared from 1-methyl-1H-benzo[d]imidazole-5-carboxylic acid (64 mg, 0.34 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μ m; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxamide hydrochloride (**compound (R)-42**) (20 mg, 17% yield) as a white solid: cSFC analytical (A) *t*_R=3.43 min., purity: 100.00%; LCMS (J): *t*_R=0.976 min., 313.1 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 9.57 (s, 1H), 8.43 (s, 1H), 8.23 (d, *J*=8.8, 1H), 8.08 (d, *J*=8.8, 1H), 4.32 (s, 1H), 4.22 (s, 3H), 3.76-3.72 (m, 2H), 2.47 (m, 1H), 2.32-2.31 (m, 1H), 2.20-2.11 (m, 2H), 2.01-1.93 (m, 1H), 1.80 (s, 3H), 1.55 (s, 3H).

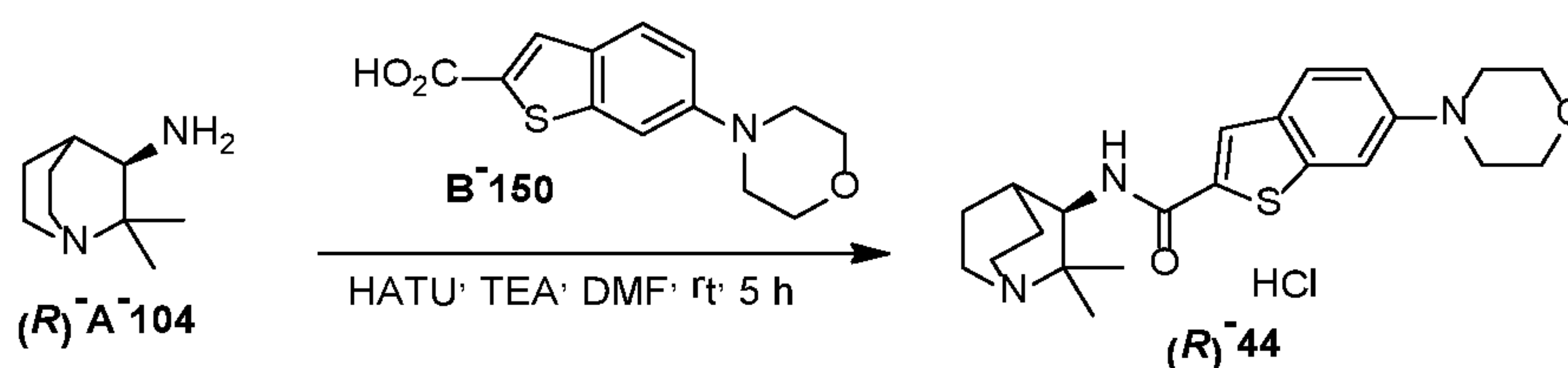
[00855] **Example 43: (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-*c*]pyridine-5-carboxamide ((*R*)-43)**



[00856] Following general procedure B, **Compound (R)-43** was prepared from **compound B-148** (70 mg, 0.39 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex SynergiC18 150×25mm, particle size: 10 µm; Mobile phase: 30-60% acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)]. The resulting solids were dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-*c*]pyridine-5-carboxamide hydrochloride (**compound (R)-43**) (35 mg, 31% yield) as a yellow solid: cSFC analytical (A) t_R=2.93 min., purity: 99.60%; LCMS (B): t_R=0.583 min., 316.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 9.60 (s, 1H), 9.09 (s, 1H), 8.84 (d, J=5.2Hz, 1H), 7.95 (d, J=5.6Hz, 1H), 4.38 (s, 1H), 3.80-3.75 (m, 2H), 3.42-3.36 (m, 2H), 2.51-2.50 (m, 1H), 2.36-2.35 (m, 1H), 2.29-2.16 (m, 2H), 2.03-1.97 (m, 1H), 1.81 (s, 3H), 1.57 (s, 3H).

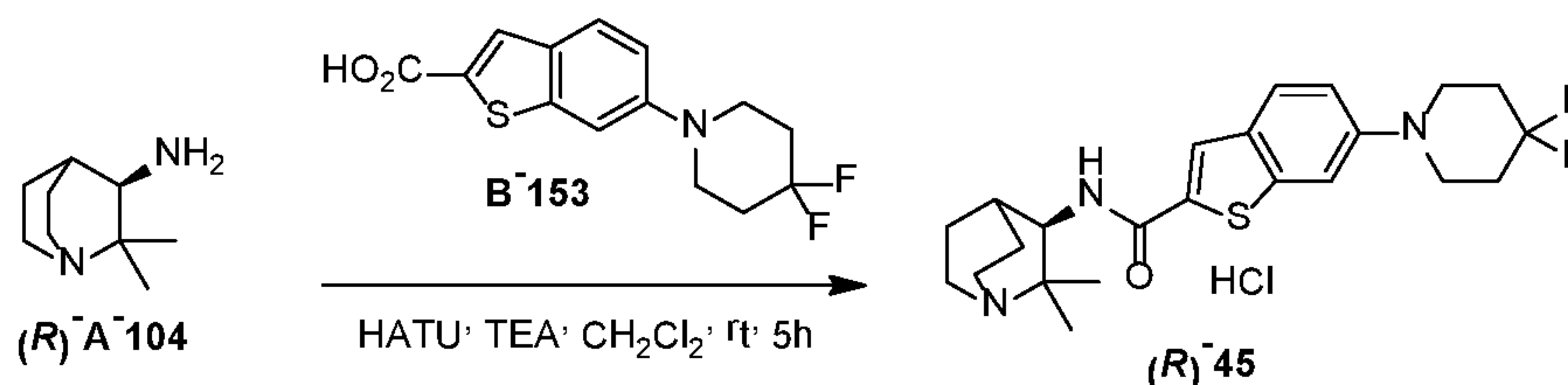
[00857] **Example 44:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-morpholinobenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-44)



[00858] Following general procedure B, **Compound (R)-44** was prepared from **compound B-150** (85 mg, 0.33 mmol) and **compound (R)-A-104** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-pack ODS-AQ C18 150×30 mm, particle size: 5 µm; Mobile phase: 20-50% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The combined fractions were treated with 0.2 M hydrochloric acid and lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-morpholinobenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-44**) (47 mg, 33% yield) as a white solid: cSFC analytical (A) t_R=3.74 min., purity: 98.92%; LCMS (K): t_R=1.328 min., (ES⁺) m/z (M+H)⁺ = 400.1; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 10.42 (s, 1H), 8.42 (d, J=7.6 Hz, 1H), 8.22 (s, 1H), 7.78 (d, J=8.8 Hz, 1H), 7.48 (s, 1H), 7.21 (d, J=8.8 Hz, 1H), 4.08 (d, J=7.6 Hz, 1H), 3.78 (m, 4H), 3.49 (m, 2H), 3.23 (t, J=4.4 Hz, 4H), 3.16-3.14 (m, 2H), 2.41 (m, 1H), 2.07 (m, 1H), 2.01 (m, 1H), 1.92-1.86 (m, 1H), 1.72-1.66 (m, 1H), 1.61 (s, 3H), 1.39 (s, 3H).

[00859] **Example 45:** (*R*)-6-(4,4-difluoropiperidin-1-yl)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-45)

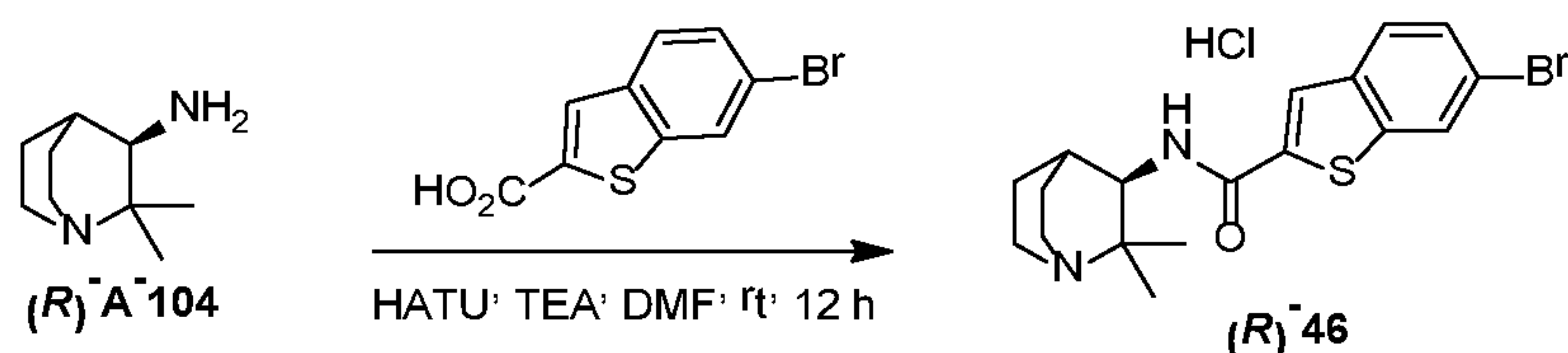


[00860] Following general procedure B, **Compound (R)-45** was prepared from **compound B-153** (70 mg, 0.24 mmol) and **compound (R)-A-104** (44 mg, 0.28 mmol), with a reaction time of 5 hours.

The product was purified by prep-HPLC [Instrument: GX-E; Column: Innoval C18 150×30 mm, particle size: 5 μm; Mobile phase: 9-39% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The solution was treated with 0.2 M hydrochloric acid solution and lyophilized to give:

(*R*)-6-(4,4-difluoropiperidin-1-yl)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (*R*)-45**) (38 mg, 34% yield) as a yellow solid: cSFC analytical (A) tR=3.41 min., purity: 100%; LCMS (N): tR=2.761 min., (ES⁺) m/z (M+H)⁺ = 434.1; ¹H-NMR (DMSO-d₆, 400 MHz): δ 10.45 (s, 1H), 8.43 (d, J=8.0 Hz, 1H), 8.23 (s, 1H), 7.77 (d, J=8.8 Hz, 1H), 7.55 (s, 1H), 7.24 (d, J=8.8 Hz, 1H), 4.08 (d, J=7.2 Hz, 1H), 3.58-3.44 (m, 6H), 3.18-3.10 (m, 2H), 2.41 (m, 1H), 2.11-1.86 (m, 7H), 1.76-1.60 (m, 4H), 1.38 (s, 3H).

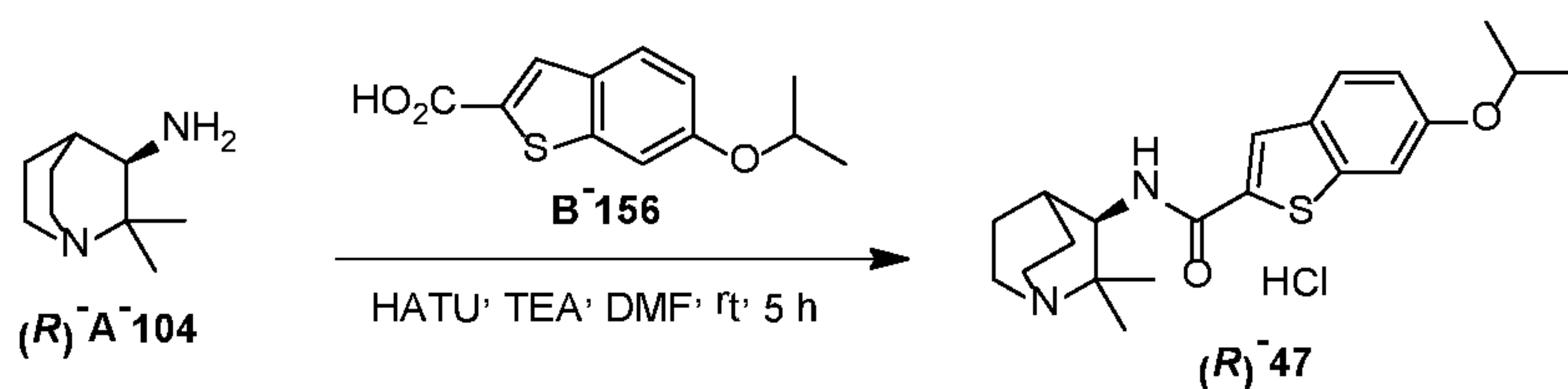
[00861] Example 46: (*R*)-6-bromo-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-46)



[00862] Following general procedure B, **Compound (R)-46** was prepared from 6-bromobenzo[b]thiophene-2-carboxylic acid (83 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 10 μm; Mobile phase: 14-44% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-6-bromo-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (*R*)-46**) (55 mg, 43% yield) as a white solid: cSFC analytical (A) tR=3.19 min., purity: 100%; LCMS (B): tR=0.714 min., (ES⁺) m/z (M+H)⁺ = 393.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.16 (s, 1H), 8.13 (s, 1H), 7.83 (d, J=8.4 Hz, 1H), 7.58 (dd, J₁=8.8 Hz, J₂=1.6, 1H), 4.25 (s, 1H), 3.73-3.66 (m, 2H), 3.36-3.31 (m, 2H), 2.41-2.40 (m, 1H), 2.27-2.26 (m, 1H), 2.17-2.10 (m, 2H), 1.96-1.94 (m, 1H), 1.74 (s, 3H), 1.48 (s, 3H).

[00863] Example 47: (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-isopropoxybenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-47)



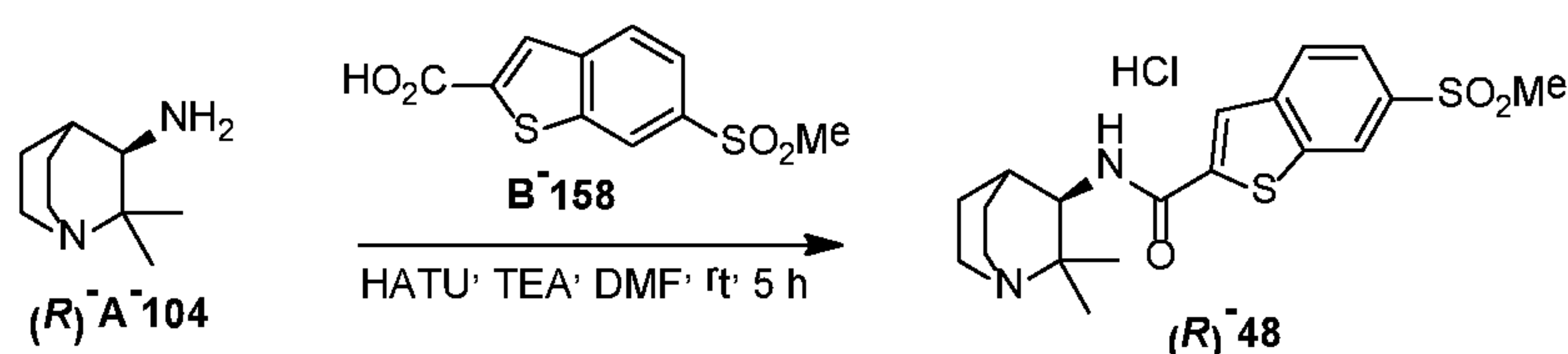
[00864] Following general procedure B, **Compound (R)-47** was prepared from **compound B-156** (77 mg, 0.33 mmol) and **compound (R)-A-104** (50 mg, 0.33 mmol), with a reaction time of 5 hours.

The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-pack ODS-AQ C18 150×30 mm, particle size: 5 µm; Mobile phase: 30-60% acetonitrile in H₂O (add 0.5% TFA, v/v)].

The combined fractions were treated with 0.2 M hydrochloric acid solution and lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-isopropoxybenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-47**) (63 mg, 48% yield) as a yellow solid: cSFC analytical (A) t_R=2.92 min., purity: 98.15%; LCMS (N): t_R=2.367 min., (ES⁺) m/z (M+H)⁺ = 373.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.02 (s, 1H), 7.76 (d, J=8.8 Hz, 1H), 7.42 (d, J=1.6 Hz, 1H), 7.02 (d, J=8.8, 2.0 Hz, 1H), 4.74-4.65 (m, 1H), 4.23 (s, 1H), 3.74-3.64 (m, 2H), 3.36-3.30 (m, 2H), 2.40-2.38 (m, 1H), 2.26-2.25 (m, 1H), 2.16-2.08 (m, 2H), 1.95-1.89 (m, 1H), 1.73 (s, 3H), 1.47 (s, 3H), 1.35 (d, J=6.0 Hz, 6H).

[00865] **Example 48:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(methylsulfonyl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-48)

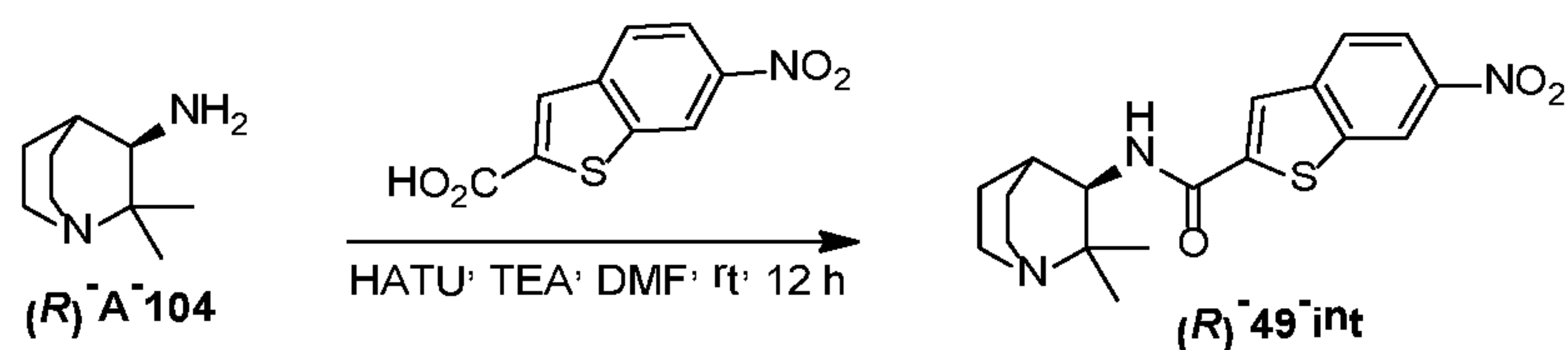


[00866] Following general procedure B, **Compound (R)-48** was prepared from **compound B-158** (83 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-pack ODS-AQ 150×30 mm, particle size: 5 µm; Mobile phase: 11-44% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The combined fractions were treated with 0.2 N HCl and lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(methylsulfonyl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-48**) (35 mg, 25% yield) as a white solid: cSFC analytical (A) t_R=3.27 min., purity: 100%; LCMS (M): t_R=1.003min., (ES⁺) m/z (M+H)⁺ = 393.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.62 (s, 1H), 8.29 (s, 1H), 8.16 (d, J=8.4 Hz, 1H), 7.97 (dd, J₁=8.4 Hz, J₂=1.2 Hz, 1H), 4.27 (s, 1H), 3.74-3.68 (m, 2H), 3.38-3.31 (m, 2H), 3.20 (s, 3H), 2.43 (m, 1H), 2.30-2.29 (m, 1H), 2.18-2.08 (m, 2H), 1.98-1.92 (m, 1H), 1.76 (s, 3H), 1.51 (s, 3H).

[00867] **Example 49:**

[00868] Preparation of (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-nitrobenzo[*b*]thiophene-2-carboxamide ((*R*)-49-int)

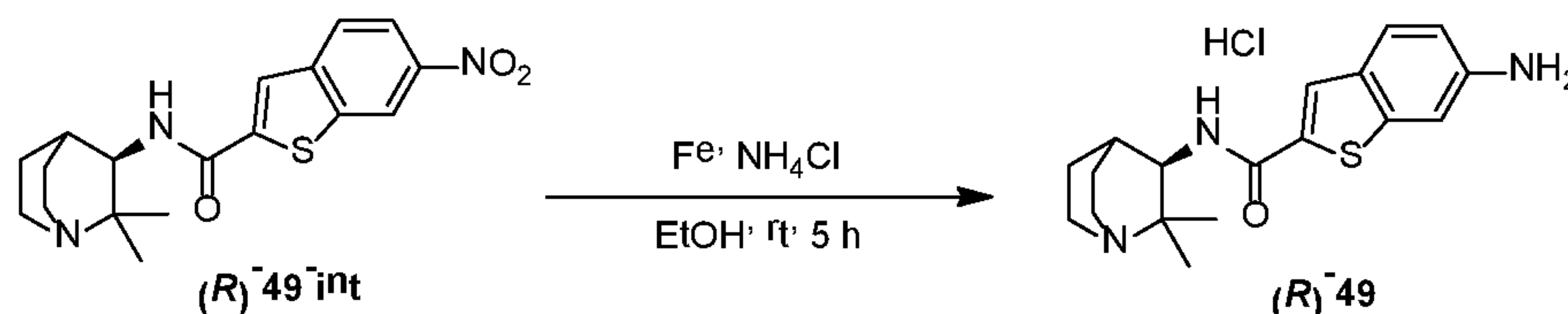


[00869] Following general procedure B, **Compound (R)-49-int** was prepared from 6-nitrobenzo[*b*]thiophene-2-carboxylic acid (72 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument:

GX-E; Column: Phenomenex SynergiC18 150×30 mm, particle size: 10 μm; Mobile phase: 10-40% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-nitrobenzo[*b*]thiophene-2-carboxamide (**compound (R)-49-int**) (45 mg, 39% yield) as a white solid.

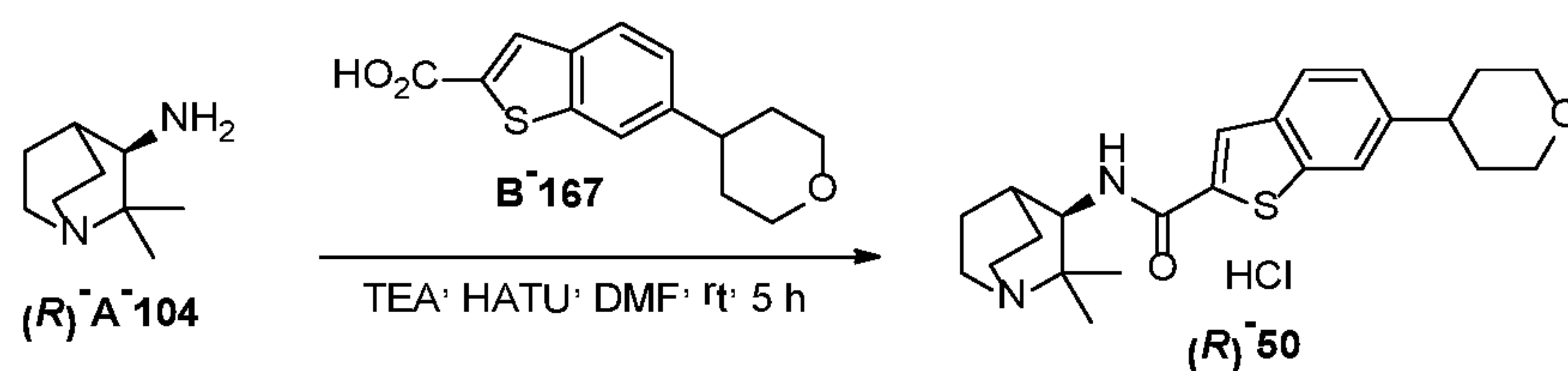
[00870] Preparation of (*R*)-6-amino-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**(R)-49**)



[00871] To a mixture of **compound (R)-49-int** (40 mg, 0.11 mmol) in EtOH (6 mL) was added iron (31 mg, 0.56 mmol) and saturated aqueous NH₄Cl (3 mL). The mixture was stirred at 25 °C for 5 hours. On completion, the mixture was filtered. The filtrate was concentrated in vacuo. The residue was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex SynergiC18 150×30 mm, particle size: 4 μm; Mobile phase: 10-40% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-6-amino-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-49**) (25 mg, 68% yield) as a white solid: cSFC analytical (C) t_R=2.24 min., purity: 100%; LCMS (M): t_R=0.812 min., (ES⁺) m/z (M+H)⁺ = 330.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.22 (s, 1H), 8.04 (d, J=8.4 Hz, 1H), 7.89 (s, 1H), 7.37 (dd, J₁=8.4 Hz, J₂=1.6 Hz, 1H), 4.26 (s, 1H), 3.73-3.71 (m, 2H), 3.38-3.31 (m, 2H), 2.43 (m, 1H), 2.28-2.27 (m, 1H), 2.17-2.16 (m, 2H), 1.97-1.1 (m, 1H), 1.75 (s, 3H), 1.50 (s, 3H).

[00872] **Example 50:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(tetrahydro-2*H*-pyran-4-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**(R)-50**)

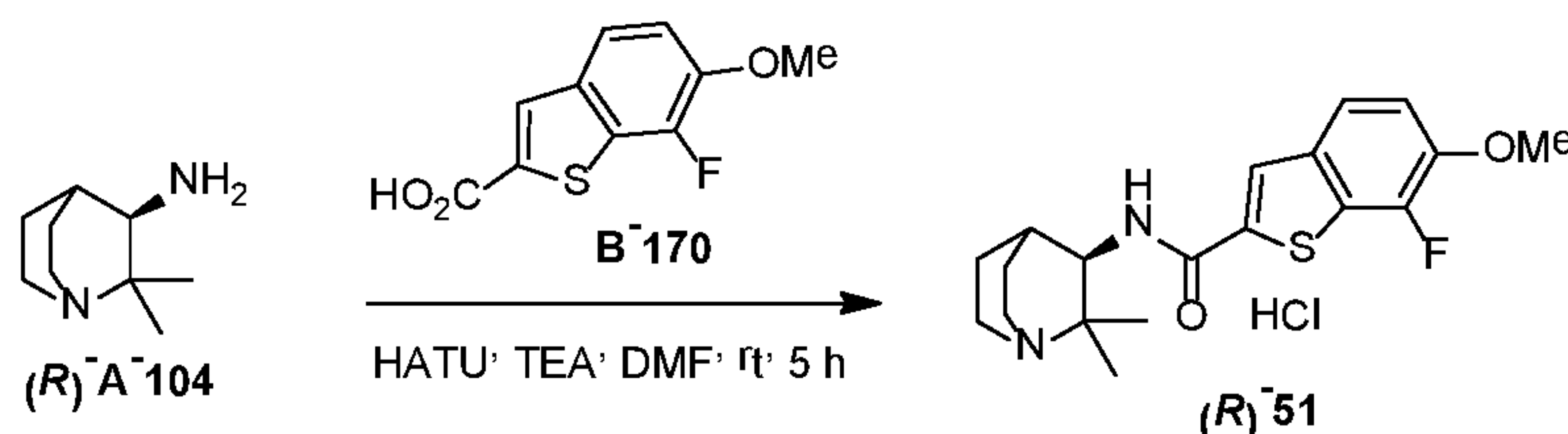


[00873] Following general procedure B, **Compound (R)-50** was prepared from **compound B-167** (54 mg, 0.33 mmol) and **compound (R)-A-104** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 16-46% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(tetrahydro-2*H*-pyran-4-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-50**) (50 mg, 51% yield) as a white solid: cSFC analytical (A) t_R=3.50 min., purity: 98.16%; LCMS (Y): t_R=0.750 min., (ES⁺) m/z (M+H)⁺ = 399.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.13 (s, 1H), 7.86 (d, J=8.4Hz, 1H), 7.80 (s, 1H), 7.36-7.34 (m, 1H), 4.24 (s, 1H), 4.07-4.04 (m, 2H), 3.72-3.67 (m, 2H), 3.61-3.55 (m, 2H), 3.36-3.31 (m, 2H), 2.94-2.93

(m, 1H), 2.42-2.31 (m, 1H), 2.26-2.25 (m, 1H), 2.15-2.12 (m, 2H), 1.96-1.81 (m, 5H), 1.74 (s, 3H), 1.50 (s, 3H).

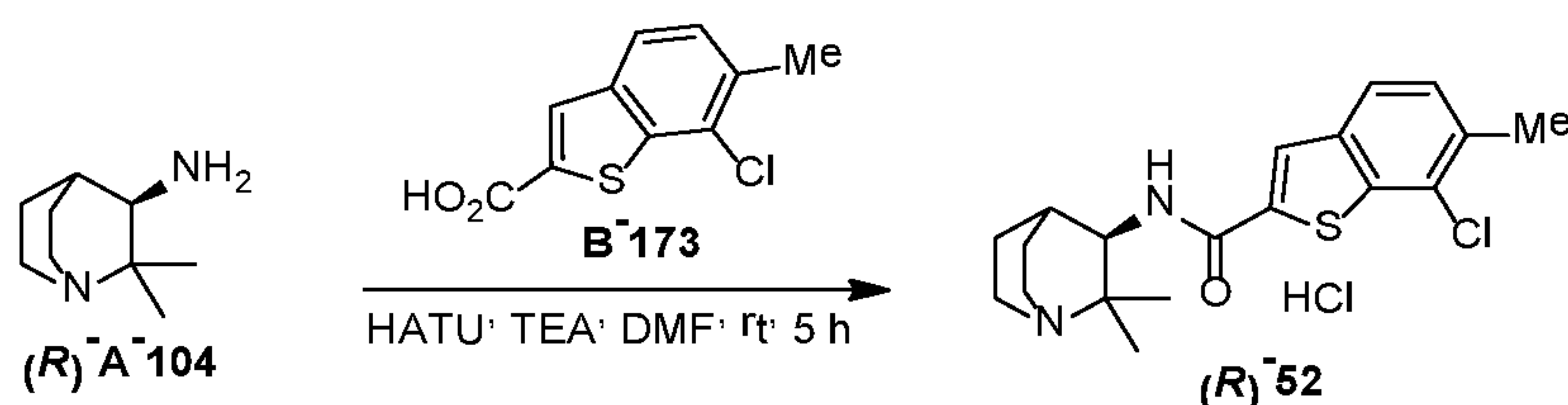
[00874] Example 51: (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methoxybenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-51)



[00875] Following general procedure B, **Compound (*R*)-51** was prepared from **compound B-170** (73 mg, 0.32 mmol) and **compound (*R*)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-pack ODS-AQ 150×30 mm, particle size: 5 μm; Mobile phase: 20-50% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The combined fractions were treated with 0.2 N HCl and lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methoxybenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (*R*)-51**) (25 mg, 19% yield) as a white solid: cSFC analytical (A) t_R=2.947 min., purity: 92.25%; LCMS (Y): t_R=0.849 min., (ES⁺) m/z (M+H)⁺ = 363.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.10 (d, J=3.2 Hz, 1H), 7.70 (d, J=8.4 Hz, 1H), 7.33 (t, J=8.0 Hz, 1H), 4.24 (s, 1H), 3.98 (s, 3H), 3.71-3.66 (m, 2H), 3.33 (m, 1H), 3.31 (m, 1H), 2.40-2.39 (m, 1H), 2.27-2.26 (m, 1H), 2.26-1.97 (m, 2H), 1.94-1.90 (m, 1H), 1.74 (m, 3H), 1.48 (s, 3H).

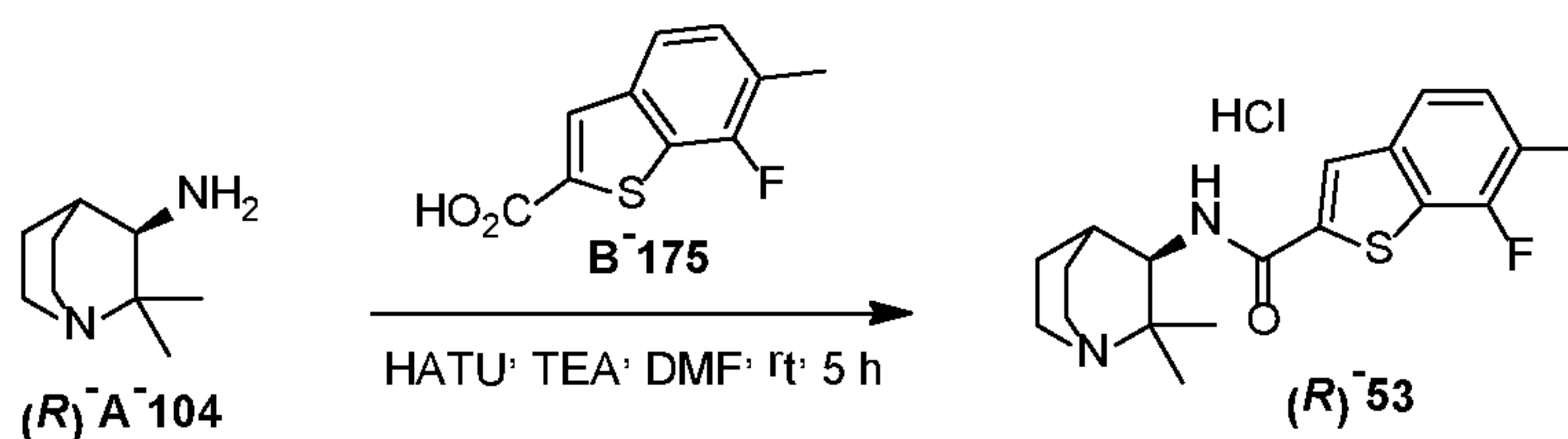
[00876] Example 52: (*R*)-7-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-52)



[00877] Following general procedure B, **Compound (*R*)-52** was prepared from **compound B-173** (73 mg, 0.32 mmol) and **compound (*R*)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-pack ODS-AQ 150×30 mm, particle size: 5 μm; Mobile phase: 25-55% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The combined fractions were treated with 0.2 N HCl and lyophilized to give:

(*R*)-7-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (*R*)-52**) (25 mg, 19% yield) as a white solid: cSFC analytical (A) t_R=3.026 min., purity: 97.65%; LCMS (Y): t_R=0.885 min., (ES⁺) m/z (M+H)⁺ = 363.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.15 (s, 1H), 7.77 (d, J=8.4 Hz, 1H), 7.40 (d, J=8.0 Hz, 1H), 4.26 (s, 1H), 3.73-3.69 (m, 2H), 3.36-3.34 (m, 1H), 3.31-3.28 (m, 1H), 2.53 (s, 3H), 2.28 (m, 1H), 2.27 (m, 1H), 2.17-2.11 (m, 2H), 2.10-1.94 (m, 1H), 1.75 (s, 3H), 1.48 (s, 3H).

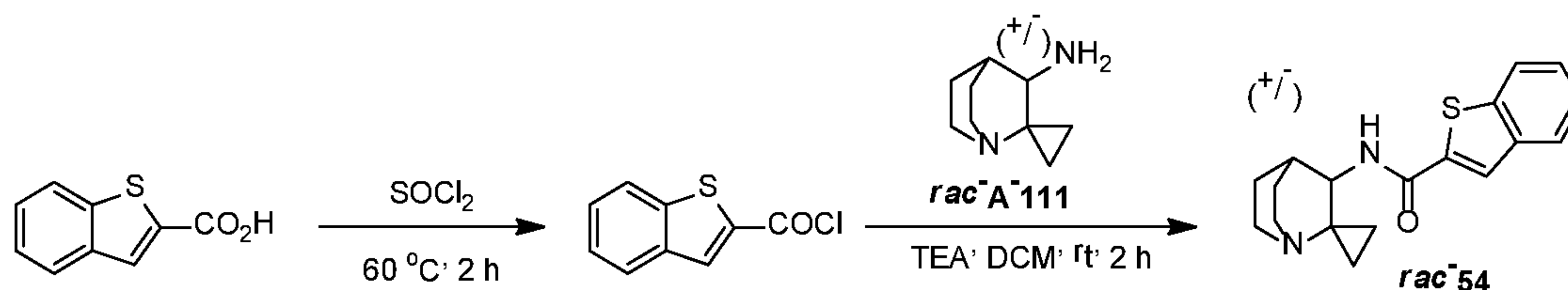
[00878] **Example 53:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-**53**)



[00879] Following general procedure B, **Compound (R)-53** was prepared from **compound B-175** (68 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 19-49% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-53**) (40 mg, 32% yield) as a white solid: cSFC analytical (A) t_R=2.728 min., purity: 96.99%; LCMS (Y): t_R=0.800 min., (ES⁺) m/z (M+H)⁺ = 347.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.14 (d, J=3.6 Hz, 1H), 7.64 (d, J=8.0 Hz, 1H), 7.33 (t, J=7.6 Hz, 1H), 4.25 (s, 1H), 3.73-3.66 (m, 2H), 3.37-3.31 (m, 2H), 2.42-2.41 (m, 4H), 2.28-2.27 (m, 1H), 2.18-2.10 (m, 2H), 1.94 (m, 1H), 1.75 (s, 3H), 1.49 (s, 3H).

[00880] **Example 54:** (+/-)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide (*rac*-**54**)



[00881] Following general procedure A, *rac*-**54** was prepared from benzo[*b*]thiophene-2-carboxylic acid and *rac*-**A-111** (1.32 g, 8.6 mmol). The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 150×25 mm, particle size: 10 μm; Mobile phase: 30-60% acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)] to give *rac*-**54** (1.6 g, 70% yield) as a white solid. LCMS: (ES⁺) m/z (M+H)⁺ = 313.1.

[00882] Chiral Separation:

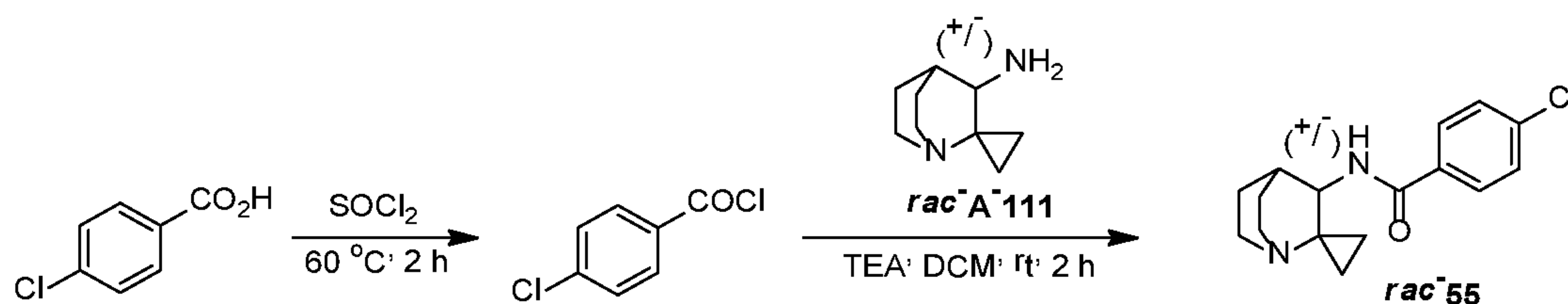
[00883] *Rac*-**54** (0.70 g, 0.22 mmol) in 5 mL of methanol was separated by SFC (Instrument: SFC 80; Column: OD-10 μm; Mobile phase: 60% methanol (0.01% NH₃ · H₂O) in CO₂) according to general procedure A to give:

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide-enantiomer1 hydrochloride (**compound 54a**) (0.33 g, 47% yield) as a white solid: cSFC analytical (A) t_R=3.15 min., purity: 99.77%; LCMS (W): t_R=0.990 min., (ES⁺) m/z (M+H)⁺ = 313.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.18 (s, 1H), 7.94-7.91 (m, 2H), 7.48-7.43 (m, 2H), 4.57 (d, J=2.4 Hz,

1H), 3.74-3.58 (m, 1H), 3.57-3.42 (m, 3H), 2.44-2.43 (m, 1H), 2.35-1.95 (m, 4H), 1.40-1.18 (m, 4H); and

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer2 hydrochloride (**compound 54b**) (0.33 g, 47% yield) as a white solid: cSFC analytical (A) tR=2.44 min., purity: 99.79%; LCMS (W): tR=0.986 min., (ES⁺) m/z (M+H)⁺ = 313.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.17 (s, 1H), 7.94-7.91 (m, 2 H), 7.48-7.43 (m, 2H), 4.57 (d, J=2.4 Hz, 1H), 3.74-3.57 (m, 1H), 3.56-3.42 (m, 3H), 2.45-2.43 (m, 1H), 2.35-1.98 (m, 4H), 1.40-1.18 (m, 4H).

[00884] **Example 55:** (+/-)-4-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide (*rac*-55)



[00885] Following general procedure A, *rac*-55 was prepared from 4-chlorobenzoic acid and *rac*-A-111 (0.45 g, 2.5 mmol). The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 150×25 mm, particle size: 10 μm; Mobile phase: 30-60% acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)] to give *rac*-55 (0.36 g, 49% yield) as a white solid. LCMS: (ES⁺) m/z (M+H)⁺ = 291.2.

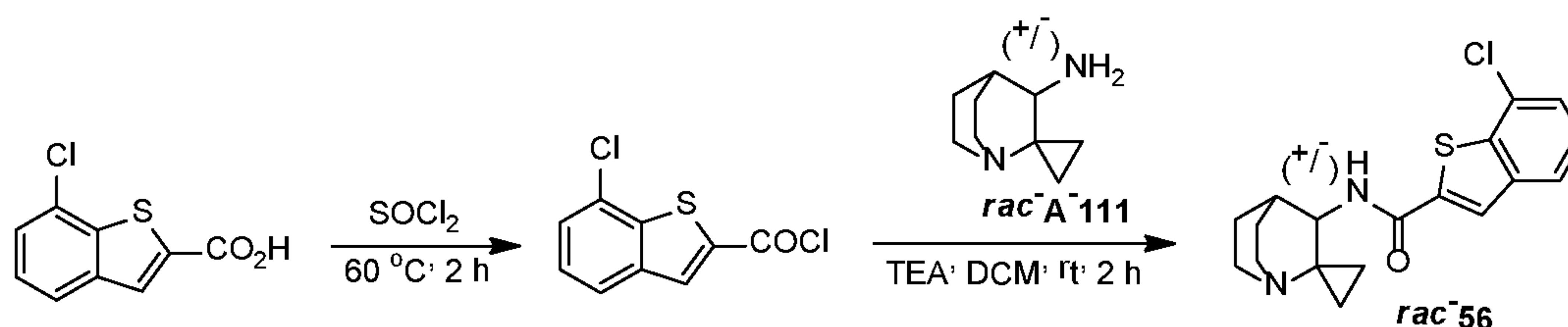
[00886] Chiral Separation:

[00887] *Rac*-55 (0.12 g, 0.41 mmol) in 3 mL of methanol was separated by SFC (Instrument: SFC 80; Column: OD-250×30mm, I.D., 10 μm; Mobile phase: 40% ethanol (0.01% NH₃ · H₂O) in CO₂) according to general procedure A to give:

4-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide -enantiomer1 hydrochloride (**compound 55a**) (60 mg, 50% yield) as a white solid : cSFC analytical (A) tR: 2.39 min., purity: 98.47%; LCMS (M): tR=0.888 min., (ES⁺) m/z (M+H)⁺ = 291.0; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 10.16 (s, 1H), 8.55 (d, J=8.8 Hz, 1H), 7.87 (d, J=8.8 Hz, 2H), 7.57 (d, J=8.8 Hz, 2H), 4.36 (d, J=5.6 Hz, 1H), 3.52-3.28 (m, 3H), 2.25-1.74 (m, 5H), 1.31-1.26 (m, 3H), 1.03-0.97 (m, 2H); and

4-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide -enantiomer2 hydrochloride (**compound 55b**) (60 mg, 50% yield) as a white solid : cSFC analytical (A) tR: 1.85 min., purity: 99.15%; LCMS (M): tR=0.898 min., (ES⁺) m/z (M+H)⁺ = 291.0; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 10.54 (s, 1H), 8.56 (d, J=8.0 Hz, 1H), 7.88 (d, J=8.8 Hz, 2H), 7.55 (d, J=8.8 Hz, 2H), 4.35 (dd, J₁=8.0Hz, J₂=2.8Hz, 1H), 3.54-3.23 (m, 3H), 2.25-1.70 (m, 5H), 1.34-1.30 (m, 3H), 1.03-0.94 (m, 2H).

[00888] **Example 56:** (+/-)-7-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide (*rac*-56)



[00889] Following general procedure A, *rac*-56 was prepared from 7-chlorobenzo[b]thiophene-2-carboxylic acid and *rac*-A-111 (0.14 g, 0.93 mmol). The product was purified by prep-HPLC

[Instrument: GX-A; Column: Phenomenex Gemini C18 150×25 mm, particle size: 10 μm; Mobile phase: 45-75% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give *rac*-56 (0.15 g, 46% yield) as a white solid. LCMS: (ES⁺) *m/z* (M+H)⁺ = 347.1.

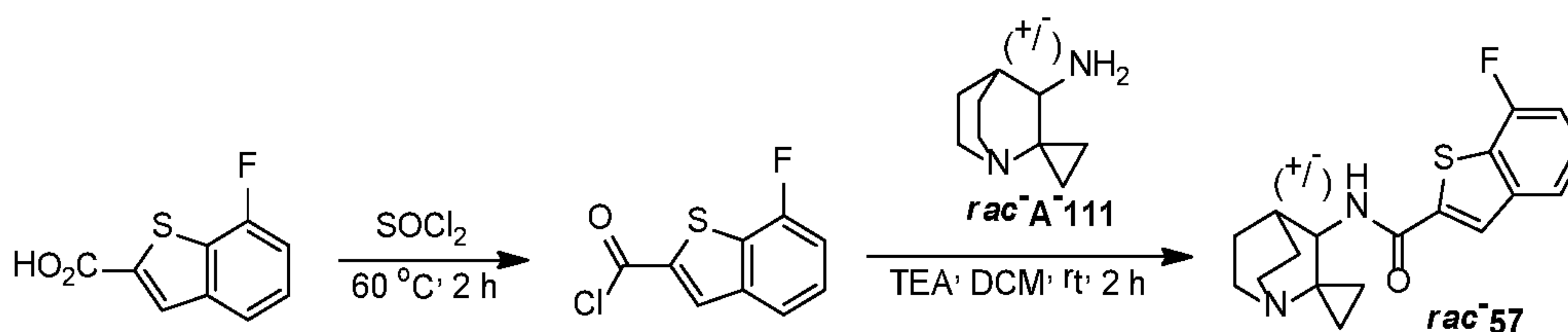
[00890] Chiral Separation:

[00891] *Rac*-56 (0.15 g, 0.43 mmol) in 5 mL of methanol was separated by SFC (Instrument: SFC 80; Column: Chiralpak OD-H 250×30 mm I.D., 10 μm; Mobile phase: 55% ethanol (0.01% NH₃·H₂O) in CO₂) according to general procedure A. The compounds were not treated with HCl but rather were isolated as the free bases:

7-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer1 (**compound 56a**) (62 mg, 41% yield) as a white solid: cSFC analytical (A) tR=2.59 min., purity: 100%; LCMS (G): tR=2.699 min., (ES⁺) *m/z* (M+H)⁺ = 347.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.17 (s, 1H), 7.87 (d, J=7.6 Hz, 1H), 7.50-7.42 (m, 2H), 4.21 (d, J=1.6 Hz, 1H), 3.28-3.25 (m, 1H), 3.08-3.07 (m, 1H), 2.93-2.85 (m, 2H), 2.11 (m, 1H), 2.01-1.93 (m, 1H), 1.87-1.84 (m, 2H), 1.61-1.53 (m, 1H), 0.91-0.87 (m, 2H), 0.78-0.75 (m, 1H), 0.70-0.64 (m, 1H); and

7-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer2 (**compound 56b**) (62 mg, 41% yield) as a white solid : cSFC analytical (B) tR=3.71 min., purity: 99.79%; LCMS (G): tR=2.697 min., (ES⁺) *m/z* (M+H)⁺ = 347.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.19 (s, 1H), 7.88 (d, J=7.6 Hz, 1H), 7.52-7.44 (m, 2H), 4.23 (d, J=2.0 Hz, 1H), 3.29-3.28 (m, 1H), 3.11-3.07 (m, 1H), 2.97-2.87 (m, 2H), 2.14-2.13 (m, 1H), 2.03-1.96 (m, 1H), 1.90-1.86 (m, 2H), 1.63-1.55 (m, 1H), 0.95-0.89 (m, 2H), 0.80-0.77 (m, 1H), 0.72-0.70 (m, 1H).

[00892] **Example 57:** (+/-)-7-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide (*rac*-57)



[00893] Following general procedure A, *rac*-**57** was prepared from benzo[b]thiophene-2-carboxylic acid and *rac*-**A-111** (0.22 g, 1.4 mmol). The product was purified by prep-HPLC [Instrument: GX-C; Column: Phenomenex Gemini C18 150×30 mm, particle size: 5 μm; Mobile phase: 35-65% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give *rac*-**57** (0.16 g, 34% yield) as a white solid. LCMS: (ES⁺) m/z (M+H)⁺ = 331.0.

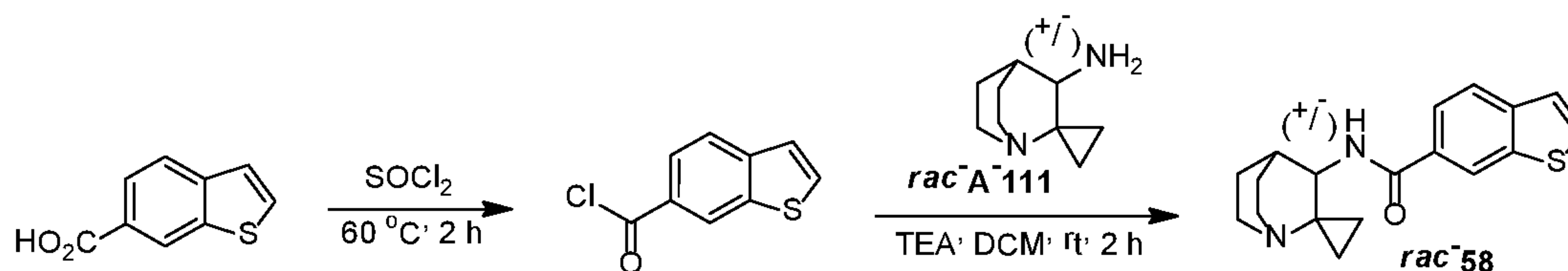
[00894] Chiral Separation:

[00895] *Rac*-**57** (0.16 g, 0.48 mmol) in 3 mL of methanol was separated by SFC (Instrument: SFC 80; Column: AD-10 μm; Mobile phase: 30% methanol (0.01% NH₃·H₂O) in CO₂) according to general procedure A to give:

7-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer1 hydrochloride (**compound 57a**) (0.02 g, 13% yield) as a white solid : cSFC analytical (A) tR: 2.22 min., purity: 99.96%; LCMS (N): tR: 1.994 min., (ES⁺) m/z (M+H)⁺ = 331.0; ¹H-NMR (MeOD, 400 MHz): δ 8.27 (d, J=3.6 Hz, 1H), 7.54 (d, J=8 Hz, 1H), 7.46-7.40 (m, 1H), 7.21-7.17 (m, 1H), 4.56 (d, J=3.6 Hz, 1H), 3.79-3.72 (m, 1H), 3.56-3.54 (m, 1H), 3.49-3.40 (m, 2H), 2.43-2.42 (m, 1H), 2.38-2.33 (m, 1H), 2.20-2.13 (m, 2H), 2.02-1.94 (m, 1H), 1.45-1.39 (m, 1H), 1.35-1.34 (m, 1H), 1.26-1.24 (m, 1H), 1.18-1.15 (m, 1H); and

7-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer2 hydrochloride (**compound 57b**) (0.02 g, 13% yield) as a white solid : cSFC analytical (A) tR: 3.11 min., purity: 98.46%; LCMS (N): tR: 2.101 min., (ES⁺) m/z (M+H)⁺ = 331.0; ¹H-NMR (MeOD, 400 MHz): δ 8.23 (d, J=3.2 Hz, 1H), 7.76 (d, J=8 Hz, 1H), 7.48-7.43 (m, 1H), 7.24-7.20 (m, 1H), 4.57 (d, J=2.4 Hz, 1H), 3.76-3.71 (m, 1H), 3.58-3.57 (m, 1H), 3.49-3.42 (m, 2H), 2.46-2.44 (m, 1H), 2.38-2.33 (m, 1H), 2.23-2.17 (m, 2H), 2.00-1.95 (m, 1H), 1.39-1.36 (m, 1H), 1.29-1.27 (m, 1H), 1.26-1.24 (m, 1H), 1.21-1.19 (m, 1H).

[00896] **Example 58:** (+/-)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide (*rac*-**58**)



[00897] Following general procedure A, *rac*-**58** was prepared from benzo[b]thiophene-6-carboxylic acid and *rac*-**A-111** (0.15 g, 0.99 mmol). The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 150×25 mm, particle size: 10 μm; Mobile phase: 25-55% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give *rac*-**58** (70 mg, 23% yield) as a white solid. LCMS: (ES⁺) m/z (M+H)⁺ = 313.2.

[00898] Chiral Separation:

[00899] *Rac*-**58** (70 mg, 0.22 mmol) in 3 mL of methanol was separated by SFC (Instrument: SFC 80; Column: Chiralpak OD-H 250×30 mm I.D., 10 μm; Mobile phase: 50% ethanol (0.01% NH₃·H₂O)

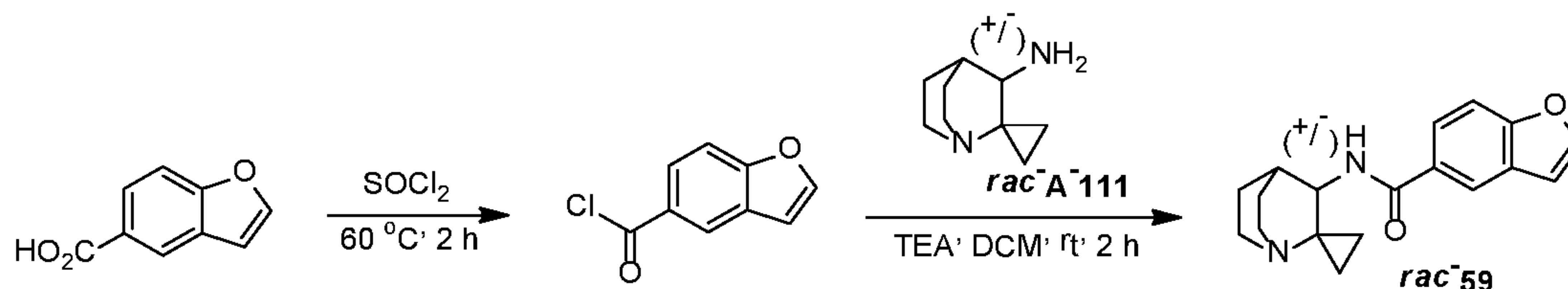
in CO₂) according to general procedure A. The compounds were not treated with HCl but rather were isolated as the free bases:

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide-enantiomer1 (**compound 58a**) (20 mg, 29% yield) as a white solid: cSFC analytical (A) tR=2.55 min., purity: 100%; LCMS (G): tR=2.230 min., (ES⁺) m/z (M+H)⁺ = 313.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.40 (s, 1H), 7.92 (d, J=8.4 Hz, 1H), 7.81-7.76 (m, 2H), 7.45 (d, J=5.6 Hz, 1H), 4.23 (d, J=2.0 Hz, 1H), 3.27-3.21 (m, 1H), 3.08-3.06 (m, 1H), 2.90-2.84 (m, 2H), 2.12-2.11 (m, 1H), 2.00-1.94 (m, 1H), 1.90-1.84 (m, 2H), 1.58-1.51 (m, 1H), 0.91-0.85 (m, 2H), 0.75-0.66 (m, 2H); and

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide-enantiomer2 (**compound 58b**) (19 mg, 27% yield) as a white solid : cSFC analytical (A) tR=3.32 min., purity: 98.60%; LCMS (G): tR=2.225 min., (ES⁺) m/z (M+H)⁺ = 313.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.40 (s, 1H), 7.92 (d, J=8.8 Hz, 1H), 7.81-7.76 (m, 2H), 7.45 (d, J=5.6 Hz, 1H), 4.23 (d, J=1.6 Hz, 1H), 3.28-3.23 (m, 1H), 3.11-3.06 (m, 1H), 2.90-2.84 (m, 2H), 2.12-2.11 (m, 1H), 1.99-1.94 (m, 1H), 1.89-1.80 (m, 2H), 1.58-1.54 (m, 1H), 0.91-0.85 (m, 2H), 0.77-0.66 (m, 2H).

[00900] Example 59:

[00901] Preparation of (+/-)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide (**rac-59**)



[00902] Following general procedure A, **rac-59** was prepared from benzofuran-5-carboxylic acid and **rac-A-111** (0.19 g, 1.2 mmol). The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 150×25 mm, particle size: 10 μm; Mobile phase: 22-52% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give **rac-59** (0.10 g, 27% yield) as a white solid. LCMS: (ES⁺) m/z (M+H)⁺ = 297.2.

[00903] Chiral Separation:

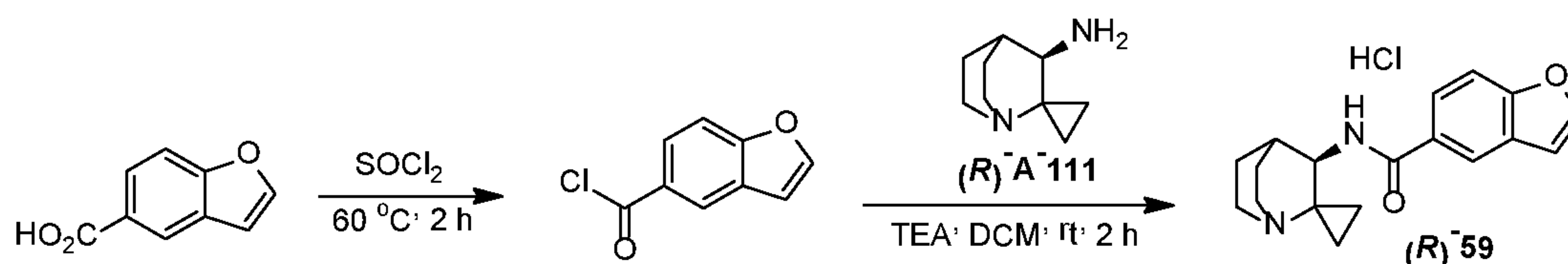
[00904] **Rac-59** (0.10 g, 0.34 mmol) in 4 mL of methanol was separated by SFC (Instrument: SFC 80; Column: Chiralpak AD-H 250×30 mm I.D., 10 μm; Mobile phase: 30% ethanol (0.01% NH₃·H₂O) in CO₂) according to general procedure A. The compounds were not treated with HCl but rather were isolated as the free bases:

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide-enantiomer1 (**compound 59a**) (38 mg, 38% yield) as a white solid: cSFC analytical (G) tR=2.28 min., purity: 99.03%; LCMS (G): tR=2.010 min., (ES⁺) m/z (M+H)⁺ = 297.2; ¹H-NMR (CD₃OD, 400 MHz): δ 8.11 (s, 1H), 7.85 (d, J=1.6 Hz, 1H), 7.77 (d, J=8.8 Hz, 1H), 7.57 (d, J=8.8 Hz, 1H), 6.95 (s,

1H), 4.21 (s, 1H), 3.26-3.21 (m, 1H), 3.07-3.04 (m, 1H), 2.91-2.84 (m, 2H), 2.11-2.10 (m, 1H), 1.99-1.94 (m, 1H), 1.86-1.80 (m, 2H), 1.58-1.50 (m, 1H), 0.90-0.85 (m, 2H), 0.74-0.65 (m, 2H); and

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide-enantiomer2 (**compound 59b**) (37 mg, 37% yield) as a white solid : cSFC analytical (G) tR=2.55 min., purity: 97.24%; LCMS (G): tR=2.008 min., (ES⁺) m/z (M+H)⁺ = 297.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.11 (s, 1H), 7.85 (d, J=1.6 Hz, 1H), 7.77 (d, J=8.8 Hz, 1H), 7.57 (d, J=8.8 Hz, 1H), 6.95 (s, 1H), 4.21 (s, 1H), 3.26-3.21 (m, 1H), 3.07-3.04 (m, 1H), 2.91-2.84 (m, 2H), 2.11-2.10 (m, 1H), 1.96-1.94 (m, 1H), 1.86-1.80 (m, 2H), 1.58-1.50 (m, 1H), 0.90-0.85 (m, 2H), 0.74-0.65 (m, 2H).

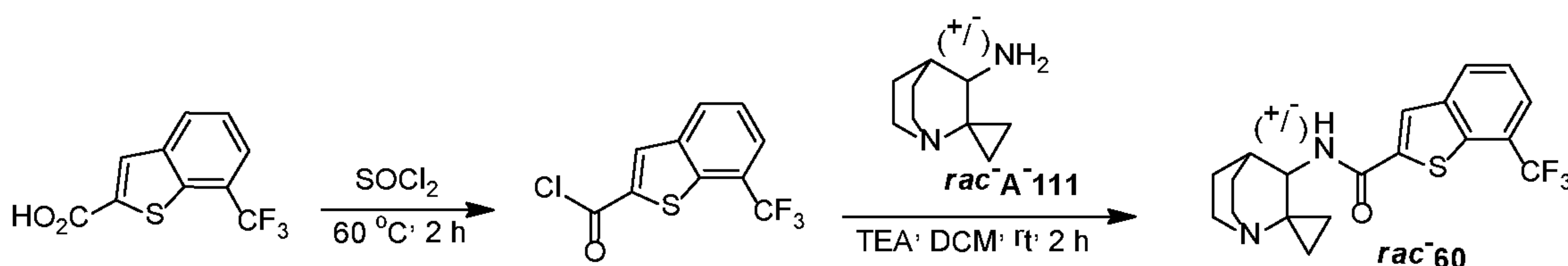
[00905] Preparation of (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide hydrochloride ((*R*)-59)



[00906] A mixture of benzofuran-5-carboxylic acid (0.25 g, 1.5 mmol) in thionyl chloride (3 mL) was stirred at 60 °C for 2 hours. On completion, the solution was concentrated in vacuo to give the acid chloride, which was used directly without further purification. This material (1.1 eq) was added to a mixture of **compound (R)-A-111** (0.20 g, 1.3 mmol) and triethylamine (0.27 g, 2.6 mmol) in dichloromethane (5 mL) at room temperature. The mixture was stirred at this temperature for 2 hours. On completion, the reaction was filtered, and the resulting filtrate was concentrated and purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 4-34% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide hydrochloride (**compound (R)-59**) (0.22 g, 57% yield) as white solid: cSFC analytical (A) tR=2.05 min., purity: 97.22%; LCMS (Z): tR=1.424 min., (ES⁺) m/z (M+H)⁺ = 297.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.17 (d, J=1.6 Hz, 1H), 7.88 (d, J=2.0 Hz, 1H), 7.81 (dd, J₁=8.4 Hz, J₂=1.6 Hz, 1H), 7.59 (d, J=8.8 Hz, 1H), 6.96 (d, J=1.2 Hz, 1H), 4.58 (d, J=2.4 Hz, 1H), 3.70-3.68 (m, 1H), 3.57-3.56 (m, 1H), 3.46-3.42 (m, 2H), 2.46-2.44 (m, 1H), 2.32-2.31 (m, 1H), 2.22-2.18 (m, 2H), 1.99-1.98 (m, 1H), 1.42-1.39 (m, 1H), 1.30-1.20 (m, 3H).

[00907] **Example 60:** (+/-)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide (*rac*-60)



[00908] Following general procedure A, *rac*-60 was prepared from 7-(trifluoromethyl)benzo[b]thiophene-2-carboxylic acid and *rac*-A-111 (0.10 g, 0.65 mmol). The

product was purified by prep-HPLC [Instrument: GX-C; Column: Phenomenex Gemini C18 150×30 mm, particle size: 5 µm; Mobile phase: 35-65% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give *rac*-**60** (0.18 g, 72% yield) as a white solid. LCMS: (ES⁺) m/z (M+H)⁺ = 381.4.

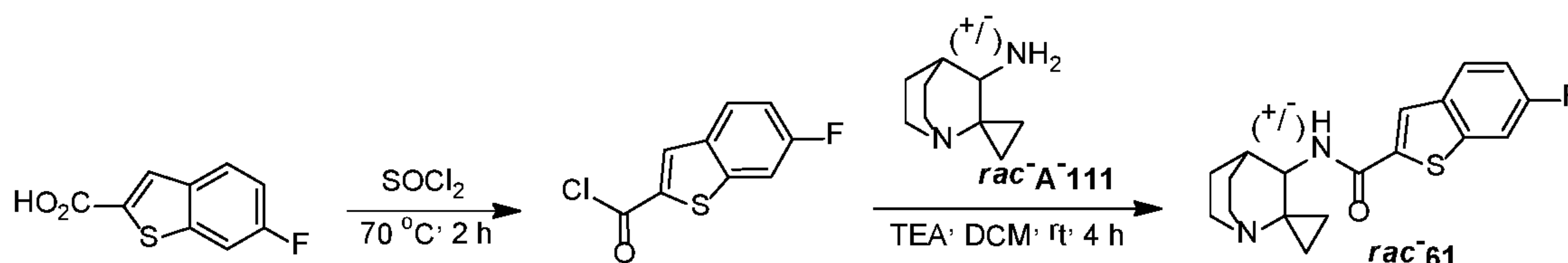
[00909] Chiral Separation:

[00910] *Rac*-**60** (0.18 g, 0.47 mmol) in 3 mL of ethanol was separated by SFC (Instrument: SFC 80; Column: Chiralpak OD-H 250 × 25 mm I.D., 10 µm; Mobile phase: 60% ethanol (0.1% NH₃·H₂O) in CO₂) according to general procedure A. The compounds were not treated with HCl but rather were isolated as the free bases:

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide-enantiomer1 (**compound 60a**) (86 mg, 48% yield) as a white solid: cSFC analytical (A) t_R=2.00 min., purity: 99.80%; LCMS (J): t_R=1.470 min., (ES⁺) m/z (M+H)⁺ = 381.4; ¹H-NMR (CD₃OD-d₄, 400 MHz): δ 8.25 (s, 1H), 8.19 (d, J=7.2 Hz, 1H), 7.83 (d, J=7.2 Hz, 1H), 7.63 (t, J=7.2 Hz, 1H), 4.23 (s, 1H), 3.27 (m, 1H), 3.10-3.08 (m, 1H), 2.95-2.85 (m, 2H), 2.13 (s, 1H), 2.00-1.87 (m, 3H), 1.58 (m, 1H), 0.91 (m, 2H), 0.82-0.69 (m, 2H); and

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide-enantiomer2 (**compound 60b**) (78 mg, 43% yield) as a white solid : cSFC analytical (A) t_R=3.18 min., purity: 99.89%; LCMS (J): t_R=1.470 min., (ES⁺) m/z (M+H)⁺ = 381.4; ¹H-NMR (CD₃OD-d₄, 400 MHz): δ 8.24 (s, 1H), 8.18 (d, J=8.0 Hz, 1H), 7.82 (d, J=7.6 Hz, 1H), 7.63 (t, J=7.6 Hz, 1H), 4.23 (s, 1H), 3.28-3.26 (m, 1H), 3.11-3.06 (m, 1H), 2.95-2.84 (m, 2H), 2.13 (s, 1H), 2.06-1.86 (m, 3H), 1.62-1.58 (m, 1H), 0.9-0.76 (m, 2H), 0.70-0.65 (m, 2H).

[00911] **Example 61:** (+/-)-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide (*rac*-**61**)



[00912] Following general procedure A, *rac*-**61** was prepared from 6-fluorobenzo[b]thiophene-2-carboxylic acid and *rac*-**A-111** (0.20 g, 1.3 mmol). The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 150×25mm, particle size: 10 µm; Mobile phase: 40-70% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give *rac*-**61** (0.16 g, 40% yield) as a green solid.

[00913] Chiral Separation:

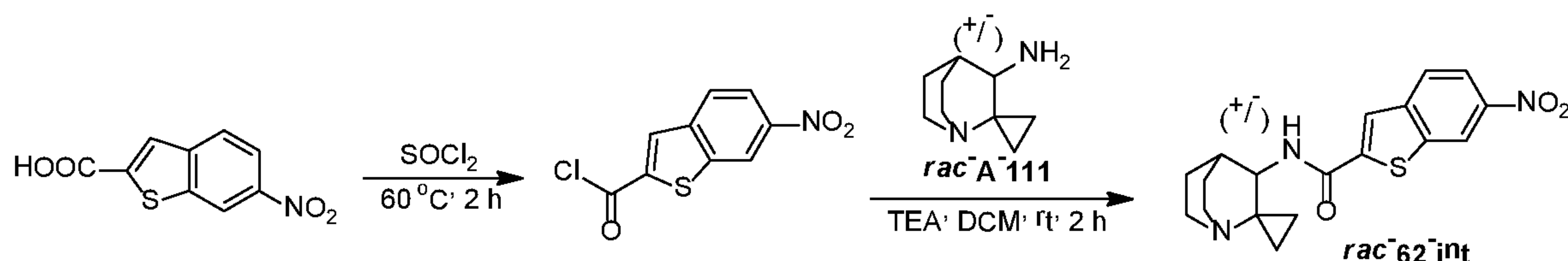
[00914] *Rac*-**61** (0.16 g, 0.48 mmol) in 3 mL of methanol was separated by SFC (Instrument: SFC 80; Column: Chiralpak OD-H 250×25 mm I.D., 10 µm; Mobile phase: 50% ethanol (0.01% NH₃·H₂O) in CO₂) according to general procedure A. The compounds were not treated with HCl but rather were isolated as the free bases:

6-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer1 (**compound 61a**) (50 mg, 31% yield) as a white solid: cSFC analytical (A) $t_R=2.17$ min., purity: 99.53%; LCMS (J): $t_R=1.287$ min., (ES^+) m/z $(M+H)^+ = 331.1$; ^1H -NMR (CD₃OD, 400 MHz): δ 8.11 (s, 1H), 7.92 (dd, $J_1=8.8$ Hz, $J_2=5.6$ Hz, 1H), 7.70 (d, $J=8.8$ Hz, 1H), 7.24 (td, $J=8.8$ Hz, 1H), 4.22 (s, 1H), 3.28-3.26 (m, 1H), 3.10-3.08 (m, 1H), 2.95-2.89 (m, 2H), 2.12 (s, 1H), 2.03-1.94 (m, 1H), 1.89-1.85 (m, 2H), 1.62-1.55 (m, 1H), 0.94-0.88 (m, 2H), 0.78-0.76 (m, 1H), 0.75-0.68 (m, 1H); and

6-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer2 (**compound 61b**) (50 mg, 31% yield) as a white solid : cSFC analytical (A) $t_R=3.24$ min., purity: 99.79%; LCMS (J): $t_R=1.285$ min., (ES^+) m/z $(M+H)^+ = 331.1$; ^1H -NMR (CD₃OD, 400 MHz): δ 8.11 (s, 1H), 7.93 (dd, $J_1=8.8$ Hz, $J_2=5.2$ Hz, 1H), 7.70 (dd, $J=8.8$ Hz, 1H), 7.24 (td, $J=8.8$ Hz, 1H), 4.22 (s, 1H), 3.30-3.27 (m, 1H), 3.11-3.09 (m, 1H), 2.97-2.86 (m, 2H), 2.12 (s, 1H), 2.04-1.96 (m, 1H), 1.90-1.86 (m, 2H), 1.63-1.59 (m, 1H), 0.95-0.89 (m, 2H), 0.79-0.78 (m, 1H), 0.72-0.69 (m, 1H).

[00915] Example 62:

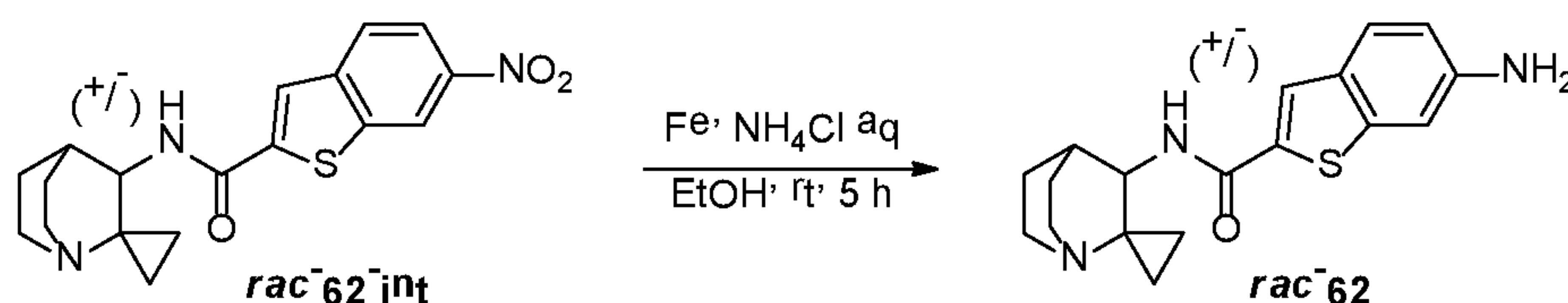
[00916] Preparation of (+/-)-6-nitro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide (**rac-62-int**)



[00917] Following general procedure A, **rac-62-int** was prepared from 6-nitrobenzo[b]thiophene-2-carboxylic acid and **rac-A-111** (0.29 g, 1.9 mmol). The product was purified by prep-HPLC

[Instrument: GX-C; Column: Phenomenex Gemini C18 150×30 mm, particle size: 5 μ m; Mobile phase: 35-65% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give **rac-62-int** (0.39 g, 57% yield) as a white solid. LCMS: (ES^+) m/z $(M+H)^+ = 358.0$.

[00918] Preparation of (+/-)-6-amino-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide (**rac-62**)



[00919] To a mixture of **rac-62-int** (0.39 g, 54 μ mol) in ethanol (200 mL) was added iron powder (0.43 g, 7.6 mmol) and saturated aqueous ammonium chloride solution. The mixture was stirred at room temperature for 5 hours. On completion, the product was purified by prep-HPLC [Instrument: GX-C; Column: Phenomenex Gemini C18 150×30 mm, particle size: 5 μ m; Mobile phase: 35-65%

acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)] to give *rac*-**62** (0.10 g, 28% yield) as a white solid.

LCMS: (ES⁺) m/z (M+H)⁺ = 328.2.

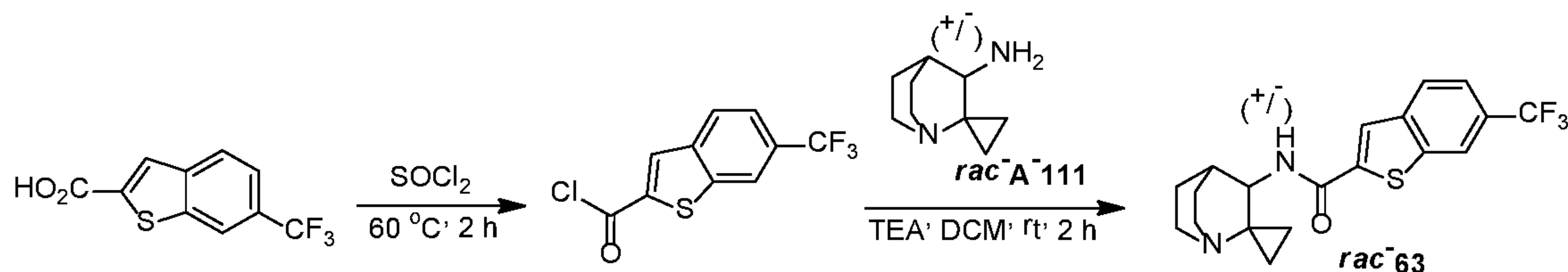
[00920] Chiral Separation:

[00921] *Rac*-**62** (0.10 g, 0.30 mmol) in 3 mL of methanol was separated by SFC (Instrument: SFC 80; Column: AD-10 μm; Mobile phase: 30% methanol (0.01% NH₃ · H₂O) in CO₂) according to general procedure A to give:

6-amino-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer1 hydrochloride (**compound 62a**) (20 mg, 20% yield) as a white solid: cSFC analytical (F) tR=3.15 min., purity: 99.67%; LCMS (N): tR=1.289 min., (ES⁺) m/z (M+H)⁺ = 328.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.35 (s, 1H), 8.09 (d, J=8.4 Hz, 1H), 8.03 (s, 1H), 7.47 (d, J=8.4 Hz, 1H), 4.56 (s, 1H), 3.83-3.76 (m, 1H), 3.56-3.52 (m, 1H), 3.49-3.39 (m, 2H), 2.43-2.35 (m, 2H), 2.20-2.14 (m, 2H), 2.02-1.95 (m, 1H), 1.45-1.36 (m, 2H), 1.27-1.25 (m, 1H), 1.15-1.12 (m, 1H); and

6-amino-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer2 hydrochloride (**compound 62b**) (20 mg, 20% yield) as a white solid: cSFC analytical (F) tR=3.94 min., purity: 96.35%; LCMS (N): tR=1.279 min., (ES⁺) m/z (M+H)⁺ = 328.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.29 (s, 1H), 8.11 (d, J=8.4 Hz, 1H), 8.01 (s, 1H), 7.46 (d, J=8.8 Hz, 1H), 4.57 (s, 1H), 3.78-3.74 (m, 1H), 3.58-3.49 (m, 1H), 3.47-3.41 (m, 2H), 2.46-2.43 (m, 1H), 2.36-2.30 (m, 1H), 2.23-2.16 (m, 2H), 2.01-1.98 (m, 1H), 1.42-1.38 (m, 1H), 1.31-1.24 (m, 2H), 1.20-1.17 (m, 1H).

[00922] **Example 63:** (+/-)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide (*rac*-**63**)



[00923] Following general procedure A, **Compound rac-63** was prepared from 6-(trifluoromethyl)benzo[b]thiophene-2-carboxylic acid and *rac*-**A-111** (0.10 g, 0.65 mmol). The product was purified by prep-HPLC [Instrument: GX-C; Column: Phenomenex Gemini C18 150×30 mm, particle size: 5 μm; Mobile phase: 35-65% acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)] to give *rac*-**63** (0.16 g, 64% yield) as a white solid.

