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(54) Titre : SELS ALCALOIDES BIS-QUATERNAIRES DE QUINQUINA A TITRE DE CATALYSEURS PAR TRANSFERT  
DE PHASE ASYMETRIQUE  
(54) Title: BIS-QUARTERNARY CINCHONA ALKALOID SALTS AS ASYMMETRIC PHASE TRANSFER CATALYSTS

(57) **Abrégé/Abstract:**

The invention is directed to novel bis-quarternary cinchona alkaloid salts and the use of bis-quarternary cinchona alkaloid salts in asymmetric phase transfer catalysis. The present invention is directed to novel bis-quarternary cinchona alkaloid salts and the use of bis-quarternary cinchona alkaloid salts in asymmetric phase transfer catalysis. On certain substrates and under specific reaction conditions, the inventors have discovered that the use of bis-quarternary cinchona alkaloid salts in asymmetric phase transfer catalysis surprisingly provides for a more active and efficient process as compared to mono-quarternary catalysts.



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(54) Title: BIS-QUARTERNARY CINCHONA ALKALOID SALTS AS ASYMMETRIC PHASE TRANSFER CATALYSTS

(57) Abstract: The invention is directed to novel bis-quarternary cinchona alkaloid salts and the use of bis-quarternary cinchona alkaloid salts in asymmetric phase transfer catalysis. The present invention is directed to novel bis-quarternary cinchona alkaloid salts and the use of bis-quarternary cinchona alkaloid salts in asymmetric phase transfer catalysis. On certain substrates and under specific reaction conditions, the inventors have discovered that the use of bis-quarternary cinchona alkaloid salts in asymmetric phase transfer catalysis surprisingly provides for a more active and efficient process as compared to mono-quarternary catalysts.

## TITLE OF THE INVENTION

BIS-QUARTERNARY CINCHONA ALKALOID SALTS AS ASYMMETRIC PHASE  
TRANSFER CATALYSTS.

## 5 BACKGROUND OF THE INVENTION

Cinchona alkaloid salts are known phase transfer catalysts useful in the  
asymmetric formation of carbon-carbon, carbon-heteroatom or carbon-halide bonds. *See* Takashi  
Ooi and Keiji Maruoka, *Recent Advances in Asymmetric Phase-Transfer Catalysis*, Angew.  
Chem. Int. Ed. **2007**, 46, 4222-4266 ("Maruoka"). Maruoka reviews the various reactions in  
10 which phase-transfer catalysis is useful, including enantioselective alkylation, Michael addition,  
aldol and related reactions and Darzens reaction. Maruoka at page 4223 discusses the advantages  
of such phase transfer catalysis processes as involving "simple experimental procedures, mild  
reaction conditions, inexpensive and environmentally benign reagents and solvents and the  
possibility of conducting large-scale preparations." Thus, asymmetric phase transfer catalysis  
15 remains an important area for organic chemistry research.

The present invention is directed to novel bis-quarternary cinchona alkaloid salts  
and the use of bis-quarternary cinchona alkaloid salts in asymmetric phase transfer catalysis. On  
certain substrates and under specific reaction conditions, the inventors have discovered that the  
use of bis-quarternary cinchona alkaloid salts in asymmetric phase transfer catalysis surprisingly  
20 provides for a more active and efficient process as compared to mono-quarternary catalysts,  
providing high efficiency rates and asymmetric products in high enantiomeric excess.

## SUMMARY OF THE INVENTION

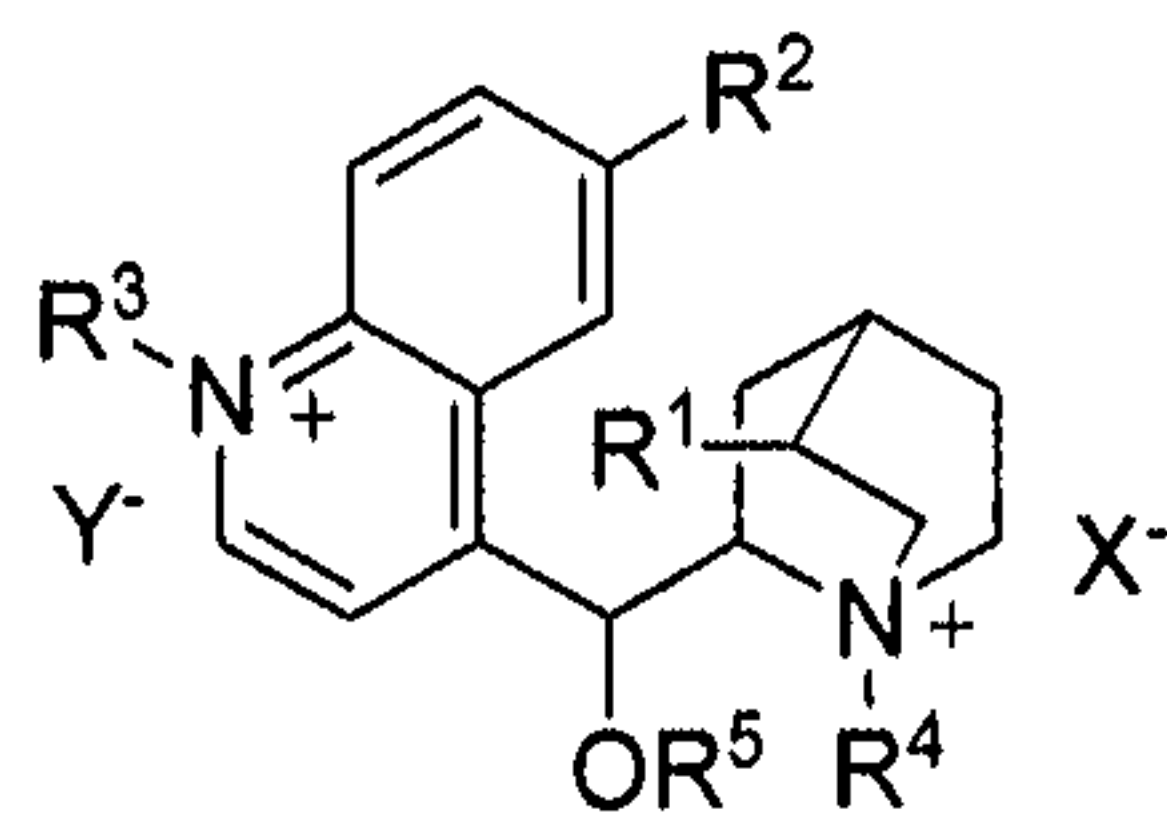
The invention is directed to novel bis-quarternary cinchona alkaloid salts and the  
25 use of bis-quarternary cinchona alkaloid salts in asymmetric phase transfer catalysis.

## DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses bis-quarternary cinchona alkaloid salts having the  
chemical structure of Formula I:

30





I

wherein:

5  $R^1$  is selected from ethyl and vinyl,

$R^2$  is selected from hydrogen and methoxy,

$R^3$  and  $R^4$  are independently selected from the group consisting of  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{3-6}$ cycloalkyl, aryl, heteroaryl,  $-C_{1-4}$ alkyl-aryl and  $-C_{1-4}$ alkyl-heteroaryl, wherein  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{3-6}$ cycloalkyl, aryl, heteroaryl and the aryl and heteroaryl  
10 portions of  $-C_{1-4}$ alkyl-aryl and  $-C_{1-4}$ alkyl-heteroaryl are optionally substituted with one to five substituents independently selected from  $R^6$ ,

$R^5$  is selected from the group consisting of hydrogen,  $C(O)R$ ,  $C(O)OR$ ,  $CONRR'$ , and  $C_{1-6}$ alkyl,

$R^6$  is selected from the group consisting of  $C_{1-4}$ alkyl,  $C_{1-4}$ haloalkyl, aryl,  $C_{1-4}$ alkoxy, hydroxy, CN,  $CO_2R$ ,  $CONRR'$ , SR,  $SO_2R$ ,  $SO_3R$ ,  $PR_2$ ,  $PO(OR)_2$ ,  $PO(OR)(NRR')$ ,  $PO(NRR')_2$ ,  $P(OR)_2$ ,

15  $P(OR)(NRR')$ ,  $P(NRR')_2$ ,  $SiRR'R''$ ,  $B(OR)_2$ ,  $C(O)R$ ,  $NRR'$ ,  $NO_2$ , and halogen,

each R, R' and R'' is independently selected from the group consisting of, H,  $C_{1-6}$ alkyl, hydroxyl,  $C_{1-6}$ alkoxy, aryl, heteroaryl,  $-CH_2$ -aryl,  $-CH_2$ -heteroaryl, and

each X and Y are independently anions selected from halide, OH,  $HSO_4$ ,  $SO_4$ ,  $BF_4$ ,  $SbF_6$ ,

carboxylate, carbonate, hydrogencarbonate,  $NO_3$ , sulfonate, hexafluorophosphate, phosphate,

20 hydrogen phosphate and perchlorate,

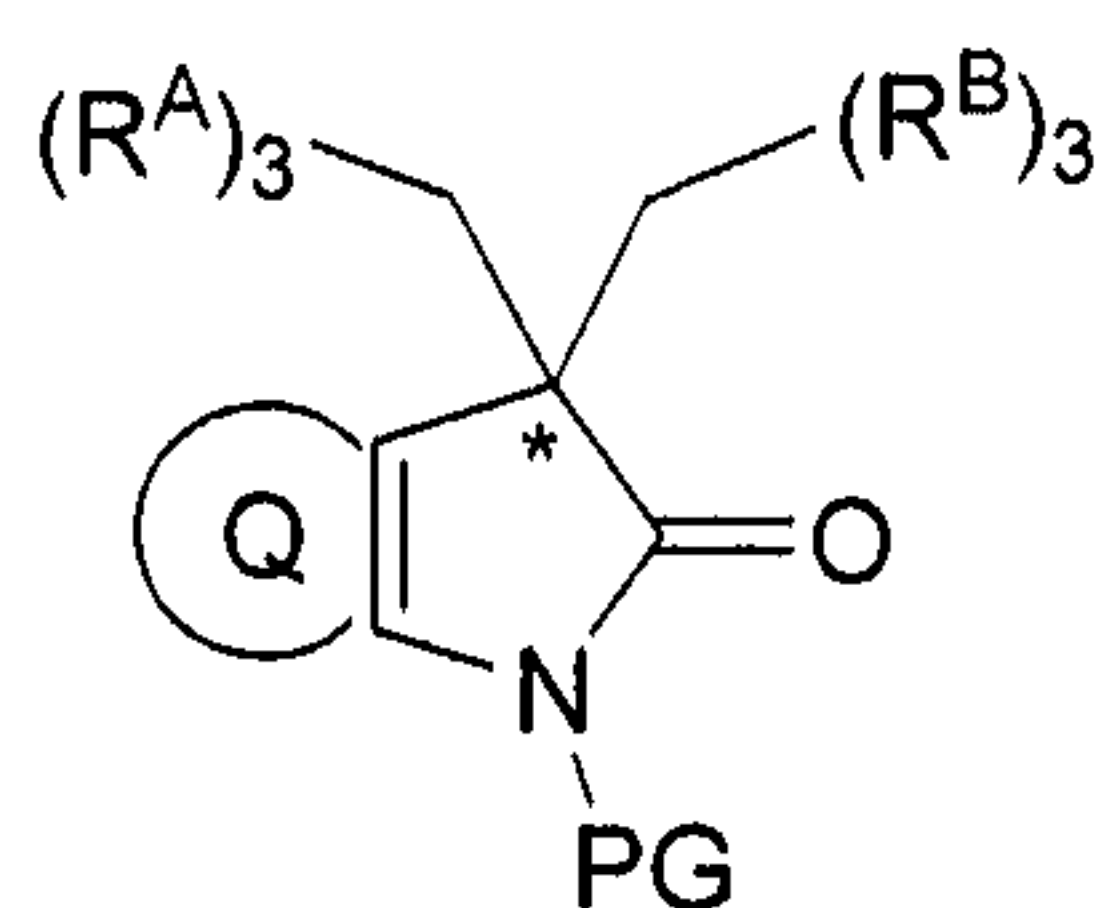
for use as phase transfer catalysts in the stereoselective formation of a carbon-carbon, carbon-heteroatom or carbon-halide bond on a substrate in a biphasic medium comprising an aqueous phase and organic phase or a micelle medium.

Unless depicted or specified otherwise, the cinchona alkaloid salts of Formula I

25 encompass all stereoisomers, including cinchonine, cinchonidine, quinine, quinidine, dihydroquinidine, and dihydroquinine.

In an embodiment, the invention encompasses the bis-quarternary cinchona alkaloid salts of Formula I for use as phase transfer catalysts in one of the following asymmetric reactions: (1) alkylation with an electrophilic alkylating agent, (2) Michael addition with an electron deficient olefin, (3) aldol reaction with an aldehyde, (4) Mannich reaction with a  $\alpha$ -imino ester, (5) Darzens reaction with an aldehyde, (6) Neber rearrangement of an oxime into an  $\alpha$ -aminoketone, (7) epoxidation of an electron deficient olefin, (8) aziridination of an electron deficient olefin, (9) dihydroxylation of an electron deficient olefins, (10) fluorination of a carbonyl substrate, and (11) sulfenylation of a  $\beta$ -keto sulfoxide. The aforementioned reactions are well know in the art and described by Maruoka.

Another embodiment of the invention encompasses a process for stereoselectively producing a compound of Formula A



A

wherein:

Q forms a fused 5- or 6-membered aromatic carbocyclic or heterocyclic ring, each optionally substituted with 1 to 4  $R^C$  groups,

each  $R^A$  and each  $R^B$  are independently hydrogen, halogen, hydroxy, amino or an organic

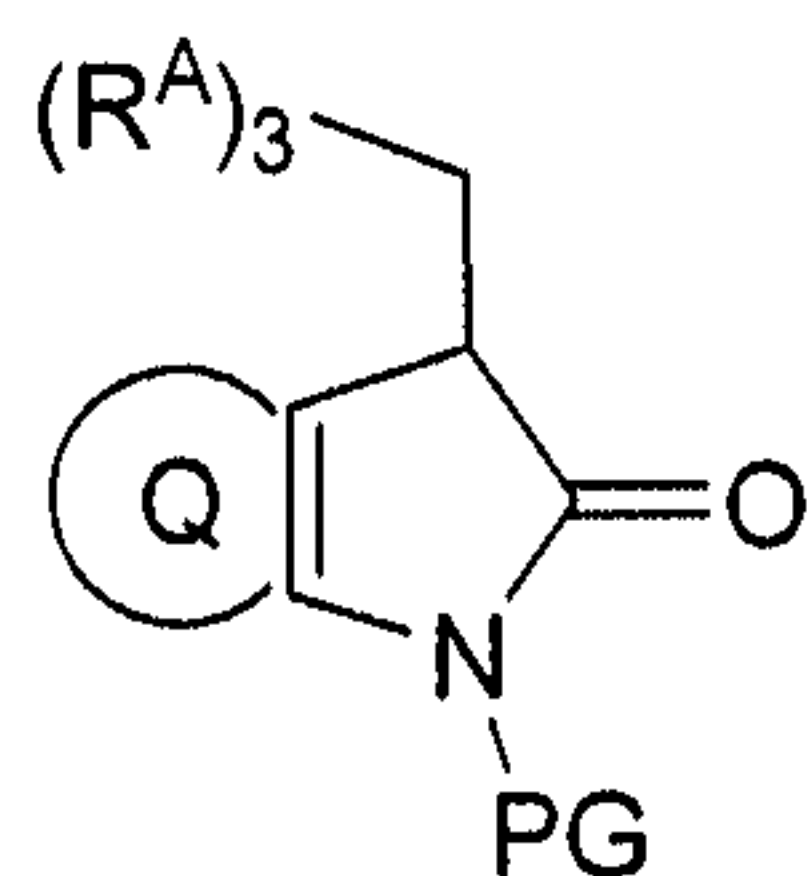
substituent group, and one  $R^A$  and one  $R^B$  may be joined together to form a mono-, bi- or tricyclic carbocyclic or heterocyclic ring system, optionally substituted with 1 to 4  $R^C$  groups,

$R^C$  is hydrogen, halogen, hydroxy, amino or an organic substituent group,

PG is a nitrogen protecting group and

\* represents an asymmetric center,

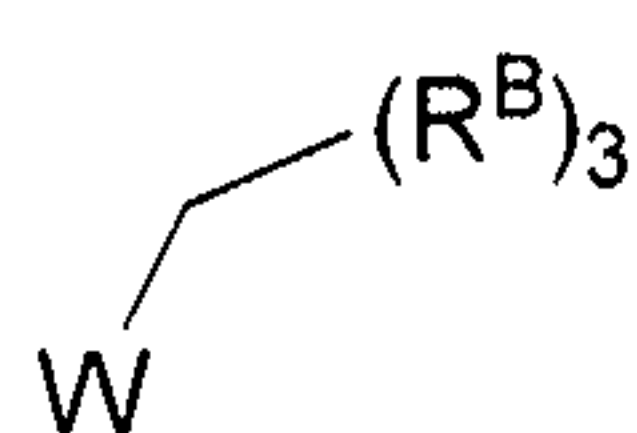
comprising initiating a reaction of a compound of Formula B



B

with a compound of Formula C

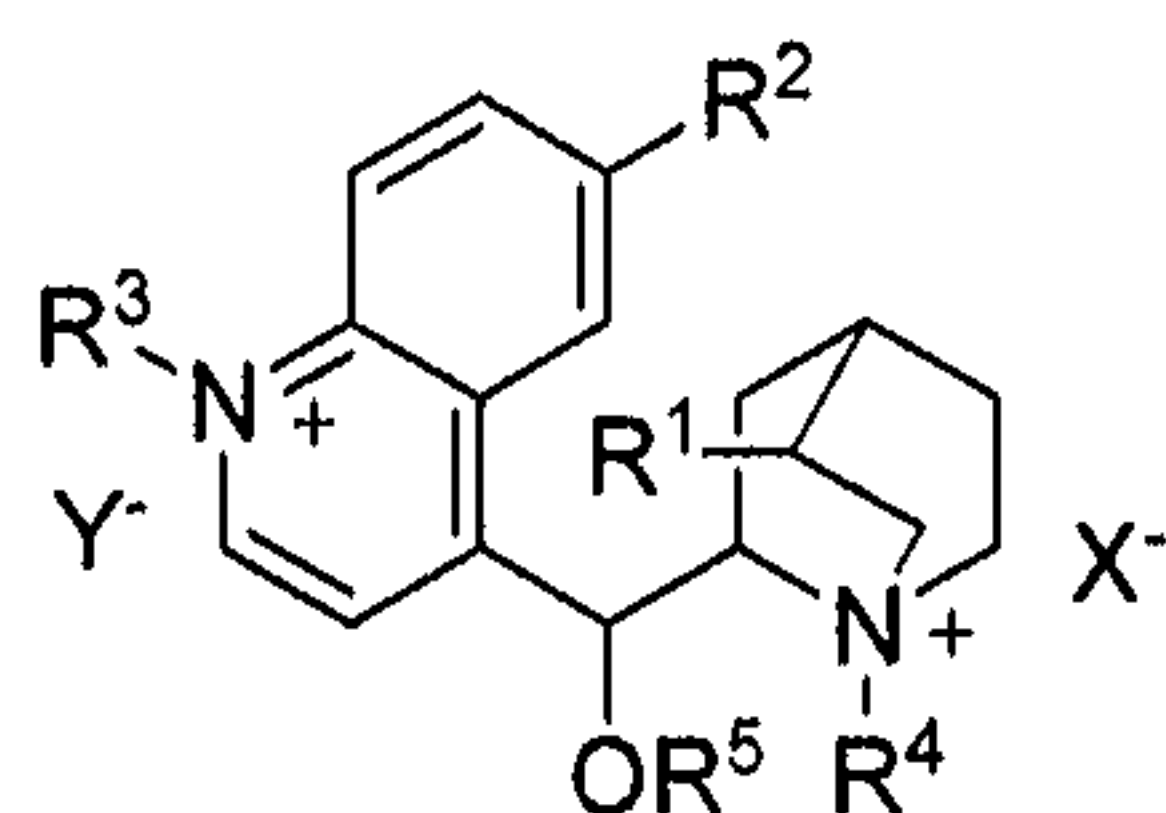
5



C

wherein W is a functional group that has leaving ability, in a water-immiscible organic phase in the presence of a bis-quarternary cinchona alkaloid salt and a base in an aqueous phase to form a biphasic medium comprising the aqueous phase and water-immiscible organic phase, wherein the bis-quarternary cinchona alkaloid salt has the chemical structure of Formula I:

10



I

15 wherein:

R<sup>1</sup> is selected from ethyl and vinyl,

R<sup>2</sup> is selected from hydrogen and methoxy,

R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>3-6</sub>cycloalkyl, aryl, heteroaryl, -C<sub>1-4</sub>alkyl-aryl and -C<sub>1-4</sub>alkyl-heteroaryl, wherein

20 C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>3-6</sub>cycloalkyl, aryl, heteroaryl and the aryl and heteroaryl portions of -C<sub>1-4</sub>alkyl-aryl and -C<sub>1-4</sub>alkyl-heteroaryl are optionally substituted with one to five substituents independently selected from R<sup>6</sup>,

R<sup>5</sup> is selected from the group consisting of hydrogen, C(O)R, C(O)OR, CONRR', and C<sub>1-6</sub>alkyl,



R<sup>6</sup> is selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>haloalkyl, aryl, C<sub>1-4</sub>alkoxy, hydroxy, CN, CO<sub>2</sub>R, CONRR', SR, SO<sub>2</sub>R, SO<sub>3</sub>R, PR<sub>2</sub>, PO(OR)<sub>2</sub>, PO(OR)(NRR'), PO(NRR')<sub>2</sub>, P(OR)<sub>2</sub>, P(OR)(NRR'), P(NRR')<sub>2</sub>, SiRR'R'', B(OR)<sub>2</sub>, C(O)R, NRR', NO<sub>2</sub>, and halogen,

each R, R' and R'' is independently selected from the group consisting of, H, C<sub>1-4</sub>alkyl, hydroxy and C<sub>1-4</sub>alkoxy, and

each X and Y are independently anions selected from halide, OH, HSO<sub>4</sub>, SO<sub>4</sub>, BF<sub>4</sub>, SbF<sub>6</sub>, carboxylate, carbonate, hydrogencarbonate, NO<sub>3</sub>, sulfonate, hexafluorophosphate, phosphate, hydrogen phosphate and perchlorate,

Within this embodiment, the invention encompasses the aforementioned process

wherein in Formula A each R<sup>A</sup> and each R<sup>B</sup> are independently selected from the group consisting of:

(i) hydrogen,

(ii) halogen,

(iii) OR<sup>7</sup>,

(iv) N(R<sup>7</sup>)<sub>2</sub>,

(v) CN,

(vi) C<sub>1-8</sub>alkyl or C<sub>2-8</sub>alkenyl, either of which optionally bears up to 3

substituents independently selected from halogen, OH, CN, CF<sub>3</sub>, OR<sup>7</sup>, SR<sup>8</sup>, SO<sub>2</sub>R<sup>8</sup>,

SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, COR<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, CON(R<sup>7</sup>)<sub>2</sub>, N(R<sup>7</sup>)<sub>2</sub>, NR<sup>7</sup>COR<sup>8</sup> and NR<sup>7</sup>SO<sub>2</sub>R<sup>8</sup>; and

(vii) C<sub>3-10</sub>cycloalkyl, C<sub>3-10</sub>cycloalkylC<sub>1-4</sub>alkyl, Het, HetC<sub>1-4</sub>alkyl, ARY or

ARY-C<sub>1-4</sub>alkyl, any of which optionally bears up to 3 substituents independently selected from

halogen, OH, oxo, CN, CF<sub>3</sub>, R<sup>8</sup>, OR<sup>7</sup>, SR<sup>8</sup>, SO<sub>2</sub>R<sup>8</sup>, SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, COR<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, CON(R<sup>7</sup>)<sub>2</sub>,

N(R<sup>7</sup>)<sub>2</sub>, NR<sup>7</sup>COR<sup>8</sup> and NR<sup>7</sup>SO<sub>2</sub>R<sup>8</sup>; where "ARY" refers to phenyl or 5- or 6-membered

heteroaryl, either of which phenyl or heteroaryl is optionally fused to a 5- or 6-membered carbocycle or heterocycle, and "Het" refers to a nonaromatic mono- or bicyclic heterocyclic system of up to 10 ring atoms;

and one of R<sup>A</sup> and R<sup>B</sup> together may complete a mono- or bicyclic carbocyclic or heterocyclic system of up to 10 ring atoms which optionally bears up to 3 substituents

independently selected from halogen, OH, oxo, CN, CF<sub>3</sub>, R<sup>8</sup>, OR<sup>7</sup>, SR<sup>8</sup>, SO<sub>2</sub>R<sup>8</sup>, SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, COR<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, CON(R<sup>7</sup>)<sub>2</sub>, N(R<sup>7</sup>)<sub>2</sub>, NR<sup>7</sup>COR<sup>8</sup> and NR<sup>7</sup>SO<sub>2</sub>R<sup>8</sup>;

R<sup>7</sup> is H or C<sub>1-6</sub>alkyl which is optionally substituted with up to 3 halogen atoms or with OH, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino or di(C<sub>1-4</sub>alkyl)amino, or R<sup>7</sup> is  
 5 phenyl, benzyl or 5- or 6-membered heteroaryl, any of which optionally bears up to 3 substituents independently selected from halogen, OH, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino and di(C<sub>1-4</sub>alkyl)amino;

or two R<sup>7</sup> groups attached to the same nitrogen atom may complete a heterocycle of up to 6 ring atoms which optionally bears up to 3 substituents independently selected from  
 10 halogen, OH, oxo, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino and di(C<sub>1-4</sub>alkyl)amino; and

R<sup>8</sup> is C<sub>1-6</sub>alkyl which is optionally substituted with up to 3 halogen atoms or with OH, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino or di(C<sub>1-4</sub>alkyl)amino, or R<sup>8</sup> is phenyl, benzyl or 5- or 6-membered heteroaryl, any of which optionally bears up to 3 substituents  
 15 independently selected from halogen, OH, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino and di(C<sub>1-4</sub>alkyl)amino;

or two R<sup>8</sup> groups attached to the same nitrogen atom may complete a heterocycle of up to 6 ring atoms which optionally bears up to 3 substituents independently selected from halogen, OH, oxo, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino and di(C<sub>1-4</sub>alkyl)amino.  
 20

Also within this embodiment, the invention encompasses the aforementioned process wherein in Formula A R<sup>C</sup> is selected from the group consisting of:

- (i) hydrogen,
- (ii) halogen,
- 25 (iii) OR<sup>7</sup>,
- (iv) N(R<sup>7</sup>)<sub>2</sub>,
- (v) CN,



(vi) C<sub>1-8</sub>alkyl or C<sub>2-8</sub>alkenyl, either of which optionally bears up to 3 substituents independently selected from halogen, OH, CN, CF<sub>3</sub>, OR<sup>7</sup>, SR<sup>8</sup>, SO<sub>2</sub>R<sup>8</sup>, SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, COR<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, CON(R<sup>7</sup>)<sub>2</sub>, N(R<sup>7</sup>)<sub>2</sub>, NR<sup>7</sup>COR<sup>8</sup> and NR<sup>7</sup>SO<sub>2</sub>R<sup>8</sup>; and

(vii) C<sub>3-10</sub>cycloalkyl, C<sub>3-10</sub>cycloalkylC<sub>1-4</sub>alkyl, Het, HetC<sub>1-4</sub>alkyl, ARY or ARY-C<sub>1-4</sub>alkyl, any of which optionally bears up to 3 substituents independently selected from halogen, OH, oxo, CN, CF<sub>3</sub>, R<sup>8</sup>, OR<sup>7</sup>, SR<sup>8</sup>, SO<sub>2</sub>R<sup>8</sup>, SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, COR<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, CON(R<sup>7</sup>)<sub>2</sub>, N(R<sup>7</sup>)<sub>2</sub>, NR<sup>7</sup>COR<sup>8</sup> and NR<sup>7</sup>SO<sub>2</sub>R<sup>8</sup>; where "ARY" refers to phenyl or 5- or 6-membered heteroaryl, either of which phenyl or heteroaryl is optionally fused to a 5- or 6-membered carbocycle or heterocycle, and "Het" refers to a nonaromatic mono- or bicyclic heterocyclic system of up to 10 ring atoms;

R<sup>7</sup> is H or C<sub>1-6</sub>alkyl which is optionally substituted with up to 3 halogen atoms or with OH, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino or di(C<sub>1-4</sub>alkyl)amino, or R<sup>7</sup> is phenyl, benzyl or 5- or 6-membered heteroaryl, any of which optionally bears up to 3 substituents independently selected from halogen, OH, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino and di(C<sub>1-4</sub>alkyl)amino;

or two R<sup>7</sup> groups attached to the same nitrogen atom may complete a heterocycle of up to 6 ring atoms which optionally bears up to 3 substituents independently selected from halogen, OH, oxo, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino and di(C<sub>1-4</sub>alkyl)amino; and

R<sup>8</sup> is C<sub>1-6</sub>alkyl which is optionally substituted with up to 3 halogen atoms or with OH, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino or di(C<sub>1-4</sub>alkyl)amino, or R<sup>8</sup> is phenyl, benzyl or 5- or 6-membered heteroaryl, any of which optionally bears up to 3 substituents independently selected from halogen, OH, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino and di(C<sub>1-4</sub>alkyl)amino;

or two R<sup>8</sup> groups attached to the same nitrogen atom may complete a heterocycle of up to 6 ring atoms which optionally bears up to 3 substituents independently selected from halogen, OH, oxo, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino and di(C<sub>1-4</sub>alkyl)amino.

Also within this embodiment, the invention encompasses the aforementioned process wherein in Formula A PG is selected from the group consisting of: C<sub>1-6</sub> alkyl, vinyl, C(O)-O-L, C(O)-L, aryl, hetroaryl, benzyl, benzhydryl, trityl and C<sub>1-6</sub>alkoxymethyl, wherein aryl, heteroaryl, benzyl, benzyhydryl and trityl optionally are substituted with 1 to 3 substituents  
 5 independently selected from methoxy and nitro, C<sub>1-6</sub>alkoxymethyl is optionally substituted with trimethylsilyl and L is C<sub>1-6</sub>alkyl, aryl or benzyl.

Also within this embodiment, the invention encompasses the aforementioned process wherein in Formula A W is selected from the group consisting of: halogen and sulfonate.

Also within this embodiment, the invention encompasses the aforementioned  
 10 process wherein the water-immiscible organic phase is selected from the group consisting of benzene, toluene, xylenes, chlorobenzene, ethyl ether, isopropyl ether, tetrahydrofuran, 2-methyl tetrahydrofuran, dioxane, methyl *tert*-butyl ether, cyclopentyl methyl ether, isopropyl acetate, ethyl acetate, hexanes, heptanes, cyclohexane, dichloromethane and dichloroethane.

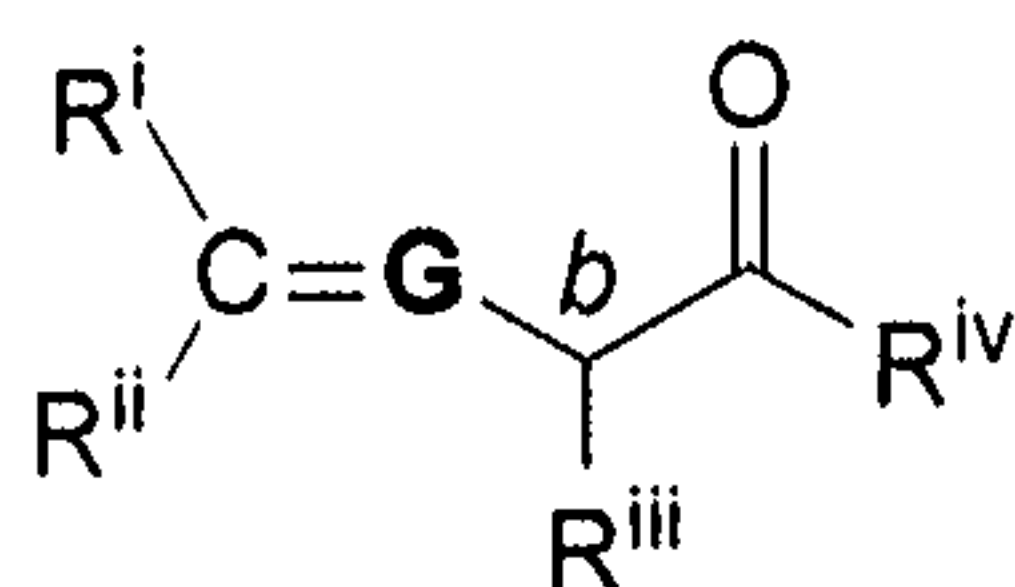
Also within this embodiment, the invention encompasses the aforementioned  
 15 process the base is selected from the group consisting of: sodium hydroxide, lithium hydroxide, potassium hydroxide, sodium carbonate, lithium carbonate, potassium carbonate, cesium hydroxide, cesium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, lithium hydrogen carbonate, cesium hydrogen carbonate, lithium fluoride, sodium fluoride, potassium fluoride, cesium fluoride, lithium *tert*-butoxide, sodium *tert*-butoxide, potassium *tert*-  
 20 butoxide, sodium phosphate, lithium phosphate and potassium phosphate.

Also within this embodiment, the invention encompasses the aforementioned process wherein the water-immiscible organic phase is toluene and the base is sodium hydroxide.

