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(54) Title: PROCESSES FOR MAKING CYCLOPROPYL AMIDE DERIVATIVES AND INTERMEDIATES ASSOCIATED  
THEREWITH

(57) **Abrégé/Abstract:**

Presented herein are processes for making cyclopropyl amide derivatives of formula I, and/or pharmaceutically acceptable salts thereof, and intermediates associated therewith. At least one cyclopropyl amide derivative of formula I, or pharmaceutically acceptable salt thereof is useful to treat at least one histamine H3 receptor associated condition.



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(57) Abstract: Presented herein are processes for making cyclopropyl amide derivatives of formula I, and/or pharmaceutically acceptable salts thereof, and intermediates associated therewith. At least one cyclopropyl amide derivative of formula I, or pharmaceutically acceptable salt thereof is useful to treat at least one histamine H3 receptor associated condition.



WO 2011/102794 A1

## PROCESSES FOR MAKING CYCLOPROPYL AMIDE DERIVATIVES AND INTERMEDIATES ASSOCIATED THEREWITH

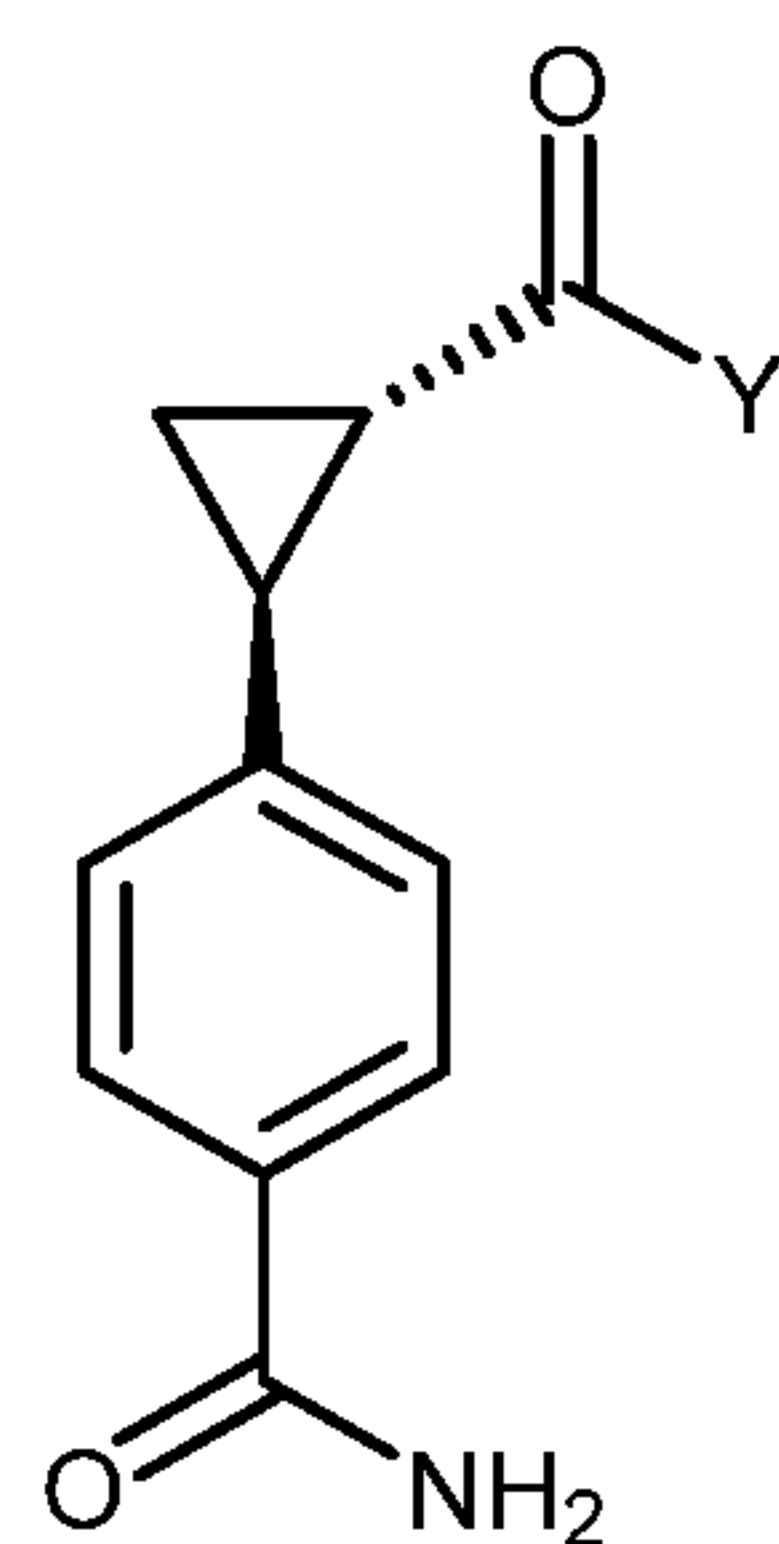
Presented herein are processes for making cyclopropyl amide derivatives of formula I, and/or pharmaceutically acceptable salts thereof, and intermediates associated therewith. At least one cyclopropyl amide derivative of formula I, or pharmaceutically acceptable salt thereof is useful to treat at least one histamine H3 receptor associated condition.

The histamine H3 receptor is of current interest in developing new medicaments. The H3 receptor is a presynaptic autoreceptor located both in the central and peripheral nervous systems, the skin, and in organs, such as, for example, the lung, the intestine, probably the spleen, and the gastrointestinal tract. Recent evidence suggests the H3 receptor has intrinsic, constitutive activity *in vitro* as well as *in vivo* (i.e., it is active in the absence of an agonist). Compounds acting as inverse agonists can inhibit this activity. The histamine H3 receptor has been shown to regulate the release of histamine and also of other neurotransmitters, such as, for example, serotonin and acetylcholine. Some histamine H3 ligands, such as, for example, a histamine H3 receptor antagonist or inverse agonist may increase the release of neurotransmitters in the brain, whereas other histamine H3 ligands, such as, for example, histamine H3 receptor agonists may inhibit the biosynthesis of histamine, as well as, inhibit the release of neurotransmitters. This suggests that histamine H3 receptor agonists, inverse agonists, and antagonists could mediate neuronal activity. As a result, efforts have been undertaken to develop new therapeutics that target the histamine H3 receptor.

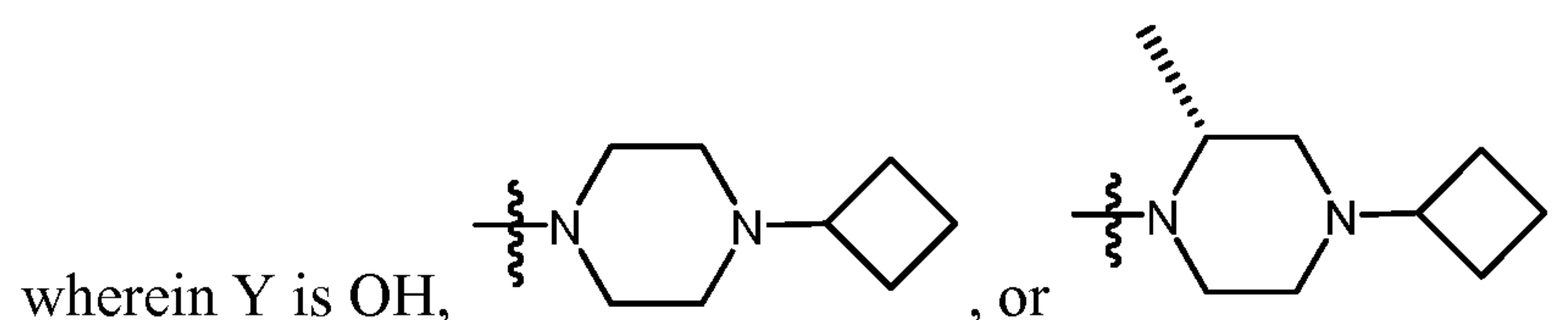
U.S. patent application publication no. 2009/0076020 describes the synthesis of a number of cyclopropyl amide derivatives, such as, for example, 4-((trans)-2-[(4-cyclobutylpiperazin-yl)carbonyl]-cyclopropyl)-benzamide (enantiomer 1; Example 43). Improved processes of making these compounds would be advantageous, especially processes amenable to large scale synthesis.

Described herein are processes of making cyclopropyl amide derivatives of formula I and pharmaceutically acceptable salts thereof:



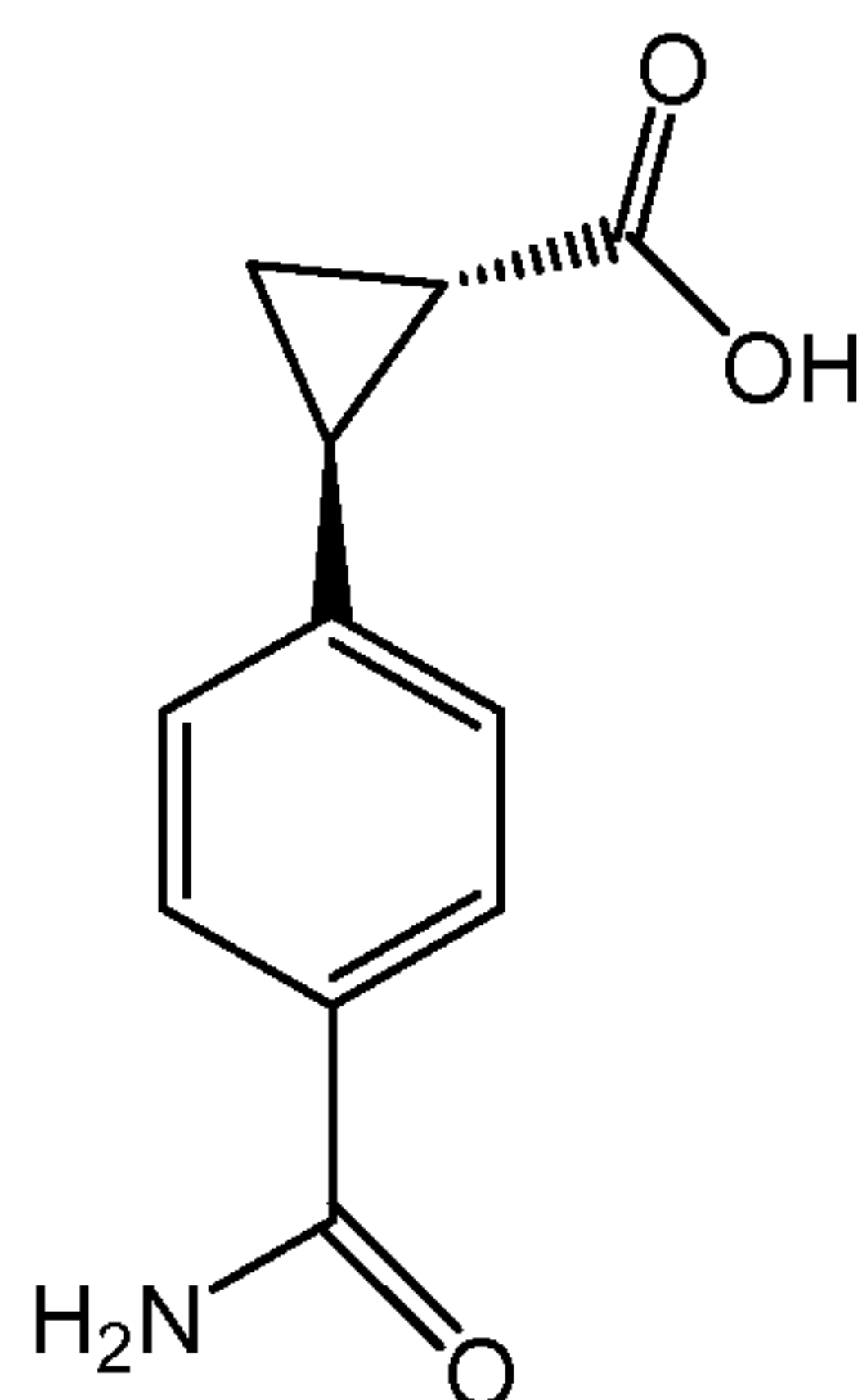


(I)



Further described herein is a compound of Formula Ia, or a pharmaceutically

5 acceptable salt thereof:



(Ia).

Throughout this disclosure it is to be understood that, where appropriate, suitable protecting groups may be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in “Protective Groups in Organic Synthesis,” T. W. Green, P. G. M. Wuts, Wiley-Interscience, New York, (1999).

A transformation of a group or substituent into another group or substituent by chemical manipulation can be conducted on any intermediate or final product on the synthetic path toward the final product; the type of transformation is limited only by the inherent incompatibility of other functional groups contained in the molecule to the conditions or reagents employed in the transformation. Such inherent incompatibilities, and ways to

circumvent them by carrying out appropriate transformations and synthetic steps in a suitable order, will be readily understood by one skilled in the art of organic synthesis.

Examples of transformations are given below, and it is understood that the described transformations are not limited only to the generic groups or substituents for which the transformations are exemplified. References and descriptions of other suitable transformations are given in "Comprehensive Organic Transformations—A Guide to Functional Group Preparations" R. C. Larock, Wiley VCH, 2<sup>nd</sup> Edition (1999).

Exemplary reaction conditions are given below, and it is understood that the described reaction conditions are not limited only to the described reaction conditions. References and descriptions of other suitable reaction conditions are described in textbooks of organic chemistry, such as, for example, "Advanced Organic Chemistry", March 6<sup>th</sup> Edition, Wiley Interscience (2007), and "Organic Synthesis", Smith, 2<sup>nd</sup> Edition, McGraw Hill, (2001).

Techniques for purification of intermediates and final products include, for example, normal and reversed phase chromatography on column or rotating plate, recrystallization, distillation and liquid-liquid or solid-liquid extraction, each of which will be readily understood by one skilled in the art.

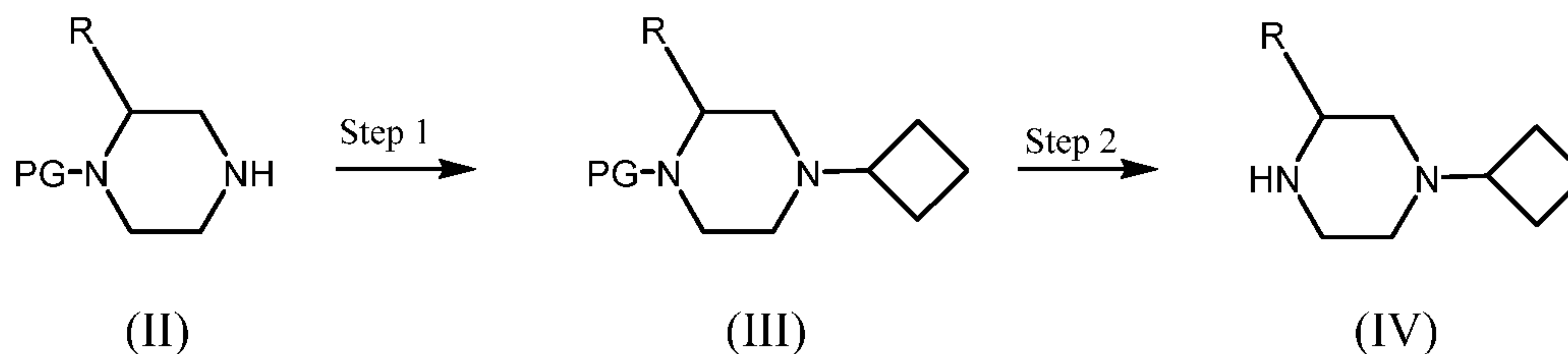
The term "amino-protecting group" refers to art-recognized moieties capable of attaching to an amino group so as to prevent the amino group from taking place in reactions occurring elsewhere on the molecule to which the amino group is attached. Acceptable amino-protecting groups, include but are not limited to, for example, amino-protecting groups described in "Protective Groups in Organic Synthesis", 4<sup>th</sup> edition, Wiley Interscience, 2006. The amino-protecting group may be, for example, a urethane type protective group (which is also referred to as a carbamate protective group), which includes but is not limited to, for example, arylalkyloxycarbonyl groups, such as, for example, benzyloxycarbonyl; and alkoxy carbonyl groups, such as, for example, methoxycarbonyl and tert-butoxycarbonyl. Typically, the amino-protecting group is tert-butoxycarbonyl.

In general, the compounds of formula I can be prepared in accordance with the following Schemes and the general knowledge of one skilled in the art and/or in accordance with the methods set forth in the Examples that follow. Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. Starting materials are commercially available or readily prepared by one skilled in the art.

The term "C<sub>1-6</sub>alkyl" refers to a straight or branched chain alkane (hydrocarbon) radical containing from 1 to 6 carbon atoms. Exemplary "C<sub>1-6</sub>alkyl" groups include, but are

not limited to, for example, methyl; ethyl; propyl; isopropyl; 1-methylpropyl; n-butyl, t-butyl; isobutyl; pentyl; hexyl; and isohexyl.

### Scheme 1



For the compounds depicted in Scheme 1, PG is an amino-protecting group; and R is H or a C<sub>1-6</sub>alkyl.

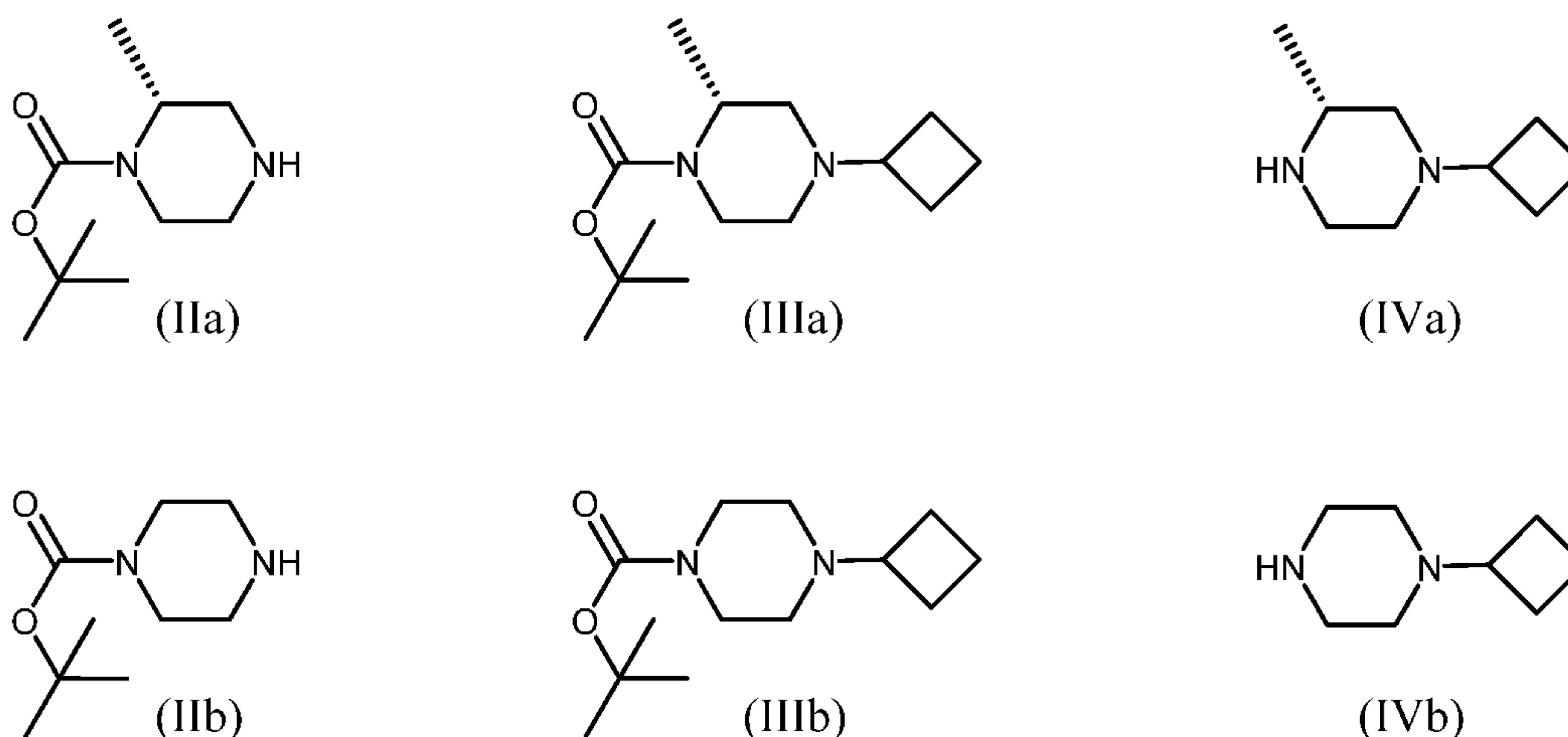
In one embodiment, C<sub>1-6</sub>alkyl is selected from methyl, ethyl, propyl, and isopropyl.