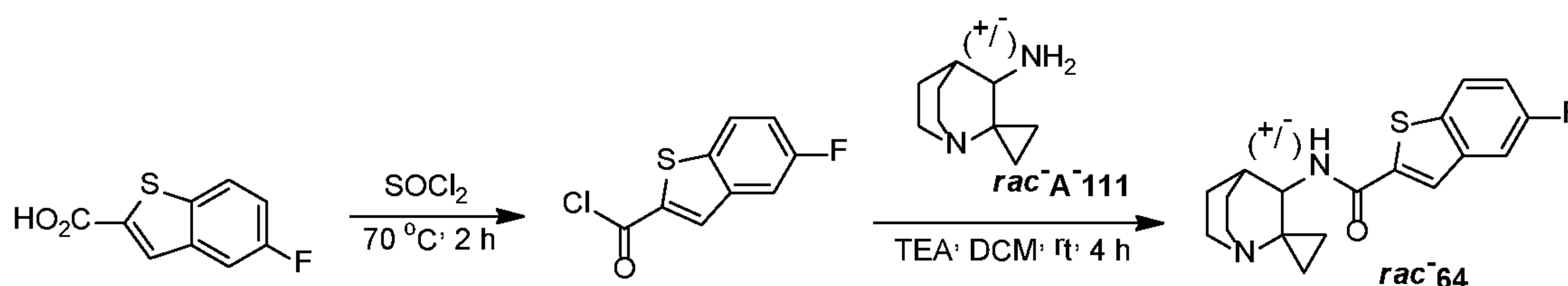
[00924] Chiral Separation:

[00925] **Racemate rac-63** (0.16 g, 0.26 mmol) in 3 mL of ethanol was separated by SFC (Instrument: SFC 80; Column: Chiralpak OD-H 250×25 mm I.D., 10 μm; Mobile phase: 60% ethanol (0.1% NH₃ · H₂O) in CO₂) according to general procedure A. The compounds were not treated with HCl but rather were isolated as the free bases:

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide-enantiomer1 (**compound 63a**) (62 mg, 62% yield) as a white solid: cSFC analytical (A) tR=1.95 min., purity: 99.08%; LCMS (J): tR=1.415 min., (ES⁺) m/z (M+H)⁺ = 381.4; ¹H-NMR (CD₃OD, 400 MHz): δ 8.31 (s, 1H), 8.19 (s, 1H), 8.07 (d, J=8.0 Hz, 1H), 7.67 (d, J=8.0 Hz, 1H), 4.23 (s, 1H), 3.27 (m, 1H), 3.08-3.07 (m, 1H), 2.94-2.84 (m, 2H), 2.20 (s, 1H), 2.12-1.85 (m, 3H), 1.58 (m, 1H), 0.91-0.69 (m, 4H); and

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide-enantiomer2 (**compound 63b**) (33 mg, 21% yield) as a white solid: cSFC analytical (A) tR=3.53 min., purity: 99.77%; LCMS (J): tR=1.41 min., (ES⁺) m/z (M+H)⁺ = 381.4; ¹H-NMR (CD₃OD, 400 MHz): δ 8.34 (s, 1H), 8.21 (s, 1H), 8.09 (d, J=8.4 Hz, 1H), 7.69 (d, J=8.8 Hz, 1H), 4.23 (s, 1H), 3.28-3.25 (m, 1H), 3.09-3.08 (m, 1H), 2.96-2.87 (m, 2H), 2.13 (s, 1H), 2.03-1.82 (m, 3H), 1.62-1.55 (m, 1H), 0.94-0.89 (m, 2H), 0.79-0.67 (m, 2H).

[00926] **Example 64:** (+/-)-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide (*rac*-64)



[00927] Following general procedure A, *rac*-64 was prepared from 5-fluorobenzo[b]thiophene-2-carboxylic acid and *rac*-A-111 (0.20 g, 1.3 mmol), with a reaction time of 4 hours in the second step. The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 150×25mm, particle size: 10 μm; Mobile phase: 38-68% acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)] to give *rac*-64 (0.16 g, 40% yield) as a brown solid.

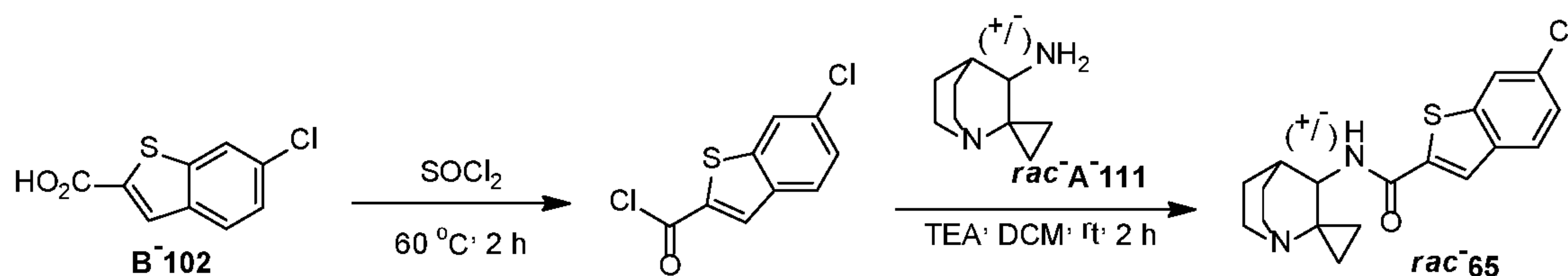
[00928] Chiral Separation:

[00929] *Rac*-64 (0.16 g, 0.48 mmol) in 3 mL of methanol was separated by SFC (Instrument: SFC 80; Column: Chiralpak OD-H 250×25 mm I.D., 10 μm; Mobile phase: 35% methanol (0.01% NH₃ · H₂O) in CO₂) according to general procedure A. The compounds were not treated with HCl but rather were isolated as the free bases:

5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer1 (**compound 64a**) (70 g, 44% yield) as a white solid: cSFC analytical (A) tR=2.17 min., purity: 99.74%; LCMS (J): tR=1.282 min., (ES⁺) m/z (M+H)⁺ = 331.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.08 (s, 1H), 7.94 (dd, J₁=8.8 Hz, J₂=4.8 Hz, 1H), 7.63 (dd, J=9.6 Hz, 1H), 7.27 (td, J=8.8 Hz, 1H), 4.22 (s, 1H), 3.30-3.26 (m, 1H), 3.09-3.08 (m, 1H), 2.95-2.88 (m, 2H), 2.11 (s, 1H), 2.02-1.96 (m, 1H), 1.89-1.85 (m, 2H), 1.62-1.54 (m, 1H), 0.93-0.88 (m, 2H), 0.78-0.77 (m, 1H), 0.70-0.67 (m, 1H); and

5-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer2 (**compound 64b**) (80 g, 50% yield) as a white solid: cSFC analytical (A) $t_R=2.88$ min., purity: 99.75%; LCMS (J): $t_R=1.282$ min., (ES^+) m/z $(M+H)^+ = 331.1$; ^1H -NMR (CD_3OD , 400 MHz): δ 8.08 (s, 1H), 7.94 (dd, $J_1=8.8$ Hz, $J_2=4.8$ Hz, 1H), 7.63 (dd, $J=9.2$ Hz, 1H), 7.27 (td, $J=9.2$ Hz, 1H), 4.22 (s, 1H), 3.30-3.26 (m, 1H), 3.12-3.08 (m, 1H), 2.96-2.88 (m, 2H), 2.12 (s, 1H), 2.03-1.97 (m, 1H), 1.89-1.85 (m, 2H), 1.62-1.59 (m, 1H), 0.94-0.88 (m, 2H), 0.79-0.78 (m, 1H), 0.71-0.68 (m, 1H).

[00930] **Example 65:** (+/-)-6-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide (**rac-65**)



[00931] Following general procedure A, **rac-65** was prepared from **compound B-102** and **rac-A-111** (0.21 g, 1.4 mmol). The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 150×25 mm, particle size: 10 μ m; Mobile phase: 36-66% acetonitrile in H_2O (add 0.5% $NH_3 \cdot H_2O$, v/v)] to give **rac-65** (0.25 g, 51% yield) as a yellow solid. LCMS: (ES^+) m/z $(M+H)^+ = 347.1$.

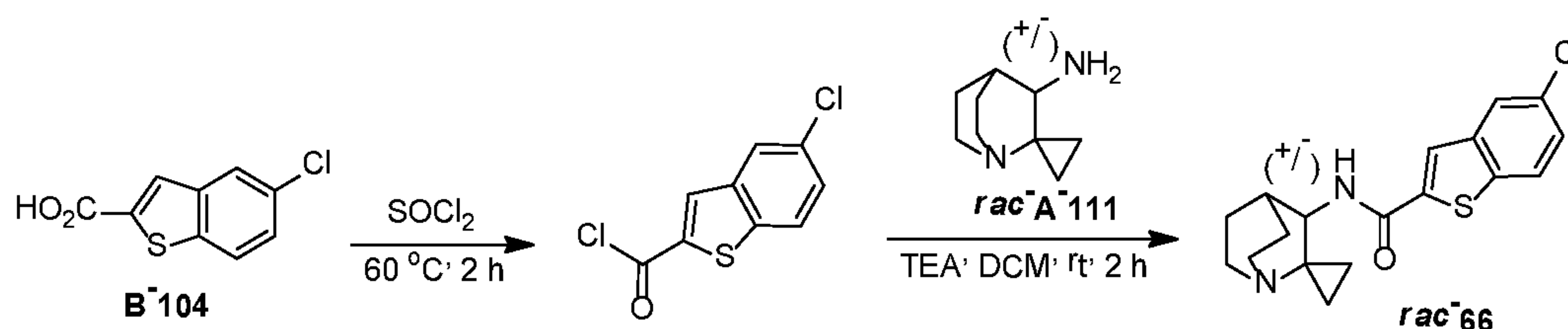
[00932] Chiral Separation:

[00933] **Rac-65** (0.25 g, 0.72 mmol) in 5 mL of ethanol was separated by SFC (Instrument: SFC 80; Column: Chiralpak OD-H 250×30 mm I.D., 10 μ m; Mobile phase: 60% ethanol (0.01% $NH_3 \cdot H_2O$) in CO_2) according to general procedure A to give:

6-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer1 hydrochloride (**compound 65a**) (0.10 g, 40% yield) as a white solid: cSFC analytical (A) $t_R=2.51$ min., purity: 100%; LCMS (B): $t_R=0.700$ min., (ES^+) m/z $(M+H)^+ = 347.1$; ^1H -NMR (CD_3OD , 400 MHz): δ 8.14 (s, 1H), 8.02 (s, 1H), 7.92 (d, $J=8.4$ Hz, 1H), 7.46 (dd, $J_1=8.4$ Hz, $J_2=1.6$ Hz, 1H), 4.59 (d, $J=2.4$ Hz, 1H), 3.75-3.71 (m, 1H), 3.61-3.60 (m, 1H), 3.52-3.45 (m, 2H), 2.47-2.46 (m, 1H), 2.36-2.33 (m, 1H), 2.26-2.18 (m, 2H), 2.03-2.00 (m, 1H), 1.40-1.35 (m, 1H), 1.29-1.21 (m, 3H); and

6-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer2 hydrochloride (**compound 65b**) (0.10 g, 40% yield) as a white solid : cSFC analytical (A) $t_R=3.77$ min., purity: 100%; LCMS (B): $t_R=0.696$ min., (ES^+) m/z $(M+H)^+ = 347.1$; ^1H -NMR (CD_3OD , 400 MHz): δ 8.17 (s, 1H), 8.01 (s, 1H), 7.921 (d, $J=8.8$ Hz, 1H), 7.46 (dd, $J_1=8.4$ Hz, $J_2=1.6$ Hz, 1H), 4.58 (d, $J=2.0$ Hz, 1H), 3.74-3.73 (m, 1H), 3.60-3.59 (m, 1H), 3.50-3.43 (m, 2H), 2.47-2.46 (m, 1H), 2.36-2.34 (m, 1H), 2.25-2.18 (m, 2H), 2.05-2.01 (m, 1H), 1.39-1.37 (m, 1H), 1.31-1.17 (m, 3H).

[00934] **Example 66:** (+/-)-5-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide (*rac*-66)



[00935] Following general procedure A, *rac*-66 was prepared from compound B-104 and *rac*-A-111 (0.20 g, 1.3 mmol). The product was purified by prep-HPLC [Instrument: GX-C; Column: Phenomenex Gemini C18 150×30 mm, particle size: 5 μm; Mobile phase: 35-65% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give *rac*-66 (0.21 g, 64% yield) as a white solid. LCMS: (ES⁺) *m/z* (M+H)⁺ = 347.0.

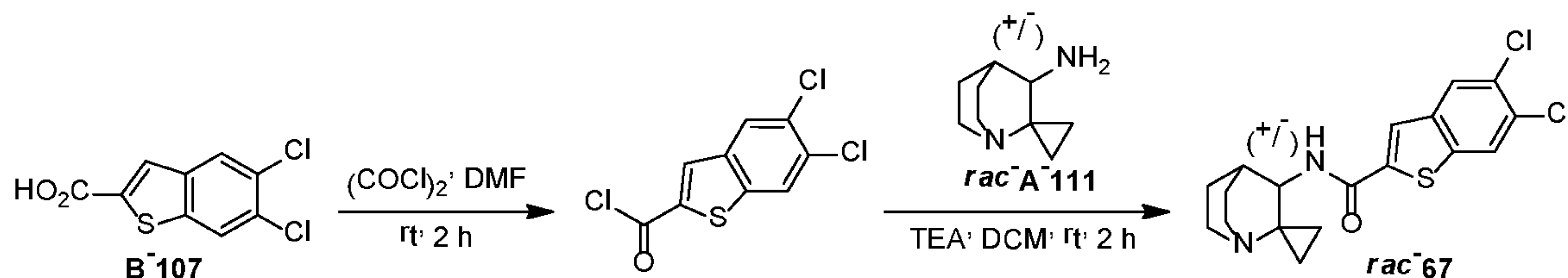
[00936] Chiral Separation:

[00937] *Rac*-66 (0.21 g, 0.58 mmol) in 3 mL of methanol was separated by SFC (Instrument: SFC 80; Column: AD-10 μm; Mobile phase: 30% methanol (0.01% NH₃·H₂O) in CO₂) according to general procedure A to give:

5-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer1 hydrochloride (**compound 66a**) (40 mg, 19% yield) as a white solid: cSFC analytical (E) *t*_R=2.60 min., purity: 100%; LCMS (N): *t*_R=2.253 min., (ES⁺) *m/z* (M+H)⁺ = 346.9; ¹H-NMR (CD₃OD, 400 MHz): δ 8.09 (s, 1H), 7.94-7.91 (m, 2H), 7.45 (dd, *J*₁=8.8 Hz, *J*₂=2.0 Hz, 1H), 4.57 (d, *J*=1.2 Hz, 1H), 3.72-3.70 (m, 1H), 3.58-3.57 (m, 1H), 3.49-3.42 (m, 2H), 2.45-2.43 (m, 1H), 2.34-2.22 (m, 1H), 2.21-2.17 (m, 2H), 2.05-1.95 (m, 1H), 1.37-1.34 (m, 1H), 1.28-1.19 (m, 3H).

5-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer1 hydrochloride (**compound 66b**) (90 mg, 42% yield) as a white solid: cSFC analytical (E) *t*_R=3.22 min., purity: 99.12%; LCMS (N): *t*_R=2.230 min., (ES⁺) *m/z* (M+H)⁺ = 347.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.09 (s, 1H), 7.94-7.91 (m, 2H), 7.45 (dd, *J*₁=8.4 Hz, *J*₂=2.0 Hz, 1H), 4.57 (d, *J*=2.8 Hz, 1H), 3.72-3.70 (m, 1H), 3.58-3.57 (m, 1H), 3.50-3.40 (m, 2H), 2.46-2.43 (m, 1H), 2.34-2.33 (m, 1H), 2.21-2.16 (m, 2H), 2.00-1.95 (m, 1H), 1.38-1.34 (m, 1H), 1.30-1.15 (m, 3H).

[00938] **Example 67:** (+/-)-5,6-dichloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide (*rac*-67)



[00939] To a solution of **compound B-107** (0.18 g, 0.73 mmol) in dichloromethane (5 mL) at 0 °C was added dropwise oxalyl chloride (0.17 g, 1.3 mmol), followed by *N,N*-dimethylformamide (1

drop). The solution was stirred at this temperature for 1 hour. On completion, the solution was concentrated in vacuo to give the acid chloride, which was used directly without further purification to prepare *rac*-**67** from *rac*-**A-111** (0.10 g, 0.66 mmol) according to general procedure A. The product was purified by prep-HPLC [Instrument: GX-C; Column: Waters Xterra C18 150*30mm, particle size: 5 μ m; Mobile phase: 36-66% acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)] to give *rac*-**67** (0.15 g, 60% yield) as a white solid. LCMS: (ES⁺) *m/z* (M+H)⁺ = 381.1.

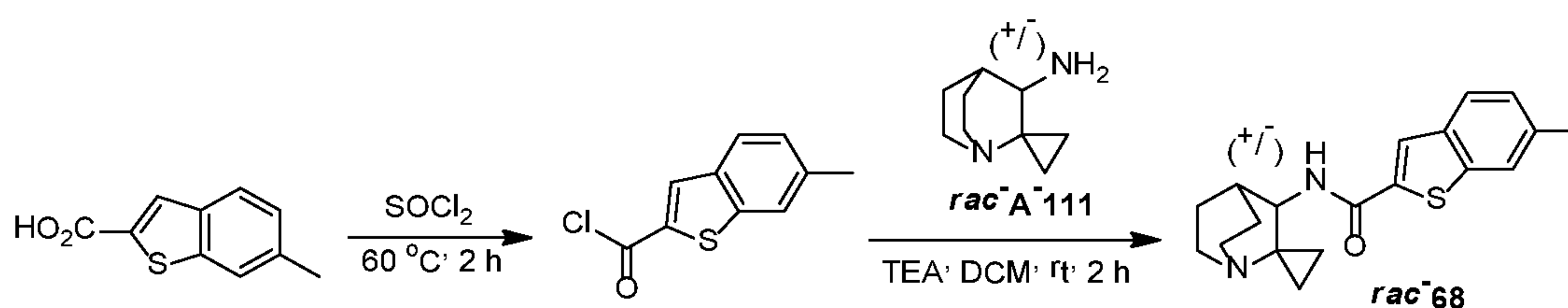
[00940] Chiral Separation:

[00941] *Rac*-**67** (0.15 g, 0.39 mmol) in 3 mL of methanol was separated by SFC (Instrument: SFC 80; Column: Chiralpak OD-H 250×30 mm I.D., 10 μ m; Mobile phase: 60% methanol (0.01% NH₃ · H₂O) in CO₂) according to general procedure A to give:

5,6-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer1 hydrochloride (**compound 67a**) (65 mg, 43% yield) as a white solid: cSFC analytical (E) *t*R=2.75 min., purity: 99.83%; LCMS (B): *t*R=0.740 min., (ES⁺) *m/z* (M+H)⁺ = 381.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.19 (s, 1H), 8.14-8.10 (m, 2H), 4.58 (s, 1H), 3.73-3.52 (m, 1H), 3.65-3.55 (m, 1H), 3.55-3.40 (m, 2H), 2.47-2.46 (m, 1H), 2.38-2.33 (m, 1H), 2.25-2.19 (m, 2H), 2.16-2.02 (m, 1H), 1.41-1.38 (m, 1H), 1.29-1.22 (m, 3H); and

5,6-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer2 hydrochloride (**compound 67b**) (0.65 mg, 43% yield) as a white solid: cSFC analytical (E) *t*R=3.29 min., purity: 99.85%; LCMS (B): *t*R=0.740 min., (ES⁺) *m/z* (M+H)⁺ = 381.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.19 (s, 1H), 8.12-8.11 (m, 2H), 4.58 (s, 1H), 3.72-3.53 (m, 1H), 3.52-3.49 (m, 1H), 3.47-3.42 (m, 2H), 2.47-2.46 (m, 1H), 2.38-2.33 (m, 1H), 2.25-2.19 (m, 2H), 2.16-2.02 (m, 1H), 1.39-1.37 (m, 1H), 1.30-1.20 (m, 3H).

[00942] **Example 68:** (+/-)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide (*rac*-**68**)



[00943] Following general procedure A, *rac*-**68** was prepared from 6-methylbenzo[b]thiophene-2-carboxylic acid and *rac*-**A-111** (0.10 g, 0.67 mmol). The product was purified by prep-HPLC [Instrument: GX-C; Column: Waters Xterra C18 150*30mm, particle size: 5 μ m; Mobile phase: 35-64% acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)] to give *rac*-**68** (0.12 g, 57% yield) as a white solid. LCMS: (ES⁺) *m/z* (M+H)⁺ = 327.0.

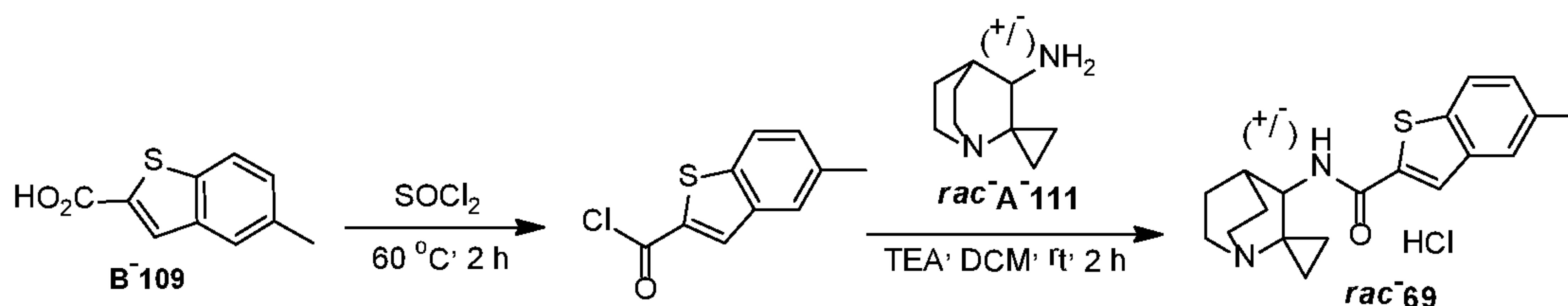
[00944] Chiral Separation:

[00945] *Rac-68* (0.12 g, 0.37 mmol) in 3 mL of methanol was separated by SFC (Instrument: SFC 80; Column: Chiralpak AD-H 250×30 mm I.D., 10 μm; Mobile phase: 40% methanol (0.01% NH₃ · H₂O) in CO₂) according to general procedure A to give:

6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer1 hydrochloride (**compound 68a**) (50 mg, 42% yield) as a white solid: cSFC analytical (A) tR=2.496 min., purity: 99.28%; LCMS (Z): tR=1.623 min., (ES⁺) m/z (M+H)⁺ = 327.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.09 (s, 1H), 7.83-7.81 (d, J=8.0 Hz, 1H), 7.74 (s, 1H), 7.31-7.29 (d, J=8.4 Hz, 1H), 4.59 (s, 1H), 3.77-3.70 (m, 1H), 3.62-3.52 (m, 1H), 3.49-3.42 (m, 2H), 2.50-2.46 (m, 4H), 2.39-2.33 (m, 1H), 2.25-2.16 (m, 2H), 2.05-1.97 (m, 1H), 1.41-1.31 (m, 1H), 1.29-1.17 (m, 3H); and

6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer2 hydrochloride (**compound 68b**) (50 mg, 42% yield) as a white solid: cSFC analytical (A) tR=3.082 min., purity: 97.83%; LCMS (Z): tR=1.606 min., (ES⁺) m/z (M+H)⁺ = 327.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.10 (s, 1H), 7.83-7.81 (d, J=8.0 Hz, 1H), 7.74 (s, 1H), 7.31-7.29 (d, J=8.4 Hz, 1H), 4.58 (s, 1H), 3.76-3.69 (m, 1H), 3.60-3.49 (m, 1H), 3.47-3.42 (m, 2H), 2.51-2.46 (m, 4H), 2.39-2.33 (m, 1H), 2.25-2.16 (m, 2H), 2.05-2.02 (m, 1H), 1.38-1.35 (m, 1H), 1.31-1.20 (m, 3H).

[00946] **Example 69:** (+/-)-5-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide (*rac-69*)



[00947] Following general procedure A, *rac-69* was prepared from **compound B-109** and *rac-A-111* (0.24 g, 1.6 mmol). The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 150×25 mm, particle size: 10 μm; Mobile phase: 44-74% acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)] to give *rac-69* (0.20 g, 64%) as a yellow solid. LCMS: (ES⁺) m/z (M+H)⁺ = 327.1.

[00948] Chiral Separation:

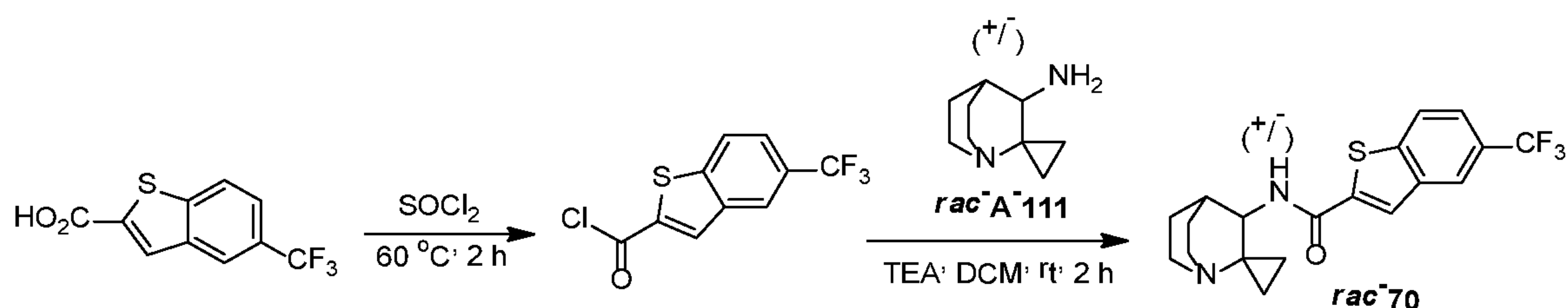
[00949] *Rac-69* (0.20 g, 0.61 mmol) in 5 mL of methanol was separated by SFC (Instrument: SFC 80; Column: OD-250×30mm, I.D., 10 μm; Mobile phase: 50% methanol (0.01% NH₃ · H₂O) in CO₂) according to general procedure A to give:

5-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer1 hydrochloride (**compound 69a**) (55 mg, 28% yield) as a white solid: cSFC analytical (A) tR=2.483 min., purity: 100.00%; LCMS (B): tR=0.686 min., (ES⁺) m/z (M+H)⁺ = 327.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.10-8.09 (m, 1H), 7.81 (d, J=8.4 Hz, 1H), 7.74 (s, 1H), 7.33 (d, J=8.4 Hz, 1H), 4.58 (s, 1H), 3.75-3.59 (m, 1H), 3.59-3.59 (m, 1H), 3.48-3.44 (m, 2H), 2.49 (s, 3H),

2.45-2.45 (m, 1H), 2.36-2.33 (m, 1H), 2.24-2.19 (m, 2H), 2.01-2.00 (m, 1H), 1.42-1.40 (m, 1H), 1.31-1.19 (m, 3H); and

5-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer2 hydrochloride (**compound 69b**) (25 mg, 13% yield) as a white solid: cSFC analytical (A) tR=3.099 min., purity: 98.88%; LCMS (B): tR=0.661 min., (ES⁺) m/z (M+H)⁺ = 327.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.09-8.09 (m, 1H), 7.81 (d, J=8.0 Hz, 1H), 7.74 (s, 1H), 7.33 (d, J=8.0Hz, 1H), 4.58 (s, 1H), 3.75-3.73 (m, 1H), 3.59-3.59 (m, 1H), 3.58-3.44 (m, 2H), 2.49 (s, 3H), 2.46-2.45 (m, 1H), 2.36-2.36 (m, 1H), 2.25-2.18 (m, 2H), 2.01-2.00 (m, 1H), 1.42-1.40 (m, 1H), 1.31-1.19 (m, 3H).

[00950] **Example 70:** (+/-)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-5-(trifluoromethyl)benzo[b]thiophene-2-carboxamide (*rac*-**70**)



[00951] Following general procedure A, *rac*-**70** was prepared from 5-(trifluoromethyl)benzo[b]thiophene-2-carboxylic acid and *rac*-**A-111** (0.10 g, 0.65 mmol). The product was purified by prep-HPLC [Instrument: GX-C; Column: Phenomenex Gemini C18 150×30 mm, particle size: 5 μm; Mobile phase: 35-65% acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)] to give *rac*-**70** (0.18 g, 72% yield) as a white solid.

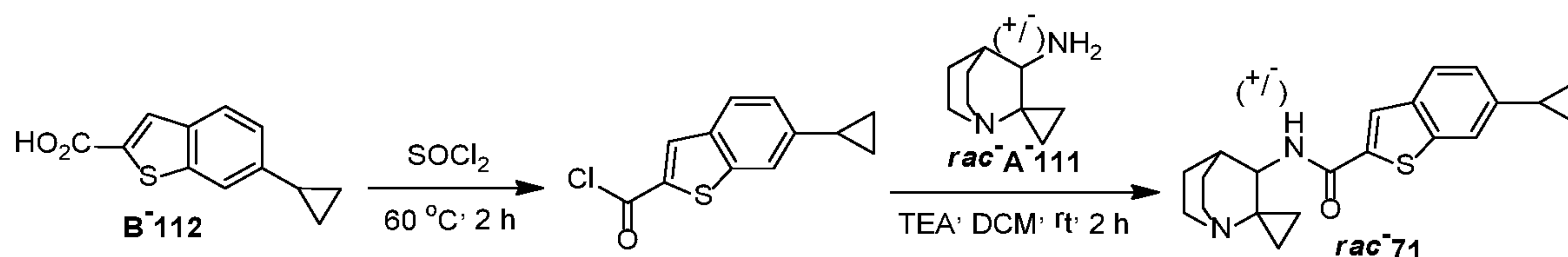
[00952] Chiral Separation:

[00953] *Rac*-**70** (0.12 g, 0.32 mmol) in 3 mL of ethanol was separated by SFC (Instrument: SFC 80; Column: Chiralpak OD-H 250×25 mm I.D., 10 μm; Mobile phase: 40% ethanol (0.1% NH₃ · H₂O) in CO₂) according to general procedure A to give:

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-5-(trifluoromethyl)benzo[b]thiophene-2-carboxamide-enantiomer1 hydrochloride (**compound 70a**) (54 mg, 45% yield) as a white solid: cSFC analytical (A) tR=1.87 min., purity: 100%; LCMS (J): tR=1.415 min., (ES⁺) m/z (M+H)⁺ = 381.4; ¹H-NMR (CD₃OD, 400 MHz): δ 8.26 (s, 1H), 8.23 (s, 1H), 8.15 (d, J=8.4 Hz, 1H), 7.72 (d, J=8.4 Hz, 1H), 4.30 (s, 1H), 3.40-3.22 (m, 1H), 3.20-3.18 (m, 1H), 3.06-2.98 (m, 2H), 2.21-2.18 (m, 1H), 2.10-1.92 (m, 2H), 1.71-1.63 (m, 1H), 1.03-0.96 (m, 1H), 0.88-0.78 (m, 2H); and

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-5-(trifluoromethyl)benzo[b]thiophene-2-carboxamide-enantiomer2 hydrochloride (**compound 70b**) (60 mg, 50% yield) as a white solid : cSFC analytical (A) tR=2.59 min., purity: 100%; LCMS (J): tR=2.63 min., (ES⁺) m/z (M+H)⁺ = 381.4; ¹H-NMR (CD₃OD, 400 MHz): δ 8.26 (s, 1H), 8.24 (s, 1H), 8.15 (d, J=8.4 Hz, 1H), 7.73-7.70 (d, J=8.4 Hz, 1H), 4.33 (s, 1H), 3.42-3.37 (m, 1H), 3.24-3.21 (m, 1H), 3.09-3.00 (m, 2H), 2.22-2.21 (m, 1H), 2.10-1.94 (m, 3H), 1.74-1.66 (m, 1H), 1.05-0.99 (m, 2H), 0.91-0.80 (m, 2H).

[00954] **Example 71:** (+/-)-6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide (*rac*-71)



[00955] Following general procedure A, *rac*-71 was prepared from compound B-112 and *rac*-A-111 (0.14 g, 0.89 mmol). The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 150×25 mm, particle size: 10 μm; Mobile phase: 44-74% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give *rac*-71 (0.20 g, 64%) as a white solid. LCMS: (ES⁺) m/z (M+H)⁺ = 353.1.

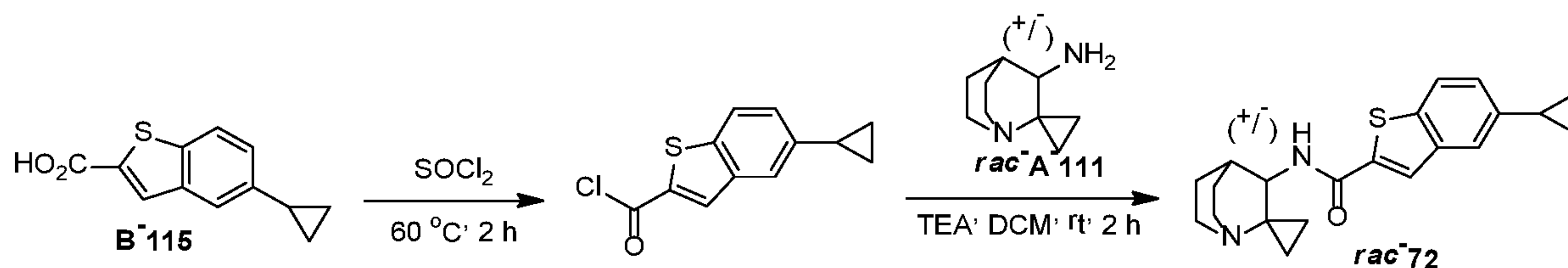
[00956] Chiral Separation:

[00957] *Rac*-71 (0.20 g, 0.57 mmol) in 5 mL of methanol was separated by SFC (Instrument: SFC 80; Column: OD-250×30mm, I.D., 10 μm; Mobile phase: 50% methanol (0.01% NH₃·H₂O) in CO₂) according to general procedure A to give:

6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer1 hydrochloride (**compound 71a**) (0.10 g, 50% yield) as a white solid: cSFC analytical (B) t_R=2.796 min., purity: 100.00%; LCMS (M): t_R=1.111 min., (ES⁺) m/z (M+H)⁺ = 353.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.05 (s, 1H), 7.78 (d, J=8.4 Hz, 1H), 7.62 (s, 1H), 7.16 (d, J=8.4 Hz, 1.4 Hz, 1H), 4.57 (d, J=2.4 Hz, 1H), 3.74-3.43 (m, 4H), 2.44-2.03 (m, 6H), 1.36-1.04 (m, 6H), 0.80-0.76 (m, 2H), and

6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer2 hydrochloride (**compound 71b**) (0.10 g, 50% yield) as a white solid: cSFC analytical (B) t_R=3.478 min., purity: 99.43%; LCMS (M): t_R=1.114 min., (ES⁺) m/z (M+H)⁺ = 353.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.05 (s, 1H), 7.78 (d, J=8.4 Hz, 1H), 7.62 (s, 1H), 7.16 (d, J=8.4 Hz, 1H), 4.55 (d, J=2.4 Hz, 1H), 3.46-3.43 (m, 4H), 2.43-2.03 (m, 6H), 1.30-1.03 (m, 6H), 0.79-0.77 (m, 2H).

[00958] **Example 72:** (+/-)-5-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide (*rac*-72)



[00959] Following general procedure A, *rac*-72 was prepared from compound B-115 and *rac*-A-111 (0.14 g, 0.89 mmol). The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 150×30 mm, particle size: 4 μm; Mobile phase: 35-65% acetonitrile in H₂O

(add 0.5% TFA, v/v)] to give ***rac*-72** (0.10 g, 31%) as a white solid. LCMS: (ES⁺) m/z (M+H)⁺ = 353.1.

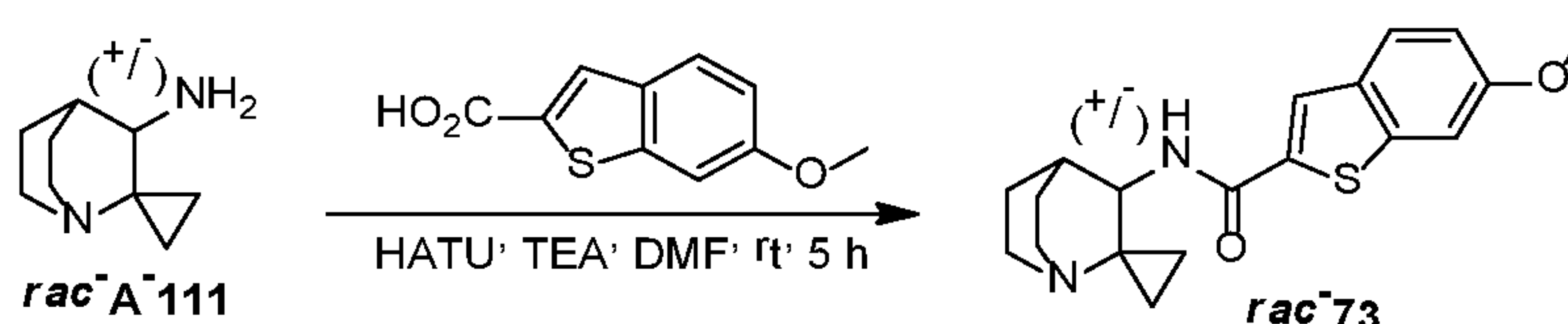
[00960] Chiral Separation:

[00961] *Rac-72* (0.10 g, 0.28 mmol) in 3 mL of methanol was separated by SFC (Instrument: SFC 80; Column: OD-250×30mm, I.D., 10 μm; Mobile phase: 50% methanol (0.01% NH₃·H₂O) in CO₂) according to general procedure A to give:

5-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer1 hydrochloride (**compound 72a**) (50 mg, 50% yield) as a white solid: cSFC analytical (A) tR: 2.70 min., purity: 100.00%; LCMS (B): tR=0.728 min., (ES⁺) m/z (M+H)⁺ = 353.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.08 (s, 1H), 7.80 (d, J=8.8 Hz, 1H), 7.65 (s, 1H), 7.23-7.21 (dd, J=8.8Hz, 1.2Hz, 1H), 4.58 (d, J=2.4 Hz, 1H), 3.73-3.44 (m, 4H), 2.46-2.07 (m, 6H), 1.39-1.03 (m, 4H), 0.78-0.76 (m, 2H); and

5-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer2 hydrochloride (**compound 72b**) (50 mg, 50% yield) as a white solid: cSFC analytical (A) tR: 3.32 min., purity: 99.22%; LCMS (B): tR=0.734 min., (ES⁺) m/z (M+H)⁺ = 353.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.08 (d, J=9.2Hz, 3.2Hz, 1H), 7.80 (d, J=8.4 Hz, 1H), 7.65 (s, 1H), 7.22 (d, J=8.8 Hz, 1H), 4.58 (s, 1H), 3.74-3.41 (m, 4H), 2.45-2.07 (m, 6H), 1.29-1.03 (m, 4H), 0.78-0.76 (m, 2H).

[00962] Example 73: (+/-)-6-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide (*rac*-**73**)



[00963] To a mixture of 6-methoxybenzo[b]thiophene-2-carboxylic acid (0.30 g, 1.4 mmol) in *N,N*-dimethylformamide (2.8 mL) was added 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate (0.66 g, 1.7 mmol), followed by ***rac*-A-111** (0.22 g, 1.4 mmol) and triethylamine (0.29 g, 2.8 mmol). The mixture was stirred at room temperature for 1 hour. On completion, the reaction was diluted with ethyl acetate and washed 4 times with water. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 150×25mm, particle size: 10 μm; Mobile phase: 36-66% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give ***racemate rac*-73** (0.13 g, 26% yield) as a white solid.

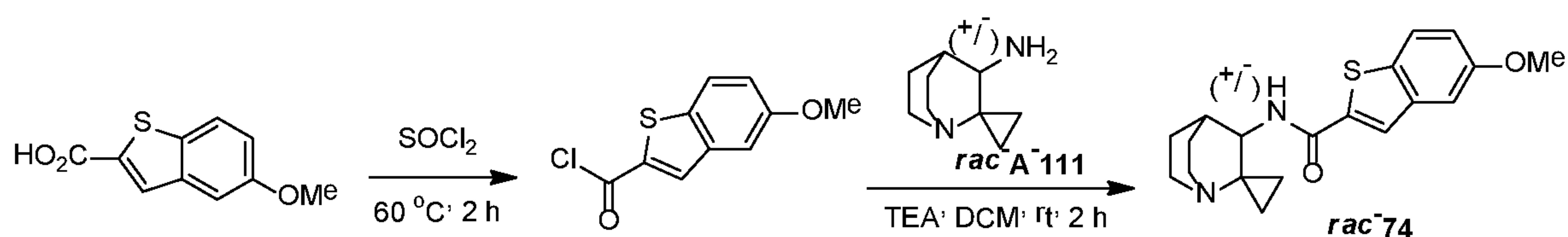
[00964] Chiral Separation:

[00965] *Rac-73* (0.13 g, 0.38 mmol) in 3 mL of methanol was separated by SFC (Instrument: SFC 80; Column: Chiralpak OD-H 250×25 mm I.D., 10 μm; Mobile phase: 50% ethanol (0.01% NH₃·H₂O) in CO₂) according to general procedure A to give:

6-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer1 hydrochloride (**compound 73a**) (70 mg, 49% yield) as a white solid: cSFC analytical (A) tR=2.61 min., purity: 100%; LCMS (J): tR=1.265 min., (ES⁺) m/z (M+H)⁺ = 343.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.04 (s, 1H), 7.79 (d, J=8.8 Hz, 1H), 7.46 (s, 1H), 7.06 (dd, J=8.8 Hz, 1H), 4.34 (s, 1H), 3.90 (s, 3H), 3.44-3.42 (m, 1H), 3.28-3.25 (m, 1H), 3.12-3.04 (m, 2H), 2.23-2.22 (m, 1H), 2.15-2.10 (m, 1H), 2.00-1.97 (m, 2H), 1.73 (m, 1H), 1.08-1.01 (m, 2H), 0.95-0.86 (m, 2H); and

6-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer2 hydrochloride (**compound 73b**) (70 mg, 49% yield) as a white solid: cSFC analytical (A) tR=3.26 min., purity: 99.63%; LCMS (J): tR=1.278 min., (ES⁺) m/z (M+H)⁺ = 343.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.06 (s, 1H), 7.79 (d, J=9.2 Hz, 1H), 7.46 (s, 1H), 7.06 (dd, J=8.8 Hz, 1H), 4.44 (s, 1H), 3.90 (s, 3H), 3.57-3.56 (m, 1H), 3.41-3.40 (m, 1H), 3.28-3.25 (m, 2H), 2.33-2.31 (m, 1H), 2.23-2.21 (m, 1H), 2.11-2.05 (m, 2H), 1.86-1.84 (m, 1H), 1.23-1.20 (m, 1H), 1.14-1.10 (m, 2H), 1.08-1.00 (m, 1H).

[00966] **Example 74:** (+/-)-5-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide (**rac-74**)



[00967] Following general procedure A, **rac-74** was prepared from 5-methoxybenzo[b]thiophene-2-carboxylic acid and **rac-A-111** (0.10 g, 0.65 mmol). The product was purified by prep-HPLC [Instrument: GX-C; Column: Phenomenex Gemini C18 150×30 mm, particle size: 5 μm; Mobile phase: 35-65% acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)] to give **rac-74** (0.12 g, 54% yield) as a white solid.

[00968] Chiral Separation:

[00969] **Rac-74** (0.10 g, 0.29 mmol) in 3 mL of ethanol was separated by SFC (Instrument: SFC 80; Column: Chiralpak OD-H 250×25 mm I.D., 10 μm; Mobile phase: 45% ethanol (0.1% NH₃ · H₂O) in CO₂) according to general procedure A to give:

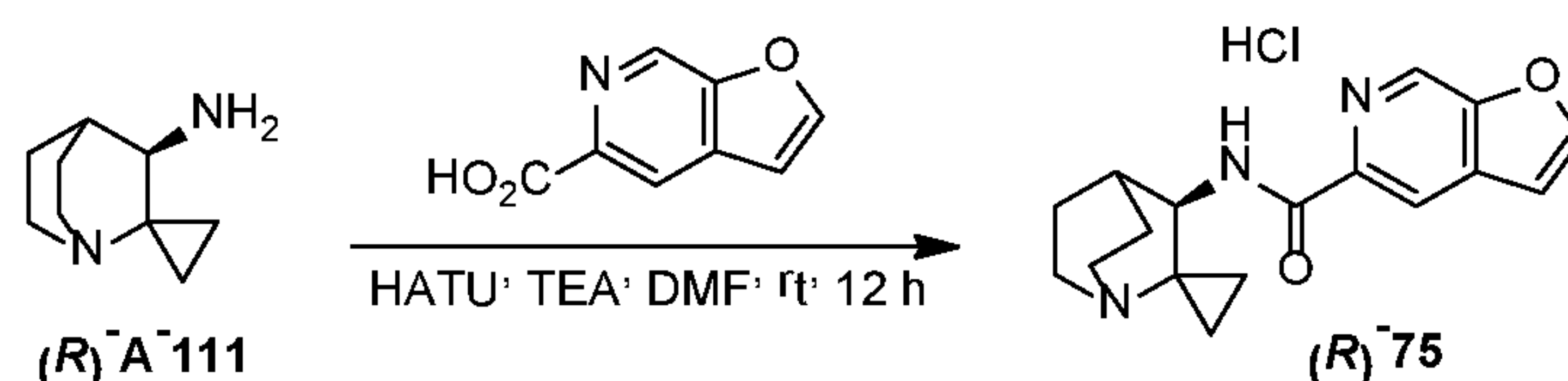
5-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer1 hydrochloride (**compound 74a**) (80 mg, 67% yield) as a white solid: cSFC analytical (A) tR=2.56 min., purity: 99.60%; LCMS (G): tR=2.231 min., (ES⁺) m/z (M+H)⁺ = 343.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.06 (s, 1H), 7.79 (d, J=8.8 Hz, 1H), 7.40 (d, J=2.4 Hz, 1H), 7.13 (dd, J₁=2.4 Hz, J₂=8.8 Hz, 1H), 4.58 (s, 1H), 3.89 (s, 3H), 3.75-3.72 (m, 1H), 3.60-3.45 (m, 3H), 2.47-2.36 (m, 2H), 2.25-2.19 (m, 2H), 1.37-1.36 (m, 1H), 1.28-1.21 (m, 3H); and

5-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide-enantiomer2 hydrochloride (**compound 74b**) (12 mg, 10% yield) as a white solid :

cSFC analytical (A) t_R =3.03 min., purity: 99.49%; LCMS (B): t_R =0.656 min., (ES^+) m/z $(M+H)^+ = 343.1$; ^1H -NMR (CD_3OD , 400 MHz): δ 8.08 (s, 1H), 7.79 (d, J =8.8 Hz, 1H), 7.40 (d, J =2.0 Hz, 1H), 7.14 (dd, J_1 =2.8 Hz, J_2 =8.8 Hz, 1H), 4.58 (s, 1H), 3.89 (s, 3H), 3.78-3.60 (m, 1H), 3.59-3.44 (m, 3H), 2.46-2.45 (m, 1H), 2.37-2.19 (m, 3H), 2.03-2.00 (m, 1H), 1.41-1.39 (m, 1H), 1.31-1.20 (m, 3H).

[00970] Example 75:

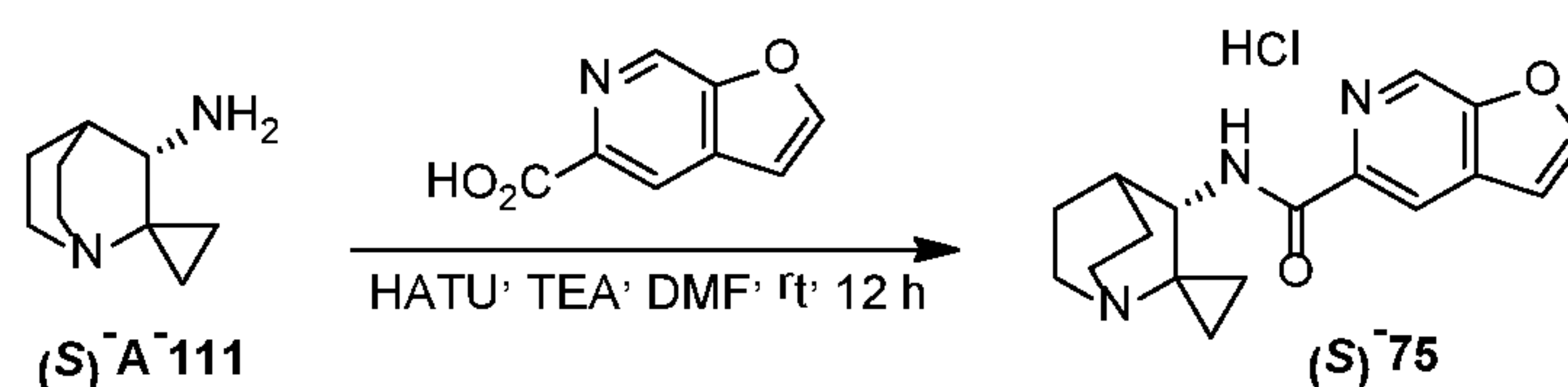
[00971] Preparation of *(R)*-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide hydrochloride (**(R)**-75)



[00972] Following general procedure B, **Compound (R)-75** was prepared from furo[2,3-c]pyridine-5-carboxylic acid (54 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μ m; Mobile phase: 16-46% acetonitrile in H_2O (add 0.5% HCl, v/v)] to give:

(R)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide hydrochloride (**compound (R)-75**) (77 mg, 79% yield) as a white solid: cSFC analytical (H) t_R =2.39 min., purity: 99.53%; LCMS (X): t_R =1.513 min., (ES^+) m/z $(M+H)^+ = 298.1$; ^1H -NMR (CD_3OD , 400 MHz): δ 9.22 (s, 1H), 8.90 (s, 1H), 8.50 (d, J =1.6 Hz, 1H), 7.39 (d, J =1.2 Hz, 1H), 4.63 (s, 1H), 3.80-3.79 (m, 1H), 3.59-3.58 (m, 1H), 3.52-3.41 (m, 2H), 2.50-2.49 (m, 1H), 2.42-2.36 (m, 1H), 2.25-2.16 (m, 2H), 2.05-2.02 (m, 1H), 1.45-1.40 (m, 1H), 1.34-1.29 (m, 2H), 1.21-1.19 (m, 1H).

[00973] Preparation of *(S)*-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide hydrochloride (**(S)**-75)



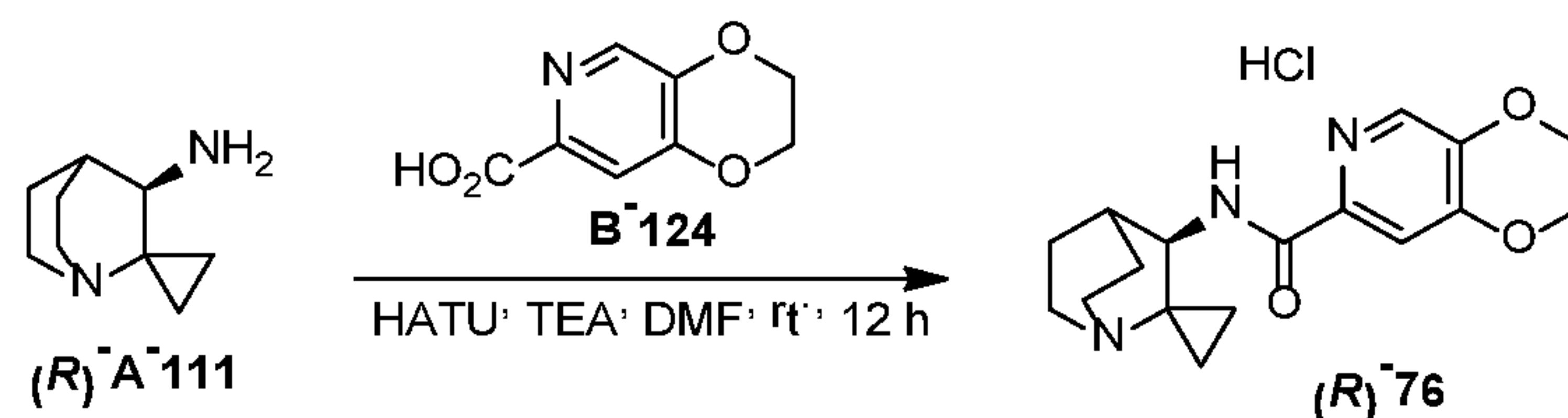
[00974] Following general procedure B, **Compound 498-SBA** was prepared from furo[2,3-c]pyridine-5-carboxylic acid (30 mg, 0.20 mmol) and **compound (S)-A-111** (0.30 g, 0.20 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μ m; Mobile phase: 16-46% acetonitrile in H_2O (add 0.5% HCl, v/v)] to give:

(S)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide hydrochloride (**compound (S)-75**) (50 mg, 85% yield) as a white solid: cSFC analytical (H) t_R =3.04 min., purity: 99.45%; LCMS (X): t_R =1.528 min., (ES^+) m/z $(M+H)^+ = 333.1$; ^1H -NMR (CD_3OD , 400 MHz): δ 9.21 (s, 1H), 8.87 (s, 1H), 8.49 (d, J =2.8 Hz, 1H), 7.38 (d, J =2.0 Hz, 1H), 4.63

(s, 1H), 3.80-3.78 (m, 1H), 3.60-3.59 (m, 1H), 3.52-3.41 (m, 2H), 2.50-2.49 (m, 1H), 2.42-2.36 (m, 1H), 2.25-2.16 (m, 2H), 2.05-2.01 (m, 1H), 1.43-1.38 (m, 1H), 1.34-1.28 (m, 2H), 1.22-1.17 (m, 1H).

[00975] Example 76:

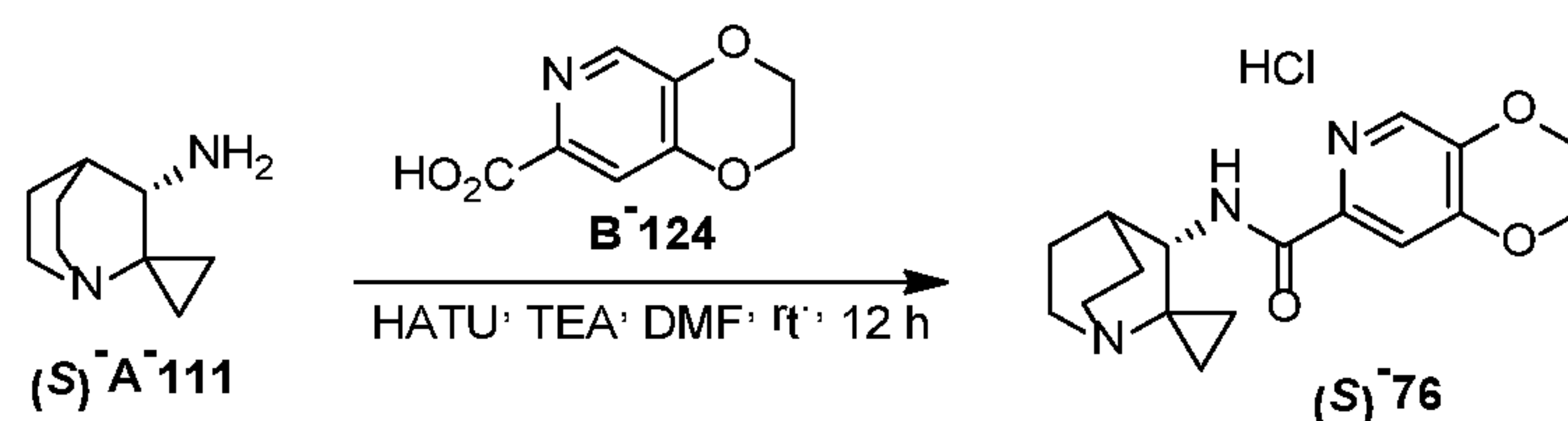
[00976] Preparation of (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydro-[1,4]dioxino[2,3-*c*]pyridine-7-carboxamide hydrochloride (**(*R*)-76**)



[00977] Following general procedure B, **Compound (*R*)-76** was prepared from **compound B-124** (60 mg, 0.33 mmol) and **compound (*R*)-A-111** (50 mg, 0.33 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 16-46% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydro-[1,4]dioxino[2,3-*c*]pyridine-7-carboxamide hydrochloride (**compound (*R*)-76**) (30 mg, 29% yield) as a white solid: cSFC analytical (G) tR = 2.73 min., purity: 99.87%; LCMS (X): tR=1.464 min., (ES⁺) m/z (M+H)⁺ = 316.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.42 (s, 1H), 8.17 (s, 1H), 4.64-4.63 (m, 2H), 4.62-4.60 (m, 1H), 4.54-4.52 (m, 2H), 3.78-3.70 (m, 1H), 3.57-3.56 (m, 1H), 3.49-3.39 (m, 2H), 2.46-2.43 (m, 1H), 2.32-2.29 (m, 1H), 2.22-2.16 (m, 2H), 2.00-1.94 (m, 1H), 1.43-1.37 (m, 1H), 1.31-1.24 (m, 2H), 1.17-1.16 (m, 1H).

[00978] Preparation of (*S*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydro-[1,4]dioxino[2,3-*c*]pyridine-7-carboxamide hydrochloride (**(*S*)-76**)

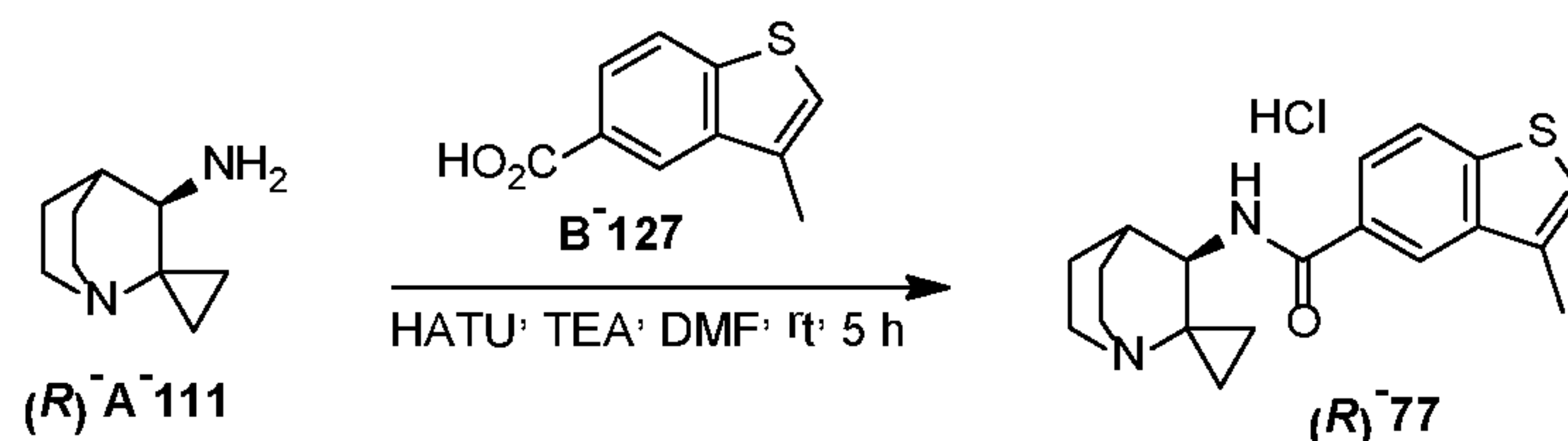


[00979] Following general procedure B, **Compound (*S*)-76** was prepared from **compound B-124** (30 mg, 0.20 mmol) and **compound (*S*)-A-111** (0.30 g, 0.20 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 16-46% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydro-[1,4]dioxino[2,3-*c*]pyridine-7-carboxamide hydrochloride (**compound (*S*)-76**) (50 mg, 85% yield) as a white solid: cSFC analytical (G) tR = 2.88 min., purity: 99.21%; LCMS (X): tR=1.464 min., (ES⁺) m/z (M+H)⁺ = 316.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.42 (s, 1H), 8.19 (s, 1H), 4.65-4.63 (m, 2H),

4.62-4.60 (m, 1H), 4.54-4.52 (m, 2H), 3.75-3.73 (m, 1H), 3.57-3.56 (m, 1H), 3.49-3.40 (m, 2H), 2.45-2.44 (m, 1H), 2.34-2.30 (m, 1H), 2.22-2.14 (m, 2H), 2.02-1.94 (m, 1H), 1.43-1.39 (m, 1H), 1.37-1.25 (m, 2H), 1.18-1.15 (m, 1H).

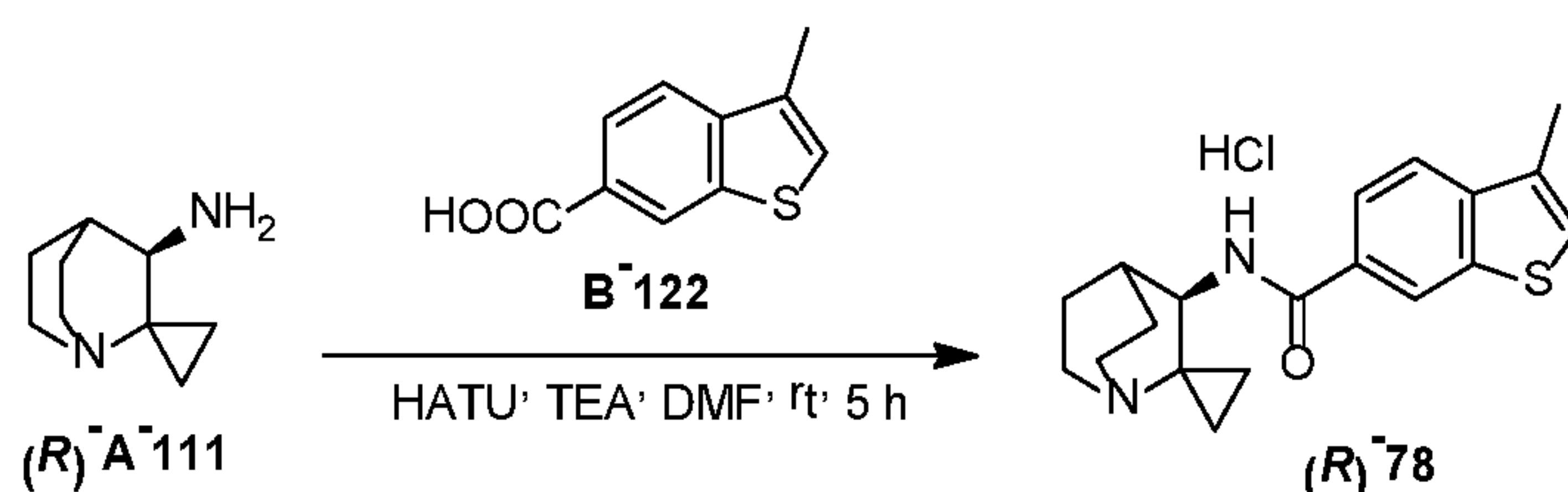
[00980] Example 77: (*R*)-3-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-5-carboxamide hydrochloride ((*R*)-77)



[00981] Following general procedure B, **Compound (*R*)-77** was prepared from **compound B-127** (63 mg, 0.32 mmol) and **compound (*R*)-A-111** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 10 μm; Mobile phase: 20-50% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-3-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-5-carboxamide hydrochloride (**compound (*R*)-77**) (60 mg, 56% yield) as a white solid: cSFC analytical (A) *t*_R=2.62 min., purity: 97.93%; LCMS (B): *t*_R=0.664 min., 327.1 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.28 (d, *J*=1.2 Hz, 1H), 7.97 (d, *J*=8.8 Hz, 1H), 7.82 (dd, *J*₁=8.4 Hz, *J*₂=1.6 Hz, 1H), 7.33 (s, 1H), 4.63 (d, *J*=2.0 Hz, 1H), 3.71-3.69 (m, 1H), 3.60-3.59 (m, 1H), 3.50-3.43 (m, 2H), 2.52 (s, 3H), 2.52-2.47 (m, 1H), 2.34 (m, 1H), 2.26-2.18 (m, 2H), 2.00-1.99 (m, 1H), 1.41-1.38 (m, 1H), 1.29-1.19 (m, 3H).

[00982] Example 78: (*R*)-3-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-6-carboxamide ((*R*)-78)

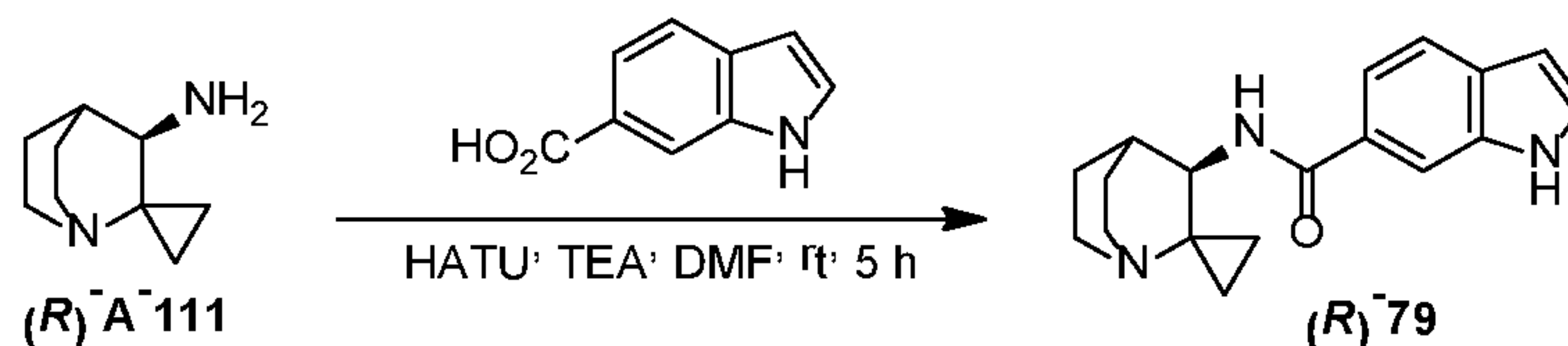


[00983] Following general procedure B, **Compound (*R*)-78** was prepared from **compound B-122** (69 mg, 0.36 mmol) and **compound (*R*)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex SynergiC18 150×30mm, particle size: 10 μm; Mobile phase: 20-50% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-3-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-6-carboxamide hydrochloride (**compound (*R*)-78**) (30 mg, 25% yield) as a white solid: cSFC analytical (A) *t*_R=2.58 min., purity: 97.59%; LCMS (B): *t*_R=0.643 min., 327.1 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.42 (s, 1H), 8.46 (d, *J*=8.0 Hz, 1H), 7.45 (s, 1H), 4.62 (d, *J*=2 Hz, 1H), 3.72-

3.70 (m, 1H), 3.61-3.60 (m, 1H), 3.52-3.42 (m, 2H), 2.54-2.50 (m, 4H), 2.34-2.20 (m, 3H), 2.04-2.01 (m, 1H), 1.40-1.37 (m, 1H), 1.30-1.22 (m, 3H).

[00984] Example 79: (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1*H*-indole-6-carboxamide ((*R*)-79)

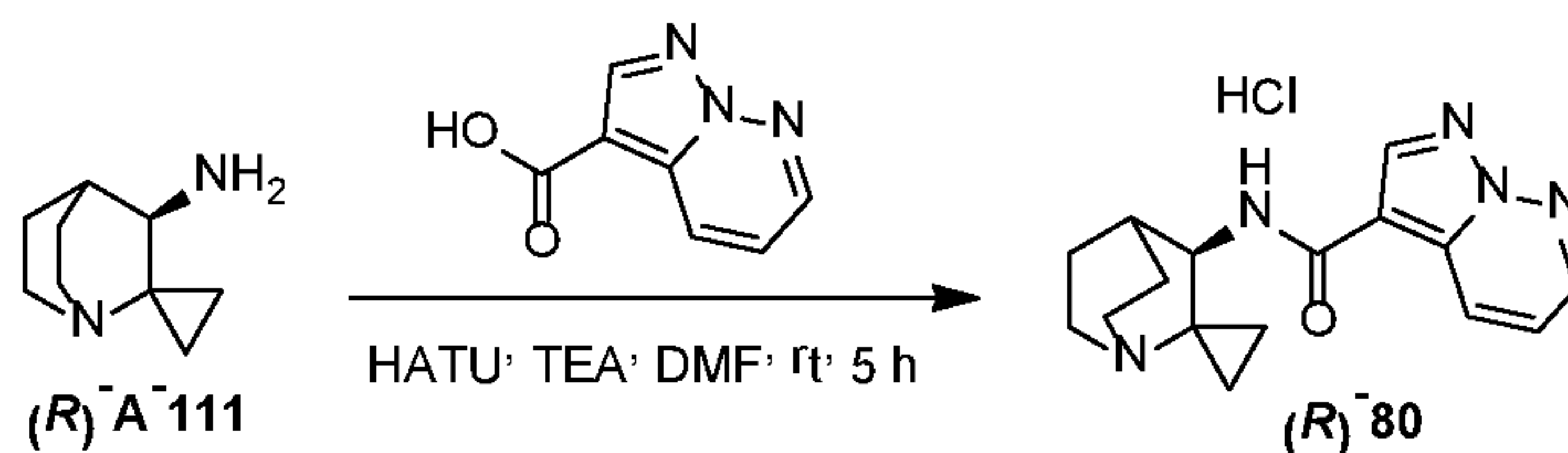


[00985] Following general procedure B, **Compound (*R*)-79** was prepared from 1*H*-indole-6-carboxylic acid (53 mg, 0.33 mmol) and **compound (*R*)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 150×30 mm, particle size: 10 μm; Mobile phase: 25-55% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1*H*-indole-6-carboxamide (**compound (*R*)-79**) (24 mg, 25% yield) as a white solid: cSFC analytical (A) t_R=2.77 min., purity: 97.84%; LCMS (G): t_R=2.234 min., (ES⁺) m/z (M+H)⁺ = 296.1; ¹H-NMR (CD₃OD, 400 MHz): δ 7.92 (s, 1H), 7.63 (d, J=8.4 Hz, 1H), 7.50 (dd, J=8.0, 1.2 Hz, 1H), 7.41 (d, J=2.8 Hz, 1H), 6.53 (d, J=2.8 Hz, 1H), 4.24 (d, J=1.6 Hz, 1H), 3.33-3.23 (m, 1H), 3.10-3.08 (m, 1H), 2.93-2.86 (m, 2H), 2.12 (d, J=3.2 Hz, 1H), 2.02-1.90 (m, 1H), 1.89-1.82 (m, 2H), 1.57 (m, 1H), 0.93-0.87 (m, 2H), 0.79-0.70 (m, 2H).

[00986] Example 80:

[00987] Preparation of (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrazolo[1,5-*b*]pyridazine-3-carboxamide hydrochloride ((*R*)-80)

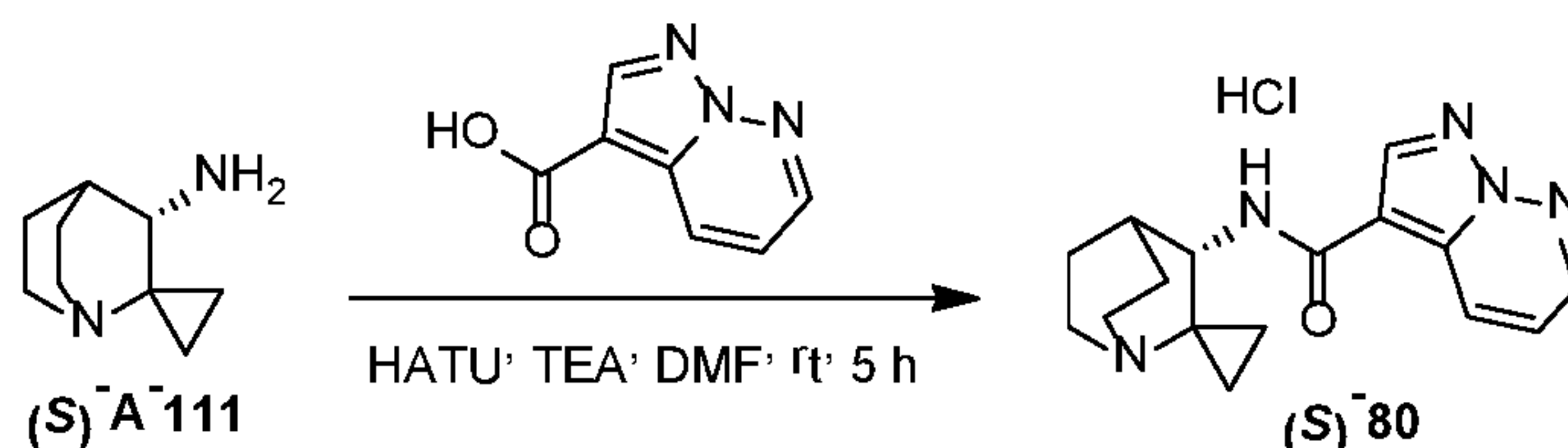


[00988] Following general procedure B, **Compound (*R*)-80** was prepared from pyrazolo[1,5-*b*]pyridazine-3-carboxylic acid (53 mg, 0.33 mmol) and **compound (*R*)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 16-46% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrazolo[1,5-*b*]pyridazine-3-carboxamide hydrochloride (**compound (*R*)-80**) (30 mg, 31% yield) as a white solid: cSFC analytical (G) t_R = 3.73 min., purity: 96.63%; LCMS (X): t_R = 1.319 min., (ES⁺) m/z (M+H)⁺ = 298.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.69 (s, 1H), 8.63 (dd, J₁ = 9.4 Hz, J₂ = 2.0 Hz, 1H), 8.53-8.51 (dd, J₁ = 4.4 Hz, J₂ = 2.0 Hz, 1H), 7.42-7.38 (m, 1H), 4.60 (d, J = 2.4 Hz, 1H), 3.69-3.58 (m, 1H), 3.57-3.47 (m,

1H), 3.45-3.41 (m, 2H), 2.44-2.42 (m, 1H), 2.36-2.30 (m, 1H), 2.23-2.18 (m, 2H), 2.00-1.97 (m, 1H), 1.39-1.34 (m, 1H), 1.26-1.20 (m, 3H).

[00989] Preparation of (*S*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrazolo[1,5-*b*]pyridazine-3-carboxamide hydrochloride ((*S*)-80)

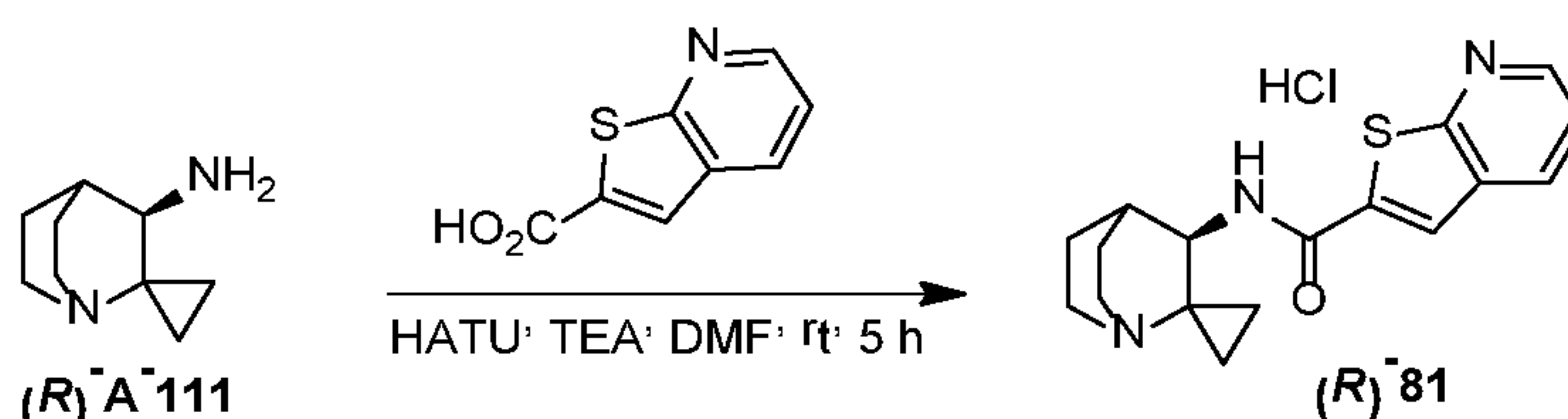


[00990] Following general procedure B, **Compound (S)-80** was prepared from pyrazolo[1,5-*b*]pyridazine-3-carboxylic acid (50 mg, 0.31 mmol) and **compound (S)-A-111** (47 mg, 0.31 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 16-46% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*S*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrazolo[1,5-*b*]pyridazine-3-carboxamide hydrochloride (**compound (S)-80**) (30 mg, 33% yield) as a white solid: cSFC analytical (G) tR = 2.98 min., purity: 99.29%; LCMS (X): tR = 1.309 min., (ES⁺) m/z (M+H)⁺ = 298.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.69 (s, 1H), 8.63 (dd, J₁ = 9.4 Hz, J₂ = 2.0 Hz, 1H), 8.52 (dd, J₁ = 4.4 Hz, J₂ = 2.0 Hz, 1H), 7.41-7.38 (m, 1H), 4.59 (d, J = 2.4 Hz, 1H), 3.73-3.72 (m, 1H), 3.57-3.47 (m, 1H), 3.45-3.41 (m, 2H), 2.44-2.42 (m, 1H), 2.36-2.29 (m, 1H), 2.24-2.18 (m, 2H), 2.00-1.96 (m, 1H), 1.39-1.34 (m, 1H), 1.23-1.17 (m, 3H).