The invention also encompasses the bis-quarternary cinchona alkaloid salts of Formula I for use as a phase transfer catalyst in one of the following reactions:

25

(1) the asymmetric formation of a carbon-carbon bond at position *b* of a substrate having the following formula



30



wherein:

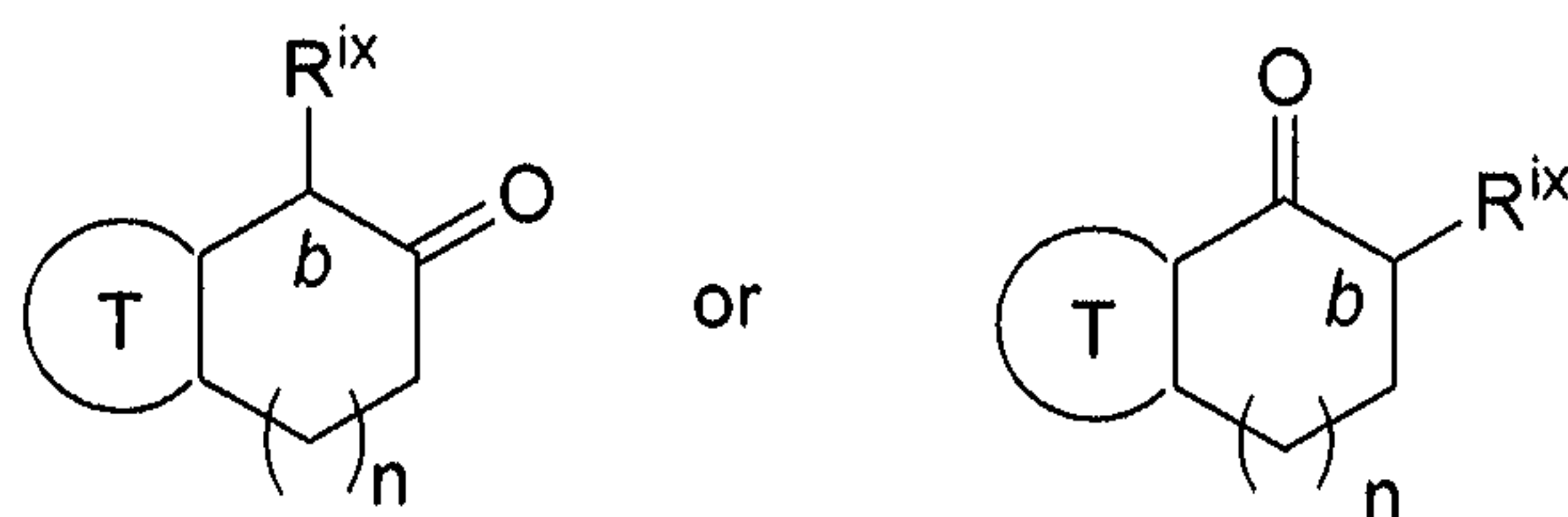
**G** is N or CH,

$R^i$ ,  $R^{ii}$  and  $R^{iii}$  are independently H, halogen or an organic substituent group

$R^{iv}$  is selected from  $-OR^v$ ,  $SR^vi$  and  $NR^{vii}R^{viii}$ , wherein  $R^v$  and  $R^vi$  are independently H or an organic substituent group,  $R^{vii}$  and  $R^{viii}$  are independently H or an organic substituent group or  $R^{vii}$  and  $R^{viii}$  may be joined together with the nitrogen to which they are attached to form a 5- or 6-membered heterocyclic ring, and

when **G** is N,  $R^{ii}$  and  $R^{iii}$  may be joined together with the atoms to which they are attached to form a 5- or 6-membered mono- or 9- or 10-membered bi-cyclic ring containing one or more heteroatoms in addition to the nitrogen, said ring optionally substituted with 1 to 5 substituents independently selected from: halogen, hydroxy, amino or an organic substituent group;

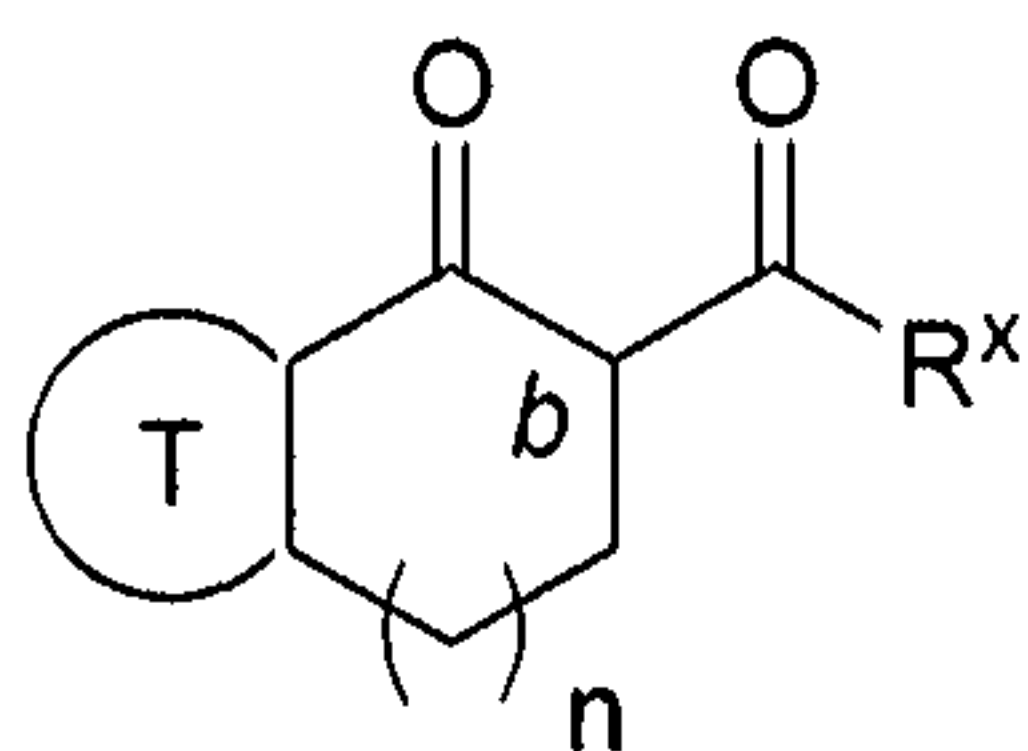
(2) the asymmetric formation of a carbon-carbon bond at position *b* of a substrate having the following formula



wherein *n* is 0 or 1, ring T is optional and forms a fused 5- or 6-membered aromatic carbocyclic or heterocyclic ring, each ring optionally substituted with hydrogen, halogen, hydroxy, amino or an organic substituent group and  $R^{ix}$  is H or an organic substituent group,

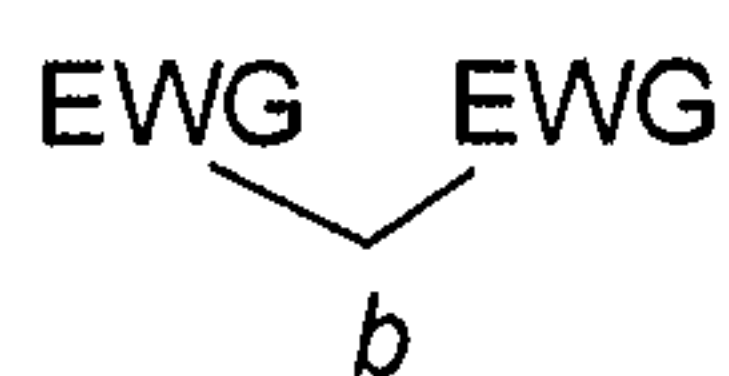
(3) the asymmetric formation of a carbon-carbon bond at position *b* of a substrate having the following formula





wherein  $n$  is 0 or 1, ring  $T$  is optional and forms a fused 5- or 6-membered aromatic carbocyclic or heterocyclic ring, each ring optionally substituted with hydrogen, halogen, hydroxy, amino or an organic substituent group and  $R^x$  is selected from  $-OR^{xi}$ ,  $SR^{xii}$  and  $NR^{xiii}R^{xiv}$ , wherein  $R^{xi}$  and  $R^{xii}$  are independently H or an organic substituent group and  $R^{xiii}$  and  $R^{xiv}$  are independently H or an organic substituent group or  $R^{xiii}$  and  $R^{xiv}$  may be joined together with the nitrogen to which they are attached to form a 5- or 6-membered heterocyclic ring;

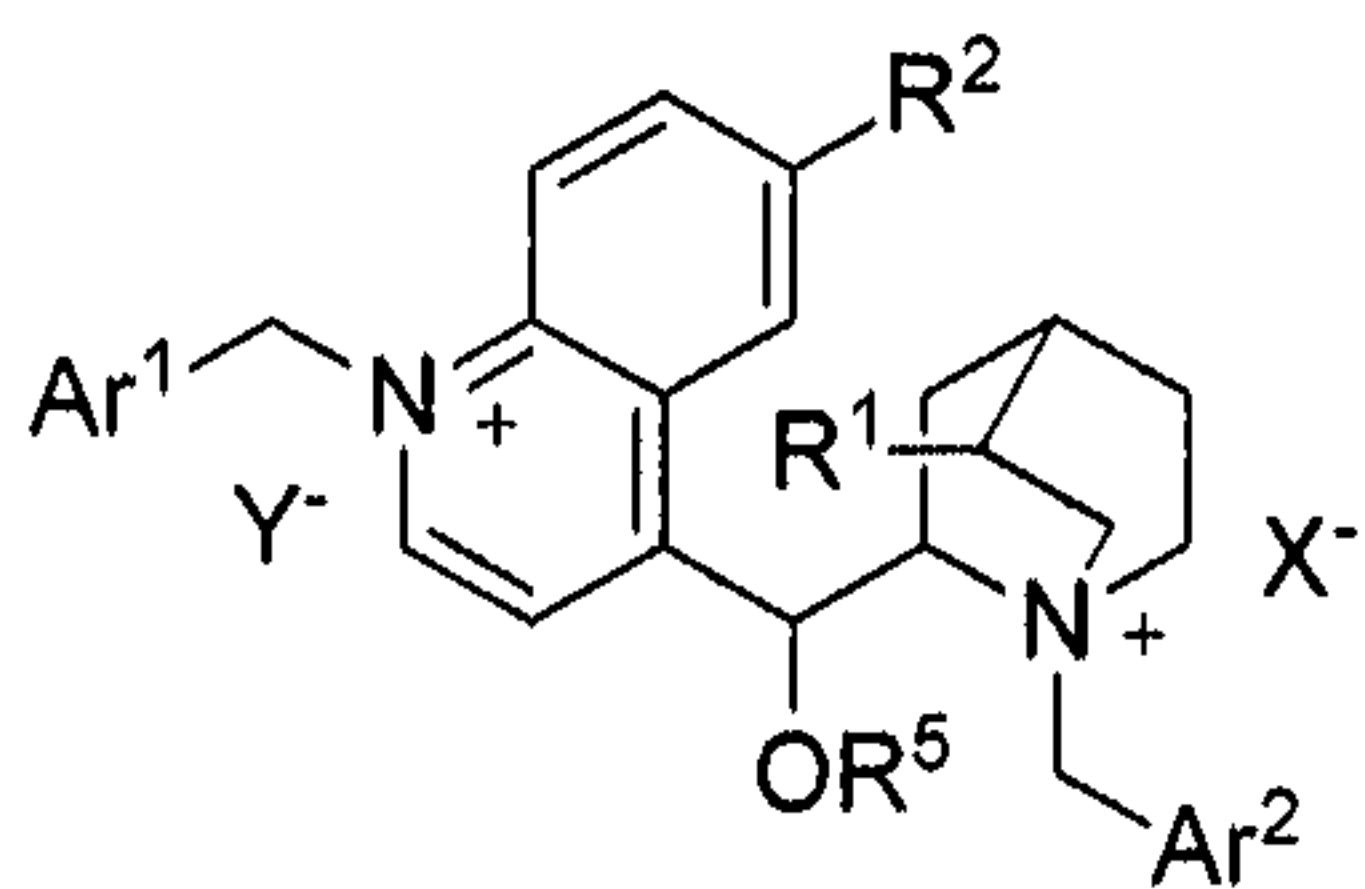
(4) the asymmetric formation of a carbon-carbon bond position  $b$  of a substrate having the following formula



wherein each EWG is independently an electron withdrawing group;

comprising reacting the substrate with electrophilic alkylating agent, an electron deficient olefin or an aldehyde in the presence of bis-quarternary cinchona alkaloid salt and a base in a biphasic medium comprising an aqueous phase and organic phase to form the carbon-carbon bond.

The invention also encompasses bis-quarternary cinchona alkaloid salts having the chemical structure of Formula II:



II

wherein:

R<sup>1</sup> is selected from ethyl and vinyl,

R<sup>2</sup> is selected from hydrogen and methoxy,

Ar<sup>1</sup> is aryl or heteroaryl, wherein said aryl and heteroaryl groups are optionally substituted with one to five substituents independently selected from R<sup>3</sup>,

Ar<sup>2</sup> is aryl or heteroaryl, wherein said aryl and heteroaryl groups are optionally substituted with one to five substituents independently selected from R<sup>3</sup>,

each R<sup>3</sup> is independently selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>haloalkyl, aryl, C<sub>1-4</sub>alkoxy, hydroxy, CN, C<sub>1-4</sub>acyl, N(R<sup>4</sup>)<sub>2</sub>, NO<sub>2</sub>, halogen, O-Phenyl and (C=O)OC<sub>1-4</sub>alkyl,

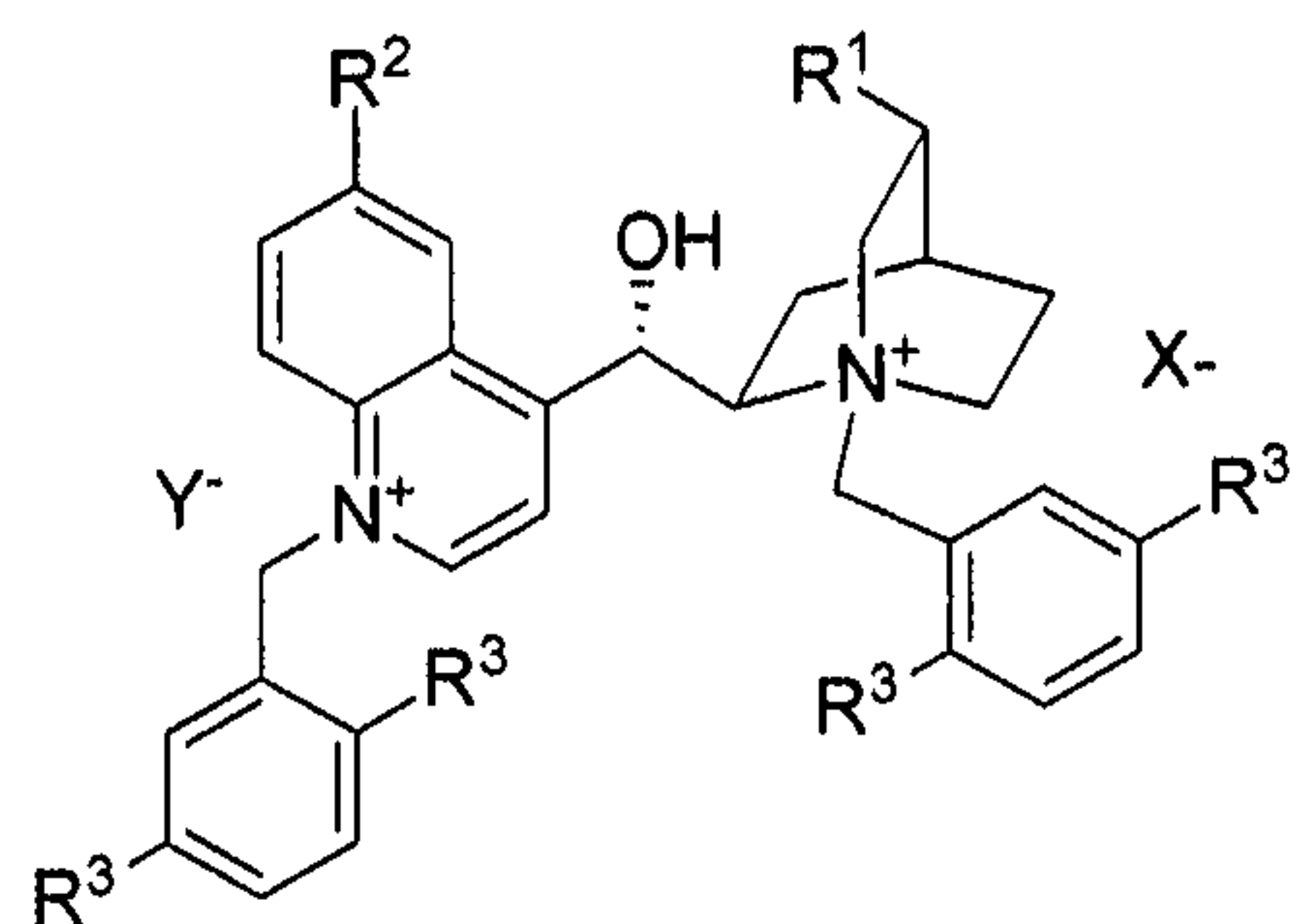
each R<sup>4</sup> is independently H or C<sub>1-4</sub>alkyl, and

each X and Y are independently anions selected from halide, OH, HSO<sub>4</sub>, SO<sub>4</sub>, BF<sub>4</sub>, SbF<sub>6</sub>, carboxylate, carbonate, hydrogencarbonate, NO<sub>3</sub>, sulfonate, hexafluorophosphate, phosphate, hydrogen phosphate and perchlorate.

Unless depicted or specified otherwise, the cinchona alkaloid salts of Formula II encompass all stereoisomers, including cinchonine, cinchonidine, quinine, quinidine, dihydroquinidine, and dihydroquinine.

An embodiment of the invention encompasses bis-quarternary cinchona alkaloid salts of Formula II wherein Ar<sup>1</sup> is phenyl which is optionally substituted with one to five substituents independently selected from R<sup>3</sup>, and Ar<sup>2</sup> is phenyl which is optionally substituted with one to five substituents independently selected from R<sup>3</sup>.

An embodiment of the invention encompasses bis-quarternary cinchona alkaloid salts of Formula IIa

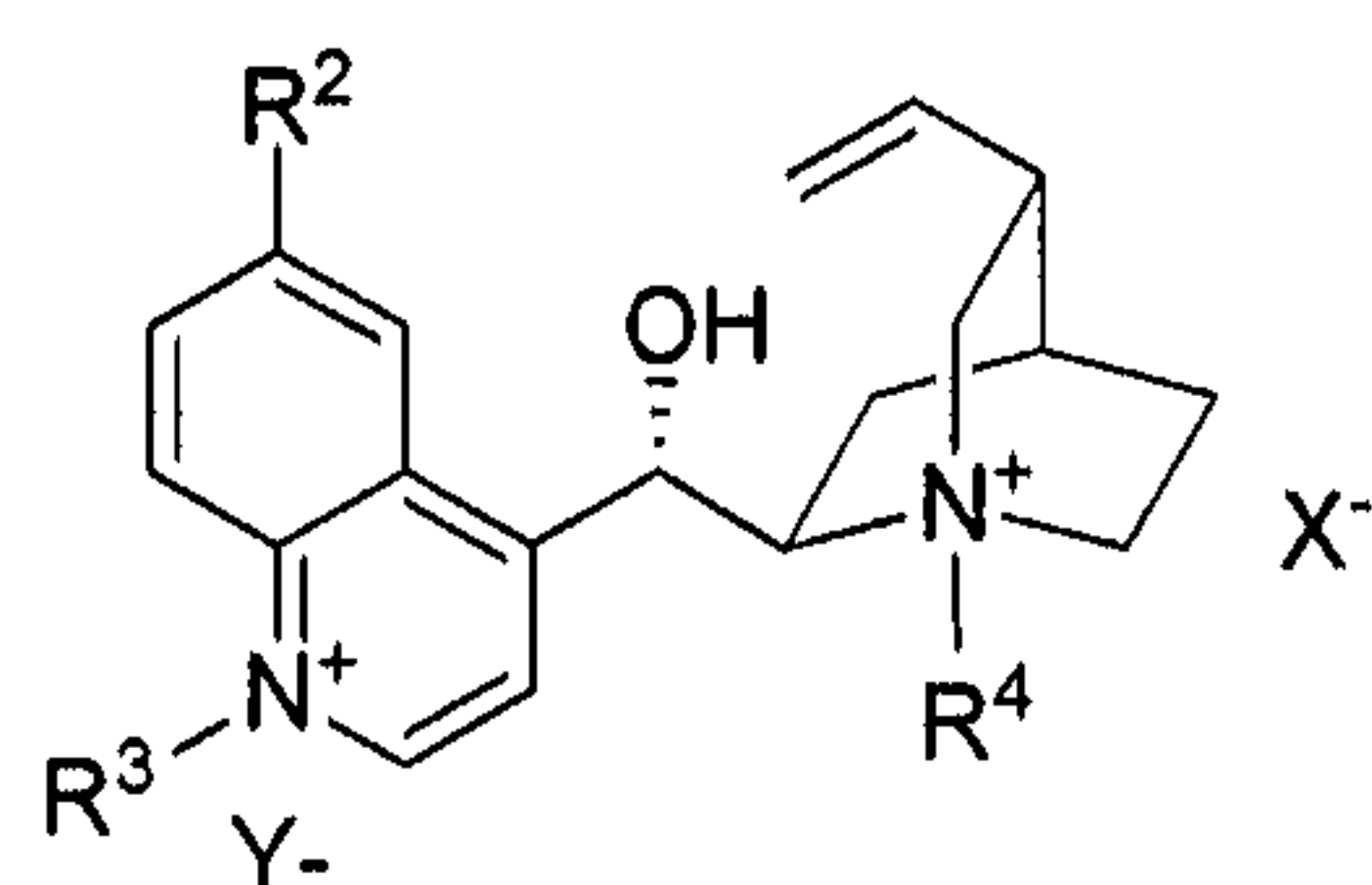


IIa,  
and otherwise as defined above.

An embodiment of the invention encompasses bis-quarternary cinchona alkaloid salts of Formula IIa wherein R<sup>1</sup> is vinyl and R<sup>2</sup> is methoxy.

Another embodiment of the invention encompasses bis-quarternary cinchona alkaloid salts of Formula IIa wherein R<sup>3</sup> is selected from halogen and methoxy.

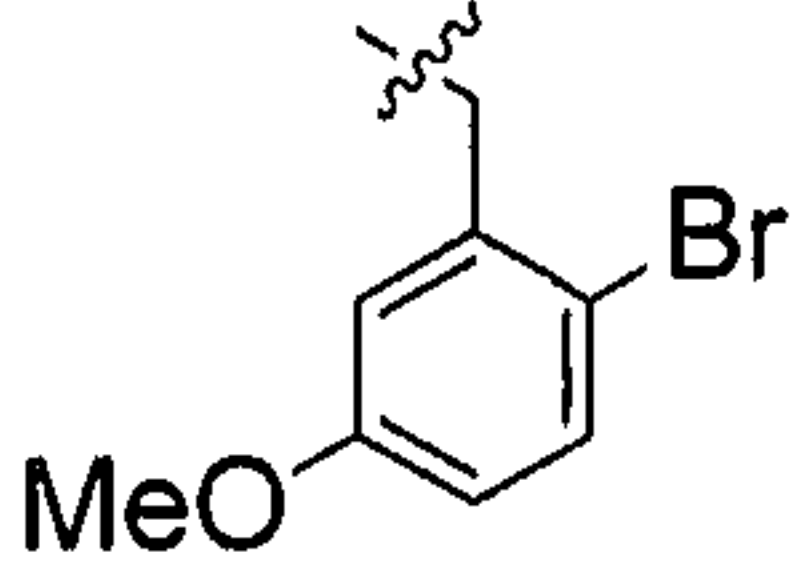
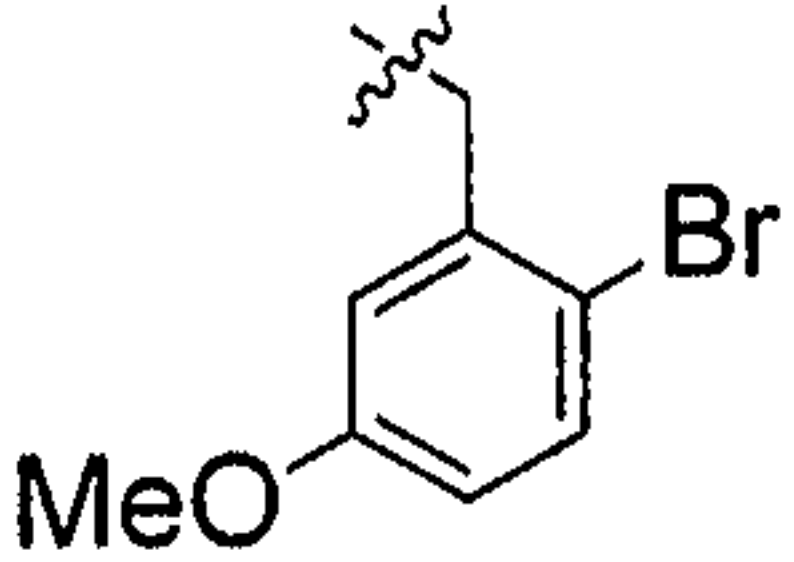
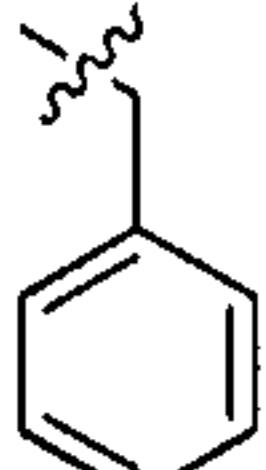
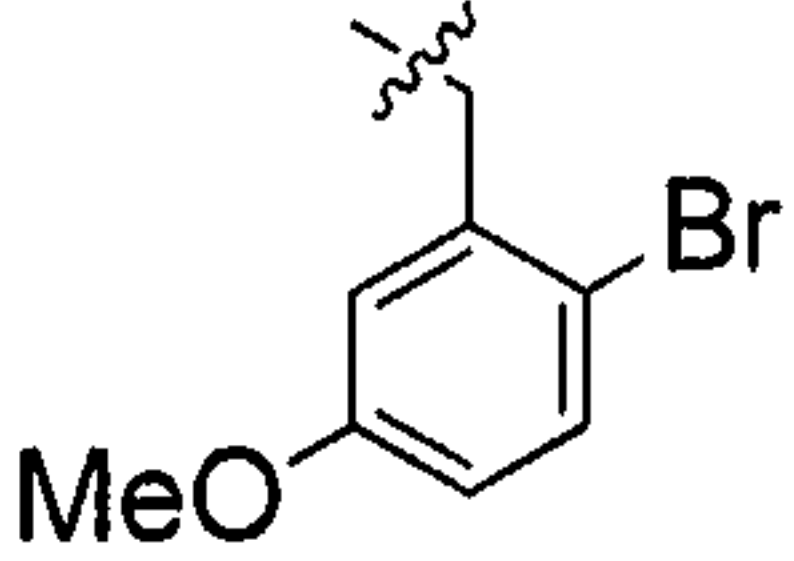
Another embodiment of the invention encompasses a bis-quarternary cinchona alkaloid salt selected from:

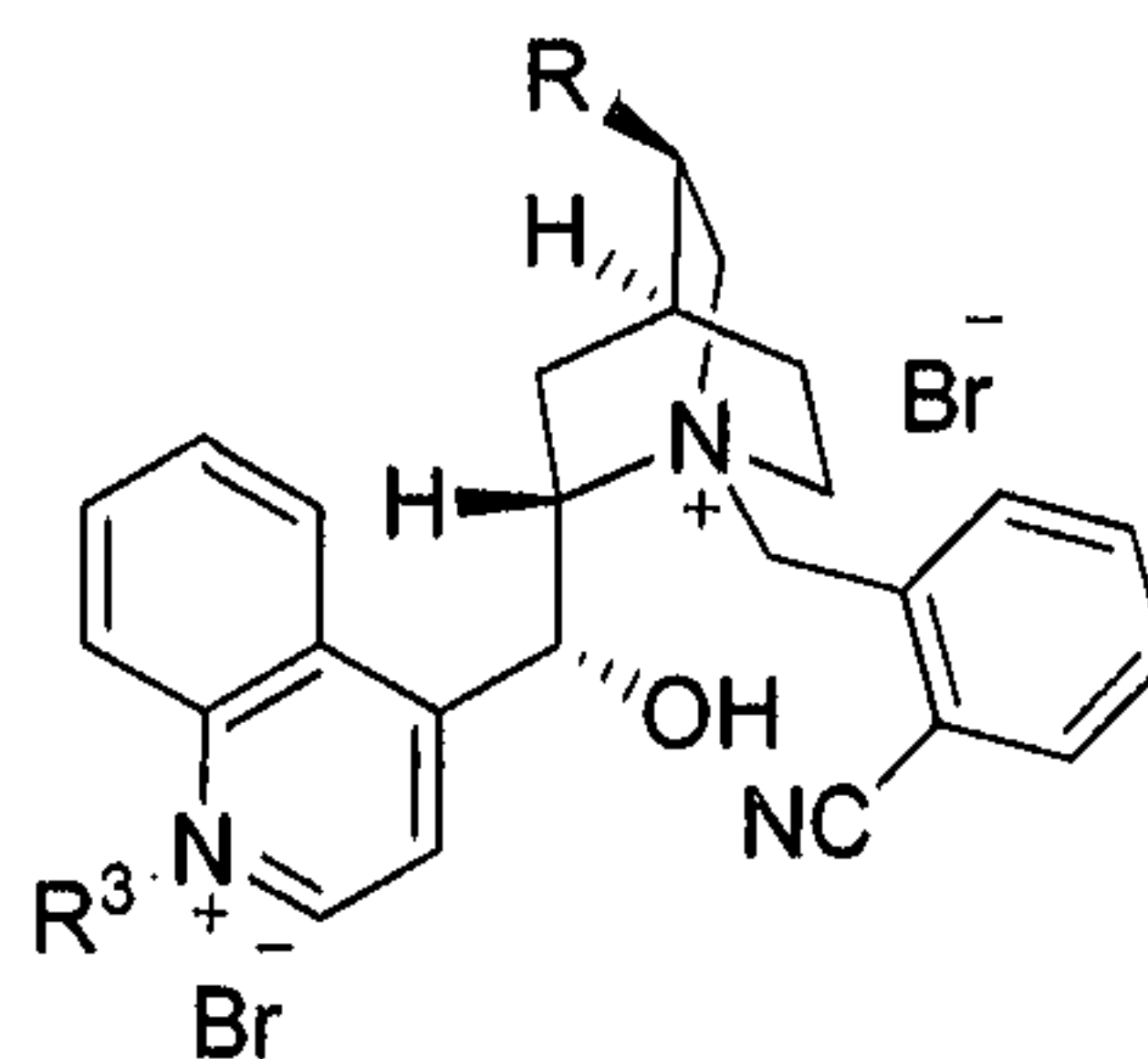


10

R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	X <sup>-</sup>	Y <sup>-</sup>
OMe			Br	Br
H			Br	Br
H			I	I
H			Br	I
H			Br	Br

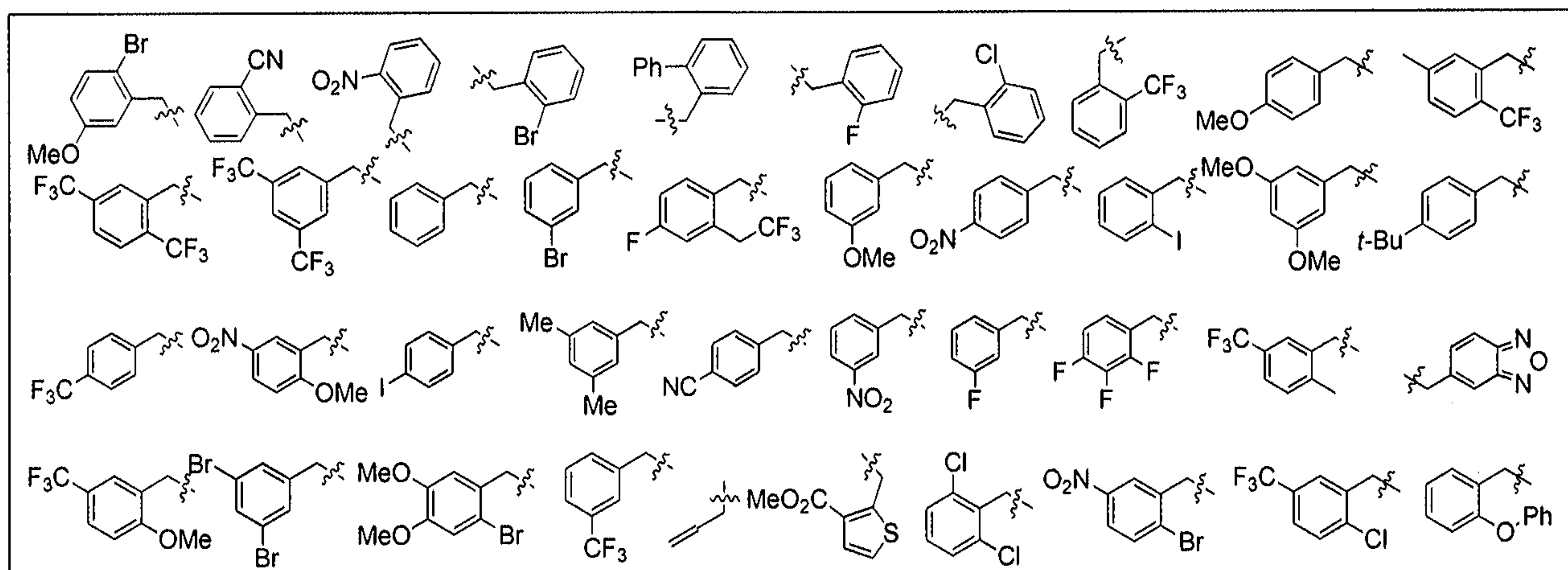


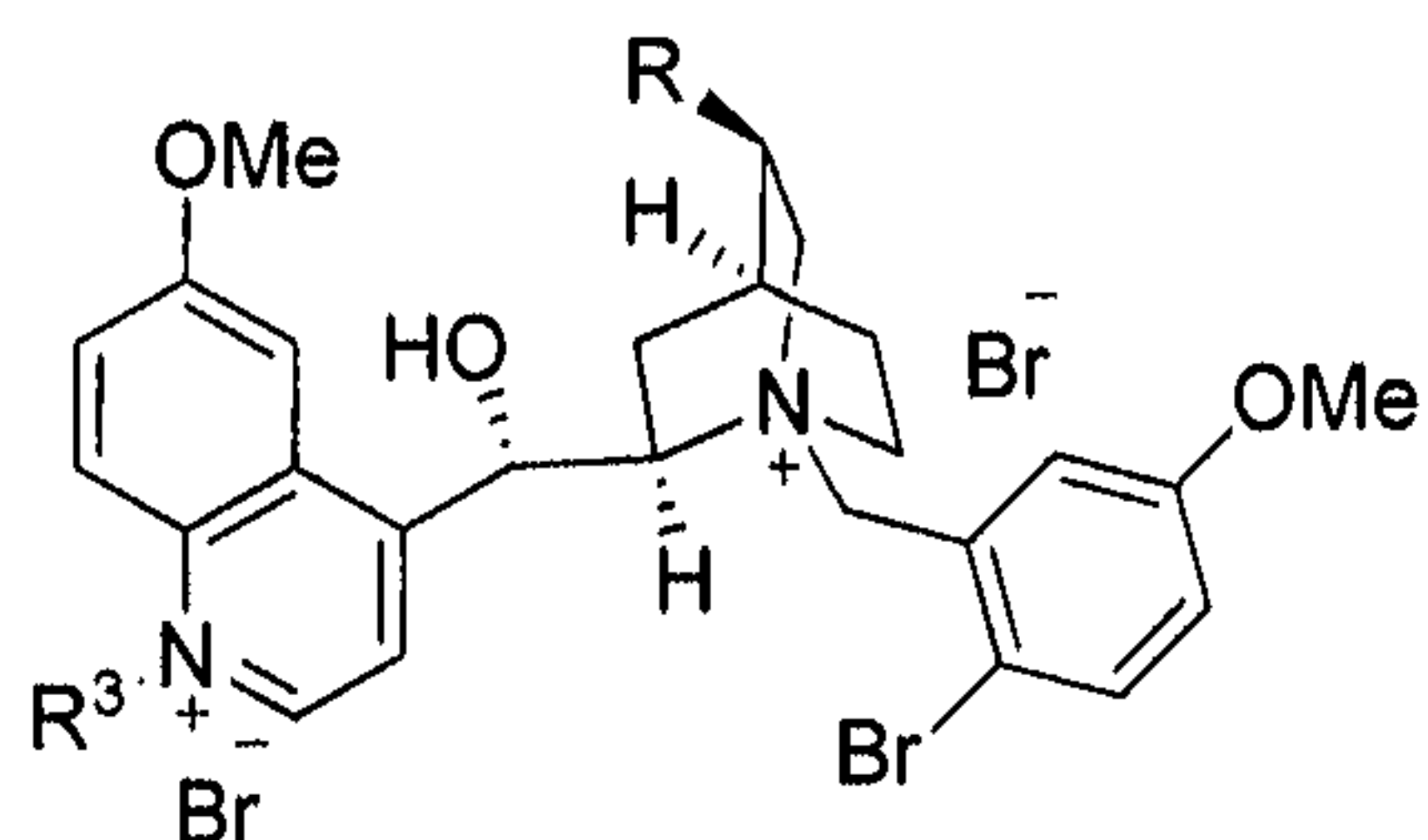
R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	X <sup>-</sup>	Y <sup>-</sup>
H	Me		Br	I
H			Br	Br
H		allyl	Br	Br



wherein R is selected from the group consisting of vinyl and ethyl;