In another embodiment, the amino protecting group is tert-butoxycarbonyl.

In a further embodiment, R is H.

In a yet another embodiment R is methyl.

In an even further embodiment, the compounds of formula II, III and IV are compounds of formula IIa, IIb, IIIa, IIIb, IVa and IVb, respectively:



In still a further embodiment, the compounds of formula II, III and IV are selected from formula IIa, formula IIb, formula IIIa, formula IIIb, formula IVa, and formula IVb.

In yet still as further embodiment, compounds in accordance with formula II, III, or IV may be in the form of a suitable salt, such as, for example, the acetate or dihydrochloride. In certain embodiments, the compounds of formula IVa and IVb may be in the form of the dihydrochloride salt.

Step 1:

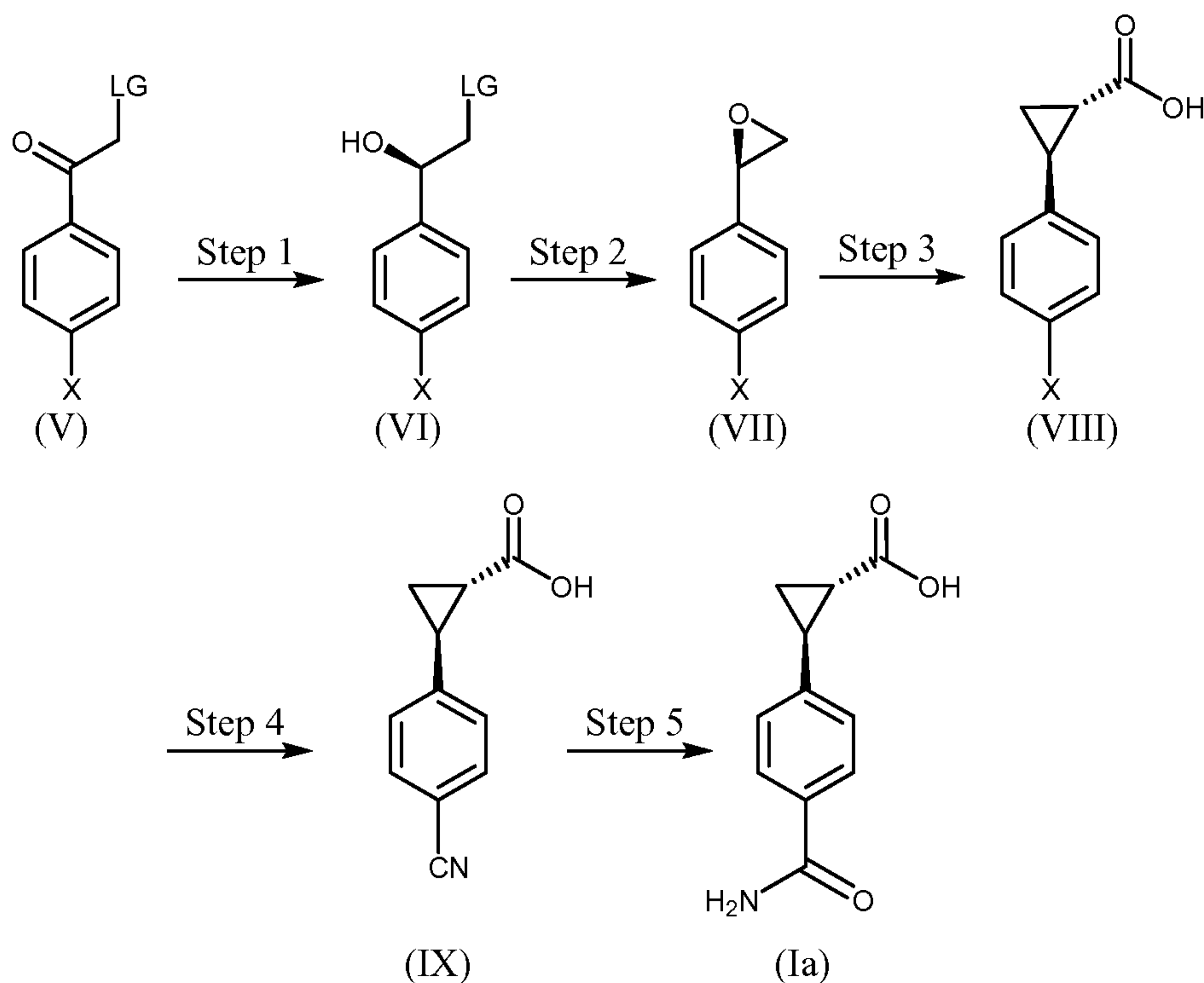


Compounds in accordance with formula III can be obtained by treating compounds in accordance with formula II with cyclobutanone and a suitable reducing agent, such as, for example, sodium triacetoxyborohydride or sodium cyanoborohydride, in a suitable solvent, such as for example, 1,2-dichloroethane, tetrahydrofuran, ethanol, or acetic acid, or a solvent mixture comprising two or more solvents, such as, for example, a solvent mixture comprising ethanol and acetic acid. Compounds in accordance with formula II are commercially available and include, for example, (*R*)-Boc-2-methylpiperazine, which is commercially available from Lanzhou Boc Chemical Co., and *N*-Boc-piperazine, which is commercially available from Sigma-Aldrich. In certain embodiments, the compounds in accordance with formula III are not isolated, but instead are carried through to step 2.

Step 2:

Compounds in accordance with formula IV can be obtained by treating compounds in accordance with formula III with a suitable reagent to deprotect the amino group, such as for example, an acid, such as for example, hydrochloric acid, trifluoroacetic acid, or sulfonic acid, in a suitable solvent, such as, for example, dioxane, dichloromethane, 2-propanol or a suitable mixture comprising two or more solvents, such as, for example, a solvent mixture comprising 2-propanol and toluene.

**Scheme 2**



For the compounds depicted in Scheme 2, X is F, Cl, Br, or I; and LG is Cl, Br, I, tosylate, brosylate, nosylate, or mesylate.

In another embodiment, X is Cl, Br, or I and LG is Cl, Br, I, tosylate, brosylate, nosylate, or mesylate. In a further embodiment, X is Br. In a still further embodiment, LG is  
5 Cl. In yet another embodiment, LG is Cl, Br, I, or tosylate. In a yet still further embodiment, X is BR and LG is Cl.

#### Steps 1 and 2:

Compounds in accordance with formula VI (step 1) and VII (steps 1 and 2, in the  
10 latter case either stepwise or in a telescope procedure) can be obtained, for example, from compound V by either enzymatic transformation, catalytic transfer hydrogenation or reduction using a chiral oxazaborolidine together with a reducing agent, followed by base treatment with or without the presence of a phase transfer catalyst in a suitable solvent. Descriptions of these transformations can be found, for example, in *Speciality Chemicals*  
15 *Magazine*, 27(8), 32-33(2007); WO2008064817; Faming Zhuanli Shenqing, 101747211; WO 2006036015; WO 2006028290; WO 2007011065; *Organic Letters* (2002), 4(24), 4373-4376; WO 2002051781; *Tetrahedron* (2004), 60(34), 7411-7417; *Organic Letters* (2007), 9(2), 255-257; and *Journal of the Chemical Society*, Perkin Transactions 1 (2001), (10), 1204-1211.

20 In one embodiment, compounds in accordance with formula VI can be obtained by adding a compound in accordance with formula V, which is dissolved in a suitable solvent, such as, for example, tetrahydrofuran, 2-methyl-tetrahydrofuran, toluene, dichloromethane, or a mixture of two or more thereof, to a solution comprising i) a suitable reducing agent, such as, for example, borane\*THF or borane dimethylsulfide in a suitable solvent, such as, for  
25 example, tetrahydrofuran, 2-methyl-tetrahydrofuran, toluene, dichloromethane, or a mixture of two or more thereof, and ii) a chiral oxazaborolidine, such as, for example, (*R*)-(+)-methyl-CBS-oxazaborolidine (CAS-No. 112022-83-0).

In another embodiment, compounds in accordance with formula VII can be obtained by treating a compound of formula VI in a suitable first solvent, such as, for example,  
30 dichloromethane, tetrahydrofuran, 2-methyl-tetrahydrofuran, or a mixture of two or more thereof, with a phase-transfer catalyst, such as, for example, an ammonium salt (e.g., methyl tributyl ammonium chloride or tetrabutylammonium chloride), a heterocyclic ammonium salt (e.g., 1,1'-dibenzyl-4,4'-bipyridinium dichloride, 1,2,3-trimethylimidazolium methyl sulfate),



or a phosphonium salt (e.g., tetrabutylphosphonium chloride or tetraphenylphosphonium chloride), with a suitable base, such as, for example, sodium hydroxide diluted in a suitable second solvent, such as, for example, water. In one embodiment, the first and second solvent form two phases when mixed together.

5 In a yet another embodiment, compounds in accordance with formula VII can be obtained by treating a compound of formula VI with a suitable base, such as, for example, sodium hydroxide or lithium hydroxide, in a suitable solvent, such as, for example, methanol, ethanol, tetrahydrofuran, dioxane, water, or a mixture of two or more thereof. In a still further embodiment, the base is sodium hydroxide when X is Br and LG is Cl.

10 Compounds in accordance with formula V are commercially available and include 1-(4-Bromo-phenyl)-2-chloro-ethanone, which is commercially available from, for example, Jiangyan Keyan Fine Chemical Co. Ltd. Compounds in accordance with formula VII are commercially available and include (R)-2-(4-Bromo-phenyl)-oxirane, which is commercially available from, for example, American Custom Chemicals Corp.

15 In certain embodiments, compounds in accordance with formula VI are not isolated, but instead carried through to step 2. In certain embodiments, compounds in accordance with formula VII are not isolated, but instead carried through to step 3.

### Step 3:

20 Compounds in accordance with formula VIII can be obtained, for example, from compounds in accordance with formula VII by methodology described, for example, in WO 2006087169 and *Org. Proc. Res. Dev.* **2002**, 6, 618.

In one embodiment, compounds in accordance with formula VIII can be obtained by preparing a solution of i) a suitable first base, such as, for example, alkyl lithium (e.g., n-hexyl lithium) in a suitable solvent, such as, for example, hexane, and ii) a suitable triC<sub>1-6</sub>alkyl phosphonoacetate (e.g., triethyl phosphonoacetate, trimethyl phosphonoacetate, and methyl diethylphosphonoacetate) in a suitable solvent, such as, for example, tetrahydrofuran, 2-methyl-tetrahydrofuran, or mixture thereof, and combining therewith a compound in accordance with formula VII in a suitable solvent, such as, for example, tetrahydrofuran, 2-methyl-tetrahydrofuran, or mixture thereof. The resulting mixture is further treated with a suitable second base, such as, for example, sodium hydroxide or lithium hydroxide. Prior to the addition of the second base, an unisolated intermediate is formed containing an alkylester, such as, for example, ethyl ester where the free carboxylic acid group of the formula VIII

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compound is present. In one embodiment, the unisolated intermediate that is formed prior to the addition of the second base is isolated.

In a further embodiment, the compound in accordance with formula VIII is purified by recrystallization using a suitable solvent, such as, for example, ethanol, water, toluene,  
5 isooctane, or a mixture of two or more thereof.

In an embodiment where X is BR, the first base is n-hexyl lithium; the triC<sub>1-6</sub>alkyl phosphonoacetate is triethylphosphonoacetate; and the second base is sodium hydroxide.

Compounds in accordance with formula V are commercially available and include (1S, 2S)-2-(4-bromophenyl)cyclopropanecarboxylic acid, which is commercially available  
10 from, for example, BOC Sciences.

#### Step 4:

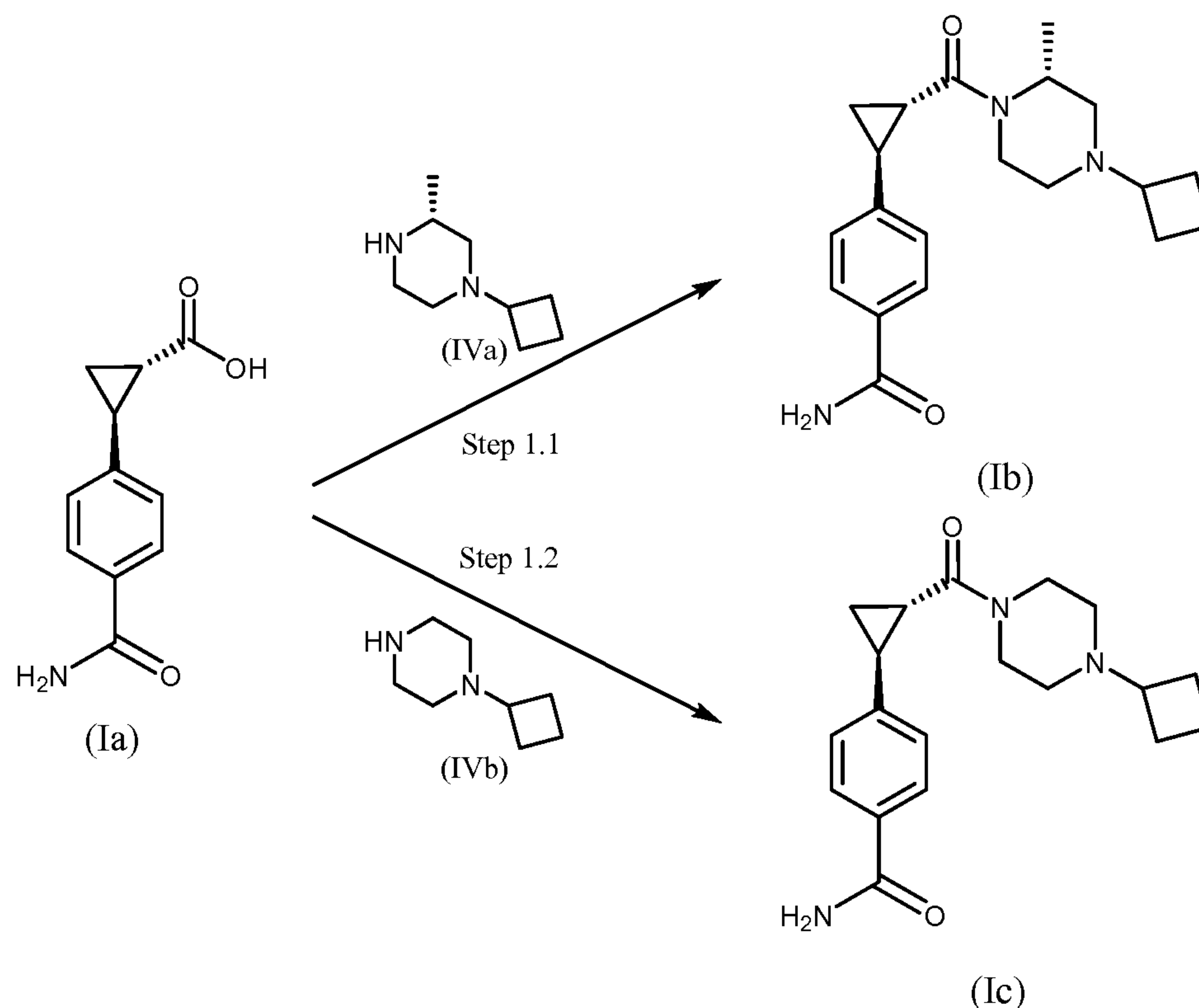
A compound in accordance with formula IX can be obtained by treating a compound in accordance with formula VIII in a suitable solvent, such as, for example,  
15 dimethylformamide with a suitable metal, such as zinc (e.g., zinc dust); a suitable catalyst, such as, for example, bis(tri-*t*-butylphosphine)palladium(0); and a suitable metal cyanide, such as, for example, zinc-(II)-cyanide.

In certain embodiments, compounds in accordance with formula IX are not isolated, but instead carried through to step 5.

#### 20 Step 5:

A compound in accordance with formula Ia can be obtained by treating a compound in accordance with formula IX in a suitable solvent, such as, for example, water, with a suitable base, such as, for example, sodium hydroxide, and a suitable peroxide, such as, for example, hydrogen peroxide, followed by treatment with a suitable acidic solution, such as,  
25 for example, an aqueous solution of sodium hydrogen sulfate.