[00991] **Example 81:**

[00992] Preparation of (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*b*]pyridine-2-carboxamide hydrochloride ((*R*)-81)

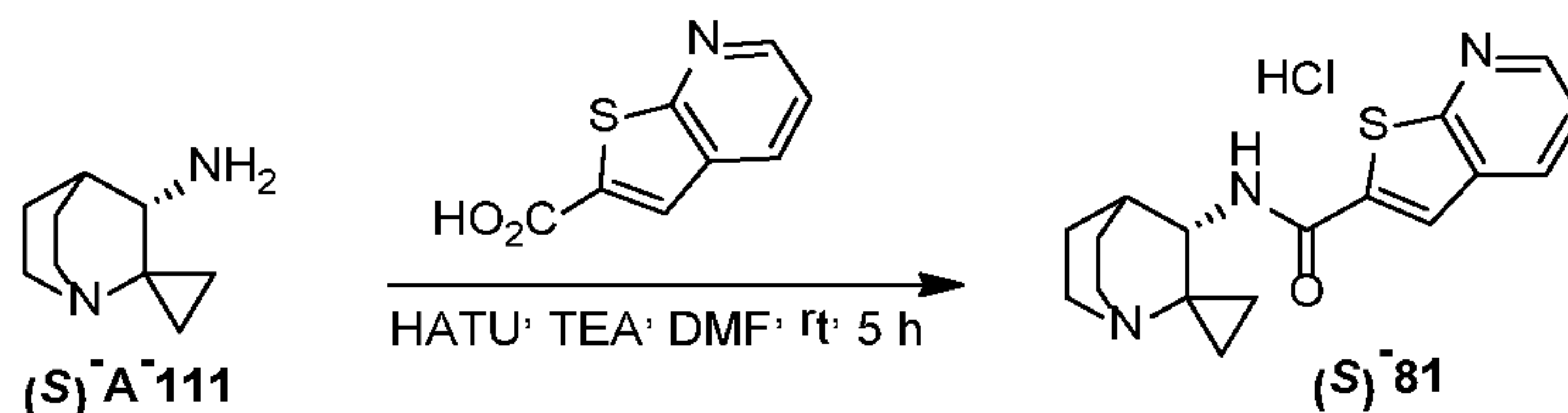


[00993] Following general procedure B, **Compound (R)-81** was prepared from thieno[2,3-*b*]pyridine-2-carboxylic acid (59 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 8-38% acetonitrile in H₂O (add 0.5% TFA, v/v)], treated with 0.2 M hydrochloric acid solution and lyophilized to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*b*]pyridine-2-carboxamide hydrochloride (**compound (R)-81**) (43 mg, 42% yield) as a yellow solid: cSFC analytical (A) tR=2.62 min., purity: 97.29%; LCMS (U): tR=1.124 min., (ES⁺) m/z (M+H)⁺ = 314.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.72 (d, J=4.8, 1.2 Hz, 1H), 8.51 (d, J=8.0, 1.2 Hz, 1H), 8.25 (s, 1H),

7.62 (d, J=8.0, 4.8 Hz, 1H), 4.58 (d, J=2.0 Hz, 1H), 3.77-3.73 (m, 1H), 3.59-3.58 (m, 1H), 3.50-3.43 (m, 2H), 2.47-2.45 (m, 1H), 2.36 (m, 1H), 2.24-2.17 (m, 2H), 2.01-1.99 (m, 1H), 1.40-1.36 (m, 1H), 1.31-1.28 (m, 2H), 1.26-1.20 (m, 1H).

[00994] Preparation of (*S*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*b*]pyridine-2-carboxamide hydrochloride ((*S*)-**81**)

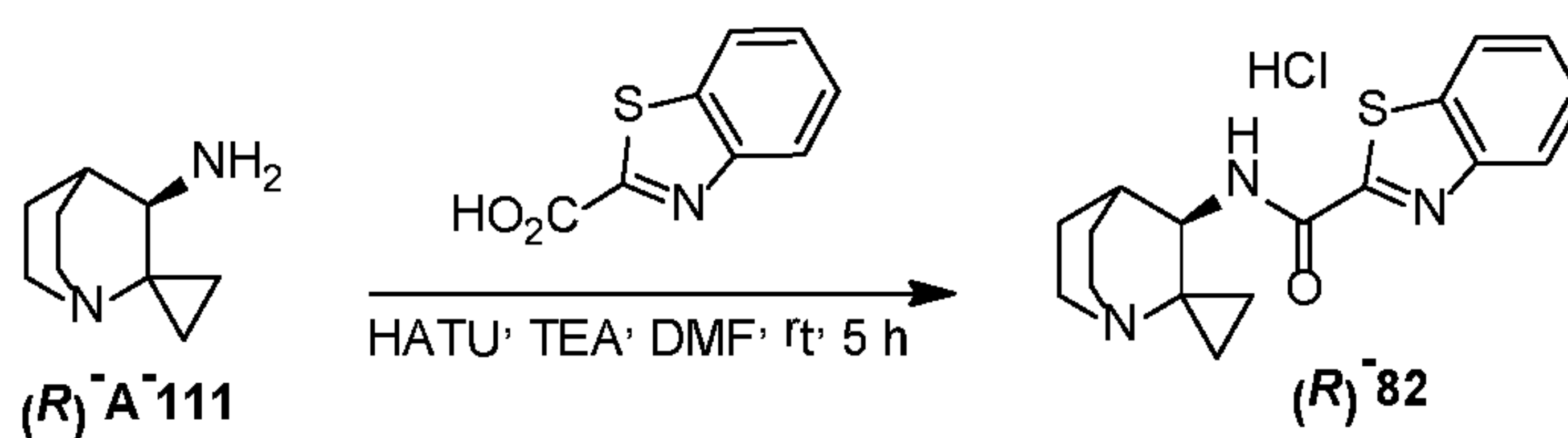


[00995] Following general procedure B, **Compound (S)-81** was prepared from thieno[2,3-*b*]pyridine-2-carboxylic acid (47 mg, 0.26 mmol) and **compound (S)-A-111** (40 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 8-38% acetonitrile in H₂O (add 0.5% TFA, v/v)], treated with 0.2 M hydrochloric acid solution and lyophilized to give:

(*S*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*b*]pyridine-2-carboxamide hydrochloride (**compound (S)-81**) (50 mg, 61% yield) as a yellow solid: cSFC analytical (A) t_R=3.52 min., purity: 97.73%; LCMS (U): t_R=1.127 min., (ES⁺) m/z (M+H)⁺ = 314.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.85-8.84 (m, 1H), 8.75 (d, J=8.4 Hz, 1H), 8.43 (s, 1H), 7.80 (d, J=8.4, 5.2 Hz, 1H), 4.59 (d, J=2.4 Hz, 1H), 3.79-3.75 (m, 1H), 3.58-3.57 (m, 1H), 3.50-3.43 (m, 2H), 2.46-2.36 (m, 2H), 2.23-2.17 (m, 2H), 2.03-1.96 (m, 1H), 1.40-1.39 (m, 1H), 1.35-1.28 (m, 2H), 1.18-1.17 (m, 1H).

[00996] **Example 82:**

[00997] Preparation of (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-2-carboxamide hydrochloride ((*R*)-**82**)

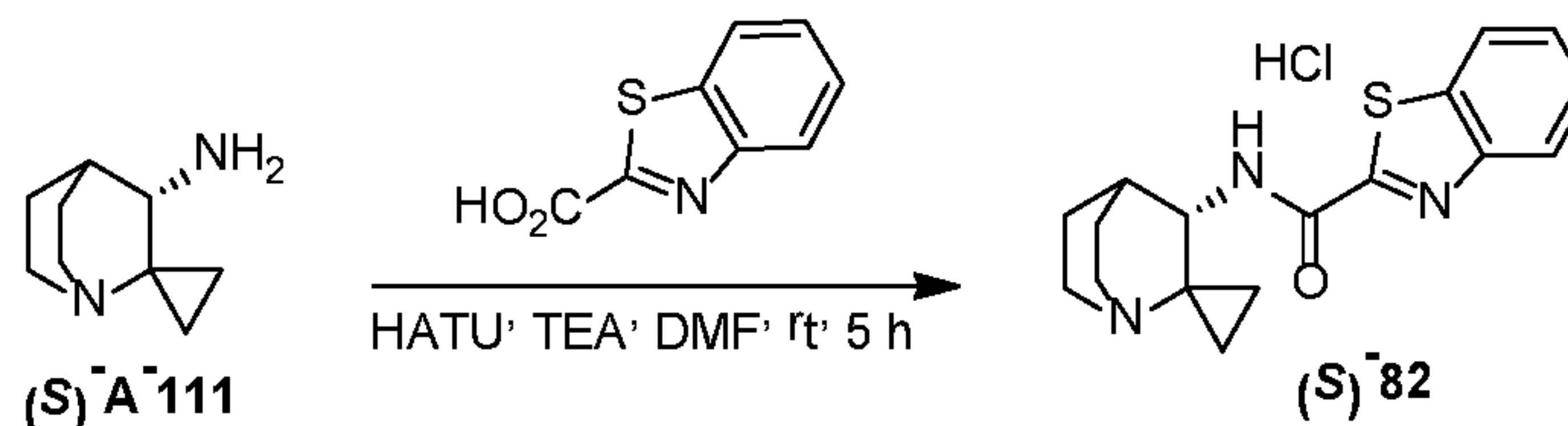


[00998] Following general procedure B, **Compound (R)-82** was prepared from benzo[d]thiazole-2-carboxylic acid (59 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-H; Column: YMC-pack ODS-AQ 150×30 mm, particle size: 5 μm; Mobile phase: 14-44% acetonitrile in H₂O (add 0.5% TFA, v/v)], treated with 0.2 M hydrochloric acid and lyophilized to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-2-carboxamide hydrochloride (**compound (R)-82**) (58 mg, 56% yield) as a white solid: cSFC analytical (A) t_R=2.10 min., purity: 97.31%; LCMS (V): t_R=2.478 min., 314.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.17 (d, J=8.4 Hz, 1H), 8.11 (d, J=7.6 Hz, 1H), 7.64 (t, J=7.6 Hz, 1H), 7.58 (t, J=7.6 Hz,

1H), 4.60 (d, J= 2.0 Hz, 1H), 3.80-3.77 (m, 1H), 3.60-3.59 (m, 1H), 3.52-3.41 (m, 2H), 2.49-2.48 (m, 1H), 2.36 (m, 1H), 2.26-2.18 (m, 2H), 2.01-1.97 (m, 1H), 1.40-1.37 (m, 1H), 1.31-1.20 (m, 3H).

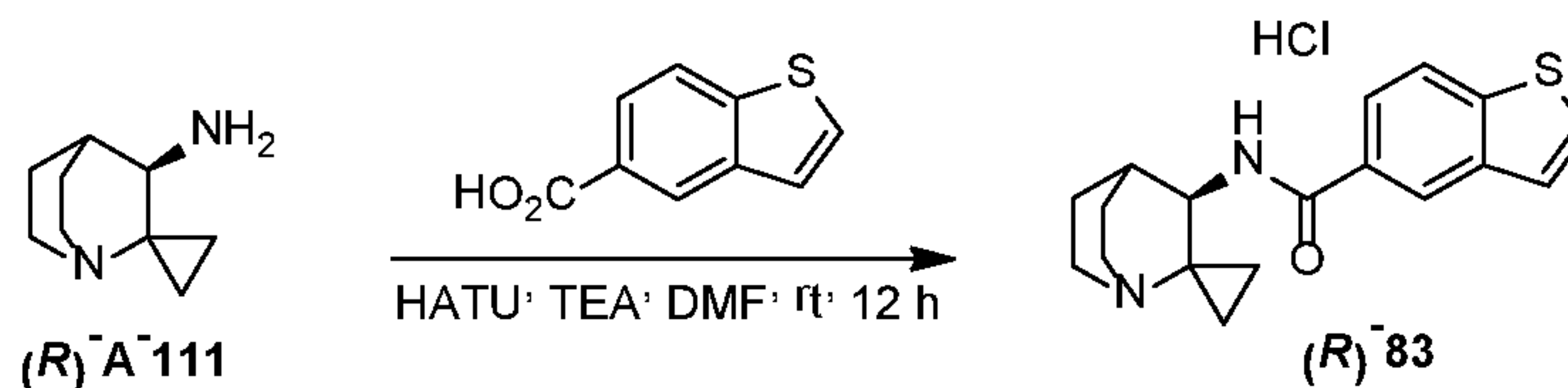
[00999] Preparation of (*S*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-2-carboxamide hydrochloride ((*S*)-**82**)



[001000] Following general procedure B, **Compound (S)-82** was prepared from benzo[d]thiazole-2-carboxylic acid (47 mg, 0.26 mmol) and **compound (S)-A-111** (40 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-H; Column: YMC-pack ODS-AQ 150×30 mm, particle size: 5 μm; Mobile phase: 14-44% acetonitrile in H₂O (add 0.5% TFA, v/v)], treated with 0.2 M hydrochloric acid and lyophilized to give:

(*S*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-2-carboxamide hydrochloride (**compound (S)-82**) (40 mg, 49% yield) as a white solid: cSFC analytical (A) t_R=2.27 min., purity: 97.78%; LCMS (V): t_R=2.469 min., 314.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.17 (d, J=8.4 Hz, 1H), 8.11 (d, J=8.0 Hz, 1H), 7.64 (t, J=7.6 Hz, 1H), 7.58 (t, J=7.6 Hz, 1H), 4.60 (s, 1H), 3.78-3.74 (m, 1H), 3.60-3.59 (m, 1H), 3.52-3.44 (m, 2H), 2.49-2.48 (m, 1H), 2.36-2.34 (m, 1H), 2.25-2.14 (m, 2H), 2.01 (m, 1H), 1.40-1.35 (m, 1H), 1.34-1.20 (m, 3H).

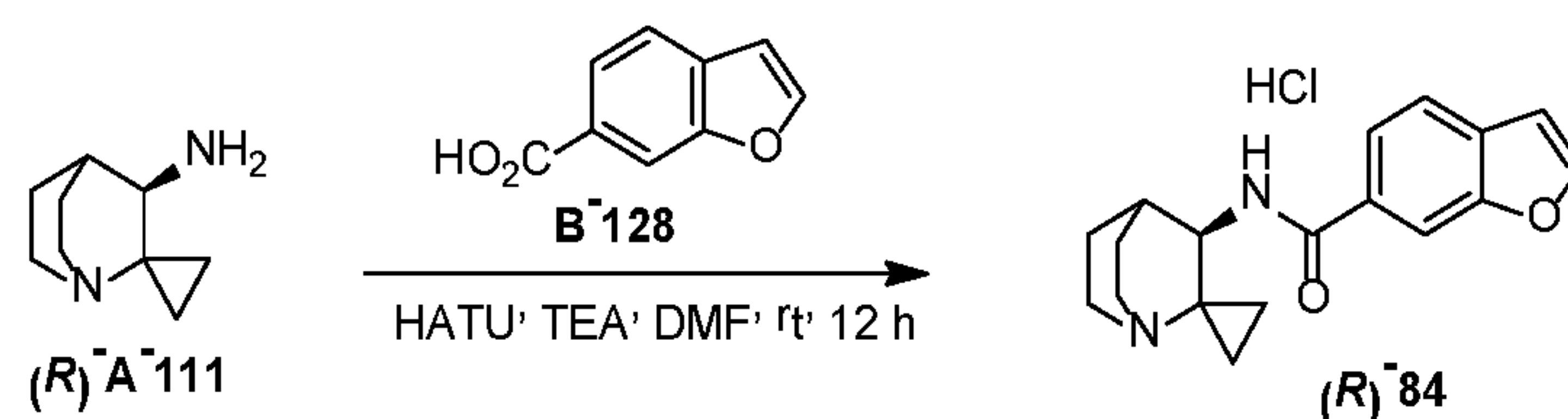
[001001] **Example 83:** (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-5-carboxamide hydrochloride ((*R*)-**83**)



[001002] Following general procedure B, **Compound (R)-83** was prepared from benzo[b]thiophene-5-carboxylic acid (64 mg, 0.36 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 10 μm; Mobile phase: 5-35% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-5-carboxamide hydrochloride (**compound (R)-83**) (15 mg, 15% yield) as a white solid: cSFC analytical (B) t_R=2.57 min., purity: 98.14%; LCMS (C): t_R=1.267 min., (ES⁺) m/z (M+H)⁺ = 313.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.38(s, 1H), 8.04 (d, J=8.0 Hz, 1H), 7.81 (d, J=8.0 Hz, 1H), 7.73 (d, J=5.2 Hz, 1H), 7.52 (d, J=5.2 Hz, 1H), 4.62(s, 1H), 3.72-3.68 (m, 1H), 3.60-3.51 (m, 1H), 3.50-3.33 (m, 2H), 2.49-2.48 (m, 1H), 2.38-2.17 (m, 3H), 2.01 (m, 1H), 1.42-1.38 (m, 1H), 1.30-1.20 (m, 3H).

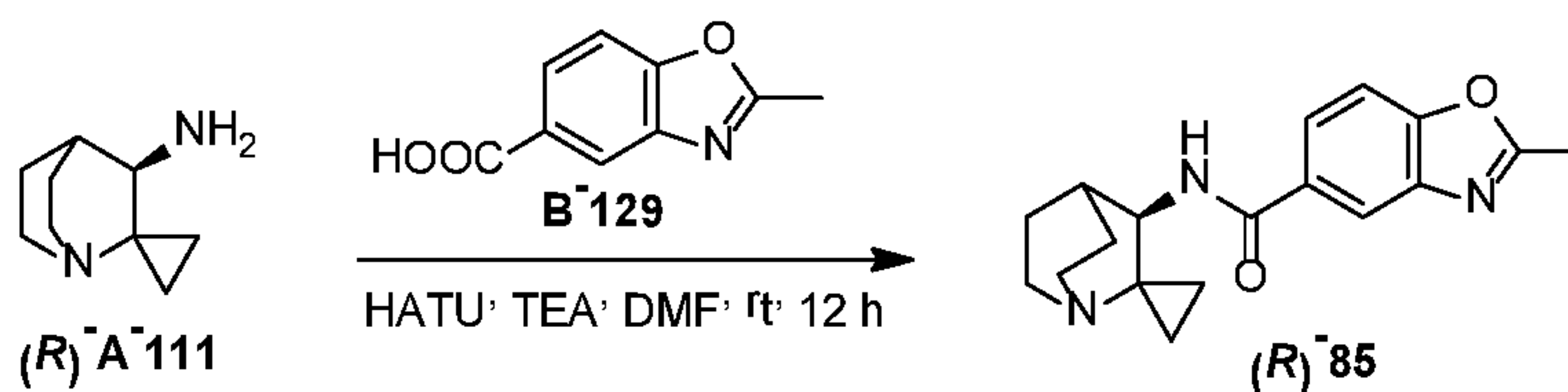
[001003] **Example 84:** (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-6-carboxamide hydrochloride ((*R*)-84)



[001004] Following general procedure B, **Compound (*R*)-84** was prepared from **compound B-128** (53 mg, 0.33 mmol) and **compound (*R*)-A-111** (50 mg, 0.33 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 10 μm; Mobile phase: 3-33% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-6-carboxamide hydrochloride (**compound (*R*)-84**) (45mg, 41% yield) as a white solid: cSFC analytical (A) t_R=2.11 min., purity: 97.07%; LCMS (R): t_R=0.417., 297.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.04 (s, 1H), 7.93 (d, J=2.4 Hz, 1H), 7.76-7.71 (m, 2H), 6.96 (d, J=1.2 Hz, 1H), 4.58 (s, 1H), 3.69-3.65 (m, 1H), 3.56-3.55 (m, 1H), 3.46-3.38 (m, 2H), 2.44 (d, J=3.2 Hz, 1H), 2.33-2.26 (m, 3H), 1.96 (s, 1H), 1.35-1.25 (m, 1H), 1.24-1.17 (m, 1H).

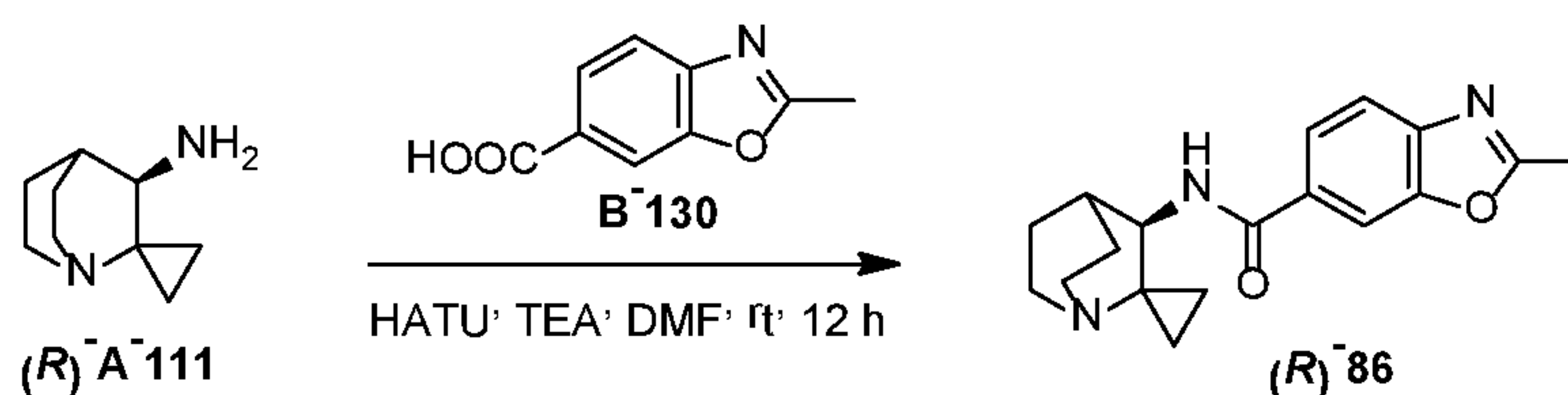
[001005] **Example 85:** (*R*)-2-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-5-carboxamide ((*R*)-85)



[001006] Following general procedure B, **Compound (*R*)-85** was prepared from **compound B-129** (0.069 g, 0.39 mmol) and **compound (*R*)-A-111** (0.051 g, 0.34 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-C; Column: Phenomenex Gemini C18 150×30 mm, particle size: 5 μm; Mobile phase: 35-65% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give:

(*R*)-2-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-5-carboxamide (**compound (*R*)-85**) (0.030 g, 29% yield) as a white solid: cSFC analytical (A) t_R=2.04 min., purity: 97.63%; LCMS (J): t_R=0.970 min., 312.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.10 (s, 1H), 7.85 (m, 1H), 7.65(d, J=8.4 Hz, 1H), 4.23 (s, 1H), 3.27-3.23 (m, 1H), 3.09-3.07 (m, 1H), 2.92-2.85 (m, 2H), 2.69 (s, 3H), 2.12-2.12 (m, 1H), 2.00-1.85 (m, 3H), 1.56-1.56 (m, 1H), 0.91-0.87 (m, 2H), 0.76-0.68 (m, 2H).

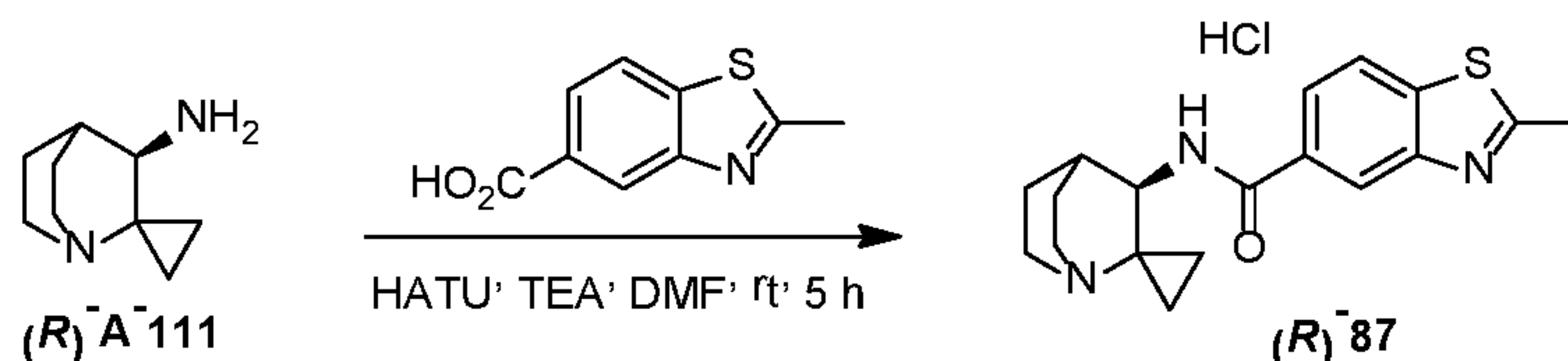
[001007] **Example 86:** (*R*)-2-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-6-carboxamide ((*R*)-86)



[001008] Following general procedure B, **Compound (R)-86** was prepared from **compound B-130** (0.060 g, 0.34 mmol) and **compound (R)-A-111** (0.052 g, 0.34 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-C; Column: Phenomenex Gemini C18 150×30 mm, particle size: 5 μm; Mobile phase: 35-65% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give:

(R)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-6-carboxamide (**compound (R)-86**) (0.040 g, 38% yield) as a white solid: cSFC analytical (A) t_R=2.14 min., purity: 97.62%; LCMS (J): t_R=0.960 min., 312.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.05 (s, 1H), 7.87-7.84 (m, 1H), 7.70 (d, J=8.4 Hz, 1H), 4.24-4.23 (s, 1H), 3.25-3.23 (m, 1H), 3.09-3.09 (m, 1H), 2.92-2.83 (m, 2H), 2.70 (s, 3H), 2.13-2.12 (m, 1H), 2.00-1.85 (m, 3H), 1.57-1.57 (m, 1H), 0.91-0.87 (m, 2H), 0.76-0.68 (m, 2H).

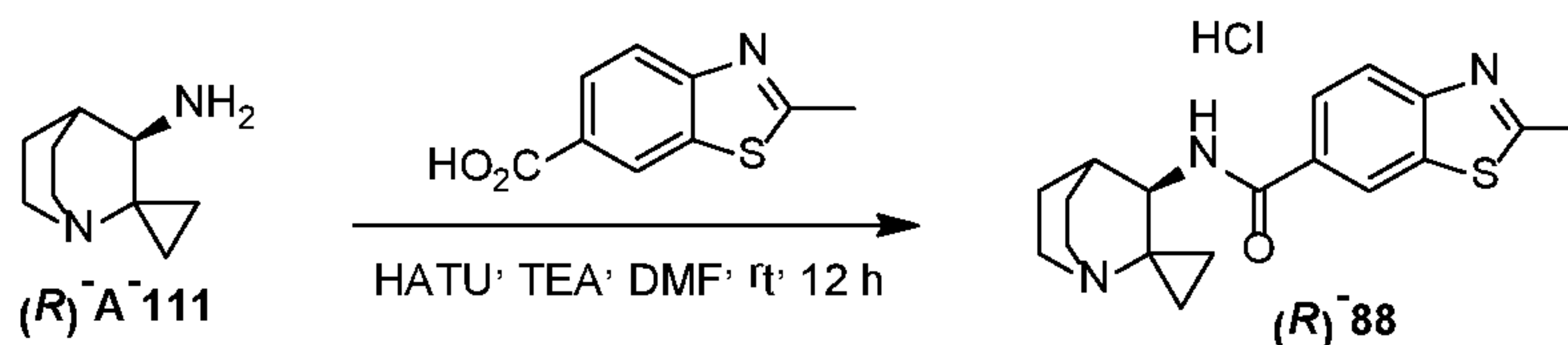
[001009] **Example 87:** (R)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-5-carboxamide hydrochloride ((R)-87)



[001010] Following general procedure B, **Compound (R)-87** was prepared from 2-methylbenzo[d]thiazole-5-carboxylic acid (63 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 8-38% acetonitrile in H₂O (add 0.5% TFA, v/v)], treated with HCl and lyophilized to give:

(R)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-5-carboxamide hydrochloride (**compound (R)-87**) (50 mg, 42% yield) as a white solid: cSFC analytical (A) t_R=2.34 min., purity: 97.73%; LCMS (K): t_R=1.210 min., (ES⁺) m/z (M+H)⁺ = 328.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.39 (s, 1H), 8.09 (d, J=8.8 Hz, 1H), 7.91 (d, J=8.0 Hz, 1H), 4.62 (s, 1H), 3.72-3.71 (m, 1H), 3.61-3.60 (m, 1H), 3.50-3.43 (m, 2H), 2.91 (s, 3H), 2.49-2.48 (m, 1H), 2.37-2.16 (m, 3H), 2.05-2.00 (m, 1H), 1.44-1.41 (m, 1H), 1.32-1.22 (m, 3H).

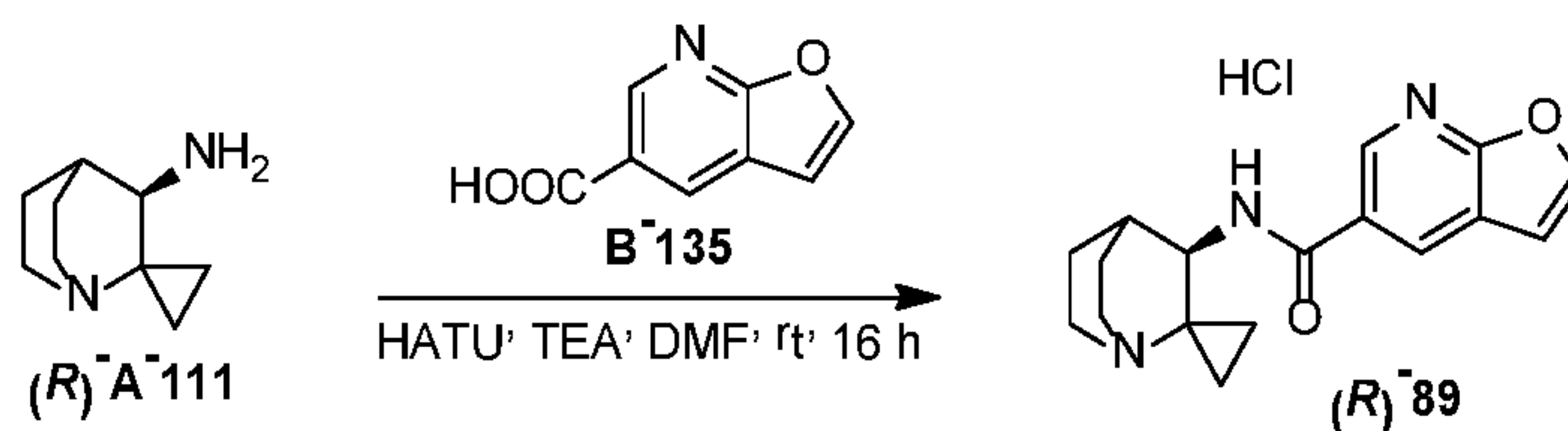
[001011] **Example 88:** (R)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-6-carboxamide hydrochloride ((R)-88)



[001012] Following general procedure B, **Compound (R)-88** was prepared from 2-methylbenzo[d]thiazole-6-carboxylic acid (63 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 8-38% acetonitrile in H₂O (add 0.5% TFA, v/v)], treated with 0.2 N HCl and lyophilized to give:

(*R*)-2-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-6-carboxamide hydrochloride (**compound (R)-88**) (48 mg, 40% yield) as a white solid: cSFC analytical (A) *t*_R=2.50 min., purity: 97.89%; LCMS (K): *t*_R=1.164 min., (ES⁺) *m/z* (M+H)⁺ = 328.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.58 (s, 1H), 8.06-7.99 (m, 2H), 4.58 (s, 1H), 3.72-3.58 (m, 1H), 3.57-3.48 (m, 1H), 3.46-3.41 (m, 2H), 2.97 (s, 3H), 2.47-2.46 (m, 1H), 2.33-2.30 (m, 1H), 2.24-2.17 (m, 2H), 2.02-1.95 (m, 1H), 1.42-1.41 (m, 1H), 1.33-1.20 (m, 3H).

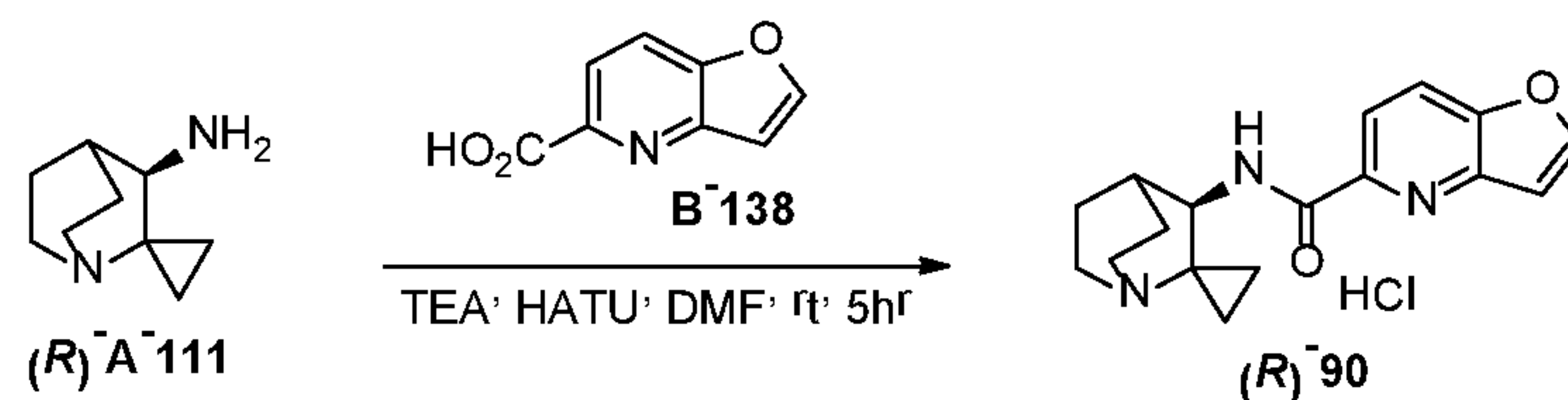
[001013] **Example 89:** (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-*b*]pyridine-5-carboxamide ((*R*)-89)



[001014] Following general procedure B, **Compound (R)-89** was prepared from **compound B-135** (54 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 16 hours. The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 150×25 mm, particle size: 10 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-*b*]pyridine-5-carboxamide hydrochloride (**compound (R)-89**) (40 mg, 38% yield) as a white solid: cSFC analytical (A) *t*_R=2.75 min., purity: 100%; LCMS (J): *t*_R=1.27 min., 298.1 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): 8.76 (d, *J*=2 Hz, 1H), 8.56 (s, 1H), 8.03 (d, *J*=2 Hz, 1H), 7.07 (d, *J*=2.4 Hz, 1H), 4.53 (s, 1H), 3.59-3.49 (m, 2H), 3.40-3.37 (m, 2H), 2.04-2.42 (m, 1H), 2.28-2.11 (m, 3H), 1.92 (m, 1H), 1.29-1.12 (m, 4H).

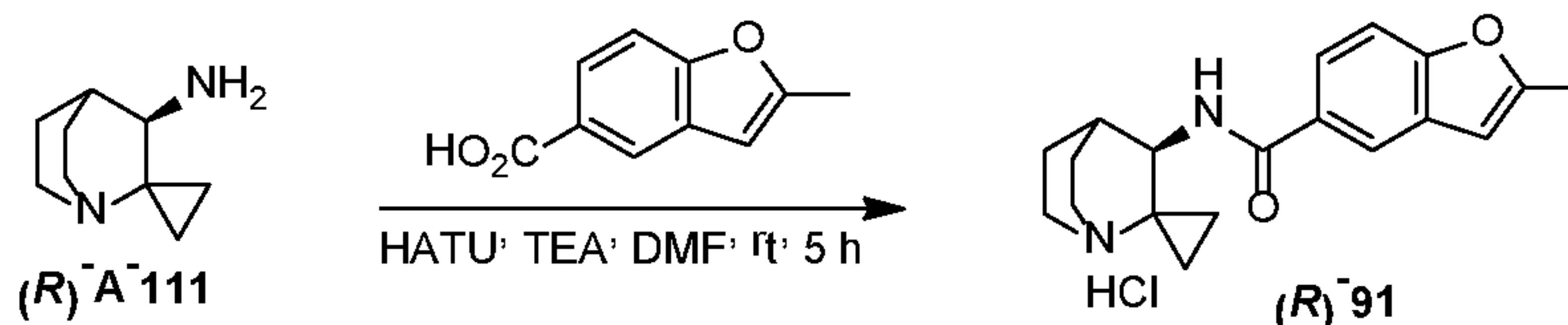
[001015] **Example 90:** (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[3,2-*b*]pyridine-5-carboxamide hydrochloride ((*R*)-90)



[001016] Following general procedure B, **Compound (R)-90** was prepared from **compound B-138** (54 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 16-46% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[3,2-*b*]pyridine-5-carboxamide hydrochloride (**compound (R)-90**) (50 mg, 51% yield) as a white solid: cSFC analytical (A) *t*_R=1.94 min., purity: 98.64%; LCMS (M): *t*_R=0.899 min., (ES⁺) *m/z* (M+H)⁺ = 298.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.34 (d, *J*=2.4 Hz, 1H), 8.26 (m, 2H), 8.21 (d, *J*=2.0 Hz, 1H), 4.60 (s, 1H), 3.77-3.75 (m, 1H), 3.59-3.58 (m, 1H), 3.50-3.44 (m, 2H), 2.47-2.46 (m, 1H), 2.39-2.33 (m, 1H), 2.22-2.19 (m, 2H), 2.02-1.99 (m, 1H), 1.32-1.30 (m, 1H), 1.26-1.11 (m, 3H).

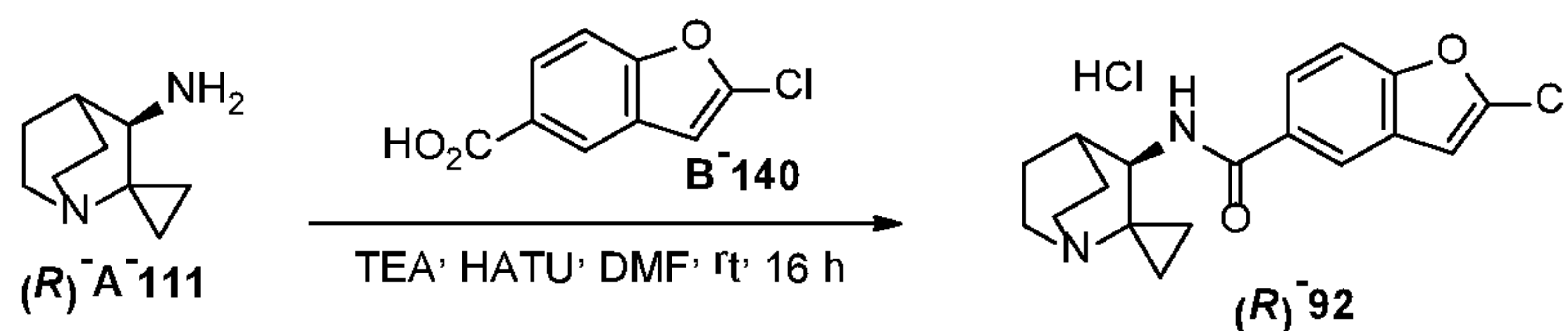
[001017] **Example 91: (R)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide hydrochloride ((R)-91)**



[001018] Following general procedure B, **Compound (R)-91** was prepared from 2-methylbenzofuran-5-carboxylic acid (60 mg, 0.34 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-pack ODS-AQ 150×30mm, particle size: 5 μm; Mobile phase: 18-48% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-2-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide hydrochloride (**compound (R)-91**) (15 mg, 13% yield) as a white solid: cSFC analytical (A) *t*_R=2.103 min., purity: 97.71%; LCMS (B): *t*_R=0.640 min., 311.1 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.02 (s, 1H), 7.73 (d, *J*=8.4, 1H), 7.49 (d, *J*=8.4, 1H), 6.58 (s, 1H), 4.60 (m, 1H), 3.69-3.61 (m, 1H), 3.60-3.59 (m, 2H), 3.50-3.44 (m, 2H), 2.47-2.46 (m, 4H), 2.33-2.19 (m, 3H), 2.01-1.99 (m, 1H), 1.40-1.36 (m, 1H), 1.27-1.20 (m, 3H).

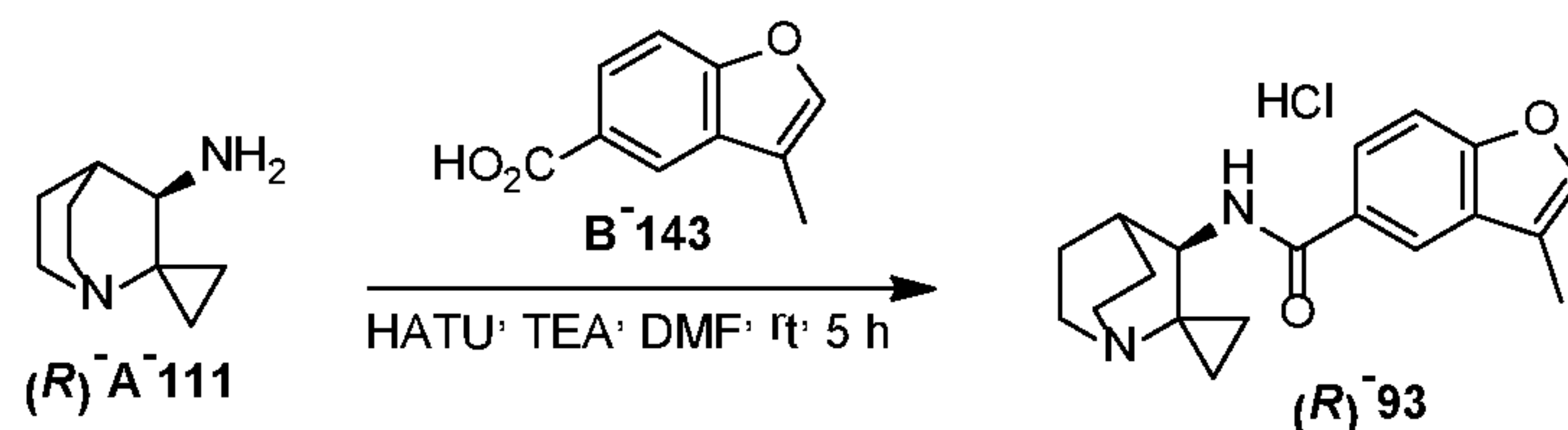
[001019] **Example 92: (R)-2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide hydrochloride ((R)-92)**



[001020] Following general procedure B, **Compound (R)-92** was prepared from **compound B-140** (71 mg, 0.36 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 16 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 10 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-2-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide hydrochloride (**compound (R)-92**) (23 mg, 21% yield) as a white solid: cSFC analytical (A) tR: 2.10 min., purity: 97.99%; LCMS (S): tR=0.89 min., (ES⁺) m/z (M+H)⁺ = 331.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.10 (d, J=1.2 Hz, 1H), 7.83 (dd, J₁=8.8 Hz, J₁=1.6 Hz, 1H), 7.60 (d, J=1.6 Hz, 1H), 6.91 (s, 1H), 4.59 (d, J=2 Hz, 1H), 3.71-3.50 (m, 2H), 3.48-3.44 (m, 2H), 2.53-2.46 (m, 1H), 2.33-2.18 (m, 3H), 2.02-1.99 (m, 1H), 1.42-1.38 (m, 1H), 1.30-1.20 (m, 3H).

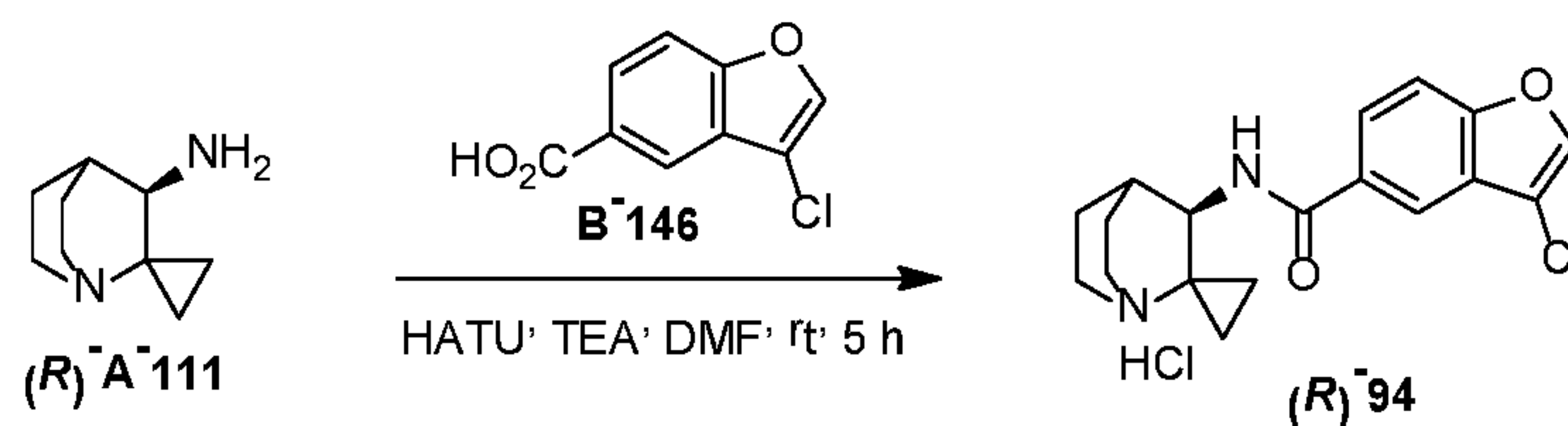
[001021] **Example 93:** (*R*)-3-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide hydrochloride (**(R)-93**)



[001022] Following general procedure B, **Compound (R)-93** was prepared from **compound B-143** (69 mg, 0.39 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 5 μm; Mobile phase: 10-40% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-3-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide hydrochloride (**compound (R)-93**) (47 mg, 41% yield) as a white solid: cSFC analytical (A) tR=2.06 min., purity: 99.42%; LCMS (B): tR=0.606 min., 311.2 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.13 (d, J=4 Hz, 1H), δ 7.81 (dd, J₁=8 Hz, J₂=4 Hz, 1H), 7.64 (d, J=4 Hz, 1H), 7.53 (d, J=8 Hz, 1H), 4.60 (m, 1H), 3.59-3.58 (m, 1H), 3.48-3.46 (m, 1H), 3.45-3.43 (m, 1H), 2.46-2.45 (m, 1H), 2.31 (m, 4H), 2.24-2.18 (m, 1H), 2.00 (m, 1H), 1.40-1.35 (m, 1H), 1.27-1.20 (m, 1H).

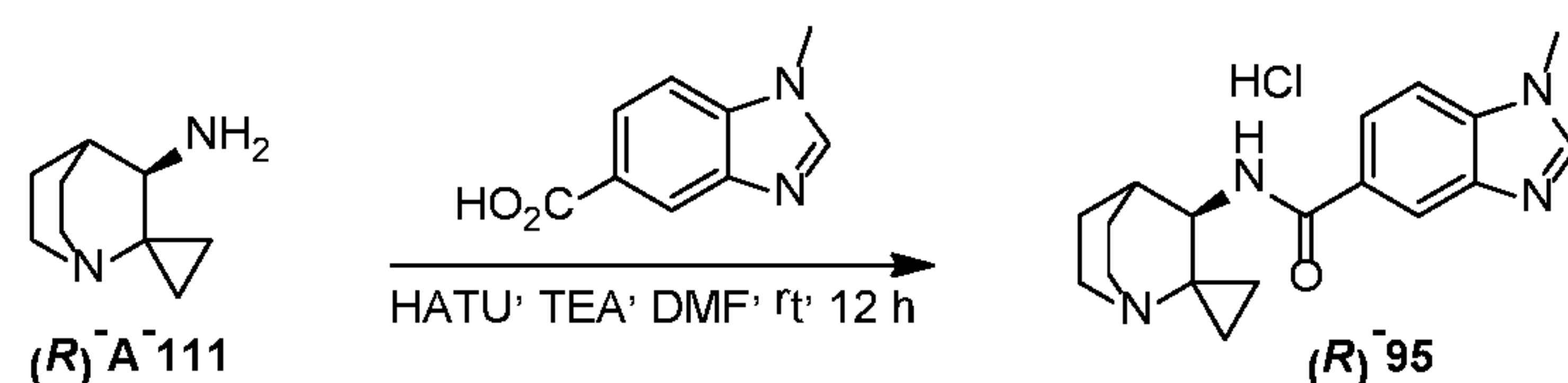
[001023] **Example 94:** (*R*)-3-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide hydrochloride (**(R)-94**)



[001024] Following general procedure B, **Compound (R)-94** was prepared from **compound B-146** (64 mg, 0.34 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 10 μm; Mobile phase: 10-40% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-3-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide hydrochloride (**compound (R)-94**) (20 mg, 17% yield) as a white solid: cSFC analytical (A) t_R=2.09 min., purity: 97.90%; LCMS (B): t_R=0.622 min., 331.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.19-8.18 (m, 1H), 8.06 (s, 1H), 7.94 (d, J=8.8, 1H), 7.67 (d, J=8.8, 1H), 3.71-3.60 (m, 2H), 3.51-3.41 (s, 2H), 2.49-2.48 (m, 1H), 2.37-2.19 (m, 3H), 2.01 (m, 1H), 1.40-1.20 (m, 5H).

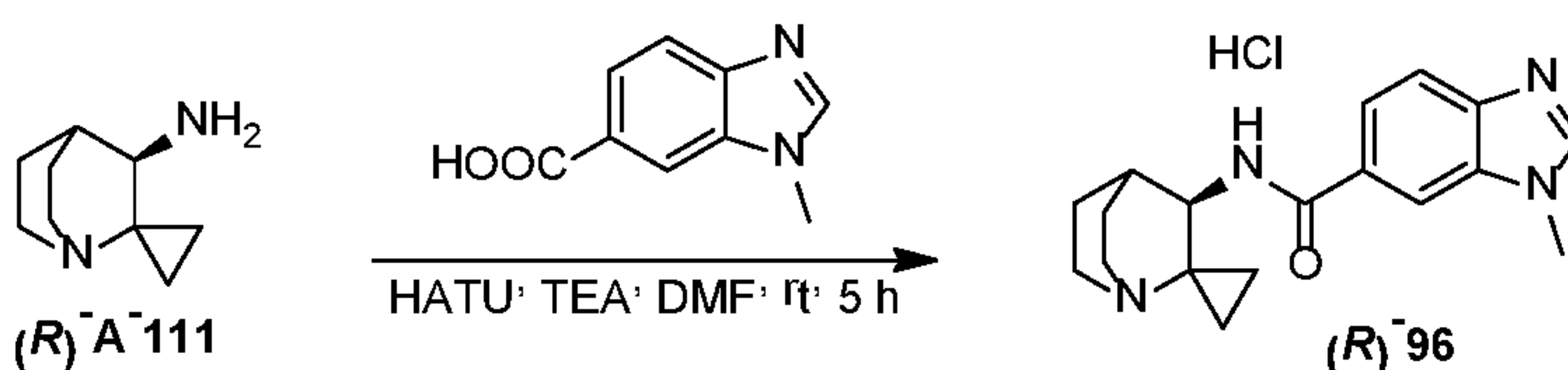
[001025] **Example 95:** (*R*)-1-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-5-carboxamide hydrochloride (**(R)-95**)



[001026] Following general procedure B, **Compound (R)-95** was prepared from 1-methyl-1H-benzo[d]imidazole-5-carboxylic acid (60 mg, 0.34 mmol) and **compound (R)-A-111** (52 mg, 0.34 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-1-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-5-carboxamide hydrochloride (**compound (R)-95**) (20 mg, 19% yield) as a white solid: cSFC analytical (A) t_R=3.01 min., purity: 97.72%; LCMS (O): t_R=1.726 min., 311.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 9.40 (s, 1H), 8.40 (s, 1H), 8.16 (d, J=8.8, 1H), 8.02 (d, J=8.8, 1H), 4.18 (s, 3H), 3.78-3.75 (m, 1H), 3.61-3.60 (m, 1H), 3.51-3.44 (m, 2H), 2.50-2.49 (m, 1H), 2.37-2.35 (m, 1H), 2.27-2.21 (m, 2H), 2.02-1.97 (m, 1H), 1.44-1.41 (m, 1H), 1.34-1.22 (m, 3H).

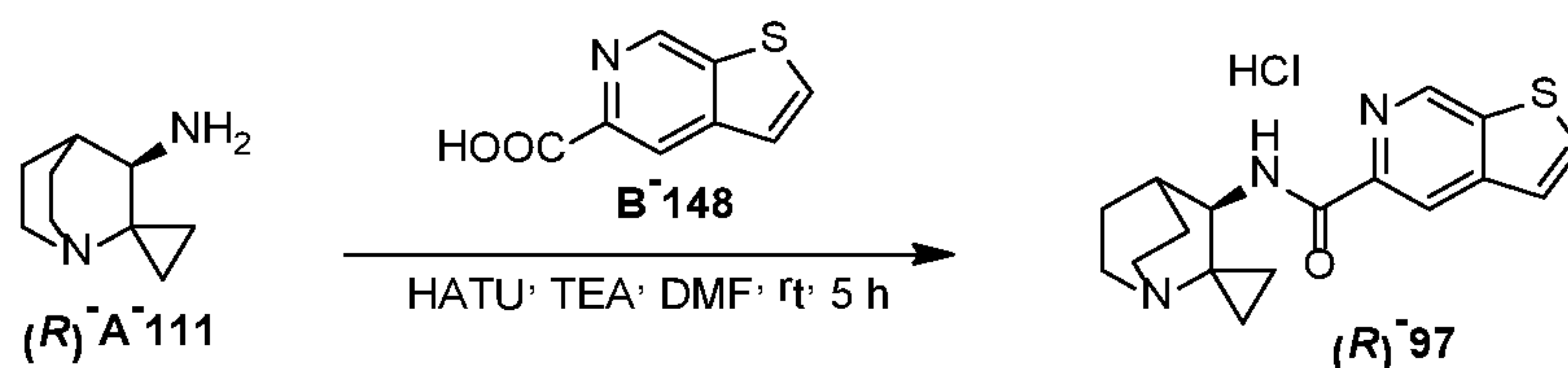
[001027] **Example 96:** (*R*)-1-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-6-carboxamide (**(R)-96**)



[001028] Following general procedure B, **Compound (R)-96** was prepared from 1-methyl-1H-benzo[d]imidazole-6-carboxylic acid (58 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-H; Column: welch Xtimate C18 150×30 mm, particle size: 5 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)]. The resulting solids were dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-1-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-6-carboxamide hydrochloride (**compound (R)-96**) (40 mg, 39% yield) as a white solid: cSFC analytical (A) t_R=2.96 min., purity: 96.48%; LCMS (Q): t_R=2.633 min., 311.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 9.53 (s, 1H), 8.60 (s, 1H), 8.19 (d, J=8.8Hz, 1H), 7.97 (d, J=8.8Hz, 1H), 4.65 (s, 1H), 4.26 (s, 1H), 3.85-3.78 (m, 1H), 3.61 (m, 1H), 3.52-3.42 (m, 2H), 2.50-2.40 (m, 2H), 2.25-2.18 (m, 2H), 2.05-2.02 (m, 1H), 1.45-1.41 (m, 1H) 1.36-1.31 (m, 2H) 1.24-1.21 (m, 1H).

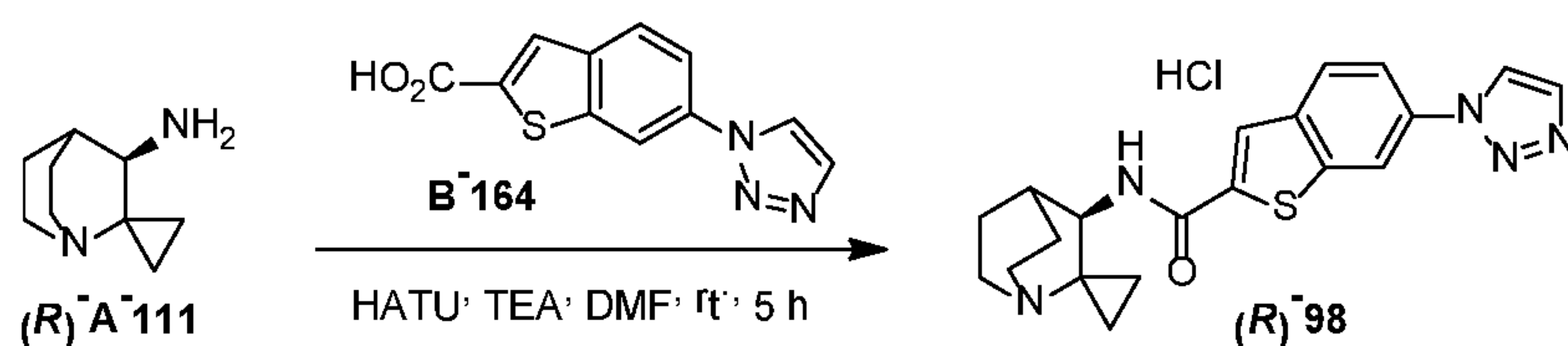
[001029] **Example 97: (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*c*]pyridine-5-carboxamide ((*R*)-97)**



[001030] Following general procedure B, **Compound (R)-97** was prepared from **compound B-148** (71 mg, 0.39 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex SynergiC18 150×25mm, particle size: 10 μm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)]. The resulting solids were dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*c*]pyridine-5-carboxamide hydrochloride (**compound (R)-97**) (40 mg, 35% yield) as a yellow solid: cSFC analytical (A) t_R=2.42 min., purity: 98.60%; LCMS (J): t_R=1.454 min., 314.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 9.46 (s, 1H), 8.87 (s, 1H), 8.43 (d, J=5.2Hz, 1H), 7.83 (d, J=5.2Hz, 1H), 4.66 (s, 1H), 3.82-3.80 (m, 1H), 3.62-3.54 (m, 1H), 3.52-3.44 (m, 1H), 2.40-2.29 (m, 1H), 2.28-2.21 (m, 2H), 2.19-2.05 (m, 1H), 1.43-1.41 (m, 1H) 1.33-1.29 (m, 1H) 1.26-1.23 (m, 1H).

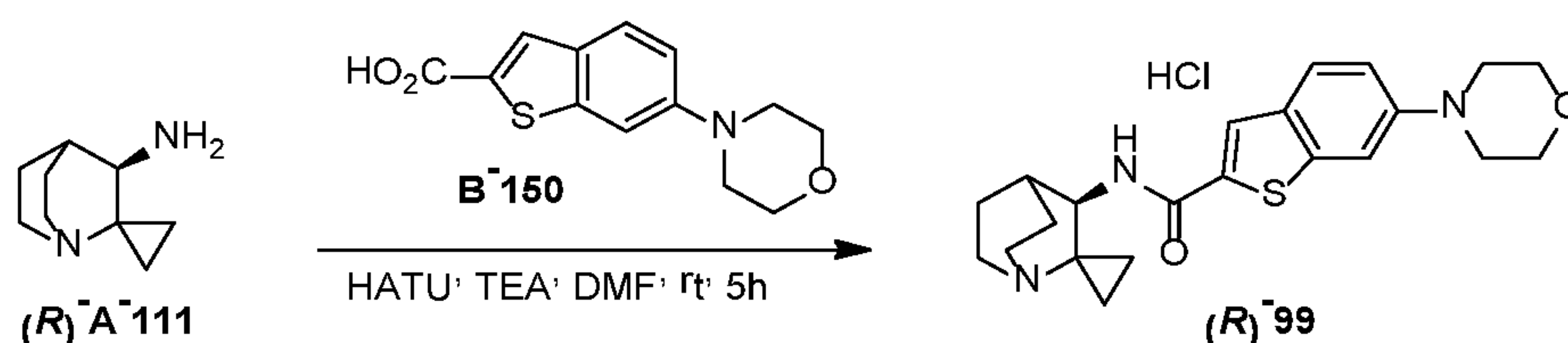
[001031] **Example 98: (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(1*H*-1,2,3-triazol-1-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-98)**



[001032] Following general procedure B, **Compound (R)-98** was prepared from **compound B-164** (80 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 16-46% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(1*H*-1,2,3-triazol-1-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-98**) (31 mg, 25% yield) as a white solid: cSFC analytical (A) t_R=3.33 min., purity: 100%; LCMS (M): t_R=0.986 min., (ES⁺) m/z (M+H)⁺ = 380.0; ¹H-NMR (D₂O, 400 MHz): δ 8.30 (d, J=0.8 Hz, 1H), 8.00 (d, J=1.6 Hz, 1H), 7.83-7.81 (m, 2H), 7.77 (s, 1H), 7.56 (dd, J₁=8.8 Hz, J₂=2.0 Hz, 1H), 4.38 (s, 1H), 3.57-3.51 (m, 2H), 3.39-3.28 (m, 2H), 2.33-2.32 (m, 1H), 2.19-2.06 (m, 2H), 2.00-1.91 (m, 1H), 1.19-1.14 (m, 2H), 1.09-1.05 (m, 2H).

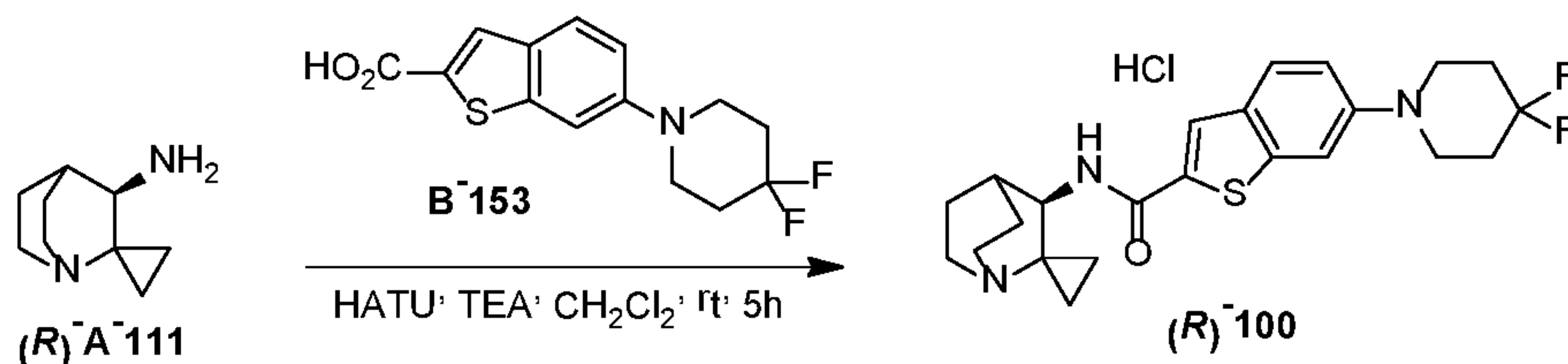
[001033] **Example 99:** (*R*)-6-morpholino-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-99)



[001034] Following general procedure B, **Compound (R)-99** was prepared from **compound B-150** (86 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-H; Column: Waters Xbridge C18 150×20 mm, particle size: 5 μm; Mobile phase: 52-70% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)]. The resulting solids were dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-6-morpholino-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-99**) (18 mg, 13% yield) as a white solid: cSFC analytical (A) t_R=3.38 min., purity: 97.39%; LCMS (L): t_R=2.827 min., (ES⁺) m/z (M+H)⁺ = 398.1; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 10.40 (s, 1H), 8.56 (d, J=8.4 Hz, 1H), 8.18 (s, 1H), 7.78 (d, J=8.8 Hz, 1H), 7.45 (s, 1H), 7.19 (d, J=8.8 Hz, 1H), 4.35 (d, J=6.0 Hz, 1H), 3.76 (t, J=4.4 Hz, 4H), 3.60 (m, 2H), 3.35-3.22 (m, 6H), 2.25 (m, 2H), 2.00-1.97 (m, 2H), 1.75 (m, 1H), 1.36-1.23 (m, 2H), 1.04-0.96 (m, 2H).

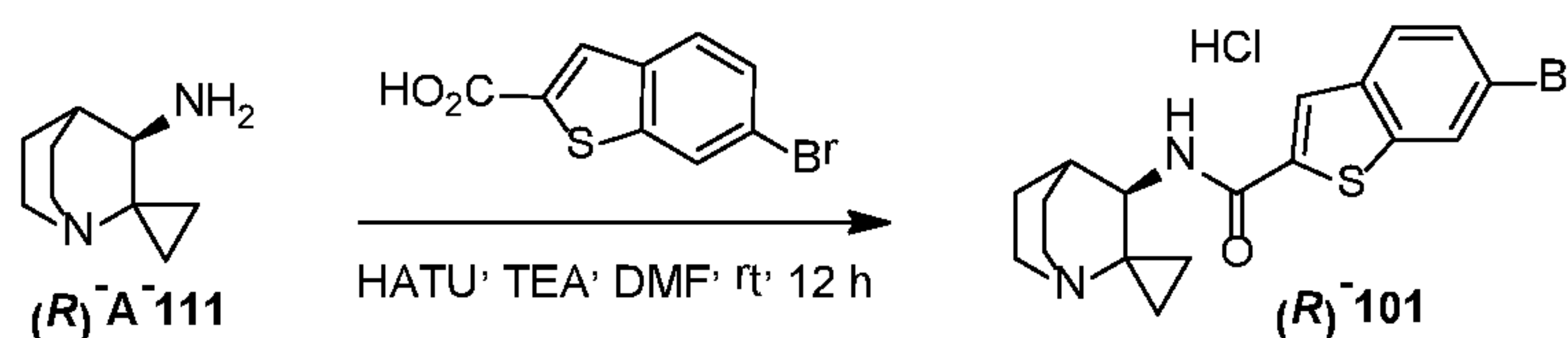
[001035] **Example 100:** (*R*)-6-(4,4-difluoropiperidin-1-yl)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-100)



[001036] Following general procedure B, **Compound (R)-100** was prepared from **compound B-153** (70 mg, 0.24 mmol) and **compound (R)-A-111** (43 mg, 0.28 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-D; Column: Boston Symmetrix C18 150×30 mm, particle size: 5 μ m; Mobile phase: 25-55% acetonitrile in H₂O (add 0.5% FA, v/v)]. The combined fractions were treated with 0.2 M hydrochloric acid solution and lyophilized to give:

(*R*)-6-(4,4-difluoropiperidin-1-yl)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-100**) (21 mg, 19% yield) as a yellow solid: cSFC analytical (A) *t*_R=3.04 min., purity: 97.13%; LCMS (X): *t*_R=2.301 min., (ES⁺) *m/z* (M+H)⁺ = 432.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.23 (s, 1H), 8.18 (s, 1H), 8.03 (d, *J*=8.4 Hz, 1H), 7.66 (d, *J*=8.8 Hz, 1H), 4.54 (d, *J*=2.0 Hz, 1H), 3.81 (t, *J*=5.6 Hz, 4H), 3.74-3.72 (m, 1H), 3.56-3.54 (m, 1H), 3.47-3.29 (m, 2H), 2.51-2.42 (m, 5H), 2.34 (m, 1H), 2.19-2.16 (m, 2H), 2.00-1.96 (m, 1H), 1.41-1.36 (m, 1H), 1.31-1.25 (m, 2H), 1.22-1.08 (m, 1H).

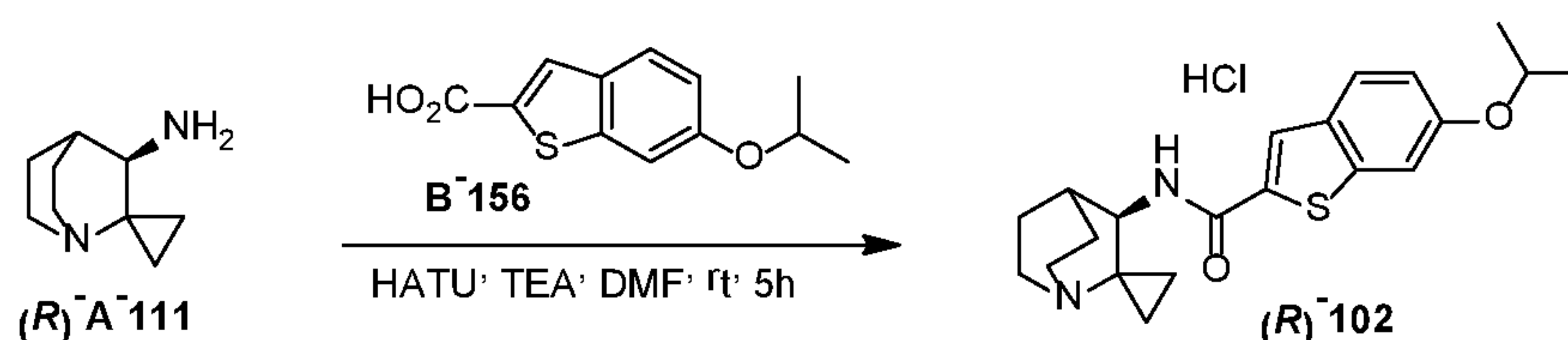
[001037] **Example 101:** (*R*)-6-bromo-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**(R)-101**)



[001038] Following general procedure B, **Compound (R)-101** was prepared from 6-bromobenzo[*b*]thiophene-2-carboxylic acid (84 mg, 0.33 mmol) and **compound (R)-A-111** (50mg, 0.33 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 10 μ m; Mobile phase: 18-48% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-6-bromo-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-101**) (63 mg, 45% yield) as a white solid: cSFC analytical (A) *t*_R=2.70 min., purity: 98.09%; LCMS (Y): *t*_R=0.797 min., (ES⁺) *m/z* (M+H)⁺ = 392.9; ¹H-NMR (CD₃OD, 400 MHz): δ 8.15-8.14 (m, 2H), 7.84 (d, *J*=8.4 Hz, 1H), 7.57 (dd, *J*₁=8.4, *J*₂=1.6, 2H), 4.56 (s, 1H), 3.71-3.58 (m, 1H), 3.58-3.57 (m, 1H), 3.50-3.31 (m, 2H), 2.45-2.44 (m, 1H), 2.37-2.34 (m, 1H), 2.23-2.14 (m, 2H), 2.00-1.99 (m, 1H), 1.38-1.35 (m, 1H), 1.28-1.15 (m, 3H).

[001039] **Example 102:** (*R*)-6-isopropoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**(R)-102**)

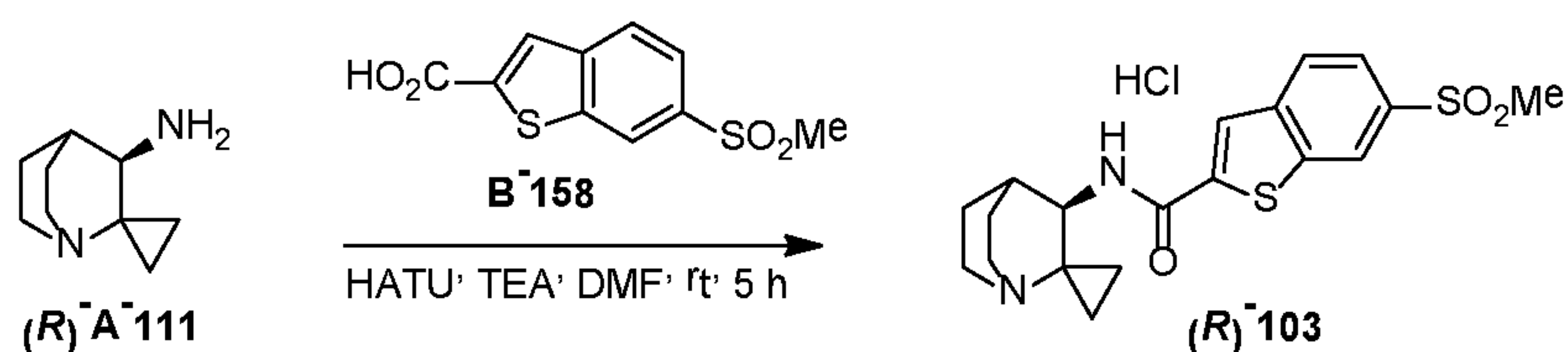


[001040] Following general procedure B, **Compound (R)-102** was prepared from **compound B-156** (78 mg, 0.33 mmol) and **compound (R)-A-104** (50 mg, 0.33 mmol), with a reaction time of 5

hours. The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 150×25 mm, particle size: 10 µm; Mobile phase: 40-70% acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)]. The resulting solids were dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-6-isopropoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-102**) (33 mg, 25% yield) as a white solid: cSFC analytical (A) t_R=2.44 min., purity: 98.84%; LCMS (N): t_R=2.381 min., (ES⁺) m/z (M+H)⁺ = 371.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.05 (d, J=2.8 Hz, 1H), 7.77 (d, J=8.8 Hz, 1H), 7.41 (s, 1H), 7.01 (dd, J=8.8, 2.0 Hz, 1H), 4.73-4.65 (m, 1H), 4.54 (s, 1H), 3.75-3.68 (m, 1H), 3.56 (m, 1H), 3.49-3.38 (m, 2H), 2.42 (s, 1H), 2.36-2.31 (m, 1H), 2.20-2.15 (m, 2H), 2.01-1.94 (m, 1H), 1.35-1.34 (m, 7H), 1.29-1.17 (m, 3H).

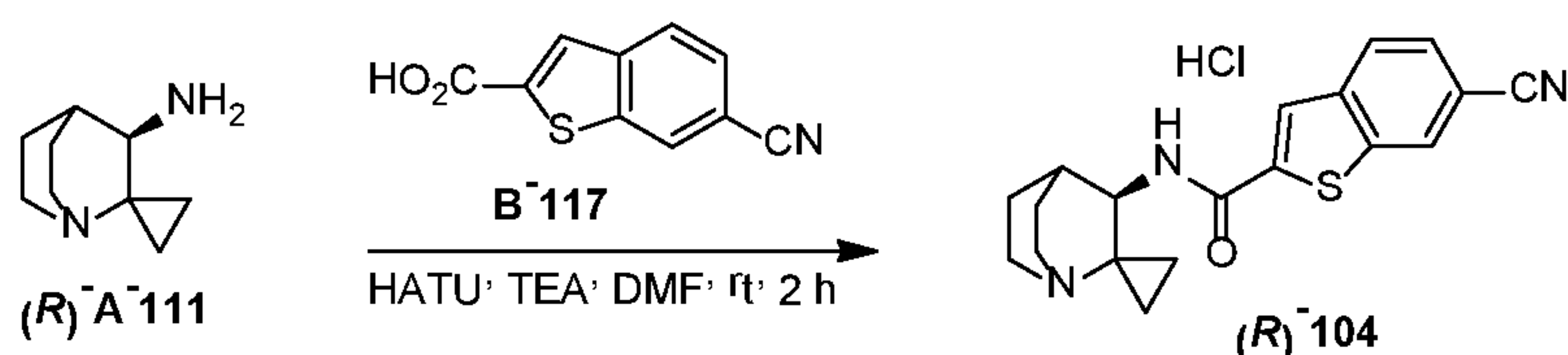
[001041] **Example 103:** (*R*)-6-(methylsulfonyl)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-103)



[001042] Following general procedure B, **Compound (R)-103** was prepared from **compound B-158** (84 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-pack ODS-AQ 150×30 mm, particle size: 5 µm; Mobile phase: 11-41% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The combined fractions were treated with 0.2 N HCl and lyophilized to give:

(*R*)-6-(methylsulfonyl)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-103**) (30 mg, 21% yield) as a white solid: cSFC analytical (A) t_R=2.94 min., purity: 100%; LCMS (M): t_R=1.016min., (ES⁺) m/z (M+H)⁺ = 391.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.64 (s, 1H), 8.27 (s, 1H), 8.16 (d, J=8.4 Hz, 1H), 7.97 (dd, J₁=8.4 Hz, J₂=1.2 Hz, 1H), 4.59 (d, J=2.4 Hz, 1H), 3.72-3.71 (m, 1H), 3.59-3.51 (m, 1H), 3.49-3.44 (m, 2H), 3.20 (s, 3H), 2.47-2.46 (m, 1H), 2.35-2.32 (m, 1H), 2.24-2.17 (m, 2H), 2.01-2.00 (m, 1H), 1.39-1.35 (m, 1H), 1.29-1.20 (m, 3H).