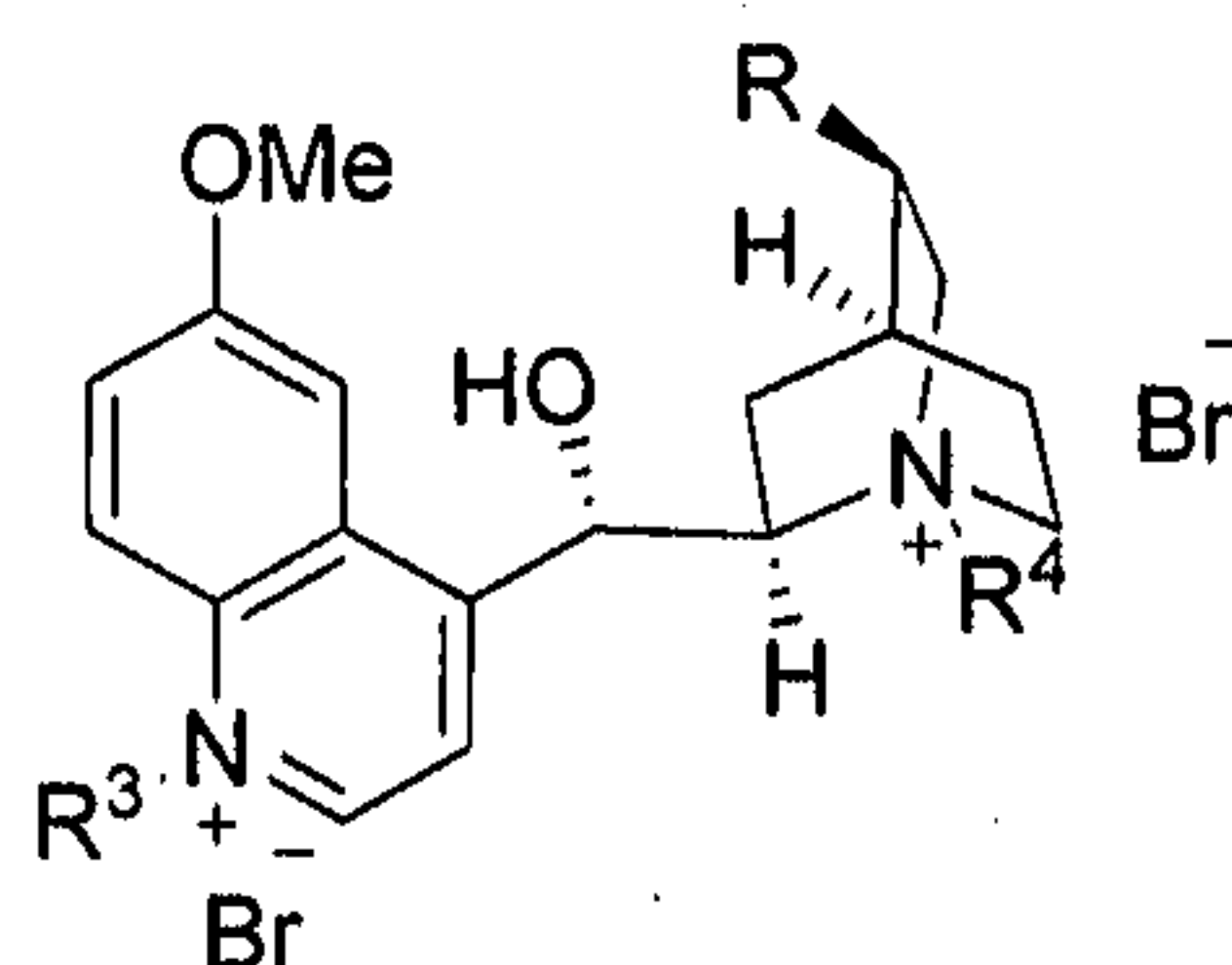
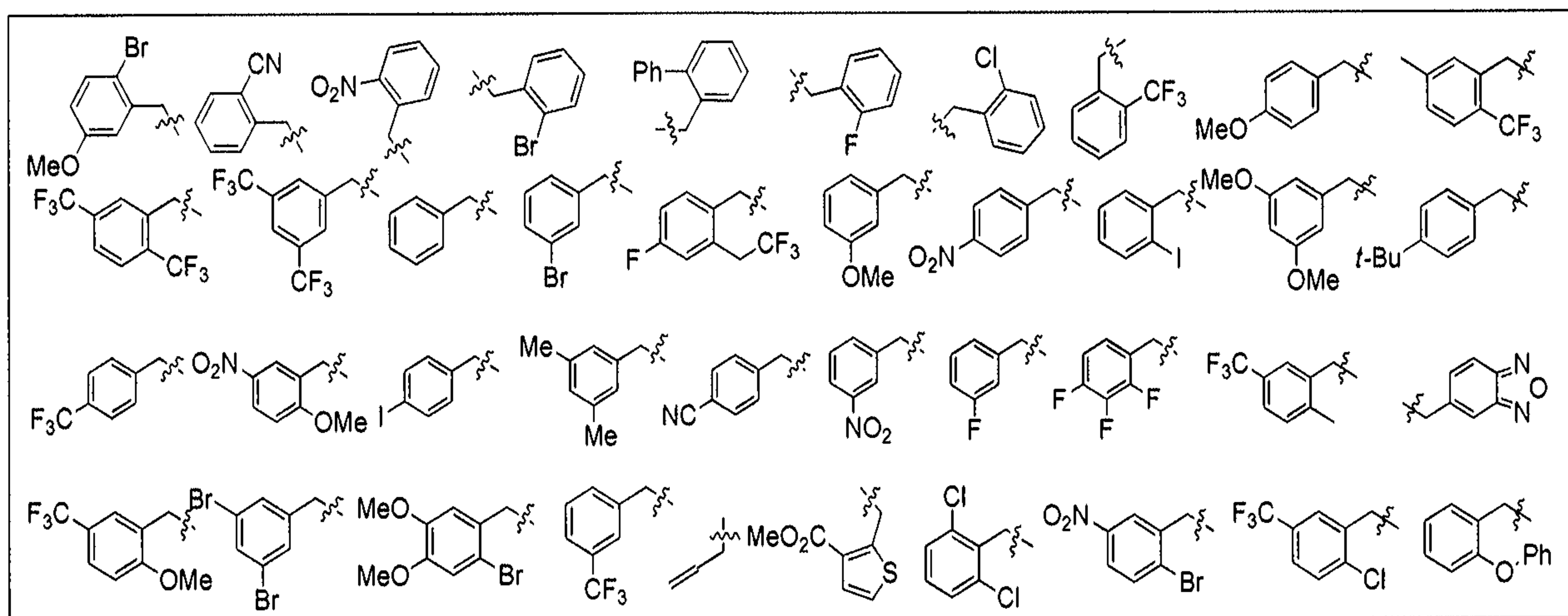
R<sup>3</sup> is selected from the following groups:





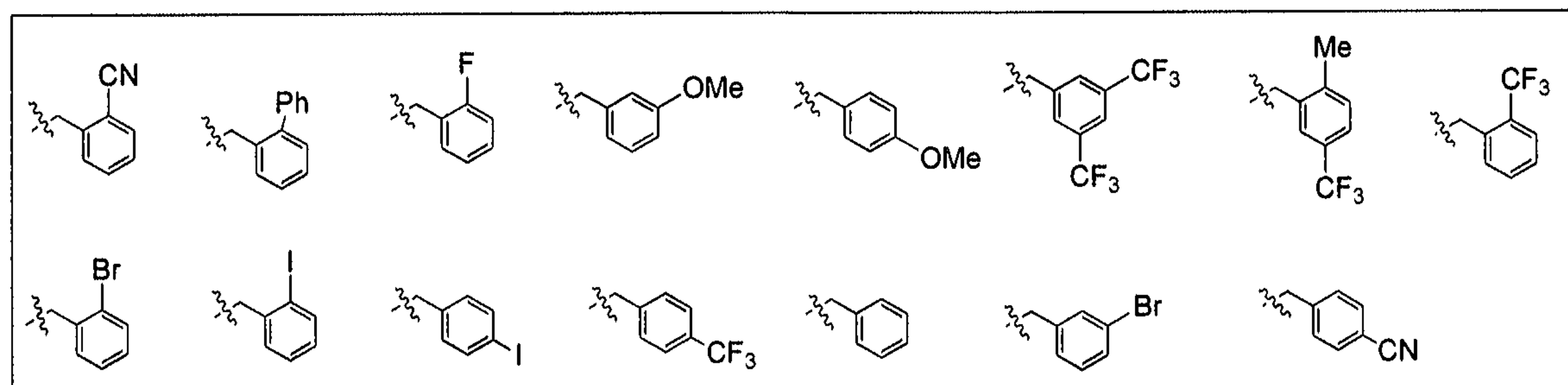
wherein R is selected from the group consisting of vinyl and ethyl;

R<sup>3</sup> is selected from the following groups:



wherein R is selected from the group consisting of vinyl and ethyl;

5 R<sup>3</sup> and R<sup>4</sup> are independently selected from the following groups:





As used herein, the term "alkyl" refers to a monovalent straight or branched chain, saturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range. Thus, for example, "C<sub>1</sub>-6 alkyl" (or "C<sub>1</sub>-C<sub>6</sub> alkyl") refers to any of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and iso- propyl, ethyl and methyl. As  
 5 another example, "C<sub>1</sub>-4 alkyl" refers to n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. As another example, "C<sub>1</sub>-3 alkyl" refers to n-propyl, isopropyl, ethyl and methyl.

The term "haloalkyl" means an alkyl radical as defined above, unless otherwise specified, that is substituted with one to five, preferably one to three halogen. Representative examples include, but are not limited to trifluoromethyl, dichloroethyl, and the like.

10 The term acyl, means -C(O)-alkyl where alkyl is as defined above.

The term "alkoxy" means -O-alkyl where alkyl is as defined above.

The term "alkenyl" refers to a monovalent straight or branched chain, saturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range and at least one carbon-carbon double bond, and otherwise carbon-carbon single bonds. Alkenyl includes for  
 15 example ethenyl, 1-methylethynyl, 2-propenenyl, 2-butenyl, 1,4-pentadienyl and the like.

The term "alkynyl" refers to a monovalent straight or branched chain, saturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range and at least one carbon-carbon triple bond, and otherwise carbon-carbon double or single bonds. Alkynyl includes for example 2-propynyl, 1-butylnyl, 3-hexen-5-ynyl and the like.

20 The term "cycloalkyl" refers to any monocyclic ring of an alkane having a number of carbon atoms in the specified range. Thus, for example, "C<sub>3</sub>-6 cycloalkyl" (or "C<sub>3</sub>-C<sub>6</sub> cycloalkyl") refers to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, and "C<sub>3</sub>-5 cycloalkyl" refers to cyclopropyl, cyclobutyl, and cyclopentyl.

The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine  
 25 (alternatively referred to as fluoro, chloro, bromo, and iodo).

The term "aryl" refers to phenyl, naphthyl, and anthranyl.

The term "heteroaryl" refers to (i) a 5- or 6-membered heteroaromatic ring containing from 1 to 3 heteroatoms independently selected from N, O and S, or (ii) is a heterobicyclic ring selected from quinolinyl, isoquinolinyl, and quinoxalinyl. Suitable 5- and 6-  
 30 membered heteroaromatic rings include, for example, pyridyl (also referred to as pyridinyl), pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thienyl, furanyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isooxazolyl, oxadiazolyl, oxatriazolyl, thiazolyl, isothiazolyl, and



thiadiazolyl. Heteroaryls of particular interest are pyrrolyl, imidazolyl, pyridyl, pyrazinyl, quinolinyl (or quinolyl), isoquinolinyl (or isoquinolyl), and quinoxalinyl.

Examples of 4- to 7-membered, saturated heterocyclic rings within the scope of this invention include, for example, azetidiny, piperidiny, morpholinyl, thiomorpholinyl, 5 thiazolidiny, isothiazolidiny, oxazolidiny, isoxazolidiny, pyrrolidiny, imidazolidiny, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, pyrazolidiny, hexahydropyrimidiny, thiazinanyl, thiazepanyl, azepanyl, diazepanyl, tetrahydropyranyl, tetrahydrothiopyranyl, and dioxanyl. Examples of 4- to 7-membered, unsaturated heterocyclic rings within the scope of this invention (see HetB) include mono-unsaturated heterocyclic rings corresponding to the saturated 10 heterocyclic rings listed in the preceding sentence in which a single bond is replaced with a double bond (e.g., a carbon-carbon single bond is replaced with a carbon-carbon double bond).

It is understood that the specific rings listed above are not a limitation on the rings which can be used in the present invention. These rings are merely representative.

Unless expressly stated to the contrary in a particular context, any of the various 15 cyclic rings and ring systems described herein may be attached to the rest of the compound at any ring atom (i.e., any carbon atom or any heteroatom) provided that a stable compound results.

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heteroaromatic ring described as containing from "1 to 4 heteroatoms" means the ring can contain 1, 2, 3 or 4 heteroatoms. It is also understood that any range cited herein includes 20 within its scope all of the sub-ranges within that range. Thus, for example, a heterocyclic ring described as containing from "1 to 4 heteroatoms" is intended to include as aspects thereof, heterocyclic rings containing 2 to 4 heteroatoms, 3 or 4 heteroatoms, 1 to 3 heteroatoms, 2 or 3 heteroatoms, 1 or 2 heteroatoms, 1 heteroatom, 2 heteroatoms, 3 heteroatoms, and 4 heteroatoms. As another example, an aryl or heteroaryl described as optionally substituted with "from 1 to 4 25 substituents" is intended to include as aspects thereof, an aryl or heteroaryl substituted with 1 to 4 substituents, 2 to 4 substituents, 3 to 4 substituents, 4 substituents, 1 to 3 substituents, 2 to 3 substituents, 3 substituents, 1 to 2 substituents, 2 substituents, and 1 substituent.

When any variable occurs more than one time in any constituent or in Formula I, II, IIa, A, B or C, or in any other formula depicting and describing compounds of the present 30 invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.



Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom in a ring (e.g., cycloalkyl, aryl, or heteroaryl) provided such ring substitution is chemically allowed and results in a stable compound.

5 The compounds of the invention contain chiral centers and, as a result of the selection of substituents and substituent patterns, can contain additional chiral centers, and thus can occur as mixtures of stereoisomers, or as individual diastereomers, or enantiomers. All isomeric forms of these compounds, whether individually or in mixtures, are within the scope of the present invention. Unless depicted or specified otherwise, the cinchona alkaloid salts of the invention encompass all stereoisomers, including cinchonine, cinchonidine, quinine, quinidine,  
10 dihydroquinidine, and dihydroquinine.

To the extent substituents and substituent patterns provide for the existence of tautomers (e.g., keto-enol tautomers) in the compounds of the invention, all tautomeric forms of these compounds, whether present individually or in mixtures, are within the scope of the present invention. Compounds of the present invention having a hydroxy substituent on a carbon atom  
15 of a heteroaromatic ring are understood to include compounds in which only the hydroxy is present, compounds in which only the tautomeric keto form (i.e., an oxo substituent) is present, and compounds in which the keto and enol forms are both present.

The term "organic substituent group" means any substituent group containing a carbon atom, which may be optionally substituted. Organic substituent groups include, but are  
20 not limited to, C<sub>1-10</sub>alkyl, C<sub>2-10</sub>alkenyl, C<sub>2-10</sub>alkynyl, aryl, heteroaryl, non- or partially aromatic heterocycles, C<sub>3-10</sub>cycloalkyl, C<sub>1-10</sub>alkoxy, C<sub>1-10</sub>alkylthio, and C<sub>1-10</sub>acyl, each optionally substituted with, for example, one or more of the following: halide, hydroxy, nitrogen containing substituents such as amino, sulfur containing substituent such as sulfates, C<sub>1-4</sub>alkoxy and C<sub>1-4</sub>alkylthio.

25 The term "nitrogen protecting group" means a substituent that protects a nitrogen atom in a reaction from a reagent or chemical environment. Nitrogen protecting groups are well known in the art and include for example, *t*-butyl, vinyl, phenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxy benzyl, *p*-nitrobenzyl, benzhydryl, trityl, trialkylsilyl, methoxymethyl ether, (2,2,2-trichloroethoxy)methyl and 2-(trimethylsilyl)ethoxymethyl, Boc, Cbz.

30 The term "functional group that has leaving ability" means an atom or atom group that leaves from a substrate in a substitution or elimination reaction, that is a leaving group, and includes for example halogen and sulfonate.

The term "electrophilic alkylating agent" means an agent that delivers the equivalent of an alkyl cation, such as for example an alkyl halide.

The term "electron deficient olefin" means an electrophilic alkene substituted with for example, a ketone, such as an  $\alpha$ ,  $\beta$ -unsaturated carbonyl, a nitrile or a nitro group.

5 The term "sulfonate" means an anion or leaving group having the formula  $R^{\#}-SO_3^-$  which is the conjugate base of sulfonic acid.  $R^{\#}$  includes for example  $C_{1-4}$ alkyl optionally substituted with 1 to 3 halogen, and aryl optionally substituted with 1 to 3 halogen or methyl or nitro. Examples include mesylate, triflate, tosylate and besylate.

The term "electron withdrawing group" is well known in the art and includes for  
 10 example, cyano, nitro,  $-C(O)OR^{xvii}$ ,  $-C(O)SR^{xviii}$  and  $-C(O)NR^{xvix}R^{xx}$ , wherein  $R^{xvii}$  and  $R^{xviii}$  are independently H or an organic substituent group and  $R^{xvix}$  and  $R^{xx}$  are independently H or an organic substituent group or  $R^{xvix}$  and  $R^{xx}$  may be joined together with the nitrogen to which they are attached to form a 5- or 6-membered heterocyclic ring;

15

## ABBREVIATIONS

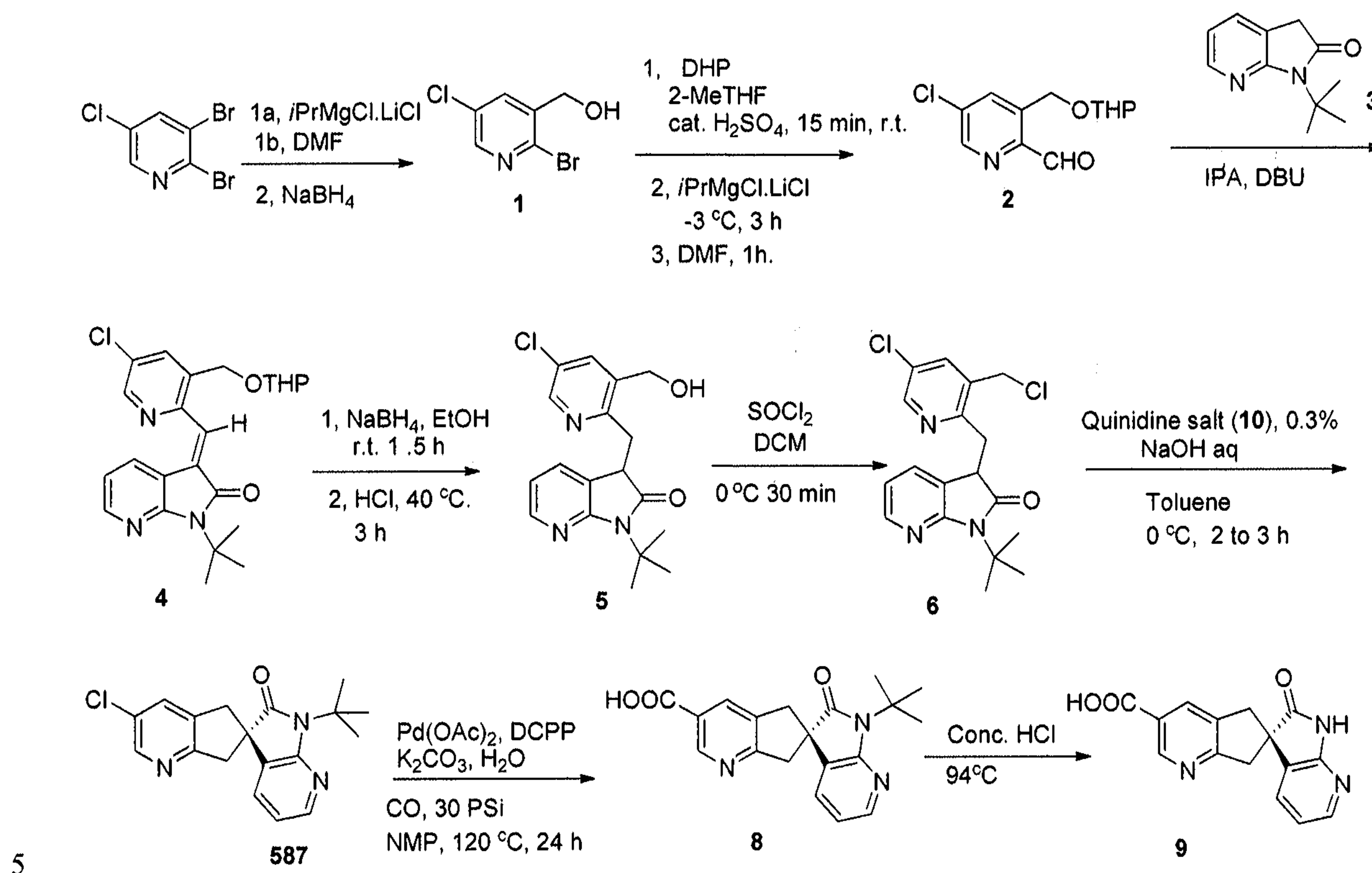
The following abbreviations are used throughout the specification.

	DCM	=	dichloromethane
20	DCPP	=	1,3-bis(dicyclohexylphosphino)propane
	DHP	=	3,4-dihydro-2H-pyran
	DMF	=	dimethylformamide
	DMSO	=	dimethyl sulfoxide
	HCl	=	hydrochloric acid
25	IPA	=	isopropyl alcohol
	LCAP	=	liquid chromatography area percent
	MTBE	=	methyl <i>tert</i> -butyl ether
	NMP	=	<i>N</i> -methyl-2-pyrrolidone
	PTC	=	phase transfer catalyst
30	RT	=	room temperature
	SFC	=	supercritical fluid chromatography
	THF	=	tetrahydrofuran

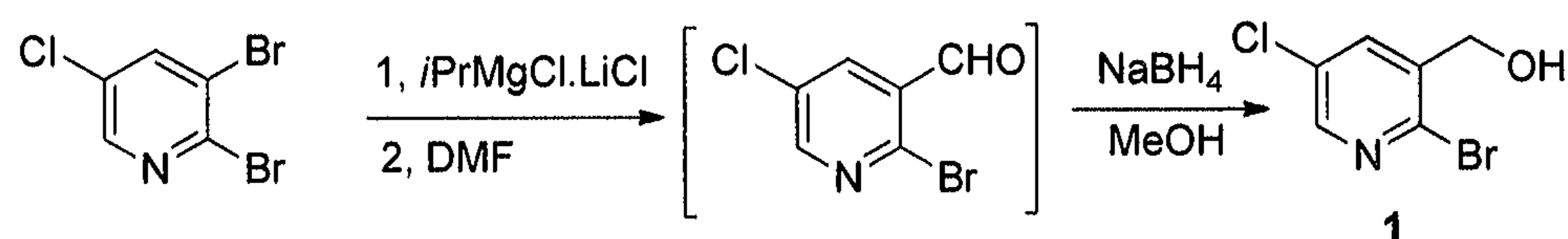


## EXAMPLE 1

## SCHEME



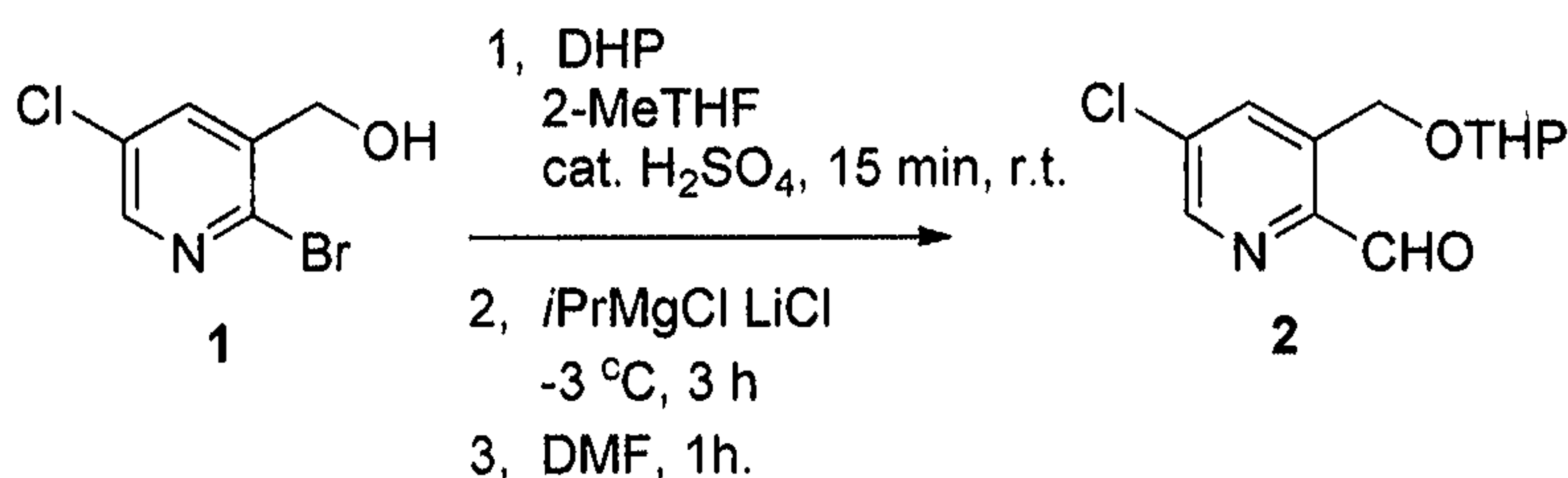
## (2-Bromo-5-chloropyridin-3-yl)methanol (1)



To a solution of 2,3-dibromo-5-chloropyridine (60 g, 221 mmol) in THF (500 mL) was added a solution of isopropylmagnesium chloride lithium chloride solution in THF (1.3M, 185 mL) at -40 °C over about 30 min. The solution was stirred for 30 min at -40 °C and DMF (50 mL) was added. The resulting solution was warmed up to room temperature and stirred for 30 min. The reaction was quenched with 1 N HCl (400 mL) and MTBE (200 mL) was added. Organic layer was separated and washed twice with 5% aqueous NaHCO<sub>3</sub> (200 mL). The solvent was removed under vacuum at 50 °C. The resulting solids (aldehyde intermediate) were dissolved in methanol (400 mL). The solution was cooled to 5 °C under an ice bath. NaBH<sub>4</sub> (3.6

g) was added slowly over 30 min while maintaining the reaction temperature below room temperature. The reaction mixture was stirred for another 30 min followed by addition of water (125 mL). The resulting mixture was concentrated under vacuum to approximately 150 ml. Solids precipitated during the concentration. The suspension was stirred vigorously at room temperature for 1 h and solids were collected by filtration. The wet cake was dried in a vacuum oven over night at 60 °C to give **1** (45.6 g, 93%) as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 8.26 (d, *J* = 2.5 Hz, 1H), 7.88 (d, *J* = 2.5 Hz, 1H), 4.73 (d, *J* = 5.8 Hz, 2H), 2.33 (t, *J* = 11.4 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 147.12, 138.48, 138.39, 136.14, 132.06, 62.76.

10 5-Chloro-3-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)picolinaldehyde (**2**)

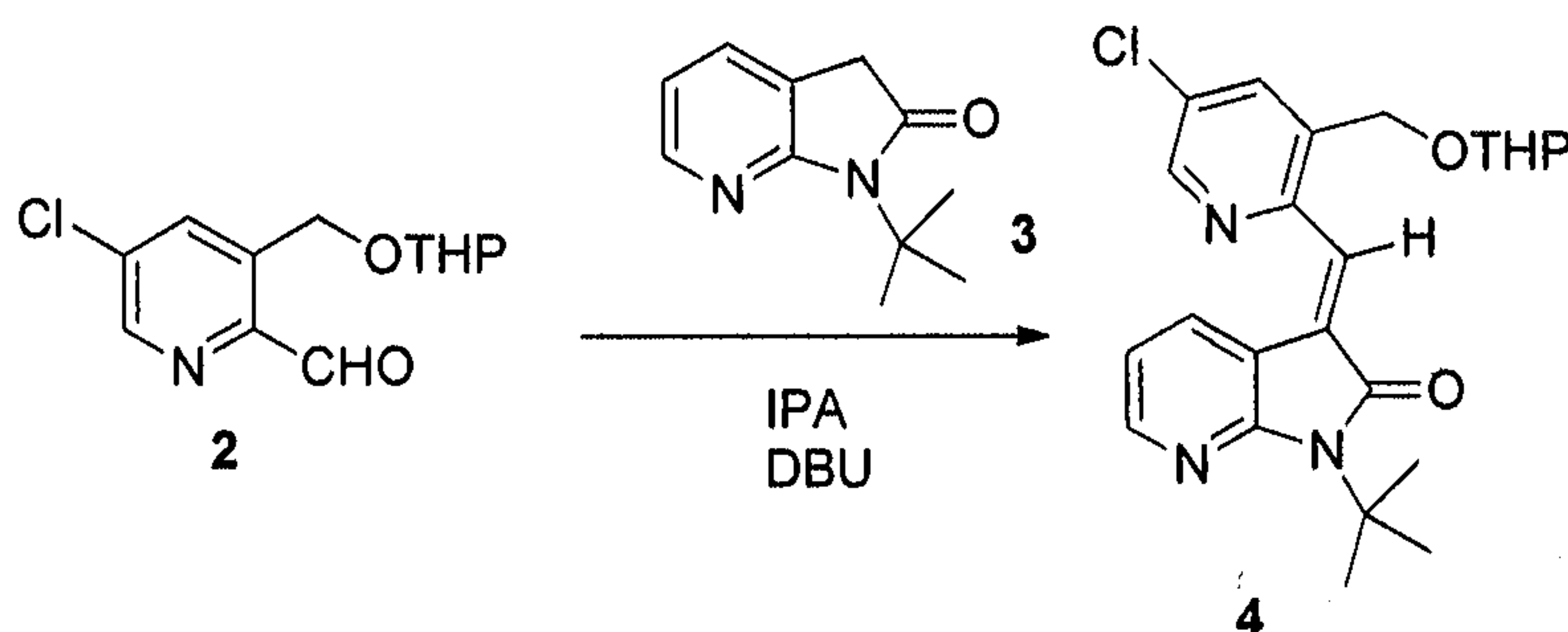


To a solution of **1** (5.0 g, 22.5 mmol) in 2-MeTHF (15 mL) was added 3,4-dihydro-2*H*-pyran (2.7 mL, 29.6 mmol) and concentrated sulfuric acid (125 mg) at room temperature. The solution was stirred for 10 min and was then cooled to -3 °C.

15 Isopropylmagnesium chloride lithium chloride solution (1.3 M, 30 mL, 39 mmol) was slowly added at -3 to 3 °C. The resulting solution was stirred at -3 °C for 3 h until a HPLC showed the conversion was greater than 97%. DMF (5 mL) was added over 15 min below 5 °C. The resulting solution was stirred for another 1 h at this temperature. The reaction mixture was quenched by addition of MTBE (50 mL), 15% aqueous citric acid (25 mL) and water (15 mL). The organic layer was separated and washed with 5% aqueous NaCl (50 mL) twice. The organic solution was concentrated under vacuum at 50 °C to give **2** as an oil (6.2 g, 68 wt%, 16.6 mmol, 74% yield). The crude product was used directly for the next step without further purification. The pure sample was isolated by flash chromatography on silica gel with 5% ethyl acetate in hexane as eluants. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 10.13 (s, 1H), 8.65 (s, 1H), 8.20 (s, 1H), 5.25 (d, *J* = 16.6 Hz, 1H), 5.01 (d, *J* = 16.6 Hz, 1H), 4.80 (m, 1H), 3.88 (m, 1H), 3.58 (m, 1H), 1.7 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 194.20, 147.06, 146.32, 138.98, 136.41, 134.87, 99.04, 64.42, 62.72, 30.53, 25.30, 19.66.