**Scheme 3****Step 1.1**

- 5 A compound in accordance with formula Ib can be obtained by treating a compound in accordance with formula Ia, with a suitable activating agent, such as, for example, 1,1'-carbonyldiimidazole, in a suitable solvent, such as, for example, tetrahydrofuran, chloroform, dimethylformamide, 2-methyl-tetrahydrofuran, or mixtures of two or more thereof, and subsequently adding a compound in accordance with formula IVa or a suitable salt thereof, such as, for example, the dihydrochloride, and a suitable base, such as, for example, triethylamine or diisopropylethylamine.
- 10

In one embodiment, a compound in accordance with formula Ib can be obtained by treating a compound in accordance with formula Ia, with a compound of formula IVa or a suitable salt thereof, such as, for example, the dihydrochloride, in the presence of a suitable base, such as, for example, N-methylmorpholine, diisopropylethylamine, or triethylamine and a suitable activating agent, such as, for example, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 1,1'-carbonyldiimidazole, or a mixture of 1-hydroxybenzotriazole and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, in

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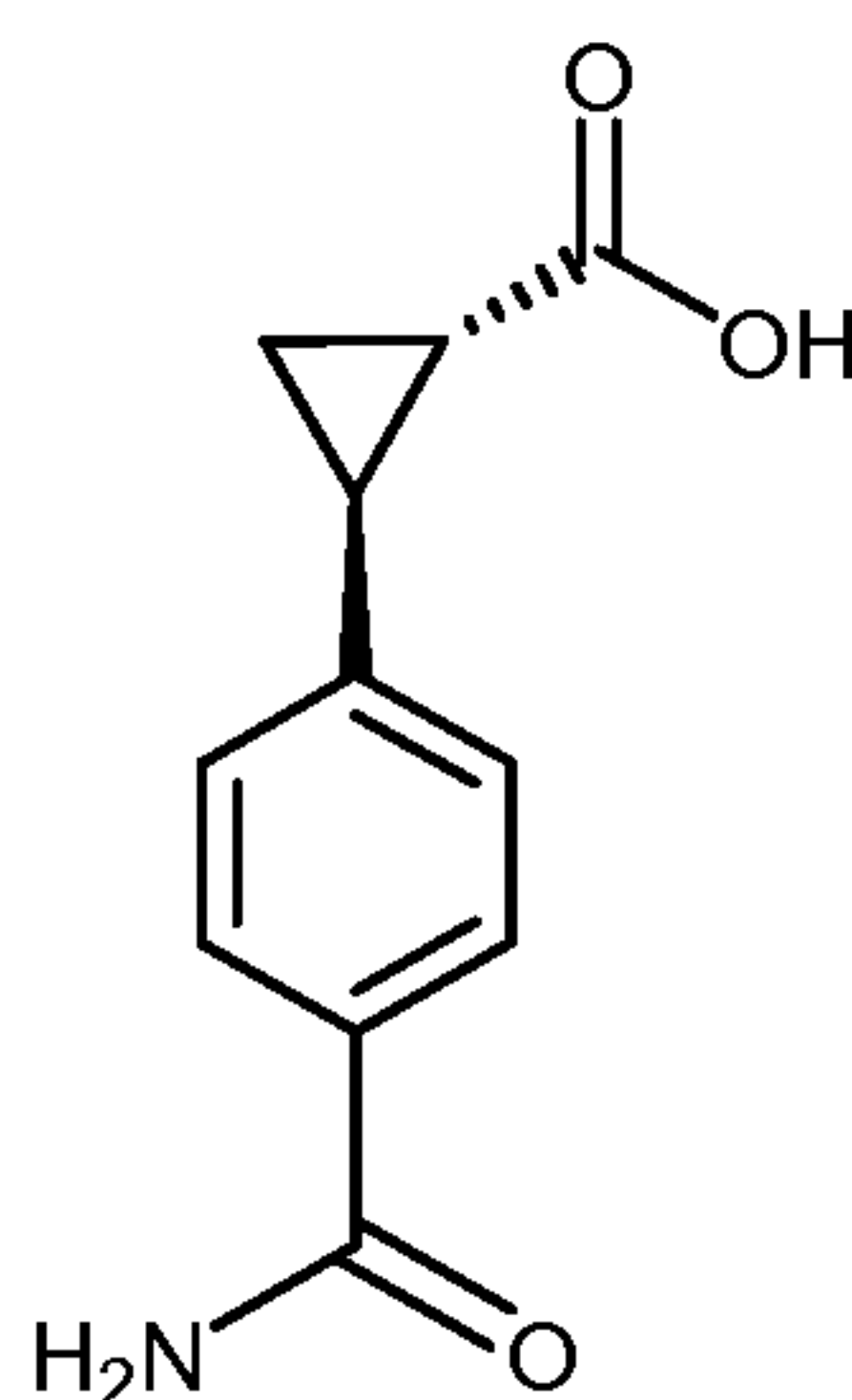
a suitable solvent, such as, for example, dimethylformamide, Me-THF, water, or mixtures thereof.

### Step 1.2

A compound in accordance with formula Ic can be obtained by treating a compound in accordance with formula Ia, with a compound of formula IVb or a suitable salt thereof, such as, for example, the dihydrochloride, in the presence of a suitable base, such as, for example, N-methylmorpholine or diisopropylethylamine, and a suitable activating agent, such as, for example, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, or a mixture of 1-hydroxybenzotriazole and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, in a suitable solvent, such as, for example, dimethylformamide, dimethylsulphoxide, water, or mixture thereof.

In one embodiment, a compound in accordance with formula Ic can be obtained by treating a compound in accordance with formula Ia, with a suitable activating agent, such as, for example, 1,1'-carbonyldiimidazole, in a suitable solvent, such as, for example, tetrahydrofuran, chloroform, dimethylformamide, 2-methyl-tetrahydrofuran, or mixture of two or more thereof, and subsequently adding a compound in accordance with formula IVb or a suitable salt thereof, such as, for example, the dihydrochloride, and a suitable base, such as, for example, triethylamine or diisopropylethylamine.

One aspect of the invention is a compound of formula Ia, or a pharmaceutically acceptable salt thereof,



(Ia)

to be used as an intermediate for the preparation of the compounds of formula Ib and Ic.



### EXAMPLES

The invention is further defined in the following Examples. It should be understood that the Examples are given by way of illustration only. From the above discussion and the Examples, one skilled in the art can ascertain the essential characteristics of the disclosure, and without departing from the spirit and scope thereof, can make various changes and modifications to adapt the disclosure to various uses and conditions. As a result, the disclosure is not limited by the illustrative examples set forth hereinbelow.

All temperatures are in degrees Celsius (°C) and are uncorrected.

Unless otherwise noted, commercial reagents used in preparing the example compounds were used as received without additional purification.

Unless otherwise noted, the solvents used in preparing the example compounds were commercial anhydrous grades and were used without further drying or purification.

All starting materials are commercially available, unless stated otherwise.

The following abbreviations may be employed herein: CBS: Corey-Bakshi-Shibata; <sup>13</sup>C NMR: carbon nuclear magnetic resonance; d: doublet; DMF: *N,N*-dimethyl formamide; DMSO: dimethyl sulfoxide; EDCI x HCl: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride; ES: electrospray; g: gram; h: hour(s); <sup>1</sup>H NMR: proton nuclear magnetic resonance; HPLC: high pressure liquid chromatography; kg: kilogram; L: liter; m: multiplet; M: molar; mL: milliliter; MHz: megahertz; min: minute(s); mmol: millimole; mol: mole; MS: mass spectrometry; NMM: *N*-methyl-morpholine; ppm: parts per million; s: singlet; 2-MeTHF: 2-methyl-tetrahydrofuran; br.: broad; Bu: butyl; calcd: calculated; Celite® : brand of diatomaceous earth filtering agent, registered trader of Celite Corporation; d: doublet; dd: doublet of doublet; ddd: doublet of doublet of doublet; dddd: doublet of doublet of doublet of doublet; DABCO: 1,4-diazabicyclo[2.2.2]octane; DCE: dichloroethane; DCM: dichloromethane; DIPEA: *N*-ethyl-*N*-isopropylpropan-2-amine; DME: dimethyl ether; DMEA: dimethyl ethylamine; dq: doublet of quartet; dt: doublet of triplet; EDC: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride; ESI: electrospray ion source; EtOAc: ethyl acetate; EtOH: ethanol; g: gram; h: hour(s); HBTU: *O*-Benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluoro-phosphate; HOBt: *N*-Hydroxybenzotriazole; HRMS: high resolution mass spectrometry; iPrOH: iso-propanol; MeOH: methanol; mg: milligram; MgSO<sub>4</sub>: anhydrous magnesium sulfate (drying agent); MPLC: medium pressure liquid chromatography; MTBE: methyl *tert*-butyl ether; NaHCO<sub>3</sub>: sodium bicarbonate; NH<sub>4</sub>Cl: ammonium chloride; q: quartet; quin: quintet; rt: room temperature; sat: saturated; t: triplet;

TEA: triethylamine; tBuOH: *tert*-butanol; td: triplet of doublet; TFA: trifluoroacetic acid; and THF: tetrahydrofuran.

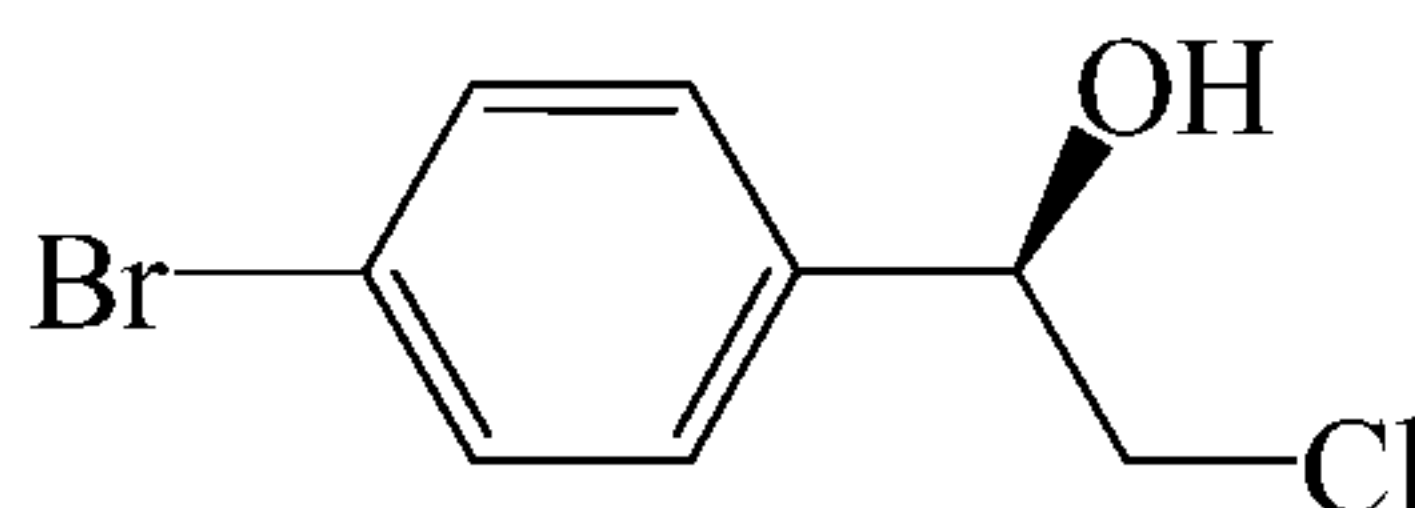
The mass spectra were recorded on a Waters MS consisting of an Alliance 2795 (LC (mobile phase: 5-90% B; A: H<sub>2</sub>O with 0.1% formic acid, B: CH<sub>3</sub>CN, 8.6 min run) on Xbridge C18 column, 3.0 x 50mm, 2.5μm particule size) and Waters Micromass ZQ detector at 120 °C. The mass spectrometer was equipped with an electrospray ion source (ESI) operated in a positive or negative ion mode. The mass spectrometer was scanned between *m/z* 120-800.

The <sup>1</sup>H NMR spectra were recorded on a Bruker UltraShield Advance 400MHz / 54mm spectrometer and processed with XWIN-NMR version 2.6 software. The chemical shifts (δ) are reported in parts-per-million from the deuterated solvent used.

The <sup>13</sup>C NMR spectra were recorded on a Bruker UltraShield Advance 125MHz / 54mm spectrometer and processed with XWIN-NMR version 2.6 software. The chemical shifts (δ) are reported in parts-per-million from the deuterated solvent used.

### Example 1

#### **(*R*)-1-(4-Bromo-phenyl)-2-chloro-ethanol**



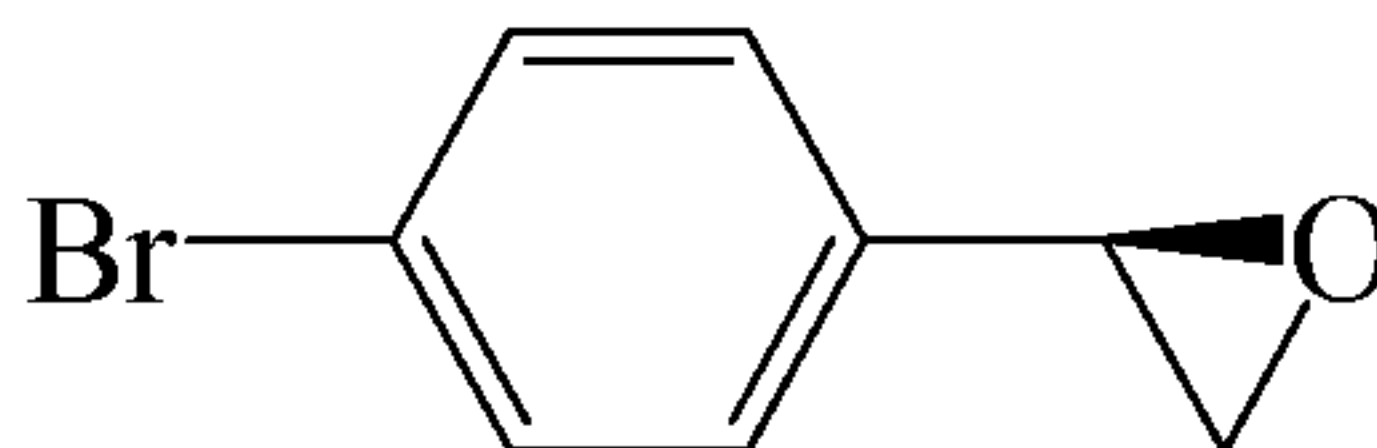
Borane dimethylsulfide (2.0 kg, 24.8 moles, 94% w/w) was mixed in toluene (8 L) at *t*<sub>jacket</sub>=20 °C. (*R*)-(+)-Methyl-CBS-oxazaborolidine (2.6 kg, 2.74 moles, 1M) as a toluene solution was added. The charging vessel was rinsed with toluene (0.5 L) and *t*<sub>jacket</sub> was set to 45 °C. 1-(4-Bromo-phenyl)-2-chloro-ethanone (7.84 kg, 33.6 moles), which is commercially available from Jiangyan Keyan Fine Chemical Co. Ltd, was dissolved in 2-MeTHF (75 L) in a separate vessel and when *t*<sub>inner</sub> was above 40 °C in the first vessel, the 2-MeTHF solution was added during 3 h. The latter vessel was rinsed with 2-MeTHF (2 L) and added to the reaction mixture, which was left stirring at *t*<sub>jacket</sub>=45 °C for 1 h. Analysis of a sample on HPLC indicated full conversion at this point using the following gradient method (mobile phase 20-95% B; A: 5% CH<sub>3</sub>CN in H<sub>2</sub>O with 0.1% TFA, B: 95% CH<sub>3</sub>CN in H<sub>2</sub>O with 0.085% TFA, 10 min run) on Chromolith Performance RP-18e, 4.6 x 100 mm. The reaction mixture was cooled to *t*<sub>jacket</sub>=10 °C before slow quench with MeOH (36 L). The first liter of MeOH was added during 30 min. and the rest during additional 30 min. MeOH was distilled off under vacuum at *t*<sub>jacket</sub>=50 °C. The organic solution left was cooled to *t*<sub>jacket</sub>=20 °C, washed with 1M HCl in H<sub>2</sub>O (7 L conc HCl + 73 L H<sub>2</sub>O) and concentrated under vacuum at



$t_{\text{jacket}}=50\text{ }^{\circ}\text{C}$  to approximately 40 L. **Example 1** obtained in a 2-MeTHF solution can be stored at  $10\text{ }^{\circ}\text{C}$  for 20 h or used directly in the next synthetic step.

### Example 2

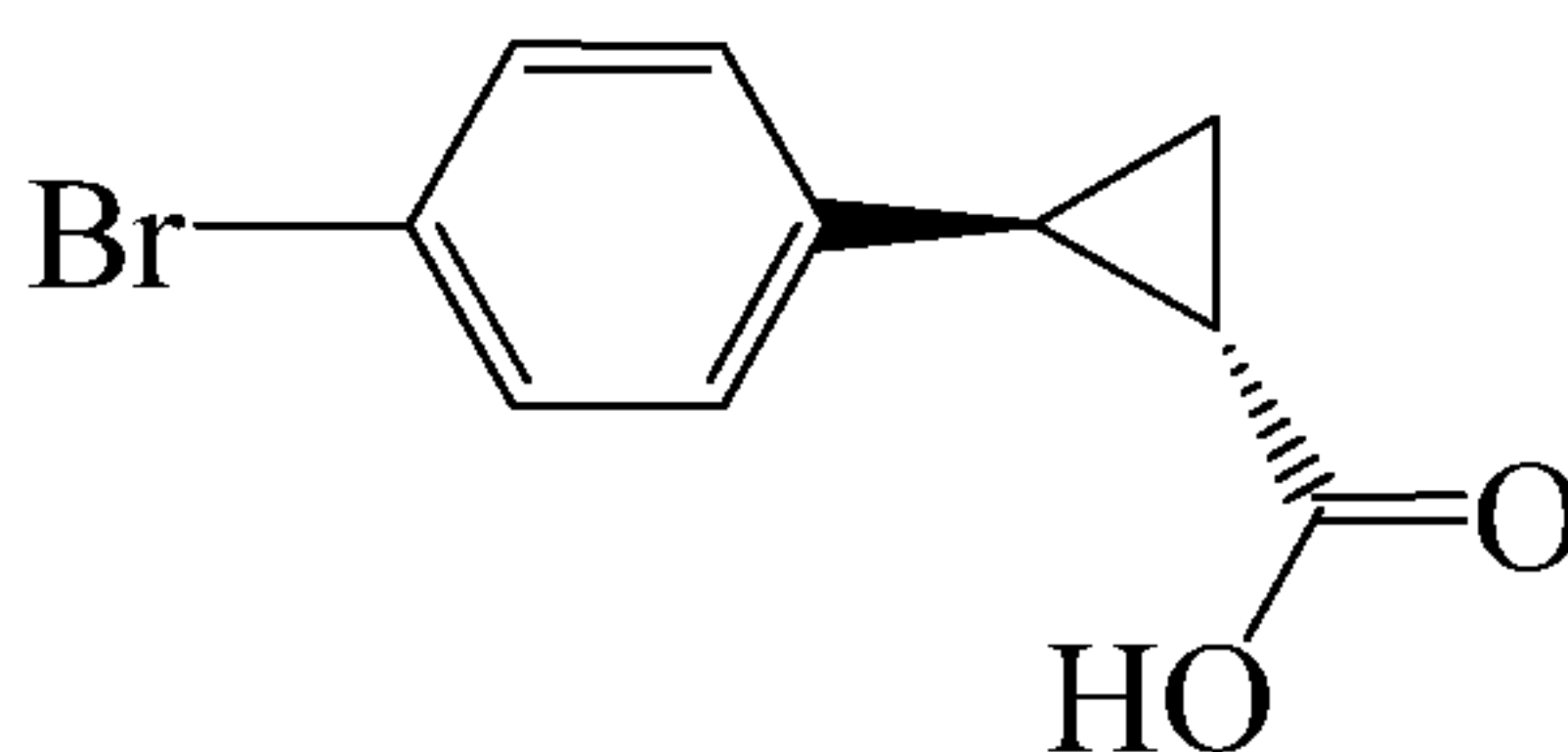
#### **(R)-2-(4-Bromo-phenyl)-oxirane**



Aliquat ® 175 (methyl tributyl ammonium chloride) (1.12 kg, 4.75 moles) was added to **Example 1** as a 2-MeTHF solution (33.6 moles, 40 L) at  $t_{\text{jacket}}=20\text{ }^{\circ}\text{C}$ . NaOH (5.1 kg, 57.4 moles, 45% w/w) diluted in H<sub>2</sub>O (2 L) was added during 20 min. The reaction mixture was left stirring at  $t_{\text{jacket}}=20\text{ }^{\circ}\text{C}$  for 2 h. Analysis of a sample on HPLC indicated full conversion at this point using the following gradient method (mobile phase 20-95% B; A: 5% CH<sub>3</sub>CN in H<sub>2</sub>O with 0.1% TFA, B: 95% CH<sub>3</sub>CN in H<sub>2</sub>O with 0.085% TFA, 10 min run) on Chromolith Performance RP-18e, 4.6 x 100 mm. The aq. phase was separated off and the organic phase washed with H<sub>2</sub>O (2 x 25 L). 2-MeTHF (25 L) was added and the organic phase concentrated under vacuum at  $t_{\text{jacket}}=50\text{ }^{\circ}\text{C}$  to approximately 30 L. **Example 2** obtained in a 2-MeTHF solution, can be stored at  $5\text{ }^{\circ}\text{C}$  for 140 h or used directly in the next synthetic step.