[001043] **Example 104:** (*R*)-6-cyano-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide ((*R*)-104)

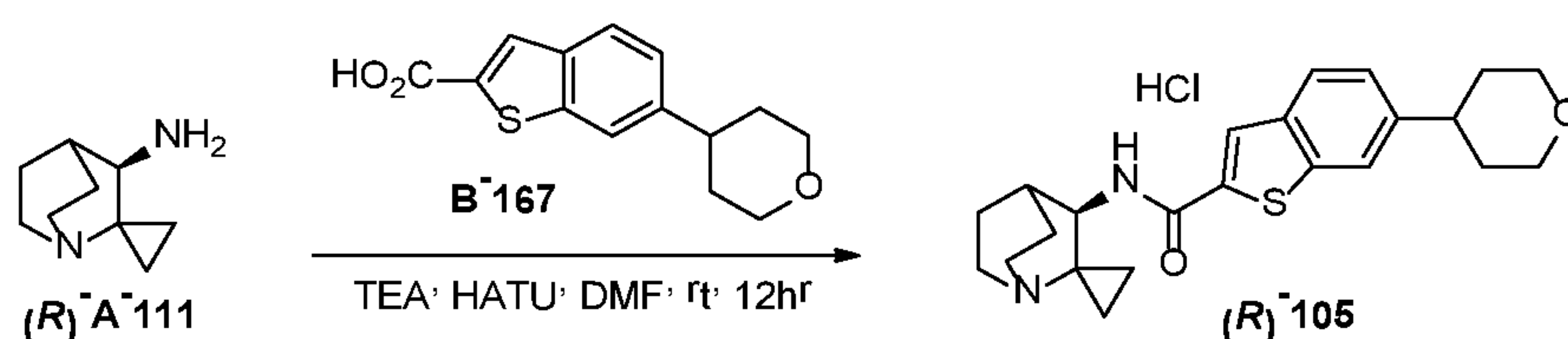


[001044] Following general procedure B, **Compound (R)-104** was prepared from **compound B-117** (67 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 2

hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 µm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-6-cyano-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-104**) (39 mg, 35% yield) as a white solid: cSFC analytical (A) t_R=2.63 min., purity: 100%; LCMS (B): t_R=0.617 min., 338.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): 8.42 (s, 1H), 8.29 (s, 1H), 8.09 (d, J=8.4 Hz, 1H), 7.72-7.70 (dd, J₁=1.2 Hz, J₂=8.4Hz, 1H), 4.59 (s, 1H), 3.79-3.75 (m, 1H), 3.62-3.45 (m, 3H), 2.48-2.35 (m, 2H), 2.25-2.16 (m, 2H), 2.06-2.02 (m, 1H), 1.42-1.20 (m, 4H).

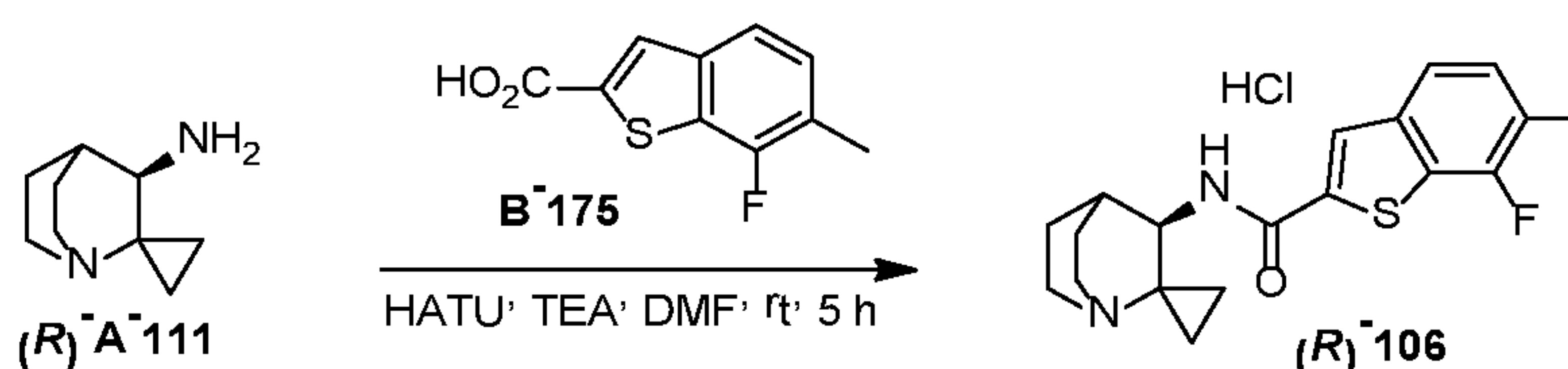
[001045] **Example 105:** (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(tetrahydro-2*H*-pyran-4-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-105)



[001046] Following general procedure B, **Compound (R)-105** was prepared from **compound B-167** (86 mg, 0.33 mmol) and **compound (R)-A-104** (50 mg, 0.33 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 µm; Mobile phase: 16-46% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(tetrahydro-2*H*-pyran-4-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-105**) (44 mg, 31% yield) as a white solid: cSFC analytical (A) t_R: 3.04 min., purity: 97.73%; LCMS (Y): t_R: 0.747 min., (ES⁺) m/z (M+H)⁺ = 397.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.14 (s, 1H), 7.85 (d, J=8.4Hz, 1H), 7.78 (s, 1H), 7.36-7.33 (m, 1H), 4.54 (d, J=2.4 Hz, 1H), 4.06-4.03 (m, 2H), 3.74-3.69 (m, 1H), 3.60-3.52 (m, 3H), 3.43-3.38 (m, 2H), 2.97-2.89 (m, 1H), 2.42-2.31 (m, 2H), 2.19-2.16 (m, 2H), 1.98 (s, 1H), 1.86-1.79 (m, 4H), 1.41-1.38 (m, 1H), 1.32-1.22 (m, 2H), 1.16-1.14 (m, 1H).

[001047] **Example 106:** (*R*)-7-fluoro-6-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-106)

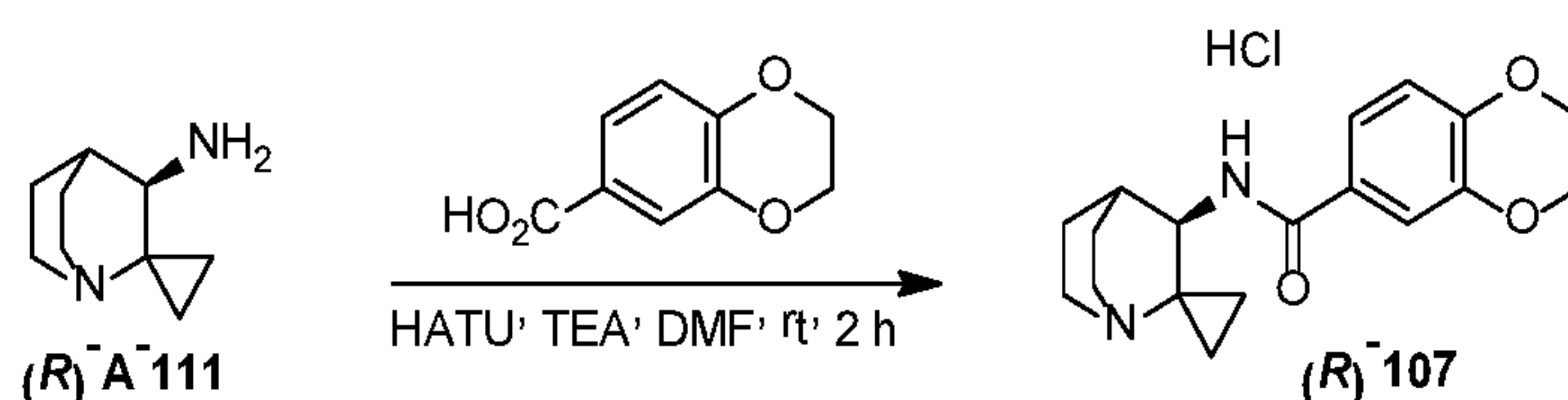


[001048] Following general procedure B, **Compound (R)-106** was prepared from **compound B-175** (69 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi

C18 150×30 mm, particle size: 4 μ m; Mobile phase: 19-49% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-7-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-106**) (85 mg, 68% yield) as a white solid: cSFC analytical (A) t_R=2.273 min., purity: 96.72%; LCMS (Y): t_R=0.807 min., (ES⁺) m/z (M+H)⁺ = 345.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.13 (d, J=3.6 Hz, 1H), 7.64 (d, J=8.0 Hz, 1H), 7.33 (t, J=8.0 Hz, 1H), 4.57 (d, J=2 Hz, 1H), 3.71-3.70 (m, 1H), 3.59-3.50 (m, 1H), 3.48-3.43 (m, 2H), 2.42-2.41 (m, 4H), 2.34-2.32 (m, 1H), 2.23-2.18 (m, 2H), 2.00-1.99 (m, 1H), 1.38-1.33 (m, 1H), 1.27-1.20 (m, 3H).

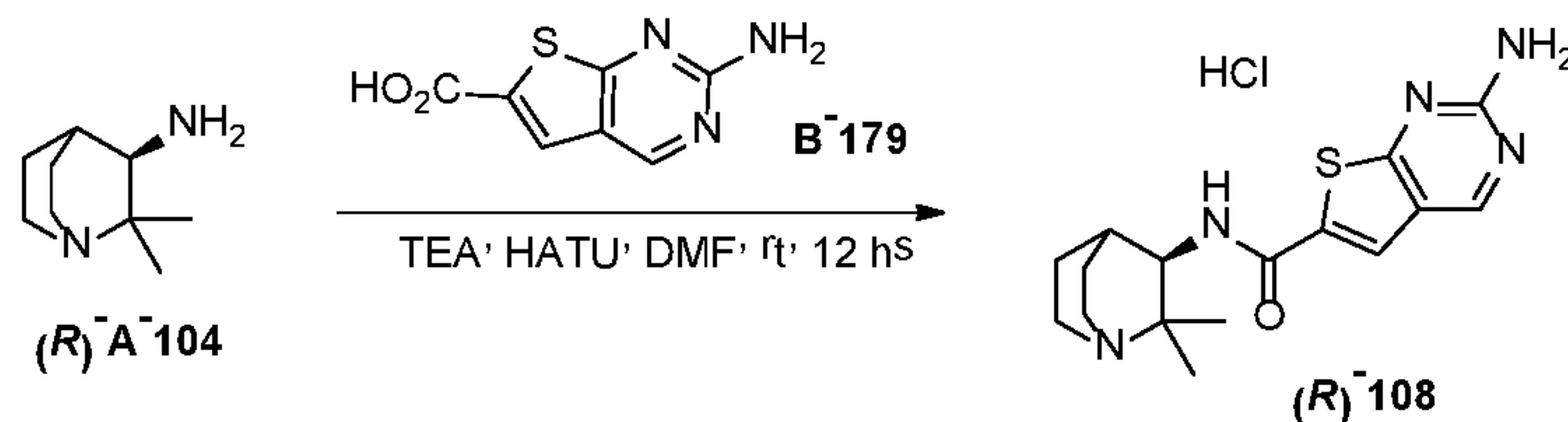
[001049] **Example 107:** (*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide ((*R*)-107)



[001050] Following general procedure B, **Compound (R)-107** was prepared from 2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylic acid (36 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 μ m; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide hydrochloride (**compound (R)-107**) (58 mg, 56% yield) as a white solid: cSFC analytical (A) t_R=2.28 min., purity: 98.41%; LCMS (W): t_R=0.817 min., 315.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): 7.40 (s, 1H), 7.38 (s, 1H), 6.93 (d, J=8.8 Hz, 1H), 4.53 (s, 1H), 4.32-4.29 (m, 4H), 3.73-3.41 (m, 4H), 2.41-2.16 (m, 4H), 1.98-1.93 (m, 1H), 1.43-1.14 (m, 4H).

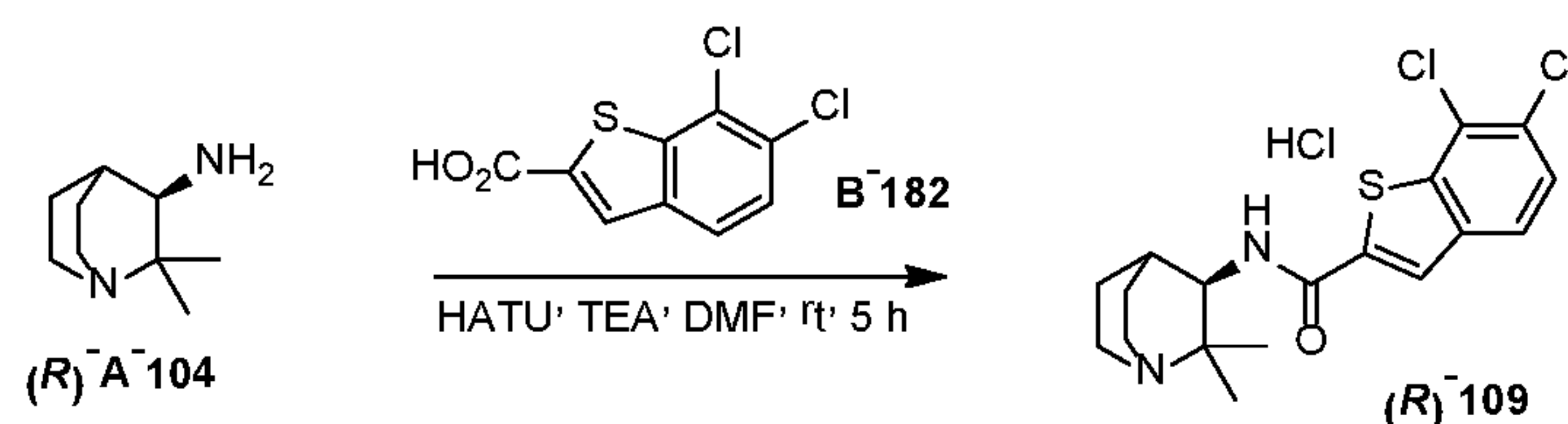
[001051] **Example 108:** (*R*)-2-amino-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-d]pyrimidine -6-carboxamide hydrochloride ((*R*)-108)



[001052] Following general procedure B, **Compound (R)-108** was prepared from **compound B-179** (60 mg, 0.31 mmol) and **compound (R)-A-104** (47 mg, 0.31 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-C; Column: Phenomenex Gemini C18 150×30 mm, particle size: 5 μ m; Mobile phase: 35-65% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-2-amino-*N*-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-*d*]pyrimidine-6-carboxamide-hydrochloride (**compound (R)-108**) (50 mg, 49% yield) as a white solid: cSFC analytical (A) *t*_R=3.42 min., purity: 99.14%; LCMS (M): *t*_R=0.812 min., 332.0 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 9.01 (s, 1H), 8.20 (s, 1H), 4.26 (m, 1H), 3.75-3.70 (m, 2H), 3.39-3.30 (m, 2H), 2.49-2.48 (m, 1H), 2.29-2.28 (m, 1H), 2.18-2.12 (m, 2H), 1.98-1.92 (m, 1H), 1.75 (s, 3H), 1.51 (s, 3H).

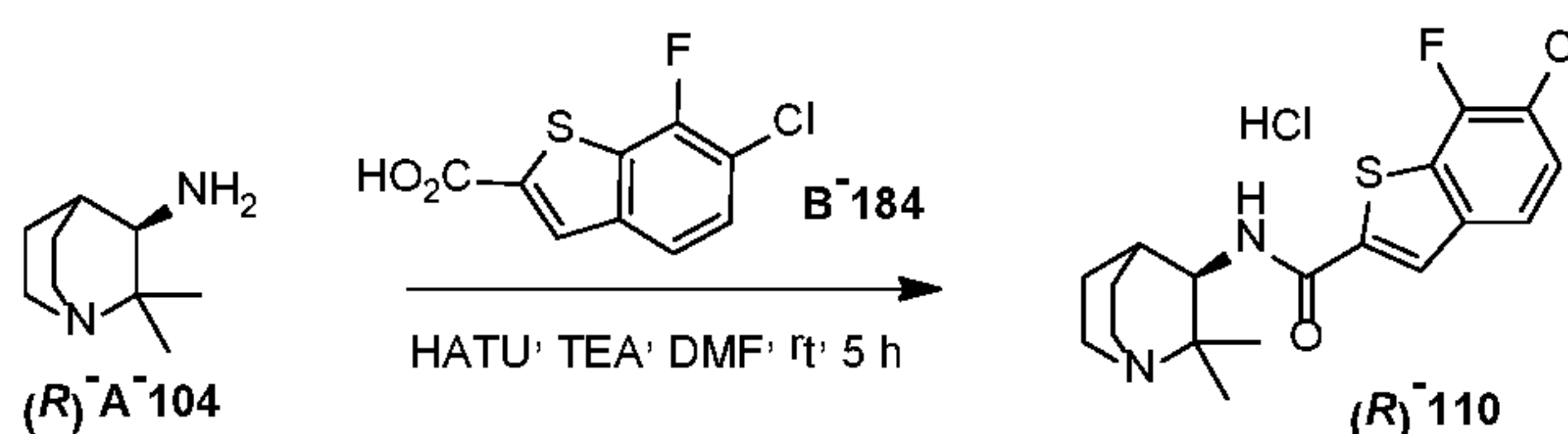
[001053] **Example 109:** (*R*)-6,7-dichloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-109)



[001054] Following general procedure B, **Compound (R)-109** was prepared from **compound B-182** (120 mg, 0.49 mmol) and **compound (R)-A-104** (75 mg, 0.49 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-D; Column: Boston Symmetrix ODS-R C18 150×30 mm, particle size: 5 μm; Mobile phase: 25-55% acetonitrile in H₂O (add 0.225% FA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-6,7-dichloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide-hydrochloride (**compound (R)-109**) (82 mg, 40% yield) as a white solid: cSFC analytical (A) *t*_R=3.22 min., purity: 97.50%; LCMS (H): *t*_R=1.786 min., (ES⁺) *m/z* (M+H)⁺ = 383.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.19 (s, 1H), 7.87 (d, *J*=8.4 Hz, 1H), 7.61 (d, *J*=8.4 Hz, 1H), 4.26 (s, 1H), 3.77-3.67 (m, 2H), 3.38-3.31 (m, 2H), 2.42-2.41 (m, 1H), 2.28 (d, *J*=2.8 Hz, 1H), 2.19-2.12 (m, 2H), 2.11-1.96 (m, 1H), 1.76 (s, 3H), 1.50 (s, 3H).

[001055] **Example 110:** (*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-7-fluorobenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-110)

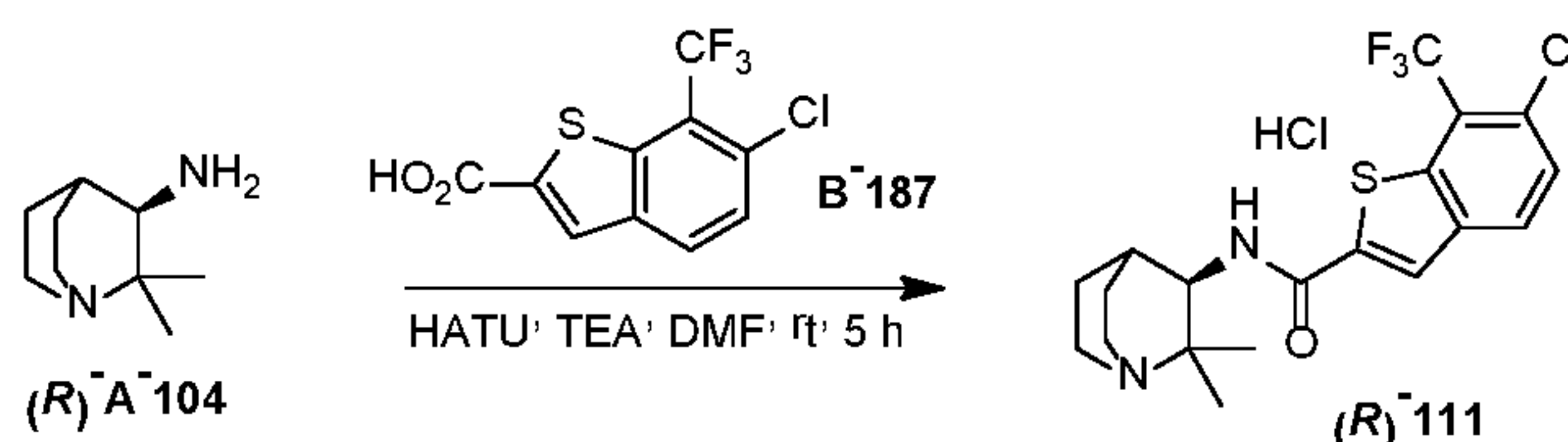


[001056] Following general procedure B, **Compound (R)-110** was prepared from **compound B-184** (120 mg, 0.52 mmol) and **compound (R)-A-104** (80 mg, 0.52 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-pack ODS-AQ 150×30 mm, particle size: 5 μm; Mobile phase: 29-59% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-7-fluorobenzo[*b*]thiophene-2-carboxamide-hydrochloride (**compound (R)-110**) (70 mg, 33% yield) as a white solid: cSFC analytical (A) *t*_R=2.946 min., purity: 97.54%; LCMS (Y): *t*_R=0.746 min., (ES⁺) *m/z* (M+H)⁺ = 367.0; ¹H-NMR

(CD₃OD, 400 MHz): δ 8.20 (d, $J=3.2$ Hz, 1H), 7.75 (d, $J=8.4$ Hz, 1H), 7.54 (dd, $J_1=8$ Hz, $J_2=6.8$ Hz, 1H), 4.26 (s, 1H), 3.75-3.67 (m, 2H), 3.38-3.35 (m, 2H), 2.42-2.41 (m, 1H), 2.28-2.27 (m, 1H), 2.18-2.09 (m, 2H), 1.95-1.91 (m, 1H), 1.75 (s, 3H), 1.49 (s, 3H).

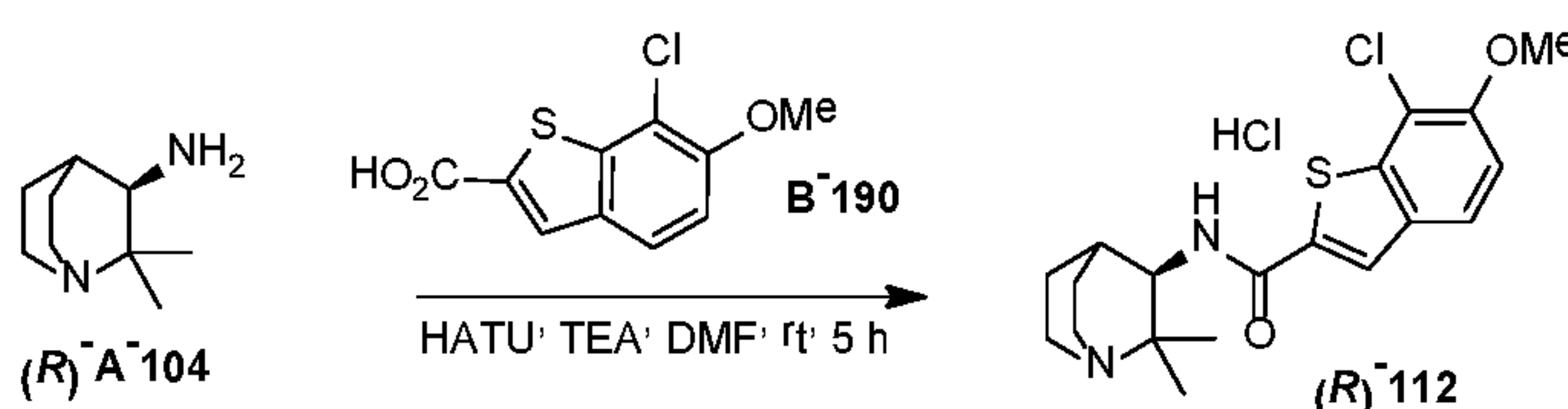
[001057] **Example 111:** (*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-111)



[001058] Following general procedure B, **Compound (*R*)-111** was prepared from **compound B-187** (146 mg, 0.52 mmol) and **compound (*R*)-A-104** (80 mg, 0.52 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150×30 mm, particle size: 5 μ m; Mobile phase: 30-60% acetonitrile in H₂O (add 0.1% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (*R*)-111**) (116 mg, 49% yield) as a white solid: cSFC analytical (A) $t_R=2.87$ min., purity: 97.89%; LCMS (H): $t_R=1.766$ min., (ES^+) m/z ($M+H$)⁺ = 417.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.24 (s, 1H), 8.14 (d, $J=8.8$ Hz, 1H), 7.67 (d, $J=8.4$ Hz, 1H), 4.26 (s, 1H), 3.75-3.66 (m, 2H), 3.37-3.32 (m, 2H), 2.41-2.39 (m, 1H), 2.27 (d, $J=2.8$ Hz, 1H), 2.17-2.10 (m, 2H), 1.97-1.80 (m, 1H), 1.75 (s, 3H), 1.49 (s, 3H).

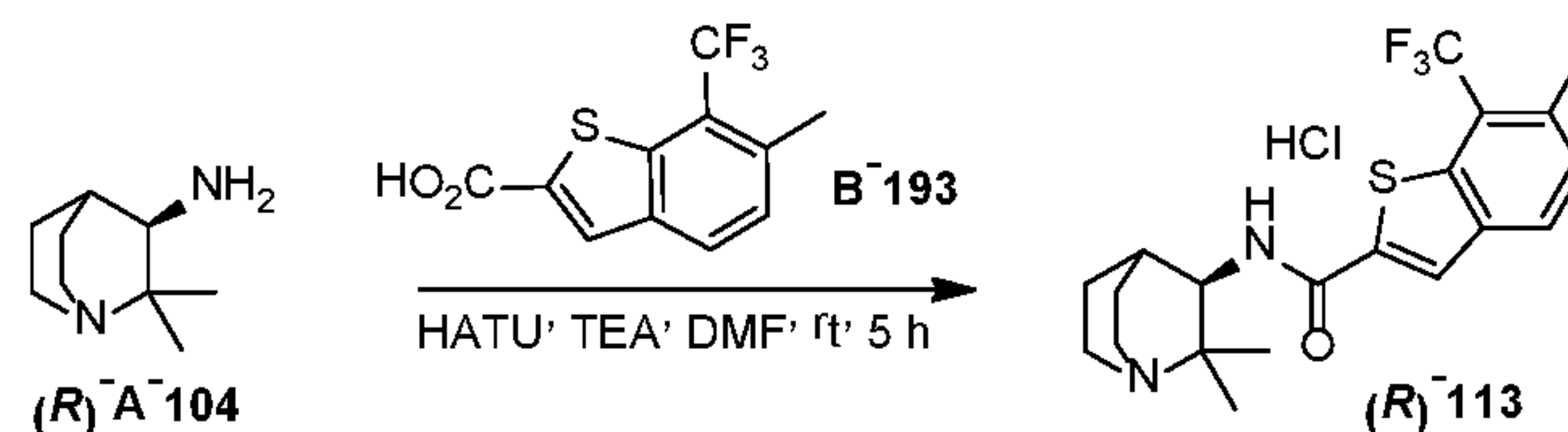
[001059] **Example 112:** (*R*)-7-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-112)



[001060] Following general procedure B, **Compound (*R*)-112** was prepared from **compound B-190** (126 mg, 0.52 mmol) and **compound (*R*)-A-104** (80 mg, 0.52 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-pack ODS-AQ 150×30 mm, particle size: 5 μ m; Mobile phase: 24-54% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-7-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (*R*)-112**) (116 mg, 53% yield) as a white solid: cSFC analytical (A) $t_R=3.267$ min., purity: 97.66%; LCMS (Y): $t_R=0.716$ min., (ES^+) m/z ($M+H$)⁺ = 379.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.12 (s, 1H), 7.86 (d, $J=8.8$ Hz, 1H), 7.32 (d, $J=8.8$, 1H), 4.25 (s, 1H), 4.00 (s, 3H), 3.76-3.66 (m, 2H), 3.37-3.36 (m, 2H), 2.41-2.40 (m, 1H), 2.27-2.26 (m, 1H), 2.18-2.04 (m, 2H), 1.94-1.90 (m, 1H), 1.75 (s, 3H), 1.49 (s, 3H).

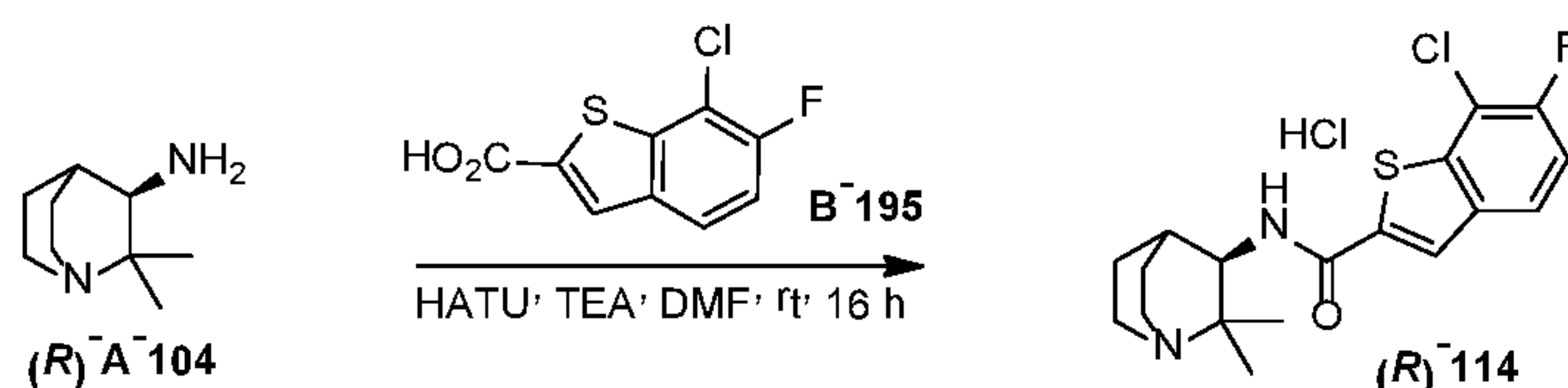
[001061] **Example 113:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-113)



[001062] Following general procedure B, **Compound (R)-113** was prepared from **compound B-193** (0.12 g, 0.45 mmol) and **compound (R)-A-104** (70 mg, 0.45 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150×30 mm, particle size: 5 μm; Mobile phase: 28-58% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide- hydrochloride (**compound (R)-113**) (0.12 g, 69% yield) as a white solid: cSFC analytical (A) t_R=2.59 min., purity: 97.70%; LCMS (DD): t_R=0.861 min., 397.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.49 (d, J=7.6 Hz, 0.5H), 8.19 (s, 1H), 8.04 (d, J=8.0 Hz, 1H), 7.47 (d, J=8.4 Hz, 1H), 4.26 (s, 1H), 3.72-3.70 (m, 2H), 3.38-3.33 (m, 2H), 2.64 (d, J=2.0 Hz, 3H), 2.42-2.41 (m, 1H), 2.28-2.27 (m, 1H), 2.18-2.06 (m, 2H), 1.97-1.91 (m, 1H), 1.75 (s, 3H), 1.50 (s, 3H).

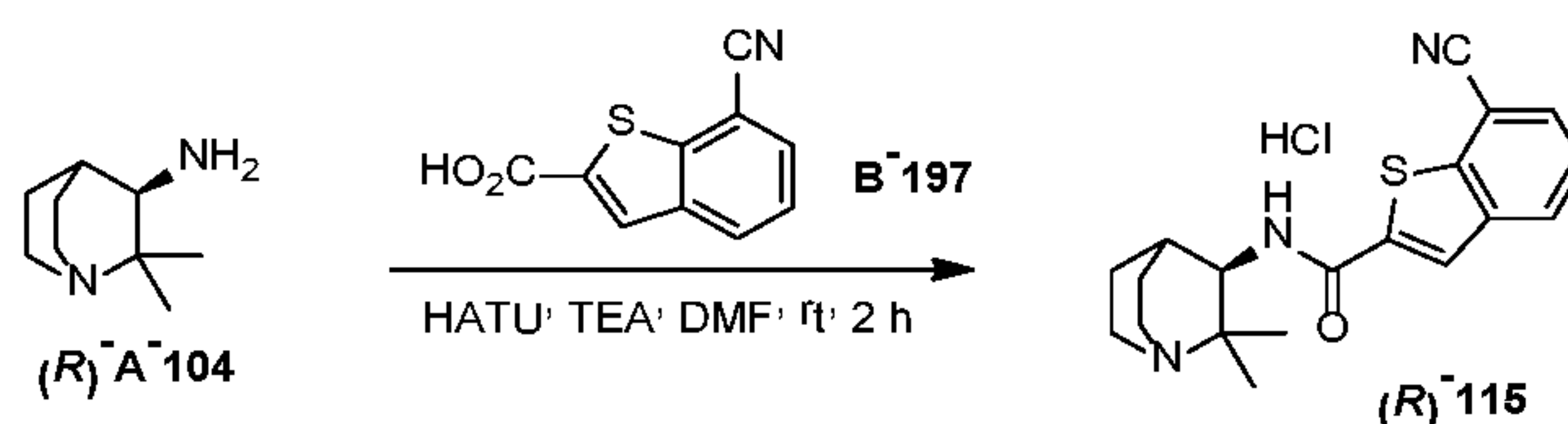
[001063] **Example 114:** (*R*)-7-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-114)



[001064] Following general procedure B, **Compound (R)-114** was prepared from **compound B-195** (0.11 g, 0.49 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 16 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-7-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide- hydrochloride (**compound (R)-114**) (0.40 g, 31% yield) as a white solid: cSFC analytical (A) t_R=2.906 min., purity: 98.17%; LCMS (M): t_R=1.095 min., 367.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.22 (s, 1H), 7.93 (dd, J₁=8.4 Hz, J₂=4 Hz, 1H), 7.42 (t, J=9.2 Hz, 1H), 4.28 (s, 1H), 3.75-3.68 (m, 2H), 3.40-3.33 (m, 2H), 2.43-2.42 (m, 1H), 2.30 (s, 1H), 2.20-2.12 (m, 2H), 2.00-1.93 (m, 1H), 1.77 (s, 3H), 1.51 (s, 3H).

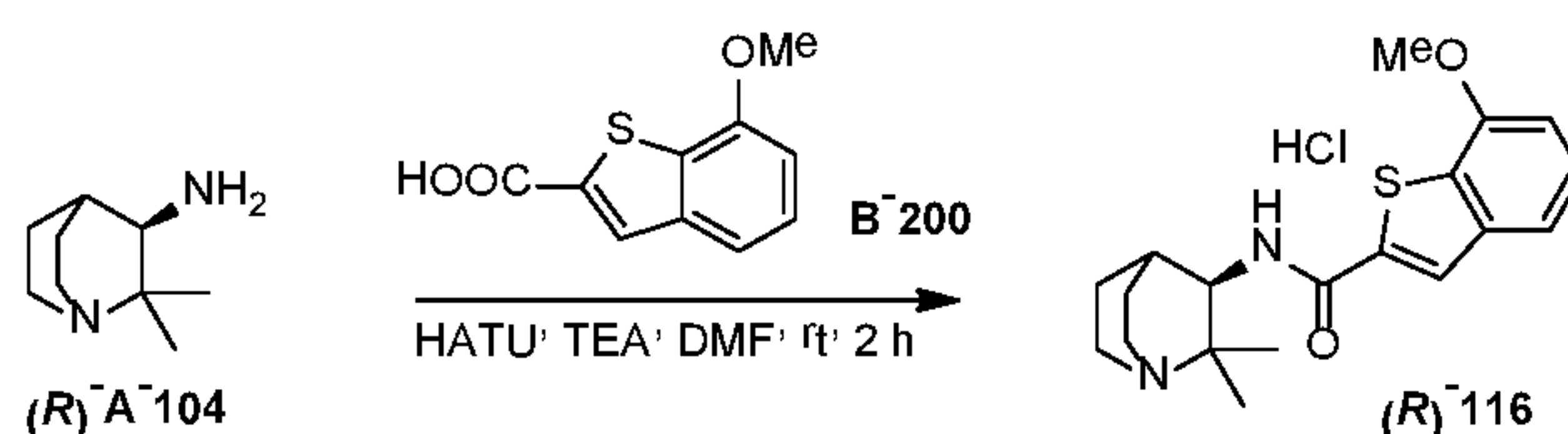
[001065] **Example 115:** (*R*)-7-cyano-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-115)



[001066] Following general procedure B, **Compound (R)-115** was prepared from **compound B-197** (as a mixture with **compound B-198**) (80 mg, 0.39 mmol) and **compound (R)-A-104** (60 mg, 0.39 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-7-cyano-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide-hydrochloride (**compound (R)-115**) (15 mg, 32% yield) as a white solid: cSFC analytical (A) *t*_R=2.30 min., purity: 99.66%; LCMS (M): *t*_R=0.973 min., 340.1 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): 8.59 (d, *J*=7.2 Hz, 1H), δ 8.30 (s, 1H), 7.26 (d, *J*=7.6 Hz, 1H), 7.94 (d, *J*=7.2 Hz, 1H), 7.64 (t, *J*=8.0 Hz, 1H), 4.29 (s, 1H), 3.79-3.69 (m, 2H), 3.40-3.36 (m, 1H), 2.45-2.44 (m, 1H), 2.31-2.13 (m, 4H), 2.00-1.94 (m, 1H), 1.78 (s, 3H), 1.52 (s, 3H).

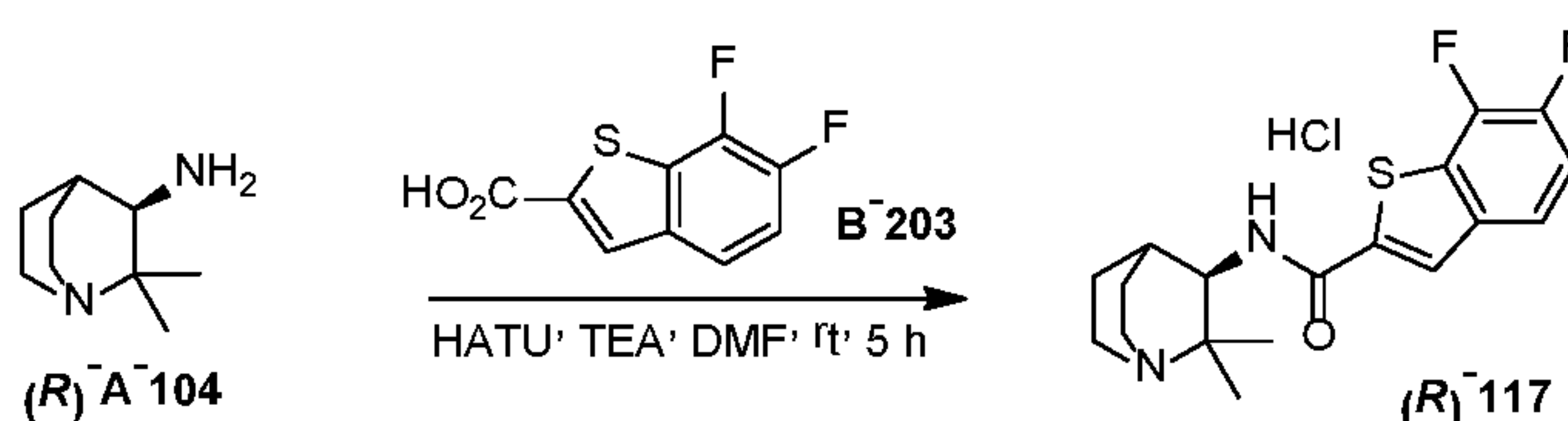
[001067] **Example 116:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-116)



[001068] Following general procedure B, **Compound (R)-116** was prepared from **compound B-200** (67 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[*b*]thiophene-2-carboxamide-hydrochloride (**compound (R)-116**) (72 mg, 65% yield) as a white solid: cSFC analytical (A) *t*_R=3.35 min., purity: 99.66%; LCMS (M): *t*_R=0.992 min., 345.1 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.13 (s, 1H), 7.53 (d, *J*=8.0 Hz, 1H), 7.44 (t, *J*=7.6 Hz, 1H), 7.01 (d, *J*=3.6 Hz, 1H), 4.27 (s, 1H), 4.03 (s, 3H), 3.78-3.68 (m, 2H), 3.39-3.36 (m, 1H), 3.30 (m, 1H), 2.47-2.42 (m, 1H), 2.30-2.29 (m, 3H), 1.98-1.92 (m, 1H), 1.77 (s, 3H), 1.51 (s, 3H).

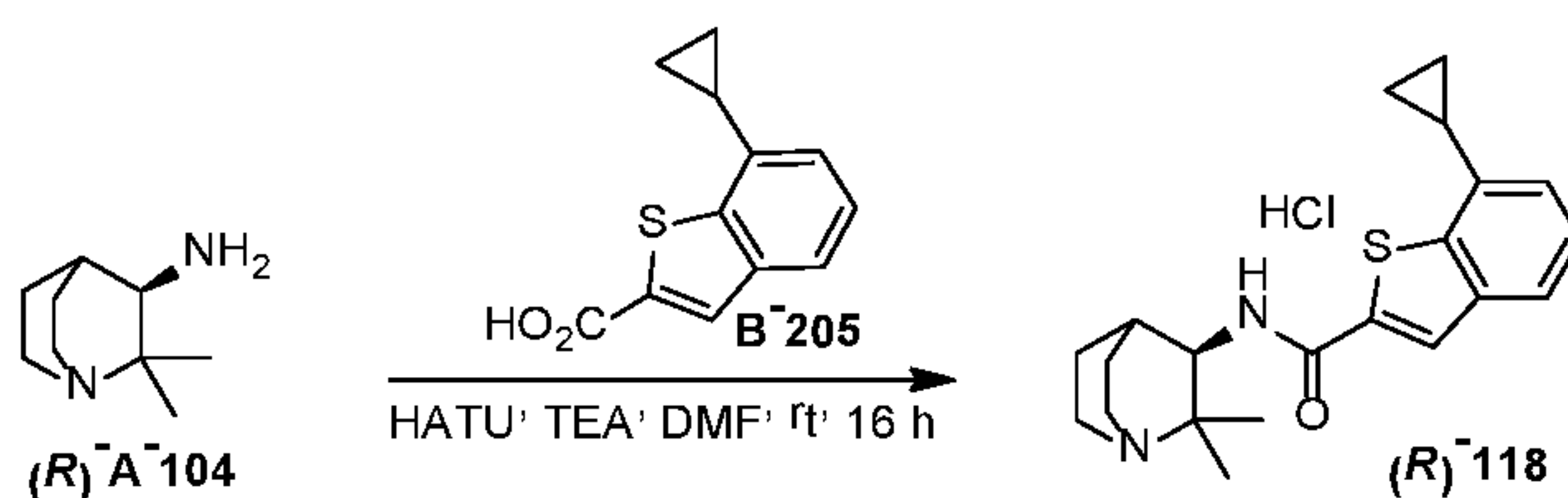
[001069] **Example 117:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6,7-difluorobenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-117)



[001070] Following general procedure B, **Compound (R)-117** was prepared from **compound B-203** (60 mg, 0.34 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 µm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6,7-difluorobenzo[b]thiophene-2-carboxamide-hydrochloride (**compound (R)-117**) (60 mg, 46% yield) as a white solid: cSFC analytical (A) t_R=2.66 min., purity: 96.66%; LCMS (B): t_R=0.702 min., 350.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.21 (d, *J*=3.2, 1H), 7.79-7.76 (m, 1H), 7.47-7.41 (m, 1H), 4.27 (s, 1H), 3.75-3.69 (m, 2H), 3.40-3.37 (m, 2H), 2.49-2.42 (m, 1H), 2.30 (d, *J*=2.8, 1H), 2.19-2.09 (m, 2H), 1.99-1.93 (m, 1H), 1.768 (s, 3H), 1.51 (s, 3H).

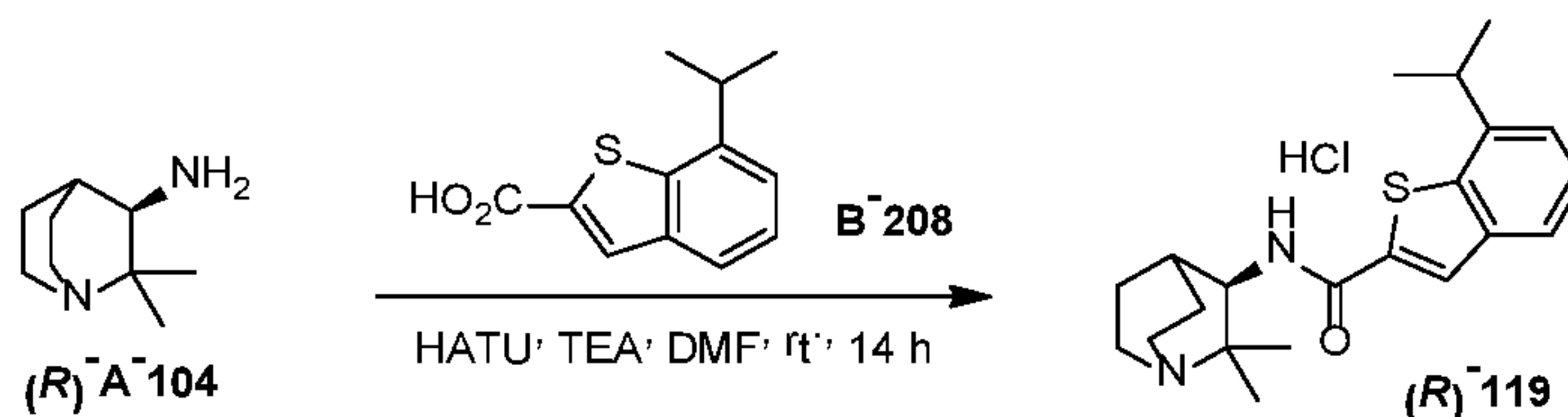
[001071] **Example 118:** (*R*)-7-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-118)



[001072] Following general procedure B, **Compound (R)-118** was prepared from **compound B-205** (0.12 g, 0.54 mmol) and **compound (R)-A-104** (70 mg, 0.45 mmol), with a reaction time of 16 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150×30 mm, particle size: 5 µm; Mobile phase: 24-54% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-7-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide - hydrochloride (**compound (R)-118**) (75 mg, 42% yield) as a white solid: cSFC analytical (A) t_R=3.228 min., purity: 100%; LCMS (B): t_R=0.711 min., 355.2 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.45 (d, *J*=7.2 Hz, 1H), 8.17 (s, 1H), 7.76 (d, *J*= Hz, 1H), 7.39 (t, *J*=7.6 Hz, 1H), 7.16 (d, *J*=7.2 Hz, 1H), 4.29 (s, 1H), 3.77-3.69 (m, 2H), 3.40-3.37 (m, 2H), 2.44-2.43 (m, 1H), 2.30 (m, 1H), 2.20-2.11 (m, 2H), 1.99-1.93 (m, 1H), 1.74 (s, 3H), 1.52 (s, 3H).

[001073] **Example 119:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-isopropylbenzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-119)

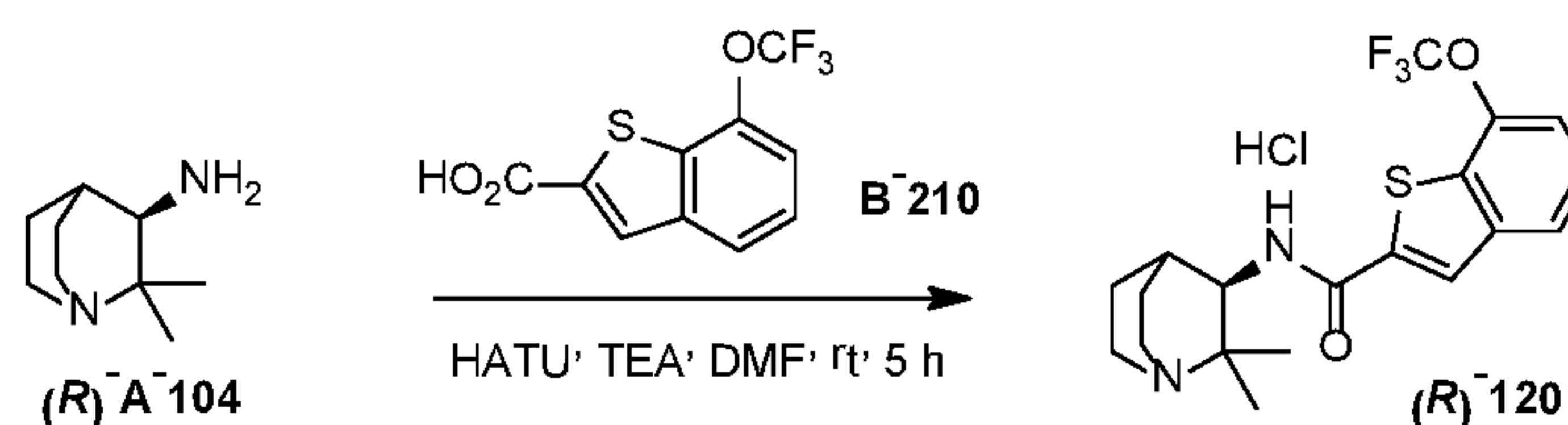


[001074] Following general procedure B, **Compound (R)-119** was prepared from **compound B-208** (0.11 g, 0.52 mmol) and **compound (R)-A-104** (80 mg, 0.52 mmol), with a reaction time of 14 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi

C18 150×30 mm, particle size: 5 μm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-isopropylbenzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-119**) (0.10 g, 49% yield) as a white solid: cSFC analytical (B) t_R=2.765 min., purity: 97.44%; LCMS (DD): t_R=0.836 min., (ES⁺) m/z (M+H)⁺ = 357.2; ¹H-NMR (CD₃OD, 400 MHz): δ8.46-8.44 (m, 1H), 7.18 (m, 1H), 7.79-7.77 (d, J=7.6 Hz, 1H), 7.47-7.39 (m, 2H), 4.28 (s, 1H), 3.78-3.68 (m, 2H), 3.40-3.35 (m, 2H), 3.28-3.23 (m, 1H), 2.44 (m, 1H), 2.30-2.20 (m, 1H), 2.16-2.11 (m, 2H), 2.09-1.93 (m, 1H), 1.78 (s, 3H), 1.52 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H).

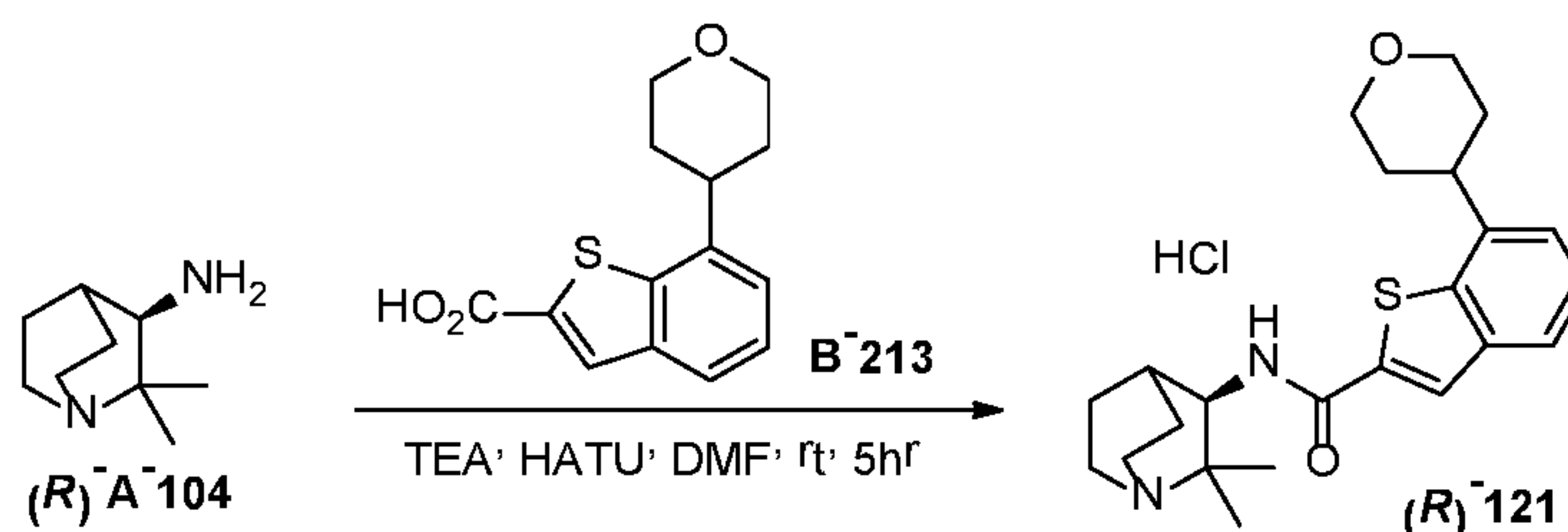
[001075] **Example 120:** (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide hydrochloride (**(R)-120**)



[001076] Following general procedure B, **Compound (R)-120** was prepared from **compound B-210** (136 mg, 0.26 mmol) and **compound (R)-A-104** (80 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150*30, particle size: 5 μm; Mobile phase: 25-55% acetonitrile in H₂O (add 0.1% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-120**) (130 mg, 57% yield) as a white solid: cSFC analytical (A) t_R=2.346 min., purity: 98.01%; LCMS (B): t_R=0.733 min., (ES⁺) m/z (M+H)⁺ = 399.1; ¹H-NMR (CD₃OD, 400 MHz): δ8.23 (s, 1H), 7.94 (d, J=8.0 Hz, 1H), 7.55 (t, J=8.0 Hz, 1H), 7.44 (d, J=8.0 Hz, 1H), 4.26 (s, 1H), 3.76-3.67 (m, 2H), 3.38-3.33 (m, 2H), 2.42-2.41 (m, 1H), 2.29-2.28 (m, 1H), 2.19-2.10 (m, 2H), 1.99-1.95 (m, 1H), 1.75 (s, 3H), 1.50 (s, 3H).

[001077] **Example 121:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(tetrahydro-2*H*-pyran-4-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**(R)-121**)

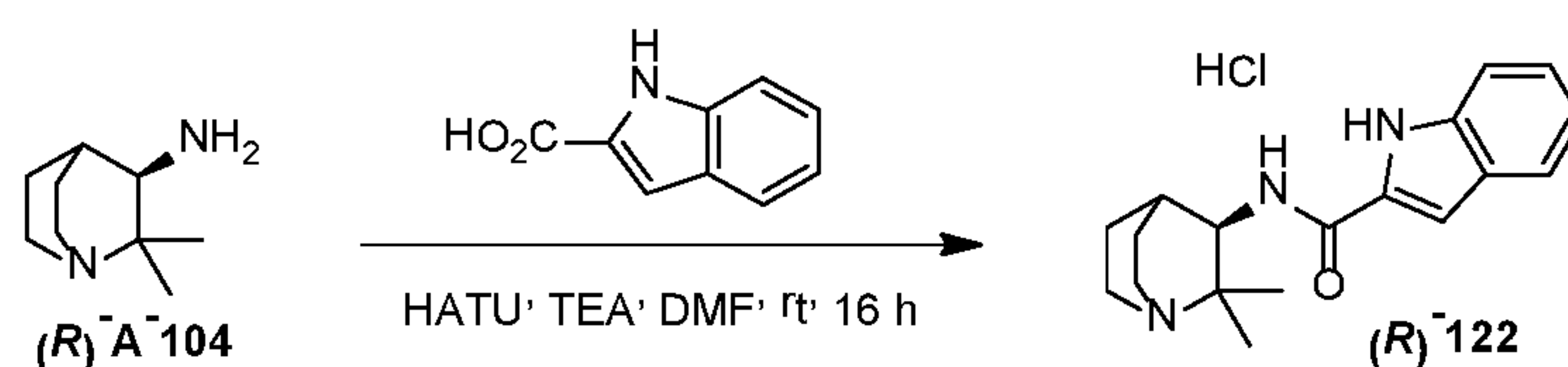


[001078] Following general procedure B, **Compound (R)-121** was prepared from **compound B-213** (119 mg, 0.45 mmol) and **compound (R)-A-104** (70 mg, 0.45 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB

C18 150×30 mm, particle size: 5 μm; Mobile phase: 19-49% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(tetrahydro-2*H*-pyran-4-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-121**) (60 mg, 33% yield) as a white solid: cSFC analytical (A) tR: 3.12 min., purity: 99.87%; LCMS (B): tR: 0.585 min., (ES⁺) m/z (M+H)⁺ = 399.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.17 (s, 1H), 7.80 (dd, J₁=7.6 Hz, J₂=0.8 Hz, 1H), 7.47-7.43 (m, 1H), 7.39 (d, J=6.8 Hz, 1H), 4.27 (dd, J₁=4.8 Hz, J₂=1.2 Hz, 1H), 4.12-4.08 (m, 2H), 3.72-3.62 (m, 4H), 3.49-3.31 (m, 2H), 3.28-3.13 (m, 1H), 2.45-2.41 (m, 1H), 2.28-2.26 (m, 1H), 2.14-2.03 (m, 2H), 2.00-1.91 (m, 5H), 1.75 (s, 3H), 1.49 (m, 3H).

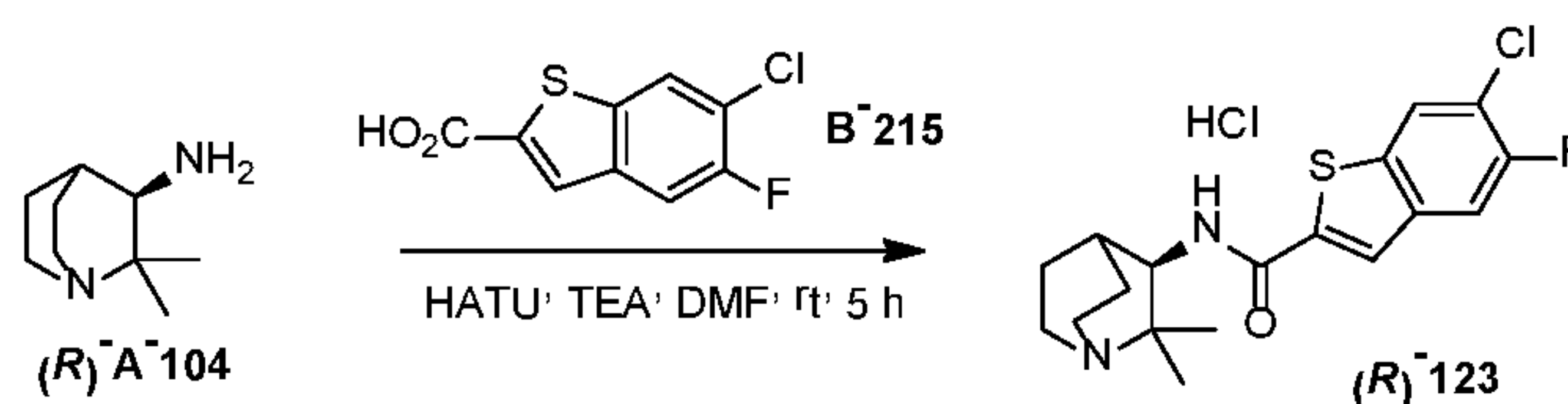
[001079] **Example 122:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-1*H*-indole-2-carboxamide hydrochloride ((*R*)-122)



[001080] Following general procedure B, **Compound (R)-122** was prepared from 1*H*-indole-2-carboxylic acid (80 mg, 0.50 mmol) and **compound (R)-A-104** (70 mg, 0.45 mmol), with a reaction time of 16 hours. The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 250*50, particle size: 10 μm; Mobile phase: 30-60% acetonitrile in H₂O (add 0.5% NH₃ · H₂O, v/v)]. The resulting solids were dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-1*H*-indole-2-carboxamide hydrochloride (**compound (R)-122**) (50 mg, 37% yield) as a yellow solid: cSFC analytical (A) tR=2.99 min., purity: 98.13%; LCMS (G): tR=2.280 min., 298.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 7.66-7.64 (d, J=8.0 Hz, 1H), 7.48-7.46 (d, J=8.4 Hz, 1H), 7.29-7.24 (m, 2H), 7.12-7.08 (t, J=7.2 Hz, 1H), 4.31 (s, 1H), 3.77-3.69 (m, 2H), 3.39-3.36 (m, 2H), 2.48-2.44 (m, 1H), 2.28-2.27 (m, 1H), 2.20-2.11 (m, 2H), 1.99-1.93 (m, 1H), 1.77 (s, 1H) 1.51 (s, 2H).

[001081] **Example 123:** (*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-123)

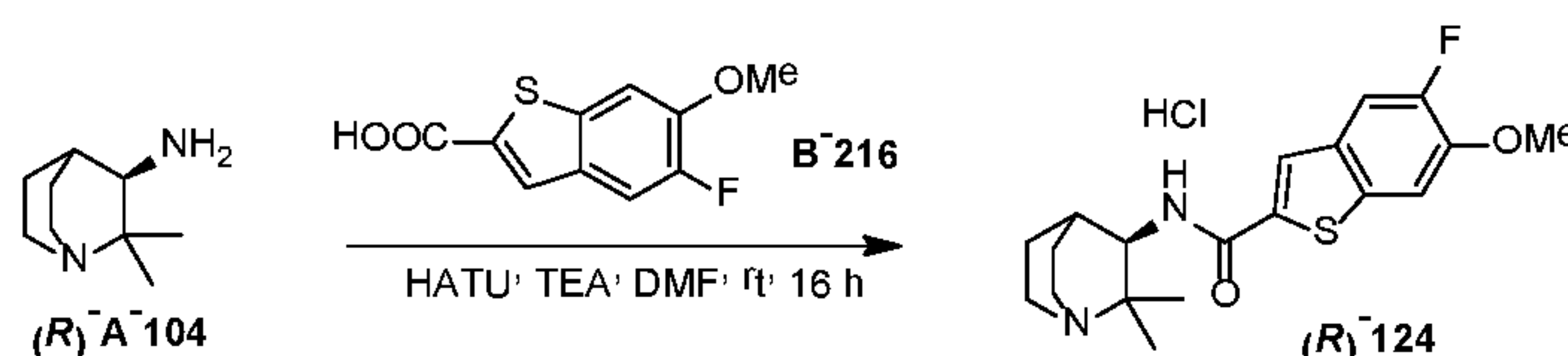


[001083] Following general procedure B, **Compound (R)-123** was prepared from **compound B-215** (0.13 g, 0.54 mmol) and **compound (R)-A-104** (70 mg, 0.45 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-D; Column: Boston Green ODS C18

150×30 mm, particle size: 5 μ m; Mobile phase: 42-72% acetonitrile in H₂O (add 0.225% FA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide-hydrochloride (**compound (R)-123**) (73 mg, 40% yield) as a white solid: cSFC analytical (A) t_R=2.98 min., purity: 96.51%; LCMS (B): t_R=0.708 min., 367.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.12-8.09 (m, 2H), 7.79-7.76 (d, J=9.6 Hz, 1H), 4.24 (m, 1H), 3.72-3.69 (m, 2H), 3.34-3.31 (m, 2H), 2.39 (m, 1H), 2.27 (m, 1H), 2.14-2.12 (m, 2H), 1.97-1.96 (m, 1H), 1.74 (s, 3H), 1.47 (s, 3H).

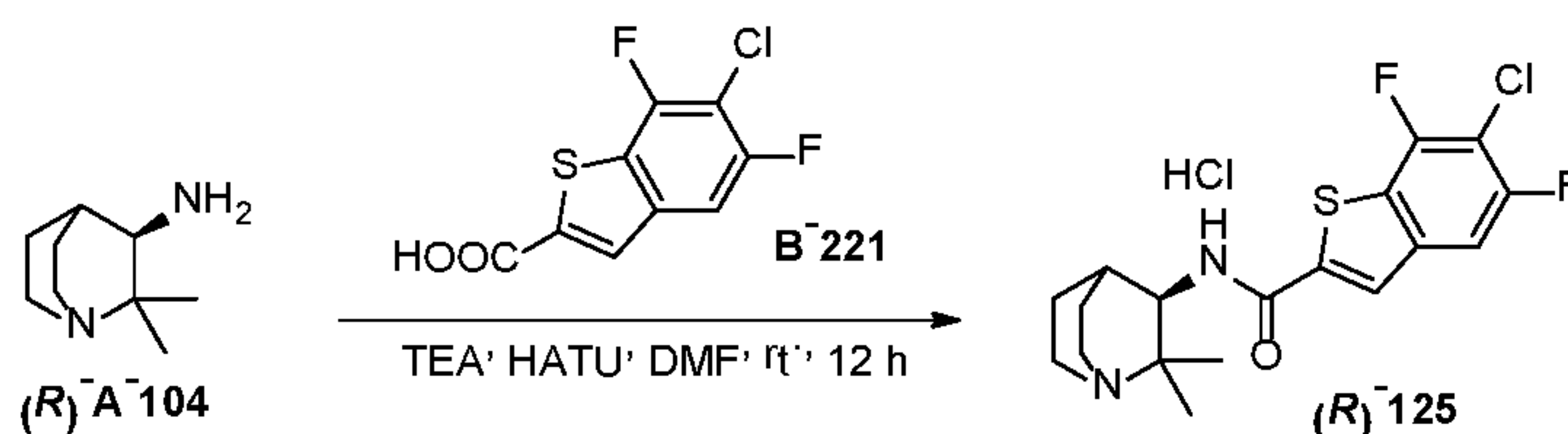
[001084] **Example 124:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-fluoro-6-methoxybenzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-124)



[001085] Following general procedure B, **Compound (R)-124** was prepared from **compound B-216** (120 mg, 0.53 mmol) and **compound (R)-A-104** (82 mg, 0.53 mmol), with a reaction time of 16 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex SynergiC18 250*21.2mm, particle size: 4 μ m; Mobile phase: 15-45% acetonitrile in H₂O (add 0.05% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-5-fluoro-6-methoxybenzo[b]thiophene-2-carboxamide-hydrochloride (**compound (R)-124**) (150 mg, 71% yield) as a white solid: cSFC analytical (A) t_R=2.54 min., purity: 97.70%; LCMS (B): t_R=0.646 min., 363.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.04 (s, 1H), 7.65-7.61 (m, 2H), 4.26 (s, 1H), 3.98 (s, 3H), 3.80-3.68 (m, 2H), 3.39-3.36 (m, 2H), 2.42-2.41 (m, 1H), 2.29-2.28 (d, J=2.8 Hz, 1H), 2.19-2.12 (m, 2H), 1.99-1.93 (m, 1H), 1.76 (s, 3H), 1.50 (m, 3H).

[001086] **Example 125:** (*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-5,7-difluorobenzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-125)

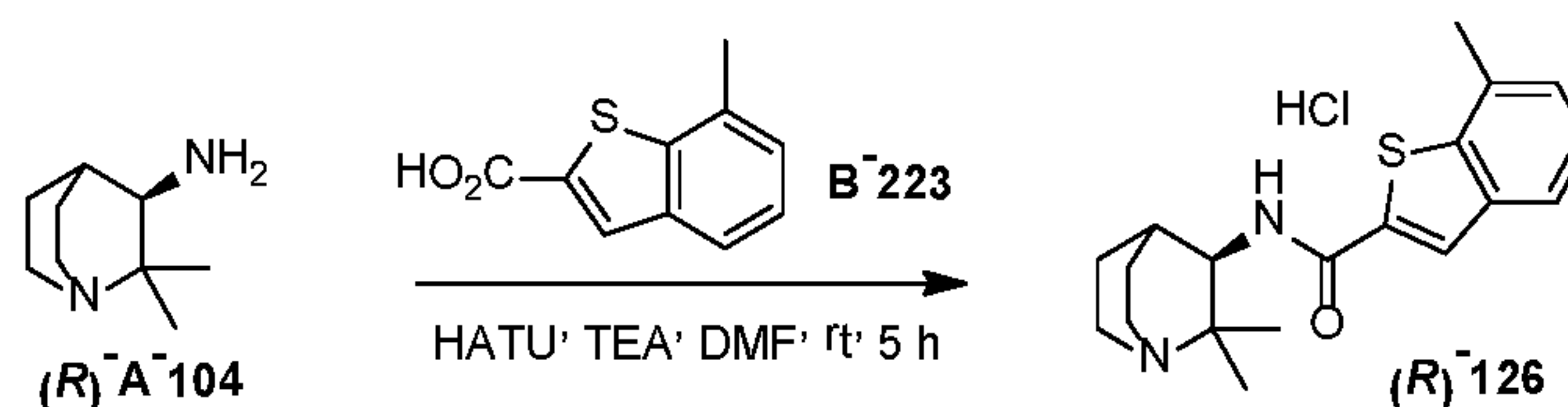


[001087] Following general procedure B, **Compound (R)-125** was prepared from **compound B-221** (70 mg, 0.28 mmol) and **compound (R)-A-104** (43 mg, 0.28 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150×30 mm, particle size: 5 μ m; Mobile phase: 25-55% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-5,7-difluorobenzo[b]thiophene-2-carboxamide-hydrochloride (**compound (R)-125**) (55 mg, 46% yield) as a yellow solid: cSFC analytical (A)

tR=2.960 min., purity: 98.11%; LCMS (FF): tR=2.570 min., 385.0 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.22-8.21 (d, J=3.2 Hz, 1H), 7.73-7.71 (dd, J₁=8.8 Hz, J₂=1.2 Hz, 1H), 4.26 (m, 1H), 3.75-3.69 (m, 2H), 3.39-3.31 (m, 2H), 2.44-2.43 (m, 1H), 2.30 (m, 1H), 2.20-2.13 (m, 2H), 2.13-1.94 (m, 1H), 1.77 (s, 3H), 1.51 (s, 3H).

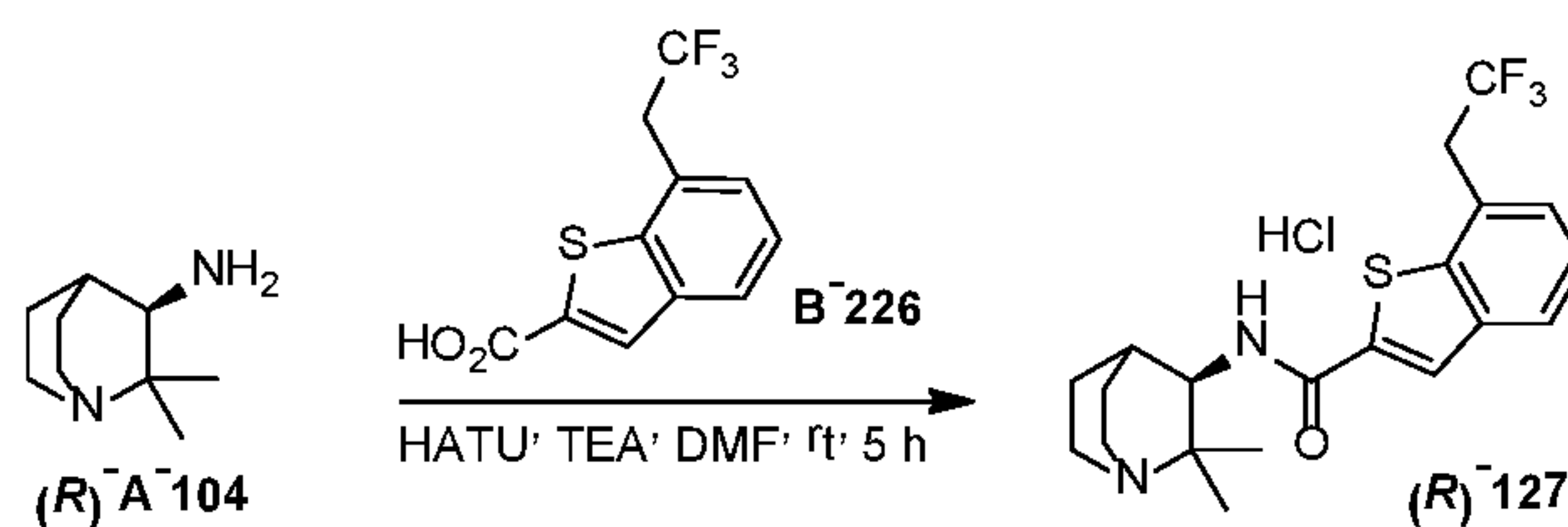
[001088] Example 126: (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-126)



[001089] Following general procedure B, **Compound (R)-126** was prepared from **compound B-223** (98 mg, 0.52 mmol) and **compound (R)-A-104** (80 mg, 0.52 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150×30 mm, particle size: 5 μm; Mobile phase: 29-59% acetonitrile in H₂O (add 0.1% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-126**) (70 mg, 37% yield) as a white solid: cSFC analytical (A) tR=3.023 min., purity: 98.27%; LCMS (B): tR=0.674 min., (ES⁺) m/z (M+H)⁺=329.2; ¹H-NMR (CD₃OD, 400 MHz): δ 8.16 (s, 1H), 7.77 (d, J=8.0 Hz, 1H), 7.38 (t, J=7.6 Hz, 1H), 7.29 (d, J=7.2 Hz, 1H), 4.27 (d, J=4.0 Hz, 1H), 3.73-3.67 (m, 2H), 3.38-3.34 (m, 2H), 2.57 (s, 3H), 2.42-2.41 (m, 1H), 2.28-2.27 (m, 1H), 2.18-2.10 (m, 2H), 2.04-1.91 (m, 1H), 1.75 (s, 3H), 1.50 (s, 3H).

[001090] Example 127: (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(2,2,2-trifluoroethyl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-127)

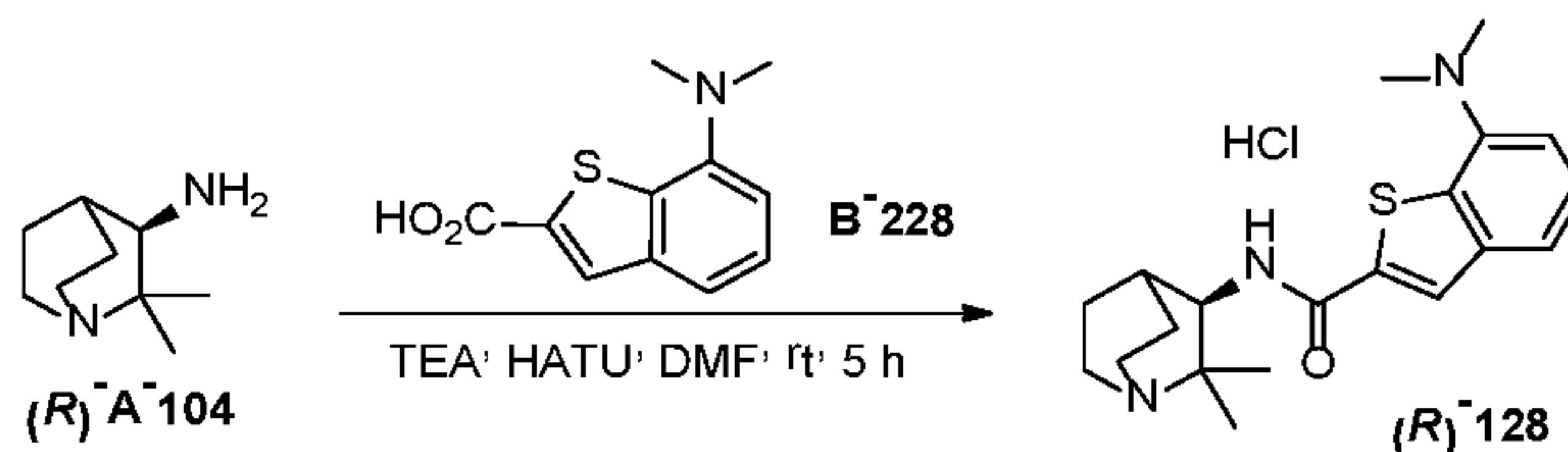


[001091] Following general procedure B, **Compound (R)-127** was prepared from **compound B-226** (84 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150×30 mm, particle size: 5 μm; Mobile phase: 25-55% acetonitrile in H₂O (add 0.1% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(2,2,2-trifluoroethyl)benzo[*b*]thiophene-2-carboxamide -hydrochloride (**compound (R)-127**) (69 mg, 54% yield) as a white solid: cSFC analytical (C) tR=0.71 min., purity: 98.06%; LCMS (DD): tR=0.806 min., 397.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.49 (d, J=7.2 Hz, 0.1H), 8.21 (s, 1H), 7.95 (dd, J₁=6.4 Hz, J₂=2.8 Hz, 1H),

7.51-7.48 (m, 2H), 4.27 (s, 1H), 3.81 (q, J=11.2 Hz, 2H), 3.73-3.67 (m, 2H), 3.38-3.33 (m, 2H), 2.44-2.41 (m, 1H), 2.29-2.28 (m, 1H), 2.17-2.10 (m, 2H), 1.98-1.91 (m, 1H), 1.76 (s, 3H), 1.50 (s, 3H).

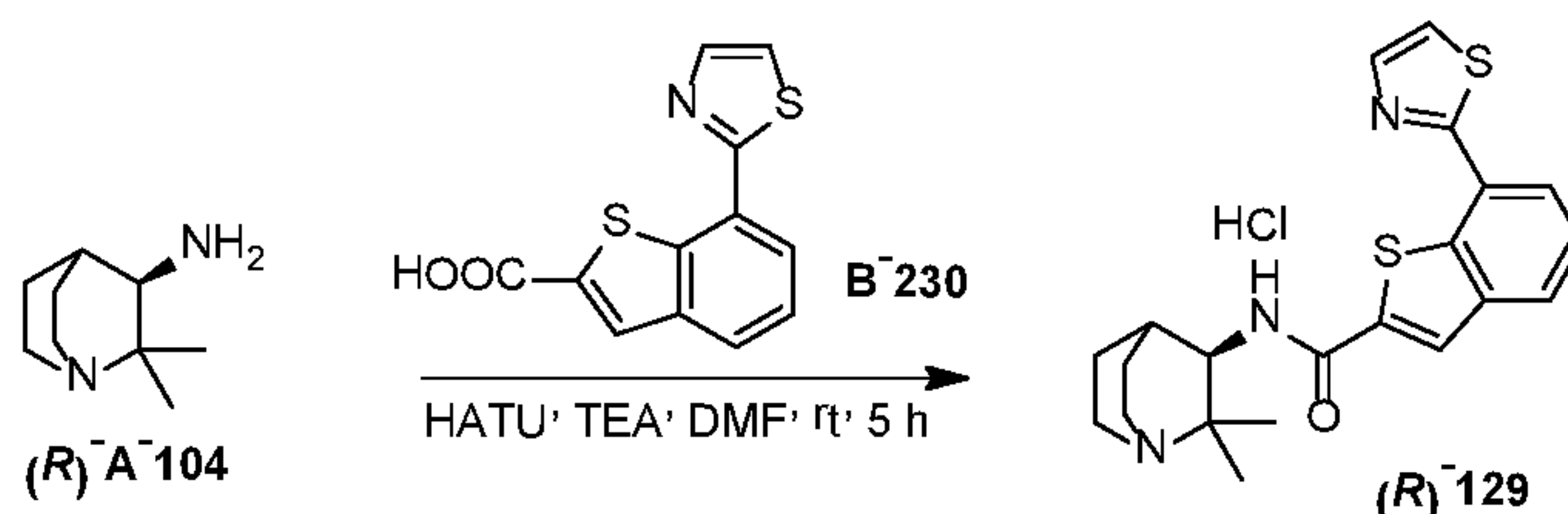
[001092] Example 128: (*R*)-7-(dimethylamino)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**(*R*)-128**)



[001093] Following general procedure B, **Compound (*R*)-128** was prepared from **compound B-228** (149 mg, crude) and **compound (*R*)-A-104** (104 mg, 0.67 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 19-49% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-7-(dimethylamino)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide-hydrochloride (**compound (*R*)-128**) (44 mg, 15% yield) as a white solid: cSFC analytical (A) t_R=3.32 min., purity: 99.66%; LCMS (FF): t_R=2.186 min., (ES⁺) m/z (M+H)⁺ = 358.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.43 (s, 1H), 8.12 (d, J=8 Hz, 1H), 8.75 (d, J=7.6 Hz, 1H), 7.68-7.64 (m, 1H), 4.28 (s, 1H), 3.75-3.69 (m, 2H), 3.48 (s, 6H), 3.36-3.30 (m, 2H), 2.48-2.47 (m, 1H), 2.30-2.29 (m, 1H), 2.18-2.11 (m, 2H), 2.10-1.95 (m, 1H), 1.76 (s, 3H), 1.52 (m, 3H).