(*E*)-1-(*tert*-Butyl)-3-((5-chloro-3-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)pyridin-2-yl)methylene)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (**4**)

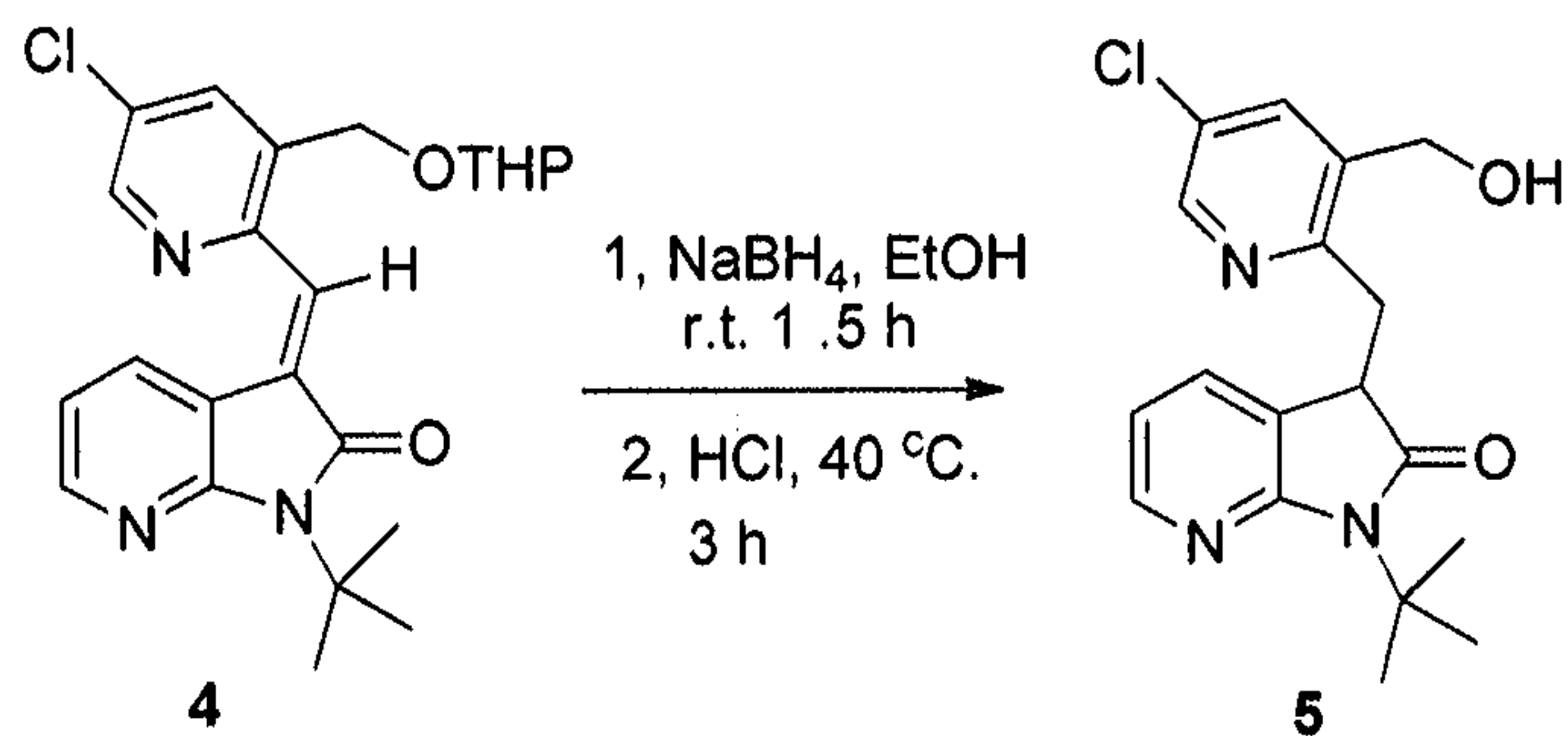


To a solution of crude **2** (6.2 g, 68 wt%, 16.6 mmol) and **3** (3.46 g, 18.3 mmol) in  
 5 isopropanol (40 mL) was added DBU (0.12 g, 0.83 mmol) at  $-2^{\circ}\text{C}$ . After stirring at  $-2^{\circ}\text{C}$  for 2  
 h, the solution was warmed up to  $10^{\circ}\text{C}$  and stirred at this temperature for 3 h. The yellow solids  
 precipitated from the solution. The suspension was stirred over night while the batch was  
 allowed to warm up to room temperature slowly. The suspension was finally warm up to  $50^{\circ}\text{C}$   
 and stirred for 4 h at this temperature. After cooling to  $30^{\circ}\text{C}$ , water (35 mL) was added dropwise  
 10 over 30 min from an additional funnel. The suspension was cooled to room temperature and  
 filtered. The cake was washed with a mixture of isopropanol (3 mL) and water (3 mL). The  
 precipitates were collected and dried in a vacuum oven over night at  $50^{\circ}\text{C}$  to give **4** (6.2 g, 87%)  
 as a solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  8.72 (dd,  $J = 7.5, 1.8$  Hz), 8.66 (d,  $J = 2.4$  Hz, 1H),  
 8.18 (dd,  $J = 5.1, 1.8$  Hz, 1H), 7.94 (d,  $J = 2.4$  Hz, 1H), 7.78 (s, 1H, 1H), 6.89 (dd,  $J = 7.5, 5.1$  Hz,  
 15 1H), 4.99 (d,  $J = 13.8$  Hz, 1H), 4.80 (m, 1H), 4.70 (d,  $J = 13.8$  Hz, 1H), 3.90 (m, 1H), 3.60 (m,  
 1H), 1.83 (s, 9H), 2.0-1.5 (m, 6H). The conformation of the double bond as *trans* isomer was  
 confirmed by NOE experiment.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  168.75, 159.64, 148.99,  
 147.85, 146.65, 137.01, 135.29, 133.56, 132.41, 129.50, 129.37, 117.27, 116.32, 98.77 64.80,  
 62.49, 58.62, 30.39, 29.01, 25.26, 19.34.

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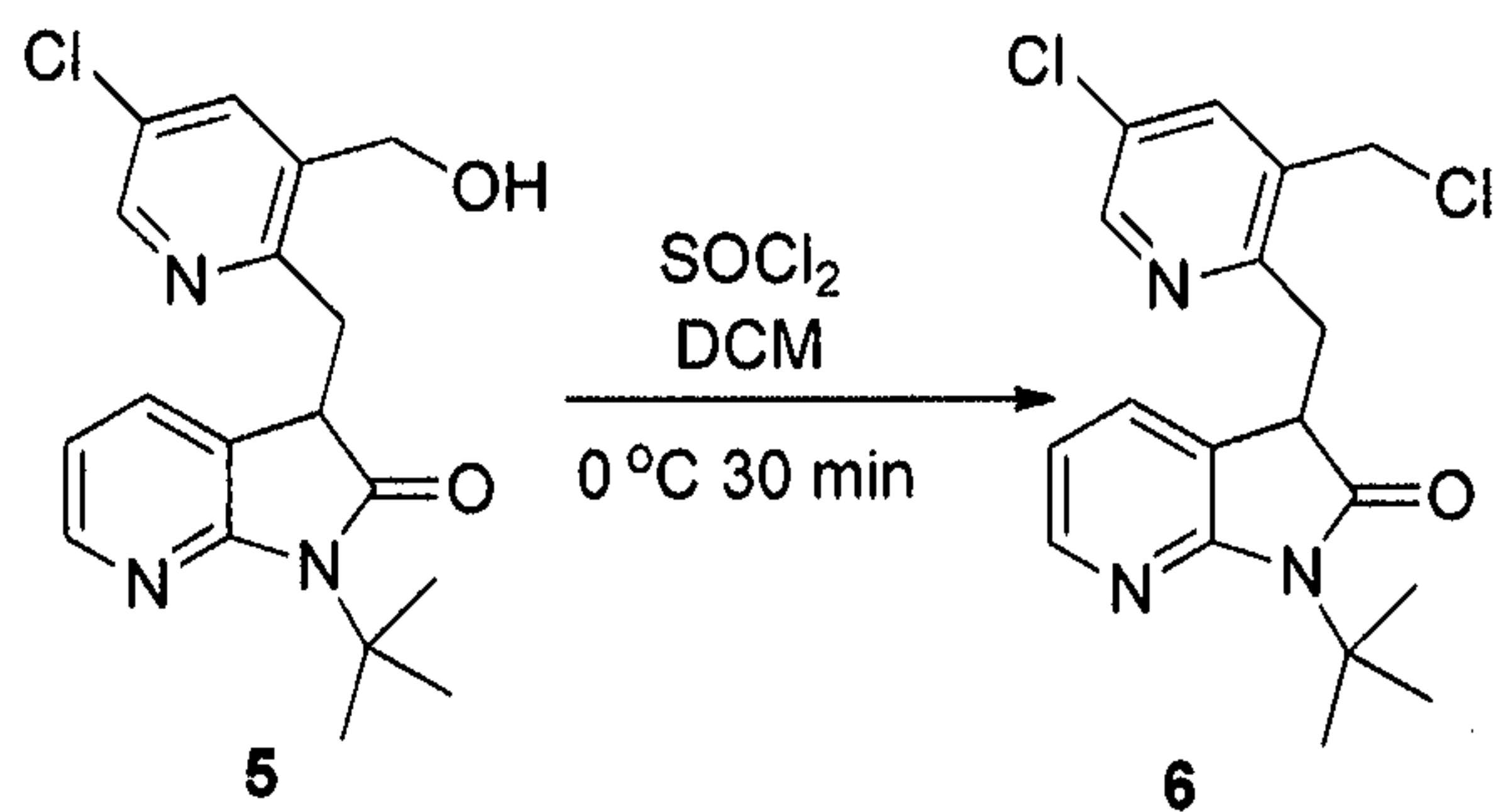


1-(*tert*-Butyl)-3-((5-chloro-3-(hydroxymethyl)pyridin-2-yl)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (**5**)



To a suspension of **4** (3.0 g, 7.0 mmol) in ethanol (25 mL) was added NaBH<sub>4</sub> (0.37 g) in one portion. The resulting suspension was stirred at room temperature for 1 h. The reaction was quenched by adding water (10 mL) followed by 6 N HCl solution in isopropanol (5 mL) slowly. The solution was warmed up to 40 °C and stirred for 3 h. The reaction mixture was mixed with MTBE (50 mL) and saturated aqueous NaCl (50 mL). The organic was separated and washed with water (50 mL). The solution was concentrated under vacuum at 50 °C and residue was triturated with hexane (30 mL). The resulting suspension was stirred at room temperature for 30 min. The precipitates were collected by filtration to give **5** (2.2 g, 86 %) as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 8.34 (s, 1H), 8.15 (d, *J* = 4.9 Hz, 1H), 7.74 (s, 1H), 7.30 (d, *J* = 7.1 Hz, 1H), 6.83 (t, *J* = 5.7 Hz, 1H), 4.73 (dd, *J* = 13.4, 4.9 Hz, 1H), 4.63 (dd, *J* = 13.4, 5.7 Hz, 1H), 4.01 (t, *J* = 6.1 Hz, 1H), 3.44 (dd, *J* = 15.4, 5.2 Hz, 1H), 3.17 (dd, *J* = 15.4, 7.2 Hz, 1H), 2.94 (t, *J* = 5.5 Hz, 1H), 1.79 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 178.72, 159.12, 153.82, 146.45, 145.83, 135.72, 135.32, 130.63, 130.27, 124.04, 117.33, 61.40, 58.70, 44.12, 34.01, 28.81.

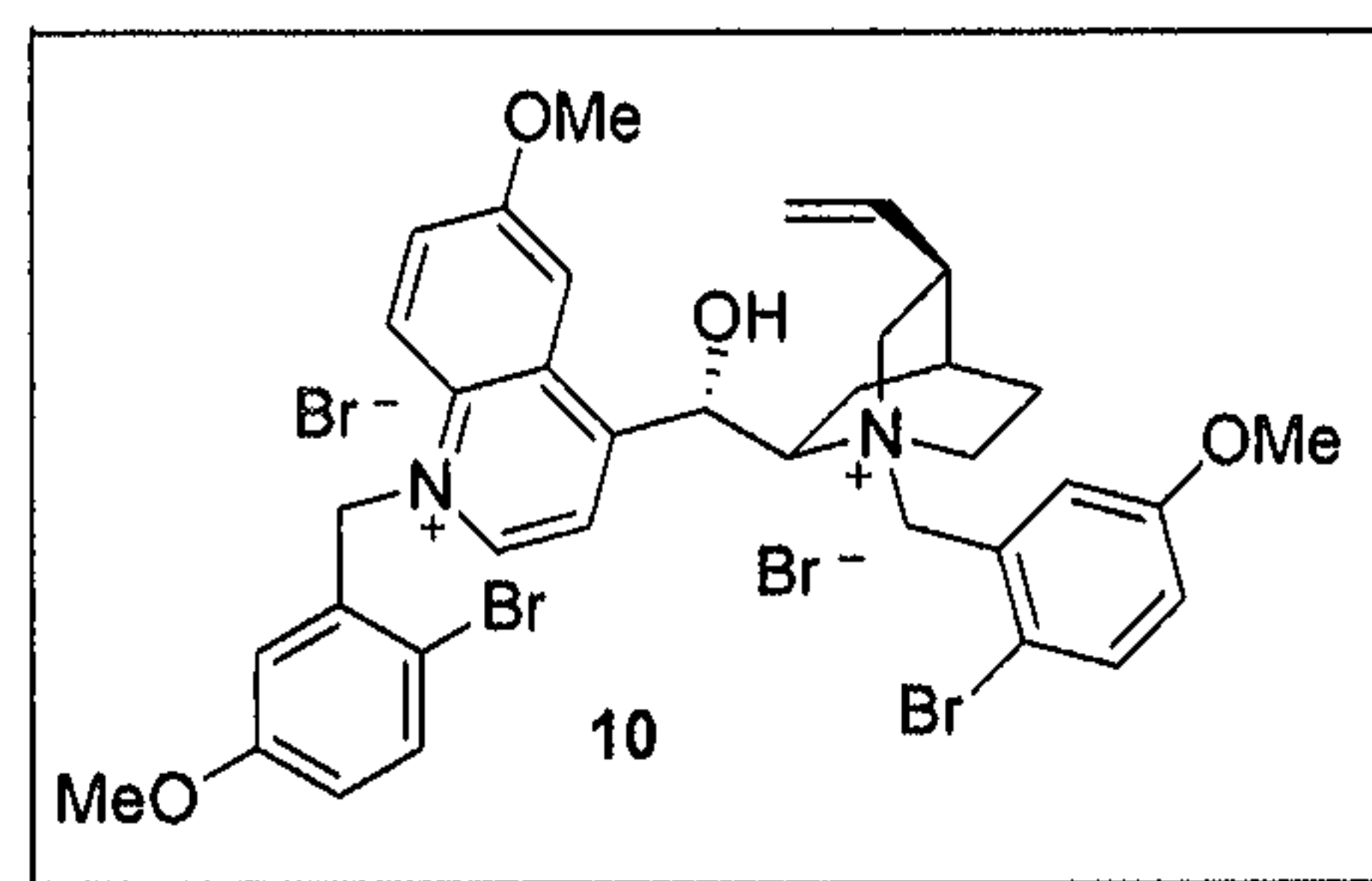
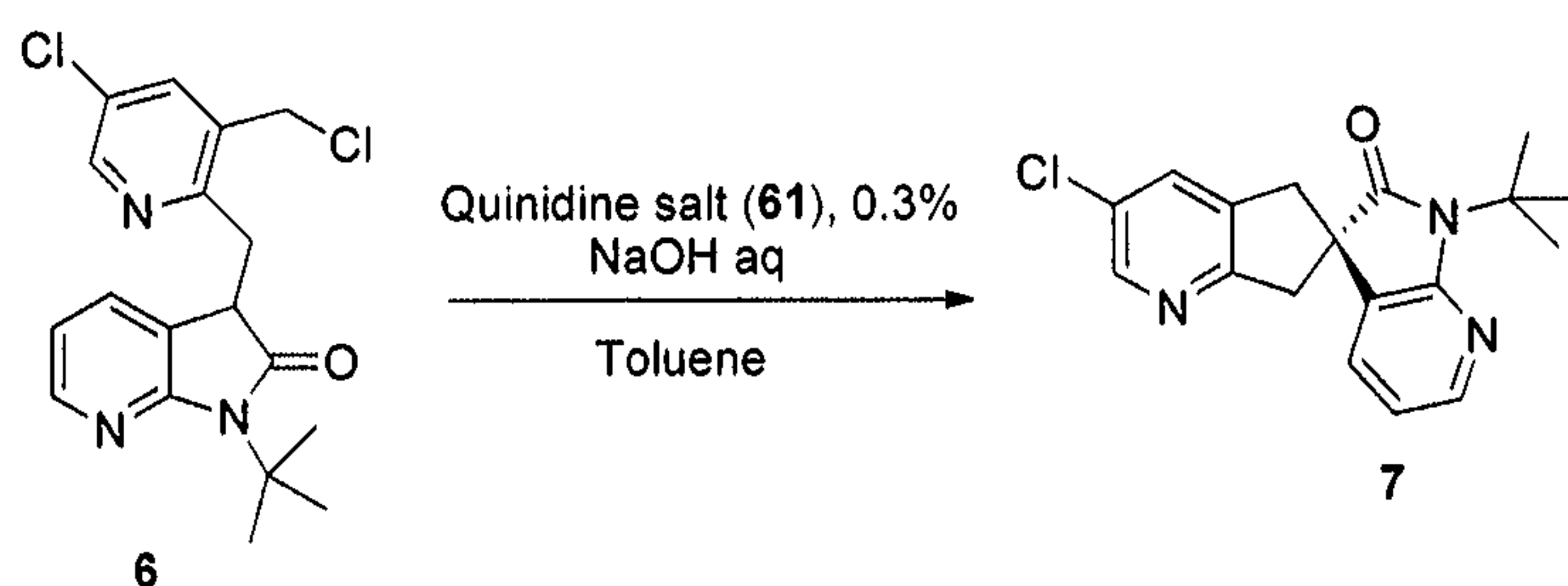
1-(*tert*-Butyl)-3-((5-chloro-3-(chloromethyl)pyridin-2-yl)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (**6**)



To a solution of **5** (5.8 g, 16.8 mmol) in dichloromethane (30 mL) was added  
 5 DMF (60  $\mu$ L) and thionyl chloride (2.2 g) at 5  $^{\circ}$ C. The mixture was stirred for 30 min at this  
 temperature followed by addition of 5% aqueous NaCl (30 mL). The organic layer was separated  
 and washed with 5% aqueous NaCl (30 mL). The solvent was removed and the residue was  
 dissolved in heptane (20 mL). The solution was stirred for 30 min and the product was  
 precipitated. The suspension was cooled to 0  $^{\circ}$ C and filtered to give **6** (5.8 g, 93%) as a solid:  $^1\text{H}$   
 10 NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  8.36 (d,  $J$  = 2.3 Hz, 1H), 8.13 (dd,  $J$  = 5.1, 1.4 Hz, 1H), 7.65 (d,  $J$  =  
 2.3 Hz, 1H), 7.19 (om, 1H), 6.78 (dd,  $J$  = 7.3, 5.2 Hz, 1H), 4.58 (m, 2H), 4.06 (m, 1H), 3.66 (dd,  
 $J$  = 16.3, 4.6 Hz, 1H), 3.32 (dd,  $J$  = 16.3, 7.5 Hz, 1H), 1.75 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100  
 MHz):  $\delta$  178.06, 159.45, 154.58, 147.39, 145.73, 136.87, 132.47, 130.42, 130.11, 123.77,  
 117.03, 58.51, 43.37, 42.25, 33.69, 28.82.

15

(*S*)-1'-(*tert*-Butyl)-3-chloro-5,7-dihydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridin]-  
 2'(1*H*)-one (**7**)



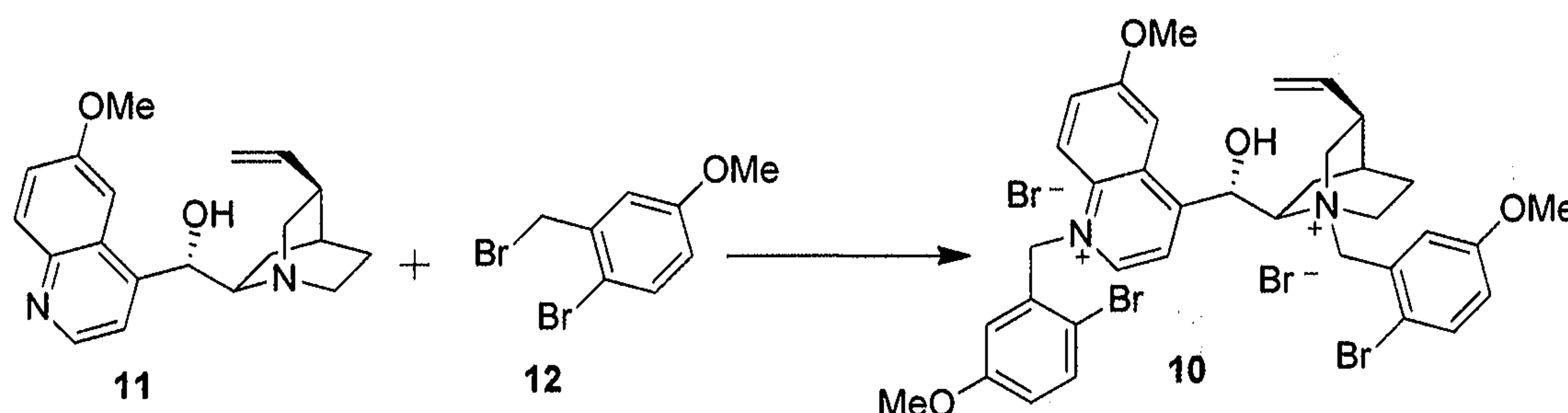
A solution of **6** (2.39 g, 6.56 mmol) in toluene (50 mL) was cooled to -2.5  $^{\circ}$ C  
 20 under nitrogen atmosphere. Compound **10** (17 mg, 0.020 mmol) was charged, and the resulting  
 solution was aged for about 15 min while cooled to -3.3  $^{\circ}$ C. A pre-cooled (-1  $^{\circ}$ C) aqueous  
 NaOH (26.2 mL, 0.3 N) was charged in over 4 min below -0.6  $^{\circ}$ C. The reaction was aged at -1.3



°C for 3 h. The reaction was quenched with water (10 ml). The organic layer was washed with water (10 mL), concentrated, flushed with IPA to give crude product **7** (2.59 g, 94.4%ee, 83% wt by NMR against 1,3,5-trimethoxybenzene as an internal standard).

The crude product was recrystallized from IPA and water, filtered and dried in an oven at 50 °C to give **58** (1.95 g, 95.7%wt, 99%ee, 87% yield) as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 8.42 (s, 1H), 8.19 (d, *J* = 5.2 Hz, 1H), 7.56 (s, 1H), 7.10 (d, *J* = 7.3 Hz, 1H), 6.83 (dd, *J* = 7.3, 5.2 Hz, 1H), 3.60 (dd, *J* = 24.9, 16.8 Hz, 2 H), 3.09 (dd, *J* = 28.6, 16.8 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz): δ 179.43, 160.54, 157.82, 147.44, 146.54, 135.80, 132.17, 130.62, 129.33, 128.36, 117.69, 58.83, 51.94, 44.35, 41.57, 28.83.

(1*S*,2*R*,4*S*,5*R*)-1-(2-Bromo-5-methoxybenzyl)-2-((*S*)-(1-(2-bromo-5-methoxybenzyl)-6-methoxyquinolin-1-ium-4-yl)(hydroxy)methyl)-5-vinylquinuclidin-1-ium bromide (**10**)

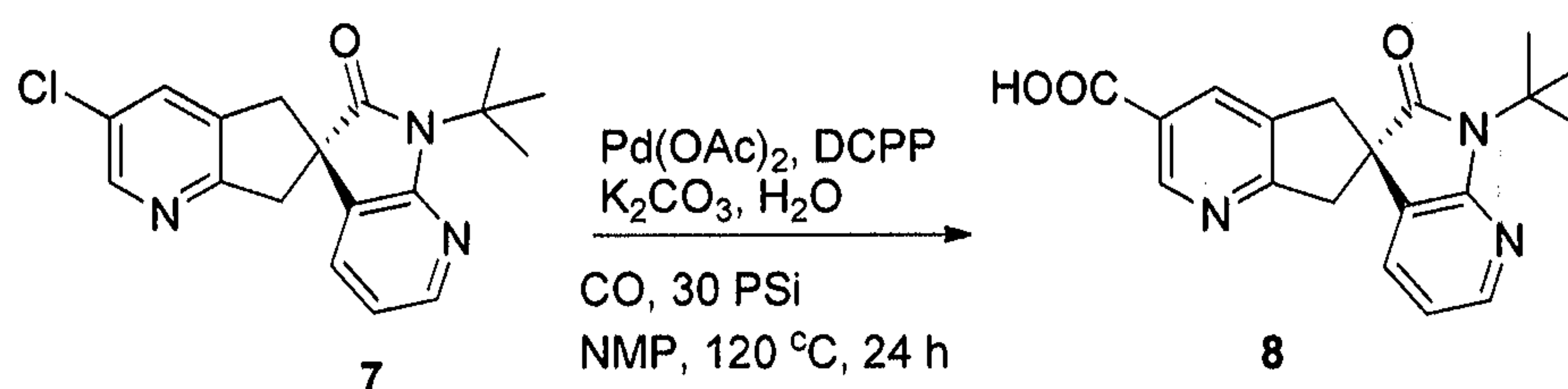


A slurry of quinidine (**11**, 8.1 g, 23.7 mmol, containing ~14% dihydroquinidine) and 2-bromo-5-methoxybenzylbromide (**12**, 16.59 g, 59.3 mmol) in IPA (4.0 ml) and DMF (28.4 mL) was degassed by vacuum and flushed with N<sub>2</sub>, then heated to 70 °C for 7 h. The reaction mixture was cooled to 22 °C, this reaction solution was charged to AcOEt (320 ml) at 22 °C over 10 min while stirring. The resulting slurry was aged at 22 °C for 1 to 2 h, filtered, rinsed with AcOEt (2 x 24 ml), then hexane (2 x 24 ml). The solid was dried under vacuum to give powder as a mixture of bis-salts (bis-quinidine salt **10** and bis-dihydroquinidine salt). (Total 19.7 g, 94% yield). The authentic sample of **10** was purified by SFC (IC column, 20 x 250 mm, 60% MeOH/CO<sub>2</sub>, 50 mL/min, 100 bar, 35°C, 220 nm, sample concentration: 133 mg/mL in MeOH; desired peak: 3 to 4.5 min). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 9.34 (d, *J* = 6.1 Hz, 1H), 8.46 (d, *J* = 6.1 Hz, 1H), 8.38 (d, *J* = 9.7 Hz, 1H), 8.0 (dd, *J* = 9.7, 2.1 Hz, 1H), 7.86 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.74 (d, *J* = 8.9 Hz, 1H), 7.60 (d, *J* = 2.5 Hz, 1H), 7.42 (d, *J* = 2.3 Hz, 1H), 7.17 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.03 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.93 (s, 1H), 6.50 (d, *J* = 2.4 Hz, 1 H), 6.06 (m, 1H), 5.24 (m, 3H), 4.95 (d, *J* = 12.9 Hz, 1H), 4.37 (m, 1H), 4.23 (m, 4H), 4.12 (m, 1H), 3.88



(s, 3H), 3.69 (s, 3H), 3.54 (m, 1H), 3.32 (s, 2H), 3.23 (m, 1H), 2.71 (m, 1H), 2.51 (s, 2H), 2.33 (m, 1H), 1.94 (br, 1H), 1.83 (br, 2H), 1.17 (br, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 100 Hz):  $\delta$  159.45, 159.07, 158.67, 156.12, 146.01, 137.08, 134.68, 134.30, 133.21, 132.98, 128.18, 128.03, 127.45, 122.13, 121.89, 121.22, 118.08, 117.5, 117.07, 116.73, 116.20, 115.81, 112.67, 105.09, 66.81, 65.51, 62.43, 56.75, 56.06, 55.91, 55.52, 54.80, 36.84, 25.91, 23.10, 20.75.

(*S*)-1'-(*tert*-Butyl)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxylic acid (**8**)

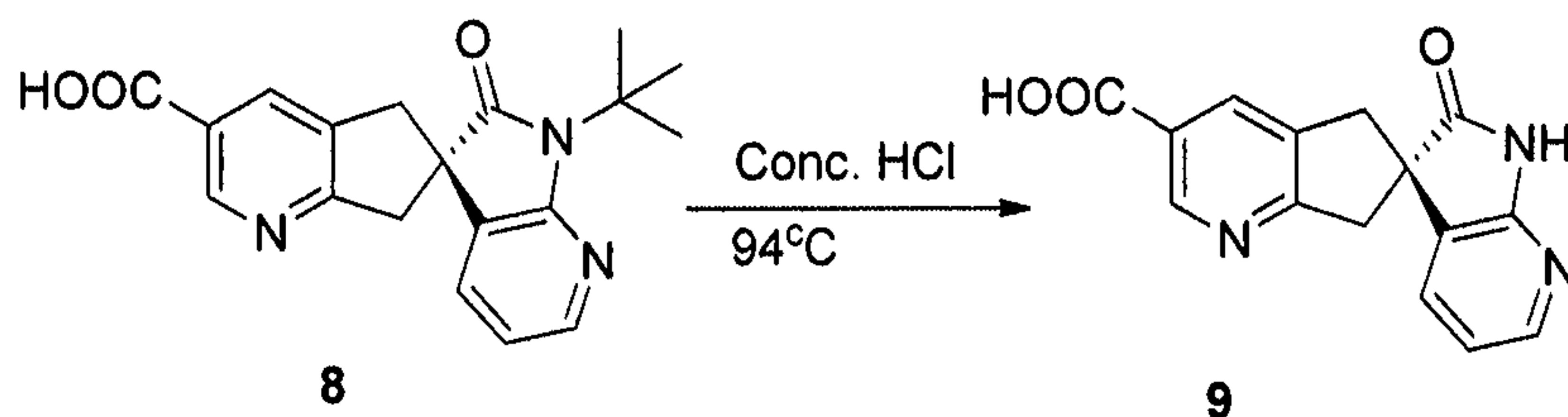


10

A mixture of **7** (5.0 g, 14.5 mmol),  $\text{K}_2\text{CO}_3$  (5.01 g, 36.2 mmol),  $\text{Pd(OAc)}_2$  (33 mg, 0.145 mmol), 1,3-bis(dicyclohexylphosphino)propane (DCPP, 127 mg, 0.290 mmol) and water (0.522 mL, 29.0 mmol) in NMP (32 mL) was heated at 120 °C under 30 psi of CO for 24 h. After cooling to room temperature, the resulted slurry was diluted with water (100 mL). The pH was slowly adjusted to 3~4 with 2 N HCl. The slurry was aged at room temperature for 1 h, filtered, rinsed with water (40 to 50 mL), dried under oven at 60 °C to give **8** (4.64 g, 95%) as a solid.  $^1\text{H}$  NMR (DMSO- $d_6$ , 500 MHz):  $\delta$  8.90 (s, 1H), 8.19 (d,  $J = 5.2$  Hz, 1H), 7.54 (d,  $J = 7.3$  Hz, 1H), 6.99 (dd,  $J = 7.3, 5.2$  Hz, 1H), 3.33 (m, 4H), 1.72 (s, 9H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 125 MHz):  $\delta$  180.16, 167.44, 166.97, 158.07, 149.76, 146.61, 135.39, 133.09, 130.36, 128.81, 125.48, 118.44, 58.19, 51.12, 44.56, 41.24, 28.91.

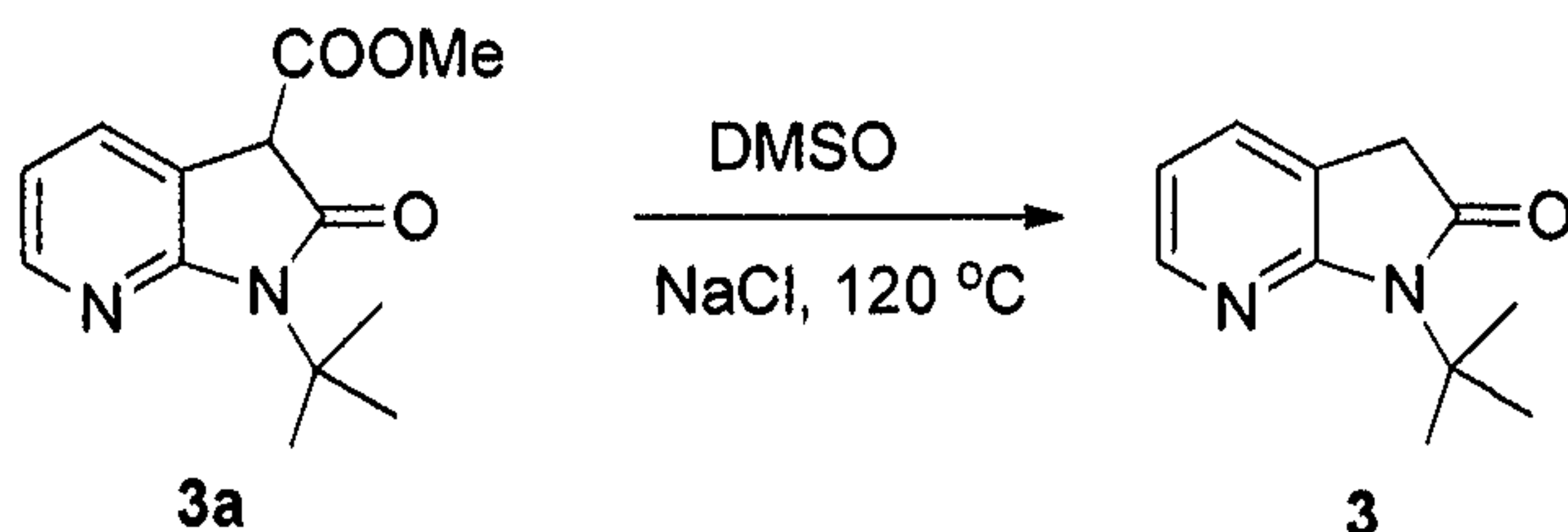
20

(*S*)-2'-Oxo-1',2',5,7-tetrahydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxylic acid (**9**)



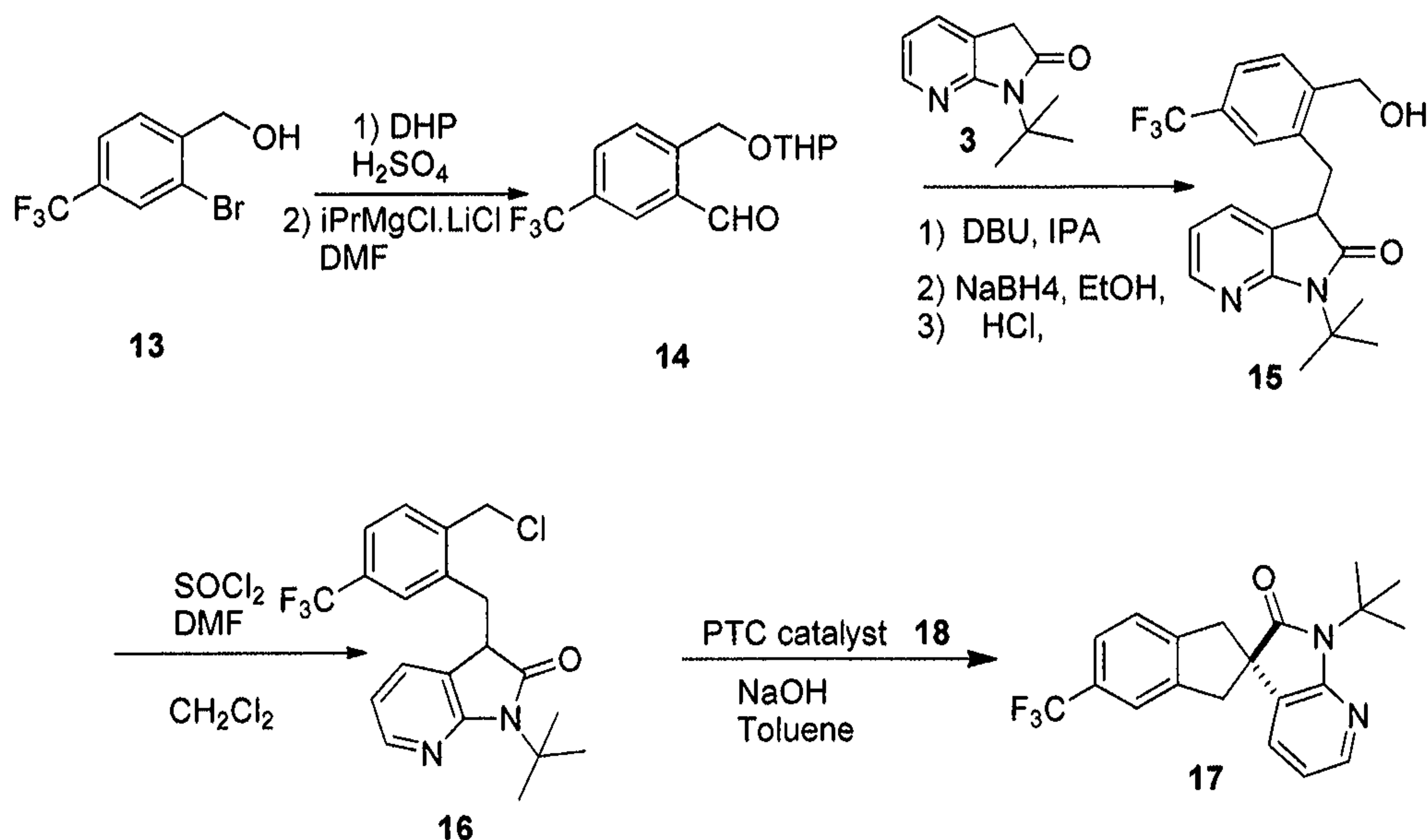
To **8** (4 g, 97%wt) was charged 37% HCl (40 to 44 mL). The slurry was heated at 94 °C for up to 48 h, cooled down to room temperature. The solvent was partially removed by reducing pressure to about total 2 vol (~ 4 mL water remained). The residue was diluted with water (20 mL) followed by adjusting pH to 2.6 with NaOH (3.5 N, 4.5 mL). The thick slurry was aged for 1 to 2 h, filtered, rinsed with water (2 x 8 mL), followed by water/acetone (1:1, 8 mL). The wet cake was dried to give compound **9** (3.1 g, 98%wt, 94%) as crystals. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 500 MHz): δ 13.31(br, 1H), 11.14 (s, 1H), 8.91 (s, 1H), 8.11 (m, 2H), 7.49 (dd, *J* = 7.3, 1.3 Hz, 1H), 6.93 (dd, *J* = 7.3, 5.3 Hz, 1H), 3.36 (m, 4H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 125 MHz): δ 181.06, 167.36, 166.95, 156.80, 149.79, 147.32, 135.37, 133.19, 130.73, 128.88, 125.50, 118.46, 51.78, 44.12, 40.70.