### Example 3

#### **(1S, 2S)-2-(4-Bromo-phenyl)-cyclopropanecarboxylic acid**



Triethyl phosphonoacetate (10.5 L, 51.9 moles, 98% w/w) was dissolved in 2-MeTHF (14 L) at  $t_{\text{jacket}}=-20\text{ }^{\circ}\text{C}$ . Hexyl lithium in hexane (21 L, 48.3 moles, 2.3 M) was added at a rate to maintain  $t_{\text{inner}}$  below  $0^{\circ}\text{C}$ . The charging vessel was rinsed with 2-MeTHF (3 L) and the reaction solution was left stirring at  $t_{\text{jacket}}=10\text{ }^{\circ}\text{C}$ . **Example 2** as a 2-MeTHF solution (33.6 moles, 30 L) was added during 20 min. The charging vessel was rinsed with 2-MeTHF (2 L) and the reaction solution was left stirring at  $t_{\text{jacket}}=65\text{ }^{\circ}\text{C}$  for at least 16 h with the last 3 h at  $t_{\text{jacket}}=75\text{ }^{\circ}\text{C}$ . Analysis of a sample on HPLC using the following gradient method (mobile phase 20-95% B; A: 5% CH<sub>3</sub>CN in H<sub>2</sub>O with 0.1% TFA, B: 95% CH<sub>3</sub>CN in H<sub>2</sub>O with 0.085% TFA, 10 min run) on Chromolith Performance RP-18e, 4.6 x 100 mm indicated full conversion to the intermediate (1S, 2S)-2-(4-bromo-phenyl)-cyclopropanecarboxylic acid

ethyl ester. The reaction solution was cooled to  $t_{\text{jacket}}=20\text{ }^{\circ}\text{C}$ . NaOH (7.6 kg, 85.5 moles, 45% w/w) diluted in  $\text{H}_2\text{O}$  (12 L) was added over 20 min. The reaction solution obtained was left stirring at  $t_{\text{jacket}}=60\text{ }^{\circ}\text{C}$  for at least 2 h. Analysis of a sample on HPLC indicated full conversion at this point using the following gradient method (mobile phase 20-95% B; A: 5%  $\text{CH}_3\text{CN}$  in  $\text{H}_2\text{O}$  with 0.1% TFA, B: 95%  $\text{CH}_3\text{CN}$  in  $\text{H}_2\text{O}$  with 0.085% TFA, 10 min run) on Chromolith Performance RP-18e, 4.6 x 100 mm. The reaction solution was cooled to  $t_{\text{jacket}}=20\text{ }^{\circ}\text{C}$ , the aq. phase was separated off and the organic phase was extracted with  $\text{H}_2\text{O}$  (37 L). The combined aq. phases were acidified to  $\text{pH} < 3.5$  with  $\text{H}_3\text{PO}_4$  (9 L, 131 moles, 85% w/w) diluted in  $\text{H}_2\text{O}$  (12.5 L). Only 17 L of the diluted  $\text{H}_3\text{PO}_4$  (aq) was used to achieve the  $\text{pH} < 3.5$ . The acidic aq. phase was extracted with 2-MeTHF ( $2 \times 15\text{ L}$ ). The combined organic phases including rinsing with 2-MeTHF (2 L) were concentrated under vacuum at  $t_{\text{jacket}}=50\text{ }^{\circ}\text{C}$  to approximately 11 L. The 2-MeTHF solution was diluted with EtOH (14.5 L) at  $t_{\text{jacket}}=35\text{ }^{\circ}\text{C}$  and  $\text{H}_2\text{O}$  (16 L) was added over 20 min. The reaction solution was cooled to  $t_{\text{jacket}}=28\text{ }^{\circ}\text{C}$ . Seed (16 g, 0.066 moles) was added and the solution was stirred for 2 h at  $t_{\text{jacket}}=28\text{ }^{\circ}\text{C}$ . The reaction mixture was cooled to  $t_{\text{jacket}}=0\text{ }^{\circ}\text{C}$  over 6 h and left stirring for at least 1 h. Additional  $\text{H}_2\text{O}$  (8 L) was added during 40 min. and the product was filtered off and washed with cold  $\text{H}_2\text{O}$  (10 L). Drying under vacuum at  $40\text{ }^{\circ}\text{C}$  gave 6.18 kg **Example 3** (21.5 moles, 84% w/w), 64% yield over four steps from 7.84 kg 1-(4-bromo-phenyl)-2-chloro-ethanone (33.6 moles).

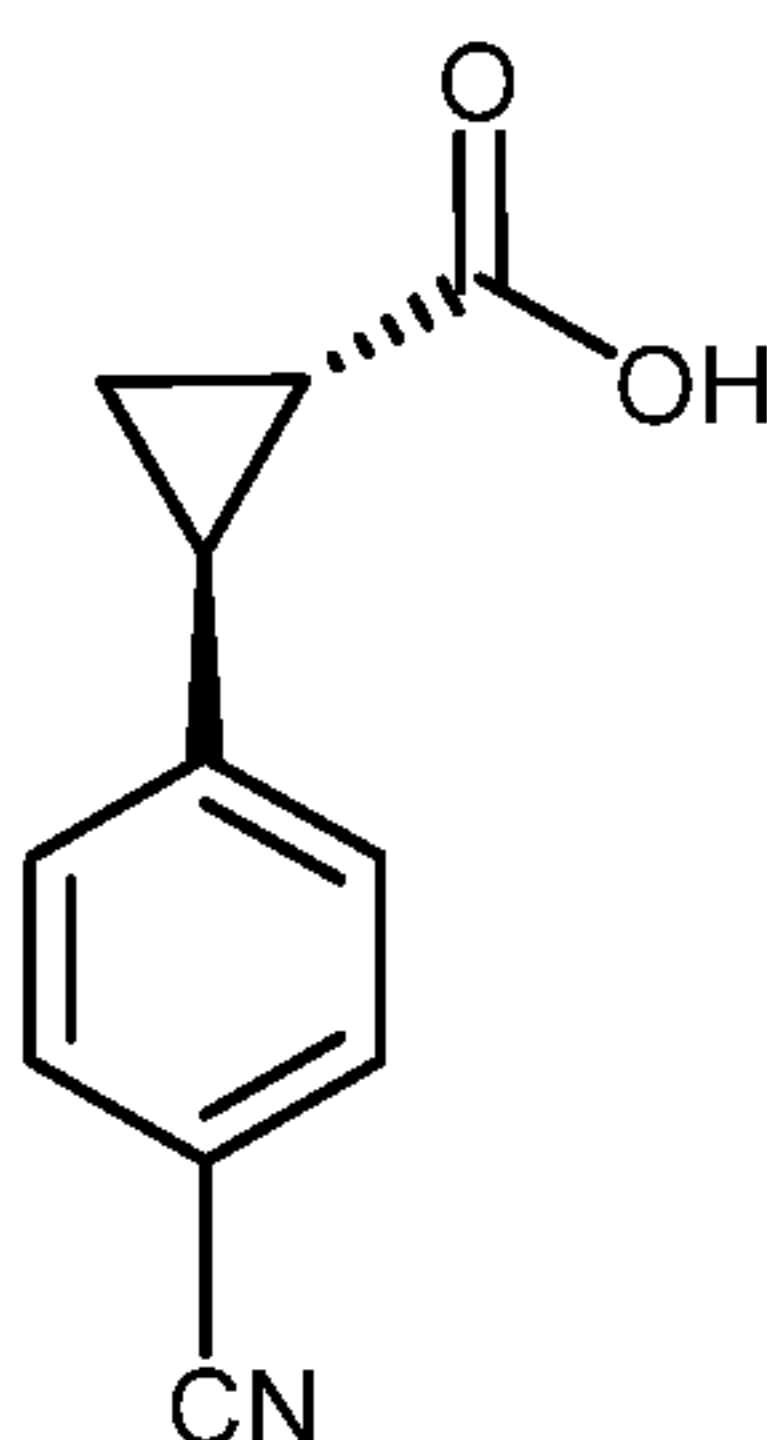
Recrystallization of **Example 3**: Two batches of **Example 3** (6.18 + 7.04 kg) were mixed in EtOH (52 L) and heated at  $t_{\text{jacket}}=70\text{ }^{\circ}\text{C}$ .  $\text{H}_2\text{O}$  (52 L) was added. The reaction solution was cooled to  $t_{\text{jacket}}=30\text{ }^{\circ}\text{C}$  over 2.5 h.  $\text{H}_2\text{O}$  (16 L) was added during 20 min. and the crystallization was cooled to  $t_{\text{jacket}}=20\text{ }^{\circ}\text{C}$  during 3 h. The product was filtered off and washed with a mixture of  $\text{H}_2\text{O}$  (8 L) and EtOH (2 L). Drying under vacuum at  $40\text{ }^{\circ}\text{C}$  gave 10.0 kg **Example 3** (41.5 moles, 88% w/w), which was redissolved in toluene (39 L) and isooctane (57 L) at  $t_{\text{jacket}}=60\text{ }^{\circ}\text{C}$ . A clear solution was obtained. The reaction solution was cooled to  $t_{\text{jacket}}=45\text{ }^{\circ}\text{C}$  and left stirring for 1 h, then cooled to  $t_{\text{jacket}}=20\text{ }^{\circ}\text{C}$  over 2 h. The product was filtered off and washed with a mixture of toluene (4 L) and isooctane (36 L) in two portions. Drying under vacuum at  $40\text{ }^{\circ}\text{C}$  gave 7.4 kg **Example 3** (29.8 moles, 97% w/w), 44% yield over four steps from 7.84 + 7.93 kg 1-(4-bromo-phenyl)-2-chloro-ethanone (67.5 moles).  $^1\text{H}$ -NMR ( $\text{DMSO-d}_6$ ):  $\delta$  12.36 (s, 1H), 7.44 (d, 2H,  $J=8\text{ Hz}$ ), 7.13 (d, 2H,  $J=8\text{ Hz}$ ), 2.39 (m, 1H), 1.81 (m, 1H), 1.43 (m, 1H), 1.33 (m, 1H);  $^{13}\text{C}$ -NMR ( $\text{DMSO-d}_6$ ):  $\delta$  173.76, 139.88, 131.20, 128.24, 119.14, 24.73, 24.31, 16.78; LC-MS (ESI):  $m/z$  239 ( $\text{M}-1$  ( $\text{Br}^{79}$ )) and



241 (M-1 ( $\text{Br}^{81}$ )).  $R_t=5.03$  min with analytical method (mobile phase: 5-90% B; A:  $\text{H}_2\text{O}$  with 0.1% formic acid, B:  $\text{CH}_3\text{CN}$ , 8.6 min run) on Xbridge C18, 3.0 x 50mm, 2.5  $\mu\text{m}$  particle size. The product was analyzed on a chiral column with UV-detection using isocratic method (mobile phase: EtOH/Isohexane/TFA (15/85/0.1 v/v/v)) on Kromosil 3-Amycoat, 150 x 4.6 mm, 3  $\mu\text{m}$  particle size, giving an enantiomeric purity of 98.9% ee,  $R_t=5.29$  min (isomer 1) and 5.97 min (isomer 2).

#### Example 4

##### **(1*S*, 2*S*)-2-(4-Cyano-phenyl)-cyclopropanecarboxylic acid**

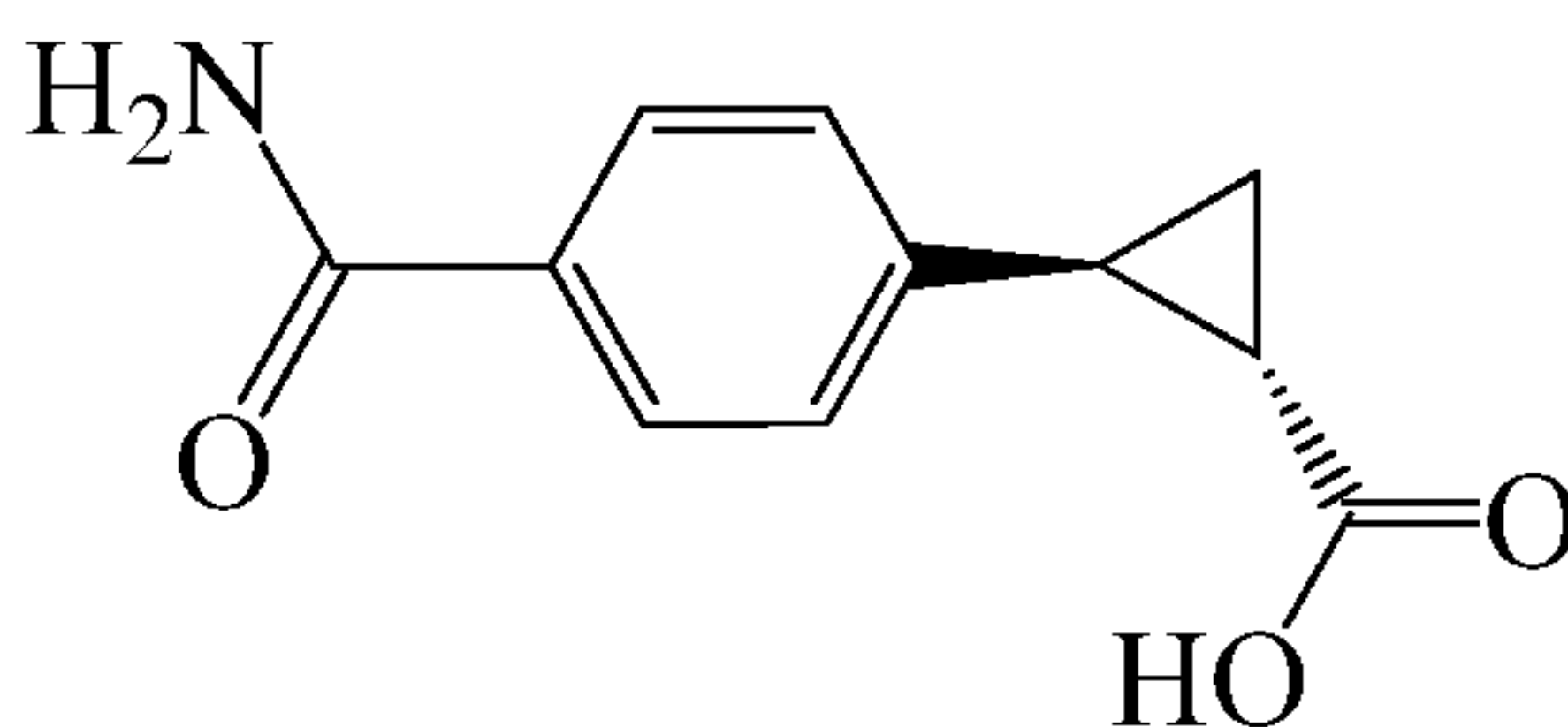


10           **Example 3** (3.7 kg, 14.9 moles, 97% w/w) and zinc-dust (98%+, <10 $\mu\text{m}$ ) (99 g, 1.51 moles) were mixed with DMF (13.5 L) and the slurry was stirred at  $t_{\text{jacket}}=20$  °C. The mixture was inerted and left with  $\text{N}_2$  pressure of 0.1-0.2 bar. Bis(tri-*t*-butylphosphine)palladium (0) (27.5 g, 0.054 moles) was added to the slurry, and the vessel was inerted and left with  $\text{N}_2$  pressure of 0.1-0.2 bar. The mixture was heated to  $t_{\text{jacket}}=45$  °C, 15  $\text{Zn}(\text{CN})_2$  (1.0 kg, 8.52 moles) was added to the suspension in one portion, and the system was inerted and left with  $\text{N}_2$  pressure of 0.1-0.2 bar (N.B. Cyanide salts are highly toxic). The resulting mixture was heated to  $t_{\text{jacket}}=75$  °C and stirred for at least 2 h. Analysis of a sample on HPLC indicated full conversion at this point using the following gradient method (mobile phase 20-95% B; A: 5%  $\text{CH}_3\text{CN}$  in  $\text{H}_2\text{O}$  with 0.05% formic acid, B: 95%  $\text{CH}_3\text{CN}$  in  $\text{H}_2\text{O}$  with 0.05% formic acid, 8 min run) on Chromolith Performance RP-18e, 4.6 x 100 mm. The reaction mixture was cooled to  $t_{\text{jacket}}=20$  °C. Thiol-functionalized silica (Silicycle, SiliaBond Thiol) (1.07 kg, 28% w/w) was added and the vessel was inerted. The reaction mixture was stirred for at least 36 h at  $t_{\text{jacket}}=20$  °C. The scavenger was filtered off via a filter with activated charcoal or equivalent (pall-filter). The vessel and the filter system were washed 20 with 2-MeTHF (53 L). The filtrate and washings were combined and stirred at  $t_{\text{jacket}}=5$  °C. A pale yellow liquid resulted. NaCl (3.5 kg) in  $\text{H}_2\text{O}$  (16.4 L) was added during 15 min. at such a rate so the inner temperature remained below 15 °C. The resulting reaction mixture was 25 heated to  $t_{\text{jacket}}=45$  °C and the aq. phase was separated off. The organic phase was washed

with  $\text{NaHSO}_4 \times \text{H}_2\text{O}$  in  $\text{H}_2\text{O}$  ( $2 \times (2.87 \text{ kg} + 16.4 \text{ L})$ ) and  $\text{NaCl}$  in  $\text{H}_2\text{O}$  ( $3.5 \text{ kg} + 16.4 \text{ L}$ ). The organic phase was cooled to  $t_{\text{jacket}}=10^\circ\text{C}$  and  $\text{NaOH}$  ( $1.54 \text{ kg}$ ,  $19.3 \text{ moles}$ ,  $50\% \text{ w/w}$ ) diluted in  $\text{H}_2\text{O}$  ( $41 \text{ L}$ ) was added during  $45 \text{ min}$ . The resulting reaction mixture was heated to  $t_{\text{jacket}}=30^\circ\text{C}$  and the organic phase separated off. The aq. phase was stirred at  $t_{\text{jacket}}=20^\circ\text{C}$  and pH adjusted to  $6.5$  with  $\text{H}_3\text{PO}_4$  ( $0.90 \text{ kg}$ ,  $7.81 \text{ moles}$ ,  $85\% \text{ w/w}$ ) diluted in  $\text{H}_2\text{O}$  ( $5.3 \text{ L}$ ) at a rate that maintained the inner temperature below  $25^\circ\text{C}$ . 2-MeTHF and  $\text{H}_2\text{O}$  were distilled off under vacuum until a volume  $85\text{--}90\%$  of the volume prior to distillation, approximately  $8 \text{ L}$ . The reaction mixture was cooled to  $t_{\text{jacket}}=0^\circ\text{C}$  and continued charging off  $\text{H}_3\text{PO}_4$  ( $1.17 \text{ kg}$ ,  $10.1 \text{ moles}$ ,  $85\% \text{ w/w}$ ) diluted in  $\text{H}_2\text{O}$  ( $8.2 \text{ L}$ ) until  $\text{pH}=4$ . The slurry was left stirring overnight at  $t_{\text{jacket}}=10^\circ\text{C}$ . The product was filtered off, washed with  $\text{H}_2\text{O}$  ( $2 \times 4 \text{ L}$ ). Drying under vacuum at  $40^\circ\text{C}$  gave **Example 4** ( $2.24 \text{ kg}$ ,  $11.2 \text{ moles}$ ,  $93.2\% \text{ w/w}$ ),  $75\%$  yield.  $^1\text{H}$ -NMR ( $\text{DMSO-d}_6$ ):  $\delta$   $12.45$  (s,  $1\text{H}$ ),  $7.72$  (d,  $2\text{H}$ ,  $J=8 \text{ Hz}$ ),  $7.37$  (d,  $2\text{H}$ ,  $J=8 \text{ Hz}$ ),  $2.50$  (m,  $1\text{H}$ ),  $1.94$  (m,  $1\text{H}$ ),  $1.50$  (m,  $1\text{H}$ ),  $1.42$  (m,  $1\text{H}$ );  $^{13}\text{C}$ -NMR ( $\text{DMSO-d}_6$ ):  $\delta$   $173.51$ ,  $146.68$ ,  $132.27$ ,  $126.93$ ,  $118.97$ ,  $108.85$ ,  $25.16$ ,  $25.04$ ,  $17.44$ ; LC-MS (ESI):  $m/z$   $186$  ( $\text{M}-1$ ).  $R_t=3.63 \text{ min}$  with analytical method (mobile phase:  $5\text{--}90\% \text{ B}$ ; A:  $\text{H}_2\text{O}$  with  $0.1\% \text{ formic acid}$ , B:  $\text{CH}_3\text{CN}$ ,  $8.6 \text{ min run}$ ) on Xbridge C18,  $3.0 \times 50\text{ mm}$ ,  $2.5 \mu\text{m}$  particle size.