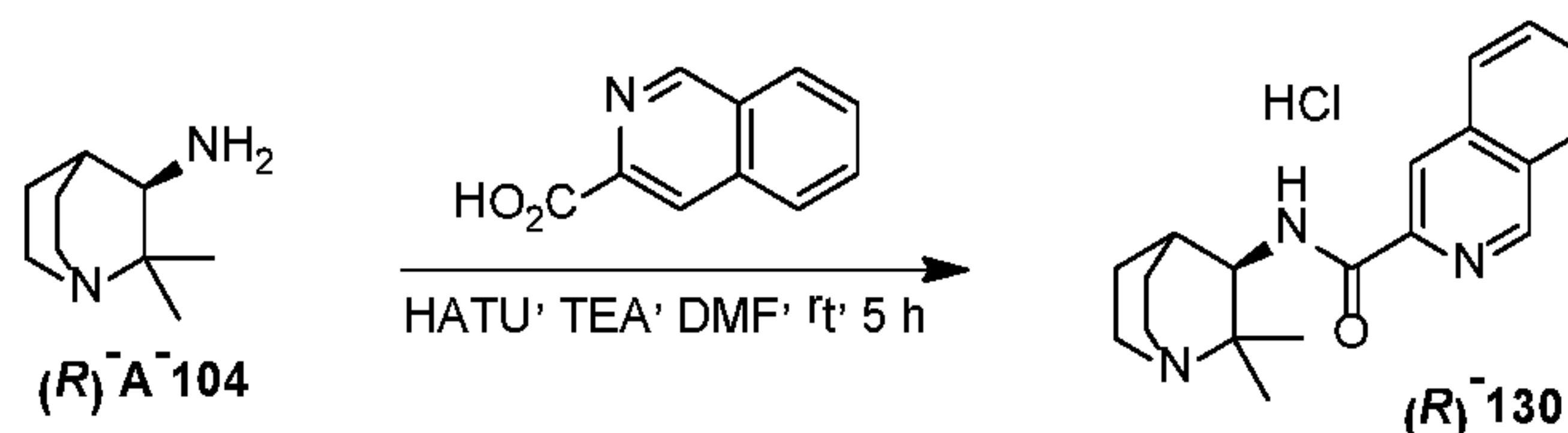
[001094] Example 129: (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(thiazol-2-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**(*R*)-129**)



[001095] Following general procedure B, **Compound (*R*)-129** was prepared from **compound B-230** (119 mg, 0.45 mmol) and **compound (*R*)-A-104** (70 mg, 0.45 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 20-50% acetonitrile in H₂O (add 0.05% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(thiazol-2-yl)benzo[*b*]thiophene-2-carboxamide-hydrochloride (**compound (*R*)-129**) (70 mg, 35% yield) as a yellow solid: cSFC analytical (C) t_R=2.054 min., purity: 100%; LCMS (EE): t_R=2.895 min., (ES⁺) m/z (M+H)⁺ = 398.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.22 (s, 1H), 8.09-8.014 (m, 3H), 7.70 (d, J=3.6 Hz, 1H), 7.59 (t, J=8.0 Hz, 1H), 4.29 (s, 1H), 3.74-3.68 (m, 2H), 3.38-3.34 (m, 2H), 2.44-2.43 (m, 1H), 2.30-2.29 (m, 1H), 2.19-2.10 (m, 2H), 1.98-1.92 (m, 1H), 1.77 (s, 3H), 1.52 (s, 3H).

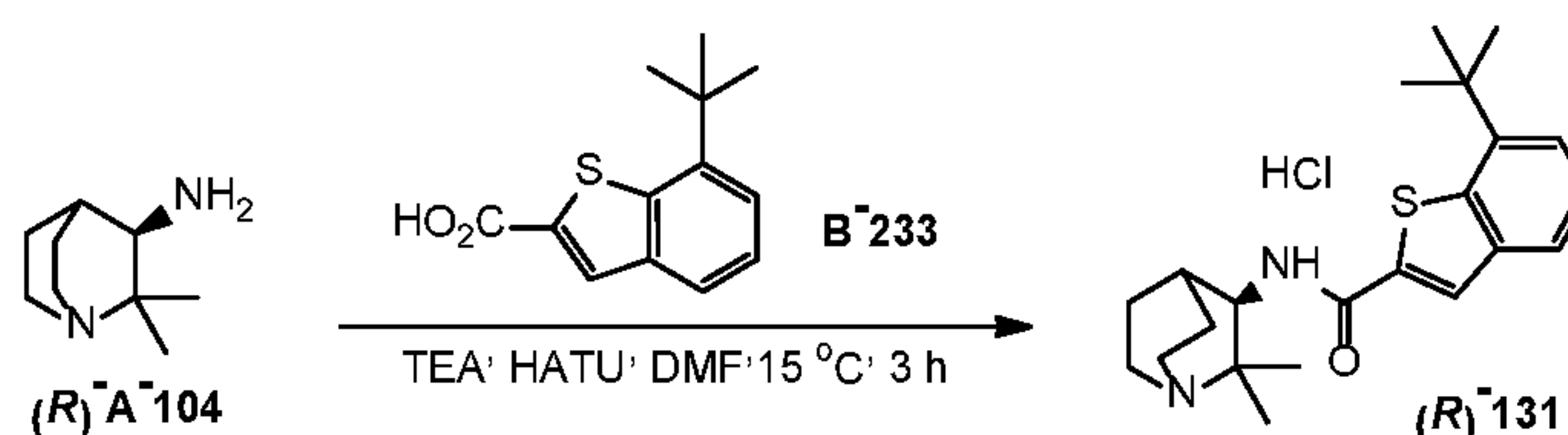
[001096] **Example 130:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)isoquinoline-3-carboxamide hydrochloride ((*R*)-130)



[001097] Following general procedure B, **Compound (R)-130** was prepared from isoquinoline-3-carboxylic acid (90 mg, 0.52 mmol) and **compound (R)-A-104** (80 mg, 0.52 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150×30 mm, particle size: 5 μm; Mobile phase: 10-40% acetonitrile in H₂O (add 0.1% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)isoquinoline-3-carboxamide- hydrochloride (**compound (R)-130**) (130 mg, 72% yield) as a white solid: cSFC analytical (A) t_R=2.741 min., purity: 100%; LCMS (B): t_R=0.575 min., (ES⁺) m/z (M+H)⁺=310.2; ¹H-NMR (CD₃OD, 400 MHz): δ 9.69 (s, 1H), 9.14 (s, 1H), 8.52 (d, J=8.4 Hz, 1H), 8.37 (d, J=8.4 Hz, 1H), 8.22 (t, J=8.0 Hz, 1H), 8.08 (t, J=8.0 Hz, 1H), 4.38 (s, 1H), 3.76-3.73 (m, 2H), 3.41-3.37 (m, 2H), 2.54-2.47 (m, 1H), 2.35 (m, 1H), 2.22-2.14 (m, 2H), 2.03-1.96 (m, 1H), 1.80 (s, 3H), 1.56 (s, 3H).

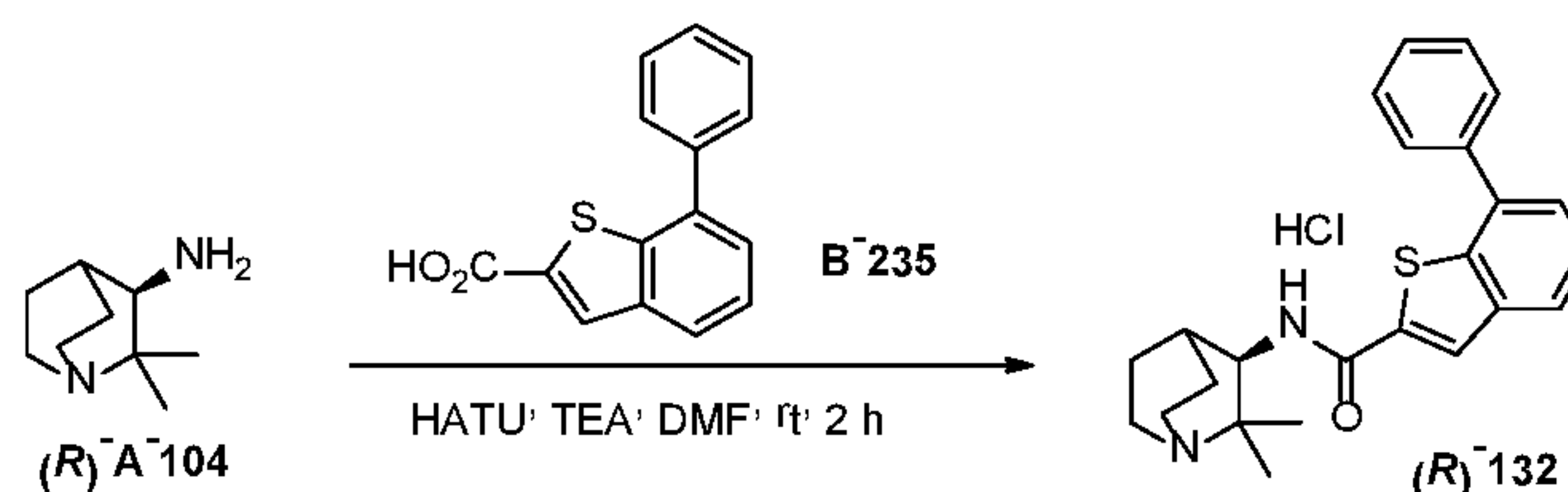
[001098] **Example 131:** (*R*)-7-(tert-butyl)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-131)



[001099] Following general procedure B, **Compound (R)-131** was prepared from **compound B-233** (96 mg, 0.49 mmol) and **compound (R)-A-104** (63 mg, 0.41 mmol), with a reaction time of 3 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 32-62% acetonitrile in H₂O (add 0.1% TFA, v/v)]. The resulting solid was dissolved in 0.2 N hydrochloric acid and again lyophilized to give:

(*R*)-7-(tert-butyl)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-2-carboxamide - hydrochloride (**compound (R)-131**) (90 mg, 45% yield) as a white solid : cSFC analytical (A) t_R=2.71 min., purity: 96.96%; LCMS (FF): t_R=2.668 min., 371.2 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.45 (d, J= 7.6 Hz, 1H), 8.17 (s, 1H), 7.81 (d, J= 7.6 Hz, 1H), 7.52-7.48 (m, 1H), 7.45-7.41 (m, 1H), 4.29 (m, 1H), 3.78-3.69 (m, 2H), 3.40-3.35 (m, 2H), 2.47-2.30 (m, 1H), 2.20-1.93 (m, 4H), 1.74 (s, 3H), 1.59 (s, 1H), 1.52 (s, 3H).

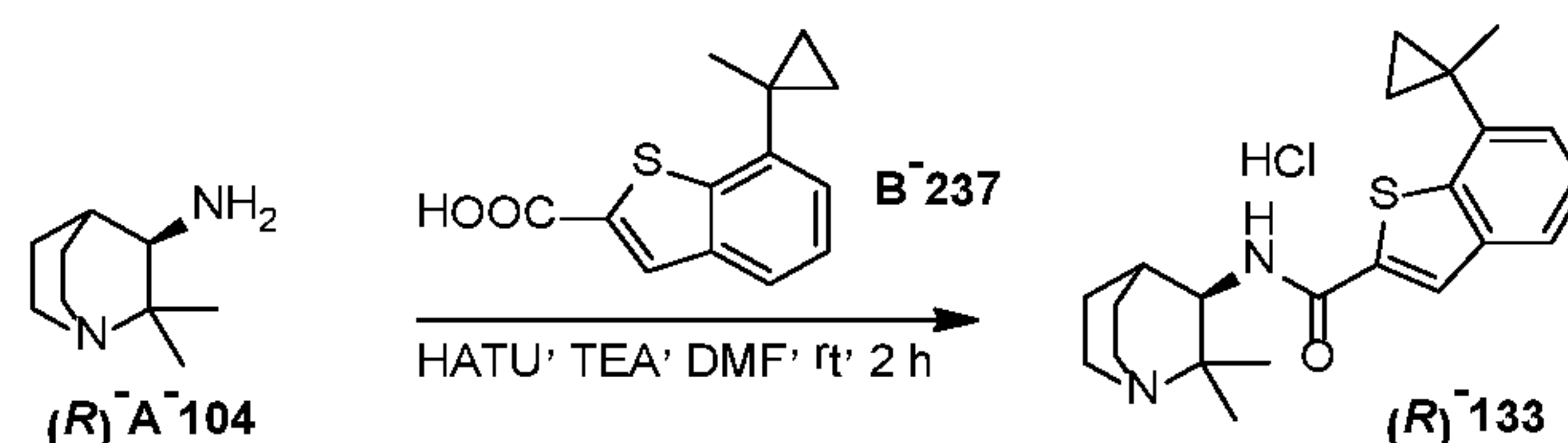
[001100] **Example 132:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-phenylbenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-132)



[001101] Following general procedure B, **Compound (R)-132** was prepared from **compound B-235** (99 mg, 0.39 mmol) and **compound (R)-A-104** (60 mg, 0.39 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 µm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-phenylbenzo[*b*]thiophene-2-carboxamide-hydrochloride (**compound (R)-132**) (70 mg, 46% yield) as a white solid: cSFC analytical (A) t_R=3.57 min., purity: 100%; LCMS (Y): t_R=0.754 min., 391.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.44 (d, J=7.2 Hz, 1H), 8.22 (s, 1H), 7.94 (d, J=7.2 Hz, 1H), 7.73 (d, J=7.2 Hz, 2H), 7.60-7.46 (m, 5H), 4.27 (s, 1H), 3.83-3.69 (m, 2H), 3.40-3.37 (m, 1H), 2.46-2.42 (m, 1H), 2.30-2.12 (m, 3H), 1.99-1.93 (m, 1H), 1.76 (s, 3H), 1.50 (s, 3H).

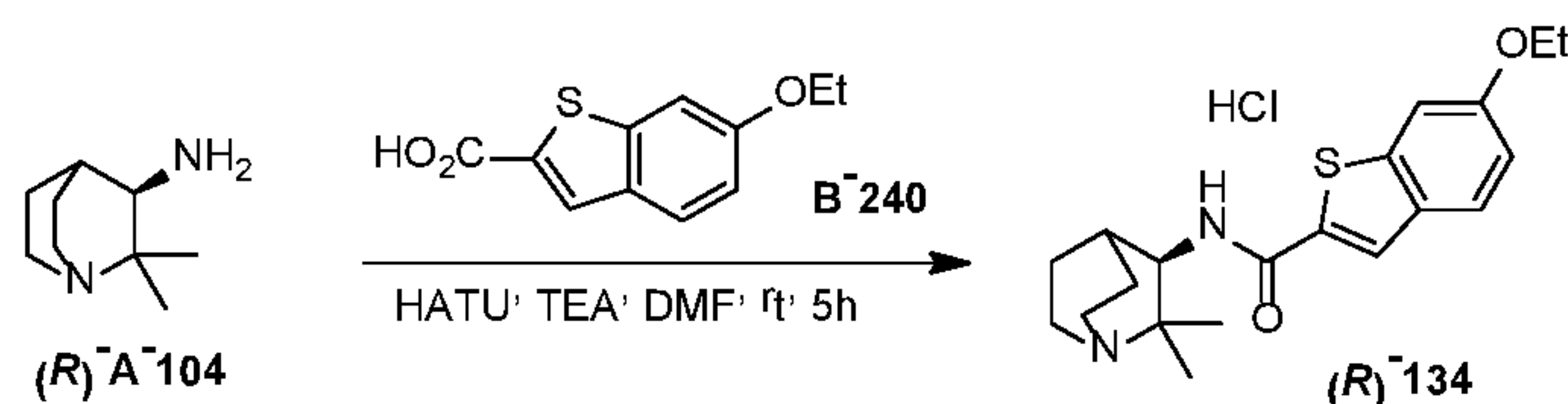
[001102] **Example 133:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(1-methylcyclopropyl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-133)



[001103] **Compound (R)-133** was prepared from **B-237** (90 mg, 0.39 mmol) and **compound (R)-A-104** (60 mg, 0.39 mmol) using general procedure B with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 µm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(1-methylcyclopropyl)benzo[*b*]thiophene-2-carboxamide –hydrochloride (**compound (R)-133**) (62 mg, 47% yield) as a white solid : cSFC analytical (A) t_R=2.76 min., purity: 98.18%; LCMS (GG): t_R=2.298 min., 369.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.42 (d, J=7.2 Hz, 1H), 8.16 (s, 1H), 7.80 (d, J=7.6 Hz, 1H), 7.46-7.39 (m, 2H), 4.29 (s, 1H), 3.79-3.69 (m, 2H), 3.40-3.37 (m, 1H), 2.47-2.42 (m, 1H), 2.31-2.30 (m, 1H), 2.20-2.10 (m, 3H), 2.00-1.94 (m, 1H), 1.78 (s, 3H), 1.51 (s, 3H), 1.48 (s, 3H), 0.96-0.92 (m, 2H), 0.89-0.86 (m, 2H).

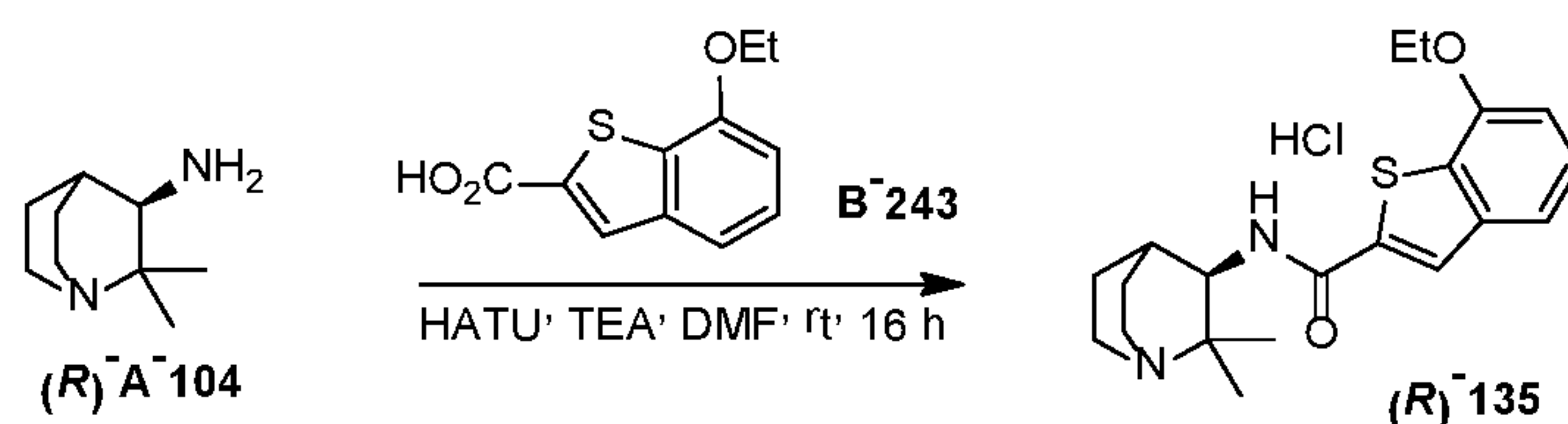
[001104] **Example 134:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-ethoxybenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-134)



[001105] Following general procedure B, **Compound (R)-134** was prepared from **compound B-240** (115 mg, 0.52 mmol) and **compound (R)-A-104** (80 mg, 0.52 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 25-55% acetonitrile in H₂O (add 0.1% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-ethoxybenzo[*b*]thiophene-2-carboxamide-hydrochloride (**compound (R)-134**) (70 mg, 34% yield) as a white solid: cSFC analytical (A) tR = 3.13 min., purity: 96.60%; LCMS (EE): tR = 2.861 min., (ES⁺) m/z (M+H)⁺ = 359.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.05 (s, 1H), 7.77 (d, J=8.8 Hz, 1H), 7.42 (d, J=1.6 Hz, 1H), 7.03 (dd, J=8.8, 2.0 Hz, 1H), 4.24-4.23 (m, 1H), 4.11 (q, J=6.8 Hz, 2H), 3.74-3.65 (m, 2H), 3.36-3.33 (m, 2H), 2.40-2.39 (m, 1H), 2.25 (d, J=2.8 Hz, 1H), 2.16-2.10 (m, 2H), 2.08-1.93 (m, 1H), 1.73 (s, 3H), 1.47 (s, 3H), 1.42 (t, J=6.8 Hz, 3H).

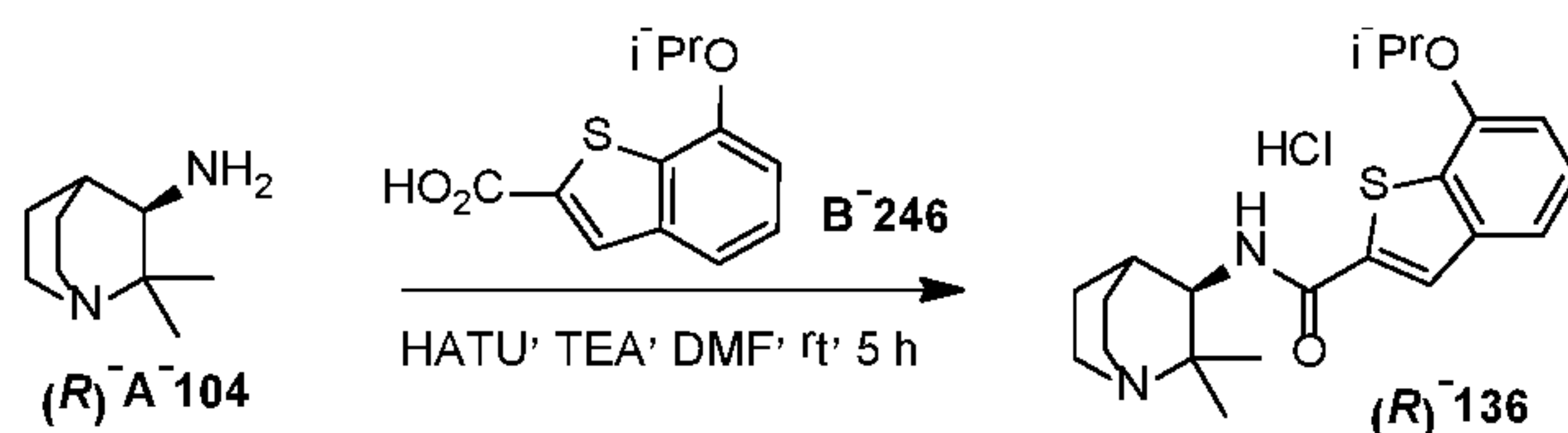
[001106] **Example 135:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-ethoxybenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-135)



[001107] Following general procedure B, **Compound (R)-135** was prepared from **compound B-243** (101 mg, 0.45 mmol) and **compound (R)-A-104** (117 mg, 0.45 mmol), with a reaction time of 16 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150×30 mm, particle size: 5 μm; Mobile phase: 25-55% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-ethoxybenzo[*b*]thiophene-2-carboxamide-hydrochloride (**compound (R)-135**) (80 mg, 41% yield) as a white solid: cSFC analytical (A) tR=3.37 min., purity: 99.52%; LCMS (GG): tR=2.096 min., (ES⁺) m/z (M+H)⁺ = 359.2; ¹H-NMR (CD₃OD, 400 MHz): 8.10 (s, 1H), 7.49 (d, J=8.0 Hz, 1H), 7.38 (m, 1H), 6.97 (d, J=7.6 Hz, 1H), 4.29-4.23 (m, 3H), 3.72-3.66 (m, 2H), 3.37-3.33 (m, 2H), 2.41-2.39 (m, 1H), 2.27-2.26 (m, 1H), 2.17-2.09 (m, 2H), 1.96-1.901 (m, 1H), 1.74 (s, 3H), 1.51-1.47 (m, 6H).

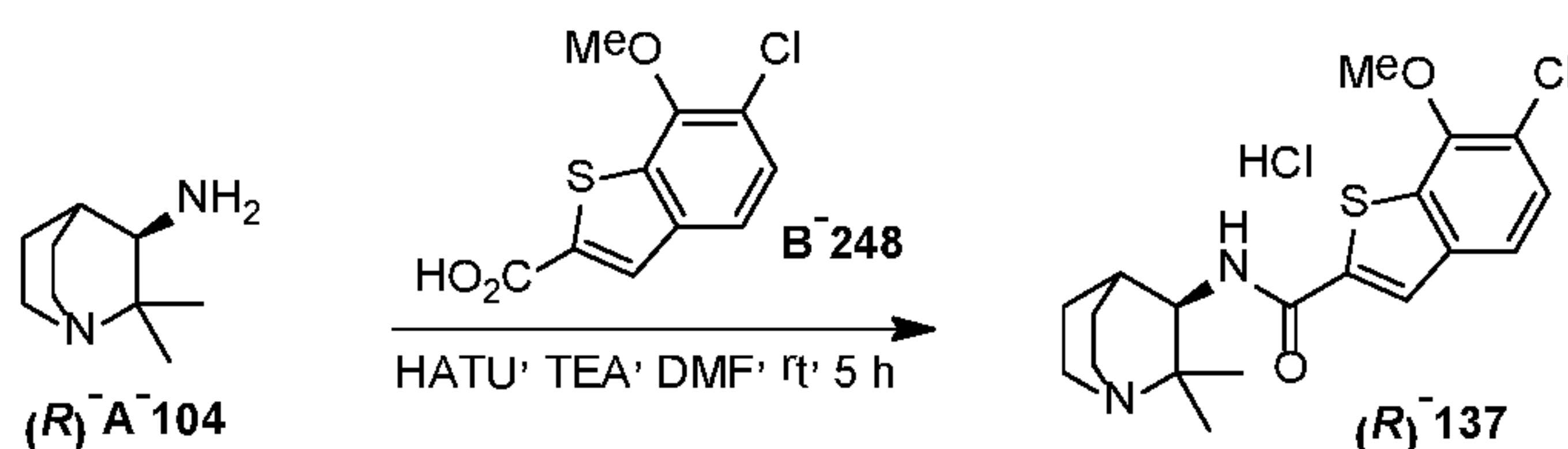
[001108] **Example 136:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-isopropoxybenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-136)



[001109] Following general procedure B, **Compound (R)-136** was prepared from **compound B-246** (107 mg, 0.45 mmol) and **compound (R)-A-104** (70 mg, 0.45 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-I; Column: Phenomenex Synergi C18 150×30mm, particle size: 4 μ m; Mobile phase: 28-58% acetonitrile in H₂O (add 0.1% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-isopropoxybenzo[b]thiophene-2-carboxamide-hydrochloride (**compound (R)-136**) (101 mg, 54% yield) as a white solid: cSFC analytical (A) t_R =2.970 min., purity: 98.63%; LCMS (EE): t_R =3.041 min., (ES⁺) m/z (M+H)⁺=373.2; ¹H-NMR (CD₃OD, 400 MHz): δ 8.09 (s, 1H), 7.49 (d, J =8.0 Hz, 1H), 7.38 (t, J =8.0 Hz, 1H), 7.00 (d, J =7.6 Hz, 1H), 4.87-4.81 (m, 1H), 4.25 (s, 1H), 3.76-3.67 (m, 2H), 3.38-3.31 (m, 2H), 2.44-2.40 (m, 1H), 2.28-2.27 (m, 1H), 2.19-2.10 (m, 2H), 1.97-1.91 (m, 1H), 1.75 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H).

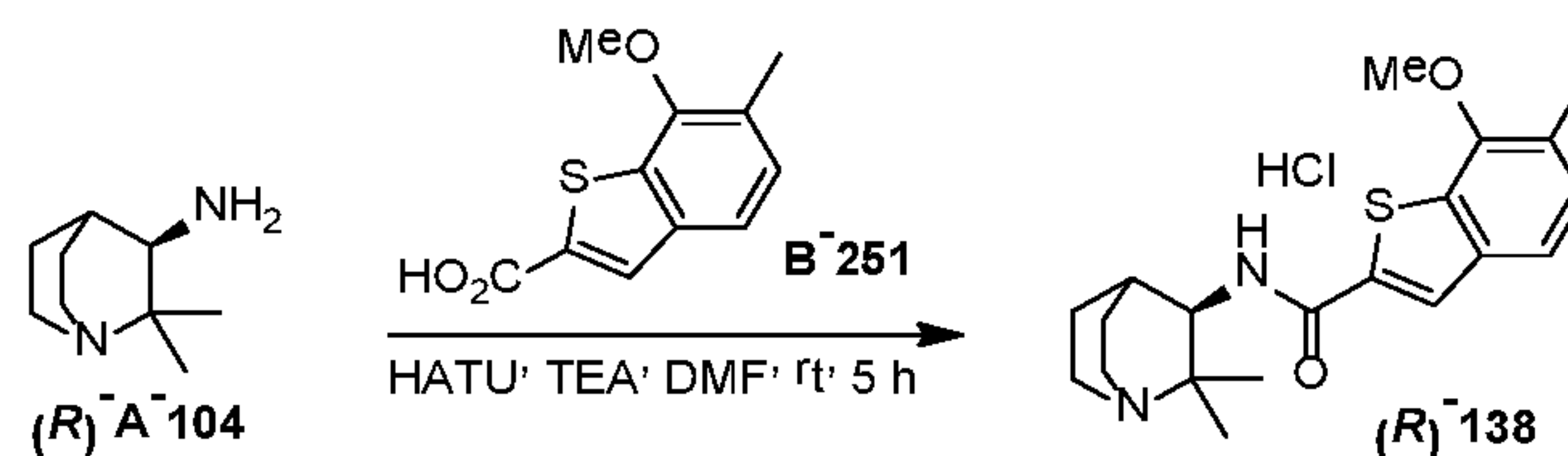
[001110] **Example 137:** (*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-137)



[001111] Following general procedure B, **Compound (R)-137** was prepared from **compound B-248** (110 mg, 0.45 mmol) and **compound (R)-A-104** (70 mg, 0.45 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150×30 mm, particle size: 5 μ m; Mobile phase: 38-68% acetonitrile in H₂O (add 0.1% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide-hydrochloride (**compound (R)-137**) (72 mg, 38% yield) as a white solid: cSFC analytical (A) t_R =2.982 min., purity: 98.64%; LCMS (FF): t_R =2.455 min., (ES⁺) m/z (M+H)⁺=379.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.13 (s, 1H), 7.66 (d, J =8.8 Hz, 1H), 7.48 (d, J =8.4 Hz, 1H), 4.25 (s, 1H), 4.04 (s, 3H), 3.76-3.66 (m, 2H), 3.38-3.33 (m, 2H), 2.42-2.39 (m, 1H), 2.28-2.27 (m, 1H), 2.17-2.09 (m, 2H), 2.04-1.91 (m, 1H), 1.75 (s, 3H), 1.48 (s, 3H).

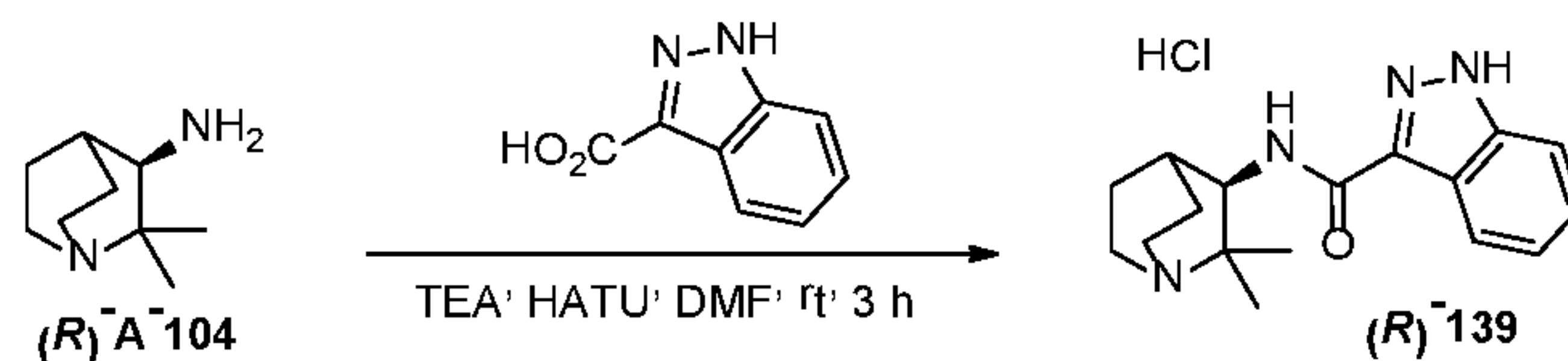
[001112] **Example 138:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-methoxy-6-methylbenzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-138)



[001113] Following general procedure B, **Compound (R)-138** was prepared from **compound B-251** (0.10 g, 0.45 mmol) and **compound (R)-A-104** (70 mg, 0.45 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 µm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.1% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-methoxy-6-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-138**) (0.11 g, 59% yield) as a white solid: cSFC analytical (A) *t*_R=2.89 min., purity: 97.99%; LCMS (EE): *t*_R=2.864 min., 359.1 *m/z* (*M*+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.41 (d, *J*=7.2 Hz, 0.6H), 8.12 (s, 1H), 7.58 (d, *J*=8.0 Hz, 1H), 7.29 (d, *J*=8.0 Hz, 1H), 4.25 (s, 1H), 3.95 (s, 3H), 3.76-3.66 (m, 2H), 3.37-3.34 (m, 2H), 2.45-2.41 (m, 4H), 2.27-2.26 (m, 1H), 2.18-2.08 (m, 2H), 1.97-1.90 (m, 1H), 1.75 (s, 3H), 1.49 (s, 3H).

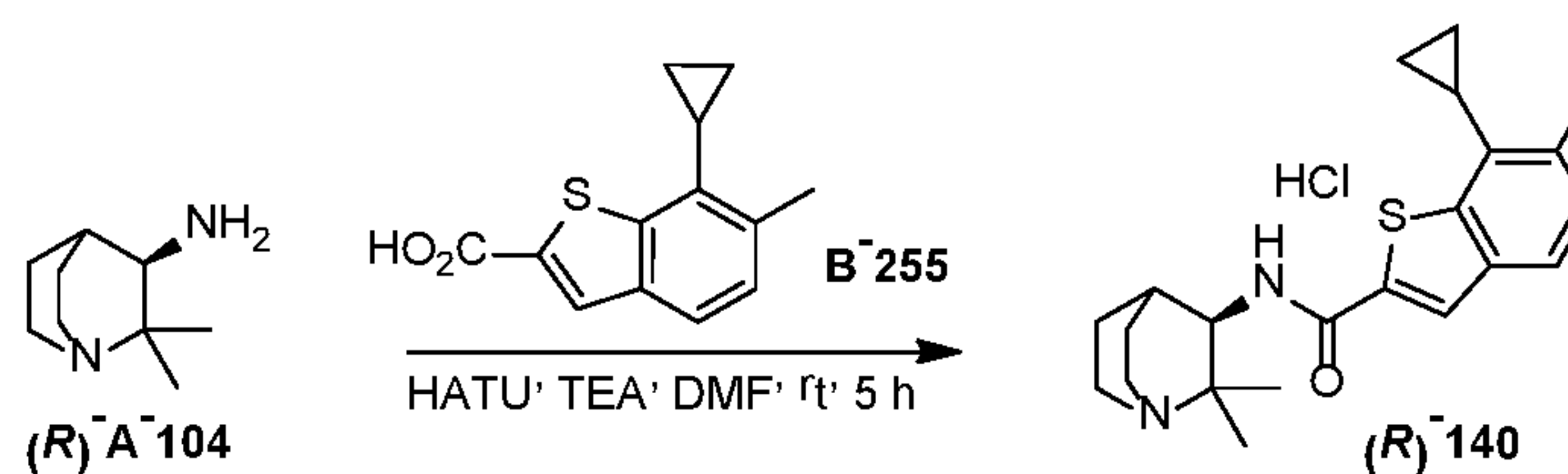
[001114] **Example 139: (R)-N-(2,2-dimethylquinuclidin-3-yl)-1H-indazole-3-carboxamide hydrochloride ((R)-139)**



[001115] Following general procedure B, **Compound (R)-139** was prepared from 1*H*-indazole-3-carboxylic acid d (0.10 g, 0.64 mmol) and **compound (R)-A-104** (90 mg, 0.58 mmol), with a reaction time of 3 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150×30 mm, particle size: 5 µm; Mobile phase: 7-37% acetonitrile in H₂O (add 0.1% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-1*H*-indazole-3-carboxamide hydrochloride (**compound (R)-139**) (62 mg, 29% yield) as a white solid: cSFC analytical (A) *t*_R=2.54 min., purity: 97.71%; LCMS (FF): *t*_R=2.004 min, 299.1 *m/z* (*M*+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.23 (d, *J*=8.4 Hz, 1H), 7.63 (d, *J*=8.5 Hz, 1H), 7.47 (t, *J*=7.4 Hz, 1H), 7.31 (t, *J*=7.5 Hz, 1H), 4.34 (s, 1H), 3.79-3.71 (m, 2H), 3.41-3.36 (m, 2H), 2.39-2.29 (m, 2H), 2.22-2.14 (m, 2H), 2.01-1.95 (m, 1H), 1.80 (s, 3H), 1.54 (s, 3H).

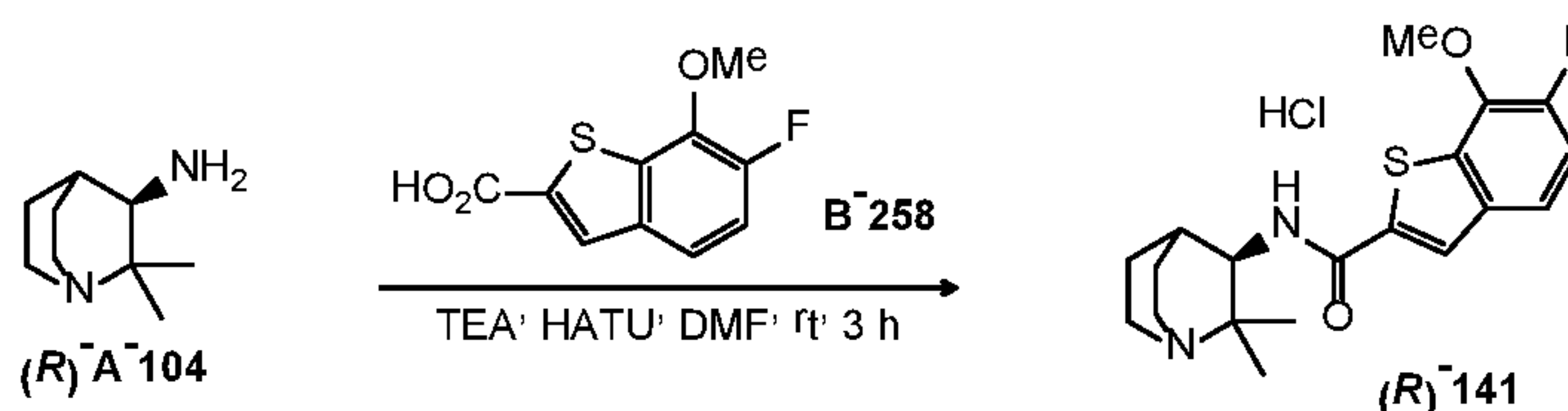
[001116] **Example 140: (R)-7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride ((R)-140)**



[001117] Following general procedure B, **Compound (R)-140** was prepared from **compound B-255** (0.14 g, 0.58 mmol) and **compound (R)-A-104** (90 mg, 0.58 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 30-60% acetonitrile in H₂O (add 0.1% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-7-cyclopropyl-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[*b*]thiophene-2-carboxamide -hydrochloride (**compound (R)-140**) (0.14 g, 67% yield) as a white solid: cSFC analytical (A) t_R=3.19 min., purity: 100%; LCMS (FF): t_R=2.536 min., 369.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.36 (d, J=7.2 Hz, 0.5H), 8.08 (s, 1H), 7.68 (d, J=8.0 Hz, 1H), 7.27 (d, J=8.0 Hz, 1H), 4.25 (s, 1H), 3.76-3.67 (m, 2H), 3.37-3.34 (m, 2H), 2.57 (s, 3H), 2.42-2.41 (m, 1H), 2.27-2.26 (m, 1H), 2.17-2.06 (m, 3H), 1.97-1.90 (m, 1H), 1.75 (s, 3H), 1.49 (s, 3H), 1.17-1.12 (m, 2H), 0.82-0.78 (m, 2H).

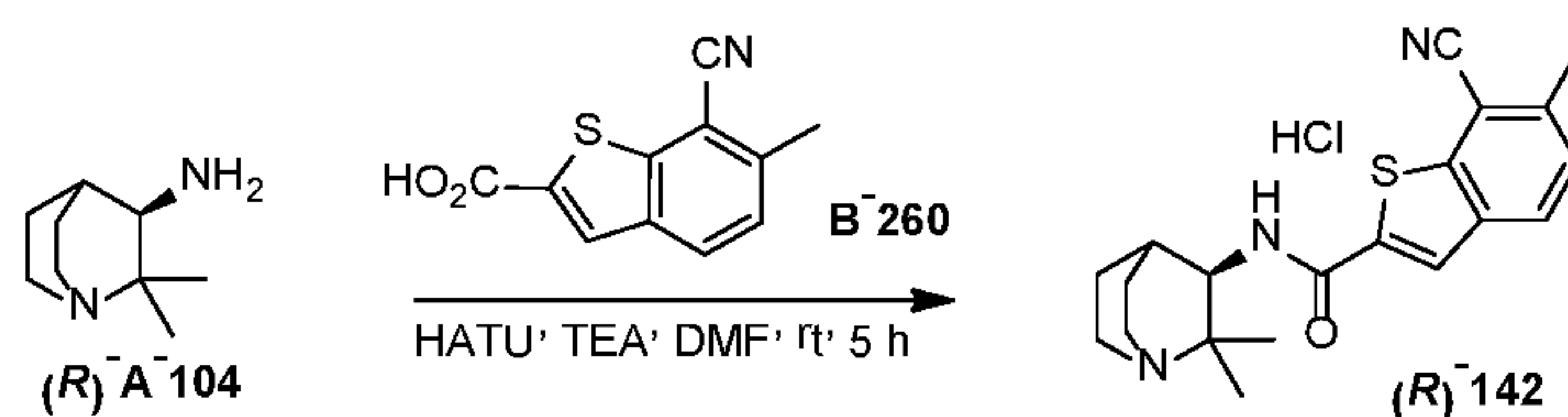
[001118] **Example 141:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-methoxybenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-141)



[001119] Following general procedure B, **compound (R)-141** was prepared from **compound B-258** (132 mg, 0.58 mmol) and **compound (R)-A-104** (90 mg, 0.58 mmol), with a reaction time of 3 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 250×21.2 mm, particle size: 4 μm; Mobile phase: 25-55% acetonitrile in H₂O (add 0.05% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-methoxybenzo[*b*]thiophene-2-carboxamide -hydrochloride (**compound (R)-141**) (119 mg, 56% yield) as a white solid: cSFC analytical (A) t_R=2.71 min., purity: 98.06%; LCMS (FF): t_R=2.356 min., 363.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.11 (s, 1H), 7.60 (dd, J₁=8.4 Hz, J₂=4.0 Hz, 1H), 7.27 (dd, J₁=12 Hz, J₂=8.4 Hz, 1H), 4.23 (s, 1H), 4.12 (d, J= 2.4 Hz, 3H), 3.72-3.65 (m, 2H), 3.38-3.28 (m, 2H), 2.40-2.38 (m, 1H), 2.27-2.25 (m, 1H), 2.15-2.10 (m, 2H), 1.97-1.93 (m, 1H), 1.74 (s, 3H), 1.47 (s, 3H).

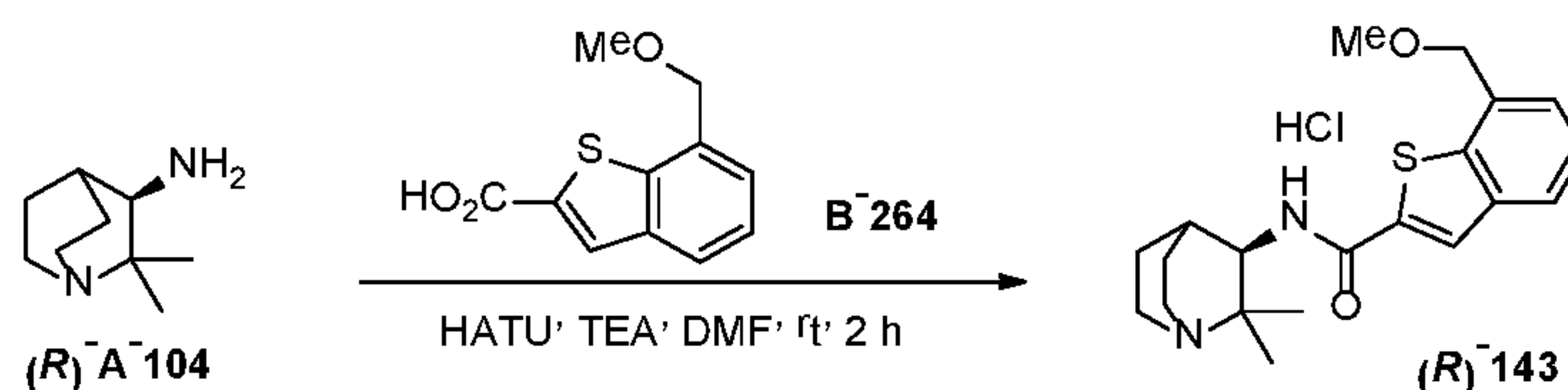
[001120] **Example 142:** (*R*)-7-cyano-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-142)



[001121] Following general procedure B, **Compound (R)-142** was prepared from **compound B-260** (0.11 g, 0.52 mmol) and **compound (R)-A-104** (80 mg, 0.52 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: Welch Ultimate AQ-C18 150×30 mm, particle size: 5 µm; Mobile phase: 25-55% acetonitrile in H₂O (add 0.1% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid and again lyophilized to give:

(*R*)-7-cyano-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[*b*]thiophene-2-carboxamide - hydrochloride (**compound (R)-142**) (0.13 g, 71% yield) as a white solid: cSFC analytical (A) *t*_R=3.05 min., purity: 100%; LCMS (GG): *t*_R=2.065 min., 354.2 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.53 (d, *J*=7.2 Hz, 0.6H), 8.22 (s, 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.50 (d, *J*=8.0 Hz, 1H), 4.26 (s, 1H), 3.76-3.67 (m, 2H), 3.38-3.33 (m, 2H), 2.69 (s, 3H), 2.46-2.41 (m, 1H), 2.29-2.28 (m, 1H), 2.18-2.10 (m, 2H), 1.98-1.91 (m, 1H), 1.75 (s, 3H), 1.50 (s, 3H).

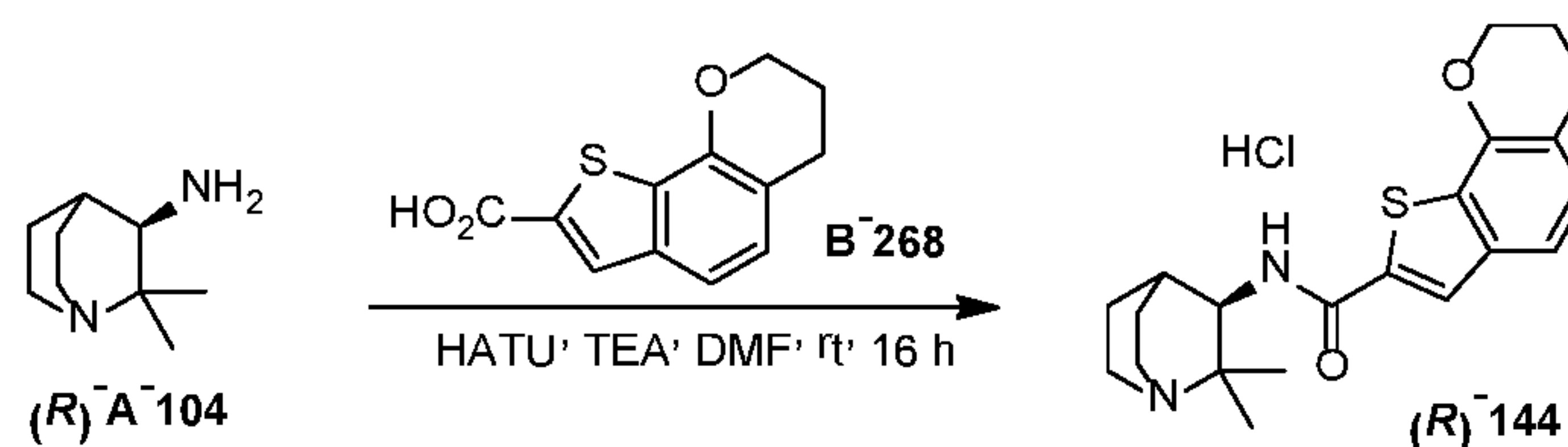
[001122] **Example 143:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(methoxymethyl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-143)



[001123] Following general procedure B, **Compound (R)-143** was prepared from **compound B-264** (0.13 g, 0.58 mmol) and **compound (R)-A-104** (90 mg, 0.58 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 µm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-(methoxymethyl)benzo[*b*]thiophene-2-carboxamide-hydrochloride (**compound (R)-143**) (135 mg, 64% yield) as a white solid : cSFC analytical (A) *t*_R=1.12 min., purity: 100%; LCMS (Y): *t*_R=2.205 min., 359.1 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.41 (d, *J*=7.2 Hz, 1H), 8.17 (s, 1H), 7.92-7.89 (m, 1H), 7.48-7.45 (m, 2H), 4.77 (s, 2H), 4.28 (d, *J*=6.8 Hz, 1H), 3.78-3.69 (m, 2H), 3.43 (s, 3H), 3.40-3.36 (m, 2H), 2.43-2.30 (m, 1H), 2.29-2.20 (m, 1H), 2.19-2.13 (m, 2H), 2.12-1.96 (m, 1H), 1.77 (s, 3H), 1.50 (s, 3H).

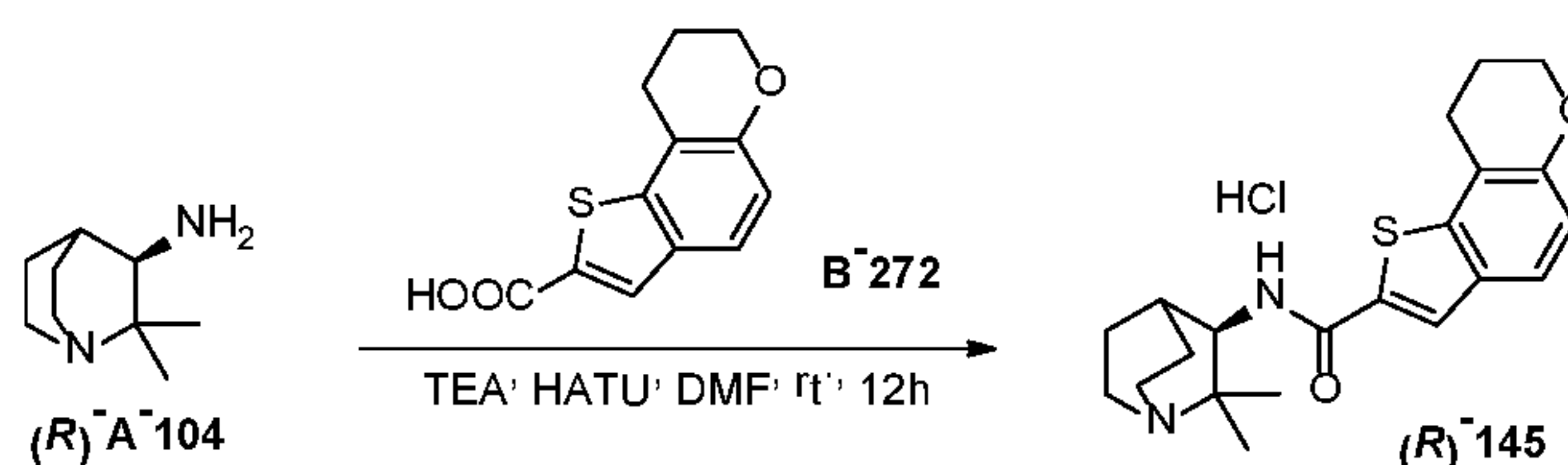
[001124] **Example 144:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-3,4-dihydro-2H-thieno[3,2-*h*]chromene-8-carboxamide ((*R*)-144)



[001125] Following general procedure B, **Compound (R)-144** was prepared from **compound B-268** (122 mg, 0.52 mmol) and **compound (R)-A-104** (80 mg, 0.52 mmol), with a reaction time of 16 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150*30mm, particle size: 4 μ m; Mobile phase: 23-43% acetonitrile in H₂O (add 0.05% HCl, v/v)] to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-3,4-dihydro-2H-thieno[3,2-h]chromene-8-carboxamide - hydrochloride (**compound (R)-144**) (150 mg, 71% yield) as a white solid: cSFC analytical (A) t_R =3.62 min., purity: 100.00%; LCMS (FF): t_R =2.391 min., (ES⁺) m/z (M+H)⁺ = 371.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.06 (s, 1H), 7.41-7.39 (d, J =8.0 Hz, 1H), 7.17-7.15 (d, J =8.4 Hz, 1H), 4.39-4.36 (t, J =5.2 Hz, 2H), 4.26 (s, 1H), 3.77-3.68 (m, 2H), 3.39-3.36 (m, 2H), 2.94-2.91 (t, J =6.4 Hz, 2H), 2.45-2.40 (m, 1H), 2.29-2.28 (m, 1H), 2.19-2.10 (m, 4H), 1.98-1.92 (m, 1H), 1.76 (s, 3H), 1.50 (s, 3H).

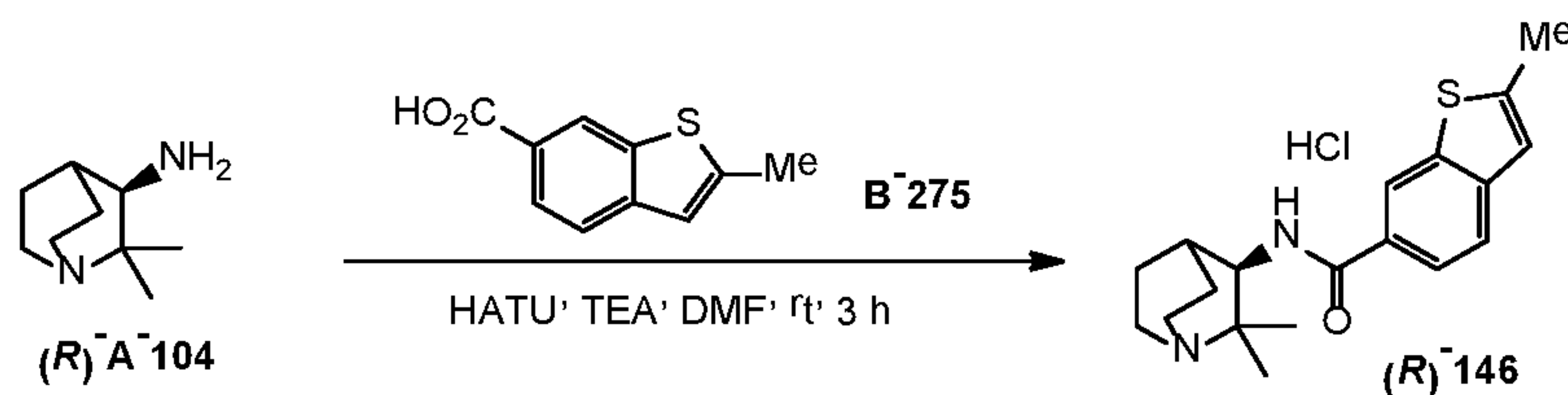
[001126] **Example 145:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-8,9-dihydro-7H-thieno[2,3-f]chromene-2-carboxamide hydrochloride (**(R)-145**)



[001127] Following general procedure B, **Compound (R)-145** was prepared from **compound B-272** (0.14 g, 0.58 mmol) and **compound (R)-A-104** (90 mg, 0.58 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150×30 mm, particle size: 5 μ m; Mobile phase: 25-55% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-8,9-dihydro-7H-thieno[2,3-f]chromene-2-carboxamide - hydrochloride (**compound (R)-145**) (70 mg, 32% yield) as a white solid: cSFC analytical (A) t_R =3.308 min., purity: 96.94%; LCMS (GG): t_R =2.058 min., 371.2 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.09 (s, 1H), 7.66-7.64 (d, J =8.8 Hz, 1H), 6.94-6.92 (d, J =8.8 Hz, 1H), 4.29-4.26 (m, 3H), 3.74-3.68 (m, 2H), 3.39-3.30 (m, 2H), 2.89-2.86 (m, 2H), 2.43-2.42 (m, 1H), 2.28 (m, 1H), 2.19-2.14 (m, 4H), 1.99-1.92 (m, 1H), 1.76 (s, 3H), 1.51 (s, 3H).

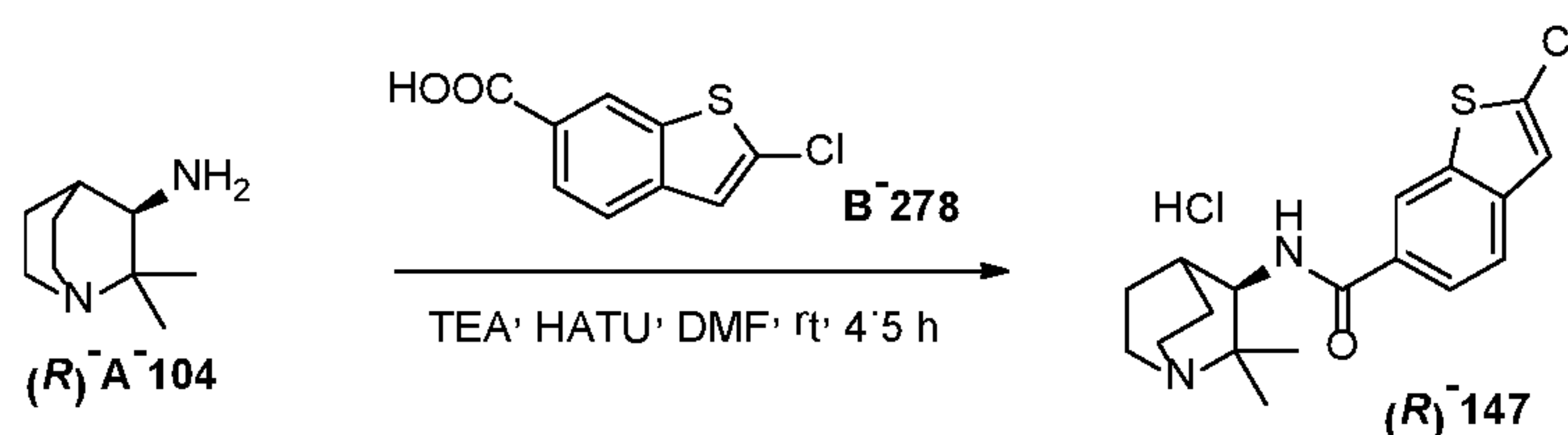
[001128] **Example 146:** (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[b]thiophene-6-carboxamide -hydrochloride (**(R)-146**)



[001129] Following general procedure B, **Compound (R)-146** was prepared from **compound B-275** (123 mg, 0.64 mmol) and **compound (R)-A-104** (90 mg, 0.58 mmol), with a reaction time of 3 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: Welch Ultimate AQ-C18 150 × 30 mm, particle size: 5 μm; Mobile phase: 20-50% acetonitrile in H₂O (add 0.1% TFA, v/v)]. The resulting solid was dissolved in 0.2 N hydrochloric acid and again lyophilized to give:

(R)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[*b*]thiophene-6-carboxamide - hydrochloride (**compound (R)-146**) (110 mg, 49% yield) as a white solid : cSFC analytical (A) t_R=2.79 min., purity: 98.20%; LCMS (GG): t_R=1.946 min., 329.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.33 (s, 1H), 7.81-7.76 (m, 2H), 7.15 (s, 1H), 4.29 (s, 1H), 3.74-3.67 (m, 2H), 3.39-3.29 (m, 2H), 2.65 (s, 3H), 2.43-2.07 (m, 4H), 1.97-1.90 (m, 1H), 1.79 (s, 3H), 1.51 (s, 3H).

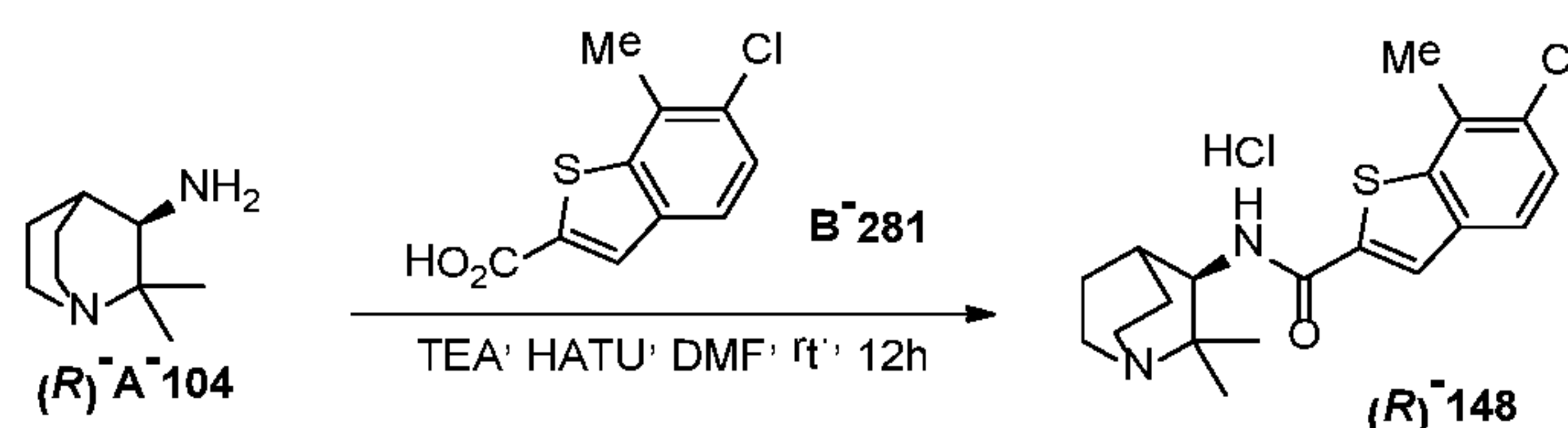
[001130] **Example 147:** *(R)*-2-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-6-carboxamide hydrochloride (**(R)-147**)



[001131] Following general procedure B, **Compound (R)-147** was prepared from **compound B-278** (69 mg, 0.32 mmol) and **compound (R)-A-104** (50 mg, 0.32 mmol), with a reaction time of 4.5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 150×30 mm, particle size: 4 μm; Mobile phase: 25-45% acetonitrile in H₂O (add 0.05% HCl, v/v)]. The resulting solution was lyophilized to give:

(R)-2-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[*b*]thiophene-6-carboxamide hydrochloride (**(R)-147**) (62 mg, 49% yield) as a white solid: cSFC analytical (A) t_R=2.85 min., purity: 98.63%; LCMS (FF): t_R=2.278 min., 349.1 m/z (M+1); ¹H-NMR (D₂O, 400 MHz): δ 8.02 (s, 1H), 7.67-7.65 (d, J=8.0Hz, 1H), 7.57-7.55 (d, J=8.0Hz, 1H), 7.24 (s, 1H), 4.11 (s, 1H), 3.62-3.55 (m, 2H), 3.27-3.18 (m, 2H), 2.17 (s, 2H), 2.05-2.03 (m, 2H), 1.99-1.83 (m, 1H), 1.63 (s, 3H), 1.39 (s, 3H).

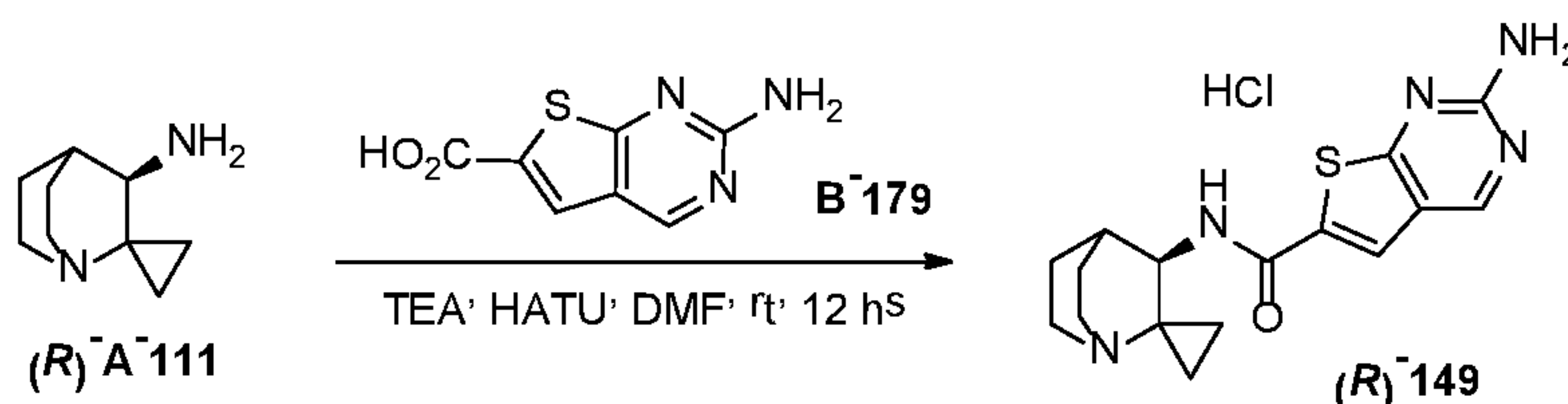
[001132] **Example 148:** *(R)*-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-methylbenzo[*b*]thiophene-2-carboxamide hydrochloride (**(R)-148**)



[001133] Following general procedure B, **Compound (R)-148** was prepared from **compound B-281** (0.15 g, 0.64 mmol) and **compound (R)-A-104** (90 mg, 0.58 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150×30 mm, particle size: 5 µm; Mobile phase: 25-55% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid and again lyophilized to give:

(*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-7-methylbenzo[*b*]thiophene-2-carboxamide - hydrochloride (**compound (R)-148**) (70 mg, 30% yield) as a white solid: cSFC analytical (A) *t*_R=2.921 min., purity: 97.21%; LCMS (FF): *t*_R=2.508 min., 363.1 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.17 (s, 1H), 7.78-7.75 (d, *J*=8.4 Hz, 1H), 7.49-7.47 (d, *J*=8.4 Hz, 1H), 4.27 (s, 1H), 3.78-3.69 (m, 2H), 3.40-3.35 (m, 2H), 2.63 (m, 3H), 2.42 (m, 1H), 2.30-2.29 (m, 1H), 2.19-2.12 (m, 2H), 1.99-1.96 (m, 1H), 1.77 (s, 3H), 1.51 (s, 3H).

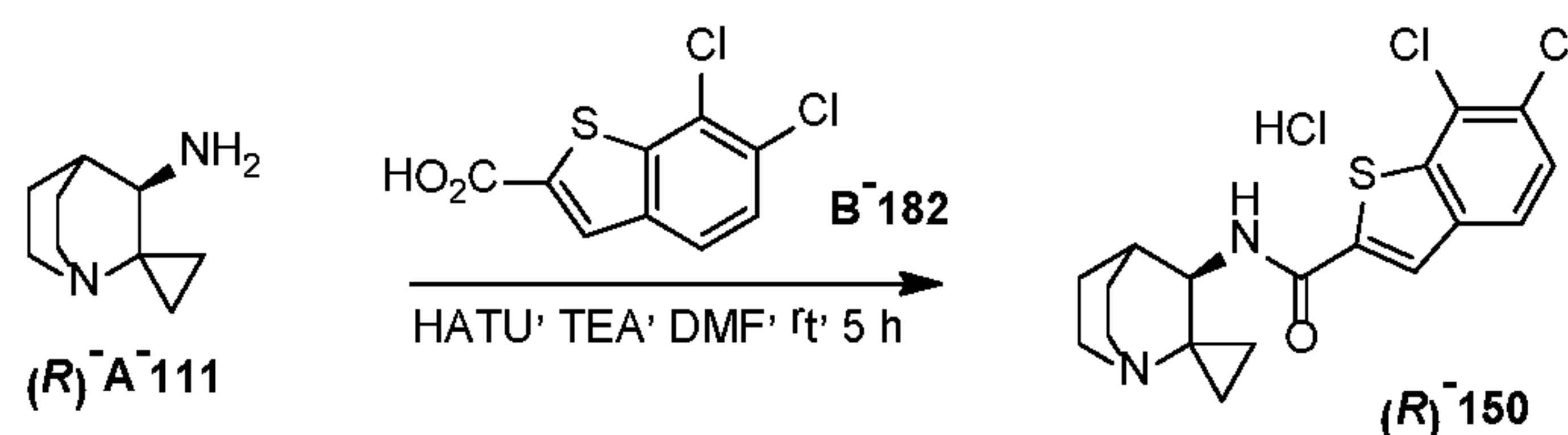
[001134] **Example 149:** (*R*)-2-amino-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*d*]pyrimidine-6-carboxamide hydrochloride ((*R*)-149)



[001135] Following general procedure B, **Compound (R)-149** was prepared from **compound B-179** (60 mg, 0.31 mmol) and **compound (R)-A-111** (47 mg, 0.31 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-C; Column: Phenomenex Gemini C18 150×30 mm, particle size: 5 µm; Mobile phase: 35-65% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-2-amino-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*d*]pyrimidine-6-carboxamide-hydrochloride (**compound (R)-149**) (40 mg, 40% yield) as a white solid: cSFC analytical (A) *t*_R=3.24 min., purity: 99.00%; LCMS (J): *t*_R=0.880 min., 330.0 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 9.04-9.04 (d, 1H), 8.27 (s, 1H), 4.56 (m, 1H), 3.81 (s, 1H), 3.58-3.33 (m, 3H), 2.44-2.37 (m, 2H), 2.21-2.19 (m, 2H), 2.01-1.99 (m, 1H), 1.43-1.27 (m, 3H), 1.19-1.16 (m, 1H).

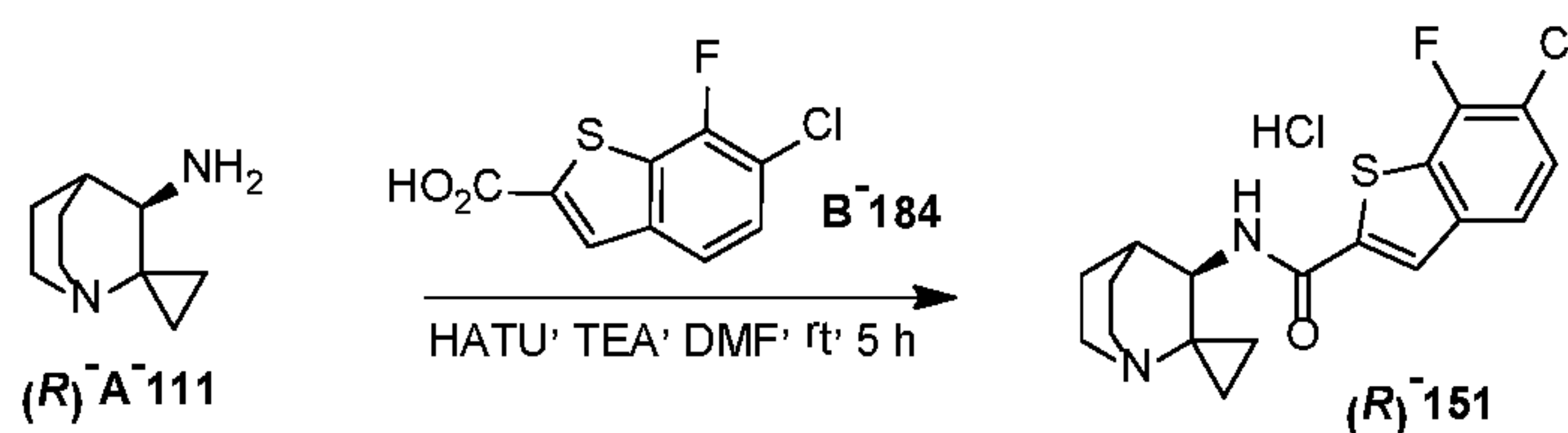
[001136] **Example 150:** (*R*)-6,7-dichloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-150)



[001137] Following general procedure B, **Compound (R)-150** was prepared from **compound B-182** (97 mg, 0.39 mmol) and **compound (R)-A-111** (60 mg, 0.39 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-D; Column: Boston Symmetrix ODS-R C18 150×30 mm, particle size: 5 µm; Mobile phase: 25-55% acetonitrile in H₂O (add 0.225% FA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-6,7-dichloro-*N*-((1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-150**) (42 mg, 26% yield) as a white solid: cSFC analytical (A) t_R=2.73 min., purity: 100%; LCMS (H): t_R=1.791 min., (ES⁺) m/z (M+H)⁺ = 381.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.21 (s, 1H), 7.86 (d, J=8.4 Hz, 1H), 7.59 (d, J=8.8 Hz, 1H), 4.56 (d, J=2.4 Hz, 1H), 3.75-3.71 (m, 1H), 3.57 (m, 1H), 3.48-3.42 (m, 2H), 2.45 (d, J=2.8 Hz, 1H), 2.34 (m, 1H), 2.24-2.16 (m, 2H), 1.99-1.98 (m, 1H), 1.41-1.38 (m, 1H), 1.36-1.26 (m, 2H), 1.25-1.19 (m, 1H).

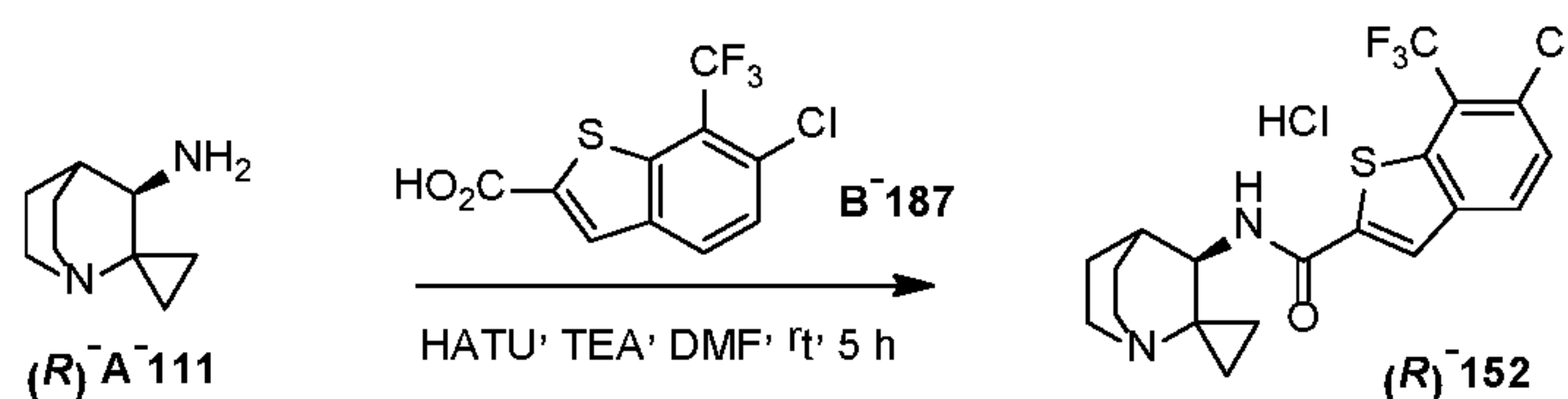
[001138] **Example 151:** (*R*)-6-chloro-7-fluoro-*N*-((1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**(R)-151**)



[001139] Following general procedure B, **Compound (R)-151** was prepared from **compound B-184** (76 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-pack ODS-AQ 150×30 mm, particle size: 5 µm; Mobile phase: 32-62% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-6-chloro-7-fluoro-*N*-((1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-151**) (60 mg, 45% yield) as a white solid: cSFC analytical (A) t_R=2.418 min., purity: 99.26%; LCMS (Y): t_R=0.819 min., (ES⁺) m/z (M+H)⁺ = 364.9; ¹H-NMR (CD₃OD, 400 MHz): δ 8.17 (d, J=3.2 Hz, 1H), 7.75 (d, J=8.4 Hz, 1H), 7.54 (dd, J₁=8.4 Hz, J₂=7.2 Hz, 1H), 4.58 (d, J=2.4 Hz, 1H), 3.70-3.69 (m, 1H), 3.59-3.52 (m, 1H), 3.51-3.44 (m, 2H), 2.47-2.46 (m, 1H), 2.34-2.31 (m, 1H), 2.24-2.18 (m, 2H), 2.04-2.00 (m, 1H), 1.38-1.34 (m, 1H), 1.28-1.22 (m, 3H).