1-(*tert*-Butyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (**3**)

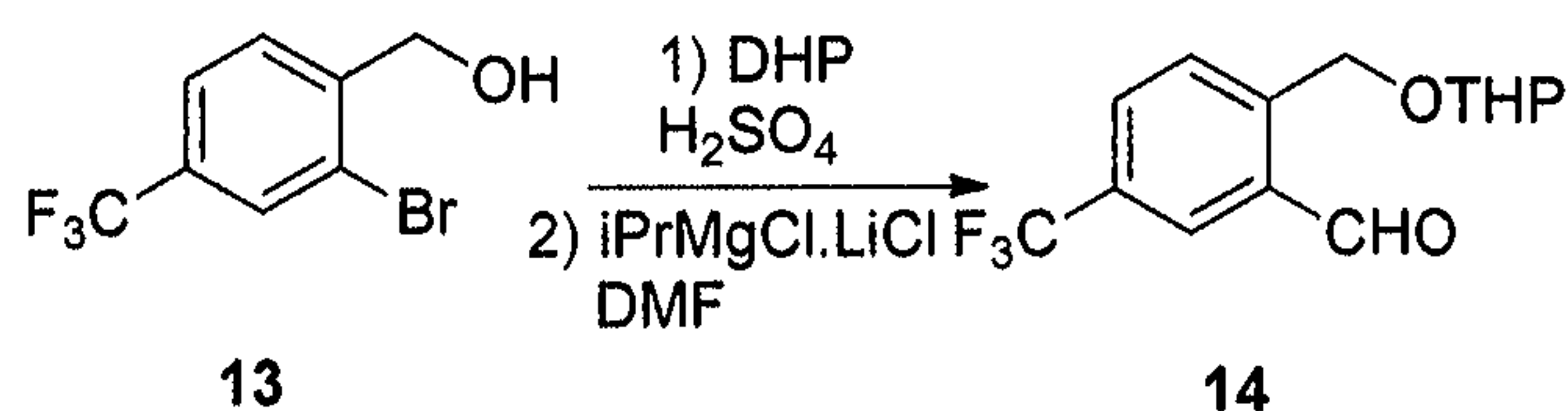


A mixture of compound **3a** (10.0 g, 40.3 mmol), NaCl (2.9g, 1.25 eq.) and water (2 mL) in DMSO (50 mL) was heated at 120 °C for 30 min. The mixture was cooled to 30 °C followed by addition of MTBE (200 mL) and water (50 mL). The organic layer was separated and the aqueous layer extracted with another MTBE (50 mL). Combined organic layer was washed three times with water (50 mL). Solvent removed under vacuum and the resulting solid was dried in a vacuum oven at 30 °C to give **3** (7.0 g, 92%) as solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 8.15 (dd, *J* = 5.2, 1.4 Hz, 1H), 7.40 (dd, *J* = 7.2, 1.4 Hz, 1H), 6.88 (dd, *J* = 7.2, 5.2 Hz, 1H), 3.45 (s, 2H), 1.78 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 174.99, 160.06, 145.82, 130.80, 119.51, 117.15, 58.53, 35.98, 28.80;



EXAMPLE 2SCHEME

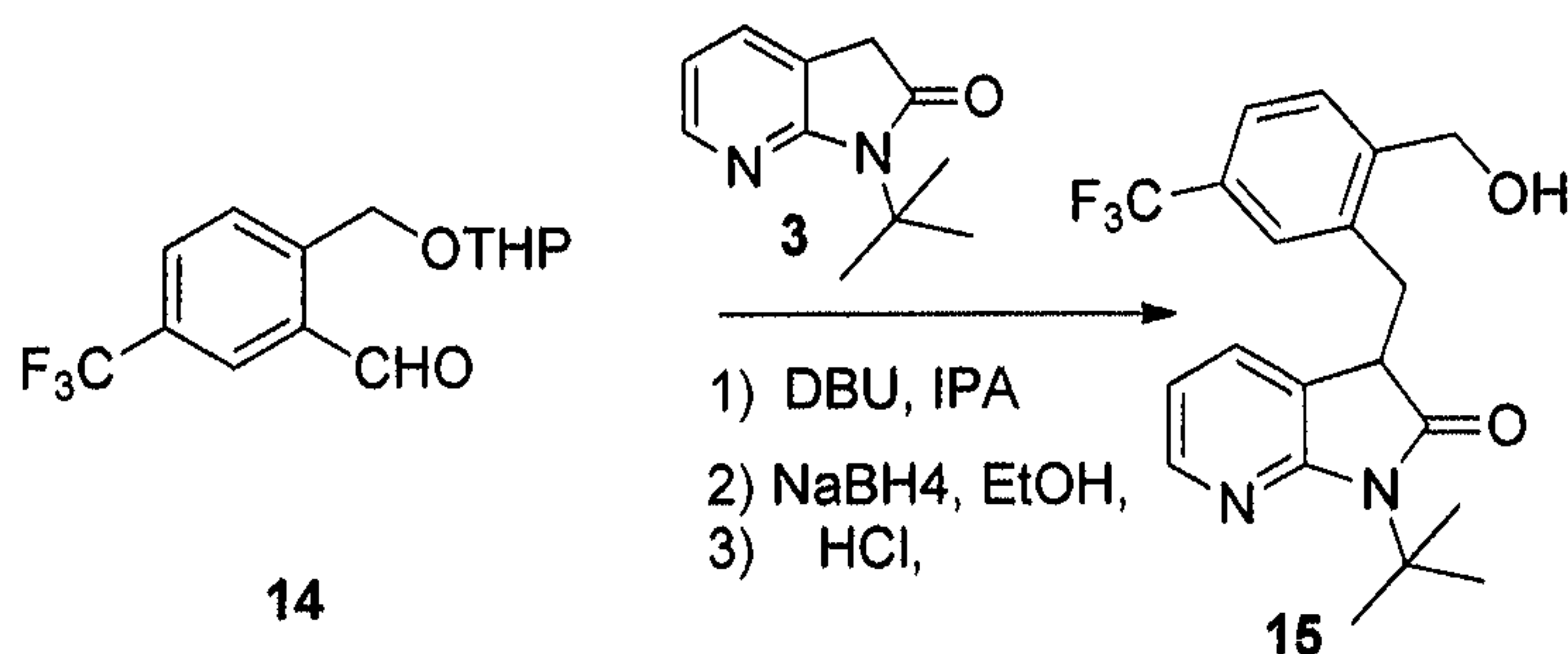
2-(((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-5-(trifluoromethyl)benzaldehyde (14)



To a solution of compound 13 (5.0 g, 15.7 mmol) in 2-MeTHF (12 mL) was added 3,4-dihydro-2H-pyran (2 mL, 20.4 mmol) and concentrated sulfuric acid (0.06 mL) at room temperature. The solution was stirred for 10 min and was then cooled to -3 °C. Isopropylmagnesium chloride lithium chloride solution (21 mL, 1.3 M, 26.7 mmol) was slowly added at -3 to 3 °C. The resulting solution was stirred at -3 °C for 3 h until a HPLC showed the conversion was greater than 97%. DMF (4 mL) was added over 15 min below 5 °C. The resulting solution was stirred for another one hour at this temperature. The reaction mixture was quenched by addition of MTBE (40 mL), 15% aqueous citric acid (20 mL) and water (12 mL). The organic layer was separated and washed twice with 5% aqueous NaCl (40 mL). The solution was concentrated under vacuum at 50 °C to give 4.65 g of 14 as oil (97 %wt, 98% yield). The crude product was used directly for the next step without further purification.



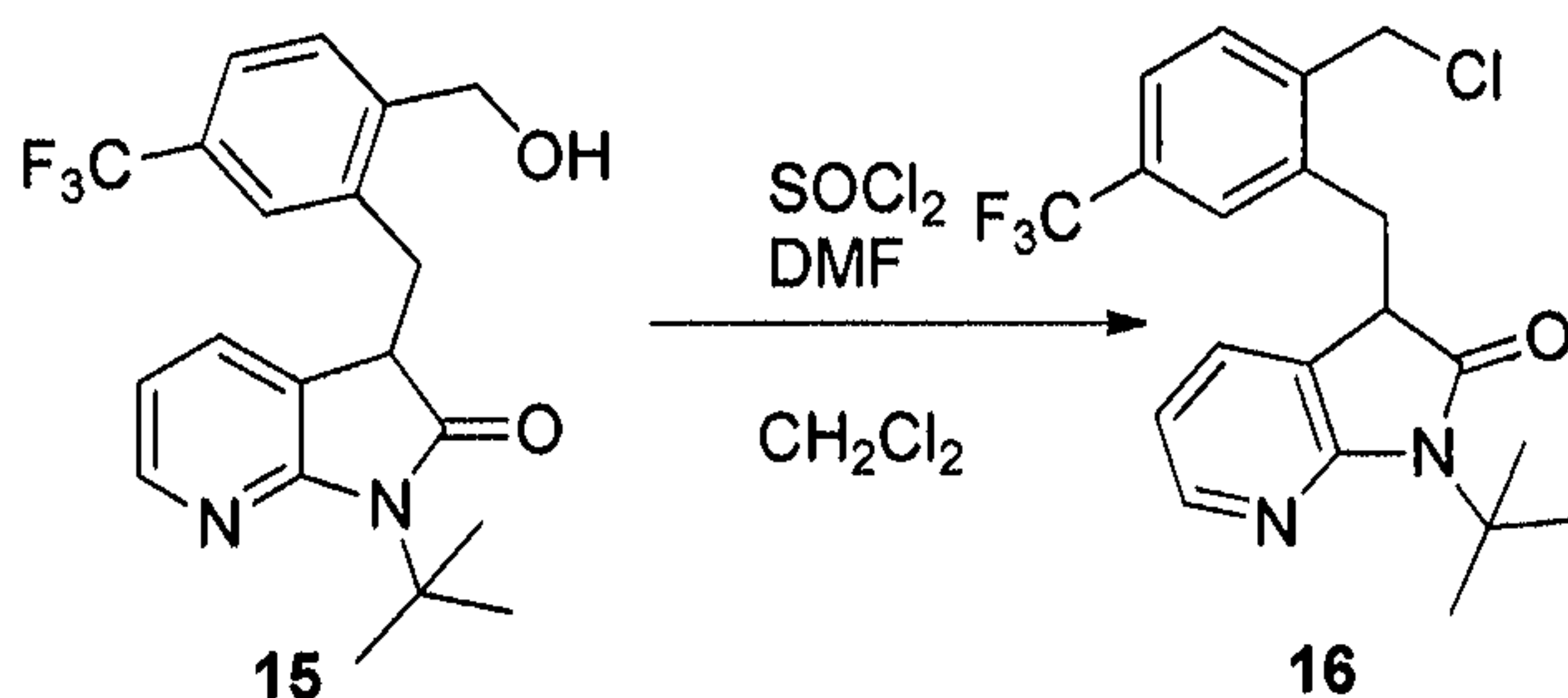
1-(*tert*-Butyl)-3-(2-(hydroxymethyl)-5-(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (**15**)



To a round bottom flask was charged **14** (4.50 g, 15.6 mmol), **3** (2.50 g, 17.2 mmol, 1.1 eq.) and IPA (25 mL). This slurry was aged until dissolved. It was cooled under an ice bath followed by charging DBU (0.12 mL, 0.8 mmol) then was aged for half hour below 5 °C and 2 h at room temperature. The reaction mixture was degassed by vacuum and flushed with N<sub>2</sub> followed by charge NaBH<sub>4</sub> (0.80g, 21.8 mmol). The reaction was aged for 2 h. After completion of the reduction, 6 N HCl (10 mL) and water (16 mL) was added in and the mixture was heated to 70 °C for 1 to 2 h until the deprotection of THP was complete. The resulting reaction mixture was concentrated followed by charge dichloromethane (60 mL) and water (27 mL). The pH of the reaction mixture was adjusted to ~10 with aqueous NaOH, and the organic layer was separated. The aqueous layer was then extracted with dichloromethane (50 mL) twice. The combined organic layer was concentrated under vacuum, and purified with silica gel column (0 to 30% of AcOEt/hexane) to give the desired product **15** as a solid (4.07 g, 78%).

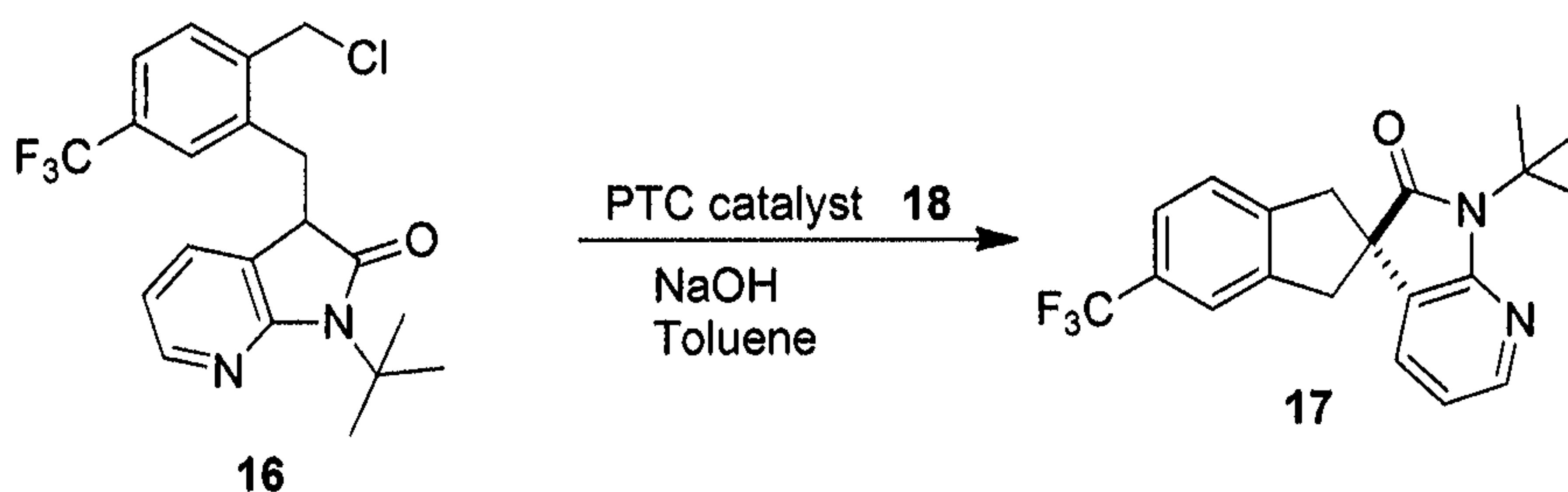
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 8.21 (dd, *J* = 5.2, 0.8 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.52 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.19 (om, 2H), 6.90 (dd, *J* = 7.3, 5.3 Hz, 1H), 4.78 (ABq, *J* = 12.9 Hz, 2H), 3.71 (m, 1H), 3.45 (dd, *J* = 14.2, 4.4 Hz, 1H), 3.22 (dd, *J* = 14.2, 4.4 Hz, 1H), 2.77 (br, 1H), 1.67 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): δ 176.6, 159.1, 146.3, 140.1, 137.4, 131.13, 131.10, 130.7 (q, *J* = 33.8 Hz), 127.3, 124.3, 123.5 (q, *J* = 272 Hz), 122.5, 117.1, 58.7, 45.7, 43.0, 33.0, 28.7.

1-(*tert*-Butyl)-3-(2-(chloromethyl)-5-(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (**16**)



To a solution of **15** (3.5g, 10.4 mmol) in dichloromethane (20 mL) was charged DMF (0.04 mL, 0.5 mmol). This solution was cooled under an ice bath. Thionyl chloride (0.85 mL, 11.5 mmol) was then added under 5 °C, and the resulting reaction was aged for 3 h at this temperature. Once the reaction was complete, 5% aqueous NaCl (16.5 mL) was added. The organic layer was separated and washed with 5% aqueous NaCl (16.5 mL). The solvent was removed via rotovap, and the crude was purified by silica gel column chromatography (0 to 10% AcOEt/hexane) to give the desired compound **16** as an oil (3.05 g, 74%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 8.20 (dd, *J* = 5.1, 1.7 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.51 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.18 (s, 1H), 7.12 (dd, *J* = 6.3, 2.7 Hz, 1H), 6.88 (dd, *J* = 7.3, 5.1 Hz, 1H), 4.77 (ABq, *J* = 12.9 Hz, 2H), 3.72 (m, 1H), 3.46 (dd, *J* = 14.2, 4.4, 1H), 3.18 (dd, *J* = 14.2, 8.7 Hz, 1H), 1.67 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): δ 177.6, 159.1, 146.5, 143.3, 136.6, 131.0, 129.7 (m, 2C), 124.0, 123.0, 123.9 (q, *J* = 271 Hz), 117.4, 126.6, 62.4, 58.8, 46.1, 32.9, 28.6.

**1'-((tert-Butyl)-5-(trifluoromethyl)-1,3-dihydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one (17)**

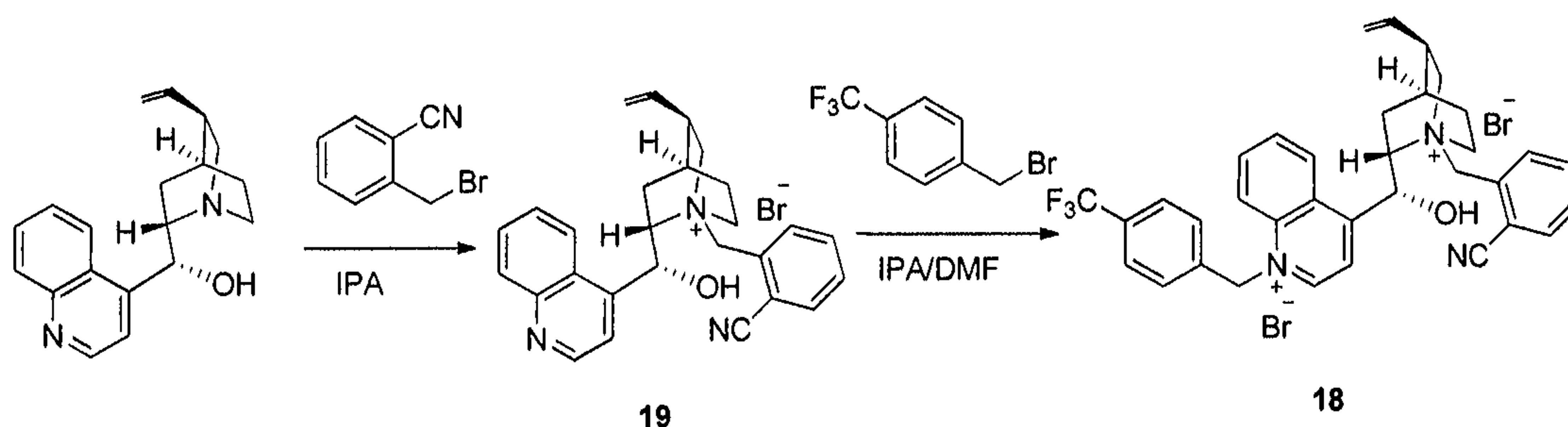


A solution of **16** (50 mg, 0.126 mmol) in toluene (2 ml) was cooled to -1 °C, degassed with vacuum and flushed N<sub>2</sub>. To this solution was charged a precooled (-2 to 0 °C) aqueous NaOH (1N, 1 mL) followed by charged a catalyst **18**. The resulted reaction was aged at -1 to 1 °C for several hours until complete conversion. The organic layer was purified with silica gel column chromatography (0 to 10% AcOEt/hexane) to give the desired compound **17** as oil (42 mg, 92%Y, 85%ee, *R* or *S* undetermined).



<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 8.17 (dd, *J* = 5.2, 1.8 Hz, 1H), 7.52 (m, 2 H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.02 (dd, *J* = 7.3, 1.8 Hz, 1H), 6.80 (dd, *J* = 7.3, 5.2 Hz, 1H), 3.64 (d, *J* = 15.9 Hz, 2H), 3.09 (d, *J* = 16.1 Hz, 2H), 1.83 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): δ 179.6, 157.6, 146.3, 145.3, 141.9, 129.8, 129.6 (q, *J* = 32 Hz), 127.6, 124.8, 124.5 (q, *J* = 271 Hz), 121.4, 117.6, 58.7, 53.8, 43.8, 43.7, 28.9.

(1*S*,2*S*,4*S*,5*R*)-1-(2-Cyanobenzyl)-2-((*R*)-hydroxy(quinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium bromide (**19**) and (1*S*,2*S*,4*S*,5*R*)-1-(2-cyanobenzyl)-2-((*R*)-hydroxy(1-(4-(trifluoromethyl)benzyl)quinolin-1-ium-4-yl)methyl)-5-vinylquinuclidin-1-ium bromide (**18**)



#### Preparation of **19**

A slurry cinchonidine (5.0 g, 16.98 mmol) and 2-cyano-benzyl bromide (4.0 g, 20.38 mmol) in 50 ml of IPA was degassed by vacuum and flushed with N<sub>2</sub>, then it was heated to 67 °C until completely conversion (4 to 5 h). It was cooled down and ~40 mL of solvent was removed by reducing pressure. This concentrated solution was added into AcOEt (160 ml) over 5 to 10 min while stirring. The resulting slurry was aged for 1 to 2 h at 22 °C, filtered, rinsed with IPA/hexane (1:1; 50 ml) and dried under vacuum to give **19** as a solid (7.43 g, 89% Y).

<sup>1</sup>H NMR(DMSO-d<sub>6</sub>, 500 MHz): δ 9.00 (d, *J* = 4.5 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 7.6 Hz, 1H), 8.12 (d, *J* = 7.6 Hz, 2H), 7.97 (t, *J* = 7.8 Hz, 1H), 7.85 (m, 3H), 7.76 (t, *J* = 8.2 Hz, 1H), 6.87 (d, *J* = 3.0 Hz, 1H), 6.58 (s, 1H), 5.72 (m, 1H), 5.33 (q, *J* = 13.1 Hz, 2H), 5.21 (d, *J* = 17.3 Hz, 1H), 4.96 (d, *J* = 10.6 Hz, 1H), 4.47 (br, 1H), 4.07 (t, *J* = 9.8 Hz, 1H), 3.94 (dt, *J* = 12.0, 3.6 Hz, 1H), 3.44 (t, *J* = 12.0 Hz, 1H), 3.30 (dt, *J* = 11.5, 4.1 Hz, 1H), 2.68 (br, 1H), 2.13 (m, 2H), 2.02 (s, 1H), 1.81 (m, 1H), 1.22 (m, 1H); <sup>13</sup>C NMR(DMSO-d<sub>6</sub>, 125 MHz): δ 150.1, 147.6, 145.0, 138.0, 135.7, 134.3, 133.6, 131.1, 130.8, 129.8, 129.4, 127.1, 124.2, 123.6, 120.0, 117.8, 116.4, 115.7, 67.7, 64.7, 60.4, 59.3, 51.2, 37.0, 25.5, 24.3, 21.1.

#### Preparation of **18**

A slurry of **19** (0.15 g, 0.306 mmol) and 2-nitrobenzyl bromide (0.104 g, 0.61

mmol) in IPA (0.075 mL) and DMF (0.53 mL) was degassed by vacuum and flushed with N<sub>2</sub>, then it was heated to 70 °C until completely conversion (4 to 5 h). It was cooled down and was added into AcOEt (6 ml) over 5 to 10 min. The resulting slurry was aged for 1 to 2 h at 22 °C, filtered, rinsed AcOEt (2 x 5 ml) and dried under vacuum to give **18** as a solid (0.19 g, 94%Y).

5 <sup>1</sup>H NMR(DMSO-d<sub>6</sub>, 500 MHz): δ 9.82 (d, *J* = 6.3 Hz, 1H), 8.81 (d, *J* = 8.5 Hz, 1H), 8.55 (m, 1H), 8.30 (t, *J* = 7.4 Hz, 1H), 8.13 (m, 3H), 8.0 (t, *J* = 7.4 Hz, 1H), 7.82 (m, 3H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 3.5 Hz, 1H), 6.86 (s, 1H), 6.50 (m, 2H), 6.5 (m, 2H), 5.70 (m, 1H), 5.33 (s, 2H), 5.21 (d, *J* = 17.4 Hz, 1H), 4.99 (d, *J* = 10.5 Hz, 1H), 4.49 (m, 1H), 4.15 (m, 1H) 3.90 (m, 1H), 3.53 (m, 1H), 3.38 (m, 1H), 2.70 (br, 1H), 2.10 (m, 3H), 1.88 (m, 1H), 1.48 (m, 1H); <sup>13</sup>C  
10 NMR(DMSO-d<sub>6</sub>, 125 MHz): δ 158.4, 149.8, 138.3, 138.0, 137.2, 135.8, 135.6, 134.3, 133.7, 131.2, 130.6, 130.5, 129.2 (q, *J* = 32.0 Hz), 128.3 (2C), 126.7, 126.2, 125.99, 125.96, 123.9 (q, *J* = 272.5 Hz), 122.8, 121.6, 119.8, 117.8, 116.7, 115.7, 67.3, 65.4, 60.4, 59.7, 59.4, 51.3, 37.0, 30.9, 25.5, 24.9, 22.0.

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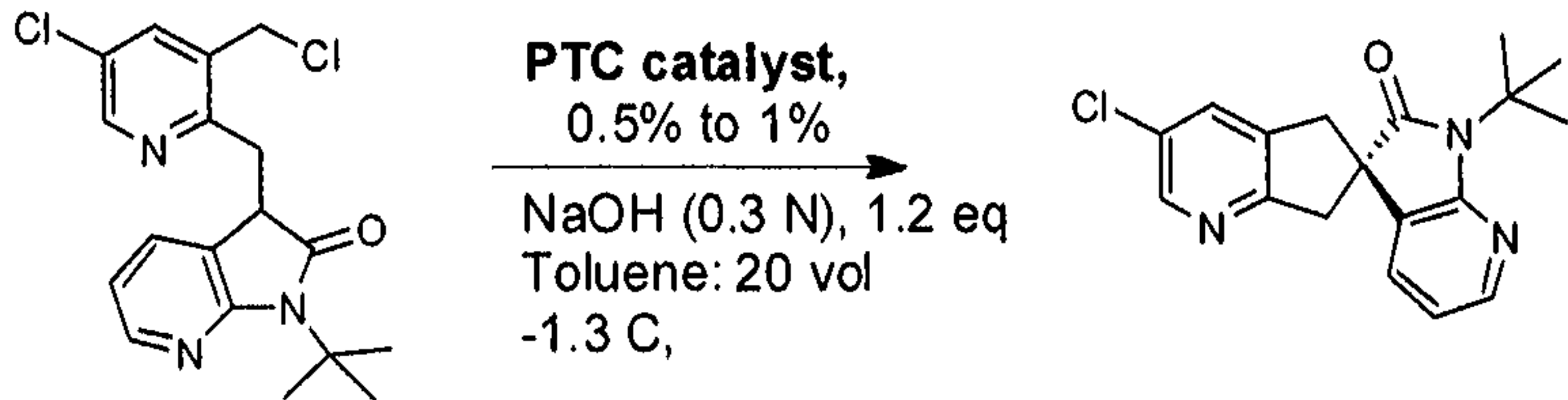
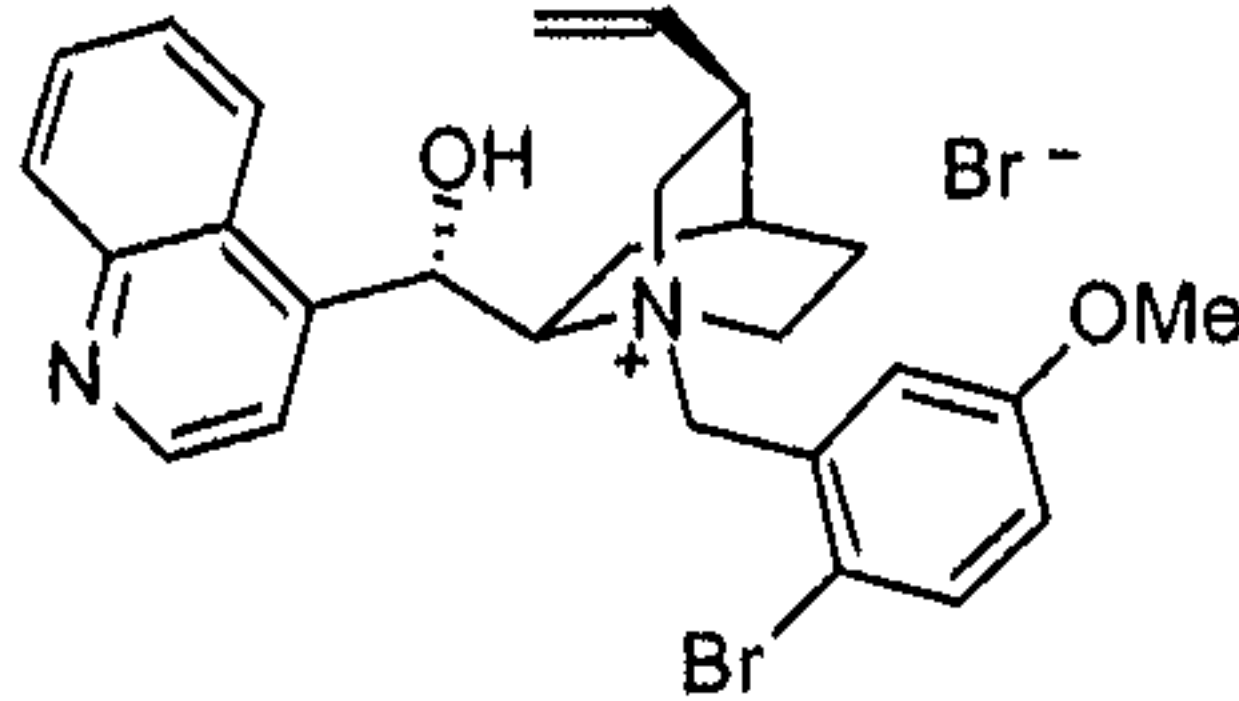
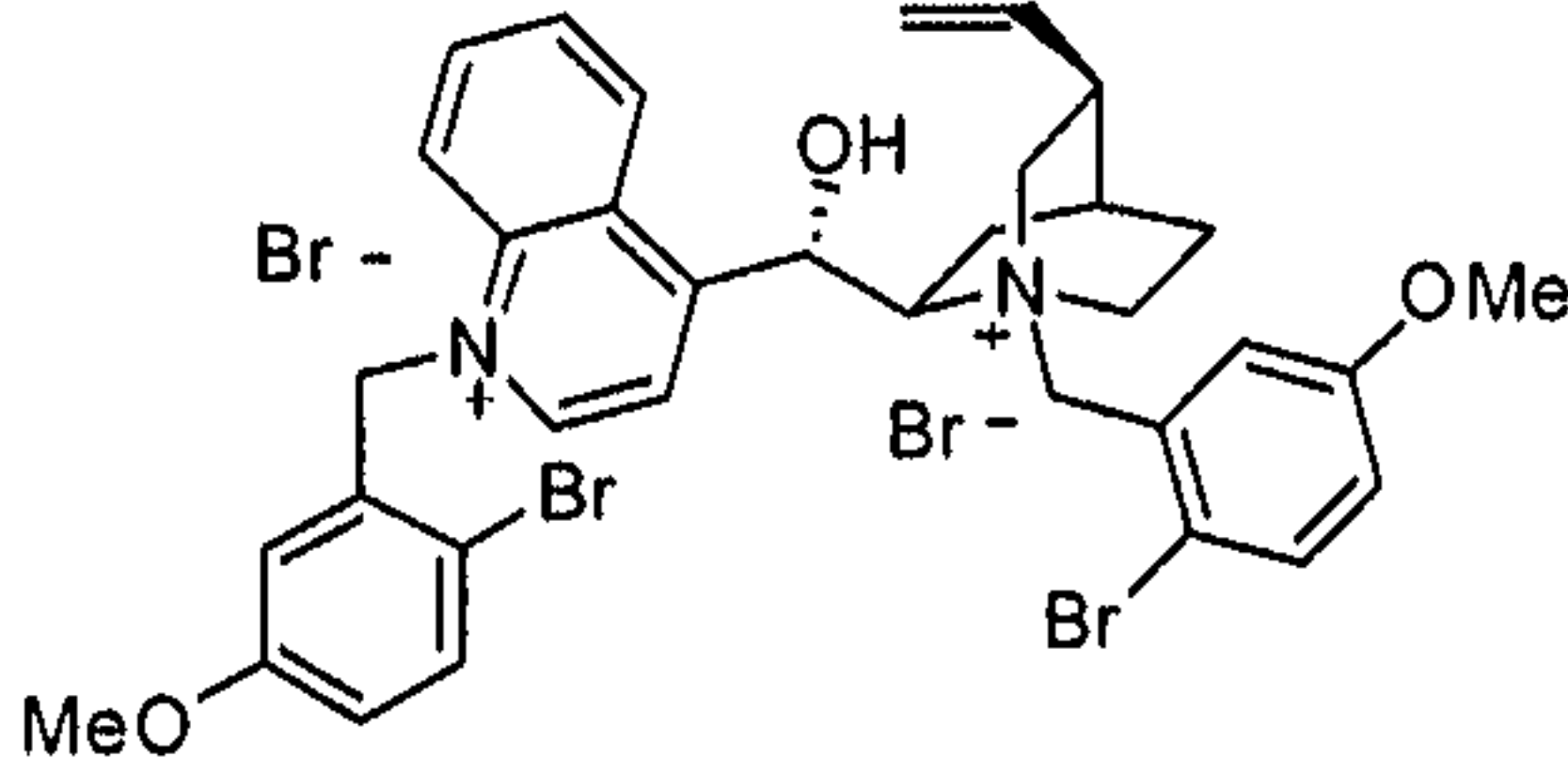
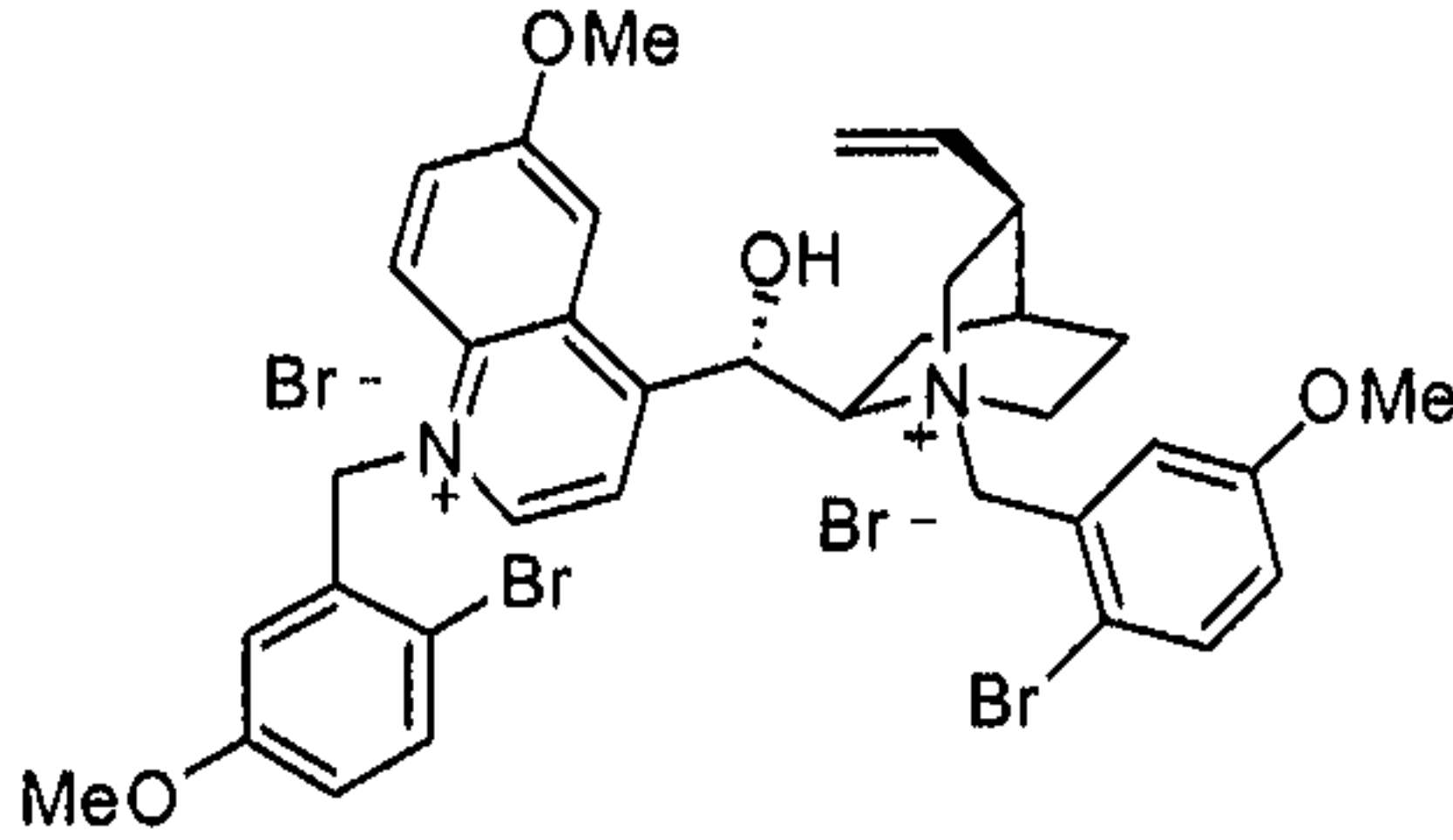
## 20 RESULTS