### Example 5

#### (1*S*, 2*S*)-2-(4-Carbamoyl-phenyl)-cyclopropanecarboxylic acid



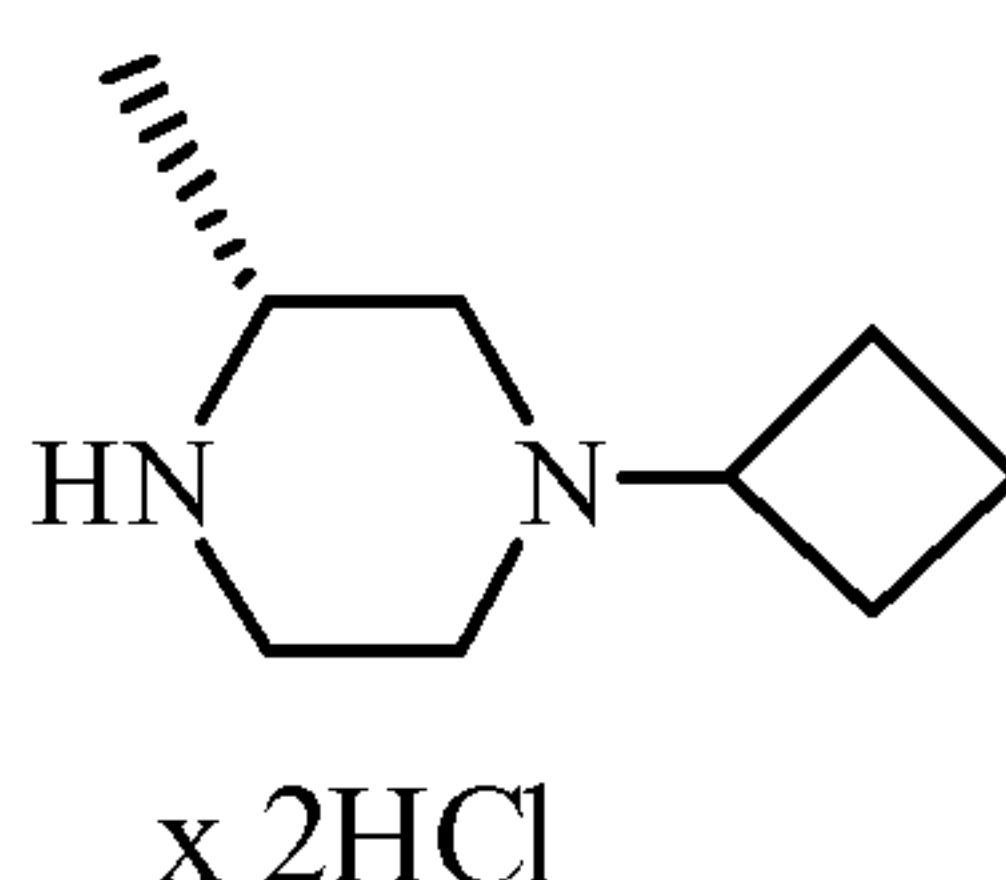
**Example 4** ( $4.46 \text{ kg}$ ,  $22.0 \text{ moles}$ ,  $92.5\% \text{ w/w}$ ) was mixed in  $\text{H}_2\text{O}$  ( $40 \text{ L}$ ) at  $t_{\text{jacket}}=30^\circ\text{C}$ .  $\text{NaOH}$  ( $2.25 \text{ kg}$ ,  $28.1 \text{ moles}$ ,  $50\% \text{ w/w}$ ) diluted in  $\text{H}_2\text{O}$  ( $6 \text{ L}$ ) was added at such a rate so  $t_{\text{inner}}$  remained below  $35^\circ\text{C}$ . The charging vessel was rinsed with  $\text{H}_2\text{O}$  ( $1 \text{ L}$ ). If the pH was not  $\geq 12$ , more  $\text{NaOH}$  was charged in the same concentration as previously. Hydrogen peroxide ( $4.89 \text{ kg}$ ,  $50.3 \text{ moles}$ ,  $35\% \text{ w/w}$ ) was added at a rate to maintain  $t_{\text{inner}}$  below  $35^\circ\text{C}$ . The charging vessel was rinsed with  $\text{H}_2\text{O}$  ( $1 \text{ L}$ ) and the reaction slurry was left stirring for  $0.5\text{--}1.0 \text{ h}$ . Analysis of a sample on HPLC indicated full conversion at this point using the following gradient method (mobile phase  $20\text{--}95\% \text{ B}$ ; A:  $5\% \text{ CH}_3\text{CN}$  in  $\text{H}_2\text{O}$  with  $0.05\% \text{ formic acid}$ , B:  $95\% \text{ CH}_3\text{CN}$  in  $\text{H}_2\text{O}$  with  $0.05\% \text{ formic acid}$ ,  $8 \text{ min run}$ ) on Chromolith Performance RP-18e,  $4.6 \times 100 \text{ mm}$ . The reaction mixture was cooled to  $t_{\text{jacket}}=0^\circ\text{C}$  and left stirring for at least  $0.5 \text{ h}$  when the temperature was reached. The sodium salt of **Example 5**



was filtered off and washed with cold H<sub>2</sub>O (2×7 L). The solid was slurry washed on the filter with NaHSO<sub>4</sub> × H<sub>2</sub>O (2.76 kg, 20.0 moles) diluted in H<sub>2</sub>O (35 L). The slurry was kept stirring at  $t_{\text{jacket}}=0$  °C for 1 h. If the pH was not < 3.7, it was adjusted with NaHSO<sub>4</sub> × H<sub>2</sub>O in H<sub>2</sub>O. The product was filtered off, washed with cold H<sub>2</sub>O (3 ×14 L). Drying under vacuum at 40 °C gave **Example 5** (4.0 kg, 18.2 moles, 93.4% w/w), 83% yield. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 12.40 (s, 1H), 7.94 (s, 1H), 7.79 (d, 2H, J=8 Hz), 7.32 (s, 1H), 7.23 (d, 2H, J=8 Hz), 2.44 (m, 1H), 1.88 (m, 1H), 1.47 (m, 1H), 1.39 (m, 1H); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ 173.83, 167.67, 143.94, 132.17, 127.68, 125.73, 25.21, 24.67, 17.11; LC-MS (ESI): *m/z* 206 (M+1). *R*<sub>t</sub>=2.13 min with analytical method (mobile phase: 5-90% B; A: H<sub>2</sub>O with 0.1% formic acid, B: CH<sub>3</sub>CN, 8.6 min run) on Xbridge C18, 3.0 x 50mm, 2.5 μm particle size. The product was analyzed on a chiral column with UV-detection using isocratic method (mobile phase: EtOH/Isohexane/TFA (15/85/0.1 v/v/v)) on Kromosil 3-Amycoat, 150 x 4.6 mm, 3 μm particle size, giving an enantiomeric purity of >99% ee, *R*<sub>t</sub>=13.40 min (isomer 1) and 22.22 min (isomer 2).

### Example 6

#### **(*R*)-1-Cyclobutyl-3-methylpiperazine × 2HCl**

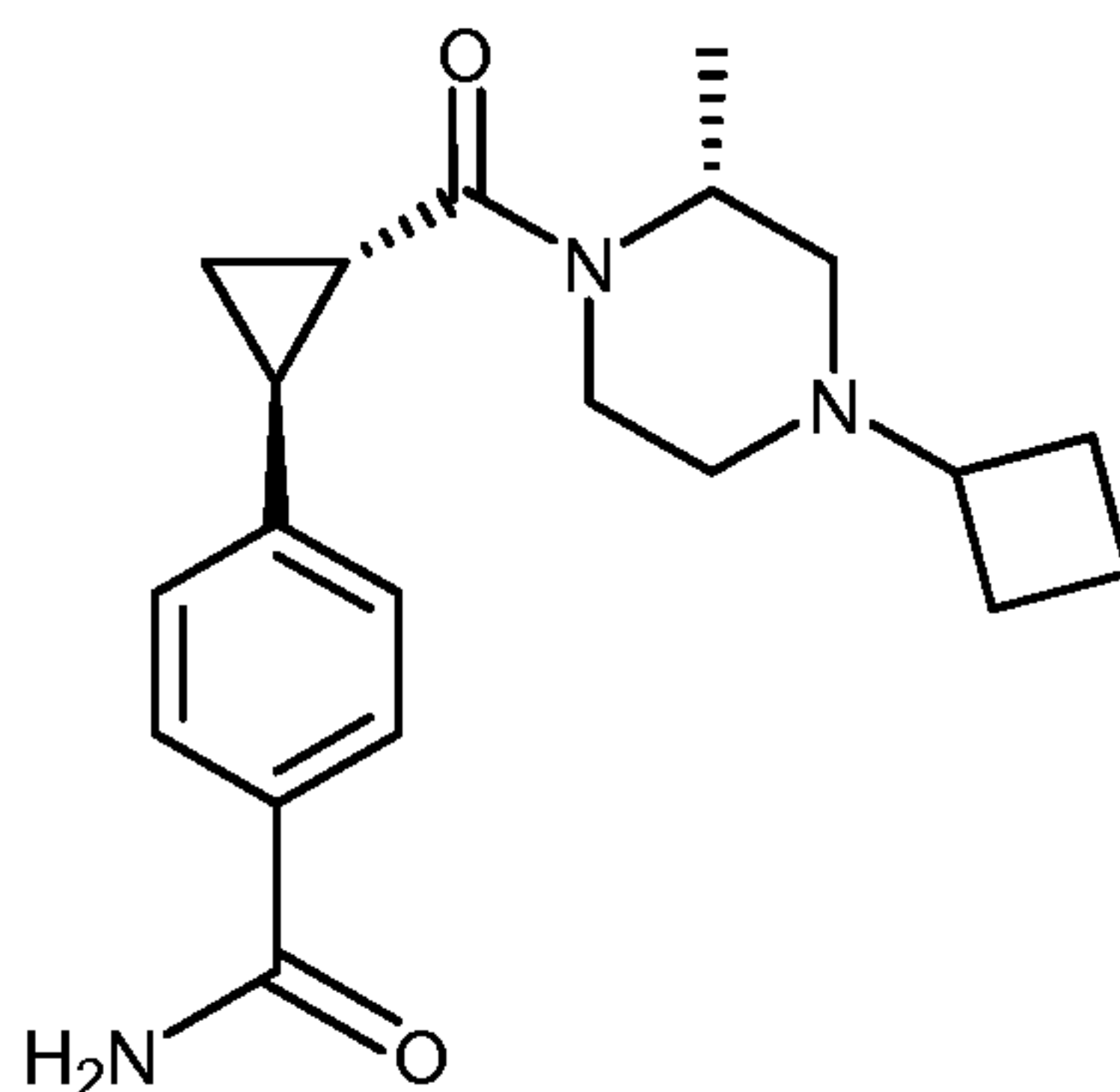


(*R*)-Boc-2-methylpiperazine (350 g, 1.71 moles, 98% w/w), which is commercially available from Lanzhou Boc Chemical Co., was dissolved in EtOH (2.75 L) at  $t_{\text{jacket}}=20$  °C. Acetic acid (1.37 L) was added in one portion followed by the addition of cyclobutanone (184 g, 2.57 moles). The charging vessel was rinsed with EtOH (250 mL) and the light yellow solution was left stirring at  $t_{\text{jacket}}=20$  °C for 1 h. NaBH(OAc)<sub>3</sub> (497 g, 2.48 moles, 95% w/w) was added in 20 portions over 90 min. EtOH (340 mL) was used for rinsing. The reaction mixture was left stirring for 2 h. A sample was analyzed on GC using HP-5MS column (length 25 m, ID 0.32 mm, Film 0.52 μm) with a gradient method (2 min at 60 °C, followed by 25 °C/min during 8 min then 2 min at 260 °C). Frontinlet temperature=200 °C using He as gas and a detector temperature=300 °C. More NaBH(OAc)<sub>3</sub> (30 g, 0.14 moles) was added to complete the reaction within 1 h. The reaction mixture was cooled to  $t_{\text{jacket}}=0$  °C before quenching with 5M NaOH (5.5 L). EtOH was distilled off under vacuum at  $t_{\text{jacket}}=$

50 °C. The H<sub>2</sub>O phase was extracted with toluene (5.5 L) at  $t_{\text{jacket}}=20$  °C. The organic phase was combined with a second batch, started with (*R*)-Boc-2-methylpiperazine (300 g, 1.47 moles, 98% w/w). The combined organic phases were concentrated under vacuum at  $t_{\text{jacket}}=50$  °C to approximately 2 L. The obtained toluene solution with the intermediate can be stored at 5 °C for several days. The toluene solution was diluted with 2-propanol (2 L) at  $t_{\text{jacket}}=10$  °C, and HCl in 2-propanol (1.06 L, 6.36 moles, 6M) diluted in 2-propanol (2 L) was added over 30 min. The reaction solution was heated to  $t_{\text{jacket}}=48$  °C. HCl in 2-propanol (2.12 L, 12.72 moles, 6M) diluted in 2-propanol (2 L) was added over 2 h at  $t_{\text{inner}}=46$  °C. The reaction solution was kept at  $t_{\text{jacket}}=48$  °C for an additional 3 h before being cooled to  $t_{\text{jacket}}=0$  °C over 1 h. A seed mixture (0.4 L reaction solution with **Example 6** (0.2 g, 0.89 mmol)) was added. The reaction mixture was left stirring at  $t_{\text{jacket}}=0$  °C overnight and the product was filtered off. Drying under vacuum at 40 °C gave **Example 6** (620 g, 2.63 moles, 96.3% w/w), 83% yield. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 12.46 (s, 1H), 10.13 (s, 2H), 3.35-3.74 (m, 6H), 3.09 (m, 1H), 2.92 (m, 1H), 2.39 (m, 2H), 2.16 (m, 2H), 1.72 (m, 2H), 1.32 (d, 3H, *J*=6.4 Hz); <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>): δ 58.50, 49.62, 48.13, 44.30, 24.48, 24.38, 15.25, 13.26

### Example 7

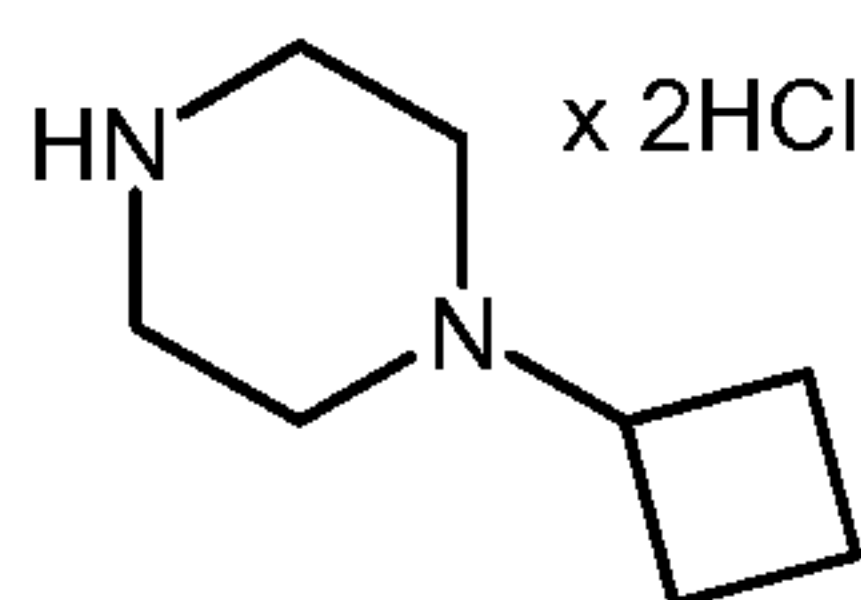
**4-{(1*S*, 2*S*)-2-[(*R*)-4-Cyclobutyl-2-methylpiperazin-1-yl]carbonyl]-cyclopropyl}-benzamide**



**Example 5** (10.0g, 48.7 mmol) was mixed in 2-MeTHF (200mL) at  $t_{\text{jacket}}=25$  °C. 1,1'-Carbonyldiimidazole (11.0 g, 53.6mmol, 82.1% w/w) was added in 1 portion. The reaction slurry was slowly heated to  $t_{\text{jacket}}=85$  °C and after approximately 5 h the reaction slurry was cooled to  $t_{\text{reaction mixture}}=25$  °C. **Example 6** (13.8 g, 58.5 mmol) and TEA (7.55 mL, 53.6mmol) were added to the reaction slurry. The reaction slurry was heated at  $t_{\text{jacket}}=70$  °C for 3h. Analysis of a sample on HPLC indicated full conversion at this point using the gradient method (mobile phase 20-95% B; A: 5% CH<sub>3</sub>CN in H<sub>2</sub>O with 0.1% TFA, B: 95% CH<sub>3</sub>CN in H<sub>2</sub>O with 0.085% TFA, 10 min run) on Chromolith Performance RP-18e,