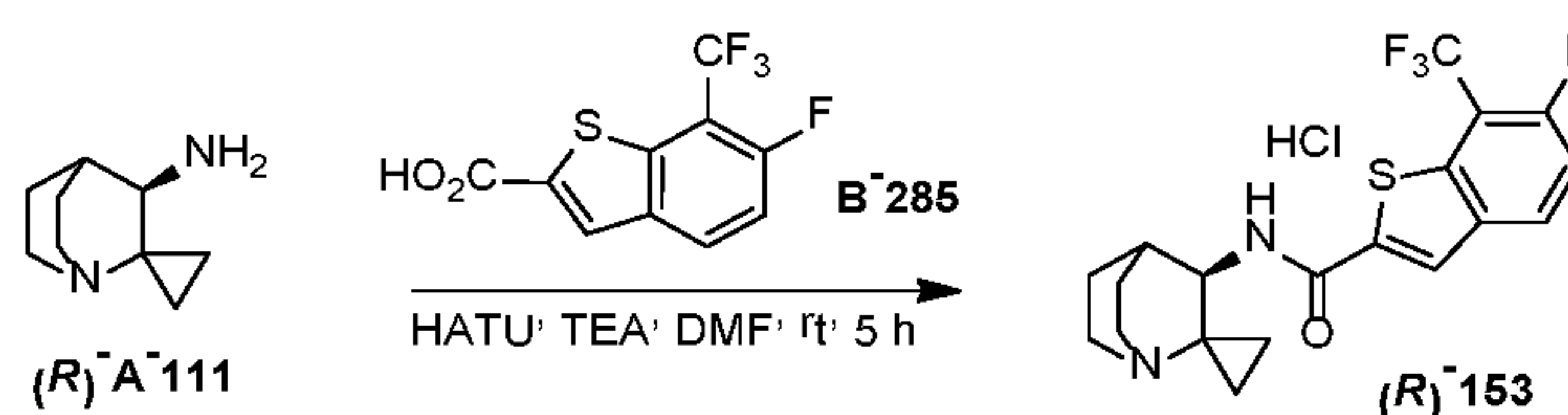
[001140] **Example 152:** (*R*)-6-chloro-*N*-((1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide hydrochloride (**(R)-152**)



[001141] Following general procedure B, **Compound (R)-152** was prepared from **compound B-187** (110 mg, 0.39 mmol) and **compound (R)-A-111** (60 mg, 0.39 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150×30 mm, particle size: 5 μ m; Mobile phase: 30-60% acetonitrile in H₂O (add 0.1% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-6-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**compound (R)-152**) (72 mg, 40% yield) as a white solid: cSFC analytical (A) *t*R=2.34 min., purity: 98.48%; LCMS (H): *t*R=1.773 min., (ES⁺) *m/z* (M+H)⁺ = 415.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.25 (s, 1H), 8.13 (d, *J*=8.4 Hz, 1H), 7.66 (d, *J*=8.4 Hz, 1H), 4.57 (d, *J*=2.4 Hz, 1H), 3.74-3.72 (m, 1H), 3.58-3.57 (m, 1H), 3.50-3.42 (m, 2H), 2.45 (d, *J*=2.8 Hz, 1H), 2.34-2.33 (m, 1H), 2.22-2.17 (m, 2H), 2.03-1.99 (m, 1H), 1.42-1.37 (m, 1H), 1.31-1.21 (m, 2H), 1.20-1.19 (m, 1H).

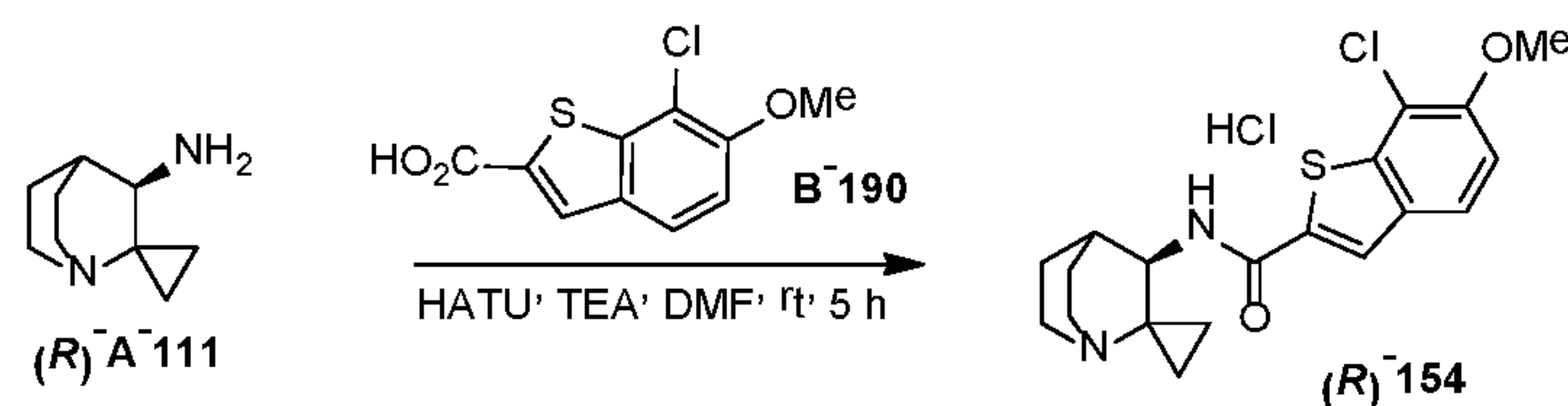
[001142] **Example 153:** (*R*)-6-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**(R)-153**)



[001143] Following general procedure B, **Compound (R)-153** was prepared from **compound B-285** (87 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: P YMC-Actus Pro C18 150×30 mm, particle size: 5 μ m; Mobile phase: 25-55% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-6-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[*b*]thiophene-2-carboxamide -hydrochloride (**compound (R)-153**) (95 mg, 72% yield) as a white solid: cSFC analytical (A) *t*R=2.07 min., purity: 98.22%; LCMS (A): *t*R=1.686 min., 399.1 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.24-8.21 (m, 2H), 7.47 (t, *J*=10.0 Hz, 1H), 4.58 (d, *J*=2.0 Hz, 1H), 3.71-3.69 (m, 1H), 3.59-3.58 (m, 1H), 3.52-3.43 (m, 2H), 2.46-2.45 (m, 1H), 2.34-2.31 (m, 1H), 2.24-2.17 (m, 2H), 2.01-1.96 (m, 1H), 1.38-1.34 (s, 1H), 1.28-1.17 (s, 3H).

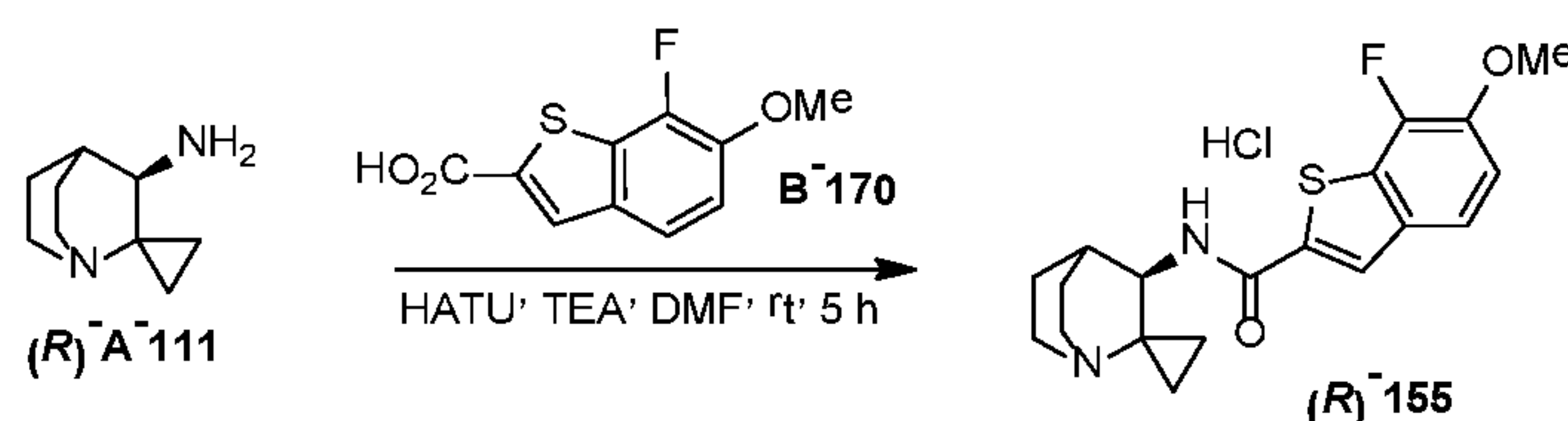
[001144] **Example 154:** (*R*)-7-chloro-6-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride (**(R)-154**)



[001145] Following general procedure B, **Compound (R)-154** was prepared from **compound B-190** (96 mg, 0.39 mmol) and **compound (R)-A-111** (60 mg, 0.39 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-pack ODS-AQ 150×30 mm, particle size: 5 µm; Mobile phase: 24-54% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-7-chloro-6-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-154**) (30 mg, 18% yield) as a white solid: cSFC analytical (A) *t*_R=2.855 min., purity: 97.05%; LCMS (Y): *t*_R=0.720 min., (ES⁺) *m/z* (M+H)⁺=377.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.11 (s, 1H), 7.86 (d, *J*=8.4 Hz, 1H), 7.32 (d, *J*=8.8, 1H), 4.56 (s, 1H), 4.00 (s, 3H), 3.74-3.70 (m, 1H), 3.59-3.58 (m, 1H), 3.50-3.43 (m, 2H), 2.45-2.44 (m, 1H), 2.34 (m, 1H), 2.24-2.17 (m, 2H), 2.16-2.00 (m, 1H), 1.38-1.33 (m, 1H), 1.26-1.21 (m, 3H).

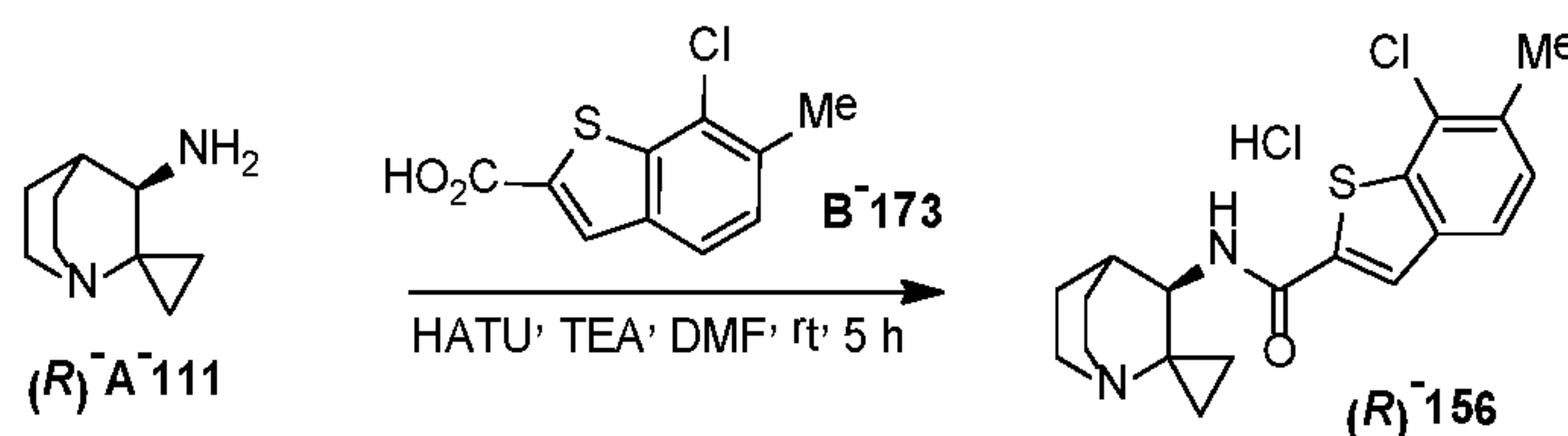
[001146] **Example 155:** (*R*)-7-fluoro-6-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**(R)-155**)



[001147] Following general procedure B, **Compound (R)-155** was prepared from **compound B-170** (74 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-pack ODS-AQ 150×30 mm, particle size: 5 µm; Mobile phase: 29-59% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-7-fluoro-6-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-155**) (40 mg, 31% yield) as a white solid: cSFC analytical (A) *t*_R=2.535 min., purity: 98.25%; LCMS (Y): *t*_R=0.768 min., (ES⁺) *m/z* (M+H)⁺=361.0; ¹H-NMR (CD₃OD, 400 MHz): δ 8.11 (d, *J*=3.6 Hz, 1H), 7.70 (d, *J*=8.8 Hz, 1H), 7.34 (t, *J*=8.4 Hz, 1H), 4.56 (d, *J*=2.4 Hz, 1H), 3.99 (s, 3H), 3.70-3.61 (m, 1H), 3.59-3.58 (m, 1H), 3.48-3.43 (m, 2H), 2.45-2.44 (m, 1H), 2.34-2.33 (m, 1H), 2.24-2.16 (m, 2H), 2.00-1.96 (m, 1H), 1.38-1.34 (m, 1H), 1.27-1.20 (m, 3H).

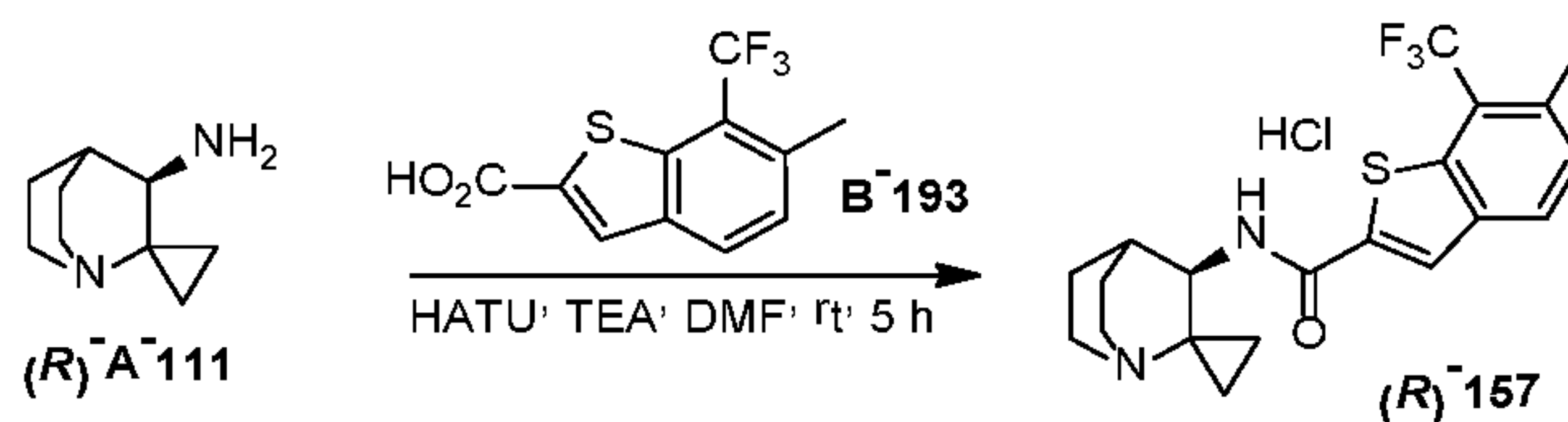
[001148] **Example 156:** (*R*)-7-chloro-6-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**(R)-156**)



[001149] Following general procedure B, **Compound (R)-156** was prepared from **compound B-173** (74 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-pack ODS-AQ 150×30 mm, particle size: 5 μ m; Mobile phase: 33-63% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-7-chloro-6-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-156**) (55 mg, 42% yield) as a white solid: cSFC analytical (B) *t*_R=2.594 min., purity: 97.66%; LCMS (B): *t*_R=0.737 min., (ES⁺) *m/z* (M+H)⁺=361.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.13 (s, 1H), 7.77 (d, *J*=8.4 Hz, 1H), 7.40 (d, *J*=8.0 Hz, 1H), 4.57 (d, *J*=3.2 Hz, 1H), 3.74-3.70 (m, 1H), 3.59-3.50 (m, 1H), 3.48-3.43 (m, 2H), 2.53 (s, 3H), 2.46-2.45 (m, 1H), 2.37-2.34 (m, 1H), 2.24-2.15 (m, 2H), 2.00-1.99 (m, 1H), 1.38-1.34 (m, 1H), 1.27-1.19 (m, 3H).

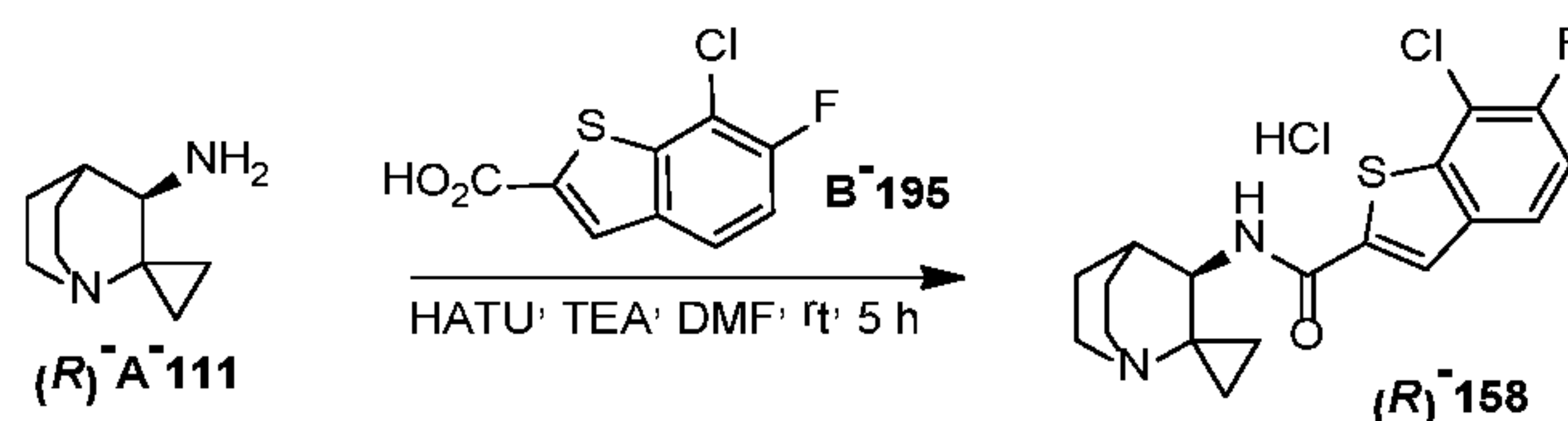
[001150] **Example 157:** (*R*)-6-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide hydrochloride (**(R)-157**)



[001151] Following general procedure B, **Compound (R)-157** was prepared from **compound B-193** (85 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 250×50 mm, particle size: 10 μ m; Mobile phase: 41-71% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-6-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide -hydrochloride (**compound (R)-157**) (50 mg, 35% yield) as a white solid: cSFC analytical (A) *t*_R=2.12 min., purity: 97.64%; LCMS (DD): *t*_R=0.829 min., 395.1 *m/z* (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.21 (s, 1H), 8.06 (d, *J*=8.0 Hz, 1H), 7.49 (d, *J*=8.4 Hz, 1H), 4.59 (d, *J*=2.0 Hz, 1H), 3.78-3.74 (m, 1H), 3.61-3.59 (m, 1H), 3.52-3.42 (m, 2H), 2.66 (d, *J*=2.0 Hz, 3H), 2.47-2.46 (m, 1H), 2.39-2.34 (m, 1H), 2.26-2.18 (m, 2H), 2.05-1.98 (m, 1H), 1.41-1.37 (m, 1H), 1.31-1.20 (m, 3H).

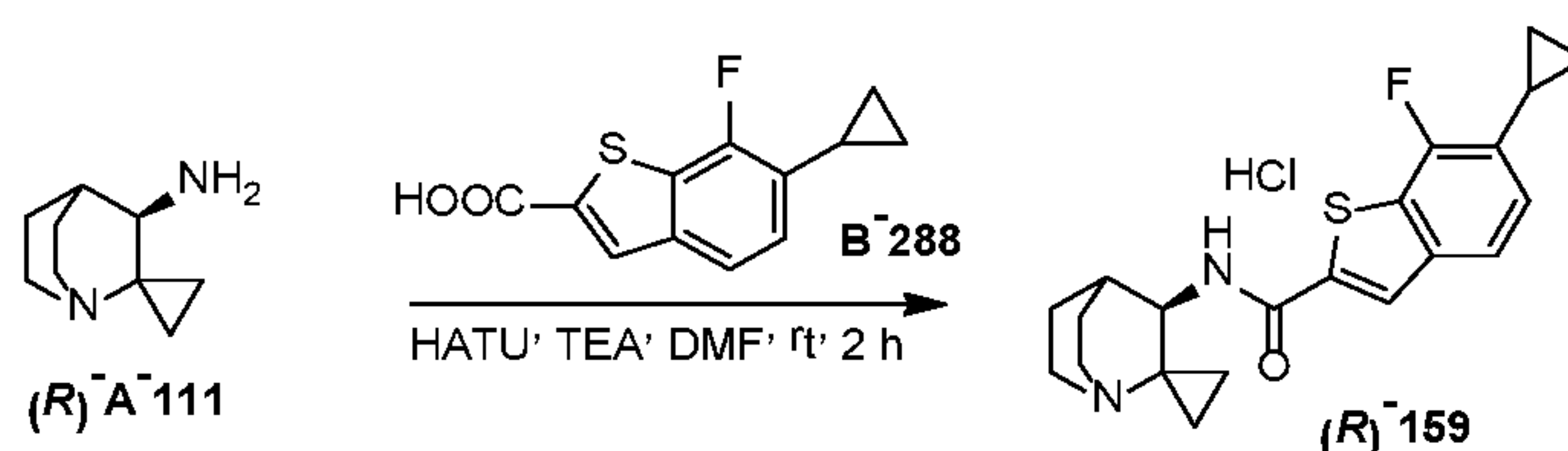
[001152] **Example 158:** (*R*)-7-chloro-6-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**(R)-158**)



[001153] Following general procedure B, **Compound (R)-158** was prepared from **compound B-195** (91 mg, 0.39 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 16 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 26-56% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-7-chloro-6-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thio-phen-2-carboxamide -hydrochloride (**compound (R)-158**) (30 mg, 23% yield) as a white solid: cSFC analytical (A) t_R=2.412 min., purity: 100%; LCMS (J): t_R=1.471 min., 365.0 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.72 (d, J=6.4 Hz, 1H), 8.228 (s, 1H), 7.94 (dd, J₁=8.8 Hz, J₂=4.4 Hz, 1H), 7.42 (t, J=8.8 Hz, 1H), 4.58 (s, 1H), 3.72 (m, 1H), 3.63-3.53 (m, 1H), 3.50-3.45 (m, 2H), 2.48-2.47 (m, 1H), 2.39-2.36 (m, 1H), 2.26-2.16 (m, 2H), 2.05-2.02 (m, 1H), 1.40-1.37 (m, 1H), 1.30-1.20 (m, 3H).

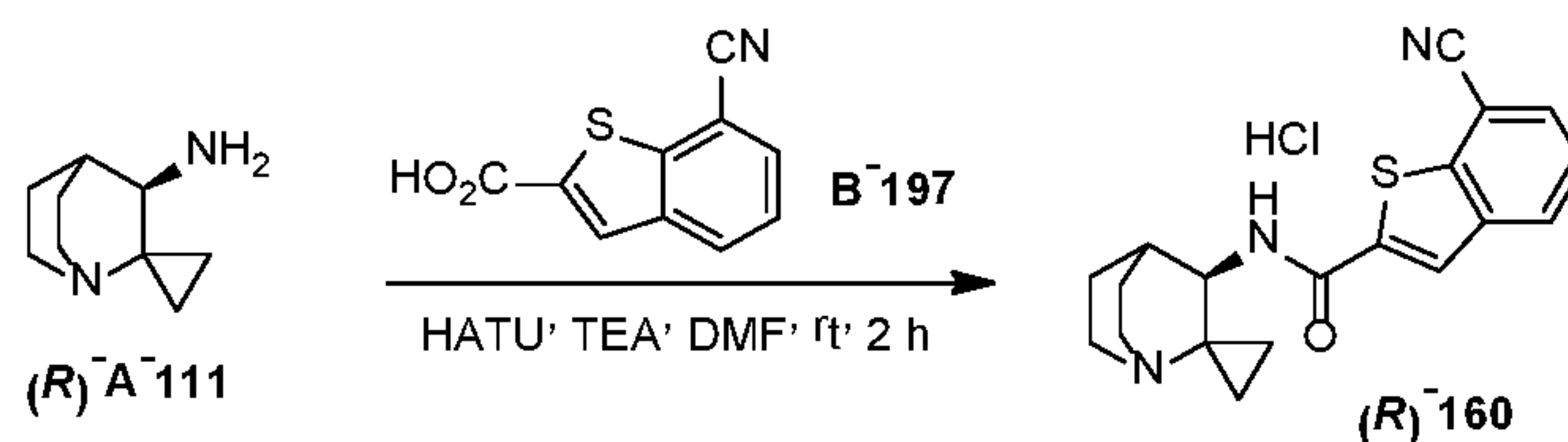
[001154] **Example 159:** (*R*)-6-cyclopropyl-7-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-159)



[001155] Following general procedure B, **Compound (R)-159** was prepared from **compound B-288** (78 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-6-cyclopropyl-7-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b] thiophene-2-carboxamide hydrochloride (**compound (R)-159**) (68 mg, 56% yield) as a white solid: cSFC analytical (A) t_R=2.55 min., purity: 97.97%; LCMS (M): t_R=1.139 min., 371.2 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.12 (d, J=3.6 Hz, 1H), 7.65 (d, J=8.0 Hz, 1H), 7.05 (t, J=7.2 Hz, 1H), 4.58 (s, 1H), 3.73-3.61 (m, 1H), 3.40-3.42 (m, 3H), 2.47-2.46 (m, 1H), 2.30-2.18 (m, 4H), 1.38-1.23 (m, 4H), 1.12-1.10 (m, 2H), 0.86-0.84 (m, 2H).

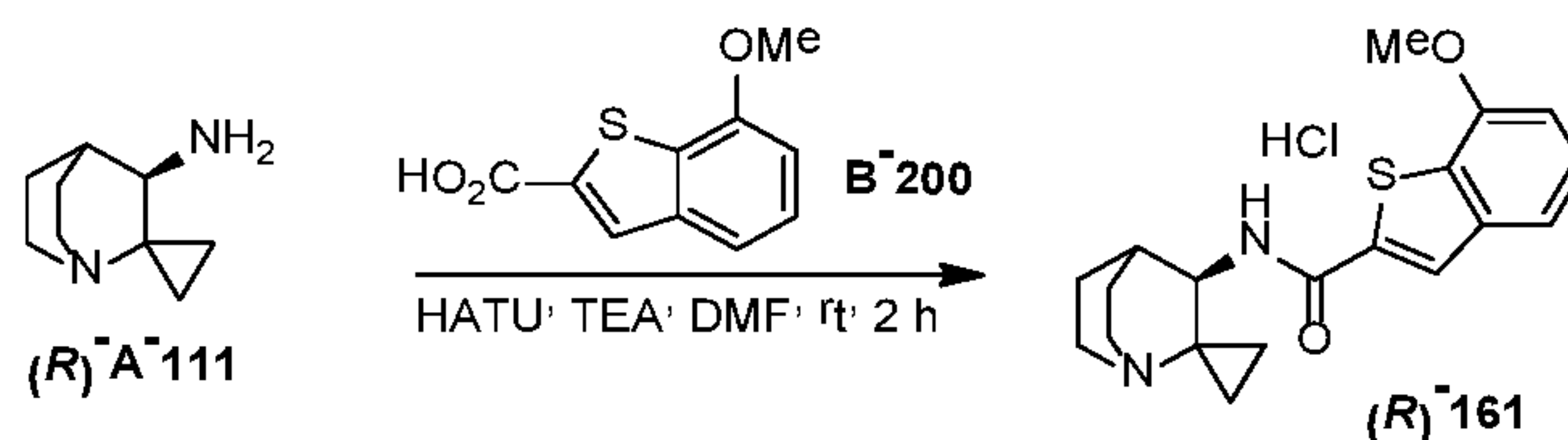
[001156] **Example 160:** (*R*)-7-cyano-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b] thiophene-2-carboxamide hydrochloride ((*R*)-160)



[001157] Following general procedure B, **Compound (R)-160** was prepared from **compound B-197** (as a mixture with **compound B-198**) (80 mg, 0.39 mmol) and **compound (R)-A-111** (59 mg, 0.39 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 µm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-7-cyano-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b] thiophene-2-carboxamide hydrochloride (**compound (R)-160**) (19 mg, 32% yield) as a white solid: cSFC analytical (A) t_R=2.52 min., purity: 100%; LCMS (M): t_R=0.860 min., 338.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): 8.25 (d, J=10.4 Hz, 2H), 7.92 (d, J=6.8 Hz, 1H), 7.63 (t, J=8.0 Hz, 1H), 7.64 (t, J=8.0 Hz, 1H), 4.34 (s, 1H), 3.42-3.37 (m, 1H), 3.25-3.22 (m, 1H), 3.13-3.06 (m, 2H), 2.24 (s, 1H), 2.14-1.93 (m, 3H), 1.73 (m, 1H), 1.14-0.85 (m, 4H).

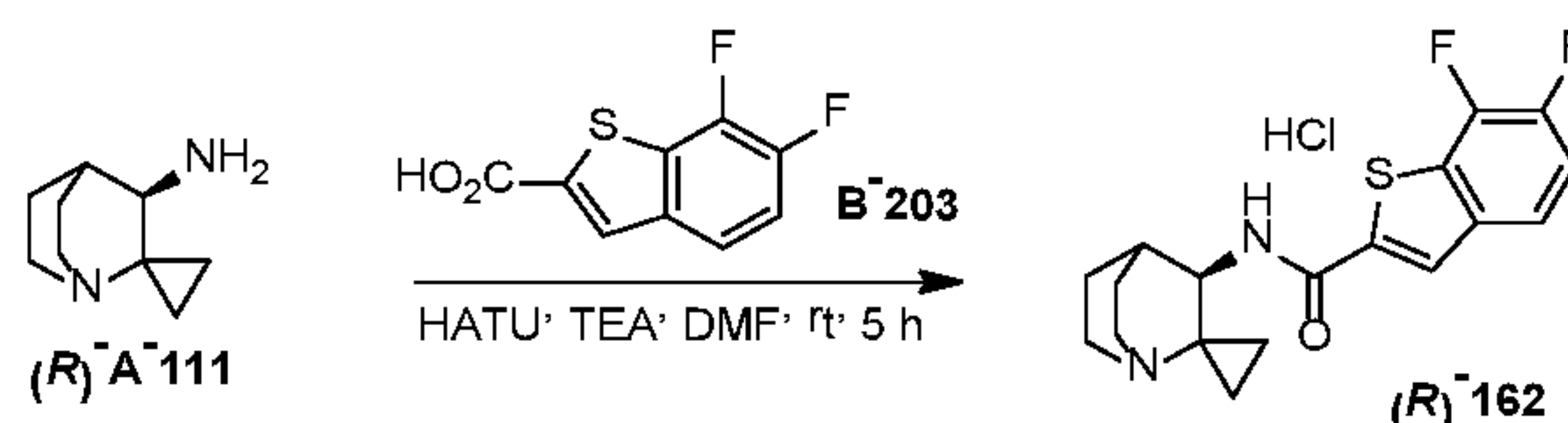
[001158] **Example 161:** (*R*)-7-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b] thiophene-2-carboxamide hydrochloride ((*R*)-161)



[001159] Following general procedure B, **Compound (R)-161** was prepared from **compound B-200** (68 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 2 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 µm; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-7-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b] thiophene-2-carboxamide hydrochloride (**compound (R)-161**) (79 mg, 71% yield) as a white solid: cSFC analytical (A) t_R=2.84 min., purity: 98.72%; LCMS (M): t_R=0.993 min., 343.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.15 (s, 1H), 7.53 (d, J=8.0 Hz, 1H), 7.42 (t, J=7.6 Hz, 1H), 7.01 (d, J=8.0 Hz, 1H), 4.58 (s, 1H), 4.02 (s, 3H), 3.77-3.59 (m, 1H), 3.59-3.41 (m, 3H), 2.46-2.33 (m, 2H), 2.25-2.18 (m, 2H), 2.04-2.00 (m, 1H), 1.41-1.20 (m, 4H).

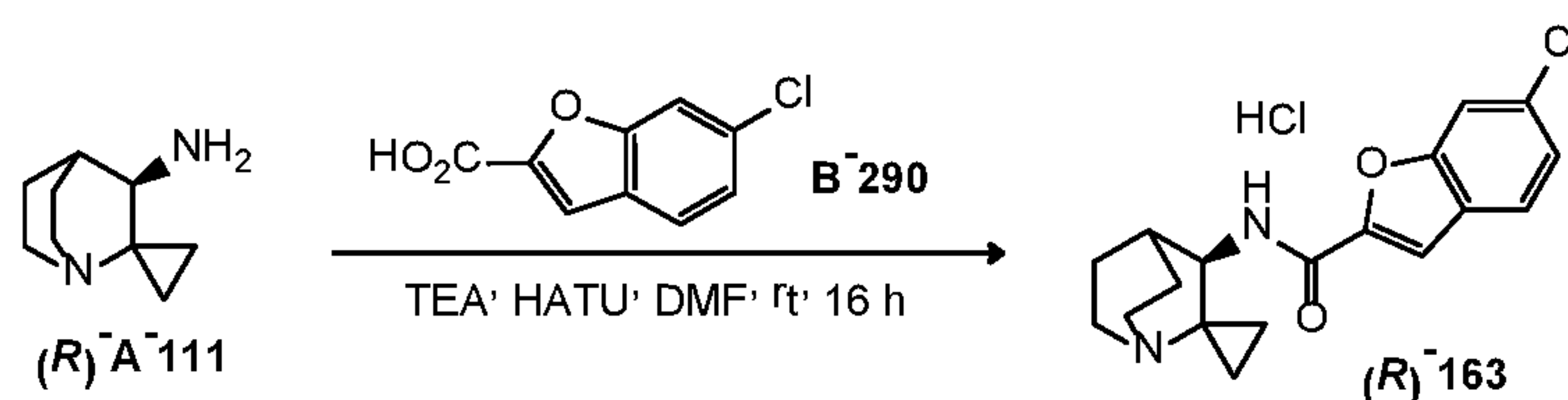
[001160] **Example 162:** (*R*)-6,7-difluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2] octan] - 3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-162)



[001161] Following general procedure B, **Compound (R)-162** was prepared from **compound B-203** (60 mg, 0.34 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×21.2 mm, particle size: 5 µm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-6,7-difluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-162**) (20 mg, 18.2% yield) as a white solid: cSFC analytical (A) t_R=2.14 min., purity: 97.6%; LCMS (DD): t_R=0.803 min., 348.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.21 (d, *J*=3.6, 1H), 7.80-7.77 (m, 1H), 7.47-7.41 (m, 1H), 4.59 (d, *J*=2.8, 1H), 3.73-3.72 (m, 1H), 3.3.61-3.60 (m, 1H), 3.54-3.42 (m, 2H), 2.47 (d, *J*=2.8, 1H), 2.36-2.33 (m, 1H), 2.26-2.19 (m, 2H), 1.98 (s, 1H), 1.42-1.36 (s, 1H), 1.30-1.21 (m, 3H).

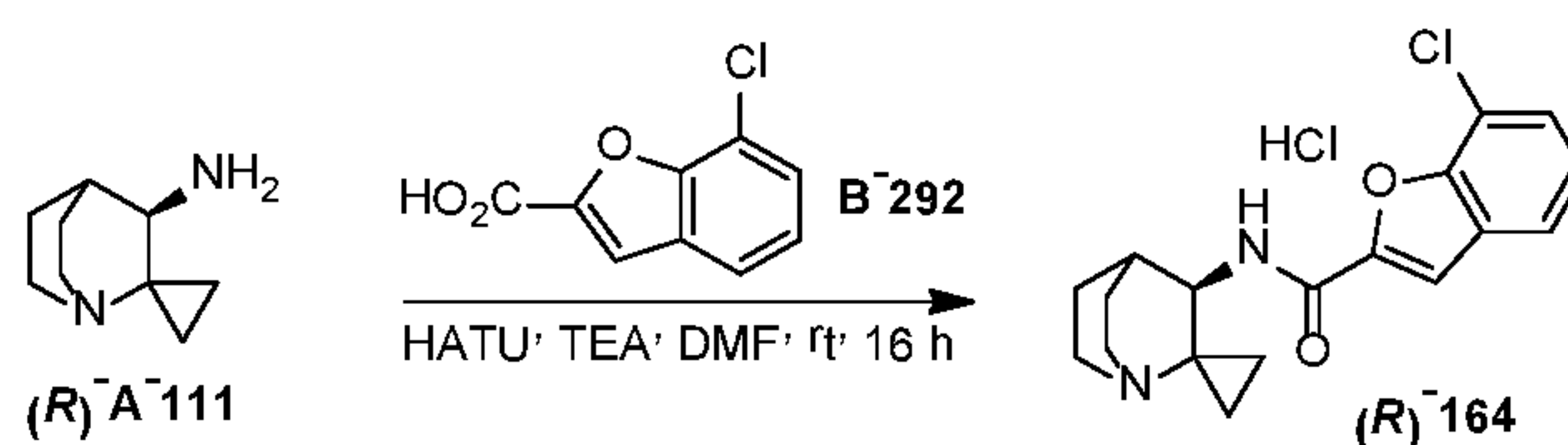
[001162] **Example 163:** (*R*)-6-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-2-carboxamide hydrochloride (**(R)-163**)



[001163] Following general procedure B, **Compound (R)-163** was prepared from **compound B-290** (77 mg, 0.39 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 16 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi C18 250×21.2 mm, particle size: 4 µm; Mobile phase: 10-40% acetonitrile in H₂O (add 0.05% HCl, v/v)] to give:

(*R*)-6-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-2-carboxamide hydrochloride (**compound (R)-163**) (50 mg, 46% yield) as a white solid: cSFC analytical (A) t_R=2.05 min., purity: 98.40%; LCMS (H): t_R=2.503 min, 331.0 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 7.74 (d, *J* = 1H), 7.70 (s, 1H), 7.57 (s, 1H), 7.37 (dd, *J*₁=8.5 Hz, *J*₂=1.8 Hz, 1H), 4.60 (s, 1H), 3.76-3.75 (m, 1H), 3.59-3.33 (m, 3H), 2.44 (m, 1H), 2.32-2.14 (m, 3H), 2.00 (m, 1H), 1.35-1.18 (m, 4H).

[001164] **Example 164:** (*R*)-7-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-2-carboxamide hydrochloride (**(R)-164**)

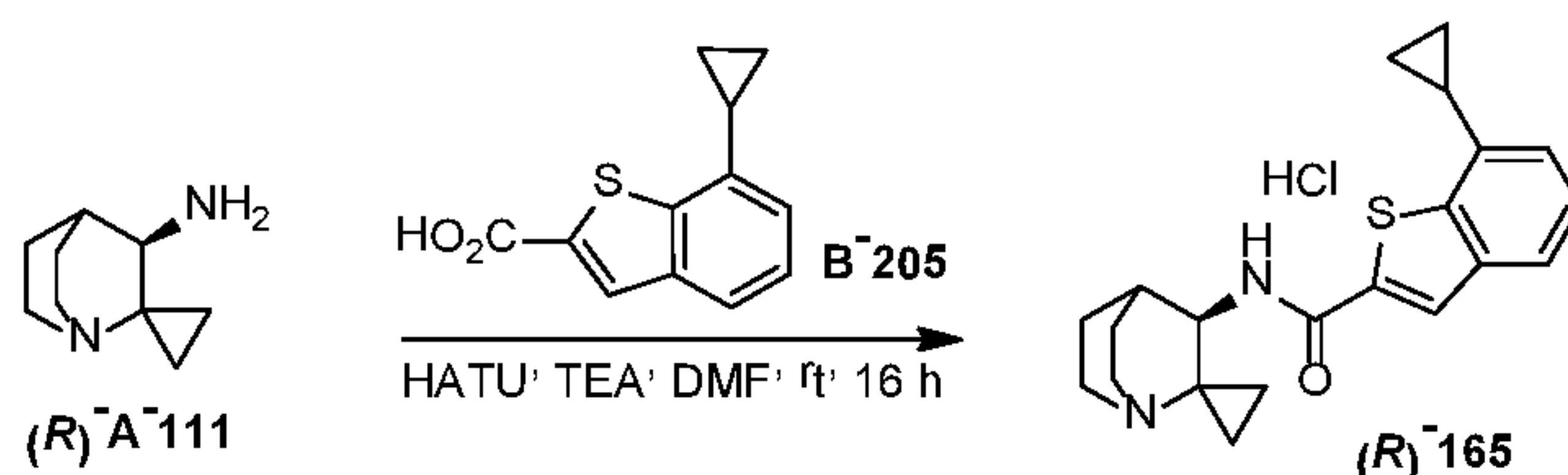


[001165] Following general procedure B, **Compound (R)-164** was prepared from **compound B-292** (77 mg, 0.39 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 16 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB

C18 150×30 mm, particle size: 5 μ m; Mobile phase: 26-56% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-7-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-2-carboxamide -hydrochloride (**compound (R)-164**) (40 mg, 33% yield) as a white solid: cSFC analytical (A) t_R=1.935 min., purity: 98.61%; LCMS (J): t_R=1.341 min., 331.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 7.72 (d, J=8 Hz, 1H), 7.67 (s, 1H), 7.54 (d, J=8 Hz, 1H), 7.35 (t, J=8 Hz, 1H), 4.63 (s, 1H), 3.80-3.77 (m, 1H), 3.61-3.53 (m, 1H), 3.51-3.44 (m, 2H), 2.49-2.48 (m, 1H), 2.36-2.33 (m, 1H), 2.27-2.19 (m, 2H), 2.03-2.01 (m, 1H), 1.40-1.20 (m, 4H).

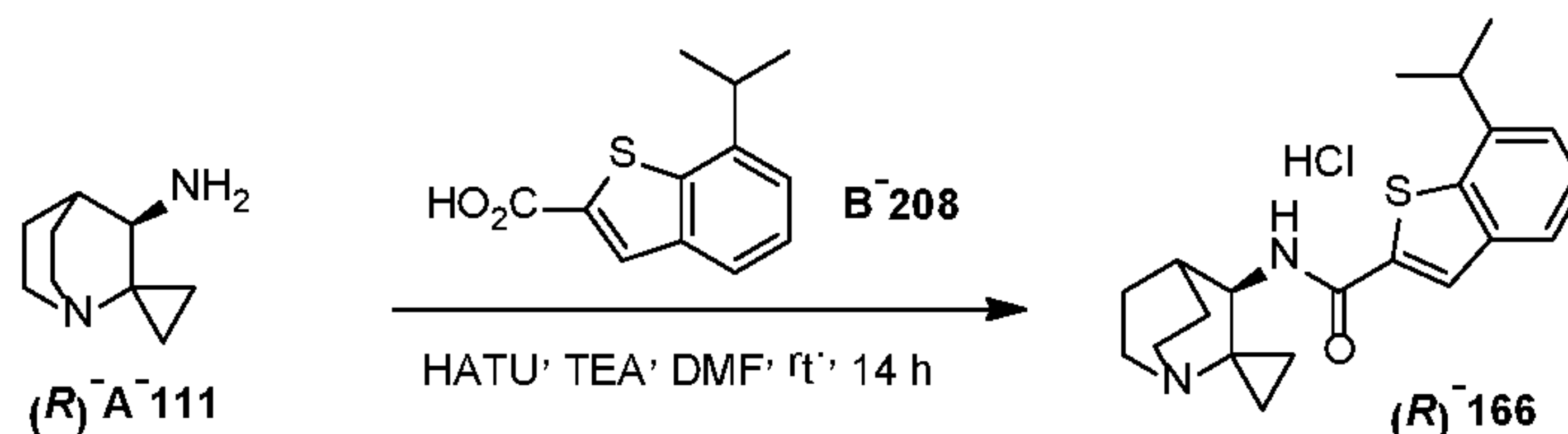
[001166] **Example 165:** (*R*)-7-cyclopropyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-165)



[001167] Following general procedure B, **Compound (R)-165** was prepared from **compound B-205** (86 mg, 0.39 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 16 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150×30 mm, particle size: 5 μ m; Mobile phase: 25-55% acetonitrile in H₂O (add 0.5% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-7-cyclopropyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide -hydrochloride (**compound (R)-165**) (25 mg, 20% yield) as a white solid: cSFC analytical (A) t_R=2.710 min., purity: 98.62%; LCMS (B): t_R=0.719 min., 353.2 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.19 (s, 1H), 7.77 (d, J=7.6 Hz, 1H), 7.39 (t, J=8 Hz, 1H), 7.15 (d, J=7.2 Hz, 1H), 4.60 (s, 1H), 3.78-3.74 (m, 1H), 3.61-3.59 (m, 1H), 3.50-3.45 (m, 2H), 2.48-2.47 (m, 1H), 2.37 (m, 1H), 2.25-2.12 (m, 3H), 2.03-2.02 (m, 1H), 1.42-1.40 (m, 1H), 1.31-1.26 (m, 3H), 1.11-1.09 (m, 2H), 0.85-0.83 (m, 2H).

[001168] **Example 166:** (*R*)-7-isopropyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-166)

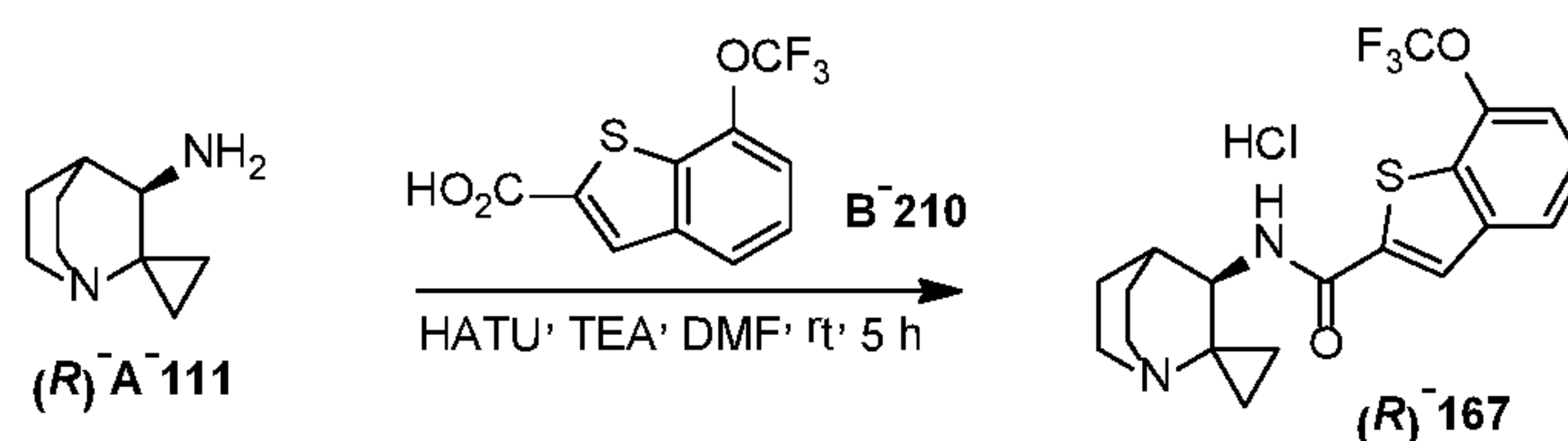


[001169] Following general procedure B, **Compound (R)-166** was prepared from **compound B-208** (86 mg, 0.40 mmol) and **compound (R)-A-111** (60 mg, 0.40 mmol), with a reaction time of 14 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex Synergi

C18 150×30 mm, particle size: 5 μ m; Mobile phase: 27-57% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-7-isopropyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-166**) (80 mg, 52% yield) as a white solid: cSFC analytical (B) t_R=2.297 min., purity: 97.72%; LCMS (DD): t_R=0.833 min., (ES⁺) m/z (M+H)⁺ = 355.2; ¹H-NMR (CD₃OD, 400 MHz): δ 8.17-8.17 (d, J=2.8 Hz, 1H), 7.79-7.77 (d, J=8.0 Hz, 1H), 7.47-7.39 (m, 2H), 4.60-4.60 (d, J=2.0 Hz, 1H), 3.78-3.73 (m, 1H), 3.60-3.49 (m, 1H), 3.48-3.42 (m, 2H), 3.29-3.23 (m, 1H), 2.48-2.47 (m, 1H), 2.39-2.29 (m, 1H), 2.26-2.17 (m, 2H), 2.06-2.01 (m, 1H), 1.44-1.38 (m, 7H), 1.30-1.24 (m, 3H).

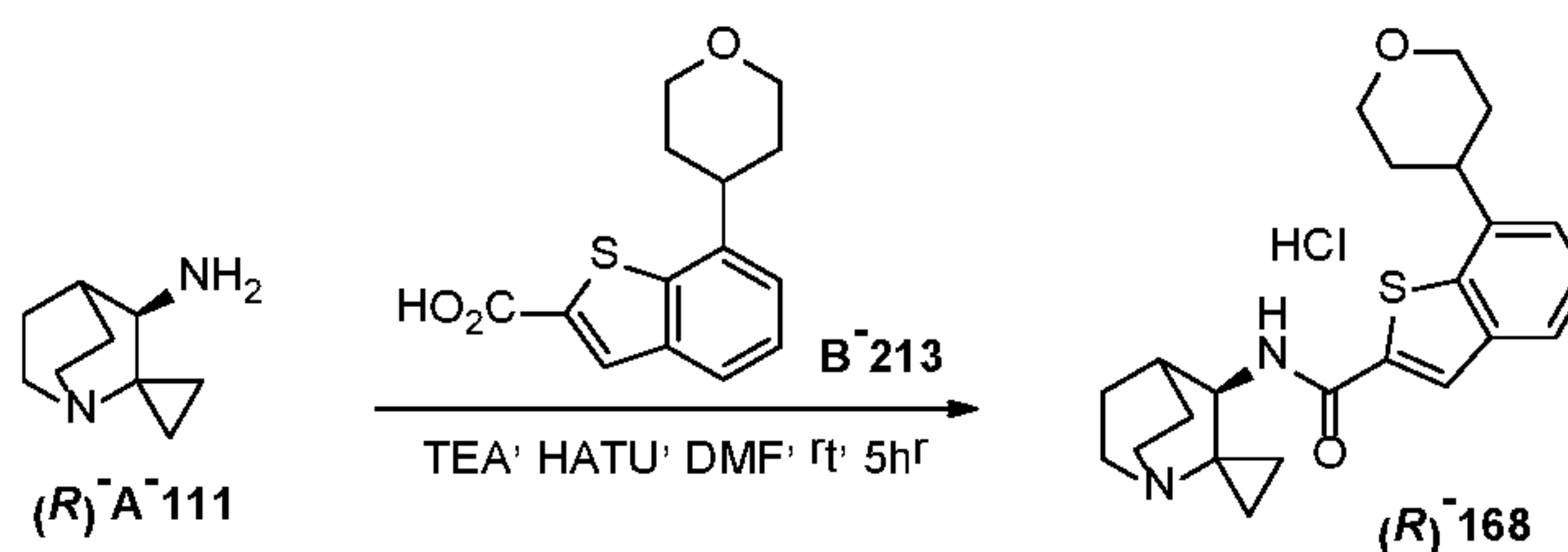
[001170] **Example 167:** (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-167)



[001171] Following general procedure B, **Compound (R)-167** was prepared from **compound B-210** (103 mg, 0.39 mmol) and **compound (R)-A-111** (60 mg, 0.39 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150×30 mm, particle size: 5 μ m; Mobile phase: 25-55% acetonitrile in H₂O (add 0.1% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-167**) (90 mg, 53% yield) as a white solid: cSFC analytical (A) t_R=1.854 min., purity: 97.78%; LCMS (B): t_R=0.723 min., (ES⁺) m/z (M+H)⁺ = 397.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.23 (s, 1H), 7.94 (d, J=8.0 Hz, 1H), 7.54 (t, J=8.4 Hz, 1H), 7.44 (d, J=7.6 Hz, 1H), 4.58 (d, J=2.4 Hz, 1H), 3.72-3.71 (m, 1H), 3.59-3.51 (m, 1H), 3.49-3.40 (m, 2H), 2.46-2.45 (m, 1H), 2.34-2.32 (m, 1H), 2.24-2.17 (m, 2H), 2.04-2.01 (m, 1H), 1.39-1.35 (m, 1H), 1.28-1.19 (m, 3H).

[001172] **Example 168:** (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(tetrahydro-2*H*-pyran-4-yl)benzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-168)

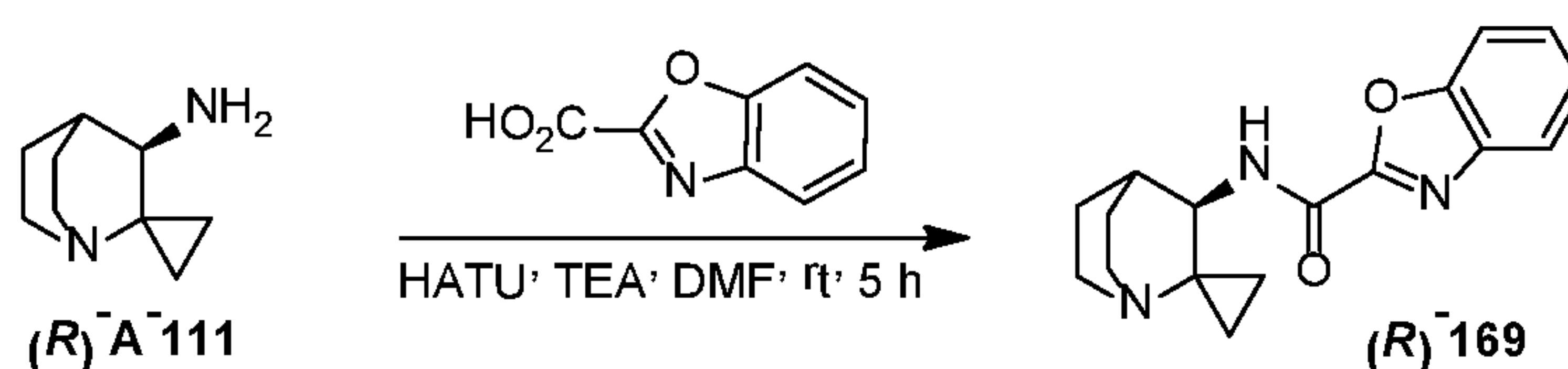


[001173] Following general procedure B, **Compound (R)-168** was prepared from **compound B-213** (86 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB

C18 150×30 mm, particle size: 5 µm; Mobile phase: 19-49% acetonitrile in H₂O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(tetrahydro-2*H*-pyran-4-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-168**) (50 mg, 38% yield) as a white solid: cSFC analytical (A) t_R=2.70 min., purity: 100%; LCMS (B): t_R=0.570 min., (ES⁺) m/z (M+H)⁺ = 397.1; ¹H-NMR (CD₃OD, 400 MHz): δ 8.21 (s, 1H), 7.80 (dd, J₁=3.6 Hz, J₂=0.8 Hz, 1H), 7.46-7.42 (m, 1H), 7.37 (d, J=6.8 Hz, 1H), 4.56 (d, J=2.4 Hz, 1H), 4.11-4.07 (m, 2H), 3.75-3.76 (m, 1H), 3.69-3.64 (m, 2H), 3.61-3.60 (m, 1H), 3.59-3.40 (m, 2H), 3.12-3.08 (m, 1H), 2.45-2.43 (m, 1H), 2.21-2.20 (m, 1H), 2.19-2.17 (m, 2H), 1.98-1.92 (m, 5H), 1.41-1.39 (m, 1H), 1.33-1.25 (m, 2H), 1.23-1.17 (m, 1H).

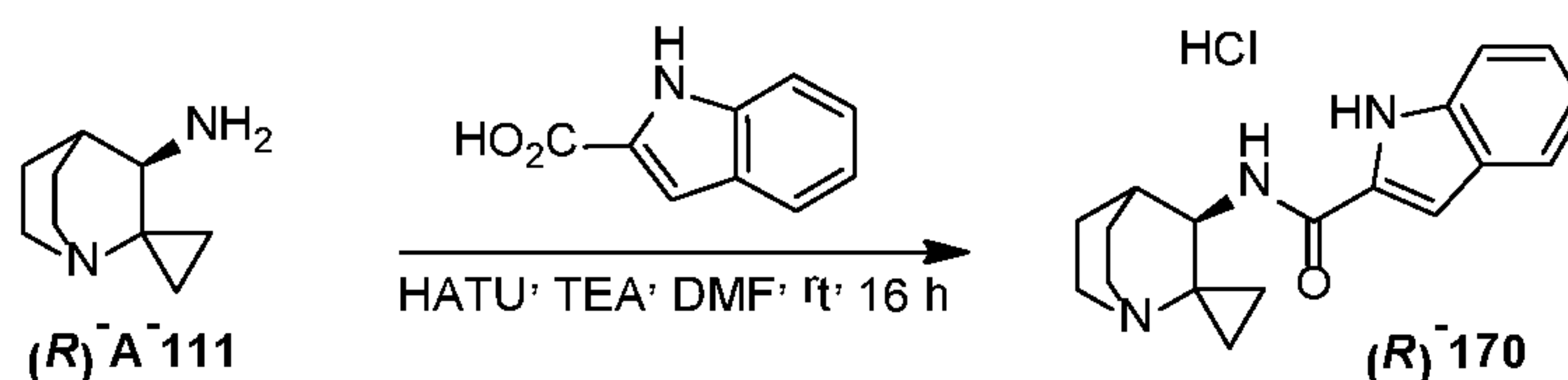
[001174] **Example 169:** (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-2-carboxamide ((*R*)-169)



[001175] Following general procedure B, **Compound (R)-169** was prepared from benzo[d]oxazole-2-carboxylic acid (53 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 250×50 mm, particle size: 10 µm; Mobile phase: 16-46% acetonitrile in H₂O (add 0.5% NH₃·H₂O, v/v)] to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-2-carboxamide (**compound (R)-169**) (50 mg, 51% yield) as a white solid: cSFC analytical (A) t_R=1.77 min., purity: 97.86%; LCMS (J): t_R=1.022 min., 298.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 7.87 (d, J=7.6 Hz, 1H), 7.75 (d, J=8.0 Hz, 1H), 7.56 (td, J₁=8.0 Hz, J₂=1.2 Hz, 1H), 7.50 (td, J₁=8.0 Hz, J₂=1.2 Hz, 1H), 4.22 (d, J=2.0 Hz, 1H), 3.23-3.22 (m, 1H), 3.08-3.05 (m, 1H), 2.94-2.86 (m, 2H), 2.15-1.13 (m, 1H), 1.97 (m, 1H), 1.87-1.83 (m, 2H), 1.58-1.54 (m, 1H), 0.92-0.88 (m, 2H), 0.77-0.74 (m, 1H), 0.70-0.65 (m, 1H).

[001176] **Example 170:** (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1*H*-indole-2-carboxamide hydrochloride ((*R*)-170)

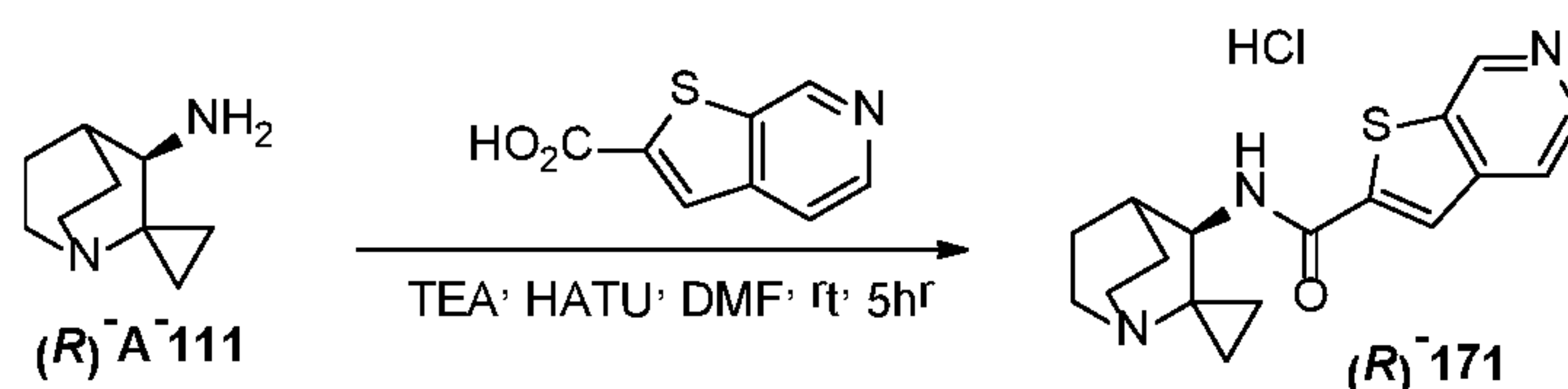


[001177] Following general procedure B, **compound (R)-170** was prepared from 1*H*-indole-2-carboxylic acid (70 mg, 0.43 mmol) and **compound (R)-A-111** (60 mg, 0.39 mmol), with a reaction time of 16 hours. The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex

Gemini C18 250*50, particle size: 10 μm ; Mobile phase: 30-60% acetonitrile in H_2O (add 0.5% $\text{NH}_3 \cdot \text{H}_2\text{O}$, v/v)]. The resulting solids were dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-2-carboxamide hydrochloride (**compound (R)-170**) (40 mg, 35% yield) as a white solid: cSFC analytical (A) t_R =2.56 min., purity: 98.54%; LCMS (J): t_R =1.11 min., 296.2 m/z ($M+1$); $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.66-7.64 (d, J =8.0 Hz, 1H), 7.48-7.46 (d, J =8.4 Hz, 1H), 7.30-7.24 (m, 2H), 7.11-7.08 (t, J =7.6 Hz, 1H), 4.62-4.61 (d, J =2.0 Hz, 1H), 3.75-3.74 (m, 1H), 3.60-3.59 (m, 1H), 3.51-3.44 (m, 2H), 2.45-2.37 (m, 2H), 2.24-2.18 (m, 2H), 2.04-2.00 (m, 1H), 1.39-1.37 (m, 1H), 1.30-1.16 (m, 3H).

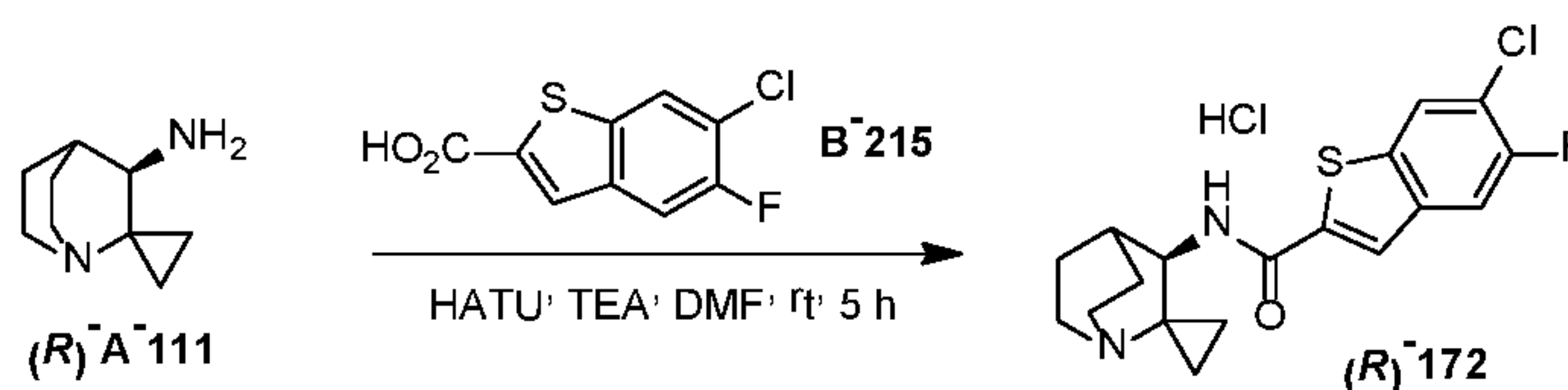
[001178] **Example 171:** (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*c*]pyridine-2-carboxamide hydrochloride ((*R*)-171)



[001179] Following general procedure B, **Compound (R)-171** was prepared from thieno[2,3-*c*]pyridine-2-carboxylic acid (59 mg, 0.33 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Agella Venusil ASB C18 150×30 mm, particle size: 5 μm ; Mobile phase: 19-49% acetonitrile in H_2O (add 0.5% HCl, v/v)] to give:

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*c*]pyridine-2-carboxamide hydrochloride (**compound (R)-171**) (40 mg, 39% yield) as a white solid: cSFC analytical (A) t_R =2.41 min., purity: 100%; LCMS (K): t_R =0.776 min., (ES^+) m/z ($M+H$) $^+$ = 314.1; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 9.73 (s, 1H), 8.70 (s, 1H), δ 8.69 (s, 1H), 8.58 (d, J =6.4 Hz 1H), 4.61 (d, J =2.8 Hz 1H), 3.86-3.81 (m, 1H), 3.60-3.55 (m, 1H), 3.47-3.40 (m, 2H), 2.48-2.37 (m, 2H), 2.24-2.15 (m, 2H), 2.03-1.99 (m, 1H), 1.43-1.30 (m, 3H), 1.18-1.16 (m, 1H).

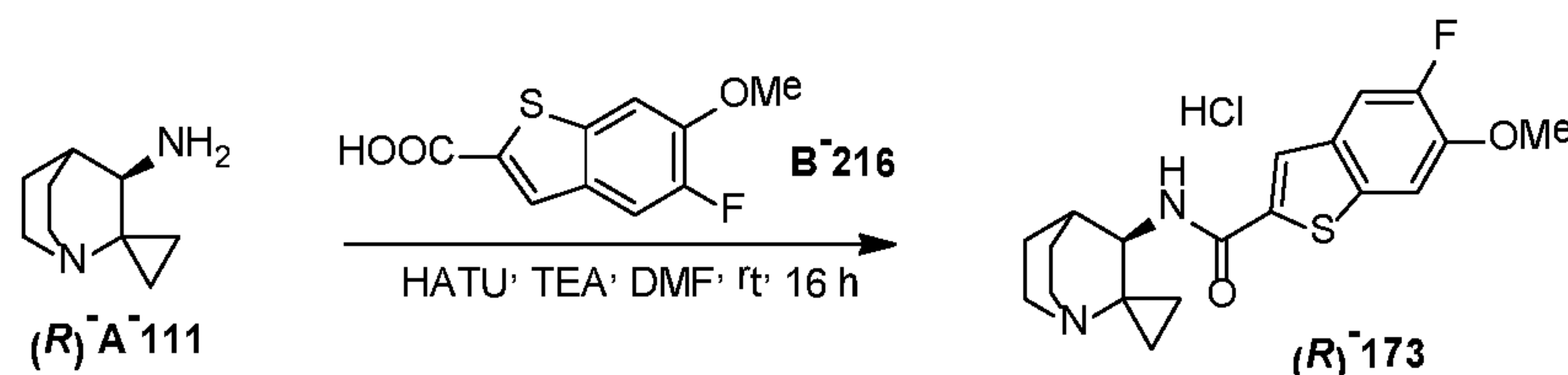
[001180] **Example 172:** (*R*)-6-chloro-5-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[*b*]thiophene-2-carboxamide hydrochloride ((*R*)-172)



[001181] Following general procedure B, **compound (R)-172** was prepared from **compound B-215** (91mg, 0.39 mmol) and **compound (R)-A-111** (50 mg, 0.33 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-D; Column: Boston Green ODS C18 150×30 mm, particle size: 5 μm ; Mobile phase: 42-72% acetonitrile in H_2O (add 0.225% FA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-6-chloro-5-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-172**) (50 mg, 38% yield) as a white solid: cSFC analytical (A) t_R=2.50 min., purity: 100%; LCMS (B): t_R=0.712 min., 365.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.12-8.11 (d, J=6.8 Hz, 1H), 8.07 (s, 1H), 7.79-7.77 (d, J=9.6 Hz, 1H), 4.56-4.55 (m, 1H), 3.69-3.68 (m, 1H), 3.59-3.58 (m, 1H), 3.49-3.44 (m, 2H), 2.45-2.44 (m, 1H), 2.33-2.30 (m, 1H), 2.23-2.16 (m, 2H), 2.01 (m, 1H), 1.37-1.33 (m, 1H), 1.25-1.18 (m, 3H).

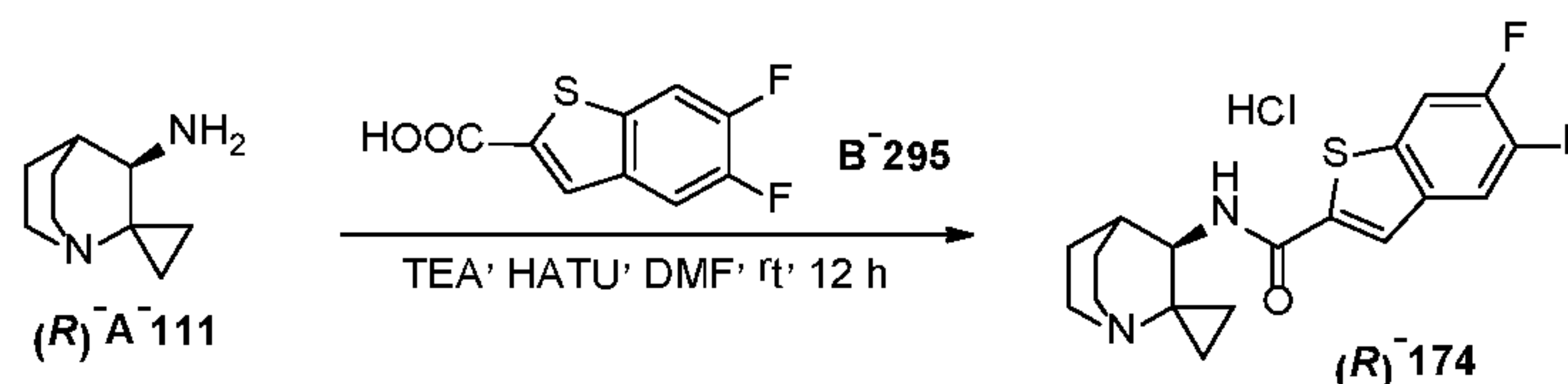
[001182] **Example 173:** (*R*)-5-fluoro-6-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**(R)-173**)



[001183] Following general procedure B, **Compound (R)-173** was prepared from **compound B-216** (60 mg, 0.27 mmol) and **compound (R)-A-111** (40 mg, 0.27 mmol), with a reaction time of 16 hours. The product was purified by prep-HPLC [Instrument: GX-E; Column: Phenomenex SynergiC18 250*21.2mm, particle size: 4 μm; Mobile phase: 15-45% acetonitrile in H₂O (add 0.05% HCl, v/v)] to give:

(*R*)-5-fluoro-6-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-173**) (80 mg, 76% yield) as a white solid: cSFC analytical (A) t_R=2.54 min., purity: 97.70%; LCMS (B): t_R=0.649 min., 361.1 m/z (M+1); ¹H-NMR (CD₃OD, 400 MHz): δ 8.04 (s, 1H), 7.64-7.61 (m, 2H), 4.57-4.56 (d, J=2.0 Hz, 1H), 3.98 (s, 3H), 3.76-3.72 (m, 1H), 3.60-3.52 (m, 1H), 3.50-3.45 (m, 2H), 2.45-2.44 (m, J=2.8 Hz, 1H), 2.35-2.34 (m, 1H), 2.25-2.18 (m, 2H), 2.02-2.01 (m, 1H), 1.41-1.36 (m, 1H), 1.28-1.19 (m, 3H).

[001184] **Example 174:** (*R*)-5,6-difluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**(R)-174**)

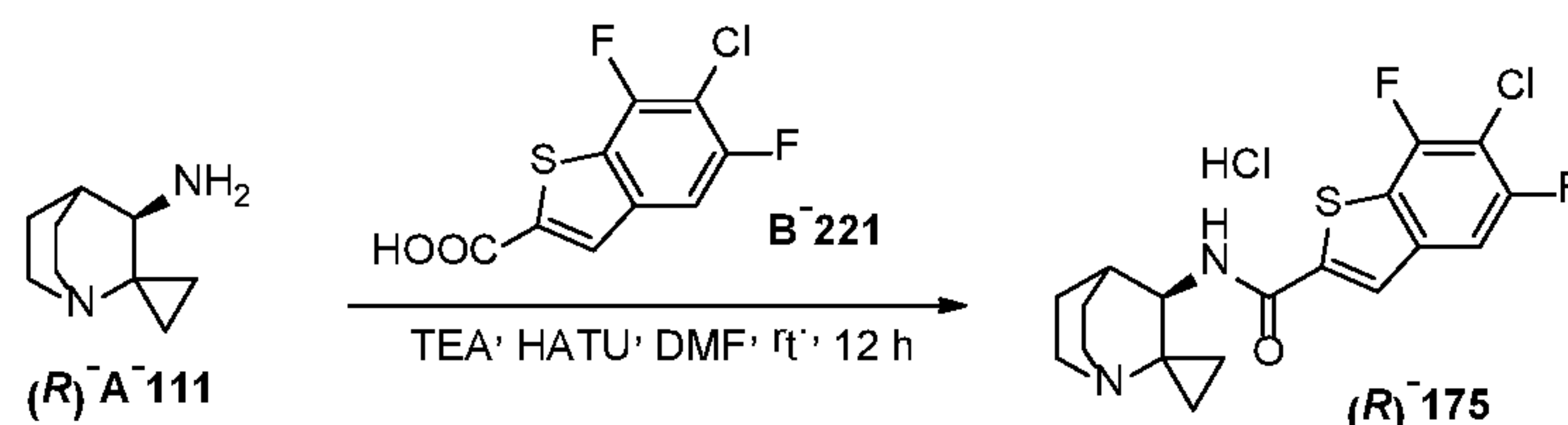


[001185] Following general procedure B, **Compound (R)-174** was prepared from **compound B-295** (0.10 g, 0.47 mmol) and **compound (R)-A-111** (71 mg, 0.47 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-A; Column: Phenomenex Gemini C18 250×50 mm, particle size: 10 μm; Mobile phase: 40-46% acetonitrile in H₂O (add 0.05% ammonia, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-5,6-difluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide -hydrochloride (**compound (R)-174**) (50 mg, 28% yield) as a

white solid: cSFC analytical (A) t_R =2.17 min., purity: 96.13%; LCMS (GG): t_R =2.016 min., 349.1 m/z (M+1); ^1H -NMR (CD_3OD , 400 MHz): δ 8.14 (s, 1H), 7.93-7.89 (q, 1H), 7.86-7.82 (q, 1H), 4.59-4.57 (m, 1H), 3.77-3.73 (m, 1H), 3.60-3.59 (m, 1H), 3.50-3.45 (m, 2H), 2.46 (m, 1H), 2.36 (m, 1H), 2.25-2.18 (m, 2H), 2.02-2.01 (m, 1H), 1.40 (m, 1H), 1.39-1.19 (m, 3H).

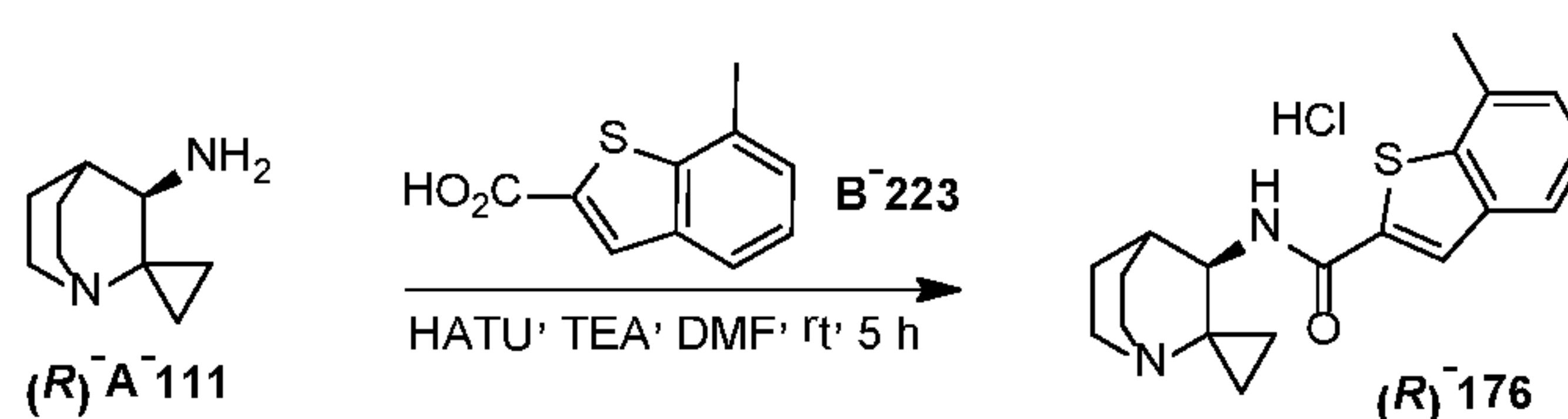
[001186] Example 175: (*R*)-6-chloro-5,7-difluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-175)



[001187] Following general procedure B, **Compound (R)-175** was prepared from **compound B-221** (40 mg, 0.16 mmol) and **compound (R)-A-111** (24 mg, 0.16 mmol), with a reaction time of 12 hours. The product was purified by prep-HPLC [Instrument: GX-B; Column: YMC-Actus Pro C18 150×30 mm, particle size: 5 μm ; Mobile phase: 25-55% acetonitrile in H_2O (add 0.5% TFA, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid and again lyophilized to give:

(*R*)-6-chloro-5,7-difluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thio-phene-2-carboxamide -hydrochloride (**compound (R)-175**) (50 mg, 74% yield) as a yellow solid: cSFC analytical (A) t_R =2.440 min., purity: 100.00%; LCMS (GG): t_R =2.353 min., 383.1 m/z (M+1); ^1H -NMR (CD_3OD , 400 MHz): δ 8.20 (d, J =2.8 Hz, 1H), 7.76-7.73 (d, J =8.8 Hz, 1H), 4.59 (m, 1H), 3.73-3.71 (m, 1H), 3.60 (m, 1H), 3.54-3.42 (m, 2H), 2.47 (m, 1H), 2.38-2.33 (m, 1H), 2.23-2.20 (m, 2H), 2.02 (m, 1H), 1.39-1.37 (m, 1H), 1.29-1.21 (m, 3H).

[001188] Example 176: (*R*)-7-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride ((*R*)-176)



[001189] Following general procedure B, **Compound (R)-176** was prepared from **compound B-223** (51 mg, 0.26 mmol) and **compound (R)-A-111** (40 mg, 0.26 mmol), with a reaction time of 5 hours. The product was purified by prep-HPLC [Instrument: GX-H; Column: Waters Xbridge 150×25, particle size: 5 μm ; Mobile phase: 34-64% acetonitrile in H_2O (add 0.05% ammonia, v/v)]. The resulting solid was dissolved in 0.2 M hydrochloric acid solution and again lyophilized to give:

(*R*)-7-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide hydrochloride (**compound (R)-176**) (40 mg, 42% yield) as a white solid: cSFC analytical (A) t_R =2.526 min., purity: 97.61%; LCMS (B): t_R =0.677 min., (ES^+) m/z (M+H) $^+$ =327.2; ^1H -NMR (CD_3OD , 400 MHz): δ 8.19 (s, 1H), 7.79 (d, J =8.0 Hz, 1H), 7.40 (t, J =7.2 Hz, 1H), 7.31 (d, J =7.2 Hz, 1H), 4.60 (d, J =3.6 Hz, 1H), 3.78-3.74 (m, 1H), 3.60-3.50 (m, 1H), 3.49-3.45 (m, 2H), 2.58

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 296

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THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 296

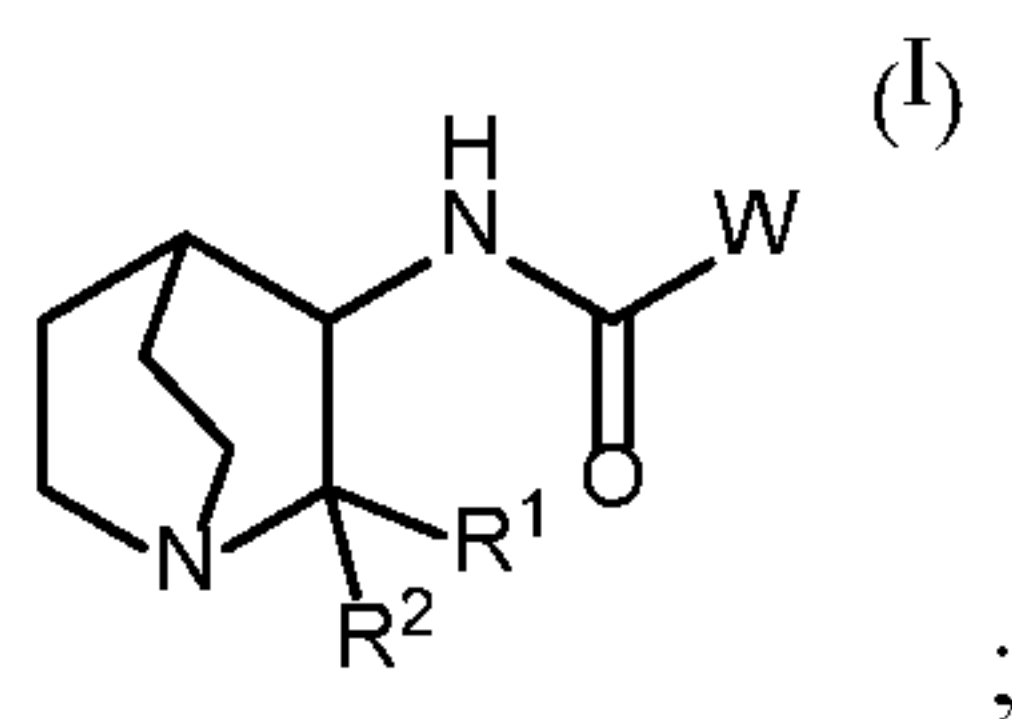
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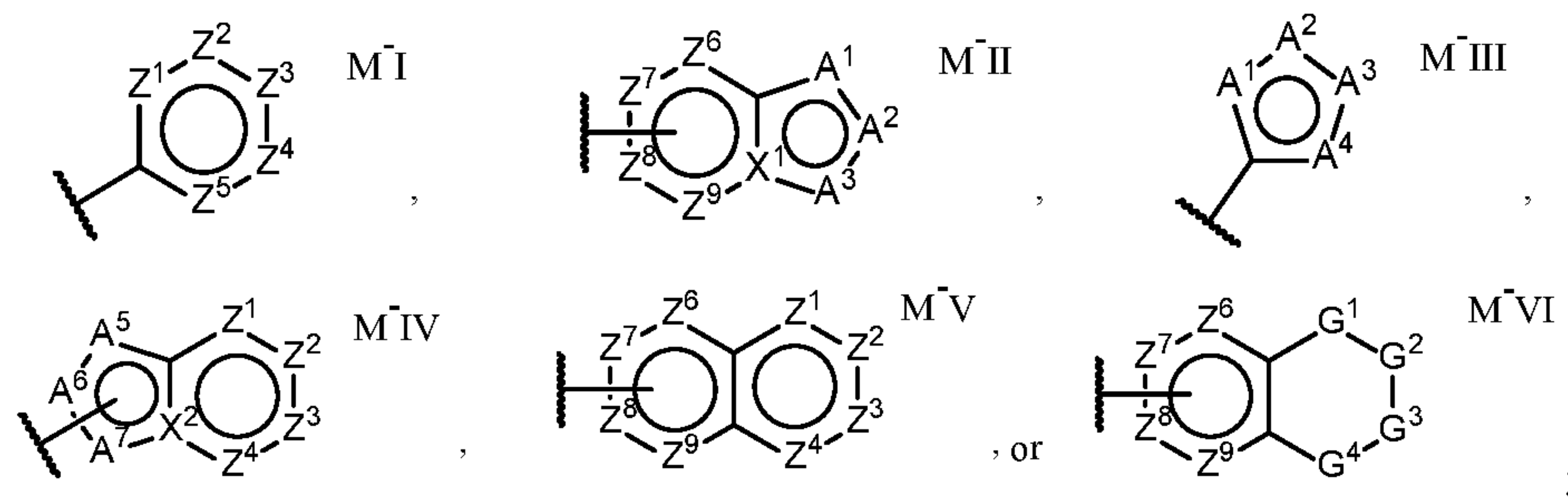
What is claimed is:

1. A geminal substituted quinuclidine amide compound represented by Formula (I):



wherein:

- R^1 and R^2 independently represent a branched or unbranched C_1 - C_4 -alkyl radical; or the $C(R^1)(R^2)$ moiety forms a (3-4 membered)-carbocycle, wherein R^1 and R^2 taken together represent a C_2 - C_3 -alkyl di-radical; wherein the C_1 - C_4 -alkyl radical and the C_2 - C_3 -alkyl di-radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, CH_3 , CH_2CH_3 , $=O$, $-OR^3$, or $-OCF_3$;
- R^3 independently represents $-H$; a branched or unbranched C_1 - C_4 -alkyl radical; C_3 - C_4 -cycloalkyl radical; wherein the C_1 - C_4 -alkyl radical and the C_3 - C_4 -cycloalkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $=O$, $-OH$, $-OC_1$ - C_4 -alkyl or $-OCF_3$; and
- W represents a moiety represented by ring system M-I, M-II, M-III, M-IV, M-V, or M-VI:



wherein:

- Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 independently represent N or CR^4 ; with the proviso that no more than two of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are N;
- R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^5$; $-N(R^5)(R^6)$; $-SO_2(CH_2)_mR^5$; $-(CO)(CH_2)_mR^5$; $-(CO)N(R^5)(R^6)$; $-OCF_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; or a heteroaryl radical; or when adjacent members of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 , is $(CR^4)(CR^4)$, the $(CR^4)(CR^4)$ may form a cycle such that the adjacent R^4 substituents taken together represents a (3-6 membered)-heteroalkyl di-

radical with at least one ring atom of the (3-6 membered)-heteroalkyl di-radical selected from the group consisting of oxygen, nitrogen, and sulfur, with the proviso that when the at least one ring atom is nitrogen, the nitrogen is substituted with $-H$, a branched or unbranched C_1 - C_4 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, $-(CO)$ -branched or unbranched C_1 - C_4 -alkyl, or $-(SO_2)$ -branched or unbranched C_1 - C_4 -alkyl, wherein the C_1 - C_4 -alkyl radical and the C_3 - C_4 -cycloalkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, halogen, $=O$, $-OH$, $-OC_1$ - C_4 -alkyl or $-OCF_3$, and with the further proviso that when the at least one ring atom is sulfur, the sulfur may substituted with 0 or 2 $=O$; wherein the C_1 - C_6 -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, the heteroaryl radical, and the alkyl portion of the (3-6 membered)-heteroalkyl di-radical, may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^5$, $-(CH_2)_mOR^5$, $-N(R^5)(R^6)$, $-(CH_2)_mN(R^5)(R^6)$, $-SO_2(CH_2)_mR^5$, $-(CO)(CH_2)_mR^5$, $-(CO)N(R^5)(R^6)$, $-OCF_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, a C_1 - C_6 -hydroxyalkyl radical, or a C_1 - C_6 -haloalkyl radical;

R^5 and R^6 independently represent $-H$; a branched or unbranched C_1 - C_6 -alkyl radical; a C_3 - C_6 -cycloalkyl radical; or the $N(R^5)(R^6)$ moiety forms a cycle, wherein R^5 and R^6 taken together represent a C_2 - C_6 -alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;

Z^6 , Z^7 , Z^8 , and Z^9 independently represent N or CR^7 ; with the proviso that no more than two of Z^6 , Z^7 , Z^8 , and Z^9 are N ;

R^7 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^8$; $-N(R^8)(R^9)$; $-SO_2(CH_2)_mR^8$; $-(CO)(CH_2)_mR^8$; $-(CO)N(R^8)(R^9)$; $-OCF_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; a heteroaryl radical; or the bond directly attaching the W moiety with the carbonyl moiety; wherein the C_1 - C_6 -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^8$, $-(CH_2)_mOR^8$, $-N(R^8)(R^9)$, $-(CH_2)_mN(R^8)(R^9)$, $-SO_2(CH_2)_mR^8$, $-(CO)(CH_2)_mR^8$, $-(CO)N(R^8)(R^9)$, $-OCF_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, a C_1 - C_6 -hydroxyalkyl radical, or a C_1 - C_6 -haloalkyl radical;

- R^8 and R^9 independently represent $-H$; a branched or unbranched C_1 - C_6 -alkyl radical; a C_3 - C_6 -cycloalkyl radical; or the $N(R^8)(R^9)$ moiety forms a cycle, wherein R^8 and R^9 taken together represent a C_2 - C_6 -alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;
- X^1 independently represents N or C;
- A^1 , A^2 , A^3 and A^4 independently represent N; NR^{10} ; $N(CH_2)_mR^{10}$; O; S; or CR^{11} ; with the proviso that only one A^1 , A^2 , A^3 and A^4 is NR^{10} , O, or S; with the further proviso that when X^1 is N, then A^1 , A^2 , and A^3 independently represent N or CR^{11} ;
- R^{10} independently represents $-H$; $-D$; $-SO_2(CH_2)_mR^{12}$; $-(CO)(CH_2)_mR^{12}$; $-(CO)N(R^{12})(R^{13})$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; or a heteroaryl radical; wherein the C_1 - C_6 -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^{12}$, $-(CH_2)_mOR^{12}$, $-N(R^{12})(R^{13})$, $-(CH_2)_mN(R^{12})(R^{13})$, $-SO_2(CH_2)_mR^{12}$, $-(CO)(CH_2)_mR^{13}$, $-(CO)N(R^{12})(R^{13})$, $-OCF_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, a C_1 - C_6 -hydroxyalkyl radical, or a C_1 - C_6 -haloalkyl radical;
- R^{11} independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^{12}$; $-N(R^{12})(R^{13})$; $-SO_2(CH_2)_mR^{12}$; $-(CO)(CH_2)_mR^{12}$; $-(CO)N(R^{12})(R^{13})$; $-OCF_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; or a heteroaryl radical; wherein the C_1 - C_6 -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^{12}$; $-(CH_2)_mOR^{12}$; $-N(R^{12})(R^{13})$; $-(CH_2)_mN(R^{12})(R^{13})$; $-SO_2(CH_2)_mR^{12}$; $-(CO)(CH_2)_mR^{12}$; $-(CO)N(R^{12})(R^{13})$; $-OCF_3$; a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, or a C_1 - C_6 -haloalkyl radical;
- R^{12} and R^{13} independently represent $-H$; a branched or unbranched C_1 - C_6 -alkyl radical; a C_3 - C_6 -cycloalkyl radical; or the $N(R^{12})(R^{13})$ moiety forms a cycle, wherein R^{12} and R^{13} taken together represent a C_2 - C_6 -alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;
- X^2 independently represents N or C;
- A^5 , A^6 , and A^7 independently represent N; NR^{14} ; $N(CH_2)_mR^{14}$; O; S; or CR^{15} ; with the proviso that only one A^5 , A^6 , and A^7 is NR^{14} , O, or S; with the further

proviso that when X^2 is N, then A^5 , A^6 , and A^7 independently represent N or CR^{15} ;

R^{14} independently represents $-H$; $-D$; $-(CH_2)_mN(R^{16})(R^{17})$; $-SO_2(CH_2)_mR^{16}$; $-(CO)(CH_2)_mR^{16}$; $-(CO)N(R^{16})(R^{17})$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; a heteroaryl radical; or the bond directly attaching the W moiety with the carbonyl moiety; wherein the C_1 - C_6 -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^{16}$, $-(CH_2)_mOR^{16}$, $-N(R^{16})(R^{17})$, $-(CH_2)_mN(R^{16})(R^{17})$, $-SO_2(CH_2)_mR^{16}$, $-(CO)(CH_2)_mR^{16}$, $-(CO)N(R^{16})(R^{17})$, $-OCF_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, or a C_1 - C_6 -haloalkyl;

R^{15} independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^{16}$; $-N(R^{16})(R^{17})$; $-SO_2(CH_2)_mR^{16}$; $-(CO)(CH_2)_mR^{16}$; $-(CO)N(R^{16})(R^{17})$; $-OCF_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; a heteroaryl radical; or the bond directly attaching the W moiety with the carbonyl moiety; wherein the C_1 - C_6 -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^{16}$; $-(CH_2)_mOR^{16}$; $-N(R^{16})(R^{17})$; $-(CH_2)_mN(R^{16})(R^{17})$; $-SO_2(CH_2)_mR^{16}$; $-(CO)(CH_2)_mR^{16}$; $-(CO)N(R^{16})(R^{17})$; $-OCF_3$; a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, or a C_1 - C_6 -haloalkyl radical;

R^{16} and R^{17} independently represent $-H$; a branched or unbranched C_1 - C_6 -alkyl radical; a C_3 - C_6 -cycloalkyl radical; or the $N(R^{16})(R^{17})$ moiety forms a cycle, wherein R^{16} and R^{17} taken together represent a C_2 - C_6 -alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;

G^1 , G^2 , G^3 , and G^4 independently represent $C(R^{18})(R^{18})$; $N(R^{19})$; $-N(CH_2)_mR^{18}$; O ; S ; SO_2 ; or $(C=O)$; with the proviso that no more than two of G^1 , G^2 , G^3 , and G^4 represent $N(R^{19})$; $-N(CH_2)_mR^{18}$; O ; S ; SO_2 ; or $(C=O)$;

R^{18} independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^{19}$; $-N(R^{19})(R^{20})$; $-SO_2(CH_2)_mR^{19}$; $-(CO)(CH_2)_mR^{19}$; $-(CO)N(R^{19})(R^{20})$; $-OCF_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; an aryl radical; or a heteroaryl radical; wherein the C_1 - C_6 -alkyl radical, the (3-6

membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: –D, –F, –Cl, –Br, –I, –CN, –NO₂, –OR¹⁹, –(CH₂)_mOR¹⁹, –N(R¹⁹)(R²⁰), –(CH₂)_mN(R¹⁹)(R²⁰), –SO₂(CH₂)_mR¹⁹, –(CO)(CH₂)_mR¹⁹, –(CO)N(R¹⁹)(R²⁰), –OCF₃, a branched or unbranched C₁-C₆-alkyl radical, a C₃-C₆-cycloalkyl radical, or a C₁-C₆-haloalkyl radical; and

R¹⁹ and R²⁰

independently represent –H; a branched or unbranched C₁-C₆-alkyl radical; a C₃-C₆-cycloalkyl radical; or the N(R¹⁹)(R²⁰) moiety forms a cycle, wherein R¹⁹ and R²⁰ taken together represent a C₂-C₆-alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical; or the C(R¹⁹)(R²⁰) moiety forms a cycle, wherein R¹⁹ and R²⁰ taken together represent a C₂-C₆-alkyl di-radical or a (3-6 membered)-heteroalkyl di-radical;

m

independently represents an integer from 1 to 6;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein R⁴ independently represents –H; –D; –F; –Cl; –Br; –I; –CN; –NO₂; –OR⁵; –N(R⁵)(R⁶); –SO₂(CH₂)_mR⁵; –(CO)(CH₂)_mR⁵; –(CO)N(R⁵)(R⁶); –OCF₃; C₁-C₆-alkyl radical; C₁-C₆-haloalkyl radical; C₃-C₆-cycloalkyl radical; (3-6 membered)-heterocycloalkyl radical; an aryl radical; or heteroaryl radical; wherein the C₁-C₆-alkyl radical, the (3-6 membered)-heterocycloalkyl radical, the aryl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: –D, –F, –Cl, –Br, –I, –CN, –NO₂, –OR⁵, –(CH₂)_mOR⁵, –N(R⁵)(R⁶), –(CH₂)_mN(R⁵)(R⁶), –SO₂(CH₂)_mR⁵, –(CO)(CH₂)_mR⁵, –(CO)N(R⁵)(R⁶), –OCF₃, a branched or unbranched C₁-C₆-alkyl radical, a C₃-C₆-cycloalkyl radical, a C₁-C₆-hydroxyalkyl radical, or a C₁-C₆-haloalkyl radical.

3. The compound of claim 1 or claim 2, wherein W represents the moiety represented by the ring system M-I.

4. The compound of claim 3, wherein Z¹ represents N; and Z², Z³, Z⁴, and Z⁵ each independently represent CR⁴.

5. The compound of claim 3, wherein Z² represents N; and Z¹, Z³, Z⁴, and Z⁵ each independently represent CR⁴.

6. The compound of claim 3, wherein Z³ represents N; and Z¹, Z², Z⁴, and Z⁵ each independently represent CR⁴.

7. The compound of claim 3, wherein Z^1 and Z^2 each represent N; and Z^3 , Z^4 , and Z^5 each independently represent CR^4 .
8. The compound of claim 3, wherein Z^1 and Z^3 each represent N; and Z^2 , Z^4 , and Z^5 each independently represent CR^4 .
9. The compound of claim 3, wherein Z^1 and Z^4 each represent N; and Z^2 , Z^3 , and Z^5 each independently represent CR^4 .
10. The compound of claim 3, wherein Z^1 and Z^5 each represent N; and Z^2 , Z^3 , and Z^4 each independently represent CR^4 .
11. The compound of claim 3, wherein Z^2 and Z^3 each represent N; and Z^1 , Z^4 , and Z^5 each independently represent CR^4 .
12. The compound of claim 3, wherein Z^2 and Z^4 each represent N; and Z^1 , Z^3 , and Z^5 each independently represent CR^4 .
13. The compound of claim 3, wherein at least one or two of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 , represent CR^4 with said R^4 independently representing $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^5$; $-N(R^5)(R^6)$; $-SO_2(CH_2)_mR^5$; $-(CO)(CH_2)_mR^5$; $-(CO)N(R^5)(R^6)$; $-OCF_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; or a (3-6 membered)-heterocycloalkyl radical; wherein the C_1 - C_6 -alkyl radical and the (3-6 membered)-heterocycloalkyl radical, may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^5$, $-(CH_2)_mOR^5$, $-N(R^5)(R^6)$, $-(CH_2)_mN(R^5)(R^6)$, $-SO_2(CH_2)_mR^5$, $-(CO)(CH_2)_mR^5$, $-(CO)N(R^5)(R^6)$, $-OCF_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, or a C_1 - C_6 -haloalkyl radical.
14. The compound of claim 13, wherein the at least one or two of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 , represent CR^4 with said R^4 independently representing $-F$; $-Cl$; $-Br$; $-I$; or $-CN$.
15. The compound of claim 3, wherein the at least one or two of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 , represent CR^4 with said R^4 independently representing an aryl radical or a heteroaryl radical; wherein the aryl radical and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^5$, $-(CH_2)_mOR^5$, $-N(R^5)(R^6)$, $-(CH_2)_mN(R^5)(R^6)$, $-SO_2(CH_2)_mR^5$, $-(CO)(CH_2)_mR^5$, $-(CO)N(R^5)(R^6)$, $-OCF_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, or a C_1 - C_6 -haloalkyl radical.

16. The compound of claim 3, wherein Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 , each independently represent CR^4 with said R^4 independently representing $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-OCH_3$; $-OCF_3$; a C_1 - C_3 -alkyl radical; $-CF_3$; or a C_3 - C_4 -cycloalkyl radical; wherein the C_1 - C_3 -alkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, a branched or unbranched C_1 - C_3 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, or a C_1 - C_3 -haloalkyl radical.

17. The compound of claim 16, wherein:

Z^1 , Z^2 , Z^4 , and Z^5 represent CR^4 with said R^4 independently representing $-H$ or $-D$; and
 Z^3 represents CR^4 with said R^4 representing $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-OCH_3$; $-OCF_3$; a C_1 - C_3 -alkyl radical; $-CF_3$; or a C_3 - C_4 -cycloalkyl radical; wherein the C_1 - C_3 -alkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, a branched or unbranched C_1 - C_3 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, or a C_1 - C_3 -haloalkyl radical.

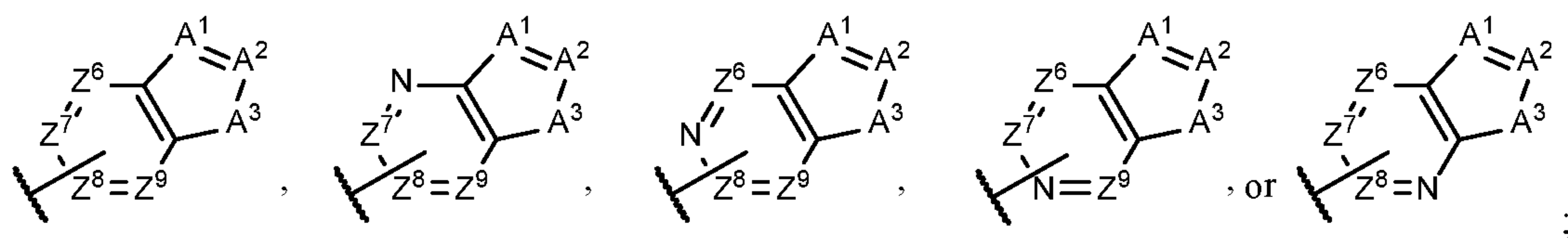
18. The compound of claim 16, wherein:

Z^1 , Z^2 , Z^4 , and Z^5 represent CR^4 with said R^4 independently representing $-H$ or $-D$; and
 Z^3 represents CR^4 with said R^4 representing $-Cl$; $-OCH_3$; $-OCF_3$; a C_1 - C_3 -alkyl radical; $-CF_3$; or a C_3 - C_4 -cycloalkyl radical.

19. The compound of claim 1 or claim 2, wherein W represents the moiety represented by the ring system M-II.

20. The compound of claim 19, wherein X^1 represents C.

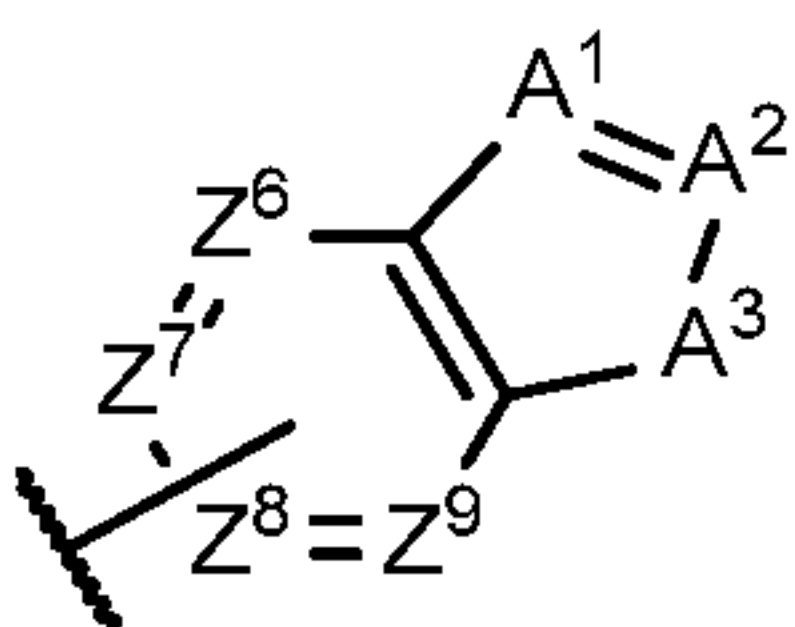
21. The compound of claim 20, wherein M-II represents a moiety represented by one of the following:



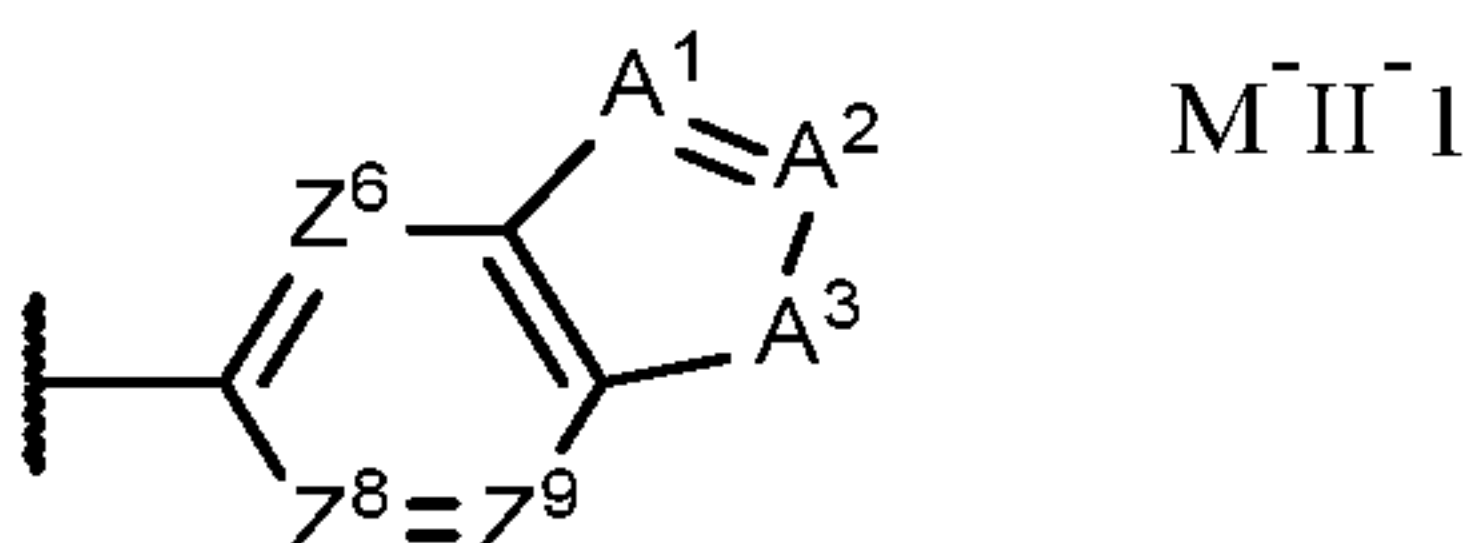
wherein:

A^1 and A^2 independently represent N or CR^{11} ; and
 A^3 represents NR^{10} ; O; or S.

22. The compound of claim 21, wherein M-II represents a moiety represented by:

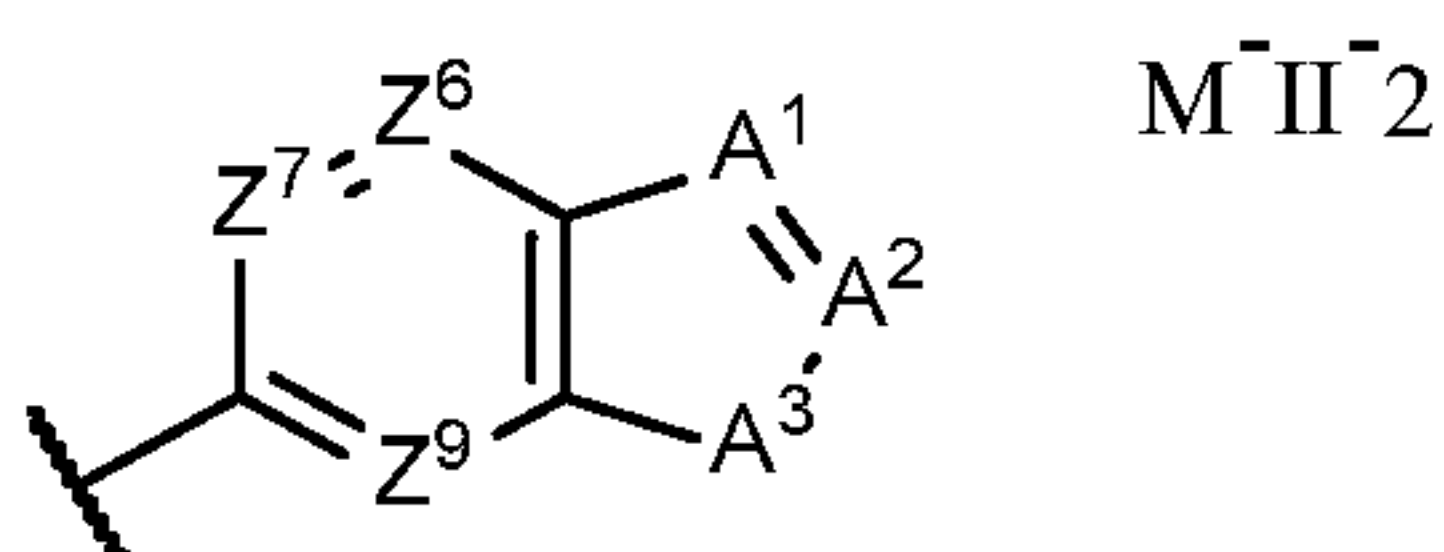


23. The compound of claim 22, wherein M-II represents a moiety represented by ring system M-II-1:



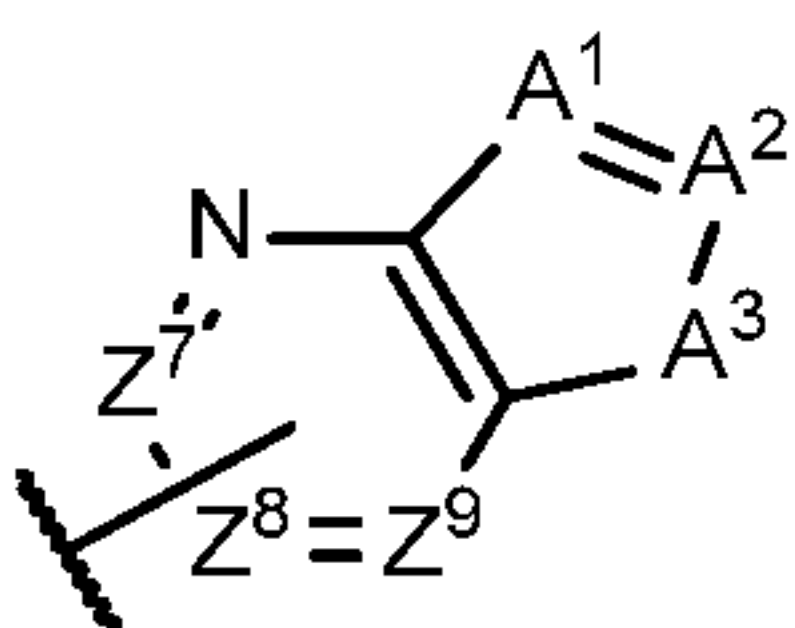
24. The compound of claim 23, wherein Z^6 , Z^8 , and Z^9 represent CR^7 .

25. The compound of claim 22, wherein M-II represents a moiety represented by ring system M-II-2:

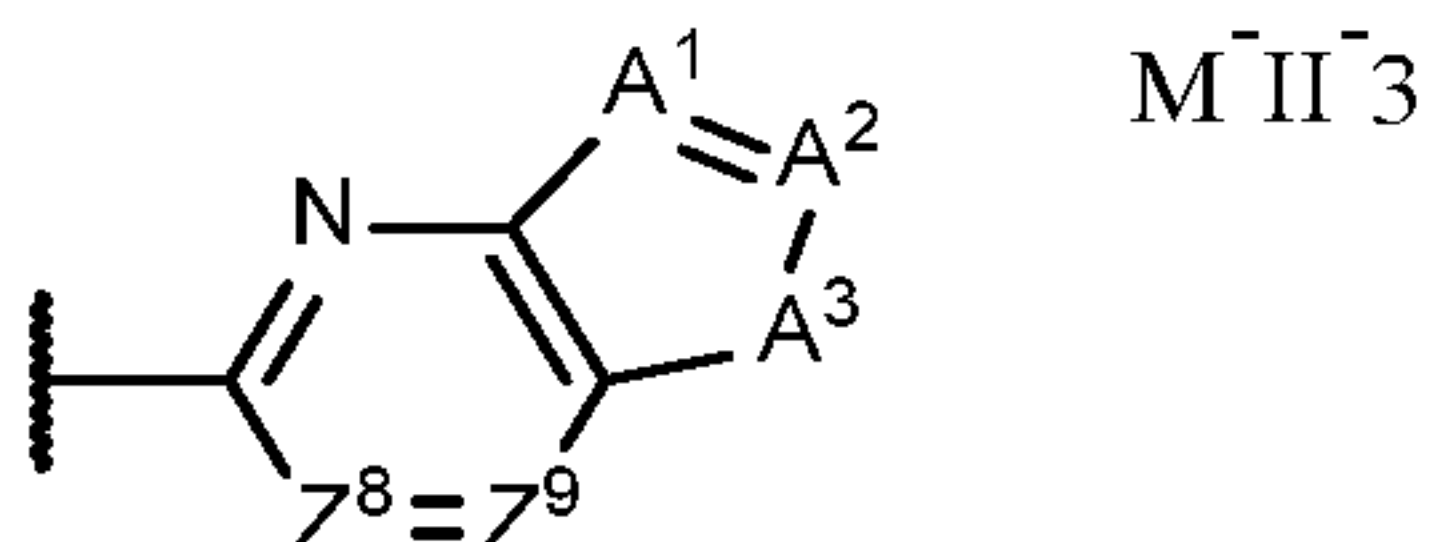


26. The compound of claim 25, wherein Z^6 , Z^7 , and Z^9 represent CR^7 .

27. The compound of claim 21, wherein M-II represents a moiety represented by:

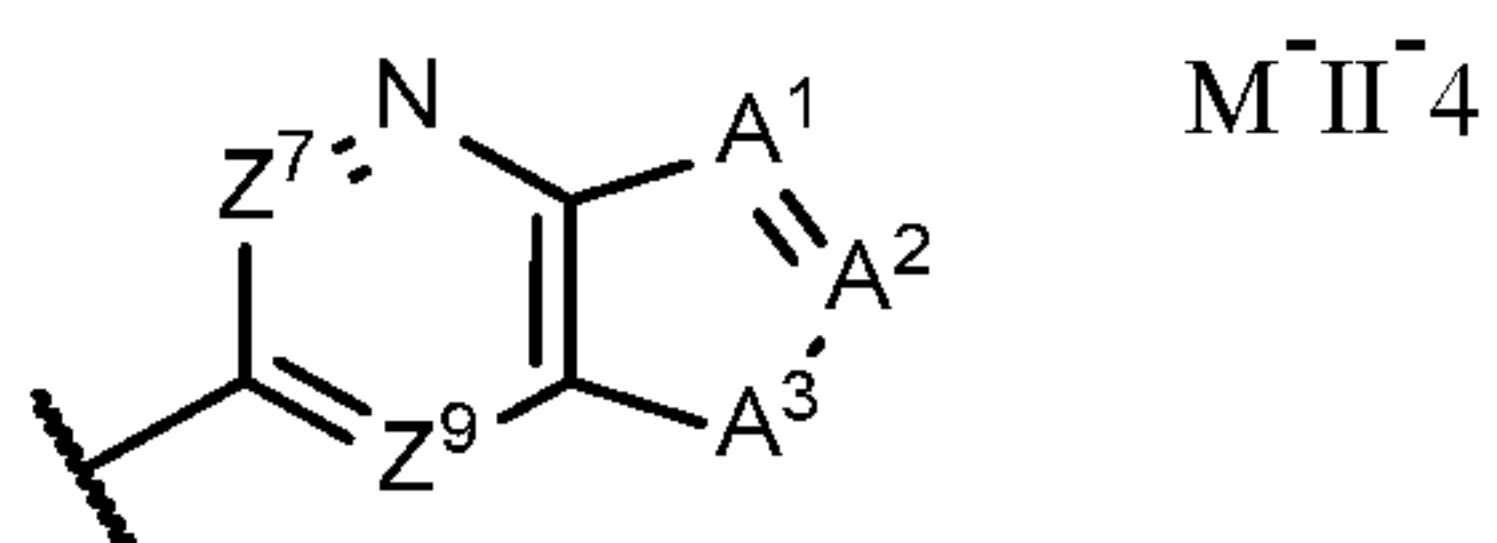


28. The compound of claim 27, wherein M-II represents a moiety represented by ring system M-II-3:



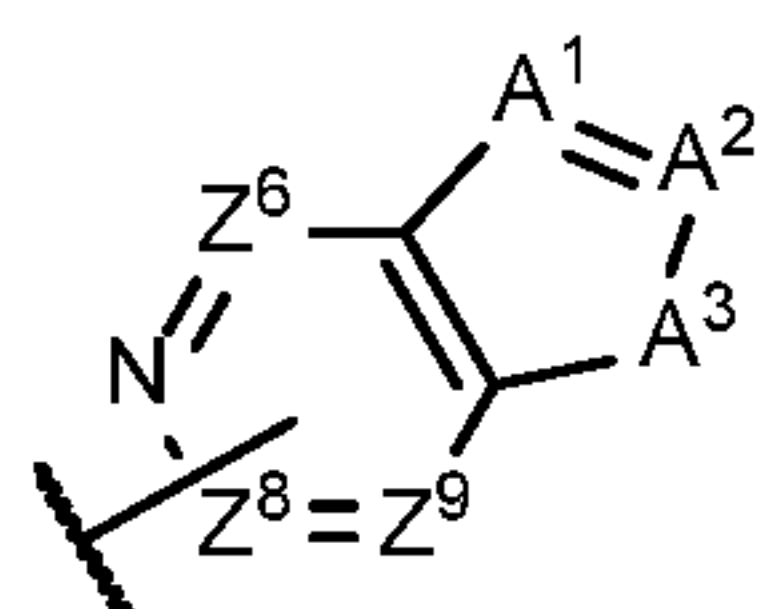
29. The compound of claim 28, wherein Z⁸ and Z⁹ represent CR⁷.

30. The compound of claim 27, wherein M-II represents a moiety represented by ring system M-II-4:

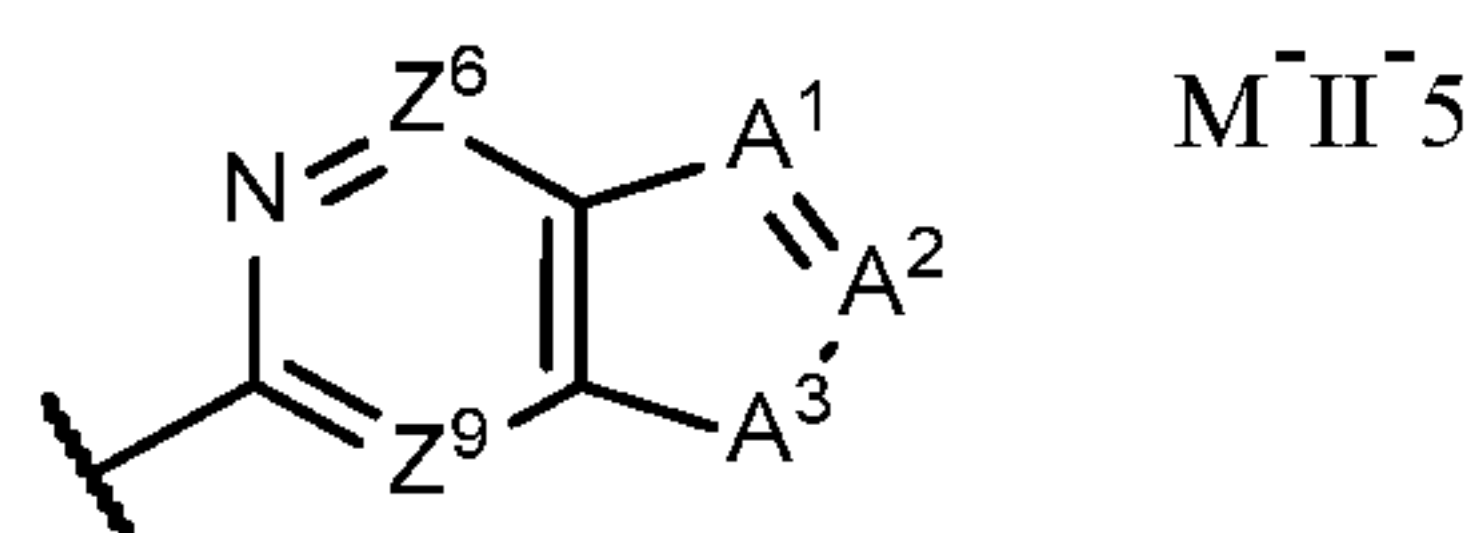


31. The compound of claim 30, wherein Z^7 and Z^9 independently represent CR^7 .

32. The compound of claim 21, wherein M-II represents a moiety represented by:

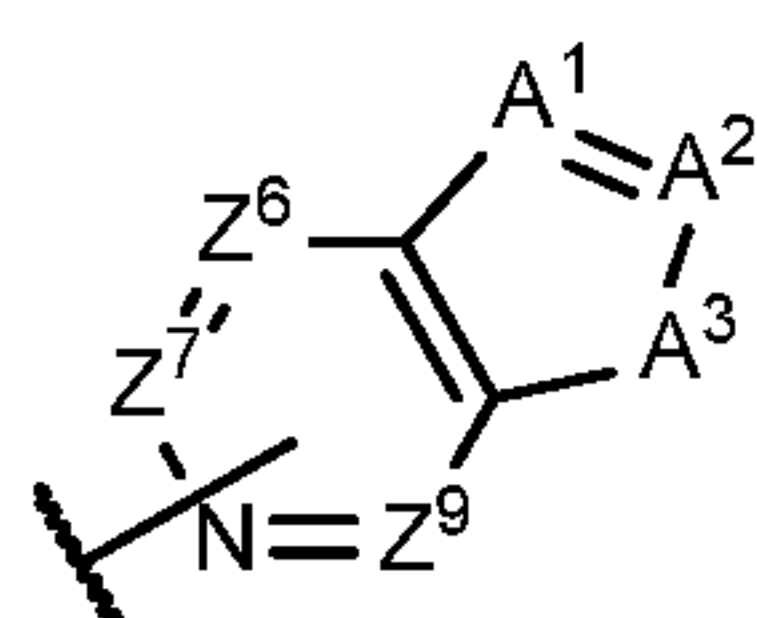


33. The compound of claim 32, wherein M-II represents a moiety represented by ring system M-II-5:

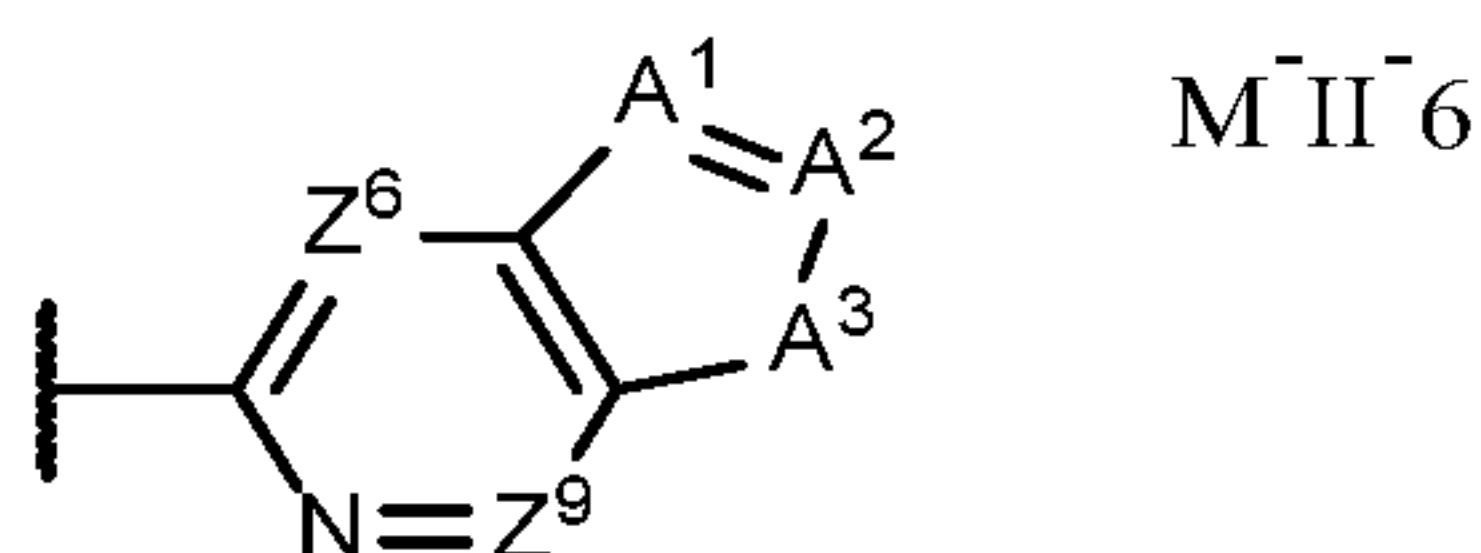


34. The compound of claim 33, wherein Z^6 and Z^9 independently represent CR^7 .

35. The compound of claim 21, wherein M-II represents a moiety represented by:

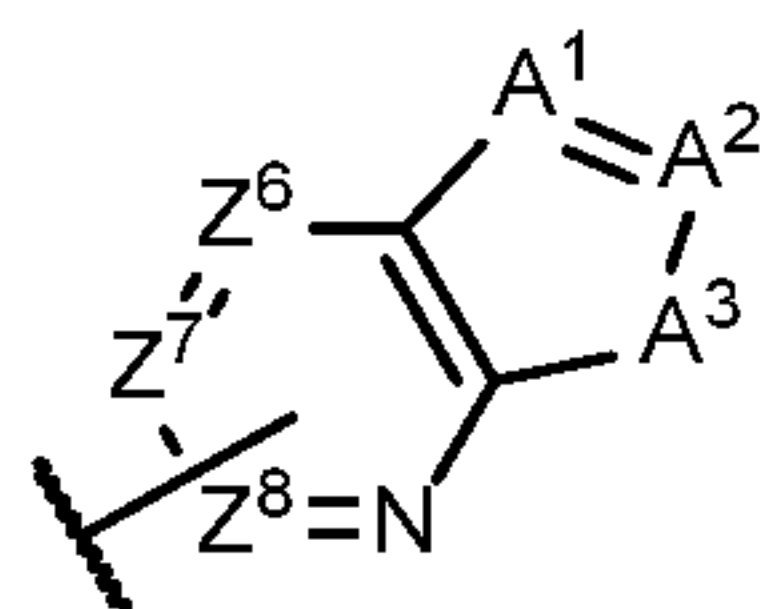


36. The compound of claim 35, wherein M-II represents a moiety represented by ring system M-II-6:

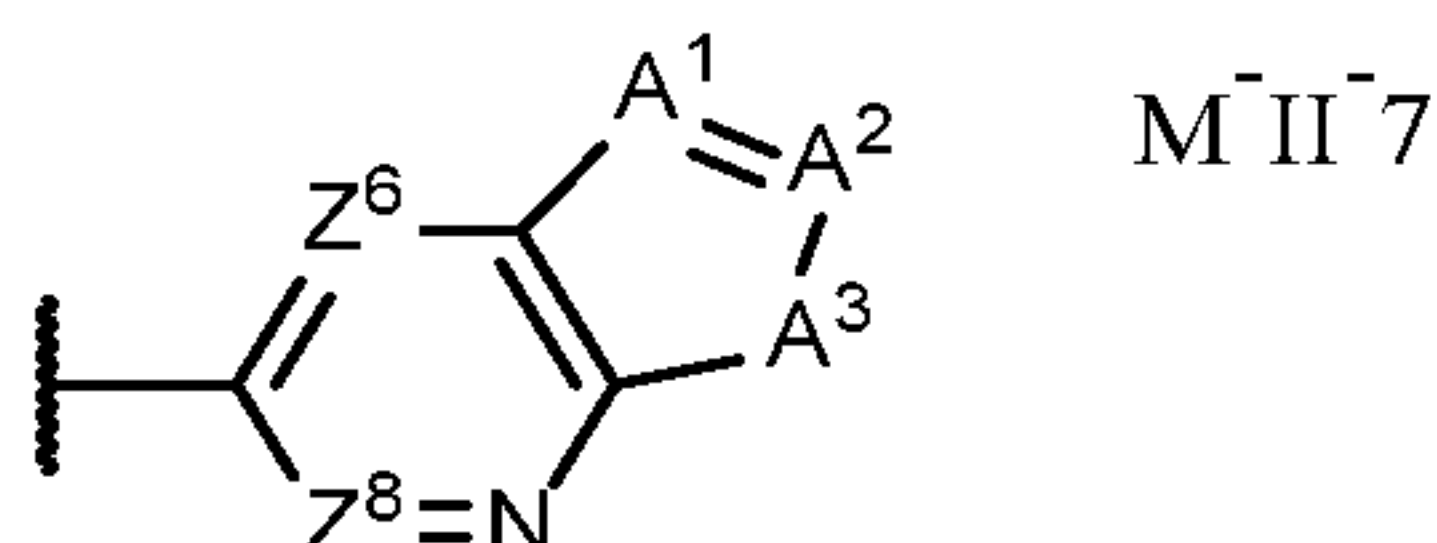


37. The compound of claim 36, wherein Z^6 and Z^9 independently represent CR^7 .

38. The compound of claim 21, wherein M-II represents a moiety represented by:

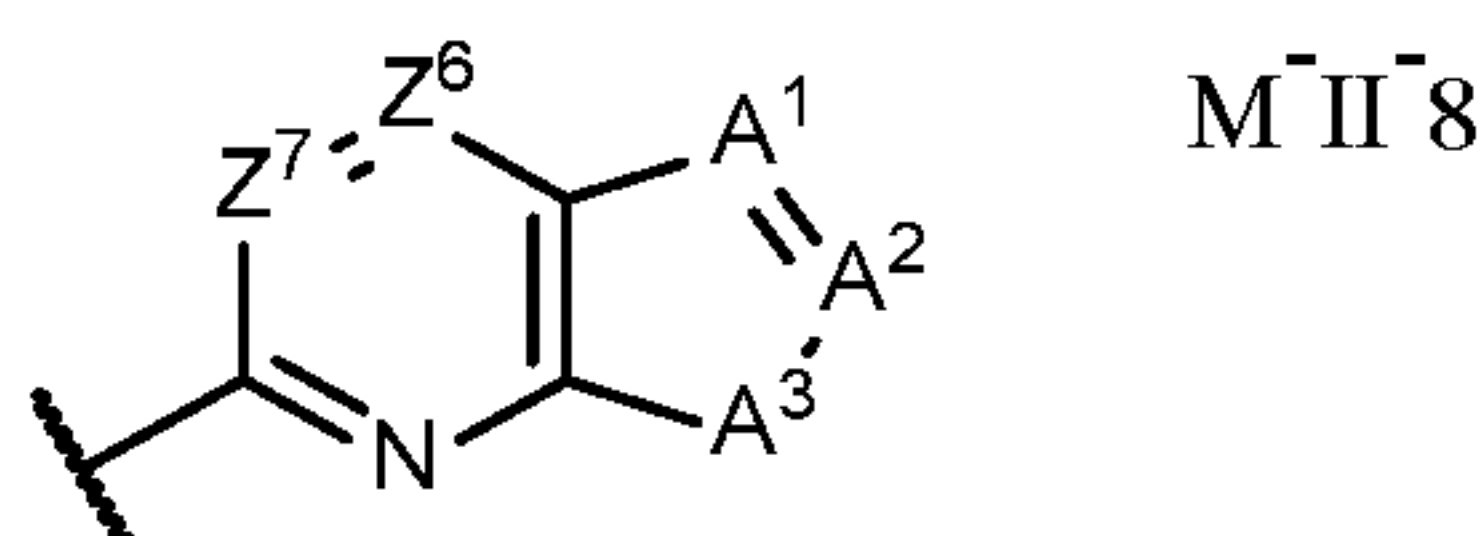


39. The compound of claim 38, wherein M-II represents a moiety represented by ring system M-II-7:



40. The compound of claim 39, wherein Z^6 and Z^8 independently represent CR^7 .

41. The compound of claim 38, wherein M-II represents a moiety represented by ring system M-II-8:



42. The compound of claim 41, wherein Z^6 and Z^7 independently represent CR^7 .

43. The compound of any one of claims 21-42, wherein A^1 and A^2 independently represent CR^{11} .

44. The compound of any one of claims 21-42, wherein A^1 represents N and A^2 represents CR^{11} .

45. The compound of any one of claims 21-44, wherein A^3 represents NR^{10} .

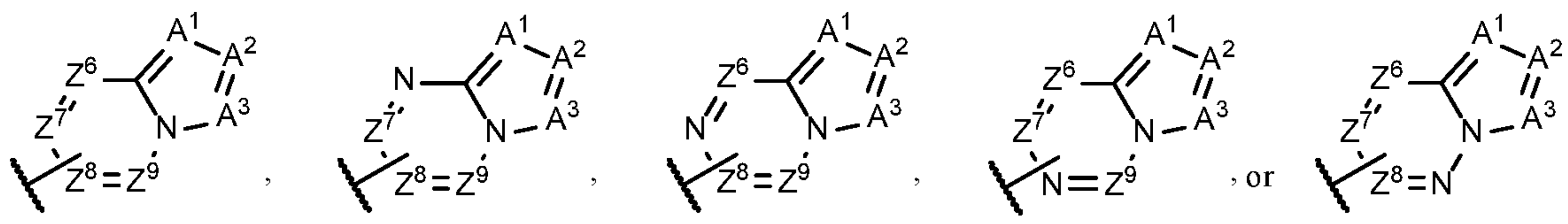
46. The compound of any one of claims 21-44, wherein A^3 represents O.

47. The compound of any one of claims 21-44, wherein A^3 represents S.

48. The compound of any one of claims 21-47, wherein R^7 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-OR^8$; $-OCF_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; wherein the C_1 - C_6 -alkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^8$, $-(CH_2)_mOR^8$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, a C_1 - C_6 -hydroxyalkyl radical, or a C_1 - C_6 -haloalkyl radical.

49. The compound of any one of claims 21-47, wherein R^7 independently represents $-H$ or $-D$.
50. The compound of any one of claims 21-49, wherein R^{11} independently represents $-H$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-OR^{12}$; $-(CH_2)_mOR^{12}$; $-OCF_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; or a C_3 - C_6 -cycloalkyl radical.
51. The compound of any one of claims 21-49, wherein R^{11} independently represents $-H$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-OR^{12}$; $-(CH_2)_mOR^{12}$; $-OCF_3$; a C_1 - C_4 -alkyl radical; or a C_1 - C_2 -haloalkyl radical.
52. The compound of any one of claims 21-49, wherein R^{11} independently represents $-H$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-OR^{12}$; $-OCF_3$; a C_1 - C_4 -alkyl radical; $-CF_3$; or a C_3 - C_4 -cycloalkyl radical.
53. The compound of any one of claims 21-52, wherein R^{12} independently represents $-H$, a branched or unbranched C_1 - C_4 -alkyl radical, or a C_3 - C_6 -cycloalkyl radical.
54. The compound of claim 19, wherein X^1 represents N.

55. The compound of claim 54, wherein M-II represents a moiety represented by one of the following:



wherein A^1 , A^2 , and A^3 , independently represent N or CR^{11} .

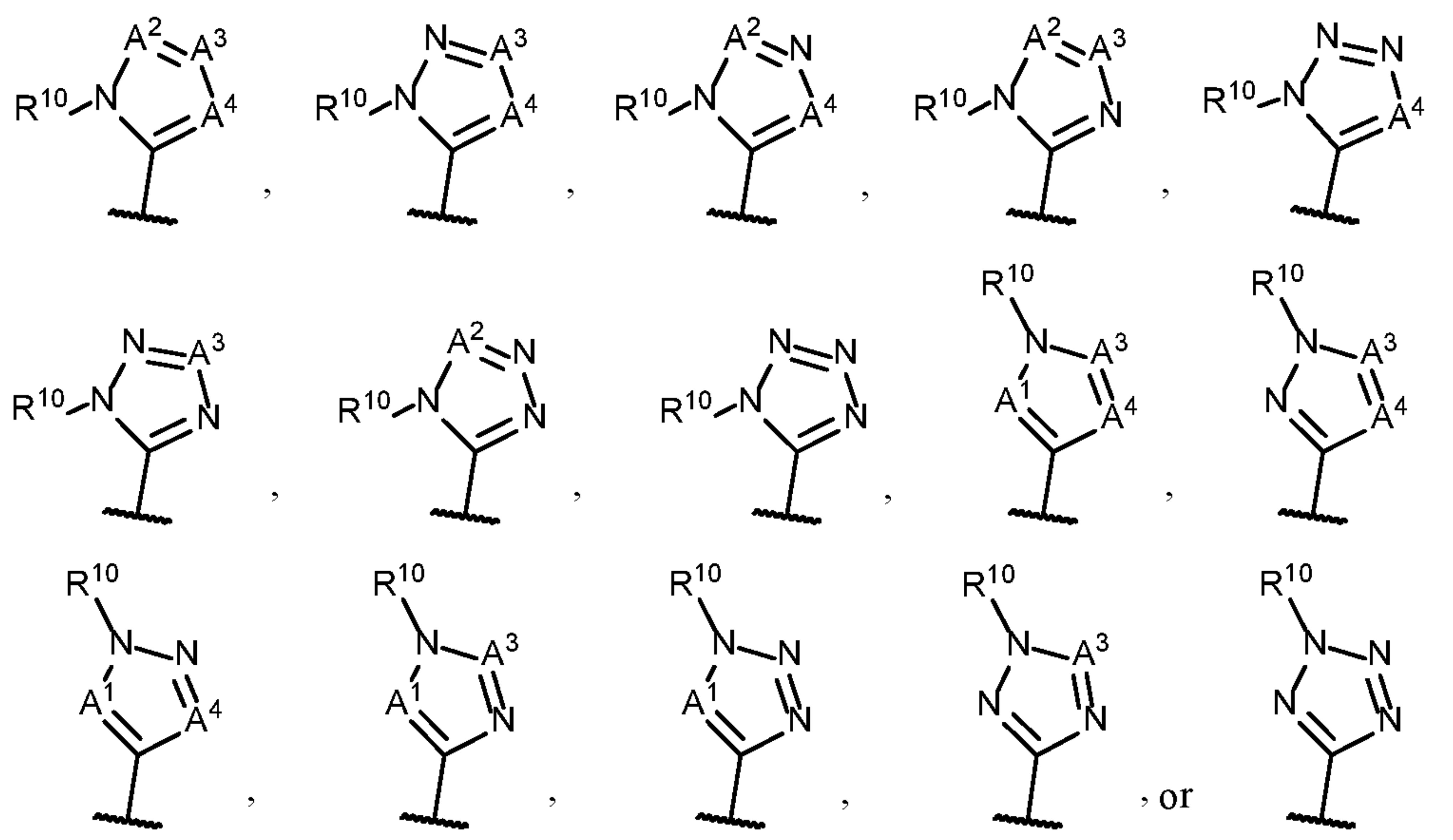
56. The compound of claim 55, wherein A^1 represents CR^{11} ; and A^2 and A^3 independently represent N or CR^{11} .
57. The compound of claim 55, wherein A^2 represents CR^{11} ; and A^1 and A^3 independently represent N or CR^{11} .
58. The compound of claim 55, wherein A^3 represents CR^{10} ; and A^1 and A^2 independently represent N or CR^{11} .
59. The compound of claim 55, wherein each of A^1 , A^2 , and A^3 , represents N.

60. The compound of any one of claims 54-59, wherein either Z^6 or Z^7 represents CR^7 with said R^7 representing the bond directly attaching the W moiety with the carbonyl moiety.

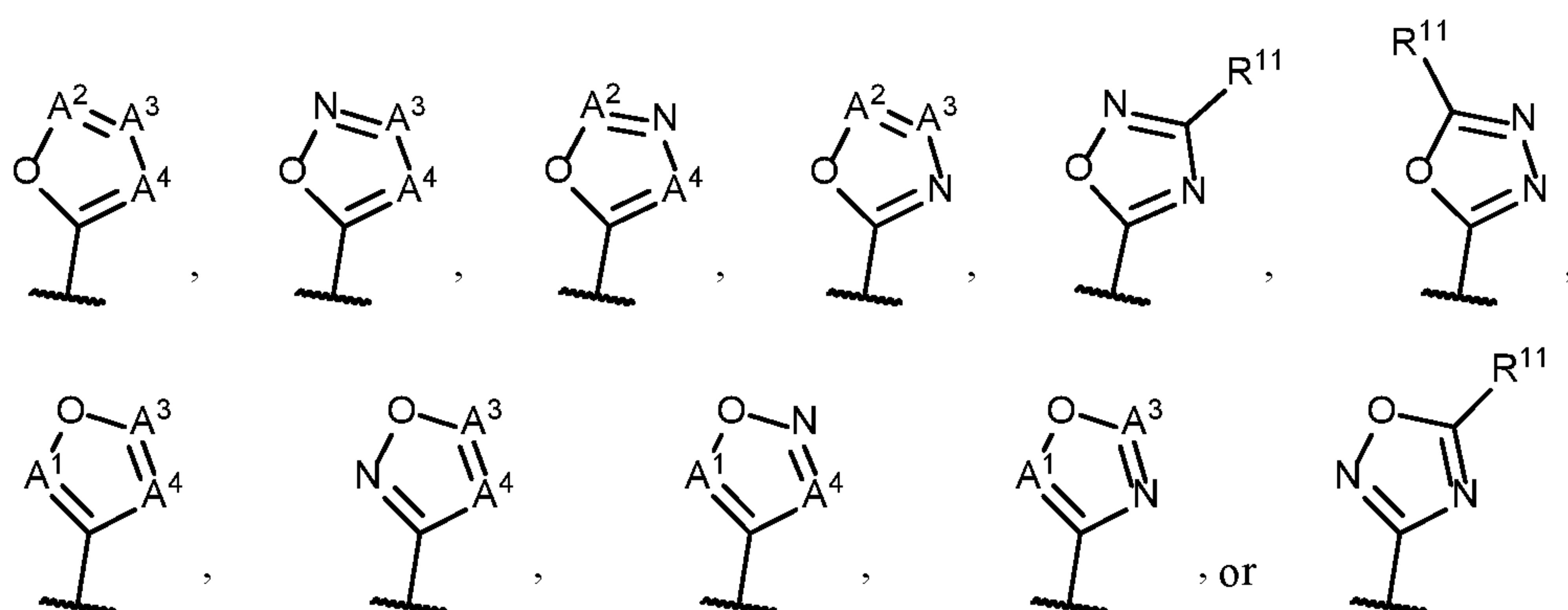
61. The compound of any one of claims 54-59, wherein either Z^8 or Z^9 represents CR^7 with said R^7 representing the bond directly attaching the W moiety with the carbonyl moiety.

62. The compound of claim 1 or claim 2, wherein W represents the moiety represented by the ring system M-III.

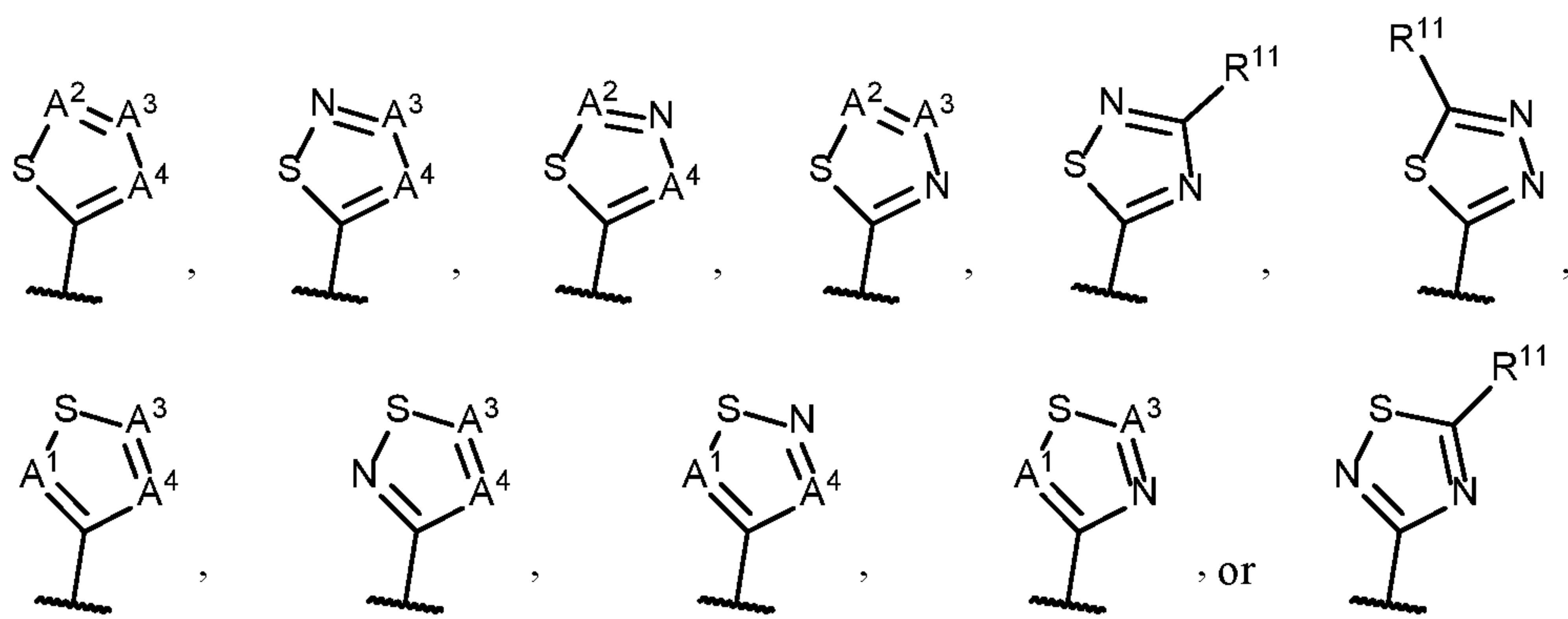
63. The compound of claim 62, wherein M-III represents a moiety represented by one of the following:



64. The compound of claim 62, wherein M-III represents a moiety represented by one of the following:



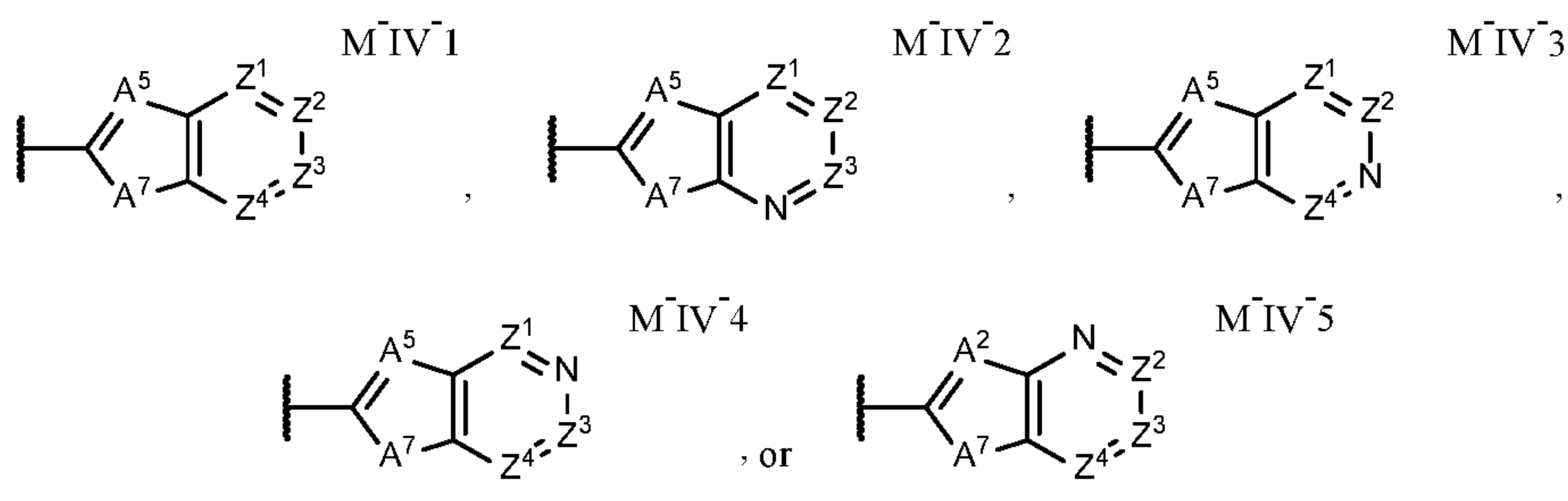
65. The compound of claim 62, wherein M-III represents a moiety represented by one of the following:



66. The compound of claim 1 or claim 2, wherein W represents the moiety represented by the ring system M-IV.

67. The compound of claim 66, wherein X^2 represents C.

68. The compound of claim 67, wherein M-IV represents a moiety represented by one of the following:

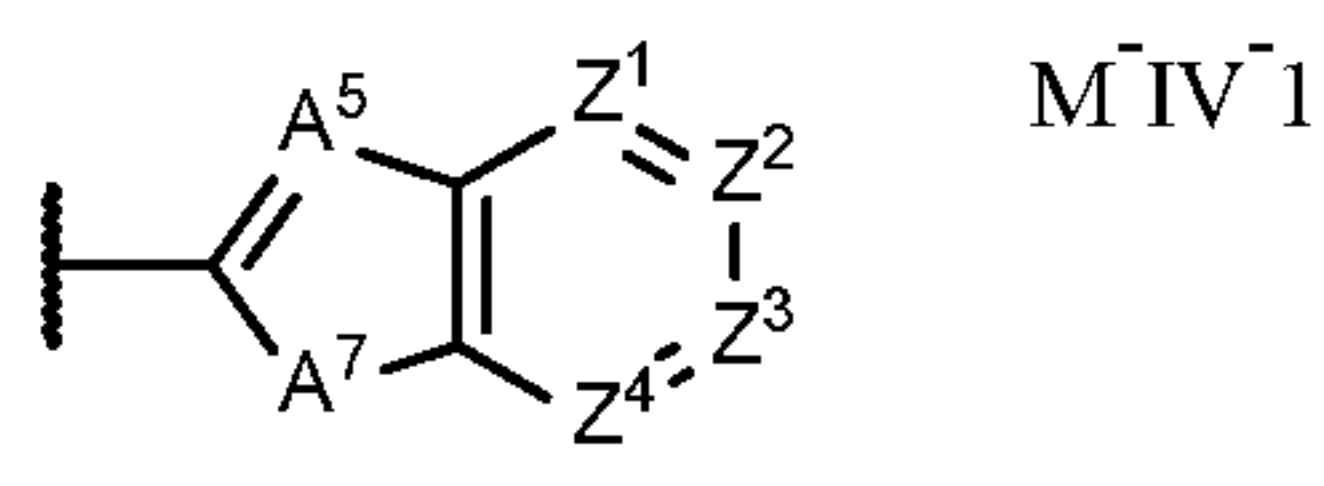


wherein:

A^5 represents N or CR^{15} ; and

A^7 represents NR^{14} ; $N(CH_2)_mR^{14}$; O; or S.

69. The compound of claim 68, wherein M-IV represents a moiety represented by ring system M-IV-1:



wherein Z^1 , Z^2 , Z^3 , and Z^4 independently represent CR^4 .

70. The compound of any one of claims 66-69, wherein A^5 represents CR^{15} .

71. The compound of any one of claims 66-69, wherein A^5 represents N.

72. The compound of any one of claims 66-71, wherein A^7 represents NR^{14} .
73. The compound of any one of claims 66-71, wherein A^7 represents $N(CH_2)_mR^{14}$.
74. The compound of any one of claims 66-71, wherein A^7 represents O.
75. The compound of any one of claims 66-71, wherein A^7 represents S.
76. The compound of any one of claims 66-75, wherein R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-I$; $-CN$; $-NO_2$; $-OR^5$; $-N(R^5)(R^6)$; $-SO_2(CH_2)_mR^5$; $-OCF_3$; a C_1 - C_6 -alkyl radical; a C_1 - C_6 -haloalkyl radical; a C_3 - C_6 -cycloalkyl radical; a (3-6 membered)-heterocycloalkyl radical; or a heteroaryl radical; wherein the C_1 - C_6 -alkyl radical, the (3-6 membered)-heterocycloalkyl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^5$, $-N(R^5)(R^6)$, $-SO_2(CH_2)_mR^5$, $-OCF_3$, a branched or unbranched C_1 - C_6 -alkyl radical, a C_3 - C_6 -cycloalkyl radical, a C_1 - C_6 -hydroxyalkyl radical, or a C_1 - C_6 -haloalkyl radical.
77. The compound of any one of claims 66-76, wherein R^5 and R^6 independently represent $-H$; a branched or unbranched C_1 - C_3 -alkyl radical; or a C_3 - C_6 -cycloalkyl radical.
78. The compound of any one of claims 66-77, wherein:
 Z^1 and Z^2 independently represent CH ; and
 Z^3 and Z^4 independently represent CR^4 , wherein R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-CN$; $-OR^5$; $-N(R^5)(R^6)$; $-SO_2(CH_2)_mR^5$; $-OCF_3$; a C_1 - C_4 -alkyl radical; $-CF_3$; a C_3 - C_4 -cycloalkyl radical; a 6 membered-heterocycloalkyl radical; or a heteroaryl radical; wherein the C_1 - C_4 -alkyl radical, the 6 membered-heterocycloalkyl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^5$, $-N(R^5)(R^6)$, $-SO_2(CH_2)_mR^5$, $-OCF_3$, a branched or unbranched C_1 - C_4 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, a C_1 - C_4 -hydroxyalkyl radical, or a C_1 - C_2 -haloalkyl radical.
79. The compound of any one of claims 66-77, wherein:
 Z^1 , Z^2 , and Z^4 independently represent CH ; and
 Z^3 represents CR^4 , wherein R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-CN$; $-OR^5$; $-N(R^5)(R^6)$; $-SO_2(CH_2)_mR^5$; $-OCF_3$; a C_1 - C_4 -alkyl radical; $-CF_3$; a C_3 - C_4 -cycloalkyl radical; a 6 membered-heterocycloalkyl radical; or a heteroaryl radical; wherein the C_1 - C_4 -alkyl radical, the 6 membered-heterocycloalkyl

radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^5$, $-N(R^5)(R^6)$, $-SO_2(CH_2)_mR^5$, $-OCF_3$, a branched or unbranched C_1 - C_4 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, a C_1 - C_4 -hydroxyalkyl radical, or a C_1 - C_2 -haloalkyl radical.