As shown in Table 1, the bis-quaternary catalyst is much more active and efficient as compared to the mono-quaternary catalyst for the spirocyclization reaction shown. For this experiment, the bis-catalysts contained ~12 to 15% of the double saturated compounds hydroquinidine or hydrocinchonine.

25

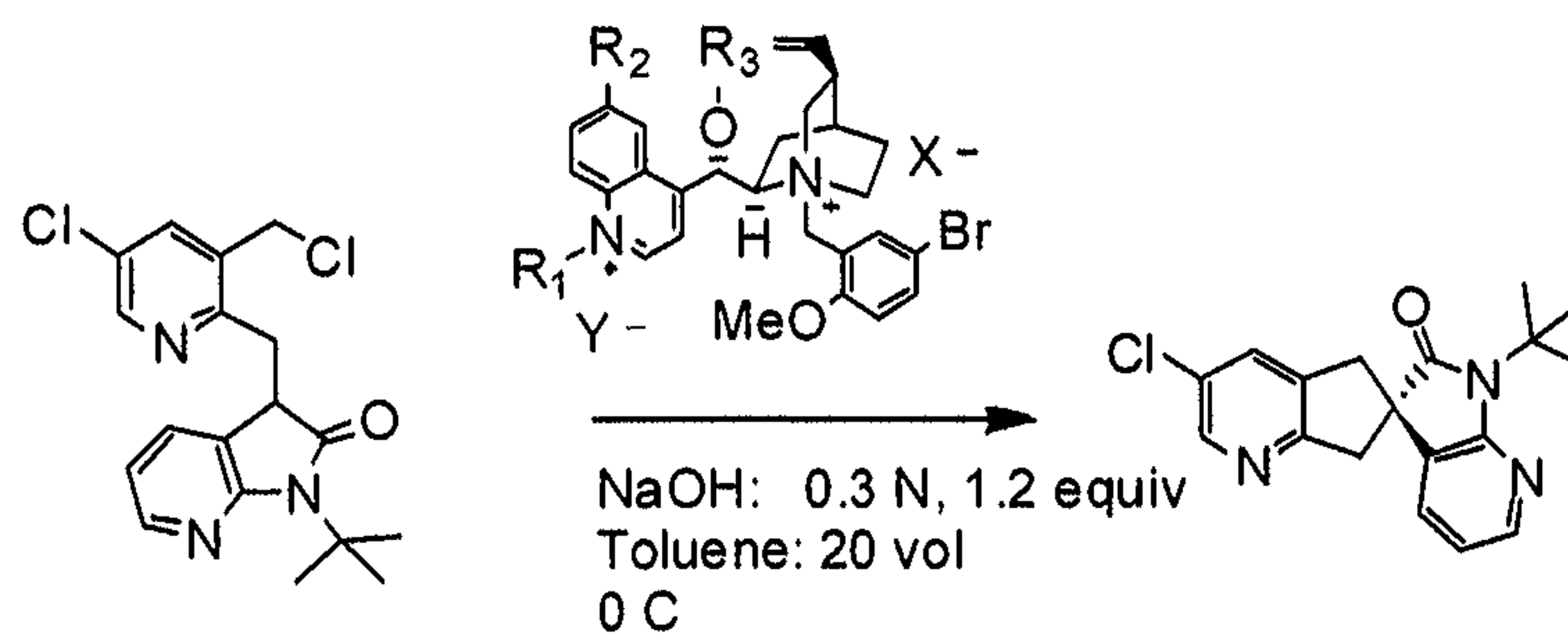


Table 1

				
PTC catalysts:	Loading	EE	conversion	Yield
	3%	58%	80%	ND
	0.3%	92%	100%	98% AY
	0.3%	94.4%	100%	100%

Tables 2 and 3 show a SAR study of bis-quaternary PTC catalysts for  
 5 spirocyclization. Both bis-quaternary quinidine and cinchonine catalysts are very efficient (Entries 2 to 5). The Bis-Quinidine catalyst is relatively better than bis-cinchonine catalyst (Entry 2 and 3). 2-Bromo-5-Methoxy-benzyl group is the optimized group for this reaction.

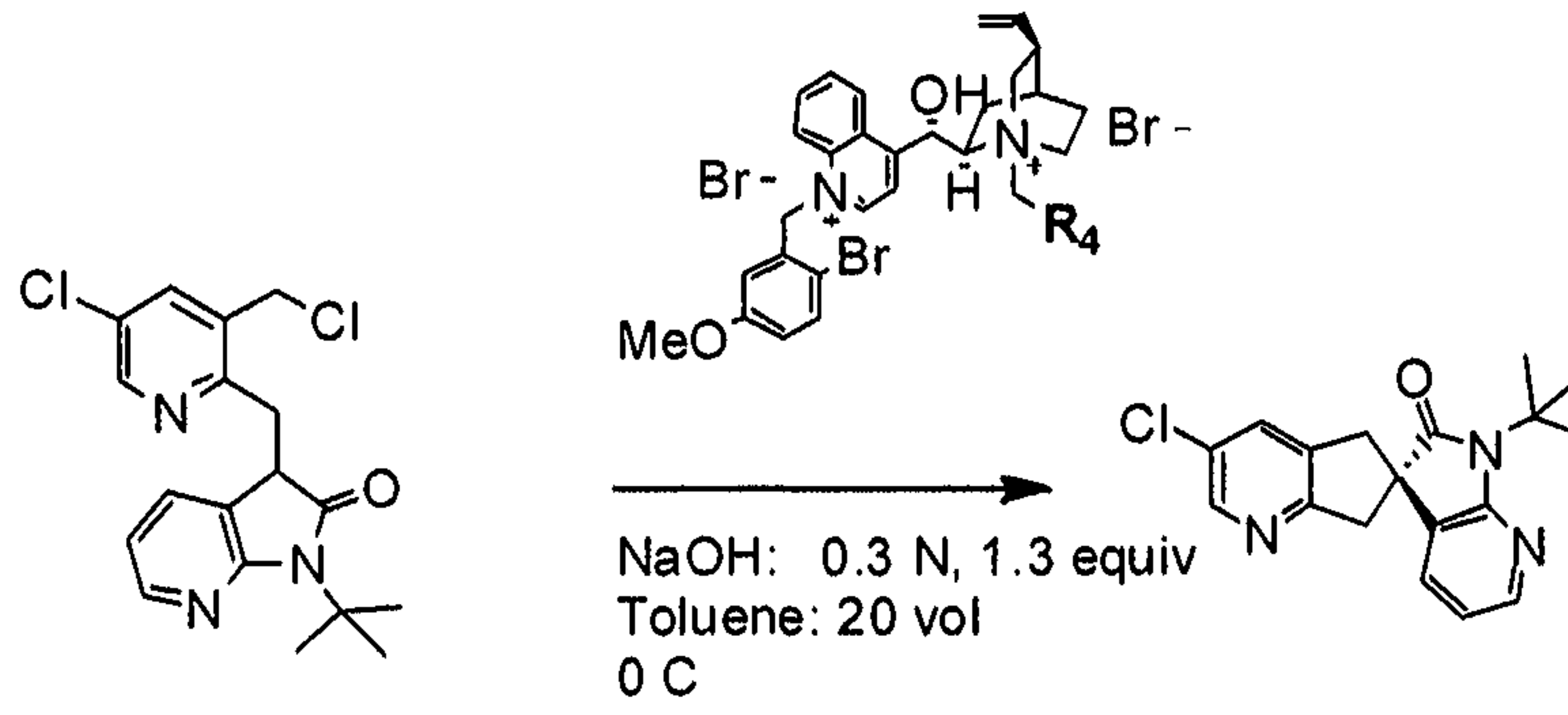
Table 2



Entry	R1	R2	R3	X	Y	%ee
1	No-substitution	H	H	Br	Br	58%ee
2		OMe	H	Br	Br	94.4%ee
3		H	H	Br	Br	90%ee
4		H	H	I	I	89.7%ee
5		H	H	Br	I	89.4%ee
6		H	H	Br	Br	84.8%ee
7	Me	H	H	Br	I	80%ee
8	No-substitution	H		Br	Br	67%ee
9		H		Br	Br	27%ee



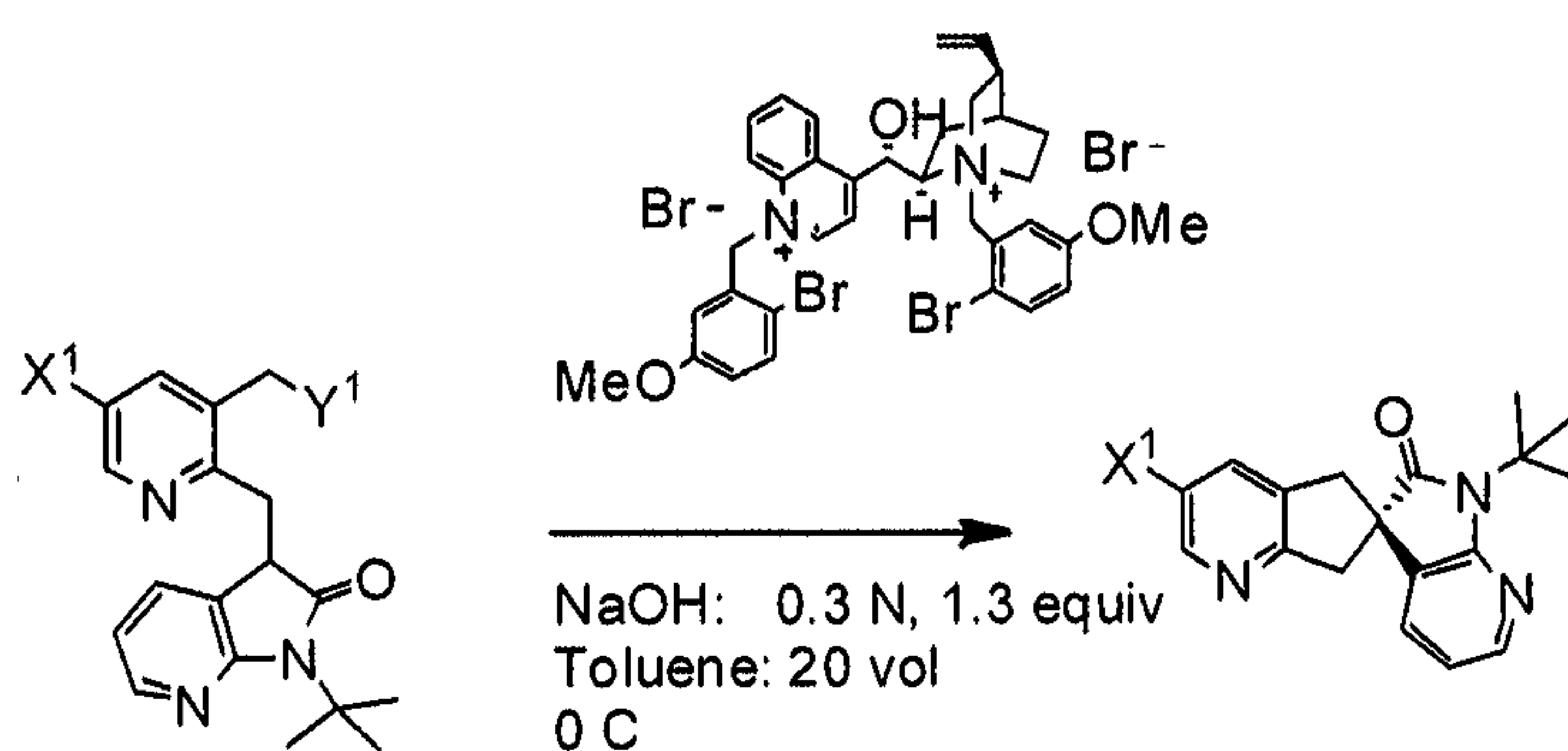
Table 3



R4	EE	Conversion
Benzyl	66.3%ee	93%
Allyl	69.7%ee	100%
2-Br-5-MeO-benzyl	92%ee	100%

5 Table 4 shows a study of different functional groups.

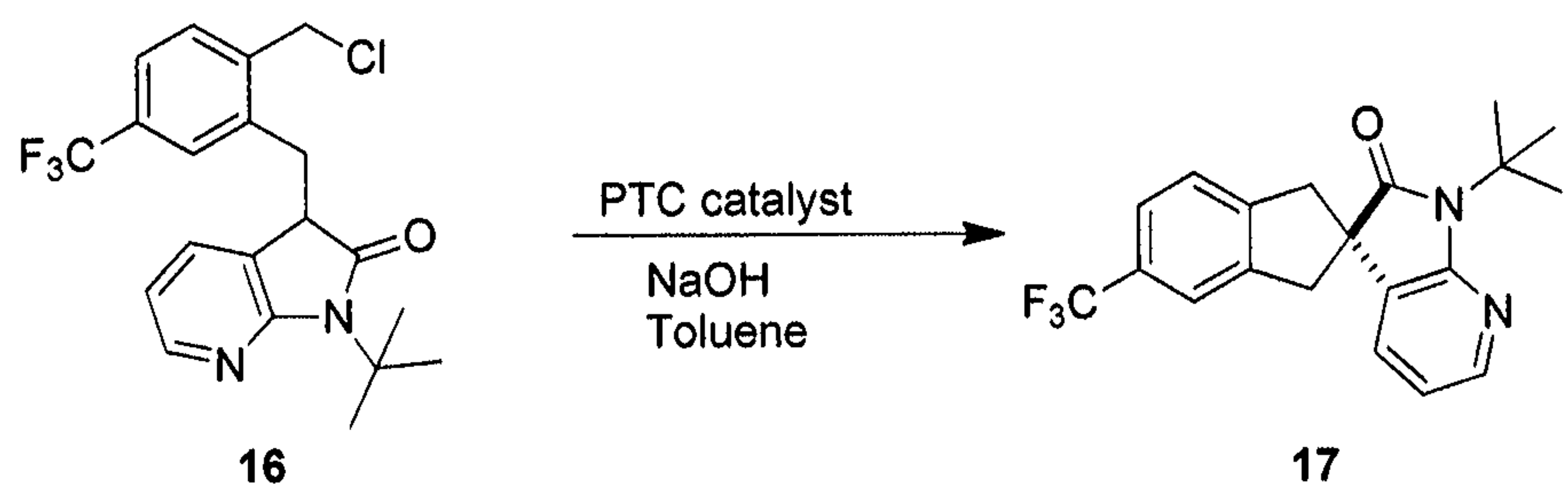
Table 4



Entry	X <sup>1</sup>	Y <sup>1</sup>	%ee
1	Cl	Cl	92
2	Br	Cl	92
3	CO <sub>2</sub> Me	Cl	92
4	Br	Tos	51
5	Br	Br	70

Table 5 shows a study of different ring systems; Doubly quaternized PTC is a more active catalyst than mono quaternized PTC.

Table 5



PTC 19: 3%ee  
PTC 18: 85%ee

Absolute configuration (*R* or *S*)  
has not been determined.

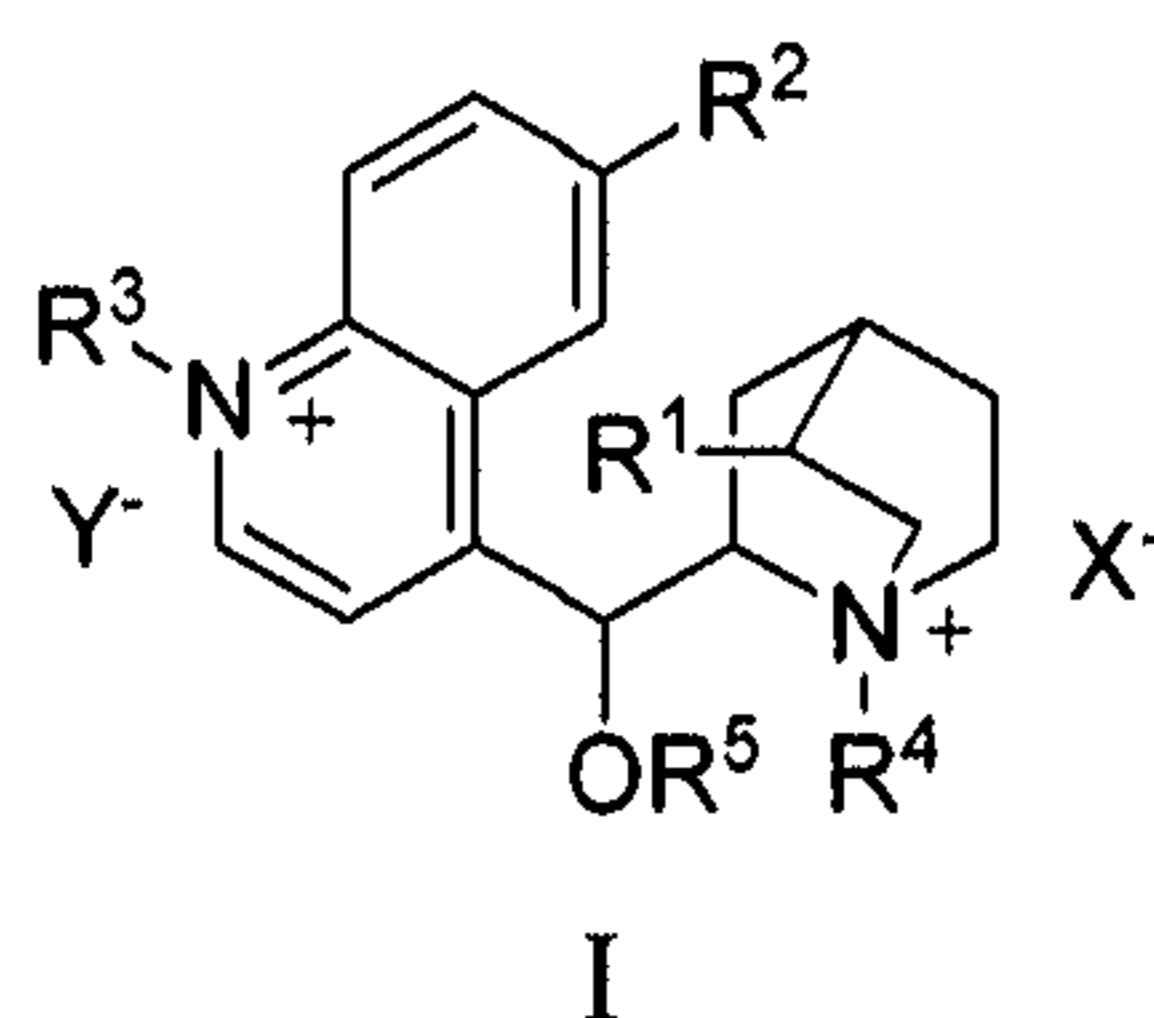
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WHAT IS CLAIMED IS:

1. A bis-quarternary cinchona alkaloid salt having the chemical structure of Formula I:

5



wherein:

10 R<sup>1</sup> is selected from ethyl and vinyl,

R<sup>2</sup> is selected from hydrogen and methoxy,

15 R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>3-6</sub>cycloalkyl, aryl, heteroaryl, -C<sub>1-4</sub>alkyl-aryl and -C<sub>1-4</sub>alkyl-heteroaryl, wherein C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>3-6</sub>cycloalkyl, aryl, heteroaryl and the aryl and heteroaryl portions of -C<sub>1-4</sub>alkyl-aryl and -C<sub>1-4</sub>alkyl-heteroaryl are optionally substituted with one to five substituents independently selected from R<sup>6</sup>,

20 R<sup>5</sup> is selected from the group consisting of hydrogen, C(O)R, C(O)OR, CONRR', and C<sub>1-6</sub>alkyl,

R<sup>6</sup> is selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>haloalkyl, aryl, C<sub>1-4</sub>alkoxy, hydroxy, CN, CO<sub>2</sub>R, CONRR', SR, SO<sub>2</sub>R, SO<sub>3</sub>R, PR<sub>2</sub>, PO(OR)<sub>2</sub>, PO(OR)(NRR'), PO(NRR')<sub>2</sub>, P(OR)<sub>2</sub>, P(OR)(NRR'), P(NRR')<sub>2</sub>, SiRR'R'', B(OR)<sub>2</sub>, C(O)R, NRR', NO<sub>2</sub>, and halogen,

25

each R, R' and R'' is independently selected from the group consisting of, H, C<sub>1-6</sub>alkyl, hydroxyl, C<sub>1-6</sub>alkoxy, aryl, heteroaryl, -CH<sub>2</sub>-aryl, -CH<sub>2</sub>-heteroaryl, and

each X and Y are independently anions selected from halide, OH, HSO<sub>4</sub>, SO<sub>4</sub>, BF<sub>4</sub>, SbF<sub>6</sub>, carboxylate, carbonate, hydrogencarbonate, NO<sub>3</sub>, sulfonate, hexafluorophosphate, phosphate, hydrogen phosphate and perchlorate,

5 for use as a phase transfer catalyst in the stereoselective formation of a carbon-carbon, carbon-heteroatom or carbon-halide bond on a substrate in a biphasic medium comprising an aqueous phase and organic phase or a micelle medium.

10 2. The bis-quarternary cinchona alkaloid salt according to claim 1 for use as a phase transfer catalyst in one of the following asymmetric reactions:

(1) alkylation with an electrophilic alkylating agent,

(2) Michael addition with an electron deficient olefin,

15

(3) aldol reaction with an aldehyde,

(4) Mannich reaction with a  $\alpha$ -imino ester,

20

(5) Darzens reaction with an aldehyde,

(6) Neber rearrangement of an oxime into an  $\alpha$ -aminoketone,

(7) epoxidation of an electron deficient olefin,

25

(8) aziridination of an electron deficient olefin,

(9) dihydroxylation of an electron deficient olefins,

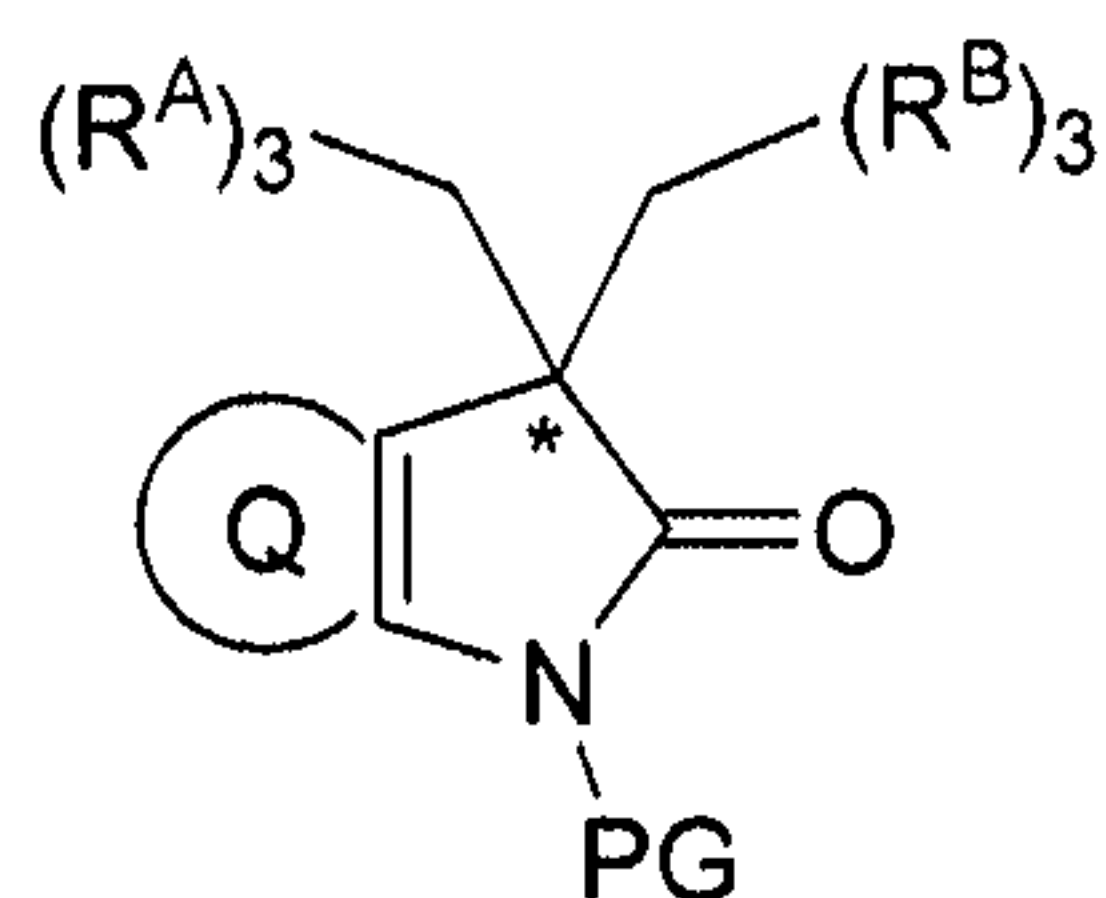
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(10) fluorination of a carbonyl substrate, and

(11) sulfenylation of a  $\beta$ -keto sulfoxide.