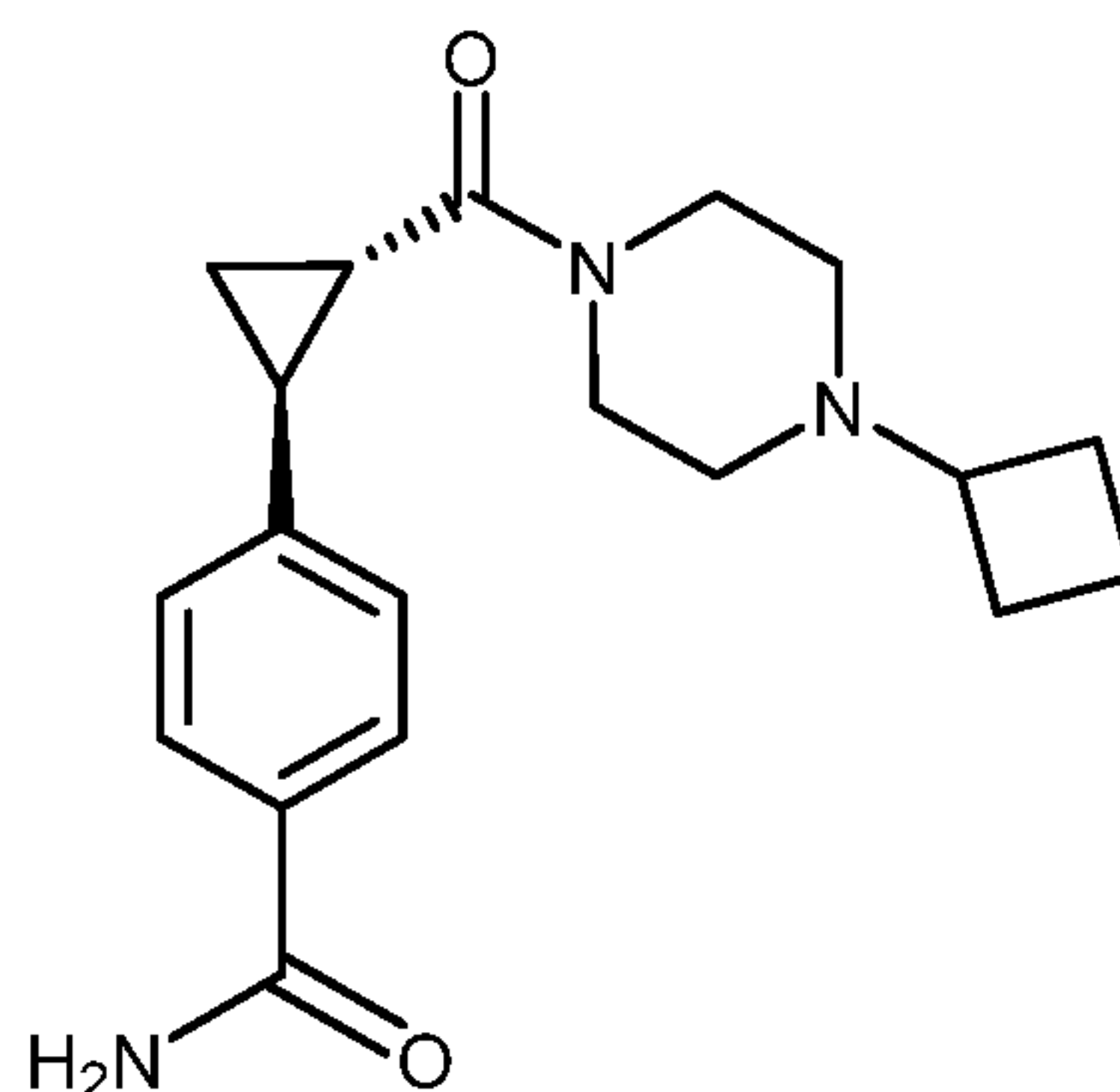
4.6 x 100 mm. The reaction slurry was cooled to  $t_{\text{jacket}}=40\text{ }^{\circ}\text{C}$ . 1M  $\text{Na}_2\text{CO}_3$  in brine (90 mL) was added. The aq. phase was separated off and the organic phase was washed with brine (2 L). The assay of **Example 7** in the organic phase was determined by  $^1\text{H}$  NMR and the volume of the organic phase was adjusted to 10 relative volumes (15.4 g of **Example 7**). The organic phase was cooled to  $t_{\text{jacket}}=15\text{ }^{\circ}\text{C}$  and extracted with 10%  $\text{H}_3\text{PO}_4$  in  $\text{H}_2\text{O}$  (charged until pH 2.5, 110 mL). The lower aq. phase was collected and the remaining organic phase was re-extracted with 10%  $\text{H}_3\text{PO}_4$  in  $\text{H}_2\text{O}$  (50 mL). The combined aq. phases were basified to pH >12 with 5M KOH and extracted with MeTHF twice (200 mL, 50 mL). The combined organic phases were extracted with brine (50 mL) and filtered to remove inorganic salts. The assay of **Example 7** in the organic phase was determined by  $^1\text{H}$  NMR and the volume of the organic phase was reduced to 6 relative volumes (14.4 g of **Example 7**, 86 mL). Crystallisation was performed starting at  $T_{\text{jacket}}=55\text{ }^{\circ}\text{C}$ . After cooling to  $t_{\text{jacket}}=40\text{ }^{\circ}\text{C}$ , heptane (21.6 mL) as well as seed (128 mg of **Example 7**) was added. The mixture was after aging cooled down to  $t_{\text{jacket}}=20\text{ }^{\circ}\text{C}$ , when a second addition of heptane (64.8 mL) was performed. The product was filtered off and washed with MeTHF/Heptane twice (2 \* 30 mL). Drying under vacuum at  $40\text{ }^{\circ}\text{C}$  gave 12.6 g **Example 7** (35.2 mmols, 98.7% w/w, 75% yield).  $^1\text{H}$ -NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.91 (br s, 1H), 7.78 (d,  $J=8.4\text{ Hz}$ , 2H), 7.30 (br s, 1H), 7.25 (d,  $J=8.0\text{ Hz}$ , 2H), 4.54 and 4.36 (br s, 1H), 4.17 and 4.01 (d,  $J=12.2\text{ Hz}$ , 1H), 3.20 and 2.80 (t,  $J=11.9\text{ Hz}$ , 1H), 2.74 (d,  $J=11.4\text{ Hz}$ , 1H), 2.67-2.55 (m, 2H), 2.33 (br s, 2H), 1.99-1.88 (m, 2H), 1.88-1.53 (m, 6H), 1.48-1.37 (m, 1H), 1.27 (br s, 3H), 1.12 (br s, 1H); LC-MS (ESI):  $m/z$  342 ( $\text{M}+1$ ).  $R_t=1.68\text{ min}$  with analytical method (mobile phase: 5-90% B; A:  $\text{H}_2\text{O}$  with 0.1% formic acid, B:  $\text{CH}_3\text{CN}$ , 8.6 min run) on Xbridge C18, 3.0 x 50mm, 2.5  $\mu\text{m}$  particle size. The LC purity of the product was analyzed on an Atlantis T3 column (3.0 x 150mm, 3.0  $\mu\text{m}$  particle size) with UV-detection (250 nm) using a gradient method (mobile phase 2-50% B; A:  $\text{H}_2\text{O}$  with 0.03% TFA, B:  $\text{CH}_3\text{CN}$  with 0.03% TFA, 30 min run), giving a purity of 99.48 area % at 12.06 min. The product was analyzed on chiral SFC (UV detection) using isocratic method (mobile phase: 55% EtOH with 0.1% DMEA, supercritical  $\text{CO}_2$ ) on ChiralPak AD-H, 10 x 250 mm, 5  $\mu\text{m}$  particle size, giving an enantiomeric purity of > 99% ee,  $R_t=1.98\text{ min}$ .

**Example 8****1-Cyclobutylpiperazine × 2HCl**

- N*-Boc-piperazine (46 g, 0.25 moles), which is commercially available from SAFC, was dissolved in EtOH (415 mL) at  $t_{\text{jacket}}=20^{\circ}\text{C}$ . Acetic acid (140 mL) was added in one portion followed by the addition of cyclobutanone (26.5 g, 0.37 moles). The charging vessel was rinsed with EtOH (25 mL) and the light yellow solution was left stirring at  $t_{\text{jacket}}=20^{\circ}\text{C}$  for 1 h.  $\text{NaBH}(\text{OAc})_3$  (80 g, 0.36 moles, 95% w/w) was added in 20 portions over 2 h. EtOH (25 mL) was used for rinsing. The reaction mixture was left stirring for 2 h. The sample analyzed on GC indicated full conversion at this point using HP-5MS column (length 25 m, ID 0.32 mm, Film 0.52  $\mu\text{m}$ ) with a gradient method (2 min at  $60^{\circ}\text{C}$ , followed by  $25^{\circ}\text{C}/\text{min}$  during 8 min then 2 min at  $260^{\circ}\text{C}$ ). Front inlet temperature= $200^{\circ}\text{C}$  using He as gas and a detector temperature= $300^{\circ}\text{C}$ . NaOH (296 g, 3.70 moles, 50% w/w) diluted in  $\text{H}_2\text{O}$  (230 mL) was added at such a rate so  $t_{\text{inner}}$  remained below  $35^{\circ}\text{C}$ .
- EtOH was distilled off under vacuum at  $t_{\text{jacket}}=45^{\circ}\text{C}$  to approximately 650 mL. The water phase was extracted with toluene (550 mL) at  $t_{\text{jacket}}=45^{\circ}\text{C}$  and the obtained organic phase was concentrated under vacuum at  $t_{\text{jacket}}=45^{\circ}\text{C}$  to approximately 250 mL. The toluene solution was diluted with 2-propanol (140 mL) at  $t_{\text{jacket}}=20^{\circ}\text{C}$  and  $\text{H}_2\text{O}$  (2.2 mL, 0.12 moles) was added. HCl in 2-propanol (82 mL, 0.49 moles, 6M) diluted in 2-propanol (140 mL) was added over 30 min at  $t_{\text{jacket}}=20^{\circ}\text{C}$ . The reaction solution was heated to  $t_{\text{jacket}}=48^{\circ}\text{C}$ . HCl in 2-propanol (164 mL, 0.99 moles, 6M) diluted in 2-propanol (276 mL) was added over 2 h at  $t_{\text{inner}}=46^{\circ}\text{C}$ . The reaction solution was kept at  $t_{\text{jacket}}=48^{\circ}\text{C}$  for an additional 4 h before cooling to  $t_{\text{jacket}}=10^{\circ}\text{C}$  over 1 h. The product was filtered off and washed with cold 2-propanol ( $2 \times 230$  mL). Drying under vacuum at  $40^{\circ}\text{C}$  gave 44 g **Example 8** (0.20 moles, 95.9% w/w), 80 % yield.  $^1\text{H}$ -NMR ( $\text{DMSO}-d_6$ ):  $\delta$  12.46 (s, 1H), 10.07 (s, 2H), 3.73 (m, 1H), 3.05-3.61 (m, 8 H), 2.37 (m, 2H), 2.14 (m, 2H), 1.70 (m, 2H);  $^{13}\text{C}$ -NMR ( $\text{DMSO}-d_6$ ):  $\delta$  58.05, 44.67, 39.59, 24.38, 13.18.

**Example 9****4-{(1S, 2S)-2-[(4-Cyclobutylpiperazin-1-yl)carbonyl]-cyclopropyl}-benzamide**





**Example 5** (5.52 g, 26.7 mmol, 99.1% w/w) and **Example 8** (6.07 g, 28.0 mmol, 98.40% w/w) were mixed in DMSO (82 mL) at  $t_{\text{jacket}}=22^{\circ}\text{C}$ . N-Methylmorpholine (2.94 mL, 27.2 mmol) was added over 5 min. The charging vessel was rinsed with DMSO (2.8 mL).

5 HOBt/NMM solution (1.80 g, 2.66 mmol, 20% w/w) was added in one portion. The charging vessel was rinsed with DMSO (2.8 mL). EDCI  $\times$  HCl (7.16 g, 38.0 mmol) was added over 10 min. at  $t_{\text{jacket}}=22^{\circ}\text{C}$ . The reaction was complete after 2 h. For analysis the following gradient method was used (mobile phase 20-95% B; A: 5% CH<sub>3</sub>CN in H<sub>2</sub>O with 0.05% formic acid, B: 95% CH<sub>3</sub>CN in H<sub>2</sub>O with 0.05% formic acid, 8 min run) on

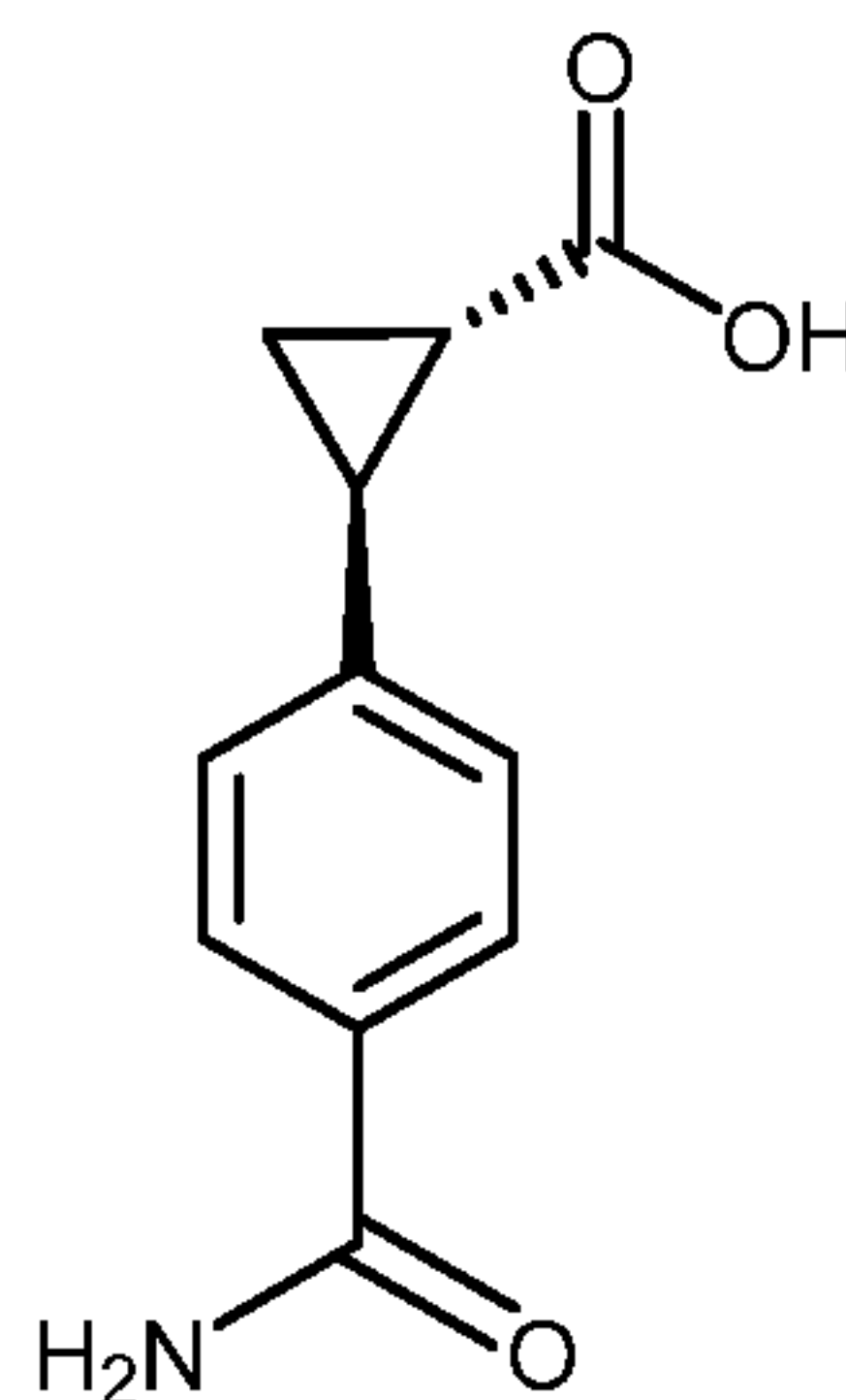
10 Chromolith Performance RP-18e, 4.6 x 100 mm. The reaction solution was heated to 60°C and pH adjusted with TEA (5.18 g, 51.2 mmol) to pH~8. The solid mixture was cooled to 20°C after which H<sub>2</sub>O (69.8 mL) was added and left to stir for 16 h. The product was filtered off, and slurry washed with cold H<sub>2</sub>O (2 x 33 mL). Drying under vacuum at 40°C gave 7.53 g **Example 9** (22.8 mmol, 99.0% w/w), 85% yield. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>):  $\delta$  7.91 (br s, 1H), 7.78 (d,  $J=8.0$  Hz, 2H), 7.29 (br s, 1H), 7.24 (d,  $J=8.0$  Hz, 2H), 3.68-3.39 (m, 4H), 2.72-2.62 (m, 1H), 2.40-2.29 (m, 2H), 2.26-2.12 (m, 4H), 1.99-1.88 (m, 2H), 1.83-1.70 (m, 2H), 1.67-1.56 (m, 2H), 1.47-1.39 (m, 1H), 1.28-1.20 (m, 1H); LC-MS (ESI):  $m/z$  328 (M+1).  $R_t$  = 1.62 min with analytical method (mobile phase: 5-90% B; A: H<sub>2</sub>O with 0.1% formic acid, B: CH<sub>3</sub>CN, 8.6 min run) on Xbridge C18, 3.0 x 50 mm, 2.5  $\mu\text{m}$  particle size. The LC purity of

20 the product was analyzed on an Atlantis T3 column (3.0 x 150 mm, 3.0  $\mu\text{m}$  particle size) with UV-detection (250 nm) using a gradient method (mobile phase 2-50% B; A: H<sub>2</sub>O with 0.03% TFA, B: CH<sub>3</sub>CN with 0.03% TFA, 30 min run) giving a purity of 97.83 area% at 11.10 min. The chiral purity of the product was analyzed on a chiral column with UV-detection (250 nm) using isocratic method (mobile phase: Heptane/EtOH (80/20) + 0.1% Diethylamine) on

25 Chiralpak AD-H, 4.6 x 150 mm, giving an enantiomeric purity of >99% ee.

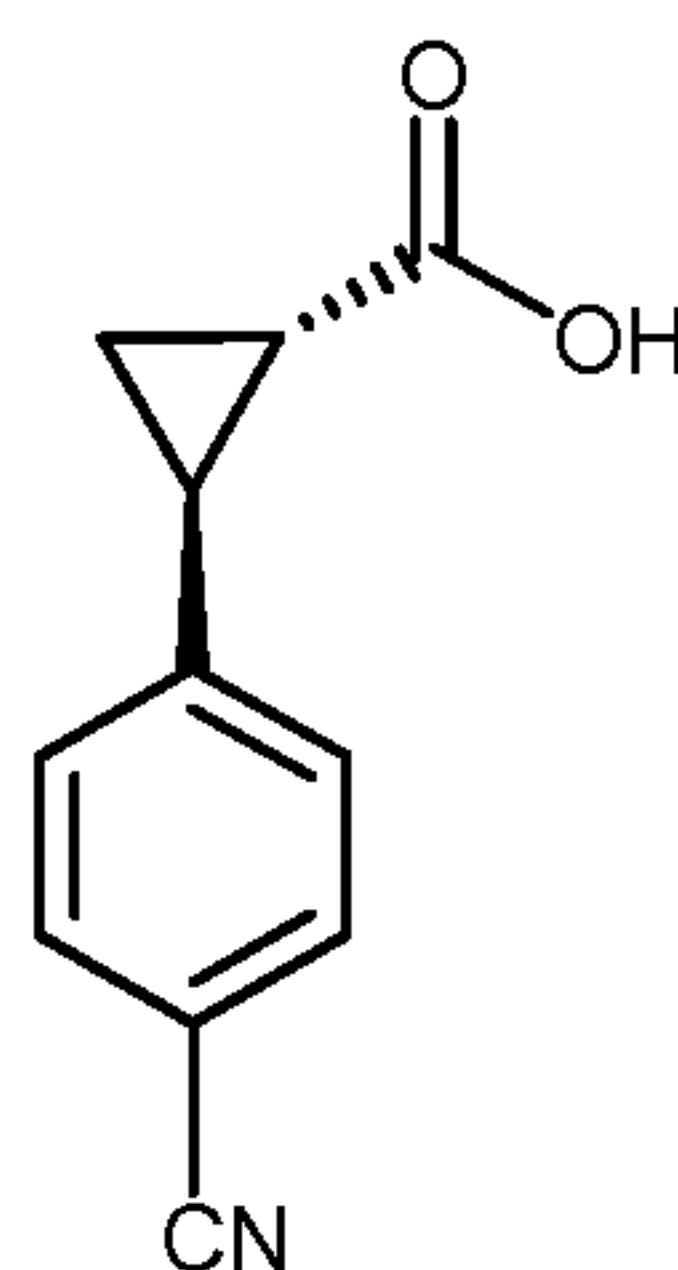
**What is claimed is:**

1. A compound of formula Ia, or a pharmaceutically acceptable salt thereof:



(Ia).

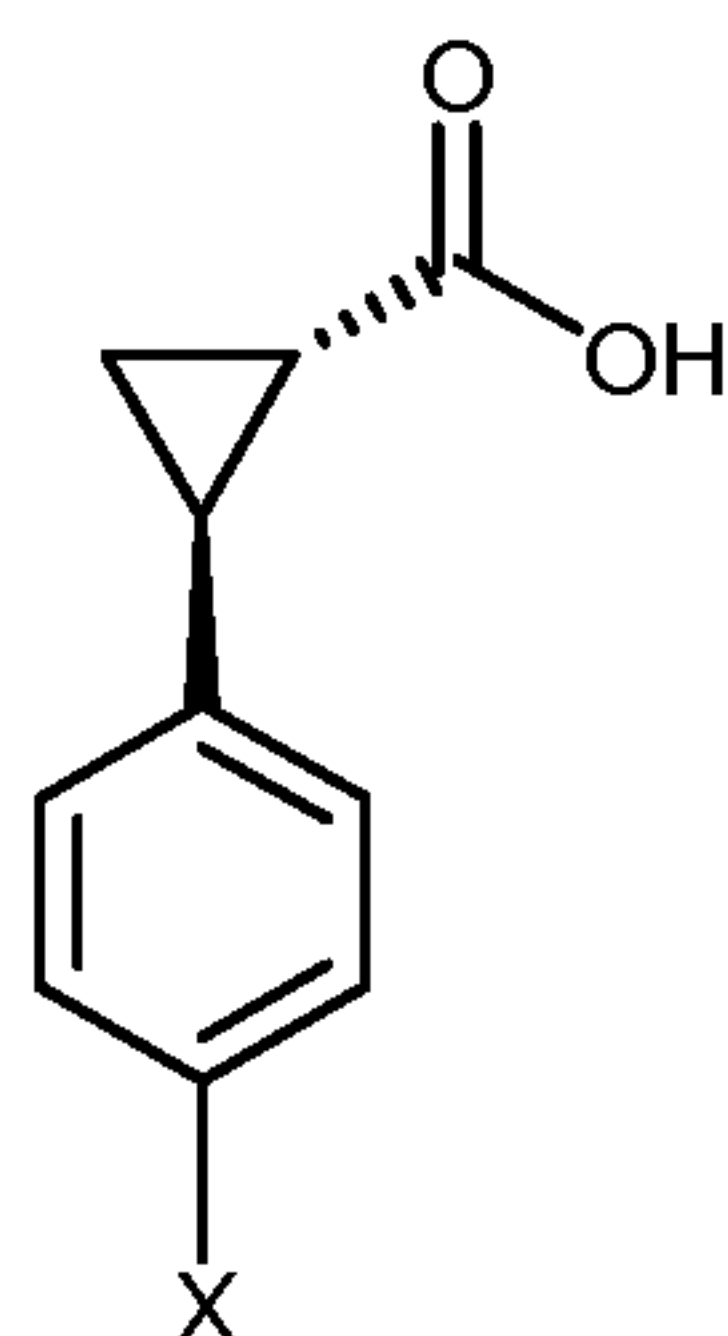
2. A process for preparing a compound according to claim 1, comprising reacting a compound of formula IX



(IX)

with (1) a base and a peroxide; and then (2) an acidic solution.

3. The process of claim 2, wherein said base is sodium hydroxide.
4. The process of claim 2 or 3, wherein said peroxide is hydrogen peroxide.
5. The process of any one of claims 2-4, wherein said acidic solution is an aqueous solution of sodium hydrogen sulfate.
6. The process of claim 2, wherein the compound of formula IX is prepared by reacting a compound of formula VIII

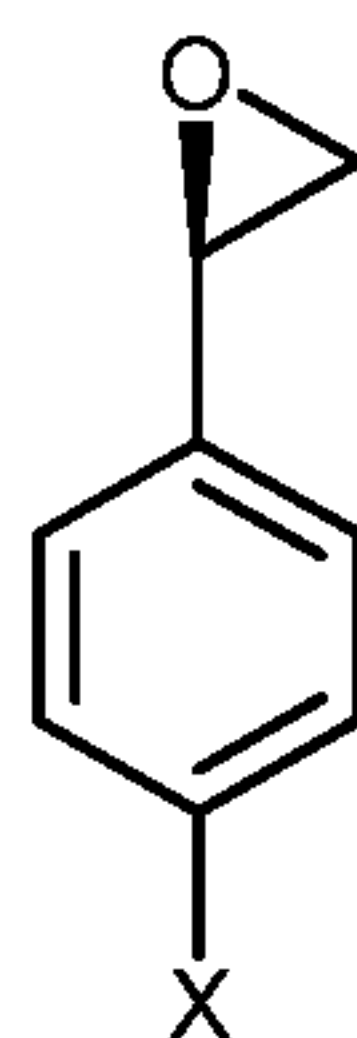


(VIII)



wherein X is Cl, Br, or I; with a metal, a metal cyanide, and a catalyst.

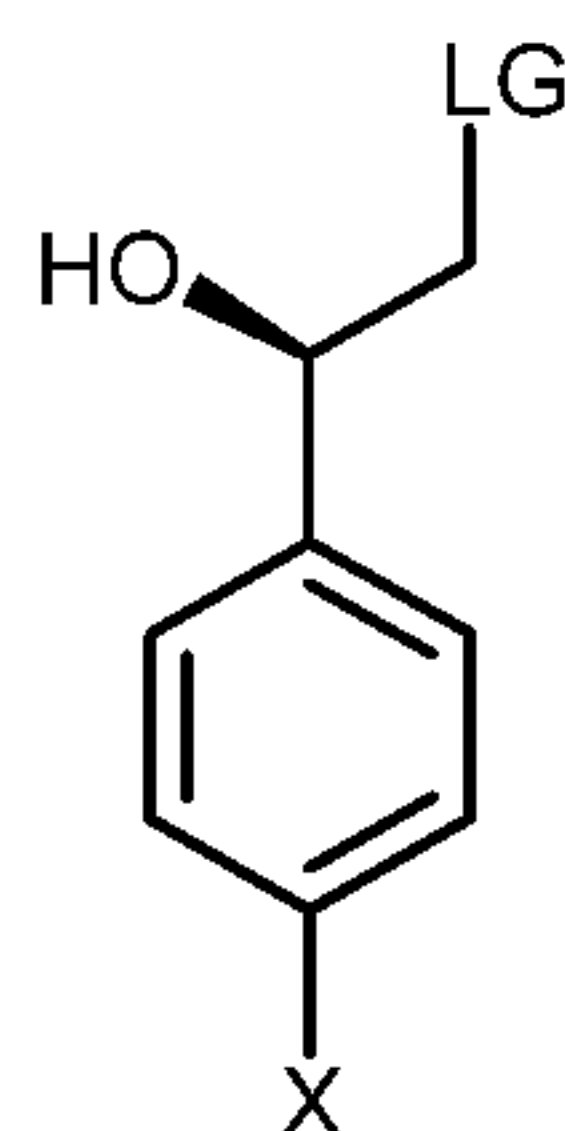
7. The process of claim 6, wherein X is Br.
8. The process of any one of claims 6 or 7, wherein said metal is zinc.
9. The process of any one of claims 6-8, wherein said metal cyanide is zinc-(II)-cyanide.
10. The process of any one of claims 6-9, wherein said catalyst is bis(tri-*t*-butylphosphine)palladium(0).
11. The process of claim 6, wherein the compound of formula VIII is prepared by reacting a compound of formula VII



(VII)

wherein X is Cl, Br, or I; with (1) a mixture of a first base and a triC<sub>1-6</sub>alkyl phosphonoacetate; and then (2) a second base.

12. The process of claim 11, wherein the compound of formula VII is prepared by reacting a compound of formula VI

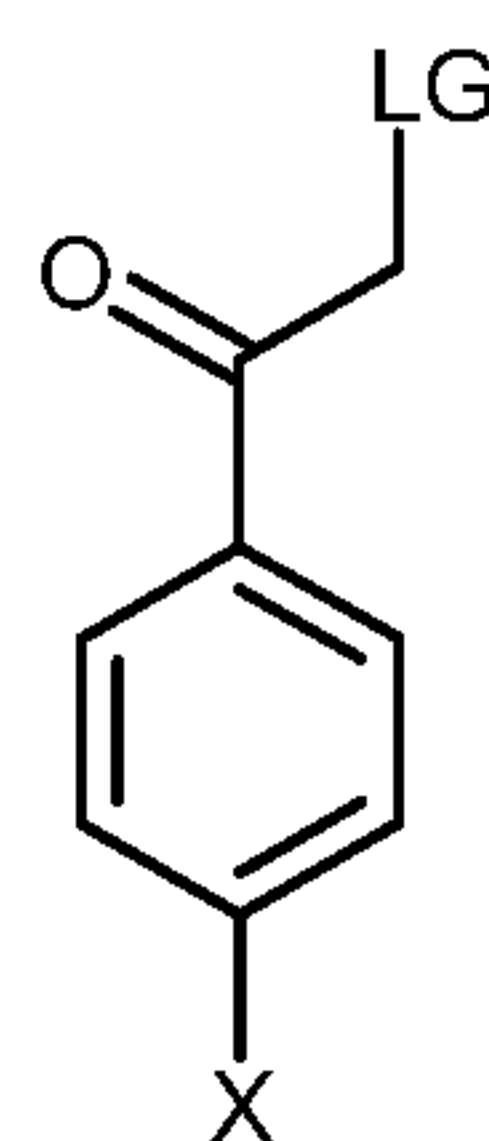


(VI)

with a base; wherein X is Cl, Br, or I and LG is Cl, Br, I, tosylate, brosylate, nosylate, mesylate, or triflate.

13. The process of claim 12, wherein the compound of formula VI is prepared by reacting a compound of formula V

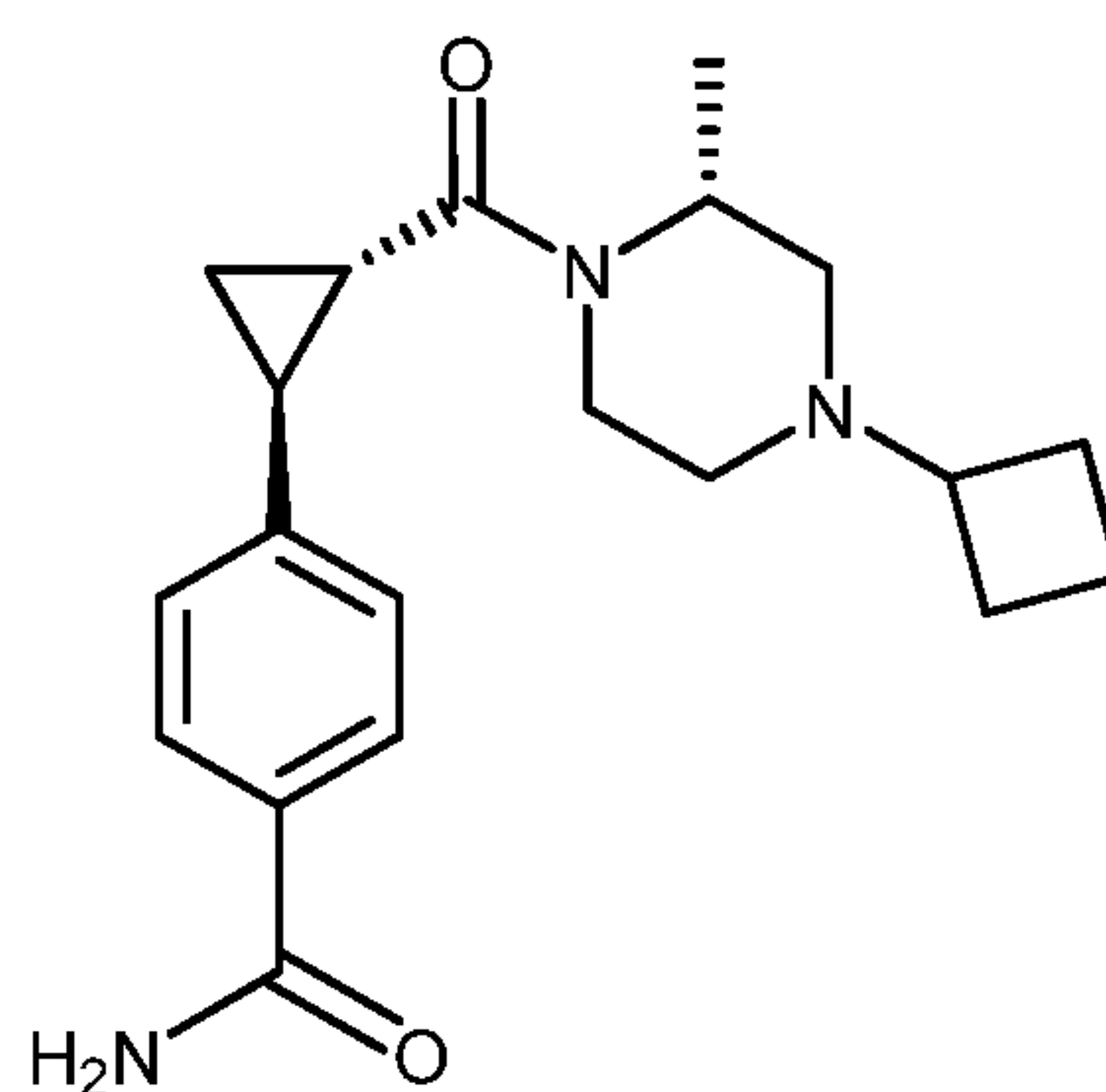
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(V)

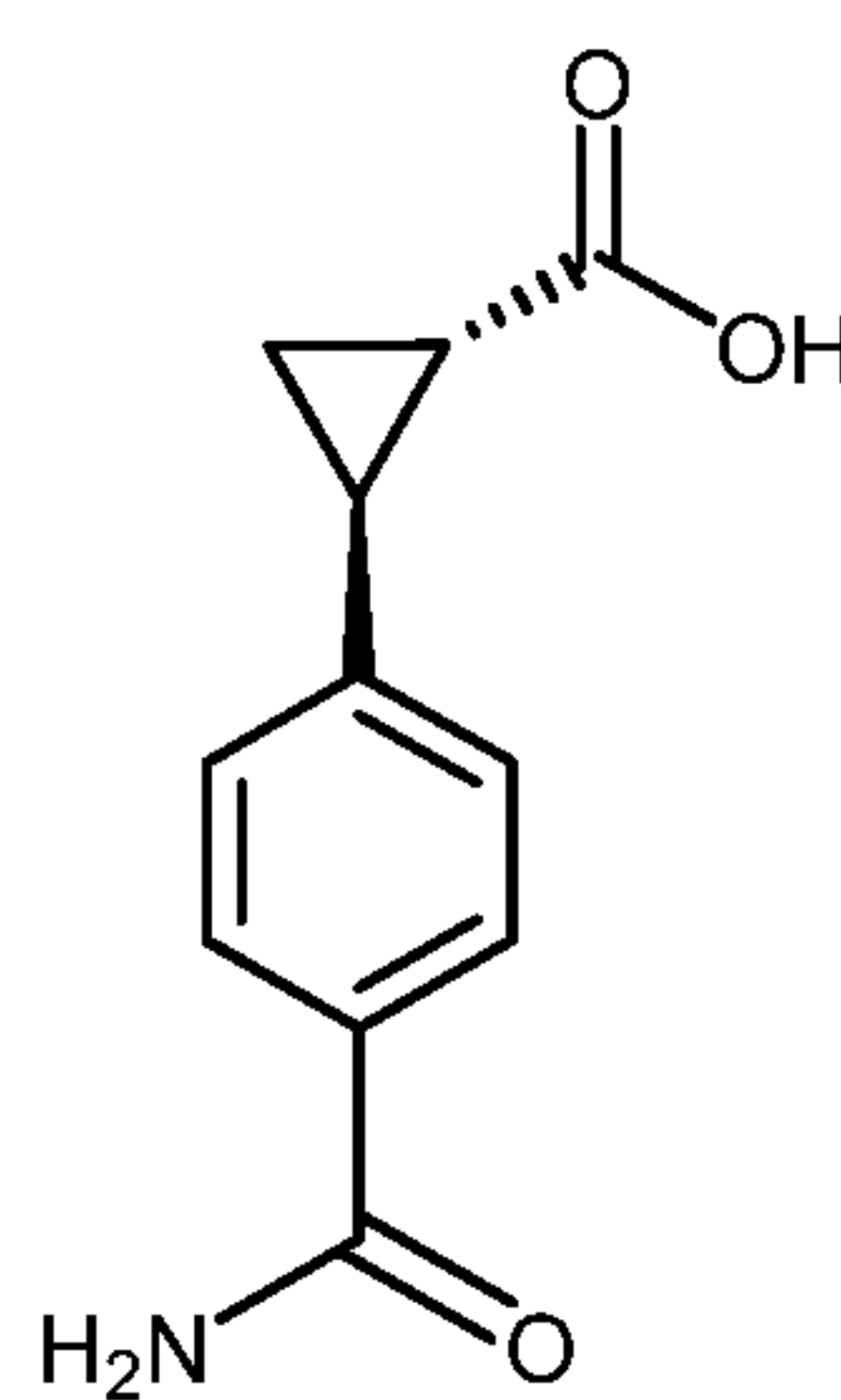
with a reducing agent and a chiral oxazaborolidine; wherein X is Cl, Br, or I and LG is Cl, Br, I, tosylate, brosylate, nosylate, mesylate, or triflate.

- 5 14. A process for preparing a compound of formula Ib, or a pharmaceutically acceptable salt thereof,



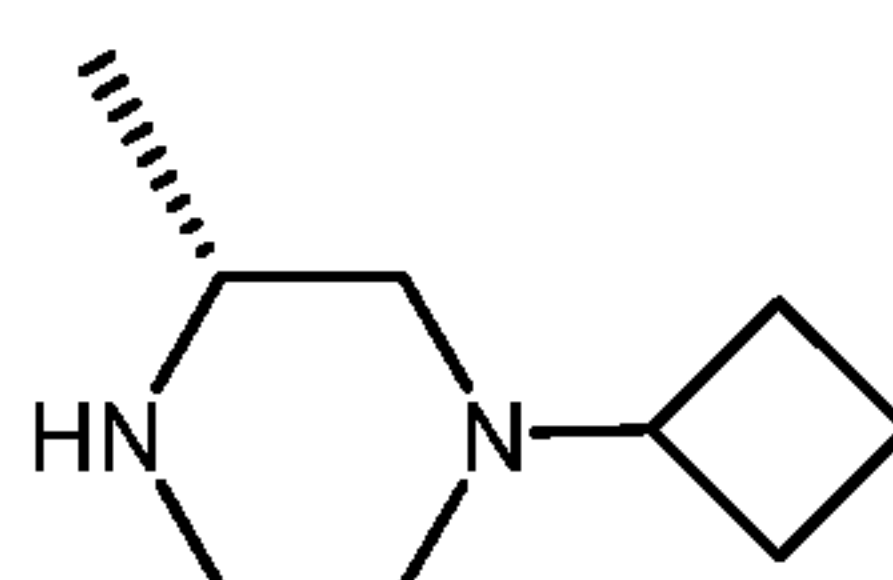
(Ib)

which process comprises reacting a compound of formula Ia



(Ia)

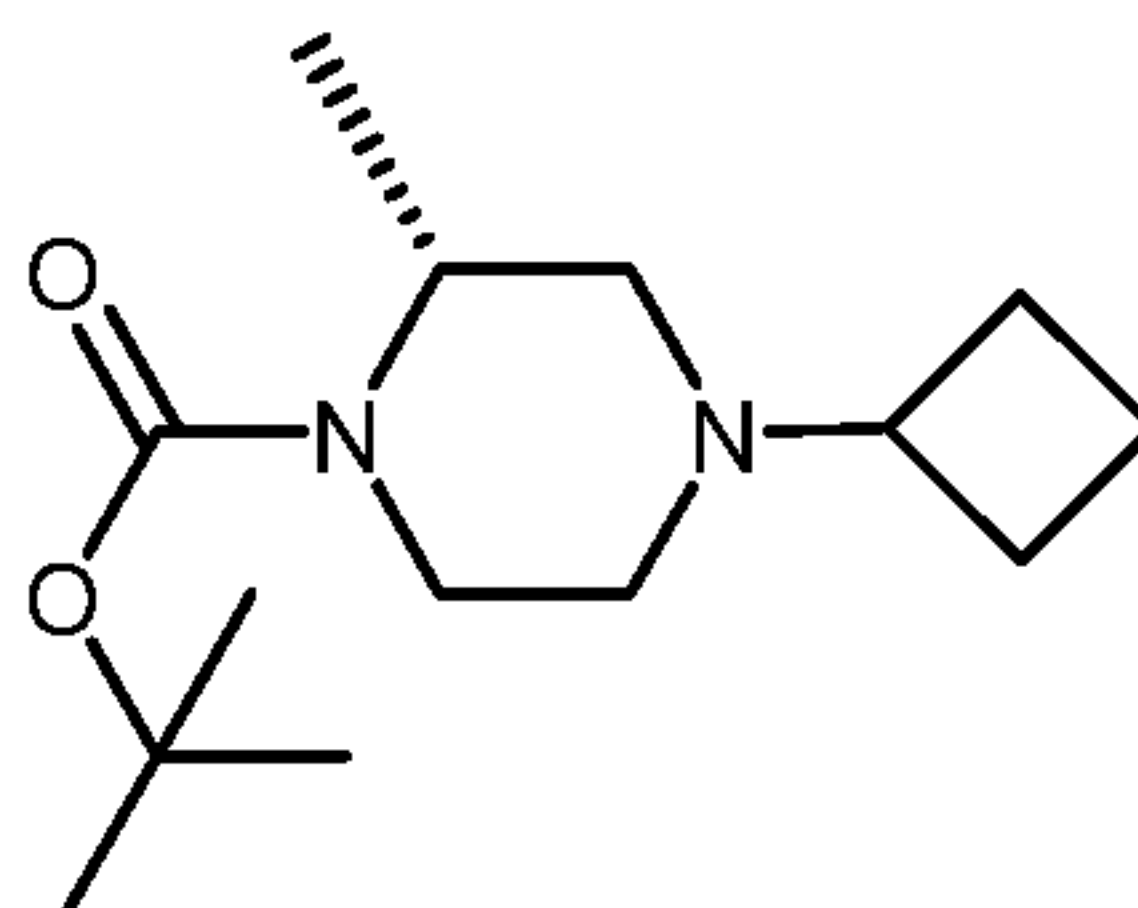
with (1) an activating agent and (2) a compound of formula IVa, or a suitable salt thereof



(IVa).



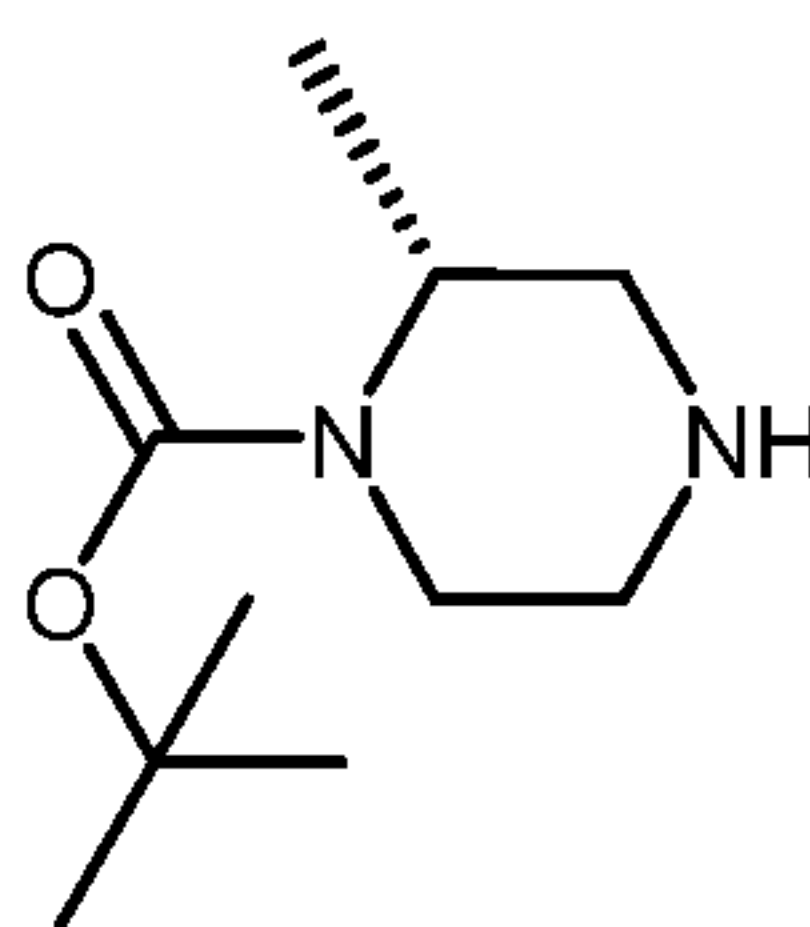
15. The process of claim 14, wherein said activating agent is 1,1'-carbonyldiimidazole.
16. The process of claim 14, wherein the compound of formula IVa, or suitable salt thereof is prepared by reacting a compound of formula IIIa



(IIIa)

with an acid.

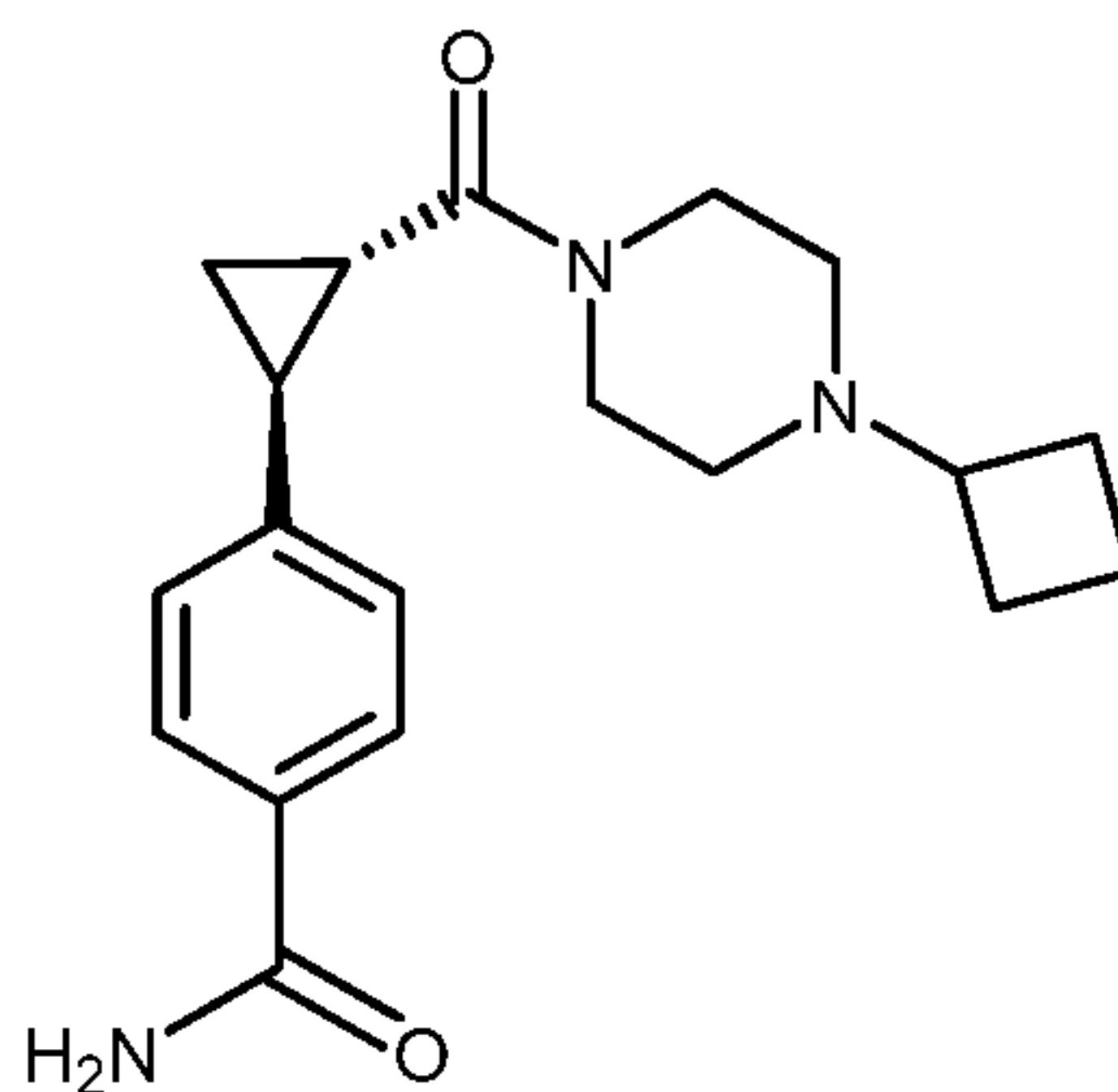
17. The process of claim 16, wherein the compound of formula IIIa is prepared by reacting a compound of formula IIa



(IIa)

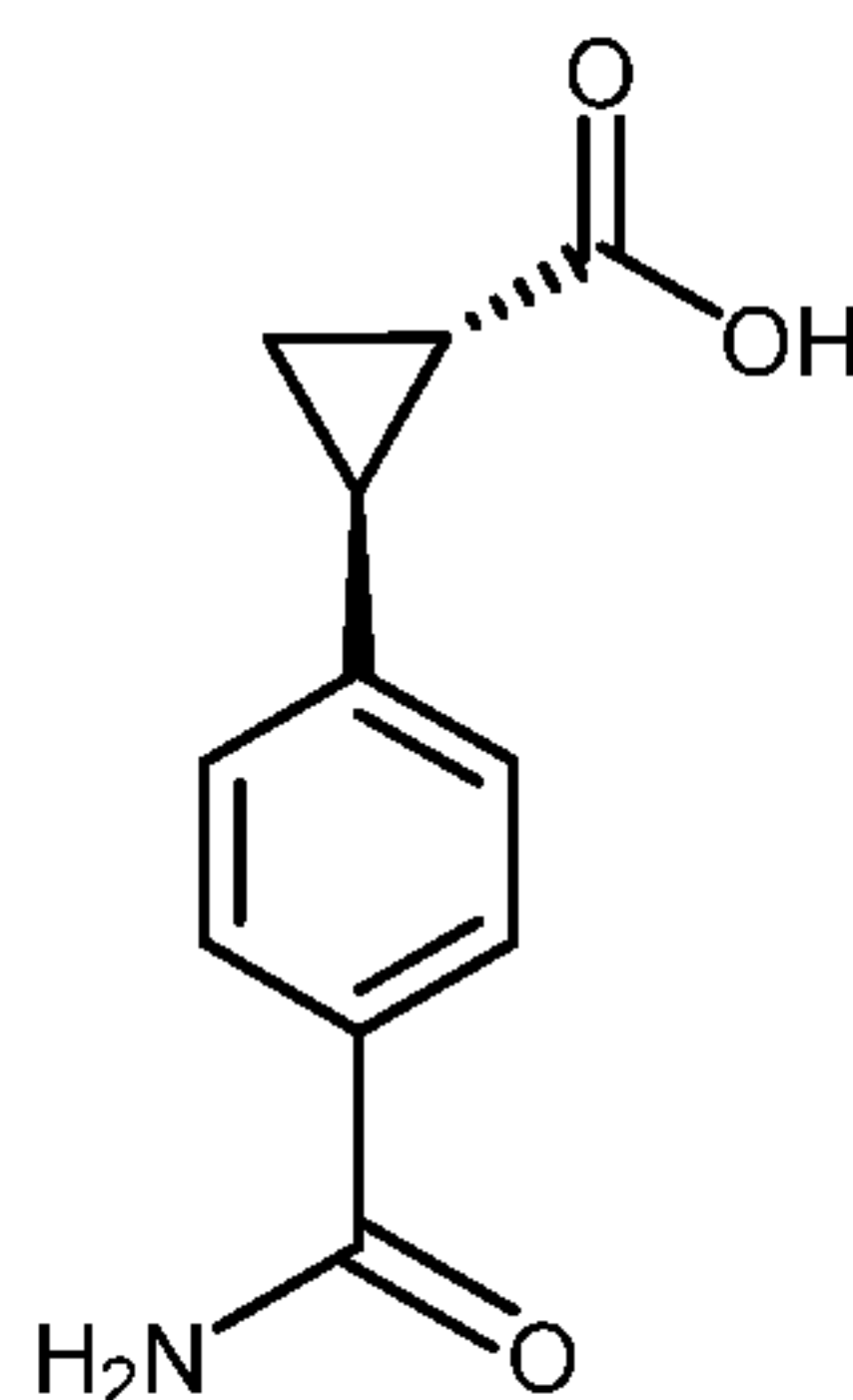
with cyclobutanone and a reducing agent.

18. A process for preparing a compound of formula Ic, or a pharmaceutically acceptable salt thereof,



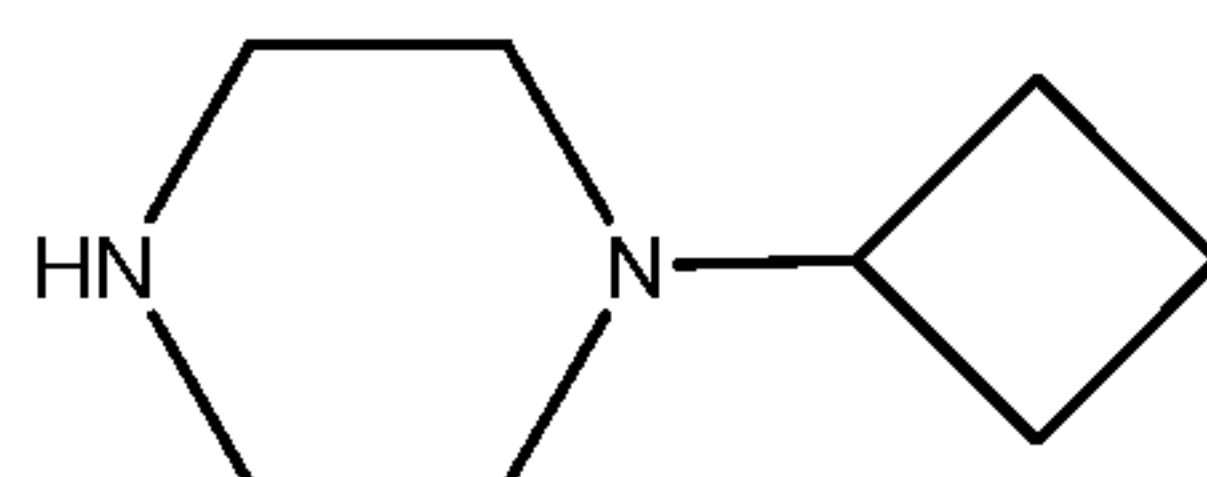
(Ic)

which process comprises reacting a compound of formula Ia



(Ia)

(1) with an activating agent and a compound of formula IVb, or a suitable salt thereof

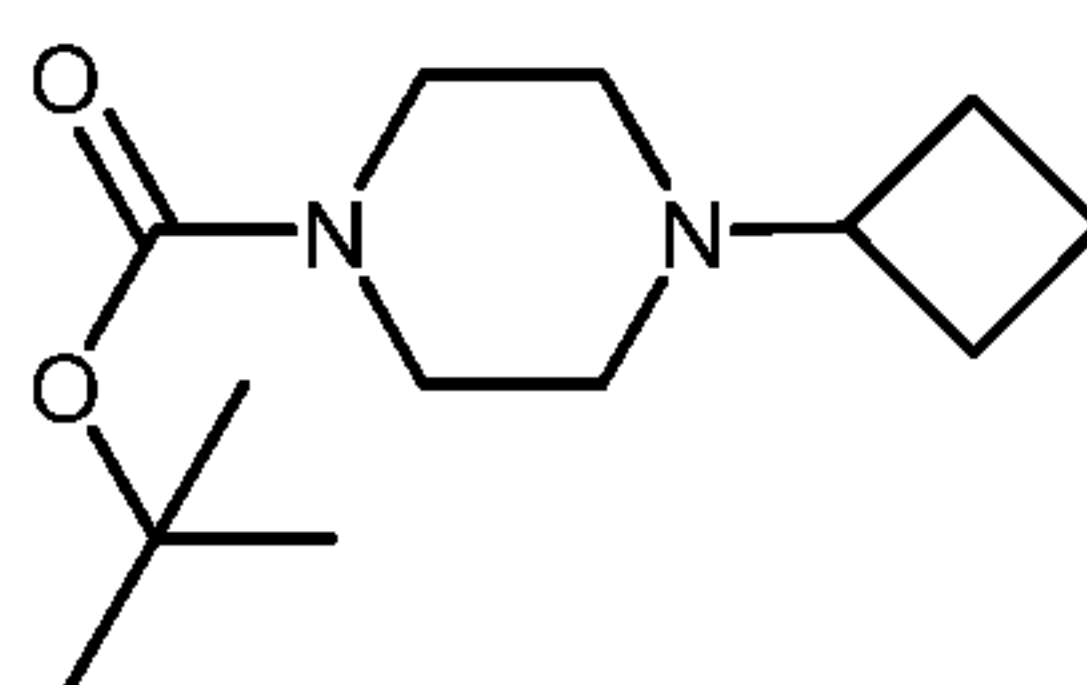


(IVb)

and (2) a base.

19. The process of claim 18, wherein the activating agent is a mixture of 1-hydroxybenzotriazole and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

20. The process of claim 18, wherein the compound of formula IVb is prepared by reacting a compound of formula IIIb

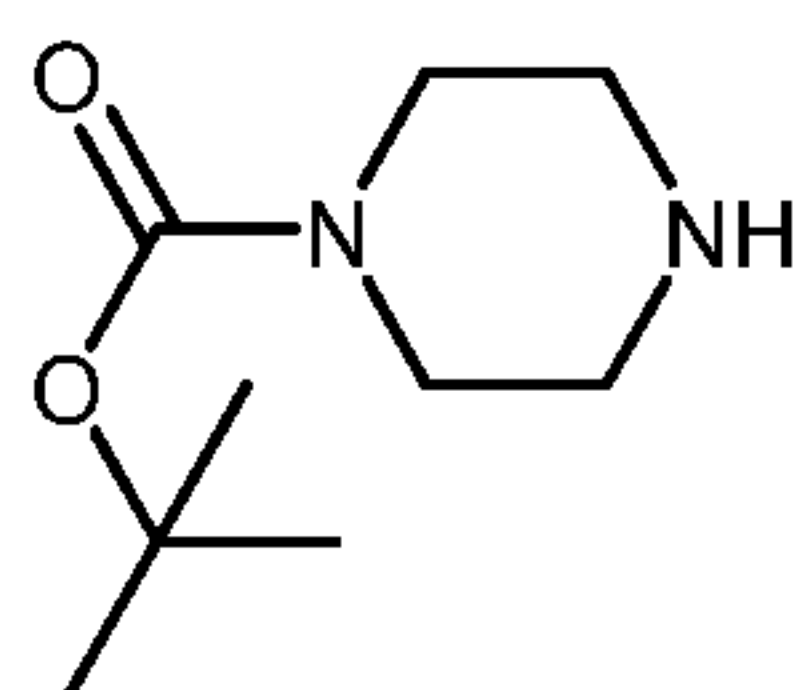


(IIIb)

with an acid.

21. The process of claim 16 or 20, wherein said acid is hydrochloric acid.

22. The process of claim 20, wherein the compound of formula IIIb is prepared by reacting a compound of formula IIb



(IIb)

with cyclobutanone and a reducing agent.

23. The process of claim 17 or 22, wherein said reducing agent is sodium triacetoxy borohydride.