80. The compound of any one of claims 66-77, wherein:

Z^1 , Z^2 , and Z^4 independently represent CH ; and

Z^3 represents CR^4 , wherein R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-OR^5$; $-N(R^5)(R^6)$; $-OCF_3$; a C_1 - C_4 -alkyl radical; $-CF_3$; or a C_3 - C_4 -cycloalkyl radical; wherein the C_1 - C_4 -alkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, a branched or unbranched C_1 - C_4 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, a C_1 - C_4 -hydroxyalkyl radical, or a C_1 - C_2 -haloalkyl radical; and wherein R^5 and R^6 independently represent $-H$; a branched or unbranched C_1 - C_3 -alkyl radical; or a C_3 - C_6 -cycloalkyl radical.

81. The compound of any one of claims 66-77, wherein:

Z^1 , Z^2 , and Z^4 independently represent CH ; and

Z^3 represents CR^4 , wherein R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-OCH_3$; $-NH_2$; $-CH_3$; $-CF_3$; or a cyclopropyl radical.

82. The compound of any one of claims 66-77, wherein:

Z^1 , Z^2 , and Z^4 independently represent CH ; and

Z^3 represents CR^4 , wherein R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-OCH_3$; $-CH_3$; or a cyclopropyl radical.

83. The compound of any one of claims 66-77, wherein:

Z^1 , Z^2 , and Z^3 independently represent CH ; and

Z^4 represents CR^4 , wherein R^4 independently represents $-H$; $-D$; $-F$; $-Cl$; $-Br$; $-CN$; $-OR^5$; $-N(R^5)(R^6)$; $-SO_2(CH_2)_mR^5$; $-OCF_3$; a C_1 - C_4 -alkyl radical; $-CF_3$; a C_3 - C_4 -cycloalkyl radical; a 6 membered-heterocycloalkyl radical; or a heteroaryl radical; wherein the C_1 - C_4 -alkyl radical, the 6 membered-heterocycloalkyl radical, and the heteroaryl radical may be substituted with up to 4 radical substituents comprising: $-D$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^5$, $-N(R^5)(R^6)$, $-SO_2(CH_2)_mR^5$, $-OCF_3$, a branched or unbranched C_1 - C_4 -alkyl radical, a C_3 - C_4 -cycloalkyl radical, a C_1 - C_4 -hydroxyalkyl radical, or a C_1 - C_2 -haloalkyl radical.

84. The compound of any one of claims 66-77, wherein:

Z^1 , Z^2 , and Z^3 independently represent CH; and
 Z^4 represents CR^4 , wherein R^4 independently represents -H; -D; -F; -Cl; -Br; -OR⁵; -N(R⁵)(R⁶); -OCF₃; a C₁-C₄-alkyl radical; -CF₃; or a C₃-C₄-cycloalkyl radical; wherein the C₁-C₄-alkyl radical may be substituted with up to 4 radical substituents comprising: -D, -F, a branched or unbranched C₁-C₄-alkyl radical, a C₃-C₄-cycloalkyl radical, a C₁-C₄-hydroxyalkyl radical, or a C₁-C₂-haloalkyl radical; and wherein R⁵ and R⁶ independently represent -H; a branched or unbranched C₁-C₃-alkyl radical; or a C₃-C₆-cycloalkyl radical.

85. The compound of any one of claims 66-77, wherein:

Z^1 , Z^2 , and Z^3 independently represent CH; and
 Z^4 represents CR^4 , wherein R^4 independently represents -H; -D; -F; -Cl; -Br; -OCH₃; -NH₂; -CH₃; -CF₃; or a cyclopropyl radical.

86. The compound of any one of claims 66-77, wherein:

Z^1 , Z^2 , and Z^3 independently represent CH; and
 Z^4 represents CR^4 , wherein R^4 independently represents -F; -Cl; -OCH₃; -CH₃; -CF₃; or a cyclopropyl radical.

87. The compound of any one of claims 66-77, wherein:

Z^1 , Z^2 , and Z^3 independently represent CH; and
 Z^4 represents CR^4 , wherein R^4 independently represents -H; -F; -CN; -OCH₂CH₃; -OCF₃; or a cyclopropyl radical.

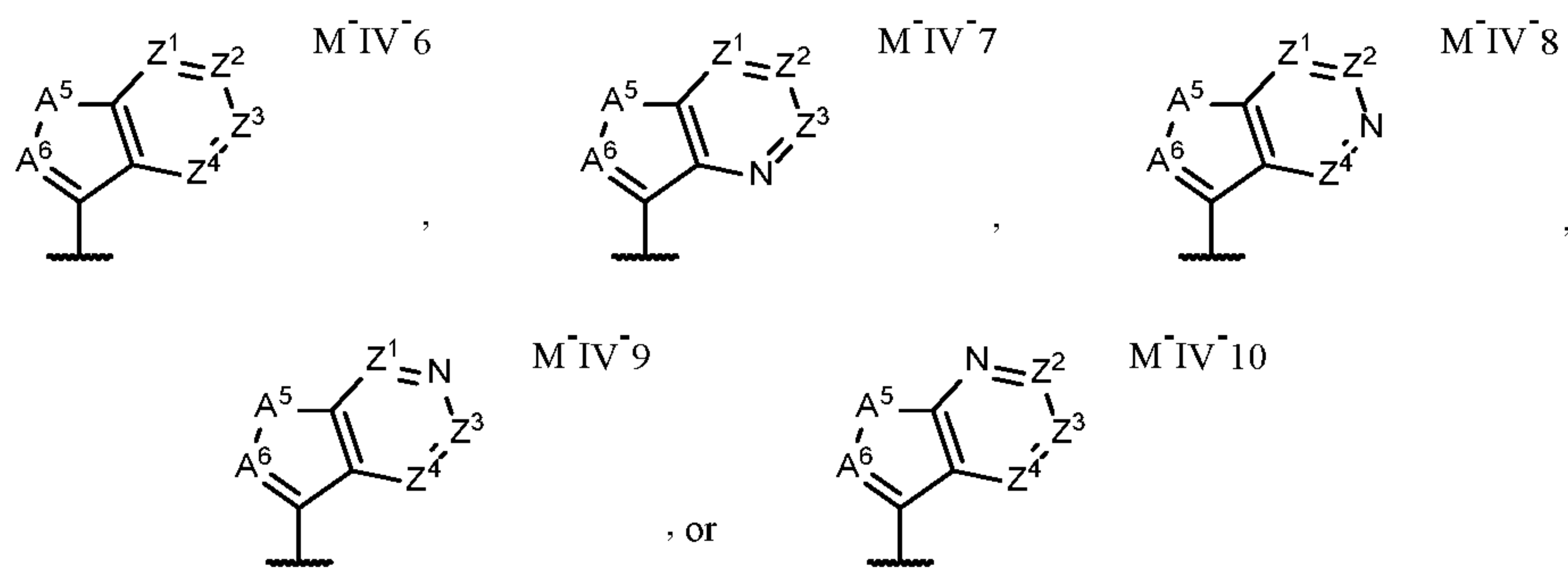
88. The compound of any one of claims 66-77, wherein:

Z^1 independently represent CH;
 Z^2 represents CR^4 , wherein R^4 independently represents -H or -F;
 Z^3 represents CR^4 , wherein R^4 independently represents -H; -D; -Cl; -Br; -OCH₃; -CH₃; or a cyclopropyl radical; and
 Z^4 represents CR^4 , wherein R^4 independently represents -H; -D; -F; -Cl; -CN; -OCH₂CH₃; -OCF₃; or a cyclopropyl radical.

89. The compound of any one of claims 66-77, wherein:

Z^1 and Z^2 independently represent CH;
 Z^3 represents CR^4 , wherein R^4 independently represents -Cl or -CH₃; and
 Z^4 represents CR^4 , wherein R^4 independently represents -F or -Cl.

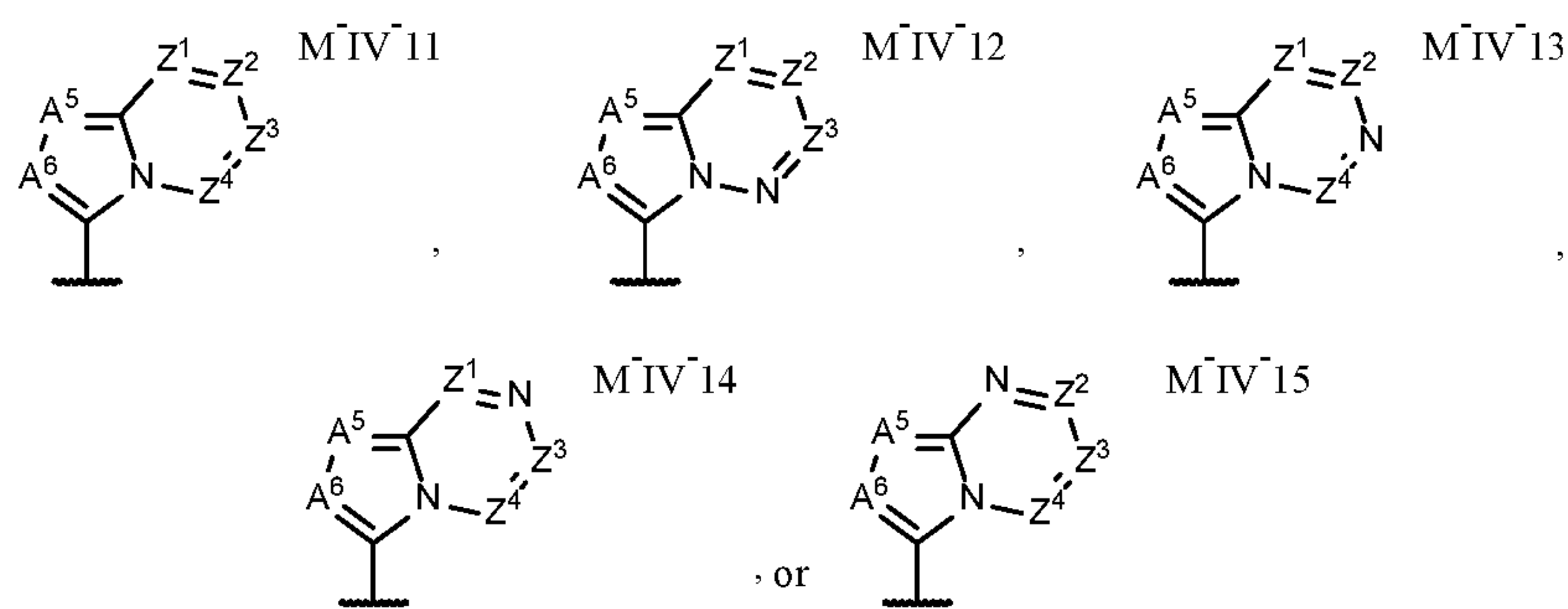
90. The compound of claim 67, wherein M-IV represents a moiety represented by one of the following:



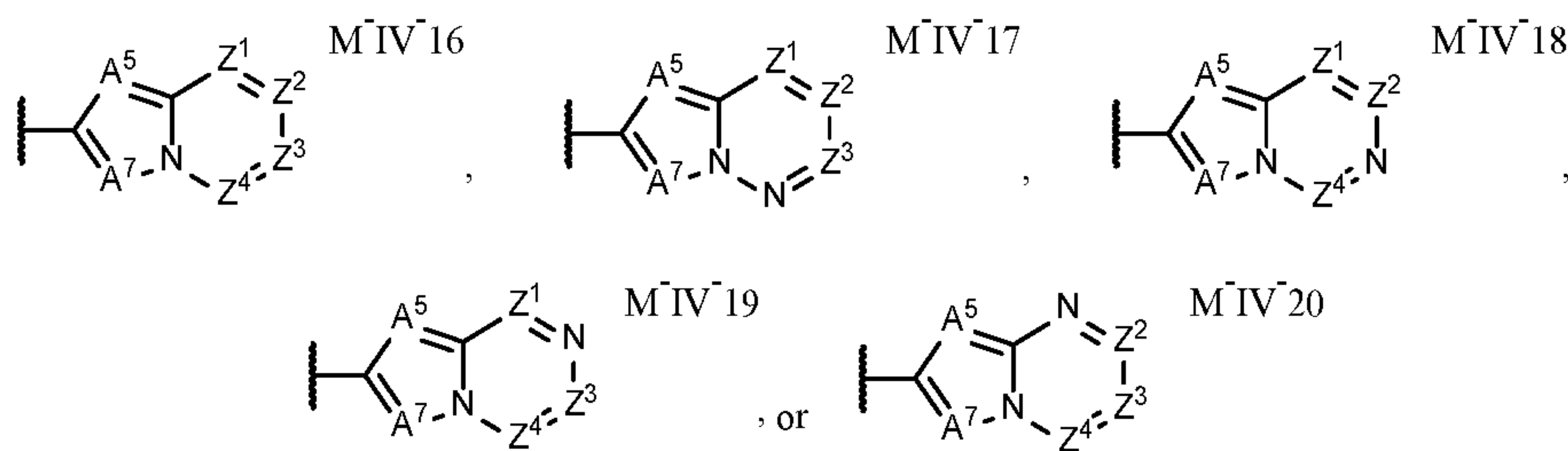
wherein A⁵ represents NR¹⁴; O; or S.

91. The compound of claim 66, wherein X² represents N.

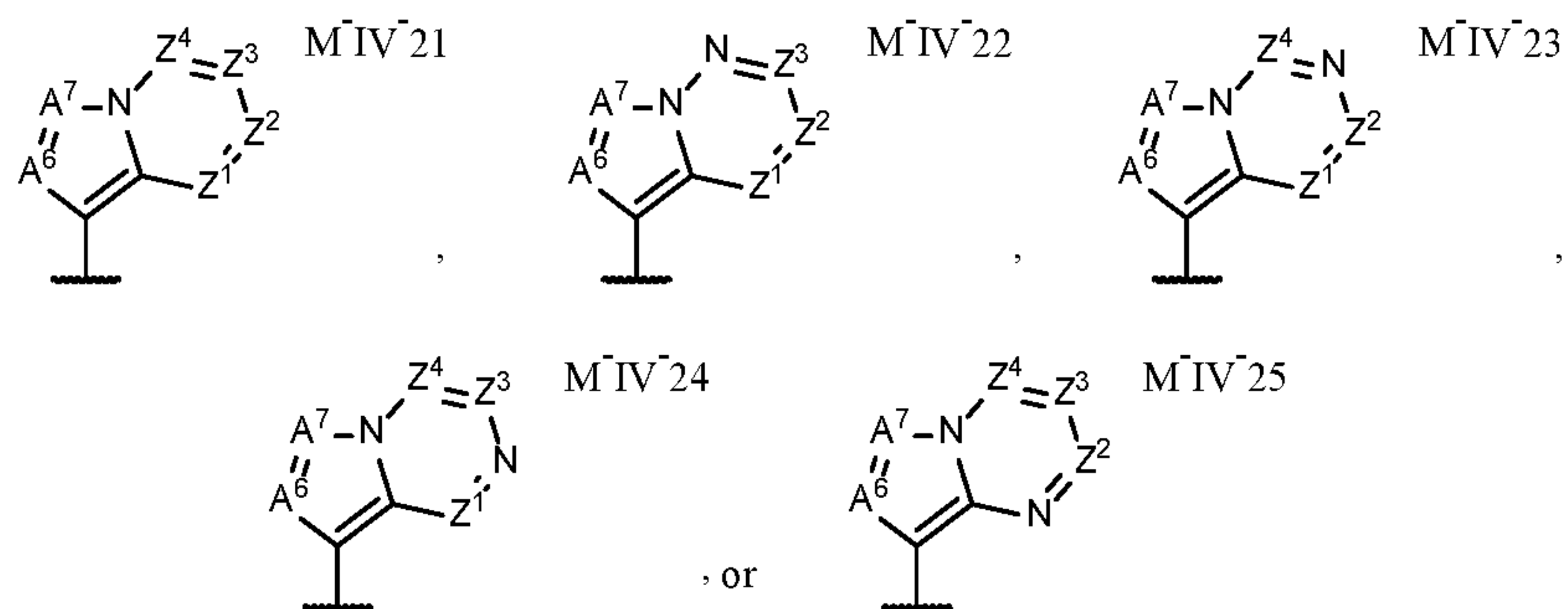
92. The compound of claim 91, wherein M-IV represents a moiety represented by one of the following:



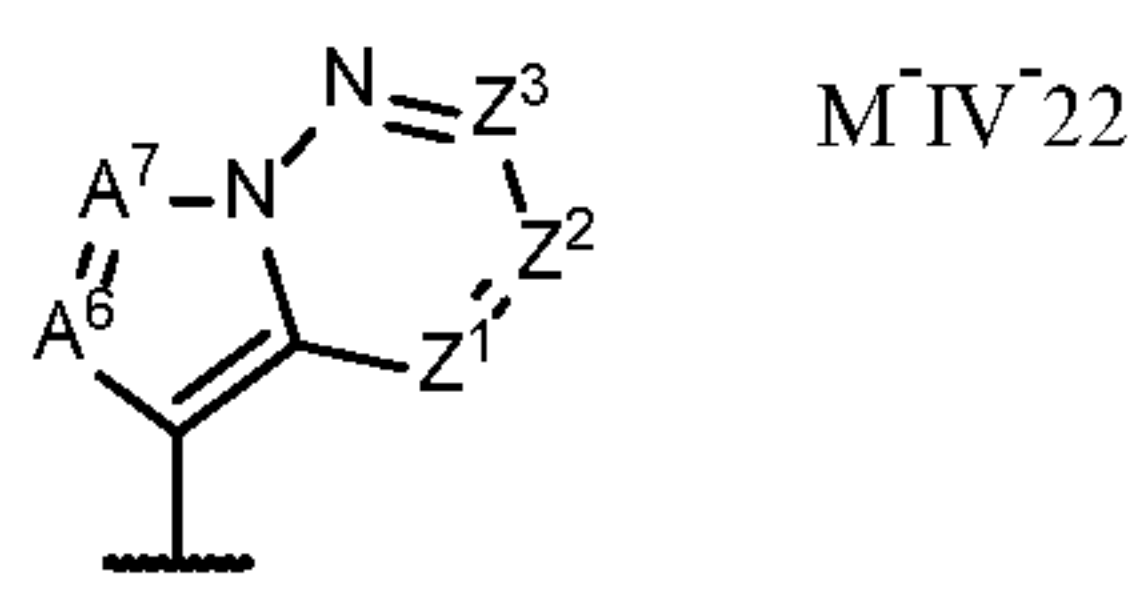
93. The compound of claim 91, wherein M-IV represents a moiety represented by one of the following:



94. The compound of claim 91, wherein M-IV represents a moiety represented by one of the following:



95. The compound of claim 94, wherein M-IV represents a moiety represented by ring system M-IV-22:

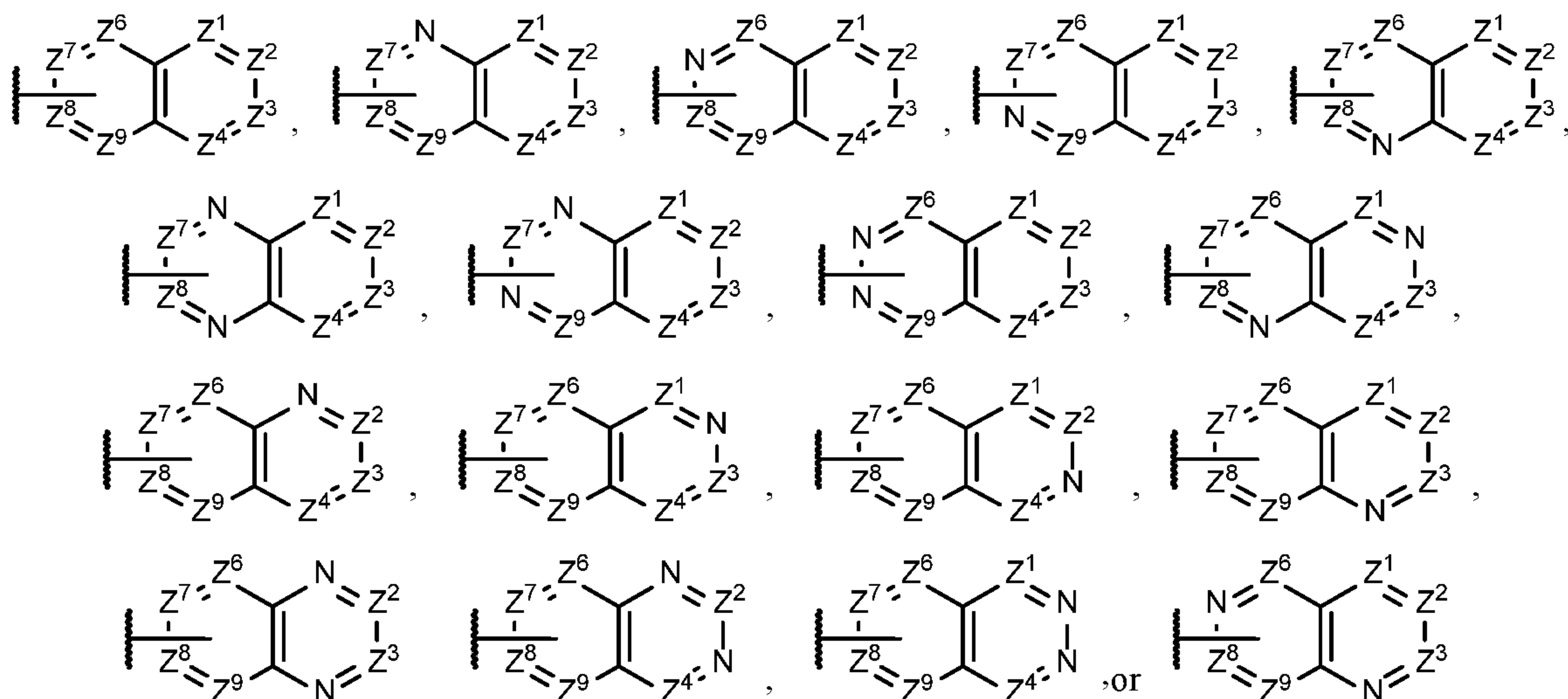


wherein:

Z^1 , Z^2 , and Z^3 independently represent CR^4 ;
 A^6 represents CR^{15} ; and
 A^7 represents N.

96. The compound of claim 1 or claim 2, wherein W represents the moiety represented by the ring system M-V.

97. The compound of claim 96, wherein M-V represents a moiety represented by one of the following:



98. The compound of any one of claims 1, 3, 66-75, or 90-97, wherein adjacent members Z^1 and Z^2 is $(CR^4)(CR^4)$, and the $(CR^4)(CR^4)$ forms a cycle such that the adjacent R^4 substituents taken

together represents a (3-6 membered)-heteroalkyl di-radical with at least one ring atom of the (3-6 membered)-heteroalkyl di-radical selected from the group consisting of oxygen, nitrogen, and sulfur, with the proviso that when the at least one ring atom is nitrogen, the nitrogen is substituted with $-H$, a branched or unbranched C_1-C_4 -alkyl radical, a C_3-C_4 -cycloalkyl radical, $-(CO)$ -branched or unbranched C_1-C_4 -alkyl, or $-(SO_2)$ -branched or unbranched C_1-C_4 -alkyl, wherein the C_1-C_4 -alkyl radical and the C_3-C_4 -cycloalkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, halogen, $=O$, $-OH$, $-OC_1-C_4$ -alkyl or $-OCF_3$, and with the further proviso that when the at least one ring atom is sulfur, the sulfur may substituted with 0 or 2 $=O$.

99. The compound of any one of claims 1, 3, 66-75, or 90-97, wherein adjacent members Z^2 and Z^3 is $(CR^4)(CR^4)$, and the $(CR^4)(CR^4)$ forms a cycle such that the adjacent R^4 substituents taken together represents a (3-6 membered)-heteroalkyl di-radical with at least one ring atom of the (3-6 membered)-heteroalkyl di-radical selected from the group consisting of oxygen, nitrogen, and sulfur, with the proviso that when the at least one ring atom is nitrogen, the nitrogen is substituted with $-H$, a branched or unbranched C_1-C_4 -alkyl radical, a C_3-C_4 -cycloalkyl radical, $-(CO)$ -branched or unbranched C_1-C_4 -alkyl, or $-(SO_2)$ -branched or unbranched C_1-C_4 -alkyl, wherein the C_1-C_4 -alkyl radical and the C_3-C_4 -cycloalkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, halogen, $=O$, $-OH$, $-OC_1-C_4$ -alkyl or $-OCF_3$, and with the further proviso that when the at least one ring atom is sulfur, the sulfur may substituted with 0 or 2 $=O$.

100. The compound of any one of claims 1, 3, 66-75, or 90-97, wherein adjacent members Z^3 and Z^4 is $(CR^4)(CR^4)$, and the $(CR^4)(CR^4)$ forms a cycle such that the adjacent R^4 substituents taken together represents a (3-6 membered)-heteroalkyl di-radical with at least one ring atom of the (3-6 membered)-heteroalkyl di-radical selected from the group consisting of oxygen, nitrogen, and sulfur, with the proviso that when the at least one ring atom is nitrogen, the nitrogen is substituted with $-H$, a branched or unbranched C_1-C_4 -alkyl radical, a C_3-C_4 -cycloalkyl radical, $-(CO)$ -branched or unbranched C_1-C_4 -alkyl, or $-(SO_2)$ -branched or unbranched C_1-C_4 -alkyl, wherein the C_1-C_4 -alkyl radical and the C_3-C_4 -cycloalkyl radical may be substituted with up to 4 radical substituents comprising: $-D$, halogen, $=O$, $-OH$, $-OC_1-C_4$ -alkyl or $-OCF_3$, and with the further proviso that when the at least one ring atom is sulfur, the sulfur may substituted with 0 or 2 $=O$.

101. The compound of any one of claims 1, 3, 66-75, or 90-97, wherein adjacent members Z^4 and Z^5 is $(CR^4)(CR^4)$, and the $(CR^4)(CR^4)$ forms a cycle such that the adjacent R^4 substituents taken together represents a (3-6 membered)-heteroalkyl di-radical with at least one ring atom of the (3-6 membered)-heteroalkyl di-radical selected from the group consisting of oxygen, nitrogen, and sulfur, with the proviso that when the at least one ring atom is nitrogen, the nitrogen is substituted with $-H$, a branched or unbranched C_1-C_4 -alkyl radical, a C_3-C_4 -cycloalkyl radical, $-(CO)$ -branched or

unbranched C₁-C₄-alkyl, or -(SO₂)-branched or unbranched C₁-C₄-alkyl, wherein the C₁-C₄-alkyl radical and the C₃-C₄-cycloalkyl radical may be substituted with up to 4 radical substituents comprising: -D, halogen, =O, -OH, -OC₁-C₄-alkyl or -OCF₃, and with the further proviso that when the at least one ring atom is sulfur, the sulfur may substituted with 0 or 2 =O.

102. The compound of any one of claims 98-101, wherein the (3-6 membered)-heteroalkyl di-radical is: -OCH₂CH₂CH₂-, -OCH₂CH₂N(H)-, -OCH₂CH₂N(C₁-C₄-alkyl)-, -N(H)CH₂CH₂O-, -N(C₁-C₄-alkyl)CH₂CH₂O-, -OCH₂CH₂O-, -OCF₂O-, or -CH₂CH₂CH₂O-.

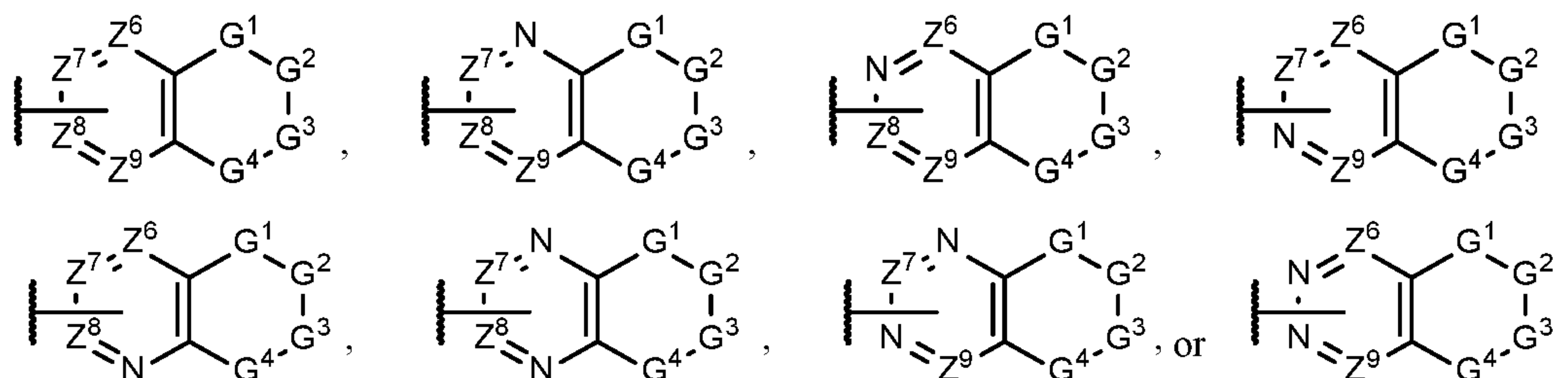
103. The compound of any one of claims 98-102, wherein M-IV represents a moiety represented by ring system M-IV-1.

104. The compound of any one of claims 98-103, wherein A⁵ represents CR¹⁵.

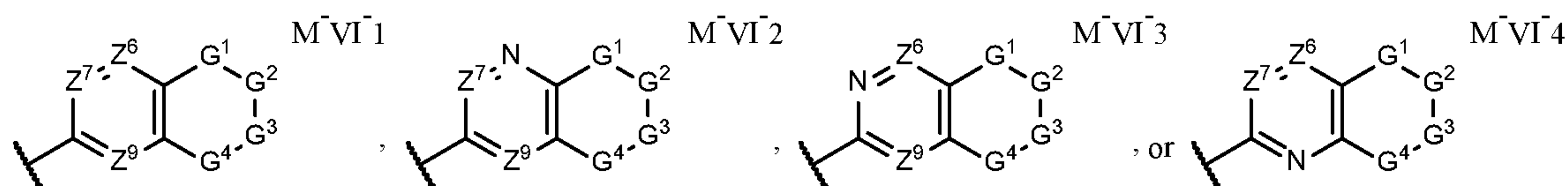
105. The compound of any one of claims 98-104, wherein A⁷ represents O or S.

106. The compound of claim 1 or claim 2, wherein W represents the moiety represented by the ring system M-VI.

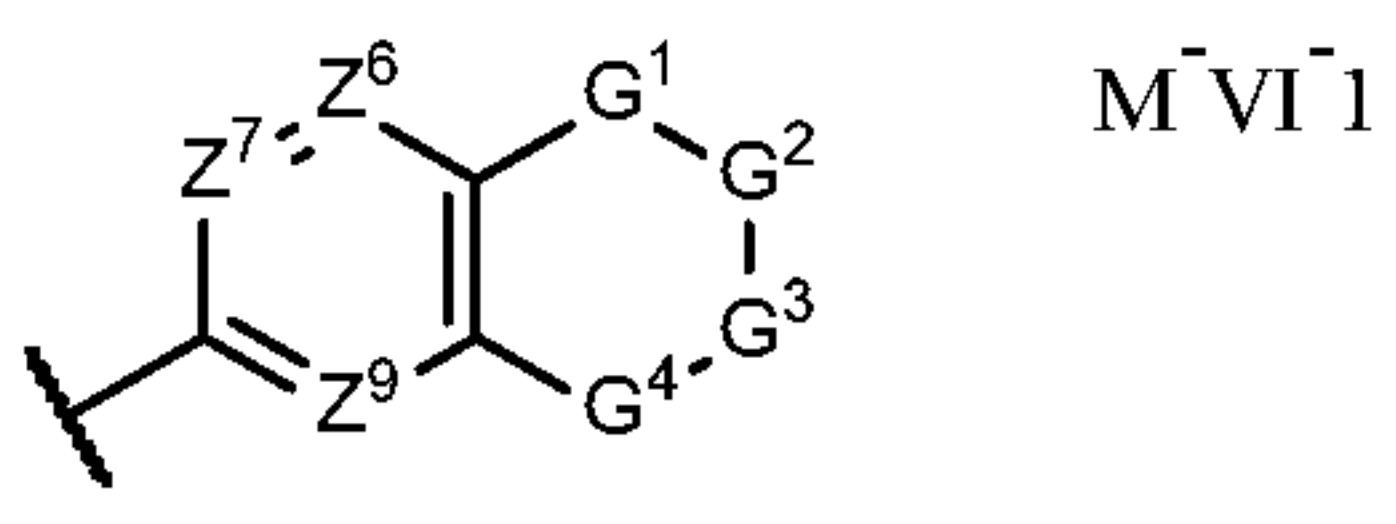
107. The compound of claim 106, wherein M-VI represents a moiety represented by one of the following:



108. The compound of claim 107, wherein M-VI represents a moiety represented by one of the following:

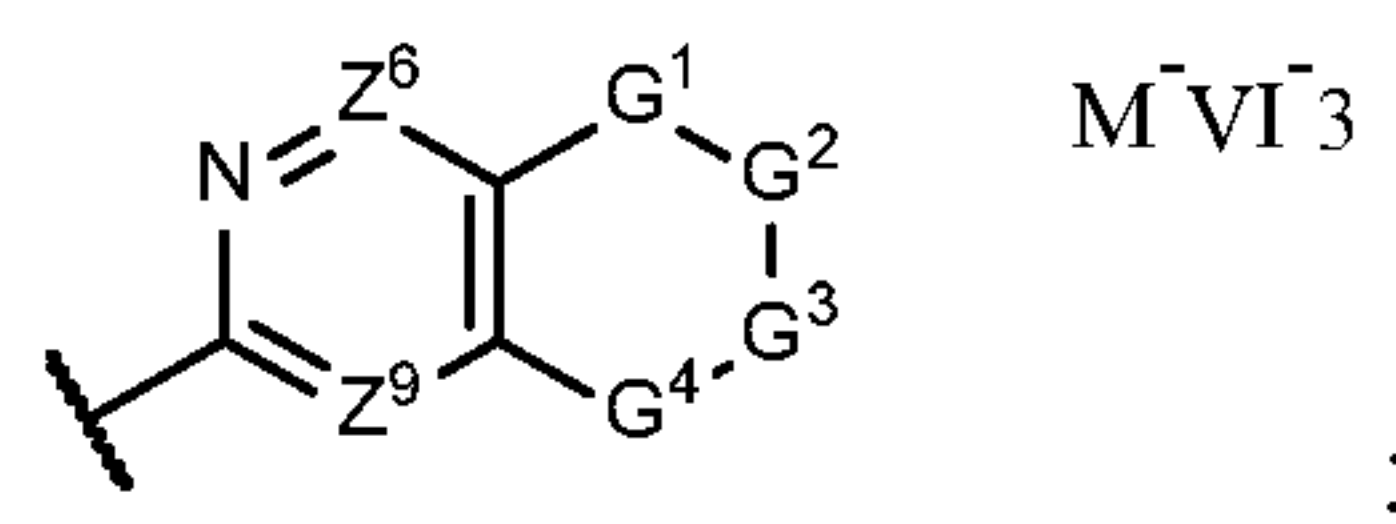


109. The compound of claim 107, wherein M-VI represents a moiety represented by ring system M-VI-1:



wherein Z^6 , Z^7 , and Z^9 independently represent CR^7 .

110. The compound of claim 107, wherein M-VI represents a moiety represented by ring system M-VI-3:

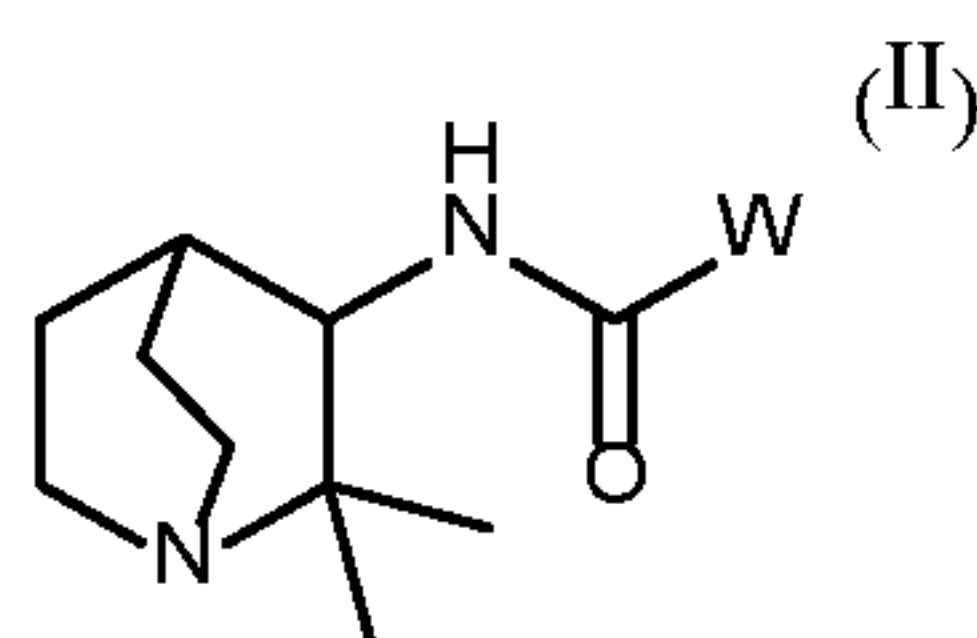


wherein Z^6 and Z^9 independently represent CR^7 .

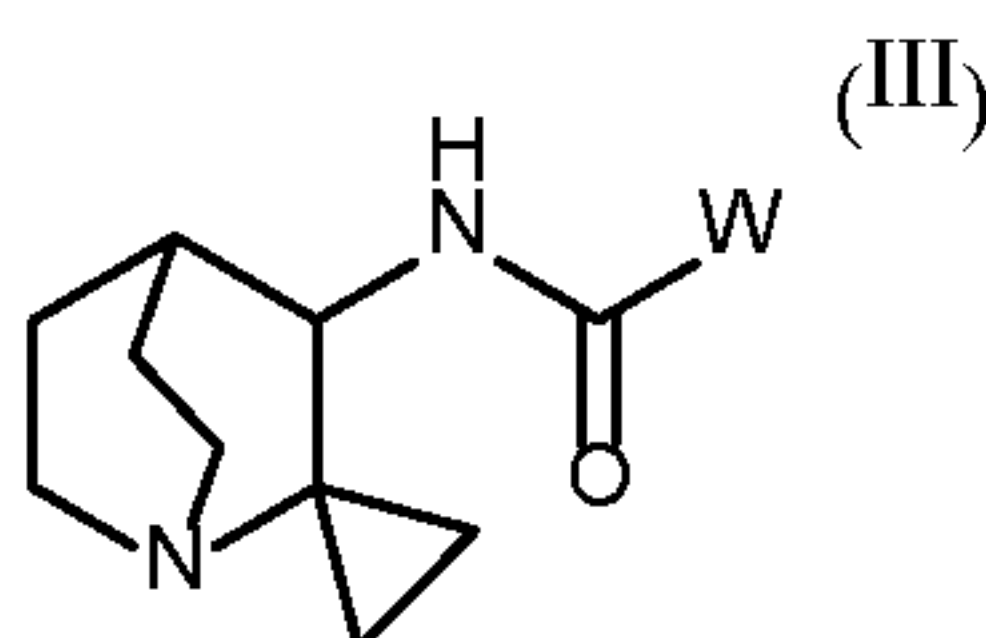
111. The compound of any one of claims 106-110, wherein G^1 and G^4 independently represent $-NH$ or O ; and G^2 and G^3 independently represent $C(R^{18})(R^{18})$.

112. The compound of any one of claims 106-110, wherein G^1 and G^4 independently represent O ; and G^2 and G^3 independently represent $C(R^{18})(R^{18})$, wherein R^{18} independently represents $-H$.

113. The compound of any one of claims 1-112, wherein R^1 and R^2 independently represent an unbranched C_1 -alkyl radical and said compound is represented by Formula (II):



114. The compound of any one of claims 1-112, wherein R^1 and R^2 taken together represent a C_2 -alkyl di-radical and said compound is represented by Formula (III):



115. The compound of any one of claims 1-114, wherein the compound is a single enantiomer or a single diastereomer.

116. The compound of claim 115, wherein the compound is a single enantiomer.

117. The compound of claim 115, wherein the compound is a single diastereomer.

118. The compound of any one of claims 1-117, wherein the compound is selected from the group consisting of:

N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 4-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzamide;
 7-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;
 6-cyano-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;
 6-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 5-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 5,6-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-5-methylbenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-5-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 5-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-5-methoxybenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-c]pyridine-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzo[b]thiophene-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzo[b]thiophene-6-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-1H-indole-6-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)pyrazolo[1,5-b]pyridazine-3-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-b]pyridine-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)benzo[d]thiazole-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)benzofuran-6-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]oxazole-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]oxazole-6-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]thiazole-5-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]thiazole-6-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-b]pyridine-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)furo[3,2-b]pyridine-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzofuran-5-carboxamide;
 2-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzofuran-5-carboxamide;
 3-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-c]pyridine-5-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-morpholinobenzo[b]thiophene-2-carboxamide;
 6-(4,4-difluoropiperidin-1-yl)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 6-bromo-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-isopropoxybenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-(methylsulfonyl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-nitrobenzo[b]thiophene-2-carboxamide;
 6-amino-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-6-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methoxybenzo[b]thiophene-2-carboxamide;
 7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 4-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;
 7-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-nitro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-amino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

5-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

5,6-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

5-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-5-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

5-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

5-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxamide;

3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-5-carboxamide;

3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1*H*-indole-6-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrazolo[1,5-*b*]pyridazine-3-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*b*]pyridine-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-5-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-6-carboxamide;

2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-5-carboxamide;

2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-6-carboxamide;

2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-5-carboxamide;

2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-6-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-*b*]pyridine-5-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[3,2-*b*]pyridine-5-carboxamide;

2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

3-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-5-carboxamide;

1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-6-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*c*]pyridine-5-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(1*H*-1,2,3-triazol-1-yl)benzo[b]thiophene-2-carboxamide;

6-morpholino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-(4,4-difluoropiperidin-1-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-bromo-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-isopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-(methylsulfonyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(tetrahydro-2*H*-pyran-4-yl)benzo[b]thiophene-2-carboxamide;

7-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide; and

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide;

and single enantiomers and pharmaceutically acceptable salts thereof.

119. The compound of any one of claims 1-117, wherein the compound is selected from the group consisting of:

2-amino-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-d]pyrimidine-6-carboxamide;

6,7-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-fluorobenzo[b]thiophene-2-carboxamide;

6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;

7-cyano-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6,7-difluorobenzo[b]thiophene-2-carboxamide;

7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-isopropylbenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-1H-indole-2-carboxamide;

6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-5-fluoro-6-methoxybenzo[b]thiophene-2-carboxamide;

6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-5,7-difluorobenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-methylbenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

7-(dimethylamino)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)isoquinoline-3-carboxamide;

7-(tert-butyl)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-phenylbenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-(1-methylcyclopropyl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-ethoxybenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-ethoxybenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-propoxybenzo[b]thiophene-2-carboxamide;

6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-methoxy-6-methylbenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-1H-indazole-3-carboxamide;

7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-methoxybenzo[b]thiophene-2-carboxamide;

7-cyano-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-(methoxymethyl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-3,4-dihydro-2H-thieno[3,2-h]chromene-8-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-8,9-dihydro-7H-thieno[2,3-f]chromene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[b]thiophene-6-carboxamide;

2-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide;

6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-methylbenzo[b]thiophene-2-carboxamide;

2-amino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-d]pyrimidine-6-carboxamide;

6,7-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

7-chloro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-chloro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

7-chloro-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-cyclopropyl-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6,7-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-2-carboxamide;

7-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-2-carboxamide;

7-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-isopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-c]pyridine-2-carboxamide;

6-chloro-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

5-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

5,6-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-5,7-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

7-(dimethylamino)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-(methylsulfonyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-morpholino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)isoquinoline-3-carboxamide;

2-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

7-(tert-butyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-(2-hydroxypropan-2-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-phenyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(1-(trifluoromethyl)cyclopropyl)benzo[b]thiophene-2-carboxamide;

7-(1-methylcyclopropyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-propoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-methoxy-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indazole-3-carboxamide;

1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-6-carboxamide;

7-cyclopropyl-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-fluoro-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-cyano-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-(methoxymethyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-(methoxymethyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-3,4-dihydro-2H-thieno[3,2-h]chromene-8-carboxamide;

2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-8,9-dihydro-7H-thieno[2,3-f]chromene-2-carboxamide;

6-chloro-7-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-6-carboxamide;

6-(tert-butyl)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-(1H-1,2,3-triazol-1-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-(oxetan-3-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-methoxy-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-7-fluorobenzo[b]thiophene-2-carboxamide;

7-chloro-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide;

6-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-2-carboxamide;

7-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)benzo[d]oxazole-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-1H-benzo[d]imidazole-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-c]pyridine-2-carboxamide;

3,4-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzamide;

N-(2,2-dimethylquinuclidin-3-yl)-4-methoxy-3-methylbenzamide;

N-(2,2-dimethylquinuclidin-3-yl)imidazo[1,2-a]pyrazine-6-carboxamide;;

N-(2,2-dimethylquinuclidin-3-yl)-5,6-difluorobenzo[b]thiophene-2-carboxamide;;

N-(2,2-dimethylquinuclidin-3-yl)-7-(methylsulfonyl)benzo[b]thiophene-2-carboxamide;;

N-(2,2-dimethylquinuclidin-3-yl)-7-morpholinobenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)quinoline-3-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)quinoline-7-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)quinoline-6-carboxamide;

2-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-(2-hydroxypropan-2-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-(1-(trifluoromethyl)cyclopropyl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-1H-indole-5-carboxamide;

6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-5-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-6-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indazole-3-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-3-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-5-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-6-carboxamide;

6-(dimethylamino)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-6-(methoxymethyl)benzo[b]thiophene-2-carboxamide;
 N-(2,2-dimethylquinuclidin-3-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;
 6-(tert-butyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;
 6-(oxetan-3-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 7-chloro-6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-2-carboxamide;
 1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-2-carboxamide;
 1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-2-carboxamide;
 3,4-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;
 4-methoxy-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)imidazo[1,2-a]pyrazine-6-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-3-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-7-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-6-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-5-carboxamide;
 6-cyclopropyl-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-5-carboxamide;
 N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-6-carboxamide;
 2,2-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d][1,3]dioxole-5-carboxamide;
 1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indazole-3-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-3-carboxamide;

1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-5-carboxamide;

6-(dimethylamino)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-(oxetan-3-yl)benzo[b]thiophene-2-carboxamide;

6-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

7-(oxetan-3-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide; and

6-cyclopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

and single enantiomers and pharmaceutically acceptable salts thereof.

120. The compound of any one of claims 1-119, wherein the compound is selected from the group consisting of:

N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;

6-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-c]pyridine-5-carboxamide;

7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;

N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-6-carboxamide;
2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

6-bromo-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6,7-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

6-chloro-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

5-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

7-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide; and

2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

and single enantiomers and pharmaceutically acceptable salts thereof.

121. The compound of any one of claims 1-117, wherein the compound is selected from the group consisting of:

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-4-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzamide;

(*S*)-4-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzamide;

(*R*)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-benzo[b]thiophene-2-carboxamide;
(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-benzo[b]thiophene-2-carboxamide;
(*R*)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide;
(*S*)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide;
(*R*)-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
(*S*)-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;
(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;
(*R*)-6-cyano-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
(*S*)-6-cyano-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;
(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;
(*R*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
(*S*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
(*R*)-5-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
(*S*)-5-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
(*R*)-5,6-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
(*S*)-5,6-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-5-methylbenzo[b]thiophene-2-carboxamide;
(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-5-methylbenzo[b]thiophene-2-carboxamide;
(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-5-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-5-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
(*R*)-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
(*S*)-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
(*R*)-5-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
(*S*)-5-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide;
(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide;
(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-5-methoxybenzo[b]thiophene-2-carboxamide;
(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-5-methoxybenzo[b]thiophene-2-carboxamide;

(R)-N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-c]pyridine-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-c]pyridine-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzo[b]thiophene-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzo[b]thiophene-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzo[b]thiophene-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzo[b]thiophene-6-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-1H-indole-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-1H-indole-6-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)pyrazolo[1,5-b]pyridazine-3-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)pyrazolo[1,5-b]pyridazine-3-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-b]pyridine-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-b]pyridine-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]thiazole-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]thiazole-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-6-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]oxazole-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]oxazole-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]oxazole-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]oxazole-6-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]thiazole-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]thiazole-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]thiazole-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[d]thiazole-6-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-b]pyridine-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-b]pyridine-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)furo[3,2-b]pyridine-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)furo[3,2-b]pyridine-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzofuran-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzofuran-5-carboxamide;
 (R)-2-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 (S)-2-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzofuran-5-carboxamide;

(S)-N-(2,2-dimethylquinuclidin-3-yl)-3-methylbenzofuran-5-carboxamide;
 (R)-3-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 (S)-3-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-c]pyridine-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-c]pyridine-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-morpholinobenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-morpholinobenzo[b]thiophene-2-carboxamide;
 (R)-6-(4,4-difluoropiperidin-1-yl)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-(4,4-difluoropiperidin-1-yl)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-6-bromo-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-bromo-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-isopropoxybenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-isopropoxybenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-(methylsulfonyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-(methylsulfonyl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-nitrobenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-nitrobenzo[b]thiophene-2-carboxamide;
 (R)-6-amino-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-amino-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methoxybenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methoxybenzo[b]thiophene-2-carboxamide;
 (R)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (S)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(R)-4-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;
 (S)-4-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;
 (R)-7-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-7-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;
 (S)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;
 (R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;
 (S)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;
 (R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (R)-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-6-nitro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-nitro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-6-amino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-amino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-5-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-5,6-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5,6-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-5-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-5-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-5-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-5-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-5-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-*c*]pyridine-5-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-*c*]pyridine-5-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydro-[1,4]dioxino[2,3-*c*]pyridine-7-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydro-[1,4]dioxino[2,3-*c*]pyridine-7-carboxamide;

(*R*)-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-5-carboxamide;

(*S*)-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-5-carboxamide;

(*R*)-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

(*S*)-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-6-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-6-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrazolo[1,5-*b*]pyridazine-3-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)pyrazolo[1,5-*b*]pyridazine-3-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*b*]pyridine-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*b*]pyridine-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-5-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-5-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-6-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-6-carboxamide;

(*R*)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-5-carboxamide;

(*S*)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-5-carboxamide;

(*R*)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-6-carboxamide;

(*S*)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-6-carboxamide;

(*R*)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-5-carboxamide;

(*S*)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-5-carboxamide;

(*R*)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-6-carboxamide;

(*S*)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]thiazole-6-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-b]pyridine-5-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-b]pyridine-5-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[3,2-b]pyridine-5-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[3,2-b]pyridine-5-carboxamide;

(*R*)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

(*S*)-2-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

(*R*)-2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

(*S*)-2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

(*R*)-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

(*S*)-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

(*R*)-3-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

(*S*)-3-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

(*R*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-5-carboxamide;

(*S*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-5-carboxamide;

(*R*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-6-carboxamide;

(*S*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-6-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-c]pyridine-5-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-c]pyridine-5-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(1H-1,2,3-triazol-1-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(1H-1,2,3-triazol-1-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-morpholino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-morpholino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-(4,4-difluoropiperidin-1-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-(4,4-difluoropiperidin-1-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-bromo-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*S*)-6-bromo-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-6-isopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*S*)-6-isopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-6-(methylsulfonyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*S*)-6-(methylsulfonyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-6-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*S*)-6-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;
 (*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-7-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*S*)-7-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide; and
 (*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide;
 and pharmaceutically acceptable salts thereof.

122. The compound of any one of claims 1-117, wherein the compound is selected from the group consisting of:

(*R*)-2-amino-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-d]pyrimidine-6-carboxamide;
 (*S*)-2-amino-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-d]pyrimidine-6-carboxamide;
 (*R*)-6,7-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (*S*)-6,7-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-fluorobenzo[b]thiophene-2-carboxamide;

(S)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-fluorobenzo[b]thiophene-2-carboxamide;
 (R)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (S)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (R)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide;
 (S)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methoxybenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-methyl-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (R)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;
 (S)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-fluorobenzo[b]thiophene-2-carboxamide;
 (R)-7-cyano-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-7-cyano-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6,7-difluorobenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6,7-difluorobenzo[b]thiophene-2-carboxamide;
 (R)-7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-isopropylbenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-isopropylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-1H-indole-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-1H-indole-2-carboxamide;
 (R)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;
 (S)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-5-fluorobenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-5-fluoro-6-methoxybenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-5-fluoro-6-methoxybenzo[b]thiophene-2-carboxamide;
 (R)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-5,7-difluorobenzo[b]thiophene-2-carboxamide;
 (S)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-5,7-difluorobenzo[b]thiophene-2-carboxamide;

(R)-N-(2,2-dimethylquinuclidin-3-yl)-7-methylbenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-methylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;
 (R)-7-(dimethylamino)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-7-(dimethylamino)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)isoquinoline-3-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)isoquinoline-3-carboxamide;
 (R)-7-(tert-butyl)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-7-(tert-butyl)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-phenylbenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-phenylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-(1-methylcyclopropyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-(1-methylcyclopropyl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-ethoxybenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-ethoxybenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-ethoxybenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-ethoxybenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-propoxybenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-propoxybenzo[b]thiophene-2-carboxamide;
 (R)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide;
 (S)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxy-6-methylbenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxy-6-methylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-1H-indazole-3-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-1H-indazole-3-carboxamide;
 (R)-7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (S)-7-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-methoxybenzo[b]thiophene-2-carboxamide;

(S)-N-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-methoxybenzo[b]thiophene-2-carboxamide;
 (R)-7-cyano-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (S)-7-cyano-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-(methoxymethyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-(methoxymethyl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-3,4-dihydro-2H-thieno[3,2-h]chromene-8-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-3,4-dihydro-2H-thieno[3,2-h]chromene-8-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-8,9-dihydro-7H-thieno[2,3-f]chromene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-8,9-dihydro-7H-thieno[2,3-f]chromene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[b]thiophene-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-2-methylbenzo[b]thiophene-6-carboxamide;
 (R)-2-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide;
 (S)-2-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-6-carboxamide;
 (R)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-methylbenzo[b]thiophene-2-carboxamide;
 (S)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)-7-methylbenzo[b]thiophene-2-carboxamide;
 (R)-2-amino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-d]pyrimidine-6-carboxamide;
 (S)-2-amino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-d]pyrimidine-6-carboxamide;
 (R)-6,7-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6,7-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-6-chloro-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-chloro-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (S)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (R)-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (S)-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (R)-7-chloro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-chloro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-chloro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-chloro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-chloro-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-chloro-6-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-cyclopropyl-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-cyclopropyl-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6,7-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6,7-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-2-carboxamide;

(*S*)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-2-carboxamide;

(*R*)-7-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-2-carboxamide;

(*S*)-7-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-2-carboxamide;

(*R*)-7-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-isopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-isopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(tetrahydro-2H-pyran-4-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]oxazole-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*c*]pyridine-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)thieno[2,3-*c*]pyridine-2-carboxamide;

(*R*)-6-chloro-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-5-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-5-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-5,6-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-5,6-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-5,7-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-5,7-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(2,2,2-trifluoroethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-(dimethylamino)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-(dimethylamino)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-(methylsulfonyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-(methylsulfonyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-morpholino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-morpholino-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)isoquinoline-3-carboxamide;

(S)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)isoquinoline-3-carboxamide;
(R)-2-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;
(S)-2-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;
(R)-7-(tert-butyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(S)-7-(tert-butyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-7-(2-hydroxypropan-2-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(S)-7-(2-hydroxypropan-2-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-7-phenyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(S)-7-phenyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(1-(trifluoromethyl)cyclopropyl)benzo[b]thiophene-2-carboxamide;
(S)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(1-(trifluoromethyl)cyclopropyl)benzo[b]thiophene-2-carboxamide;
(R)-7-(1-methylcyclopropyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(S)-7-(1-methylcyclopropyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-6-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(S)-6-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-7-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(S)-7-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-7-propoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(S)-7-propoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-chloro-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-methoxy-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-methoxy-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indazole-3-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indazole-3-carboxamide;

(*R*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-6-carboxamide;

(*S*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-6-carboxamide;

(*R*)-7-cyclopropyl-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyclopropyl-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-fluoro-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-fluoro-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-cyano-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-cyano-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-(methoxymethyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-(methoxymethyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-(methoxymethyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-(methoxymethyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-3,4-dihydro-2H-thieno[3,2-h]chromene-8-carboxamide;

(*S*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-3,4-dihydro-2H-thieno[3,2-h]chromene-8-carboxamide;

(*R*)-2-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

(*S*)-2-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

(*R*)-2-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

(*S*)-2-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-8,9-dihydro-7H-thieno[2,3-f]chromene-2-carboxamide;

(*S*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-8,9-dihydro-7H-thieno[2,3-f]chromene-2-carboxamide;

(*R*)-6-chloro-7-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-chloro-7-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-6-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-6-carboxamide;

(*R*)-6-(tert-butyl)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-(tert-butyl)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(1H-1,2,3-triazol-1-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(1H-1,2,3-triazol-1-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(oxetan-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-(oxetan-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-fluoro-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methoxy-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-6-methoxy-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-7-fluorobenzo[b]thiophene-2-carboxamide;

(*S*)-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-7-fluorobenzo[b]thiophene-2-carboxamide;

(*R*)-7-chloro-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-chloro-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide;

(*R*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-2-carboxamide;

(*S*)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-2-carboxamide;

(*R*)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-2-carboxamide;

(*S*)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]oxazole-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]oxazole-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-1H-benzo[d]imidazole-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-1H-benzo[d]imidazole-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-benzo[d]imidazole-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-c]pyridine-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)thieno[2,3-c]pyridine-2-carboxamide;

(*R*)-3,4-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzamide;

(*S*)-3,4-dichloro-N-(2,2-dimethylquinuclidin-3-yl)benzamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-4-methoxy-3-methylbenzamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-4-methoxy-3-methylbenzamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)imidazo[1,2-a]pyrazine-6-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)imidazo[1,2-a]pyrazine-6-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-5,6-difluorobenzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-5,6-difluorobenzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-(methylsulfonyl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-7-(methylsulfonyl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-morpholinobenzo[b]thiophene-2-carboxamide;

(S)-N-(2,2-dimethylquinuclidin-3-yl)-7-morpholinobenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)quinoline-3-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)quinoline-3-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)quinoline-7-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)quinoline-7-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)quinoline-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)quinoline-6-carboxamide;
 (R)-2-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 (S)-2-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-(2-hydroxypropan-2-yl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-(2-hydroxypropan-2-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-7-(1-(trifluoromethyl)cyclopropyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-7-(1-(trifluoromethyl)cyclopropyl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-1H-indole-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-1H-indole-5-carboxamide;
 (R)-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide;
 (S)-6-cyclopropyl-N-(2,2-dimethylquinuclidin-3-yl)-7-methoxybenzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-6-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indazole-3-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indazole-3-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-3-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)benzo[d]isoxazole-3-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-5-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-5-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-6-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-1-methyl-1H-indole-6-carboxamide;

(R)-6-(dimethylamino)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-(dimethylamino)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-6-(methoxymethyl)benzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-6-(methoxymethyl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(2,2-dimethylquinuclidin-3-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;
 (S)-N-(2,2-dimethylquinuclidin-3-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;
 (R)-6-(tert-butyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-(tert-butyl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;
 (S)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-6-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;
 (R)-6-(oxetan-3-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-6-(oxetan-3-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (S)-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethyl)benzo[b]thiophene-2-carboxamide;
 (R)-7-chloro-6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (S)-7-chloro-6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-2-carboxamide;
 (S)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-2-carboxamide;
 (R)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-2-carboxamide;
 (S)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-benzo[d]imidazole-2-carboxamide;
 (R)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-2-carboxamide;

(*S*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-2-carboxamide;

(*R*)-3,4-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;

(*S*)-3,4-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;

(*R*)-4-methoxy-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;

(*S*)-4-methoxy-3-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)imidazo[1,2-a]pyrazine-6-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)imidazo[1,2-a]pyrazine-6-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-3-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-3-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-7-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-7-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-6-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)quinoline-6-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-5-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-5-carboxamide;

(*R*)-6-cyclopropyl-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-cyclopropyl-7-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-5-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-5-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-6-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-6-carboxamide;

(*R*)-2,2-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d][1,3]dioxole-5-carboxamide;

(*S*)-2,2-difluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d][1,3]dioxole-5-carboxamide;

(*R*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indazole-3-carboxamide;

(*S*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indazole-3-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-3-carboxamide;

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[d]isoxazole-3-carboxamide;

(*R*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-5-carboxamide;

(*S*)-1-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-5-carboxamide;

(*R*)-6-(dimethylamino)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-(dimethylamino)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide; and

(*S*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)-7-(oxetan-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-N-(2,2-dimethylquinuclidin-3-yl)-7-(oxetan-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-6-cyclopropoxy-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-(oxetan-3-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*S*)-7-(oxetan-3-yl)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-6-cyclopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide; and

(*S*)-6-cyclopropoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

and pharmaceutically acceptable salts thereof.

123. The compound of any one of claims 1-117 or 121-122, wherein the compound is selected from the group consisting of:

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;

(R)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-benzo[b]thiophene-2-carboxamide;
(R)-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;
(R)-6-chloro-N-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
(R)-N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-c]pyridine-5-carboxamide;
(R)-7-chloro-N-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
(R)-N-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;
(R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;
(R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;
(R)-6-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-6-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-c]pyridine-5-carboxamide;
(R)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-6-carboxamide;
(R)-2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;
(R)-6-bromo-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-7-fluoro-6-methyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-6,7-dichloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-6-chloro-7-fluoro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-7-cyano-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
(R)-7-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;
 (*R*)-5-fluoro-6-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-7-ethoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide; and
 (*R*)-2-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;
 and pharmaceutically acceptable salts thereof.

124. The compound of claim 1-2, 66-89, 113-114, or 121-123, wherein the compound is selected from the group consisting of:

(*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-benzo[b]thiophene-2-carboxamide;
 (*R*)-6-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-7-chloro-*N*-(2,2-dimethylquinuclidin-3-yl)-6-methylbenzo[b]thiophene-2-carboxamide;
 (*R*)-*N*-(2,2-dimethylquinuclidin-3-yl)-7-fluoro-6-methylbenzo[b]thiophene-2-carboxamide;
 (*R*)-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-6-chloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-6-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-6-cyclopropyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-6-methoxy-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-6-bromo-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-7-fluoro-6-methyl-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-6,7-dichloro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-6-chloro-7-fluoro-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;
 (*R*)-7-cyano-*N*-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-7-cyclopropyl-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-7-(trifluoromethoxy)benzo[b]thiophene-2-carboxamide;

(*R*)-5-fluoro-6-methoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide; and

(*R*)-7-ethoxy-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-2-carboxamide;

and pharmaceutically acceptable salts thereof.

125. The compound of claim 1-2, 19-24, 43, 46, 48-53, 113-114, or 121-123, wherein the compound is selected from the group consisting of:

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)benzofuran-5-carboxamide;

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

and

(*R*)-2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzofuran-5-carboxamide;

and pharmaceutically acceptable salts thereof.

126. The compound of claim 1-2, 35-37, 43, 46, 48-53, 113-114, or 121-123, wherein the compound is selected from the group consisting of:

(*R*)-N-(2,2-dimethylquinuclidin-3-yl)furo[2,3-*c*]pyridine-5-carboxamide; and

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)furo[2,3-*c*]pyridine-5-carboxamide;

and pharmaceutically acceptable salts thereof.

127. The compound of claim 1-2, 25-26, 43, 45, 48-53, 113-114, or 121-123, wherein the compound is:

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)-1H-indole-6-carboxamide; and pharmaceutically acceptable salts thereof.

128. The compound of claim 1, 25-26, 43, 47-53, 113-114, or 121-123, wherein the compound is:

(*R*)-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide; and

(*R*)-2-chloro-N-(1'-azaspiro[cyclopropane-1,2'-bicyclo[2.2.2]octan]-3'-yl)benzo[b]thiophene-6-carboxamide;

and pharmaceutically acceptable salts thereof.

129. A pharmaceutical composition, comprising:

- i) the compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-128; and
- ii) at least one pharmaceutically acceptable carrier, excipient or diluent.

130. A method of treating a patient in need thereof, comprising administering to the patient the compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-128.

131. A method of treating a patient in need thereof, comprising administering to the patient the pharmaceutical composition of claim 129.

132. A method of improving cognition of a patient in need thereof, comprising: administering to the patient the compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-128.

133. A method of improving cognition of a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising:

- i) the compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-128; and
- ii) at least one pharmaceutically acceptable carrier, excipient or diluent.

134. A method of treating or improving one or more symptoms associated with a cognitive disease and/or a cognitive impairment in a patient in need thereof, comprising: administering to the patient the compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-128.

135. A method of treating or improving one or more symptoms associated with a cognitive disease and/or a cognitive impairment in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising:

- i) the compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-128; and
- ii) at least one pharmaceutically acceptable carrier, excipient or diluent.

136. The method of any one of claims 130-135, wherein the patient suffers from a cognitive impairment, suffers from a cognitive loss associated with a cognitive impairment, or suffers from one or more symptoms associated with a cognitive impairment.

137. The method of claim 136, wherein the cognitive impairment comprises Limited Cognitive Impairment (LCI), Mild Cognitive Impairment (MCI), Alzheimer's disease, dementia of an Alzheimer's-type, schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional

disorder, positive symptoms of schizophrenia, negative symptoms of schizophrenia, or schizophrenia with dementia.

138. The method of claim 136, wherein the cognitive impairment is Limited Cognitive Impairment (LCI).

139. The method of claim 136, wherein the cognitive impairment is Mild Cognitive Impairment (MCI).

140. The method of claim 136, wherein the cognitive impairment is Alzheimer's disease.

141. The method of claim 136, wherein the cognitive impairment is dementia of an Alzheimer's-type.

142. The method of claim 136, wherein the cognitive impairment is schizophrenia.

143. The method of claim 136, wherein the cognitive impairment is schizophreniform disorder, schizoaffective disorder, or delusional disorder.

144. The method of claim 136, wherein the cognitive impairment comprises positive symptoms of schizophrenia.

145. The method of claim 136, wherein the cognitive impairment comprises negative symptoms of schizophrenia.

146. The method of claim 136, wherein the cognitive impairment is schizophrenia with dementia.

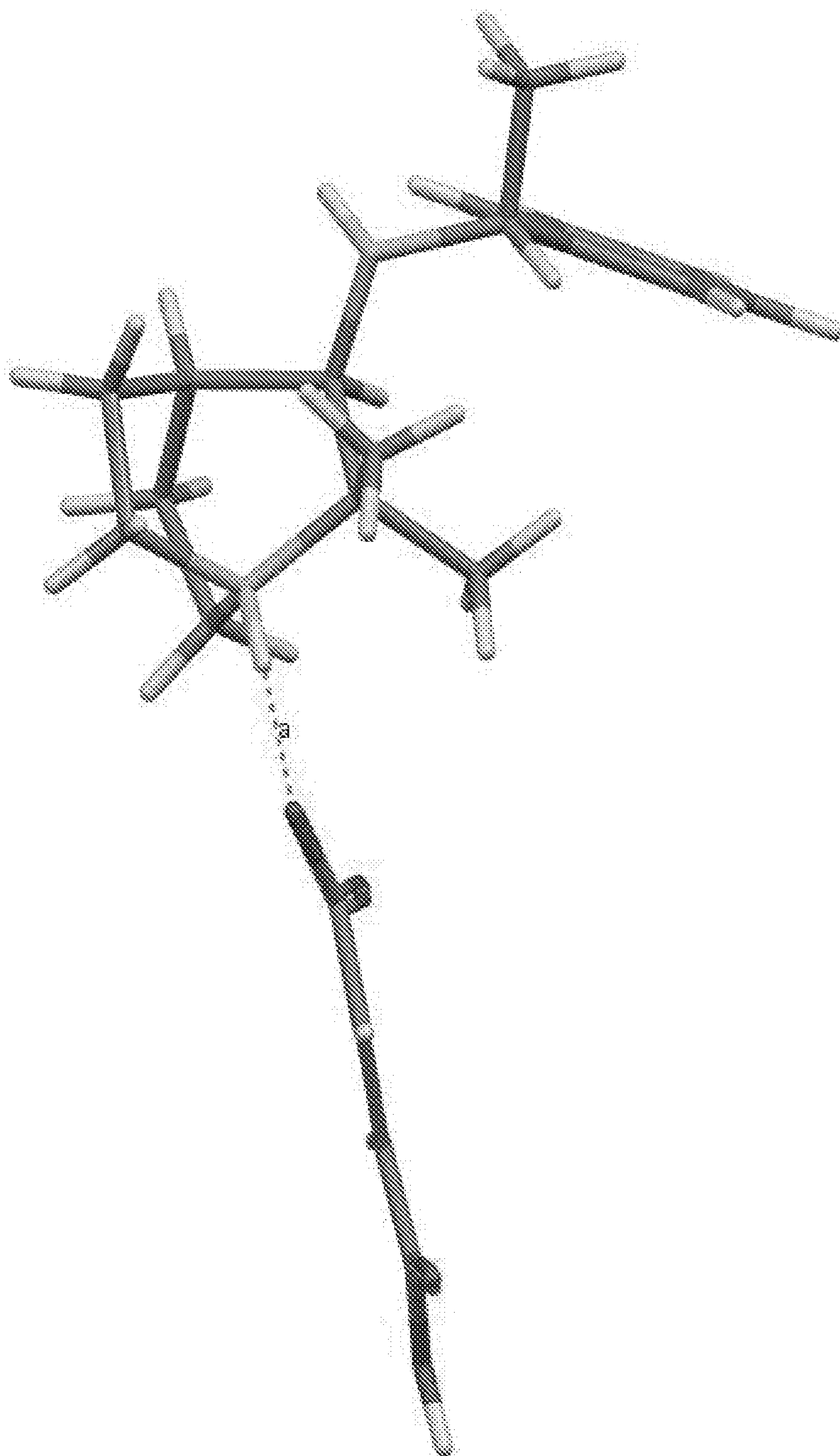


FIGURE 1

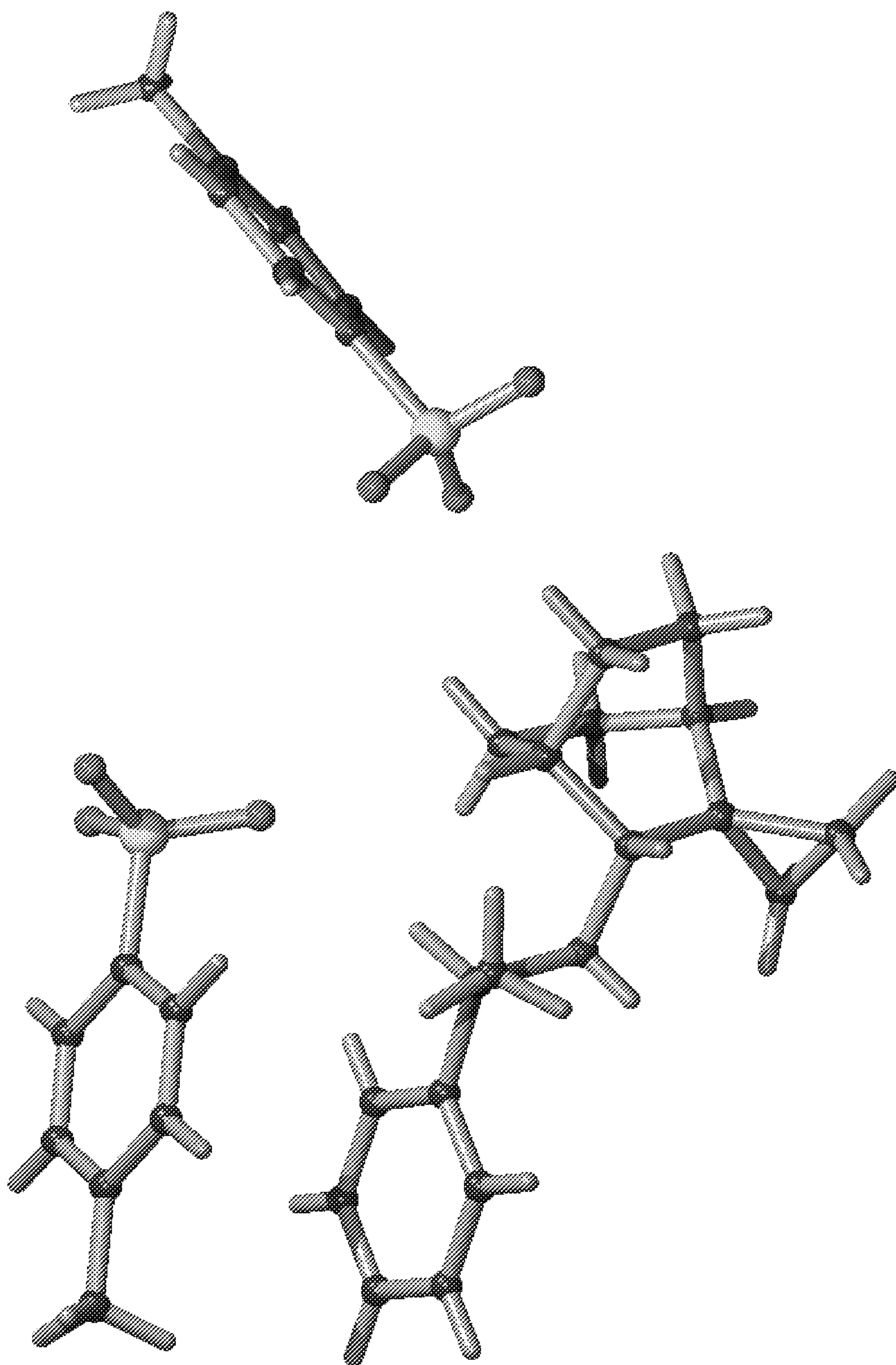


FIGURE 2

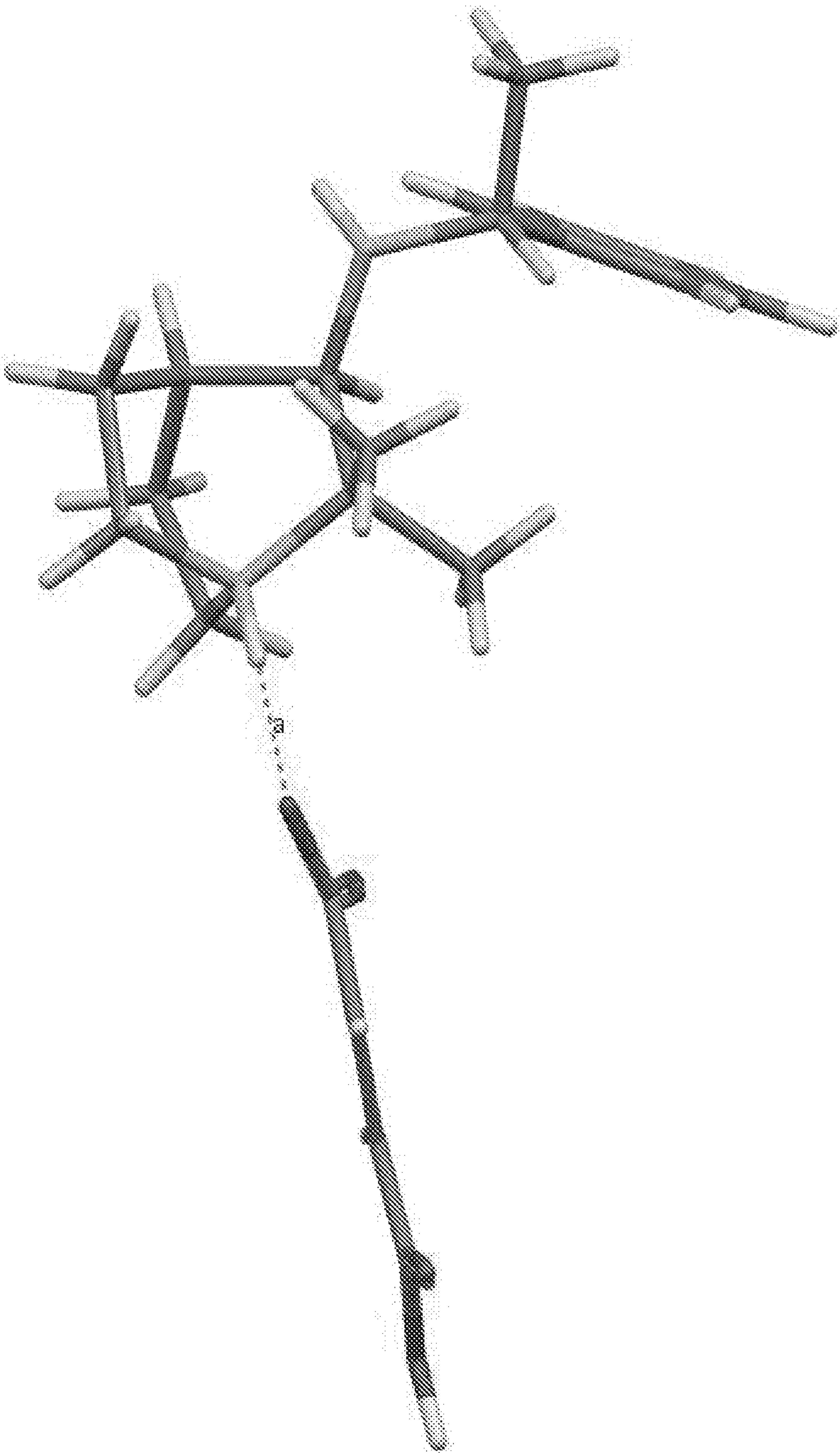


FIGURE 1