## 3. A process for stereoselectively producing a compound of Formula A



5 A

wherein:

Q forms a fused 5- or 6-membered aromatic carbocyclic or heterocyclic ring, each optionally  
 10 substituted with 1 to 4  $R^C$  groups,

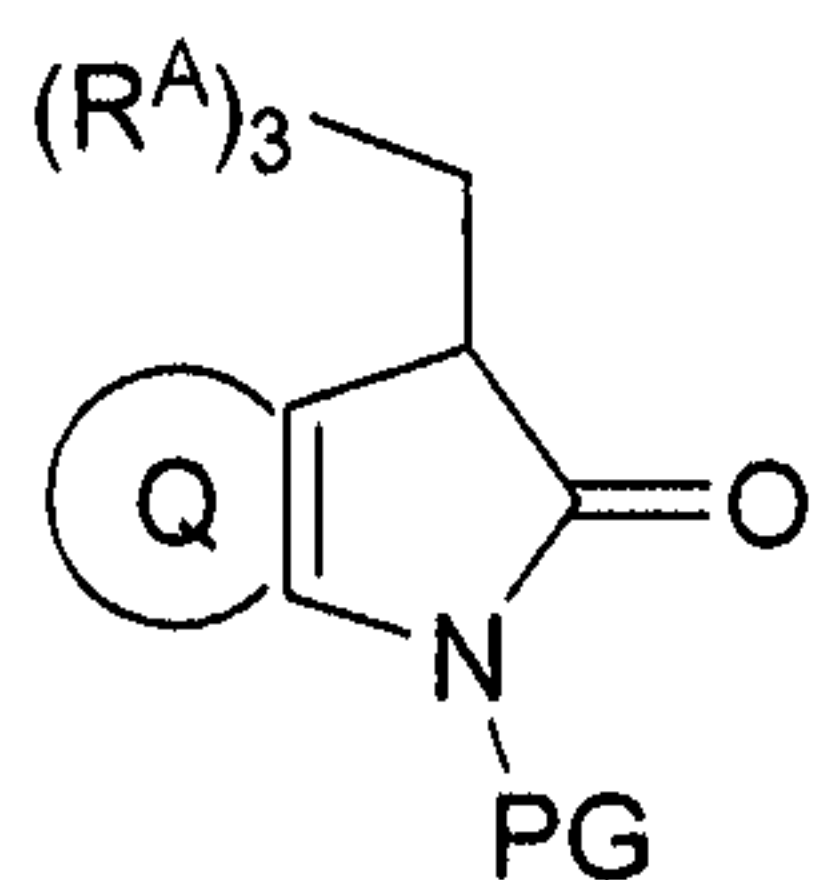
each  $R^A$  and each  $R^B$  are independently hydrogen, halogen, hydroxy, amino or an organic  
 substituent group, and one  $R^A$  and one  $R^B$  may be joined together to form a mono-, bi- or  
 tricyclic carbocyclic or heterocyclic ring system, optionally substituted with 1 to 4  $R^C$  groups,  
 15

$R^C$  is hydrogen, halogen, hydroxy, amino or an organic substituent group,

PG is a nitrogen protecting group and

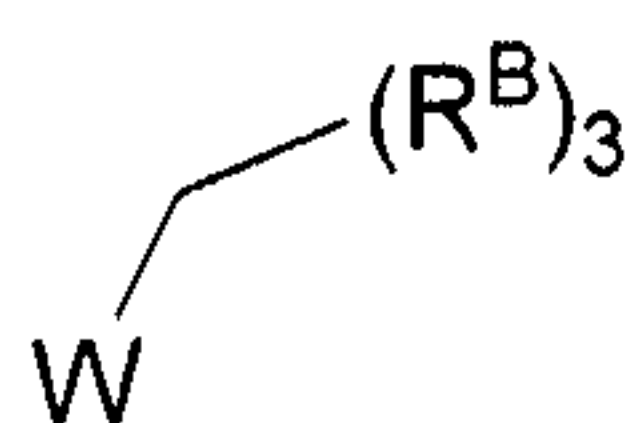
20 \* represents an asymmetric center,

comprising initiating a reaction of a compound of Formula B



25 B

with a compound of Formula C

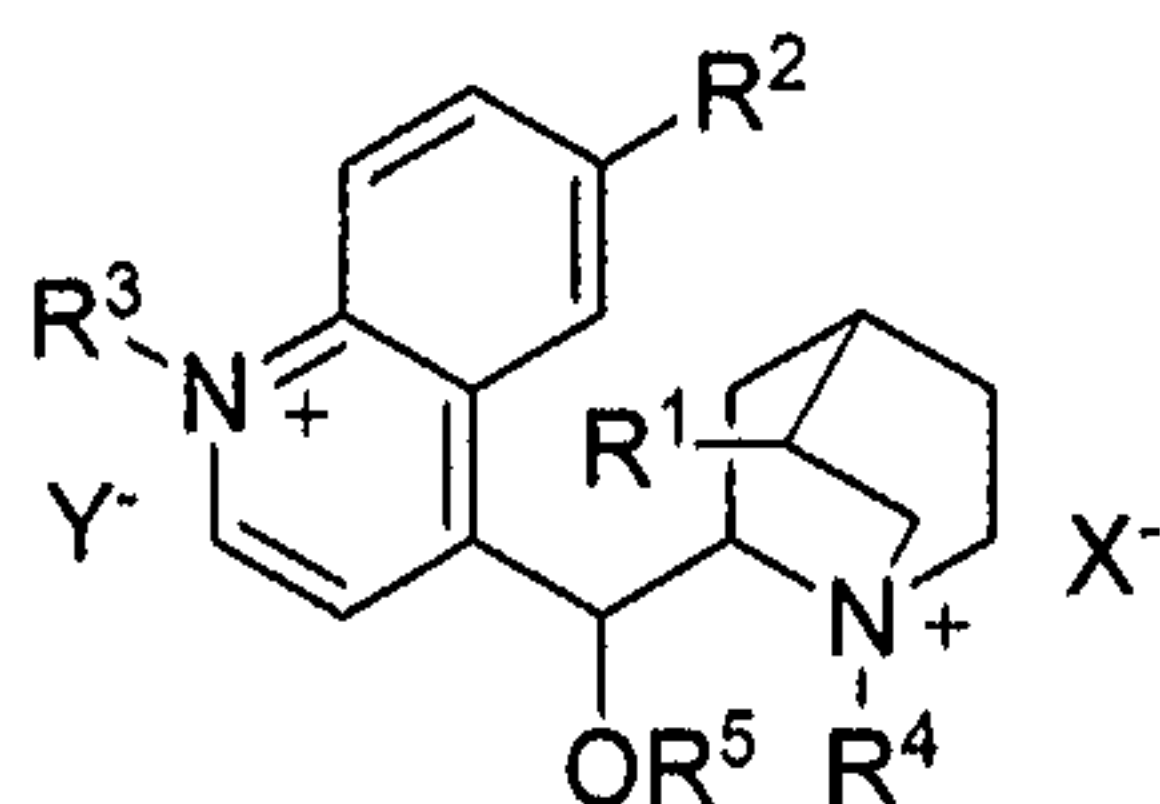


5 C

wherein W is a functional group that has leaving ability, in a water-immiscible organic phase in the presence of a bis-quarternary cinchona alkaloid salt and a base in an aqueous phase to form a biphasic medium comprising the aqueous phase and water-immiscible organic phase,

10

wherein the bis-quarternary cinchona alkaloid salt has the chemical structure of Formula I:



15 I

wherein:

R<sup>1</sup> is selected from ethyl and vinyl,

20 R<sup>2</sup> is selected from hydrogen and methoxy,

R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>3-6</sub>cycloalkyl, aryl, heteroaryl, -C<sub>1-4</sub>alkyl-aryl and -C<sub>1-4</sub>alkyl-heteroaryl, wherein C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>3-6</sub>cycloalkyl, aryl, heteroaryl and the aryl and heteroaryl portions of -C<sub>1-4</sub>alkyl-aryl and -C<sub>1-4</sub>alkyl-heteroaryl are optionally substituted with one to five substituents independently selected from R<sup>6</sup>,

25



R<sup>5</sup> is selected from the group consisting of hydrogen, C(O)R, C(O)OR, CONRR', and C<sub>1-6</sub>alkyl,

R<sup>6</sup> is selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>haloalkyl, aryl, C<sub>1-4</sub>alkoxy, hydroxy, CN, CO<sub>2</sub>R, CONRR', SR, SO<sub>2</sub>R, SO<sub>3</sub>R, PR<sub>2</sub>, PO(OR)<sub>2</sub>, PO(OR) (NRR'), PO(NRR')<sub>2</sub>, P(OR)<sub>2</sub>,  
 5 P(OR)(NRR'), P(NRR')<sub>2</sub>, SiRR'R'', B(OR)<sub>2</sub>, C(O)R, NRR', NO<sub>2</sub>, and halogen, ,

each R, R' and R'' is independently selected from the group consisting of, H, C<sub>1-4</sub>alkyl, hydroxy and C<sub>1-4</sub>alkoxy, and

10 each X and Y are independently anions selected from halide, OH, HSO<sub>4</sub>, SO<sub>4</sub>, BF<sub>4</sub>, SbF<sub>6</sub>, carboxylate, carbonate, hydrogencarbonate, NO<sub>3</sub>, sulfonate, hexafluorophosphate, phosphate, hydrogen phosphate, and perchlorate,

4. The process according to Claim 3 wherein each R<sup>A</sup> and each R<sup>B</sup> are  
 15 independently selected from the group consisting of:

- (i) hydrogen,
- (ii) halogen,
- (iii) OR<sup>7</sup>,
- 20 (iv) N(R<sup>7</sup>)<sub>2</sub>,
- (v) CN,
- (vi) C<sub>1-8</sub>alkyl or C<sub>2-8</sub>alkenyl, either of which optionally bears up to 3 substituents independently selected from halogen, OH, CN, CF<sub>3</sub>, OR<sup>7</sup>, SR<sup>8</sup>, SO<sub>2</sub>R<sup>8</sup>, SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, COR<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, CON(R<sup>7</sup>)<sub>2</sub>, N(R<sup>7</sup>)<sub>2</sub>, NR<sup>7</sup>COR<sup>8</sup> and NR<sup>7</sup>SO<sub>2</sub>R<sup>8</sup>; and
- 25 (vii) C<sub>3-10</sub>cycloalkyl, C<sub>3-10</sub>cycloalkylC<sub>1-4</sub>alkyl, Het, HetC<sub>1-4</sub>alkyl, ARY or ARY-C<sub>1-4</sub>alkyl, any of which optionally bears up to 3 substituents independently selected from halogen, OH, oxo, CN, CF<sub>3</sub>, R<sup>8</sup>, OR<sup>7</sup>, SR<sup>8</sup>, SO<sub>2</sub>R<sup>8</sup>, SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, COR<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, CON(R<sup>7</sup>)<sub>2</sub>, N(R<sup>7</sup>)<sub>2</sub>, NR<sup>7</sup>COR<sup>8</sup> and NR<sup>7</sup>SO<sub>2</sub>R<sup>8</sup>; where "ARY" refers to phenyl or 5- or 6-membered heteroaryl, either of which phenyl or heteroaryl is optionally fused to a 5- or 6-membered

carbocycle or heterocycle, and "Het" refers to a nonaromatic mono- or bicyclic heterocyclic system of up to 10 ring atoms;

and one of R<sup>A</sup> and R<sup>B</sup> together may complete a mono- or bicyclic carbocyclic or heterocyclic system of up to 10 ring atoms which optionally bears up to 3 substituents

5 independently selected from halogen, OH, oxo, CN, CF<sub>3</sub>, R<sup>8</sup>, OR<sup>7</sup>, SR<sup>8</sup>, SO<sub>2</sub>R<sup>8</sup>, SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, COR<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, CON(R<sup>7</sup>)<sub>2</sub>, N(R<sup>7</sup>)<sub>2</sub>, NR<sup>7</sup>COR<sup>8</sup> and NR<sup>7</sup>SO<sub>2</sub>R<sup>8</sup>;

R<sup>7</sup> is H or C<sub>1-6</sub>alkyl which is optionally substituted with up to 3 halogen atoms or with OH, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino or di(C<sub>1-4</sub>alkyl)amino, or R<sup>7</sup> is phenyl, benzyl or 5- or 6-membered heteroaryl, any of which optionally bears up to 3 substituents  
10 independently selected from halogen, OH, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino and di(C<sub>1-4</sub>alkyl)amino;

or two R<sup>7</sup> groups attached to the same nitrogen atom may complete a heterocycle of up to 6 ring atoms which optionally bears up to 3 substituents independently selected from halogen, OH, oxo, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino and di(C<sub>1-4</sub>alkyl)amino; and  
15

R<sup>8</sup> is C<sub>1-6</sub>alkyl which is optionally substituted with up to 3 halogen atoms or with OH, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino or di(C<sub>1-4</sub>alkyl)amino, or R<sup>8</sup> is phenyl, benzyl or 5- or 6-membered heteroaryl, any of which optionally bears up to 3 substituents independently selected from halogen, OH, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino and di(C<sub>1-4</sub>alkyl)amino;  
20

or two R<sup>8</sup> groups attached to the same nitrogen atom may complete a heterocycle of up to 6 ring atoms which optionally bears up to 3 substituents independently selected from halogen, OH, oxo, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino and di(C<sub>1-4</sub>alkyl)amino.  
25

5. The process according to Claim 3 wherein R<sup>C</sup> is selected from the group consisting of:

(i) hydrogen,



(ii) halogen,

(iii) OR<sup>7</sup>,

(iv) N(R<sup>7</sup>)<sub>2</sub>,

(v) CN,

5 (vi) C<sub>1-8</sub>alkyl or C<sub>2-8</sub>alkenyl, either of which optionally bears up to 3

substituents independently selected from halogen, OH, CN, CF<sub>3</sub>, OR<sup>7</sup>, SR<sup>8</sup>, SO<sub>2</sub>R<sup>8</sup>,

SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, COR<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, CON(R<sup>7</sup>)<sub>2</sub>, N(R<sup>7</sup>)<sub>2</sub>, NR<sup>7</sup>COR<sup>8</sup> and NR<sup>7</sup>SO<sub>2</sub>R<sup>8</sup>; and

(vii) C<sub>3-10</sub>cycloalkyl, C<sub>3-10</sub>cycloalkylC<sub>1-4</sub>alkyl, Het, HetC<sub>1-4</sub>alkyl, ARY or

ARY-C<sub>1-4</sub>alkyl, any of which optionally bears up to 3 substituents independently selected from

10 halogen, OH, oxo, CN, CF<sub>3</sub>, R<sup>8</sup>, OR<sup>7</sup>, SR<sup>8</sup>, SO<sub>2</sub>R<sup>8</sup>, SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, COR<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, CON(R<sup>7</sup>)<sub>2</sub>,

N(R<sup>7</sup>)<sub>2</sub>, NR<sup>7</sup>COR<sup>8</sup> and NR<sup>7</sup>SO<sub>2</sub>R<sup>8</sup>; where "ARY" refers to phenyl or 5- or 6-membered

heteroaryl, either of which phenyl or heteroaryl is optionally fused to a 5- or 6-membered

carbocycle or heterocycle, and "Het" refers to a nonaromatic mono- or bicyclic heterocyclic

system of up to 10 ring atoms;

15 R<sup>7</sup> is H or C<sub>1-6</sub>alkyl which is optionally substituted with up to 3 halogen atoms

or with OH, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino or di(C<sub>1-4</sub>alkyl)amino, or R<sup>7</sup> is

phenyl, benzyl or 5- or 6-membered heteroaryl, any of which optionally bears up to 3 substituents

independently selected from halogen, OH, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, amino, C<sub>1-</sub>

4alkylamino and di(C<sub>1-4</sub>alkyl)amino;

20 or two R<sup>7</sup> groups attached to the same nitrogen atom may complete a heterocycle

of up to 6 ring atoms which optionally bears up to 3 substituents independently selected from

halogen, OH, oxo, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino and di(C<sub>1-</sub>

4alkyl)amino; and

R<sup>8</sup> is C<sub>1-6</sub>alkyl which is optionally substituted with up to 3 halogen atoms or

25 with OH, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino or di(C<sub>1-4</sub>alkyl)amino, or R<sup>8</sup> is phenyl,

benzyl or 5- or 6-membered heteroaryl, any of which optionally bears up to 3 substituents

independently selected from halogen, OH, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, amino, C<sub>1-</sub>

4alkylamino and di(C<sub>1-4</sub>alkyl)amino;

or two R<sup>8</sup> groups attached to the same nitrogen atom may complete a heterocycle of up to 6 ring atoms which optionally bears up to 3 substituents independently selected from halogen, OH, oxo, CN, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, amino, C<sub>1-4</sub>alkylamino and di(C<sub>1-4</sub>alkyl)amino.

5

6. The process according to Claim 3 wherein PG is selected from the group consisting of: C<sub>1-6</sub> alkyl, vinyl, C(O)-O-L, C(O)-L, aryl, heteroaryl, benzyl, benzhydryl, trityl and C<sub>1-6</sub>alkoxymethyl, wherein aryl, heteroaryl, benzyl, benzyhydryl and trityl optionally are substituted with 1 to 3 substituents independently selected from methoxy and nitro, C<sub>1-6</sub>alkoxymethyl is optionally substituted with trimethylsilyl and L is C<sub>1-6</sub>alkyl, aryl or benzyl.

10

7. The process according to Claim 3 wherein W is selected from the group consisting of: halogen and sulfonate.

15

8. The process according to Claim 3 wherein the water-immiscible organic phase is selected from the group consisting of benzene, toluene, xylenes, chlorobenzene, ethyl ether, isopropyl ether, tetrahydrofuran, 2-methyl tetrahydrofuran, dioxane, methyl *tert*-butyl ether, cyclopentyl methyl ether, isopropyl acetate, ethyl acetate, hexanes, heptanes, cyclohexane, dichloromethane and dichloroethane.

20

9. The process according to Claim 3 wherein the base is selected from the group consisting of: sodium hydroxide, lithium hydroxide, potassium hydroxide, sodium carbonate, lithium carbonate, potassium carbonate, cesium hydroxide, cesium carbonate, sodium hydrogen carbonate, cesium hydrogen carbonate, potassium hydrogen carbonate, lithium hydrogen carbonate, lithium fluoride, sodium fluoride, potassium fluoride, cesium fluoride, lithium *tert*-butoxide, sodium *tert*-butoxide, potassium *tert*-butoxide, cesium *tert*-butoxide, sodium phosphate, lithium phosphate and potassium phosphate.

25

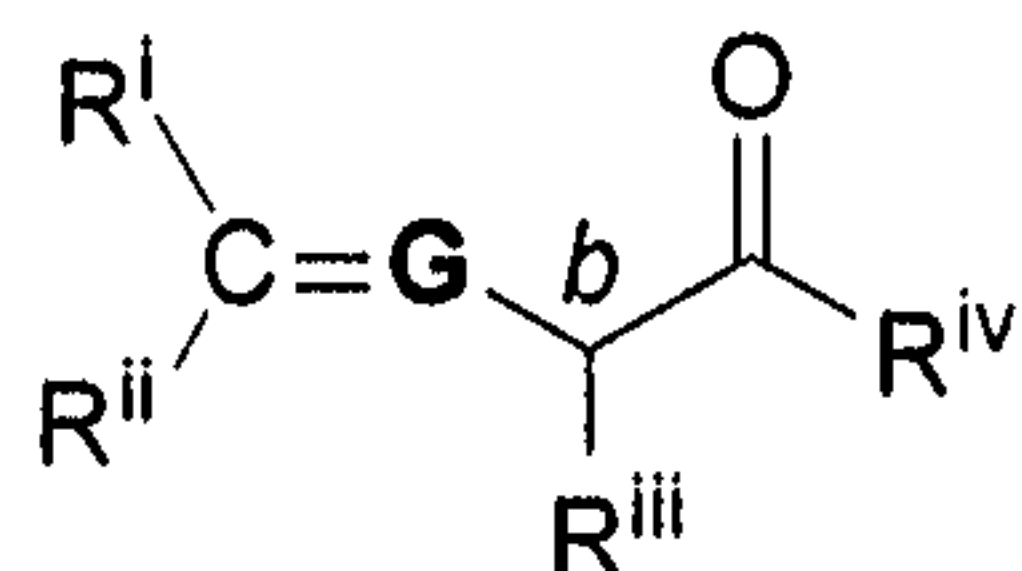
10. The process according to Claim 3 wherein the water-immiscible organic phase is toluene and the base is sodium hydroxide.

30



11. The bis-quarternary cinchona alkaloid salt according to claim 1 for use as a phase transfer catalyst in one of the following reactions:

(1) the asymmetric formation of a carbon-carbon bond at position *b* of a substrate  
5 having the following formula



wherein:

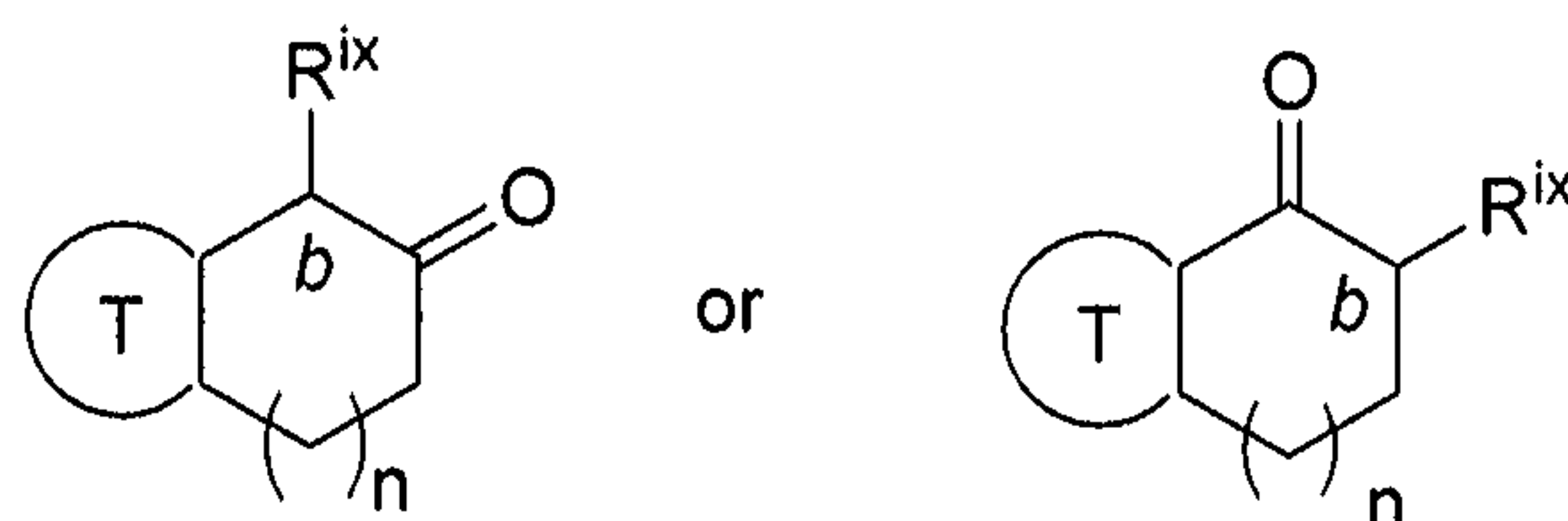
10 **G** is N or CH,

$R^I$ ,  $R^{II}$  and  $R^{III}$  are independently H, halogen or an organic substituent group

$R^{IV}$  is selected from  $-OR^V$ ,  $SR^{VI}$  and  $NR^{VII}R^{VIII}$ , wherein  $R^V$  and  $R^{VI}$  are independently H or an  
15 organic substituent group,  $R^{VII}$  and  $R^{VIII}$  are independently H or an organic substituent group or  
 $R^{VII}$  and  $R^{VIII}$  may be joined together with the nitrogen to which they are attached to form a 5- or  
6-membered heterocyclic ring, and

when **G** is N,  $R^{II}$  and  $R^{III}$  may be joined together with the atoms to which they are attached to  
20 form a 5- or 6-membered mono- or 9- or 10-membered bi-cyclic ring containing one or more  
heteroatoms in addition to the nitrogen, said ring optionally substituted with 1 to 5 substituents  
independently selected from: halogen, hydroxy, amino or an organic substituent group;

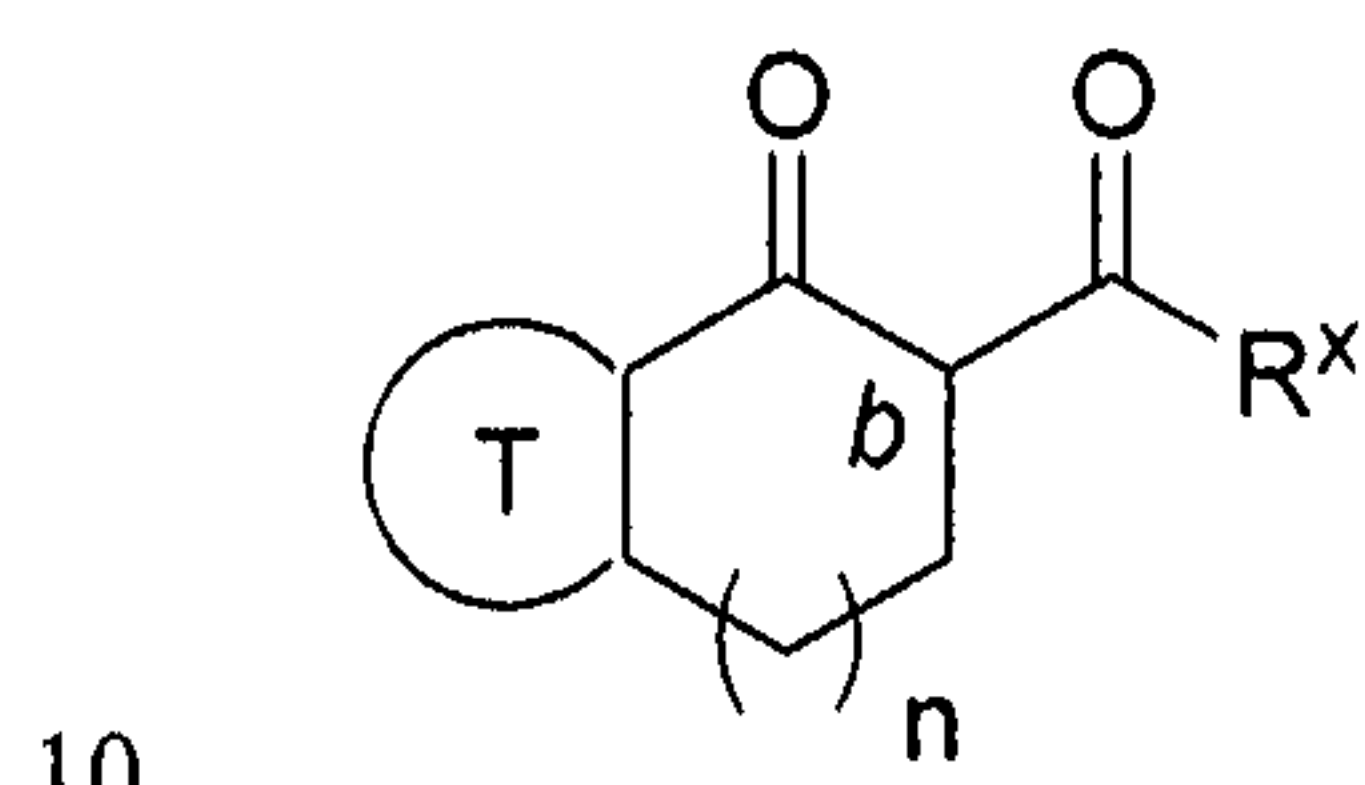
(2) the asymmetric formation of a carbon-carbon bond at position *b* of a substrate  
25 having the following formula





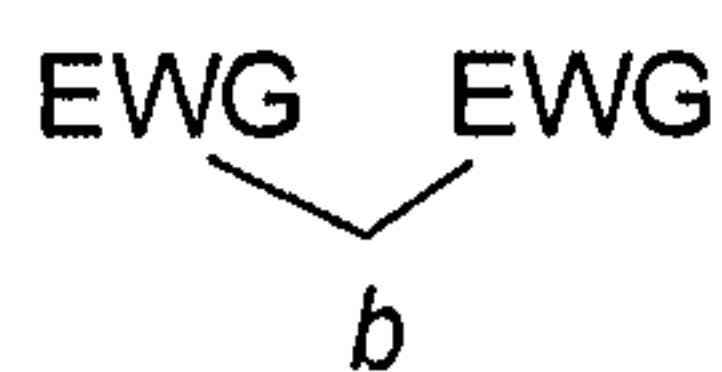
wherein  $n$  is 0 or 1, ring  $T$  is optional and forms a fused 5- or 6-membered aromatic carbocyclic or heterocyclic ring, each ring optionally substituted with hydrogen, halogen, hydroxy, amino or  
 5 an organic substituent group and  $R^{ix}$  is H or an organic substituent group,

(3) the asymmetric formation of a carbon-carbon bond at position  $b$  of a substrate having the following formula



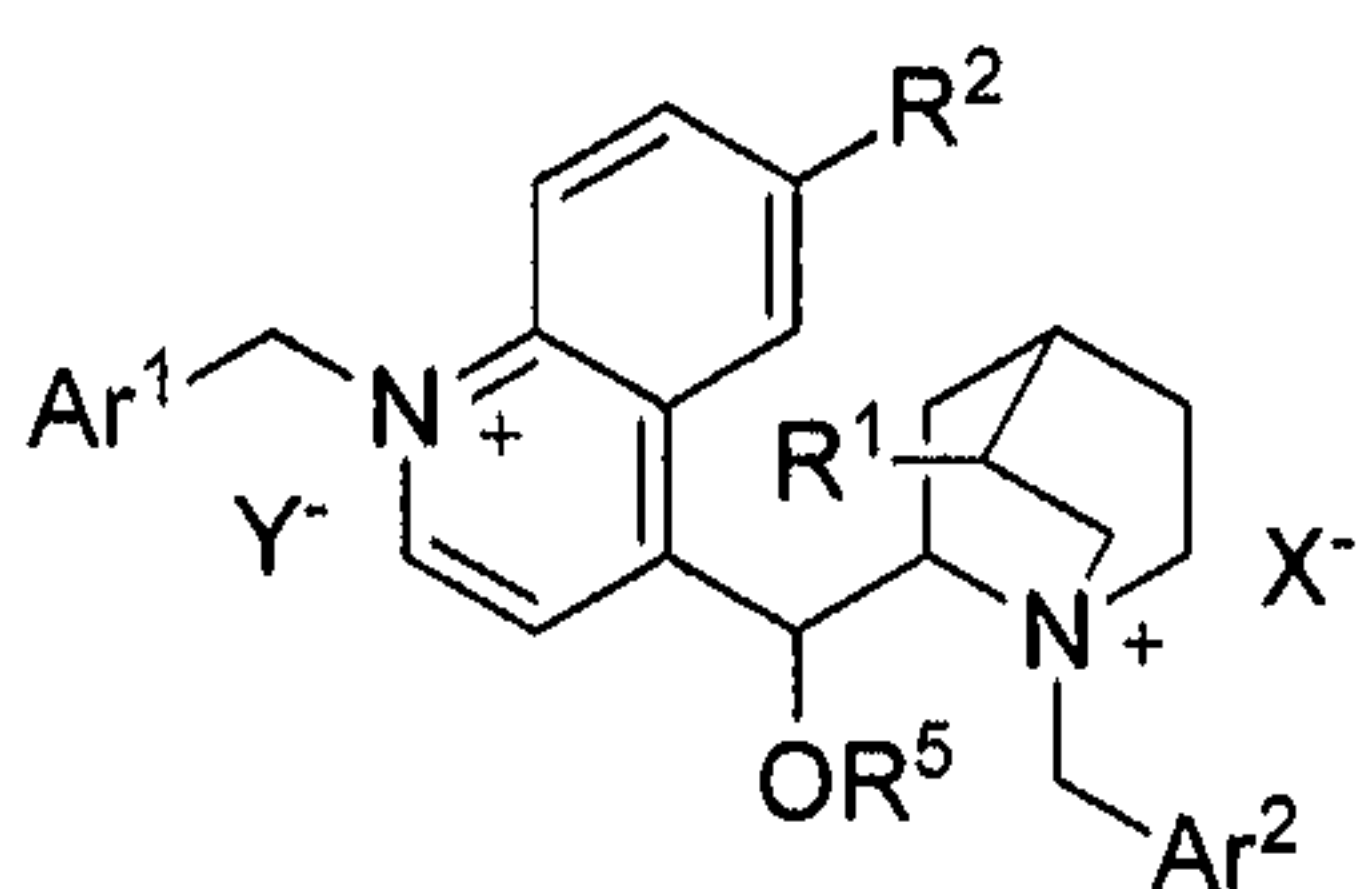
wherein  $n$  is 0 or 1, ring  $T$  is optional and forms a fused 5- or 6-membered aromatic carbocyclic or heterocyclic ring, each ring optionally substituted with hydrogen, halogen, hydroxy, amino or  
 15 an organic substituent group and  $R^x$  is selected from  $-OR^{xi}$ ,  $SR^{xii}$  and  $NR^{xiii}R^{xiv}$ , wherein  $R^{xi}$  and  $R^{xii}$  are independently H or an organic substituent group and  $R^{xiii}$  and  $R^{xiv}$  are independently H or an organic substituent group or  $R^{xiii}$  and  $R^{xiv}$  may be joined together with the nitrogen to which they are attached to form a 5- or 6-membered heterocyclic ring;

20 (4) the asymmetric formation of a carbon-carbon bond position  $b$  of a substrate having the following formula



25 wherein each EWG is independently an electron withdrawing group;

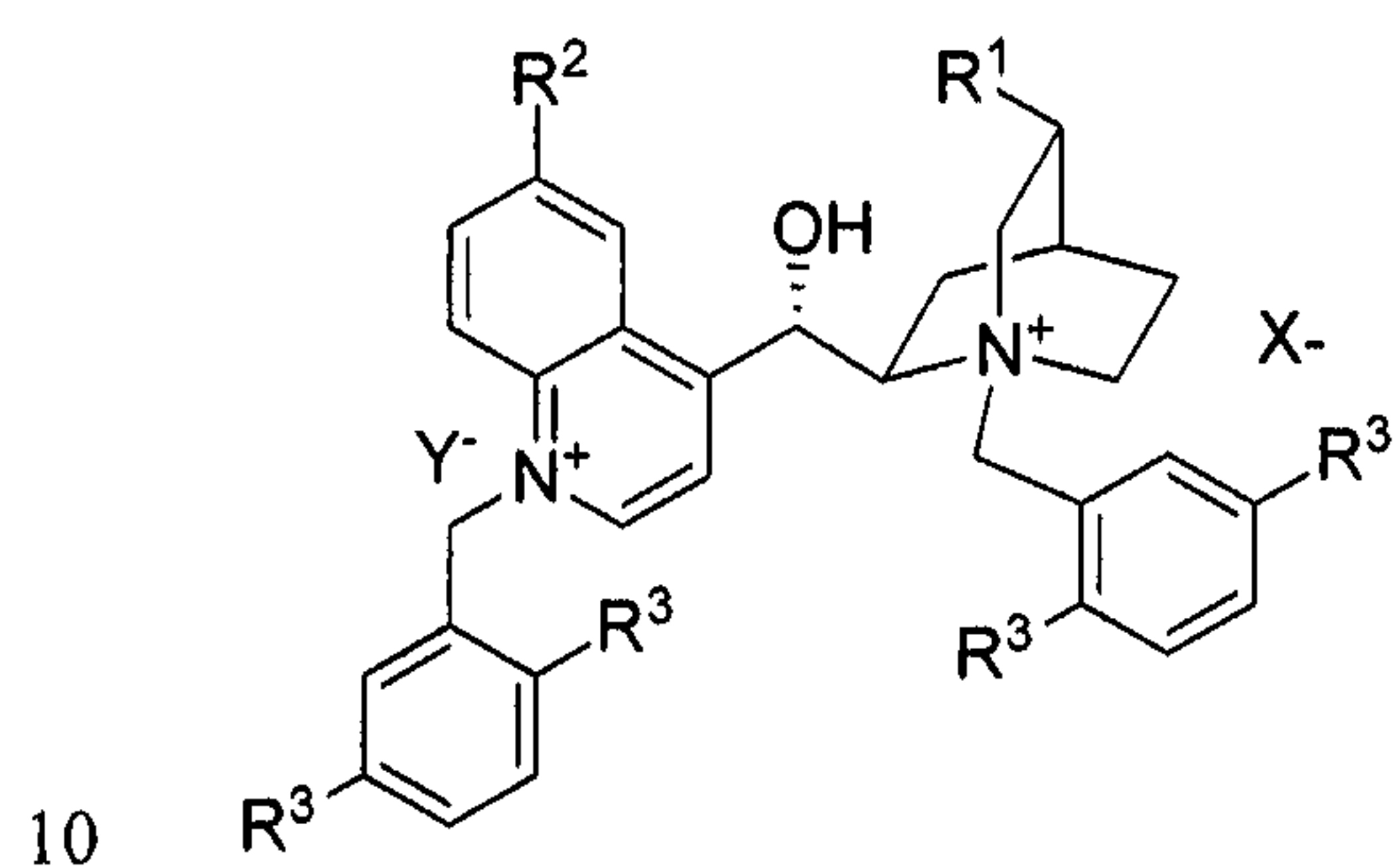
5                      12.        A bis-quarternary cinchona alkaloid salt having the chemical structure of  
Formula II:



- 46 -

13. The bis-quarternary cinchona alkaloid salt of claim 12 wherein Ar<sup>1</sup> is phenyl optionally substituted with one to five substituents independently selected from R<sup>3</sup>, and Ar<sup>2</sup> is phenyl optionally substituted with one to five substituents independently selected from R<sup>3</sup>.

14. The bis-quarternary cinchona alkaloid salt of claim 13 having the chemical structure of Formula IIa

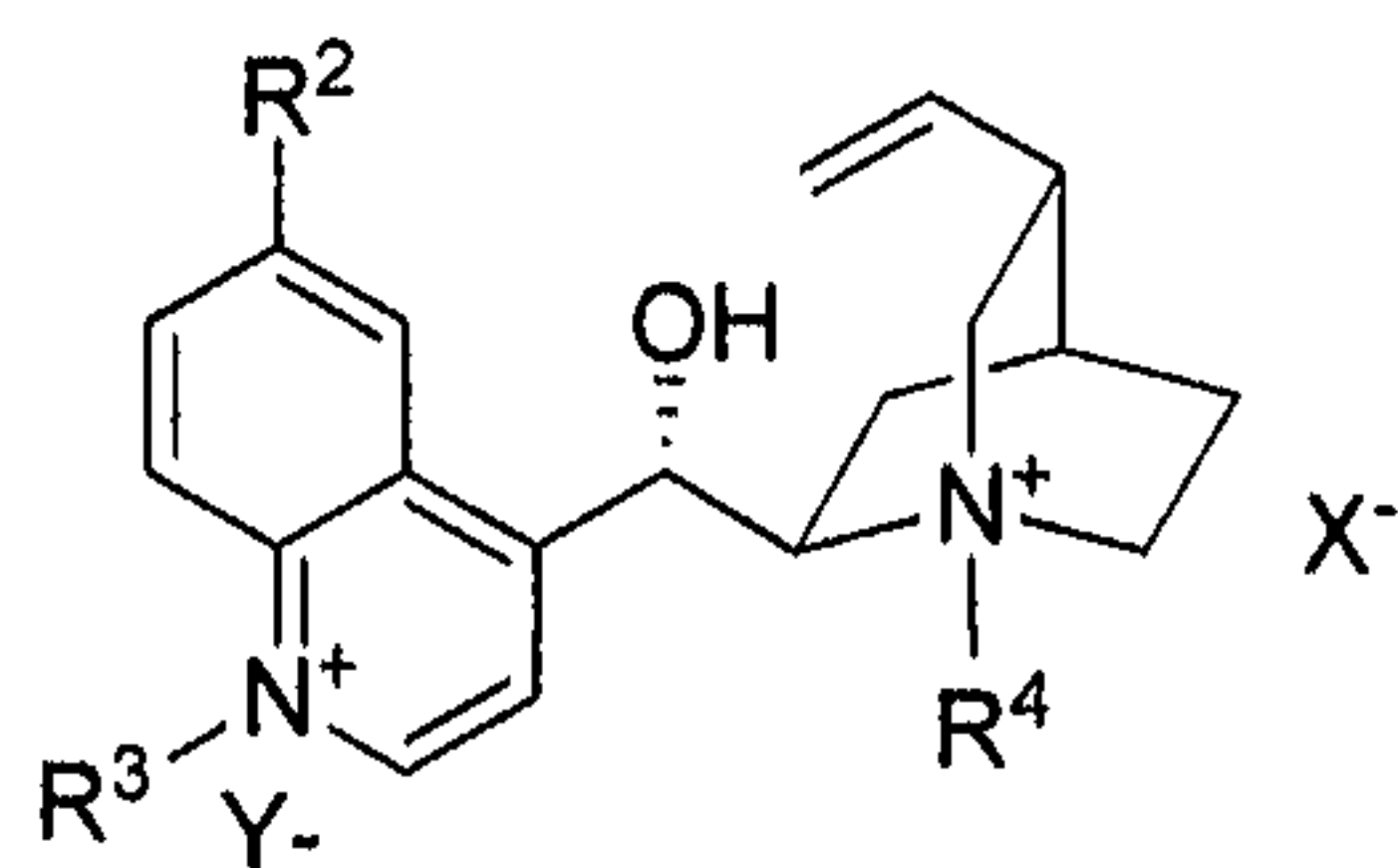


IIa.

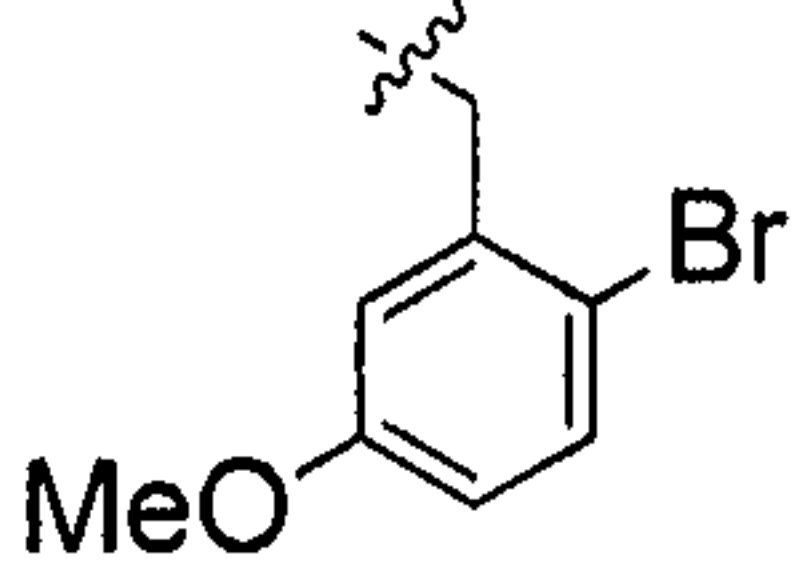
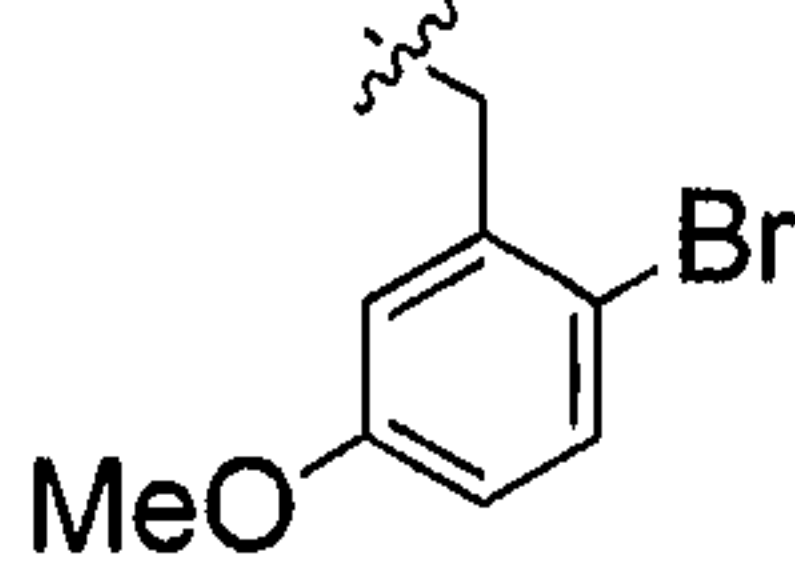
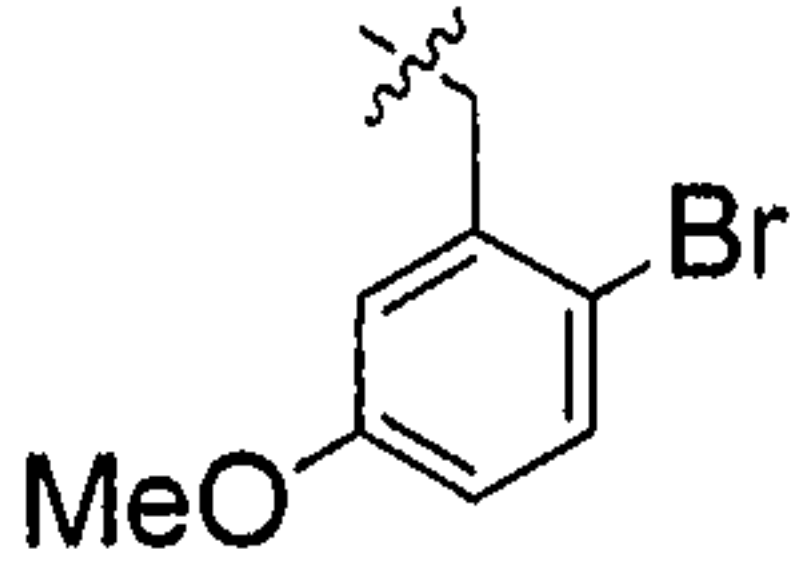
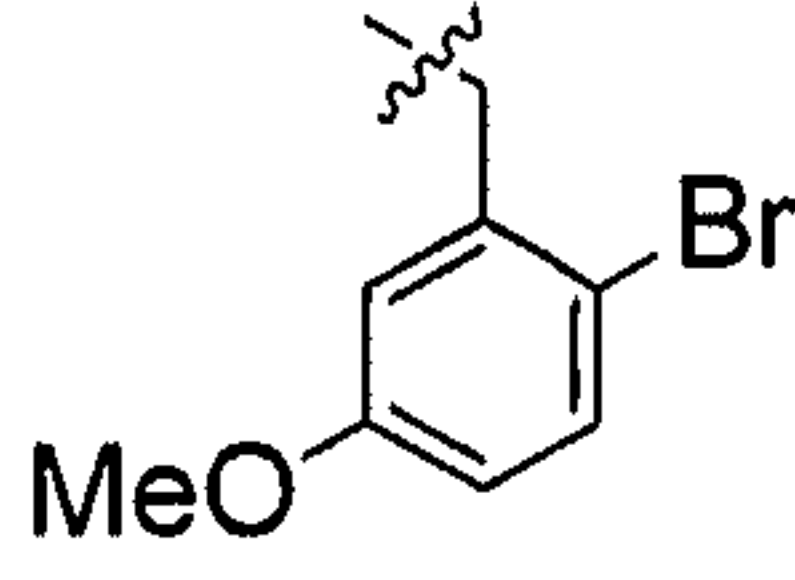
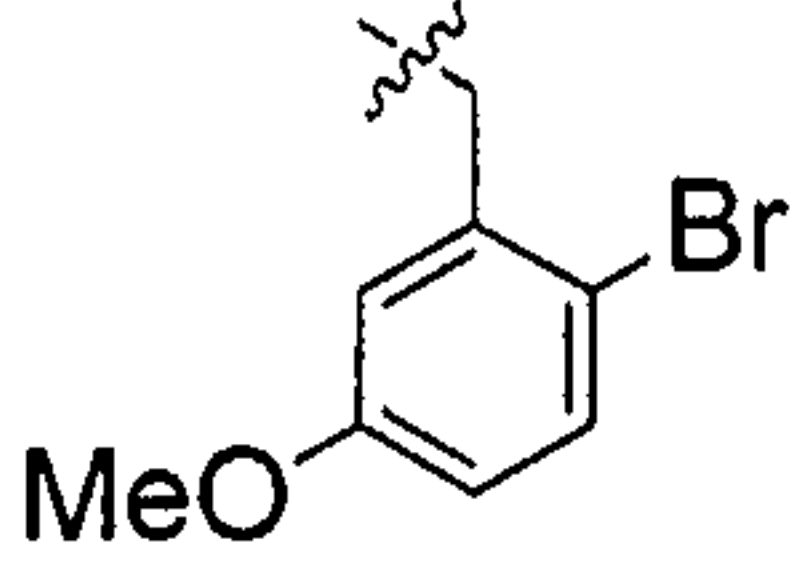
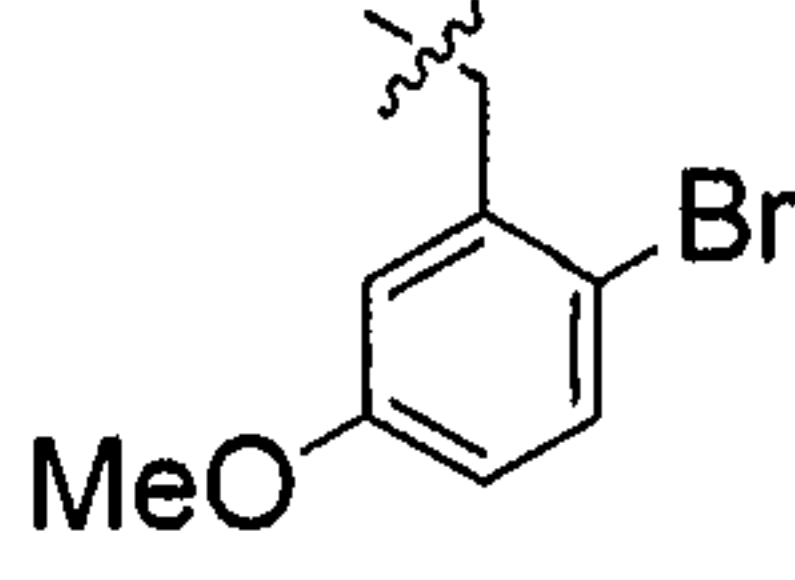
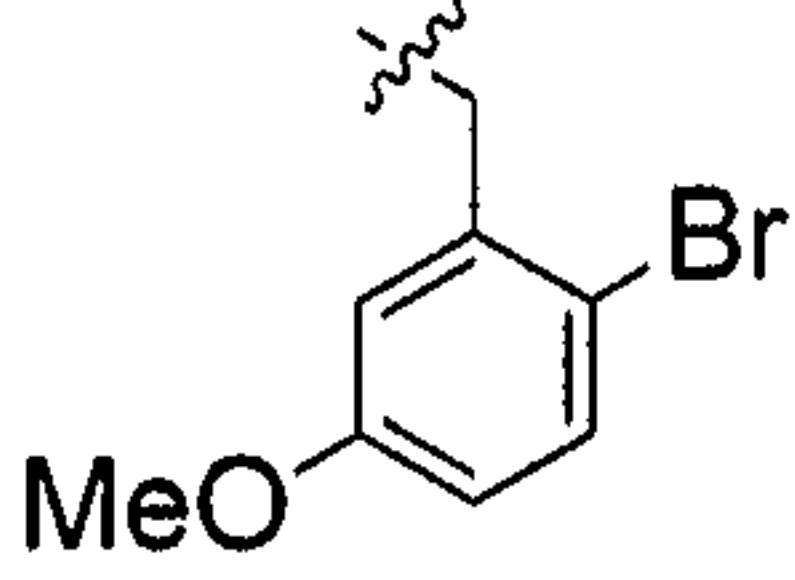
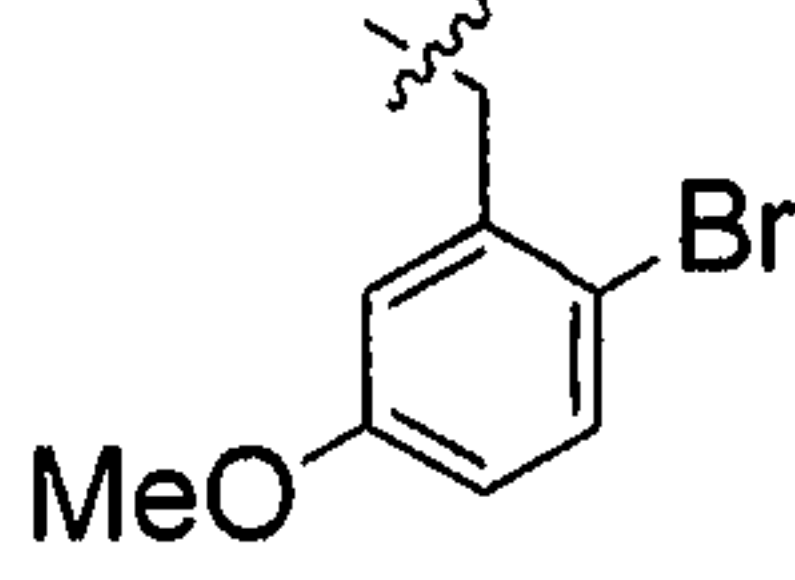
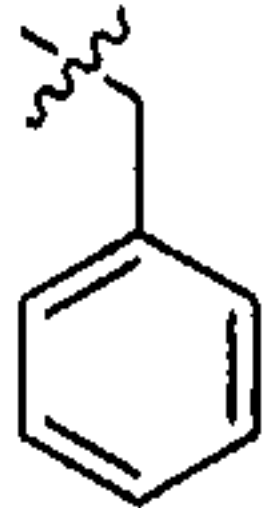
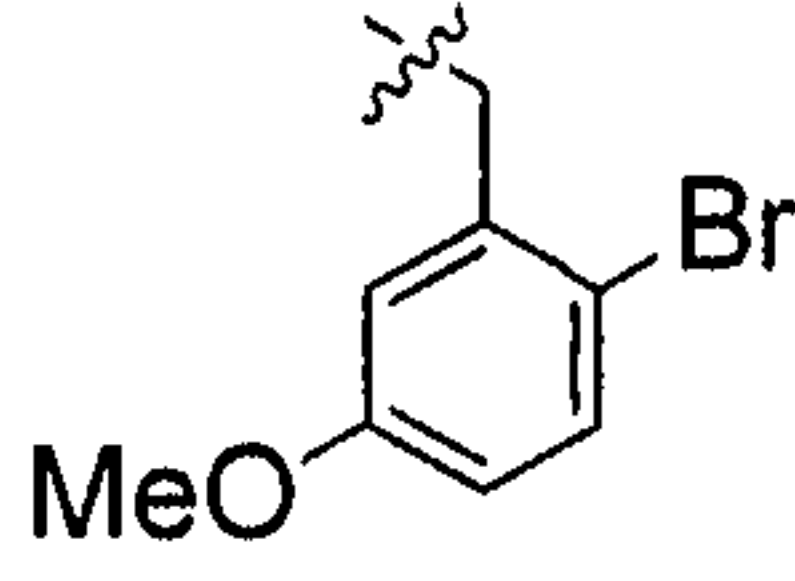
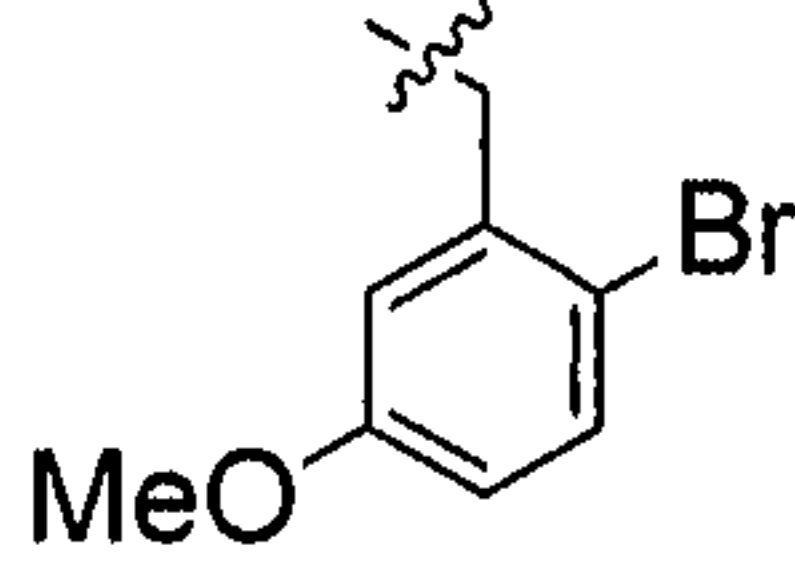
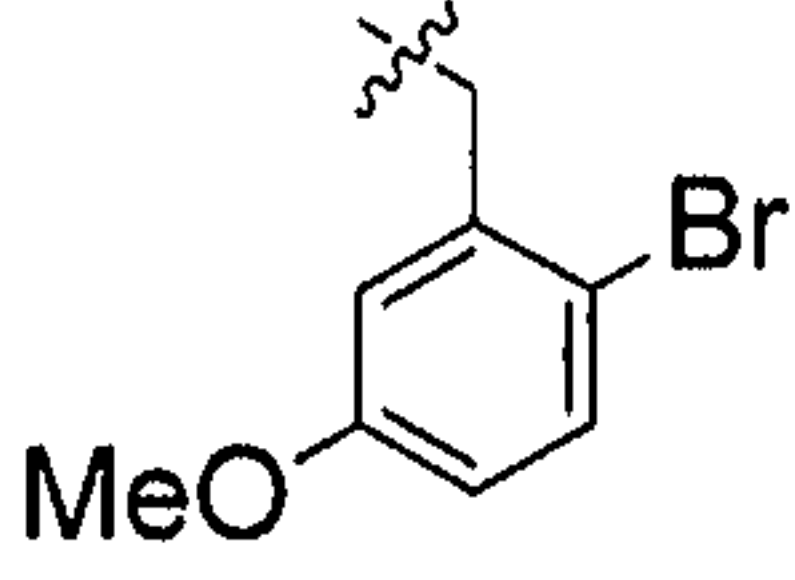
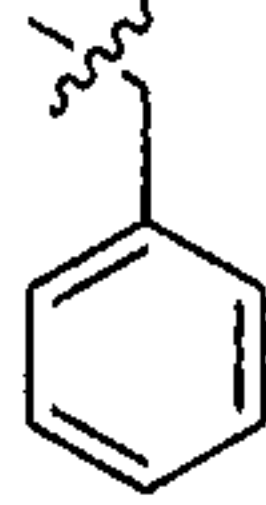
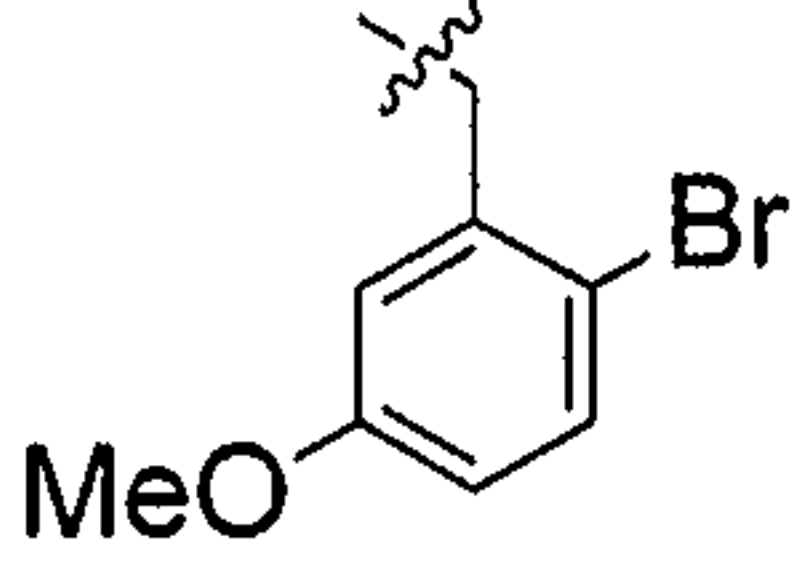
15. The bis-quarternary cinchona alkaloid salt of claim 14 wherein R<sup>1</sup> is vinyl and R<sup>2</sup> is methoxy.

16. The bis-quarternary cinchona alkaloid salt of claim 15 wherein R<sup>3</sup> is selected from halogen and methoxy.

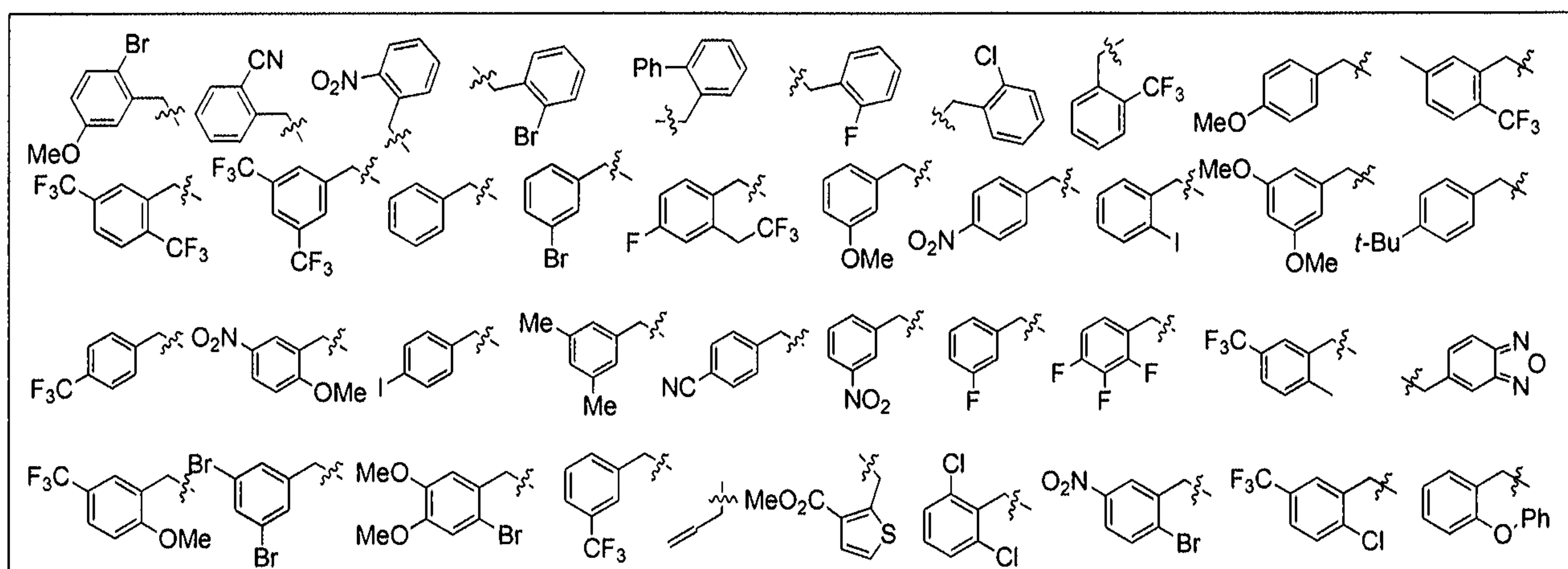
17. A bis-quarternary cinchona alkaloid salt selected from:



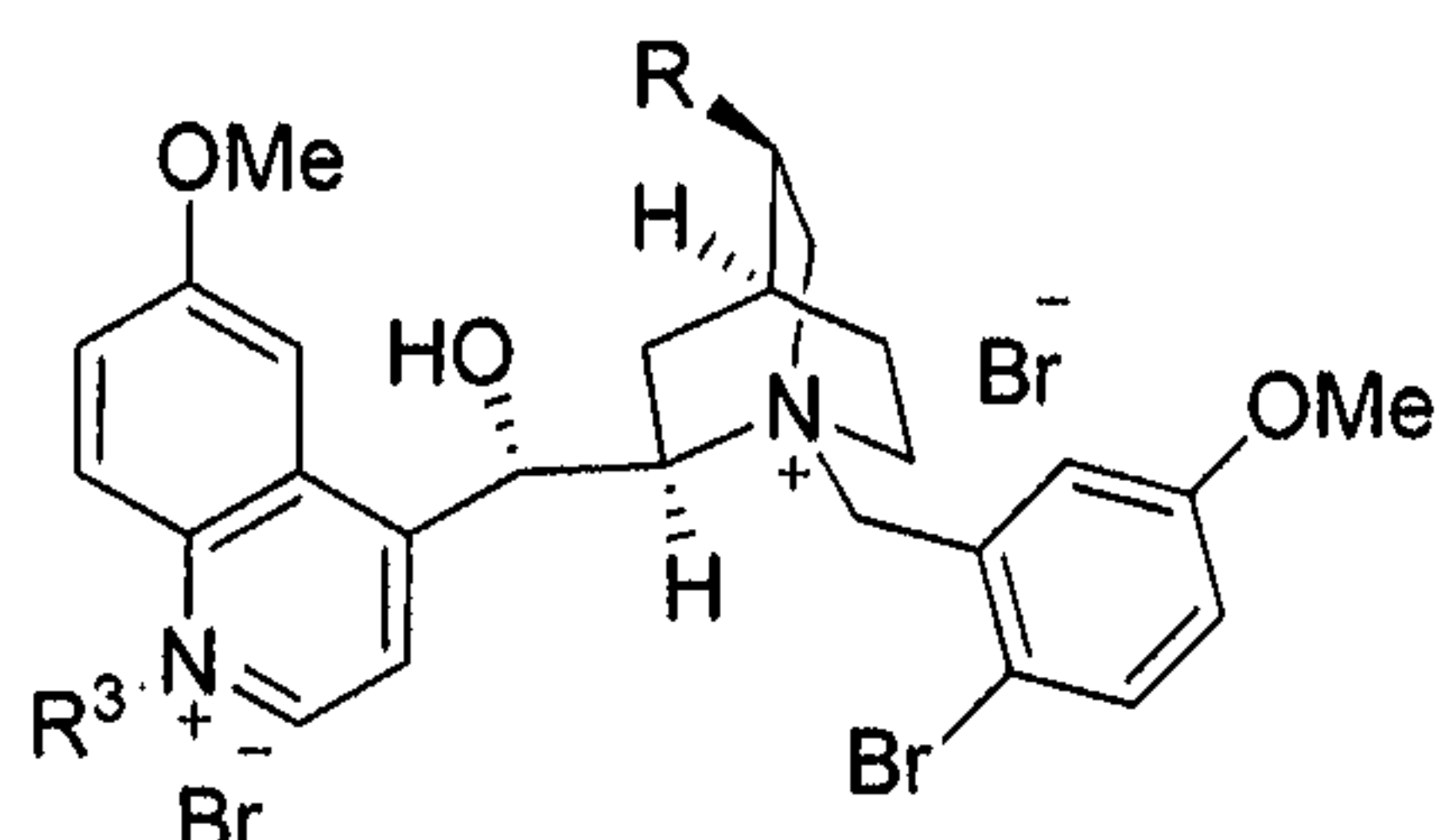


R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	X <sup>-</sup>	Y <sup>-</sup>
OMe			Br	Br
H			Br	Br
H			I	I
H			Br	I
H			Br	Br
H	Me		Br	I
H			Br	Br
H		allyl	Br	Br

$R^3$  is selected from the following groups:

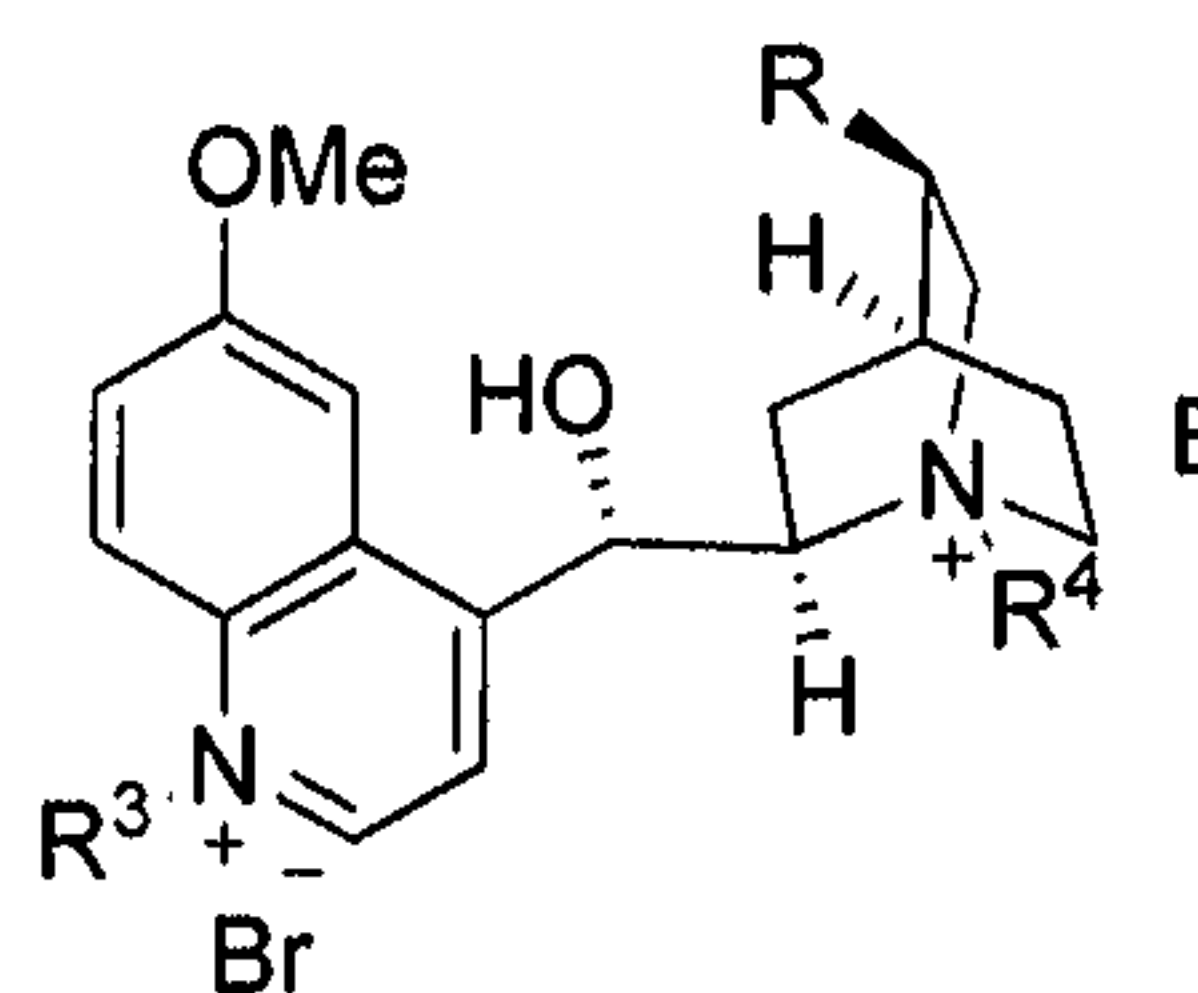
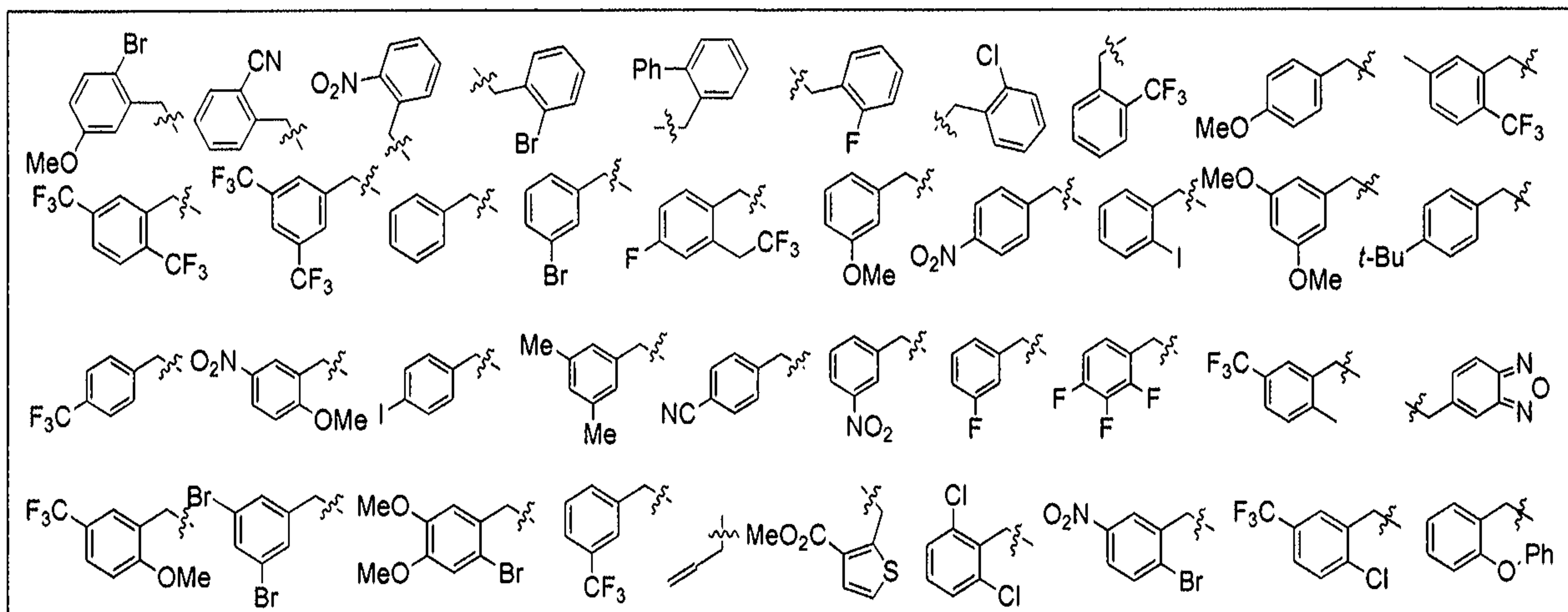


5



wherein R is selected from the group consisting of vinyl and ethyl;

$R^3$  is selected from the following groups:



wherein R is selected from the group consisting of vinyl and ethyl;

$R^3$  and  $R^4$  are independently selected from the following groups:

