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(54) Title: ENANTIOMERIC COMPOUNDS

(57) Abstract: The present invention relates to enantiomeric compounds, their use in stereospecific reactions and to a method of preparing enantiomeric compounds.



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Enantiomeric Compounds

[0001] The present invention relates to enantiomeric compounds, the use of these enantiomeric compounds in stereospecific reactions, and to a method of preparing these enantiomeric compounds.

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BACKGROUND

[0002] Asymmetric synthetic methods are of critical importance in the pharmaceutical industry to produce enantiomeric drug molecules.

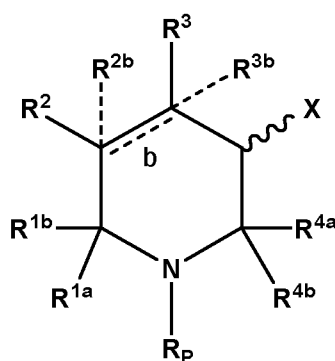
[0003] Tetrahydropyridines constitute an important subgroup of heterocycles that are found in a wide range of biologically active compounds, including alkaloids and iminosugars.³ Moreover, they are precursors of various drug molecules that comprise a piperidine moiety with specific stereochemistry (see, for example, the drug structures shown in Figure 1).⁴

[0004] There is, however, a need for improved methods of acquiring stereospecific tetrahydropyridines for use as building blocks in the synthesis of drug molecules that comprise a stereospecific piperidine moiety.

[0005] The present invention was devised with the foregoing in mind.

BRIEF SUMMARY OF THE DISCLOSURE

[0006] In a first aspect of the invention there is provided a compound according to Formula (I) or a salt, hydrate or solvate thereof, as shown below, with an enantiomeric excess of at least 20%:



Formula (I)

25

wherein:

bond **b** is independently selected from a single bond or double bond;

X is a leaving group;

R_P is a protecting group, hydrogen, (1-8C)alkyl, (3-10C)cycloalkyl or aryl;

5 wherein R^{1a} and R^{1b} are identical and R^{4a} and R^{4b} are identical; and R^{1a}, R^{1b}, R^{4a} and R^{4b} are selected from hydrogen, carbonyl, (1-8C)alkyl, (3-10C)cycloalkyl, (3-10C)cycloalkenyl, aryl, heteroaryl and heterocyclic wherein R^{1a}, R^{1b}, R^{4a} and R^{4b} are optionally further substituted by one or more substituent groups independently selected from halo, (1-4C)alkyl and (1-4C)haloalkyl;

10 when bond **b** is a double bond, R^{2b} and R^{3b} are absent, R² is selected from hydrogen, halo, (1-8C)alkyl, (3-10C)cycloalkyl, (1-8C)alkoxy, hydroxyl and R³ is selected from hydrogen, halo (1-8C)alkyl, (3-10C)cycloalkyl, (3-10C)cycloalkenyl, (1-8C)alkoxy, hydroxyl, epoxide and aryl; or

15 when bond **b** is a single bond, R² and R^{2b} are identical and are selected from hydrogen, halo, (1-8C)alkyl and (3-10C)cycloalkyl; and R³ and R^{3b} are identical and selected from hydrogen, halo (1-8C)alkyl, (3-10C)cycloalkyl, (3-10C)cycloalkenyl, (1-8C)alkoxy, hydroxyl, epoxide and aryl; and

20 wherein R², R³ and, if present, R^{2b} and R^{3b}, are optionally substituted by one or more substituent groups independently selected from halo, (1-4C)alkyl and (1-4C)haloalkyl.

[0007] The compounds defined herein may have an enantiomeric excess of the (R)- or (S)-enantiomer of the compound.

[0008] X may be a leaving group which is readily displaceable by nucleophilic attack or elimination. X may be selected from alkoxy, halo, tosylate, mesylate, triflate and
25 perfluoroalkylsulfonates. Preferably, X is halo, e.g. chloro, bromo, fluoro. Most preferably, X is chloro.

[0009] R_P may be a protecting group selected from acyl, arylmethyl (e.g. benzyl), arylmethoxycarbonyl (e.g. benzyloxycarbonyl) and alkoxycarbonyl, or R_P may be
30 hydrogen, (1-8C)alkyl or (3-10C)cycloalkyl. Preferably, R_P is benzyl, benzyloxycarbonyl, hydrogen or (1-8C)alkyl. Most preferably, R_P is benzyl or benzyloxycarbonyl.

[0010] R^{1a} and R^{1b} are identical. R^{1a} and R^{1b} may both be selected from hydrogen, (1-8C)alkyl, (3-10C)cycloalkyl, (3-10C)cycloalkenyl and aryl. Preferably, R^{1a} and R^{1b} are hydrogen or (1-4C)alkyl. R^{1a} and R^{1b} may optionally be further substituted by one or more substituent groups independently selected from (1-4C)alkyl and (1-4C)haloalkyl.

35 **[0011]** R^{4a} and R^{4b} are identical. R^{4a} and R^{4b} may both be selected from hydrogen, (1-8C)alkyl, (3-10C)cycloalkyl, (3-10C)cycloalkenyl and aryl. Preferably, R^{1a} and R^{1b} are

hydrogen or (1-4C)alkyl. R^{4a} and R^{4b} may optionally be further substituted by one or more substituent groups independently selected from (1-4C)alkyl and (1-4C)haloalkyl.

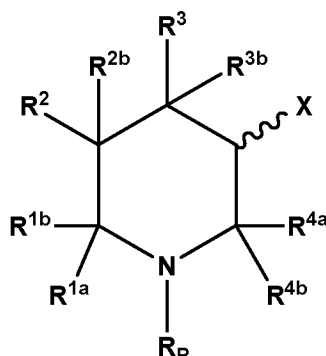
[0012] R^{1a} and R^{1b} must be identical but may be different to R^{4a} and R^{4b} . For example, R^{1a} and R^{1b} may both be hydrogen, whilst R^{4a} and R^{4b} may both be (1-4C)alkyl, or vice versa.

5 **[0013]** R^2 may be selected from hydrogen, halo, (1-8C)alkyl or (3-10C)cycloalkyl. Preferably, R^2 is selected from hydrogen, halo or (1-8C)alkyl. R^{2b} , if present, will be identical to R^2 .

[0014] R^3 may be selected from hydrogen, halo (1-8C)alkyl, (3-10C)cycloalkyl, (3-10C)cycloalkenyl and aryl. Preferably, R^3 is selected from hydrogen, halo, (1-8C)alkyl or
10 aryl. R^{3b} , if present, will be identical to R^3 .

[0015] Preferably, each of R^{1a} , R^{1b} , R^2 , R^3 , R^{4a} , R^{4b} and, if present, R^{2b} and R^{3b} are hydrogen.

[0016] If bond **b** is a single bond, R^{2b} and R^{3b} are present. As such, the compound has the formula (II) below:

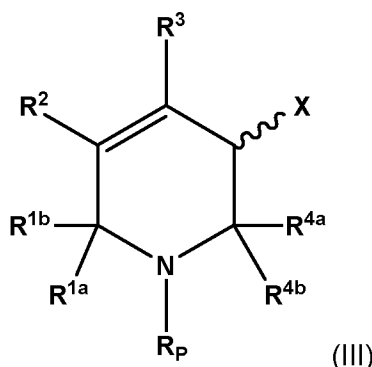


15

Formula (II)

wherein X , R^{1a} , R^{1b} , R^2 , R^{2b} , R^3 , R^{3b} , R^{4a} , R^{4b} and R_P are as defined herein.

[0017] Bond **b** may be a double bond. As such, R^{2b} and R^{3b} will be absent and the compound has the formula (III) below:



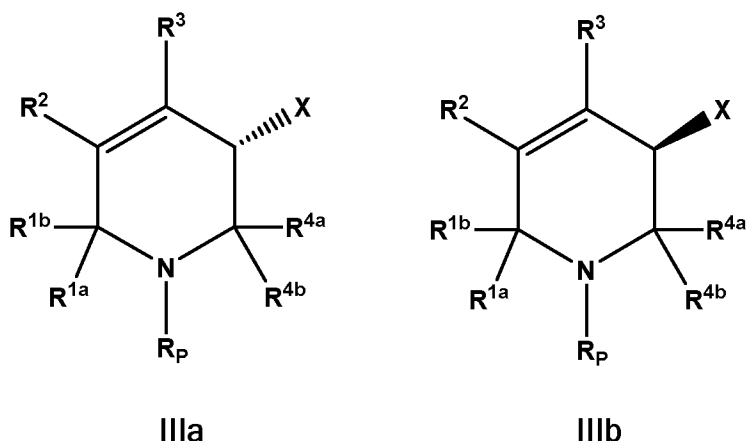
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(III)

wherein X, R^{1a}, R^{1b}, R², R³, R^{4a}, R^{4b} and R_P are as defined herein.

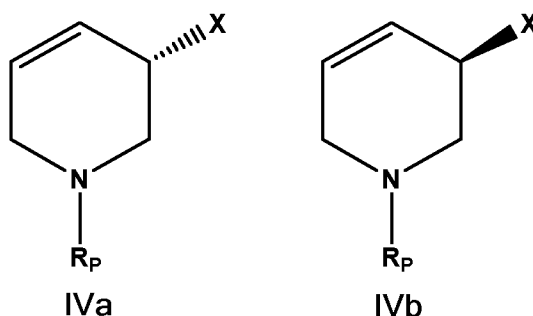
[0018] Preferably, the compound is a compound according to Formula (III) and each of R^{1a}, R^{1b}, R², R³, R^{4a}, R^{4b} are hydrogen.

[0019] The compound may be a compound having the formula (IIIa) or (IIIb), shown below:



wherein each of X, R^{1a}, R^{1b}, R², R³, R^{4a}, R^{4b} and R_P are as defined herein.

[0020] The compound may be a compound having the formula (IIIa) or (IIIb), shown below:

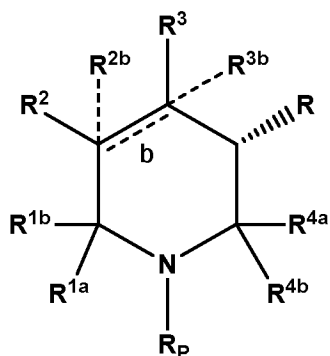


wherein X and R_P are as defined herein.

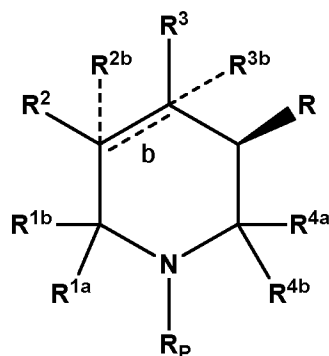
[0021] The compounds according to Formulas (I) to (IVb), defined herein, may have an enantiomeric excess of at least 40%, at least 60%, at least 80%, at least 90%, at least 95%, at least 98% or at least 99%.

[0022] In a second aspect, there is provided the use of a compound according to formulas (I) to (IVb) defined herein, in stereospecific reactions. The use may be in nucleophilic substitution reactions.

[0023] In a third aspect, there is provided a method of producing a compound having the formula (Va) or (Vb):



(Va)



(Vb)

wherein R is a substituent group; and

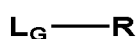
- 5 bond **b**, R^{1a}, R^{1b}, R², R^{2b}, R³, R^{3b}, R^{4a}, R^{4b} and R_P are as defined herein, and
 wherein the compound of formula (Va) or (Vb) has an enantiomeric excess of at least 20%;
 and

- wherein the process comprises reacting a compound according to any one of
 Formulas (I) to (IVb) defined above, with a nucleophilic compound comprising a R group,
 10 such that the X-group in the compound according to any one of Formulas (I) to (IVb)
 defined above is replaced by the R group to form a compound of formula (Va) or (Vb).

- [0024]** A person skilled in the art will readily appreciate that there is a wide range of
 possible nucleophilic compounds comprising R groups that could be used in the reaction
 defined above. For example, the nucleophilic compound comprising the R group may be
 15 selected from organolithium compounds, alkenes, Grignard reagents, alcohols (including
 phenols), carboxylic acids, carbonyls, enols, sulphides, thiols, peroxides, azides, amines,
 nitrites, hydroxylamines, hydrazines, carbazides, phenylhydrazines, semicarbazides, and
 amides.

- [0025]** It will be appreciated that the R group may be any substituent group. There are a
 20 wide range of R groups that it might be desirable to couple to a compound of any one of
 Formulas (I) to (IVb), as evidenced by the structures shown in Figures 1 and 2 herein. The
 present invention is not limited by the nature of the R group in any way. For instance, the
 R group may be selected from the group consisting of alkyl, aryl, arylalkyl, heteroaryl,
 heteroarylalkyl, oxide, carboxylate, amine, amide, cyanide, sulphide, sulfoxide, halogen
 25 (e.g. fluoro), azide or hydroxide.

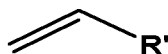
[0026] The nucleophilic compound comprising the R group may be a compound of the
 formula:



wherein L_G is a leaving group (e.g. halo) that is displaced during the reaction with a compound of any one of formulae (I) to (IVb).

[0027] Alternatively, the nucleophilic compound may be an alkene, e.g. a compound with the formula:

5



wherein R' is a remainder of the R substituent group. It will be appreciated that the alkene moiety reacts with the compound of any one of formulae (I) to (IVb) to form a R substituent group of the formula $-CH_2-CH_2-R'$.

10 [0028] In the method of the third aspect, the compound according to Formulas (I) to (IVb) above, may be the racemic form of the compound or may have an enantiomeric excess of either the (R)- or (S)- enantiomer.

[0029] The method of the third aspect may favour the formation of one enantiomer over the other. The method may therefore increase the enantiomeric excess of one of the enantiomers of the starting materials. Thus, the starting material may be enantiomerically
15 enriched by the method of the third aspect of the invention.

[0030] The compound of formula (Va) or (Vb) has an enantiomeric excess of at least 40%, at least 60%, at least 80%, at least 90%, at least 95% or at least 99%.

[0031] The method may further comprise the step of removing the protecting group on the compound according to Formula (Va) or (Vb).

20

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] Embodiments of the invention are further described hereinafter with reference to the accompanying drawings, in which:

Figure 1: Selected piperidine drug molecules with substituents at C3 and/or C5 positions.

25 Figure 2: Selected piperidine drug molecules with substituents at C2 and/or C6 positions.

DETAILED DESCRIPTION

Definitions

[0033] Throughout the description and claims of this specification, the words “comprise”
30 and “contain” and variations of them mean “including but not limited to”, and they are not intended to (and do not) exclude other moieties, additives, components, integers or steps. Throughout the description and claims of this specification, the singular encompasses the

plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

[0034] Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

[0035] The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

[0036] The term "enantiomeric excess" (ee) is well understood by those skilled in the art, and herein refers to the excess of one enantiomer relative to the opposite enantiomer within an enantiomeric mixture. Enantiomeric excess within is typically calculated using equation (1), where R and S refer to the respective mole fractions of the (R)- and (S)-enantiomers such that $R + S = 1$.

$$ee = ((R-S)/(R+S)) \times 100 \quad \text{Equation (1)}$$

[0037] Herein, the term "enantiomerically enriched" as applied to a composition comprising a mixture of enantiomers, means said composition that comprises an excess of one enantiomer. A composition may be considered "enantiomerically enriched" relative to another composition where the enantiomeric excess differs between the two.

[0038] In this specification the term "alkyl" includes both straight and branched chain alkyl groups. References to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched chain alkyl groups such as "isopropyl" are specific for the branched chain version only. For example, "(1-6C)alkyl" includes (1-4C)alkyl, (1-3C)alkyl, propyl, isopropyl and *t*-butyl. A similar convention applies

to other radicals, for example "phenyl(1-6C)alkyl" includes phenyl(1-4C)alkyl, benzyl, 1-phenylethyl and 2-phenylethyl.

[0039] The term "alkenyl" will be understood to include both straight and branched hydrocarbon groups comprising one or more carbon-carbon double bonds. Reference to, for example, "(2-6C)alkenyl" will be understood to refer to alkene groups containing from 3 to 6 carbon atoms and may includes, for example, hexenyl, pentenyl, butenyl, propenyl and ethylenyl.

[0040] The term "alkynyl" will be understood to include both straight and branched hydrocarbon groups comprising one or more carbon-carbon triple bonds. Again, reference to "(2-6C)alkynyl" groups will be understood to refer to alkyne groups containing from 3 to 6 carbon atoms and may includes, for example hexynyl, pentynyl, butynyl, propynyl and acetylenyl.

[0041] The term "(m-nC)" or "(m-nC) group" used alone or as a prefix, refers to any group having m to n carbon atoms.

[0042] An "alkylene," "alkenylene," or "alkynylene" group is an alkyl, alkenyl, or alkynyl group that is positioned between and serves to connect two other chemical groups. Thus, "(1-6C)alkylene" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, for example, methylene, ethylene, propylene, 2-methylpropylene, pentylene, and the like.

[0043] "(3-10C)cycloalkyl" means a hydrocarbon ring containing from 3 to 10 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl.

[0044] "(3-10C)cycloalkenyl" means a hydrocarbon ring containing from 3 to 10 carbon atoms and at least one double bond, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl, such as 3-cyclohexen-1-yl, or cyclooctenyl.

[0045] The term "heterocyclyl", "heterocyclic" or "heterocycle" means a non-aromatic saturated or partially saturated monocyclic, fused, bridged, or spiro bicyclic heterocyclic ring system(s). Monocyclic heterocyclic rings contain from about 3 to 12 (suitably from 3 to 7) ring atoms, with from 1 to 5 (suitably 1, 2 or 3) heteroatoms selected from nitrogen, oxygen or sulfur in the ring. Bicyclic heterocycles contain from 7 to 17 member atoms, suitably 7 to 12 member atoms, in the ring. Bicyclic heterocyclic(s) rings may be fused, spiro, or bridged ring systems. Examples of heterocyclic groups include cyclic ethers such as oxiranyl, oxetanyl, tetrahydrofuranyl, dioxanyl, and substituted cyclic ethers. Heterocycles containing nitrogen include, for example, azetidiny, pyrrolidinyl, piperidinyl,

piperazinyl, tetrahydrotriazinyl, tetrahydropyrazolyl, and the like. Typical sulfur containing heterocycles include tetrahydrothienyl, dihydro-1,3-dithiol, tetrahydro-2*H*-thiopyran, and hexahydrothiepine. Other heterocycles include dihydro-oxathiolyl, tetrahydro-oxazolyl, tetrahydro-oxadiazolyl, tetrahydrodioxazolyl, tetrahydro-oxathiazolyl, hexahydrotriazinyl, tetrahydro-oxazinyl, morpholinyl, thiomorpholinyl, tetrahydropyrimidinyl, dioxolinyl, octahydrobenzofuranyl, octahydrobenzimidazolyl, and octahydrobenzothiazolyl. For heterocycles containing sulfur, the oxidized sulfur heterocycles containing SO or SO₂ groups are also included. Examples include the sulfoxide and sulfone forms of tetrahydrothienyl and thiomorpholinyl such as tetrahydrothiene 1,1-dioxide and thiomorpholinyl 1,1-dioxide. A suitable value for a heterocyclyl group which bears 1 or 2 oxo (=O) or thioxo (=S) substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl. Particular heterocyclyl groups are saturated monocyclic 3 to 7 membered heterocyclyls containing 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulfur, for example azetidiny, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, tetrahydrothienyl, tetrahydrothienyl 1,1-dioxide, thiomorpholinyl, thiomorpholinyl 1,1-dioxide, piperidinyl, homopiperidinyl, piperazinyl or homopiperazinyl. As the skilled person would appreciate, any heterocycle may be linked to another group via any suitable atom, such as via a carbon or nitrogen atom. However, reference herein to piperidino or morpholino refers to a piperidin-1-yl or morpholin-4-yl ring that is linked via the ring nitrogen.

[0046] The term “heteroaryl” or “heteroaromatic” means an aromatic mono-, bi-, or polycyclic ring incorporating one or more (for example 1-4, particularly 1, 2 or 3) heteroatoms selected from nitrogen, oxygen or sulfur. The term heteroaryl includes both monovalent species and divalent species. Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring, for example a bicyclic structure formed from fused five and six membered rings or two fused six membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulfur and oxygen. Typically, the heteroaryl ring will contain up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general, the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

[0047] Examples of heteroaryl include furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, isoindolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzothiazolyl, indazolyl, purinyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalyl, cinnolyl, pteridinyl, naphthyridinyl, carbazolyl, phenazinyl, benzoquinolyl, pyridopyrazinyl, thieno[2,3-*b*]furanyl, 2H-furo[3,2-*b*]-pyranal, 5H-pyrido[2,3-*d*]-o-oxazinyl, 1H-pyrazolo[4,3-*d*]-oxazolyl, 4H-imidazo[4,5-*d*]thiazolyl, pyrazino[2,3-*d*]pyridazinyl, imidazo[2,1-*b*]thiazolyl, imidazo[1,2-*b*][1,2,4]triazinyl. "Heteroaryl" also covers partially aromatic bi- or polycyclic ring systems wherein at least one ring is an aromatic ring and one or more of the other ring(s) is a non-aromatic, saturated or partially saturated ring, provided at least one ring contains one or more heteroatoms selected from nitrogen, oxygen or sulfur. Examples of partially aromatic heteroaryl groups include for example, tetrahydroisoquinolyl, tetrahydroquinolyl, 2-oxo-1,2,3,4-tetrahydroquinolyl, dihydrobenzthienyl, dihydrobenzfuranyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,3]dioxolyl, 2,2-dioxo-1,3-dihydro-2-benzothienyl, 4,5,6,7-tetrahydrobenzofuranyl, indolyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl, 1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazinyl and 3,4-dihydro-2H-pyrido[3,2-*b*][1,4]oxazinyl.

[0048] Examples of five membered heteroaryl groups include but are not limited to pyrrolyl, furanyl, thienyl, imidazolyl, furazanyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl and tetrazolyl groups.

[0049] Examples of six membered heteroaryl groups include but are not limited to pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl and triazinyl.

[0050] The term "aryl" means a cyclic or polycyclic aromatic ring having from 5 to 12 carbon atoms. The term aryl includes both monovalent species and divalent species. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl, anthracenyl and the like. In particular embodiment, an aryl is phenyl.

[0051] The term "halo" refers to any suitable halogen and may be selected from fluoro, chloro, bromo and iodo groups. Suitably, the term halo refers to fluoro, chloro or bromo groups, and most suitably, chloro groups.

[0052] The term "alcohol" means a compound which comprises a hydroxyl group, for example, methanol, phenol, primary alcohols, and substituted or unsubstituted secondary alcohols, tertiary alcohols.

[0053] The term "alcohol" refers to saturated and unsaturated alcohols (e.g. phenols), alcohol having one hydroxyl group per alcohol molecule (mono-alcohol) and alcohol having

a plurality of hydroxyl groups per alcohol molecule (di-alcohol, tri-alcohol, etc.), (iii) primary, secondary, and tertiary alcohol, (iv) alcohol having a terminal hydroxyl group (1-alcohol) and alcohol having a hydroxyl group in a non-terminal position (2-alcohol, 3-alcohol, etc.),

- 5 **[0054]** The term "optionally substituted" refers to either groups, structures, or molecules that are substituted and those that are not substituted. The term "wherein a/any CH, CH₂, CH₃ group or heteroatom (i.e. NH) within a R¹ group is optionally substituted" suitably means that (any) one of the hydrogen radicals of the R¹ group is substituted by a relevant stipulated group.
- 10 **[0055]** The term "leaving group" (LG), as used herein, means a chemical moiety that can be or is displaced by a nucleophile to form a new chemical bond, generally via an S_N2 type displacement mechanism. Thus, leaving group is a term well known in the art and usually used without definition. Reference leaving groups can be found in (a) Thomas H. Lowry and Kathleen Schueller Richardson, *Mechanism and Theory in Organic Chemistry*,
- 15 Harper & Row, New York, 1976, p. 192; and (b) Jerry March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th Ed., John Wiley and Sons, New York, 1992, pp. 352-357.

Synthesis

- 20 **[0056]** In the description of the synthetic methods described herein and in any referenced synthetic methods that are used to prepare the starting materials, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be selected by a person skilled in the art.
- 25 **[0057]** It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reaction conditions utilised.

- [0058]** It will be appreciated that during the synthesis of the compounds of the invention in the processes defined herein, or during the synthesis of certain starting materials, it may
- 30 be desirable to protect certain substituent groups to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed.

- [0059]** For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green
- 35 (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient

method described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with the minimum disturbance of groups elsewhere in the molecule.

- 5 [0060] Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

[0061] By way of example, a suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxy carbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or t-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxy carbonyl group or an aroyl group may be removed by, for example, hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively, an acyl group such as a *tert*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

[0062] A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium, sodium hydroxide or ammonia. Alternatively, an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

[0063] A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a t-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

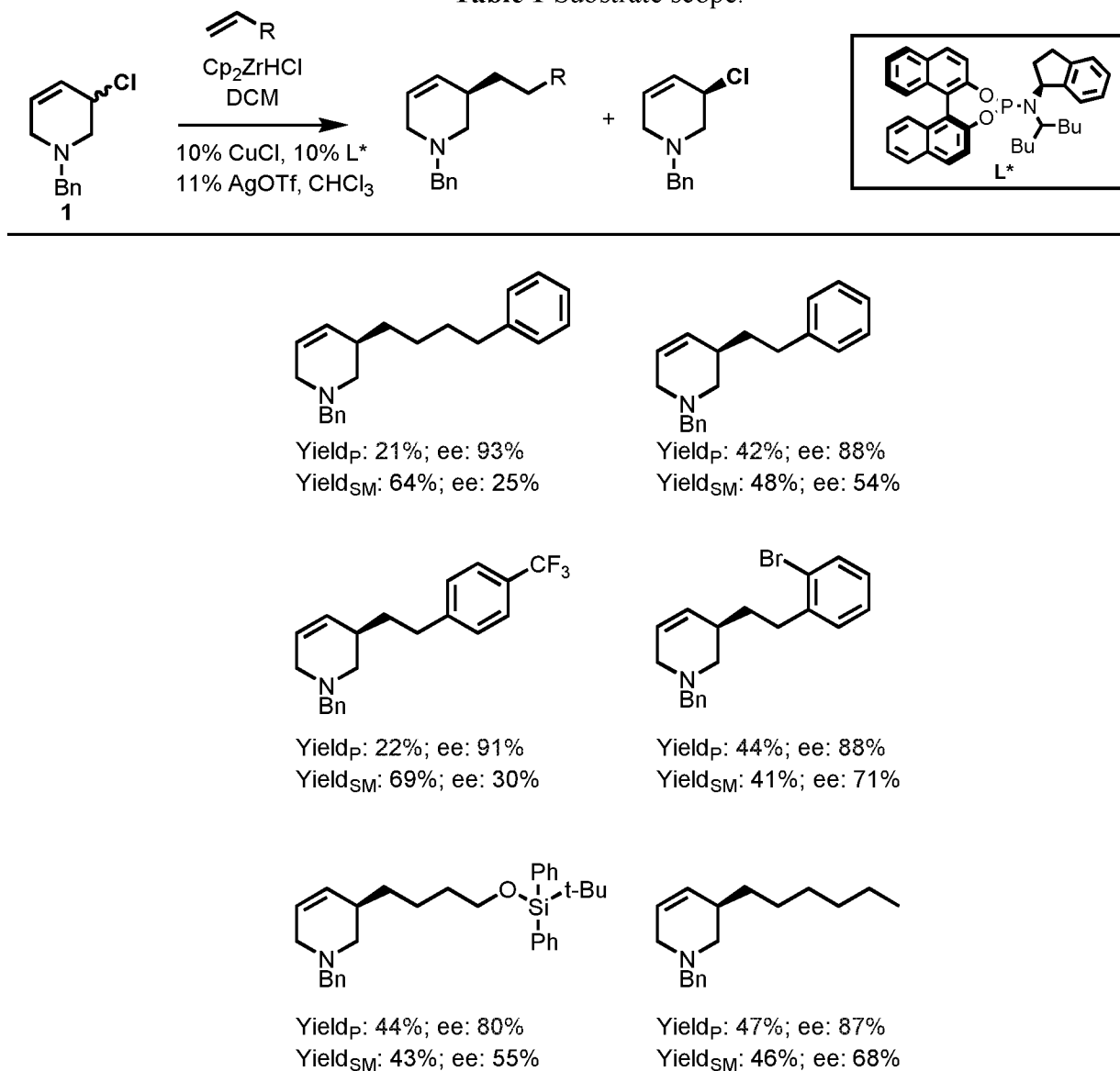
Experimental

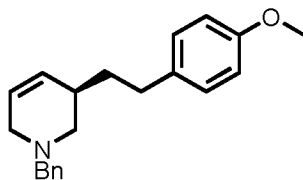
[0064] The present inventors have developed copper catalysed-asymmetric allylic alkylations (AAA's) of *in situ* formed, non-stabilized alkylzirconocene nucleophiles with various cyclic allylic halides and pseudohalides.

- Racemic 3-chloro-1,2,3,6-tetrahydropyridines were subjected to Cu-catalysed AAA reactions and under optimized conditions allyl chloride **1** lead to enantioselective formation of novel 1,2,3,6-tetrahydropyridines (Table 1). More importantly unreacted allyl chloride was recovered with an elevated enantiomeric excess, showing the reaction is a kinetic resolution of racemic substrate (Table 1).

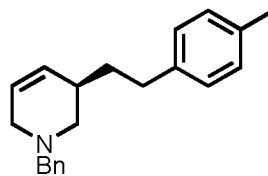
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Table 1 Substrate scope.

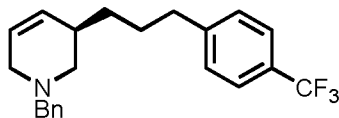




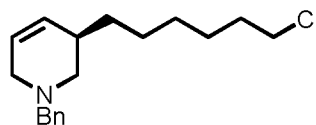
Yield_P: 33%; ee: 93%
Yield_{SM}: 64%; ee: 37%



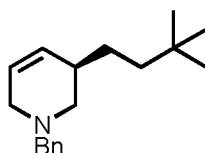
Yield_P: 27%; ee: 93%
Yield_{SM}: 71%; ee: 25%



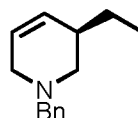
Yield_P: 24%; ee: 83%
Yield_{SM}: 70%; ee: 23%



Yield_P: 37%; ee: 86%
Yield_{SM}: 46%; ee: 43%

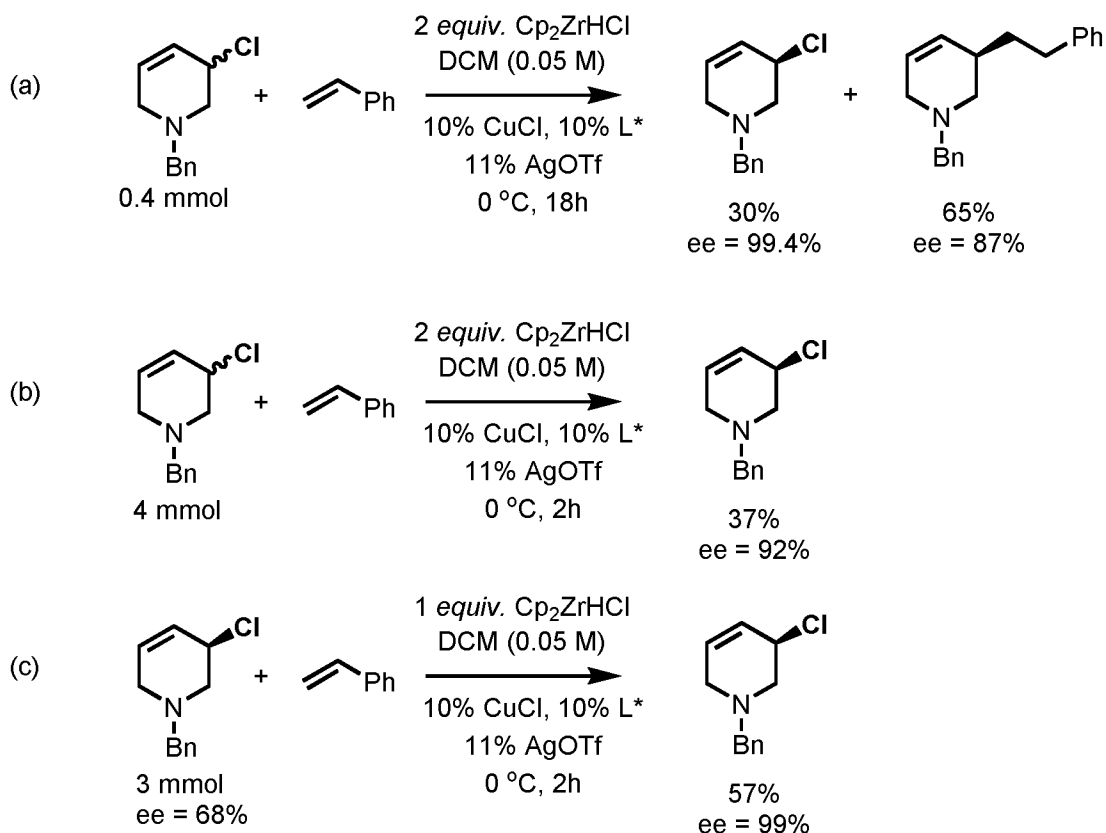


Yield_P: 31%; ee: 88%
Yield_{SM}: 64%; ee: 30%

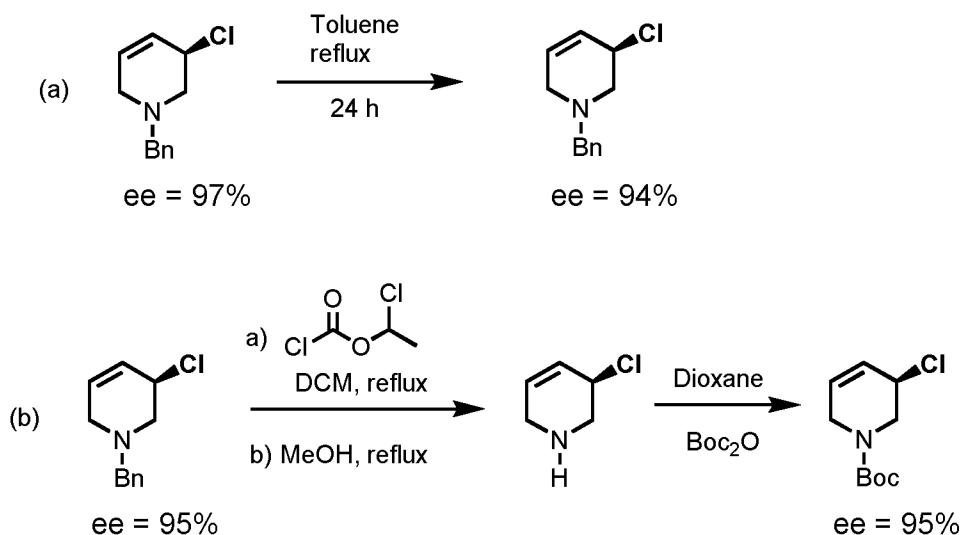


Yield_P: 25%; ee: 90%
Yield_{SM}: 63%; ee: 34%

[0065] Further alteration of reaction conditions allowed the complete resolution of tetrahydropyridine allyl chloride (Scheme 1a). We showed that larger amounts of racemic substrate can be enantiomerically enriched (Scheme 1b) and resolution is successful on recycled substrates using lower equivalences of Schwartz reagent (Scheme 1c).

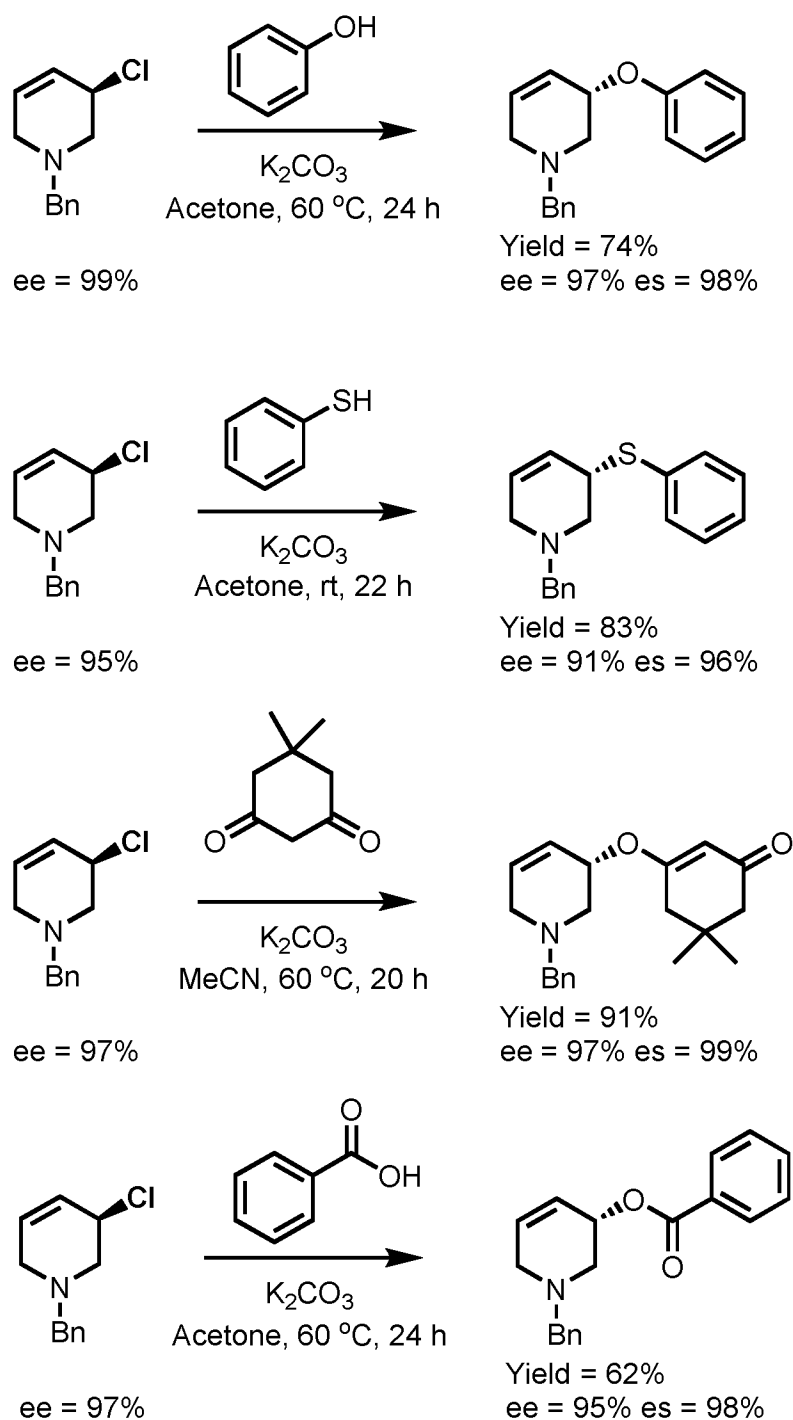
Scheme 1 Kinetic resolution of tetrahydropyridine allyl chloride **1**.

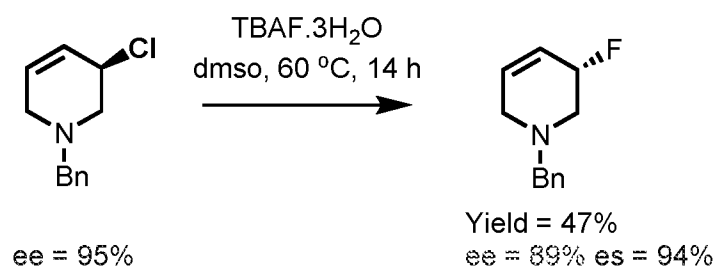
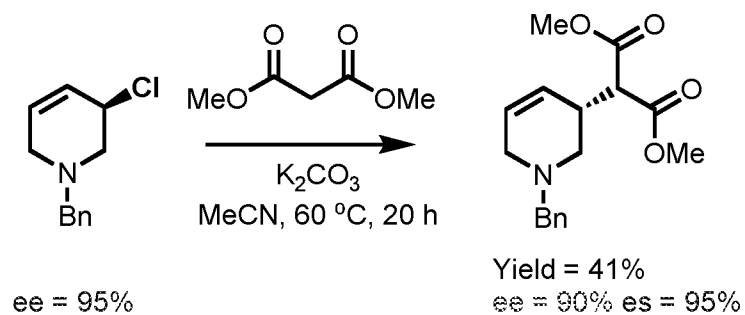
[0066] Enantiopure allyl chloride was proven quite *robust* and *versatile*. The enantiomeric excess was preserved even under harsh reaction conditions (Scheme 2a). Removal of benzyl protecting group did not affect the stereochemical structure allowing, access to various tetrahydropyridine allyl chlorides with different functionalities on the N atom (Scheme 2b).

Scheme 2 Test reactions on enantiomeric allyl chloride.

[0067] Resolved allyl chloride went through simple but practical substitution reactions with phenol, thiophenol, dimedone, benzoic acid, dimethyl malonate and tetrabutylammonium fluoride with high stereospecificity (Scheme 3).

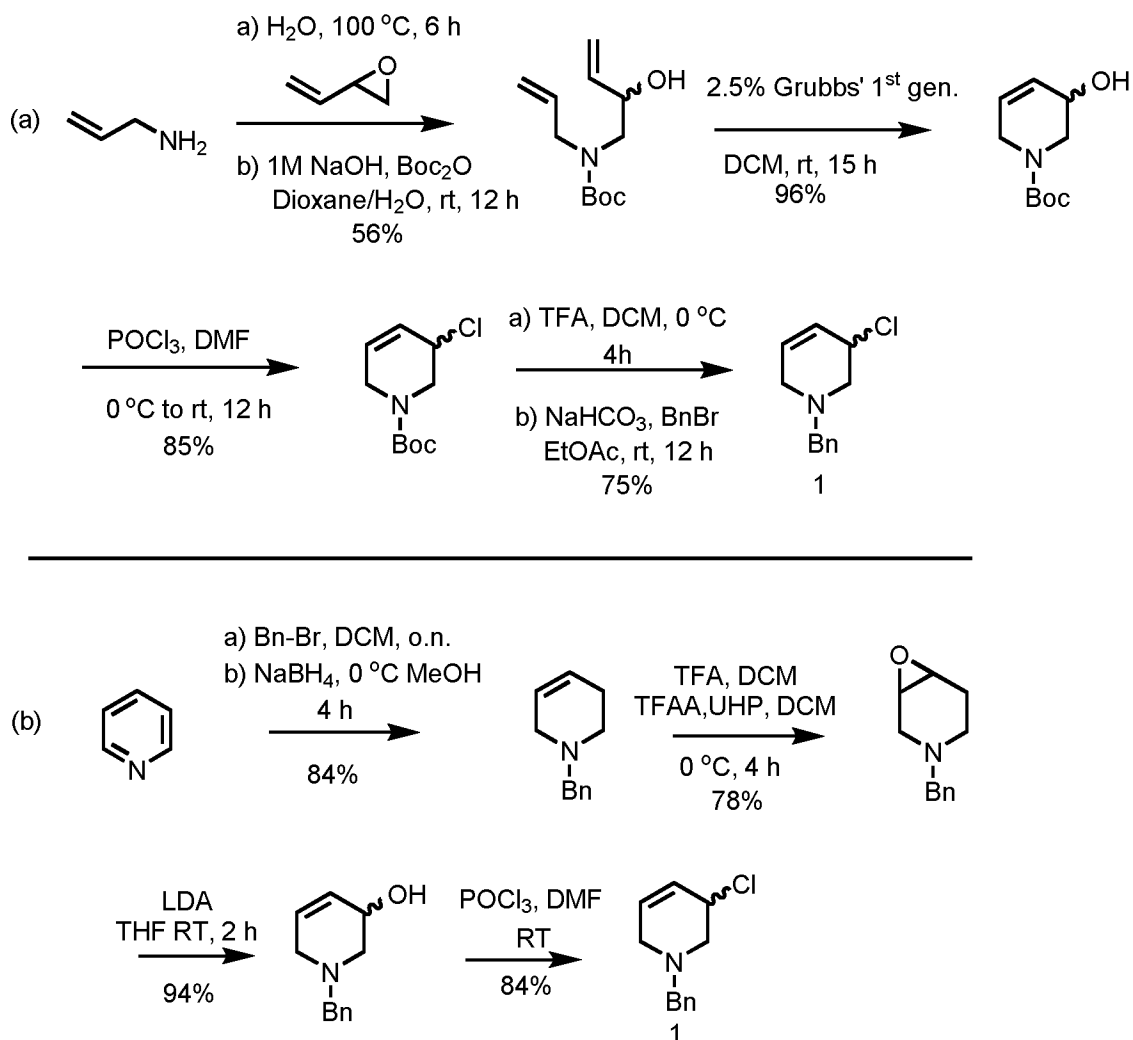
5 **Scheme 3** Stereospecific substitution reactions of enantiomeric tetrahydropyridine allyl chloride.



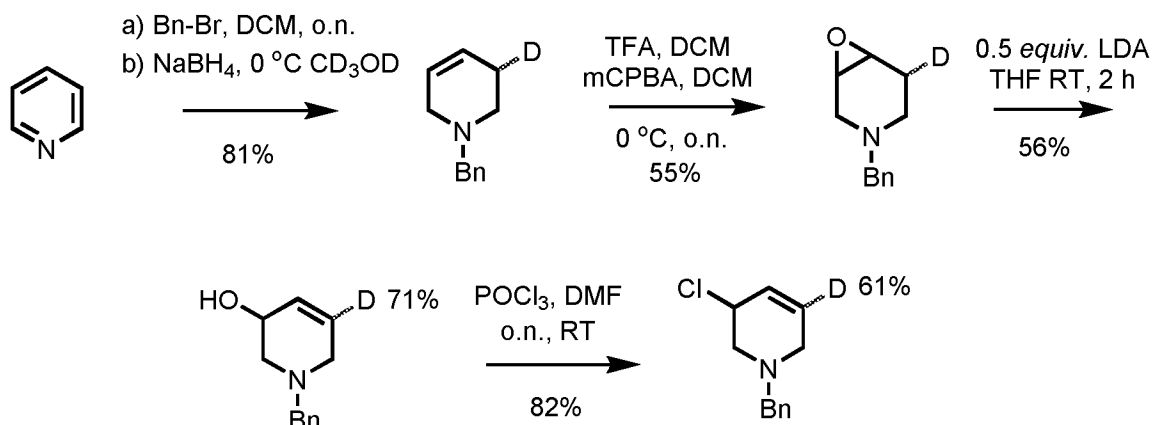


[0068] Racemic 3-chloro-1,2,3,6-tetrahydropyridine **1** was prepared via two alternative synthesis methods (Scheme 4). While first method involved a ring closing metathesis and protecting group exchange (Scheme 4a), second method was more straightforward with

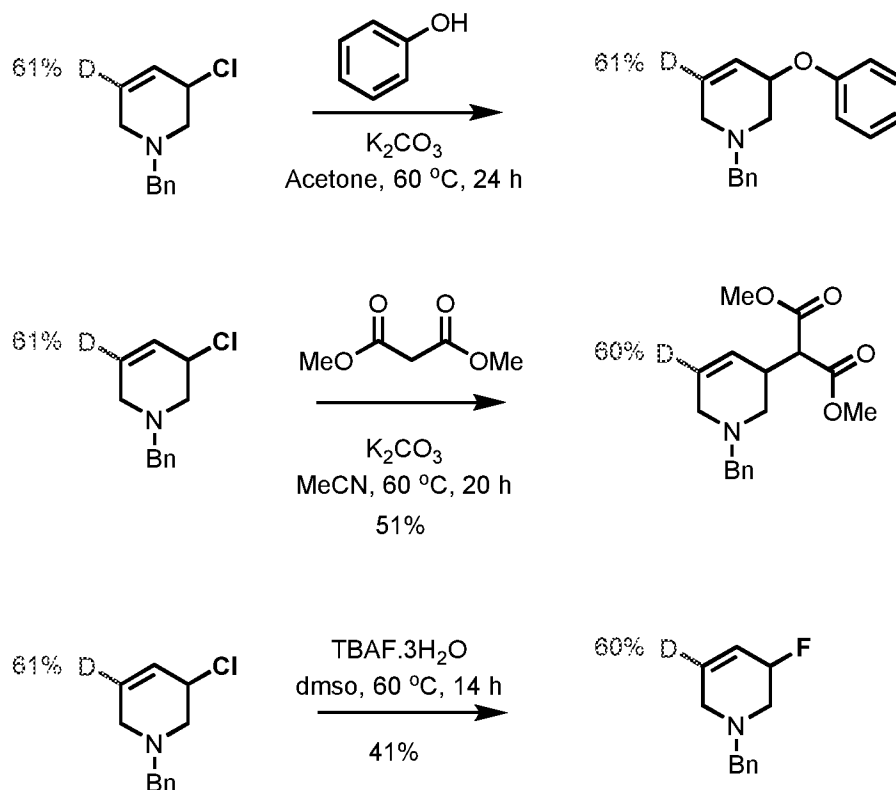
5 key steps of formation and opening of oxa-3-azabicycloheptane (Scheme 4b).⁵

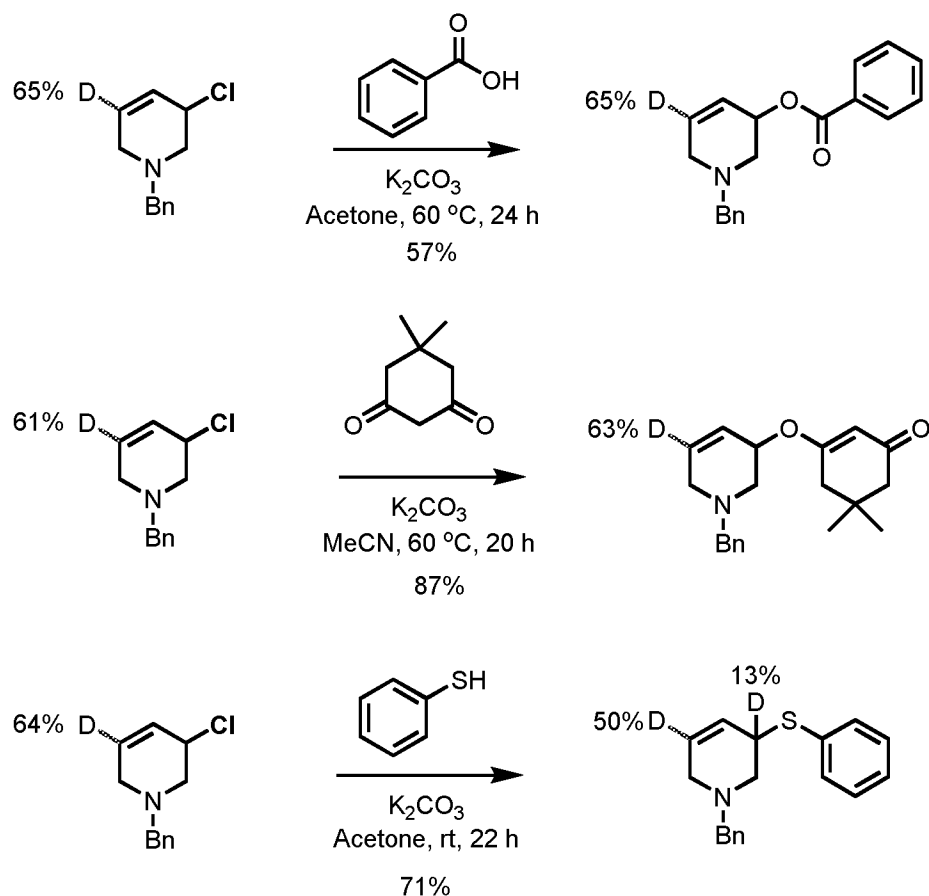
Scheme 4 Preparation of racemic allyl chloride.

- 5 **[0069]** Latter method was utilized to synthesize deuterium labelled 3-chloro-1,2,3,6-tetrahydropyridine (Scheme 5). Reduction of benzylpyridinium bromide in deuterated methanol selectively substituted the deuterium atom on to C3 position and deuterium saturation was preserved during epoxide formation. A kinetic isotope effect was observed in the epoxide opening step leading to 71% deuterium saturation at C5 position. Final
- 10 product was obtained with a reasonable 61% deuterium saturation (Scheme 5).

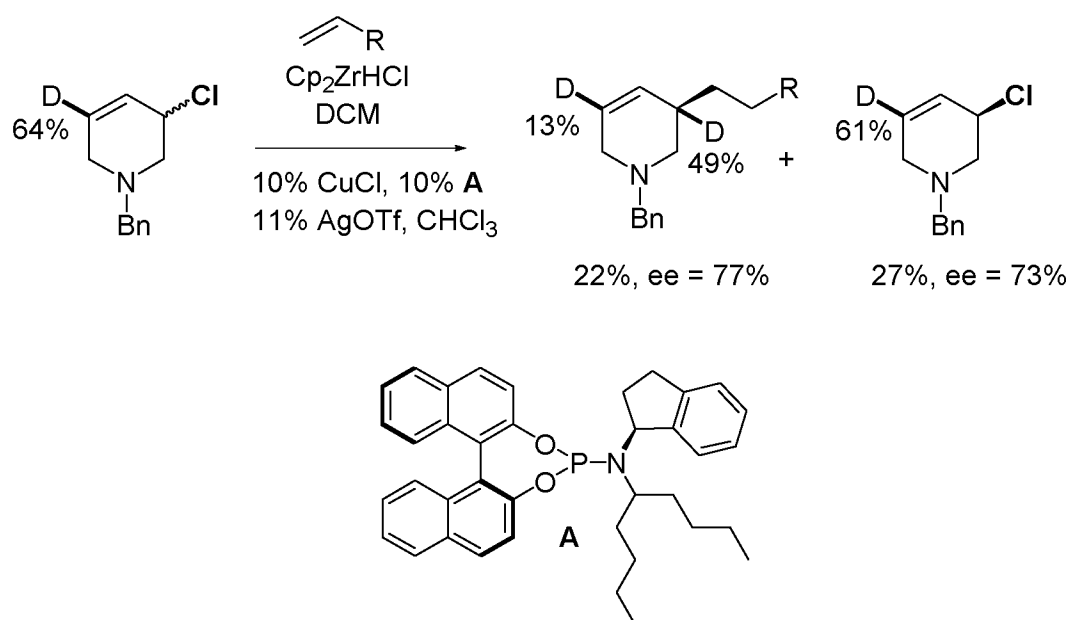
Scheme 5 Deuterium labelling reactions.

[0070] Above mentioned nucleophilic substitution reactions (Scheme 3) were performed with deuterium-labelled allyl chloride in order to determine mechanistic pathway and absolute configurations of compounds in hand, mainly enantiopure allyl chloride (Table 1). Through out the reactions D atom percentage at C5 position was conserved, strongly suggesting an S_N2 pathway (Scheme 6). Copper catalyzed asymmetric allylic alkylation reaction was also performed with D-labelled allyl chloride starting material, showing an S_N2' pathway is mainly preferred.

Scheme 6 Nucleophilic substitution reactions with deuterium labelled allylic chloride.



Scheme 7 Cu-catalyzed asymmetric allylic alkylation with D-labelled allyl chloride.



5 References:

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5 Thapa, B.; Tran, F.; Crook, R. *J. Catal.* **2018**, *360*, 97. (c) Kubota, K.; Watanabe, Y.;
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Org. Process. Res. Dev. **2014**, *18*, 1097. (e) Long, H.; Wang, G.; Lu, R.; Xu, M.; Zhang, K.;
Qi, S.; He, Y.; Bu, Y.; Liu, L. *Org. Lett.* **2017**, *19*, 4146.
5. Grishina, G. V.; Borisenko, A. A.; Veselov, I. S.; Petrenko, A. M. *Russ. J. Org.*
10 *Chem.* **2005**, *41*, 272.

Experimental Details and Spectral Data

General Information:

[0071] Procedures using oxygen/moisture-sensitive materials were performed with
15 anhydrous solvents under an atmosphere of anhydrous argon in flame-dried flasks, using
standard Schlenk techniques. Analytical thin-layer chromatography was performed on
precoated glass-backed plates (Silica Gel 60 F254; Merck), and visualized using a
combination of UV light (254 nm) and aqueous basic potassium permanganate (KMnO₄)
stain and developed upon heating. Flash column chromatography was carried out using
20 Apollo Scientific silica gel 60 (0.040 – 0.063 mm), Merck 60 Å silica gel, VWR (40-63 µm)
silica gel and Sigma Aldrich silica gel. Pressure was applied at the column head via a flow
of nitrogen with the solvent system used in parentheses.

[0072] Reactions at 0 °C were performed using an ice-water bath, covered with cotton
wool and aluminum foil if overnight stirring is needed. Other temperatures were obtained
25 using a Julabo FT902 immersion cooler or the heating plate of the stirrer.

[0073] NMR spectra were recorded at room temperature on Bruker AVIII HD 400 or AVIII
HD 500 spectrometers and calibrated to the solvent signal (CDCl₃ δ = 7.26 ppm for ¹H
NMR, δ = 77.0 ppm for ¹³C NMR, C₆D₆ δ = 7.16 ppm for ¹H NMR, δ = 128.0 ppm for ¹³C
NMR). Chemical shifts are reported in ppm from the residual solvent peak. Chemical shifts
30 (δ) are given in ppm and coupling constants (J) are quoted in hertz (Hz). Resonances are
described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or b (broadened).

[0074] Chiral HPLC separations were achieved using an Agilent 1230 Infinity series
normal phase HPLC unit and HP Chemstation software. Chiralpak® columns (250 × 4.6
mm), fitted with matching Chiralpak® Guard Cartridges (10 × 4 mm), were used as

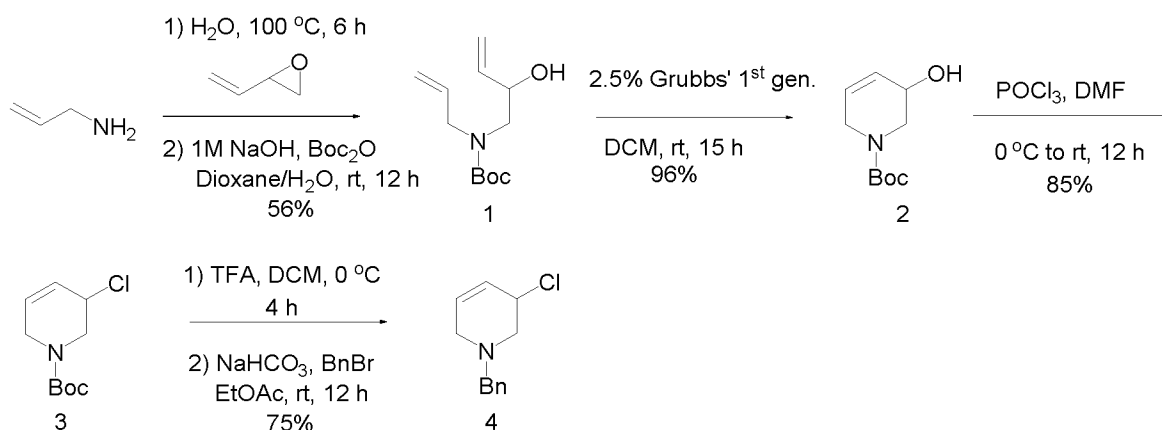
specified in the text. Solvents used were of HPLC grade (Fisher Scientific, Sigma Aldrich or Honeywell); all eluent systems were isocratic. Chiral SFC (supercritical fluid chromatography) separations were conducted on a Waters Acquity UPC2 system using Waters Empower software. Chiralpak® columns (150 × 3 mm, particle size 3 µm) were used as specified in the text. Solvents used were of HPLC grade (Fisher Scientific, Sigma Aldrich or Honeywell).

[0075] Low-resolution mass spectra were recorded using a Walters LCT premier XE. High resolution mass spectra (EI and ESI) were recorded using a Bruker MicroTOF spectrometer by the internal service at the University of Oxford. Infrared measurements (neat, thin film) were carried out using a Bruker Tensor 27 FT-IR with internal calibration in the range 600-4000 cm⁻¹. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 25°C in a 10 cm cell in the stated solvent; [α]_D values are given in 10⁻¹ deg.cm² g⁻¹ (concentration c given as g/100 mL).

[0076] Dry THF, CHCl₃, DMF, 1,4-dioxane, toluene, MTBE and CH₂Cl₂ were collected fresh from an mBraun SPS-5 solvent purification system having been passed through anhydrous alumina columns. All other dry solvents used were dried over 3 Å or 4 Å molecular sieves and stored under argon. All other solvents were used as purchased from Sigma Aldrich, Honeywell or Fisher Scientific. Unless stated otherwise, commercially available reagents were purchased from Sigma-Aldrich, Fisher Scientific, Apollo Scientific, Acros Organics, Strem Chemicals, Alfa Aesar or TCI UK and were used without purification. Petroleum ether refers to light petroleum boiling in the range 40-60 °C. Deuterated solvents were purchased from Sigma-Aldrich. Schwartz reagent was prepared according to the literature¹ from Cp₂ZrCl₂ purchased from Acros or Strem Chemicals. Phosphoramidite ligands were prepared according to literature.²

25 **Synthesis of 1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine (4):**

Method A:



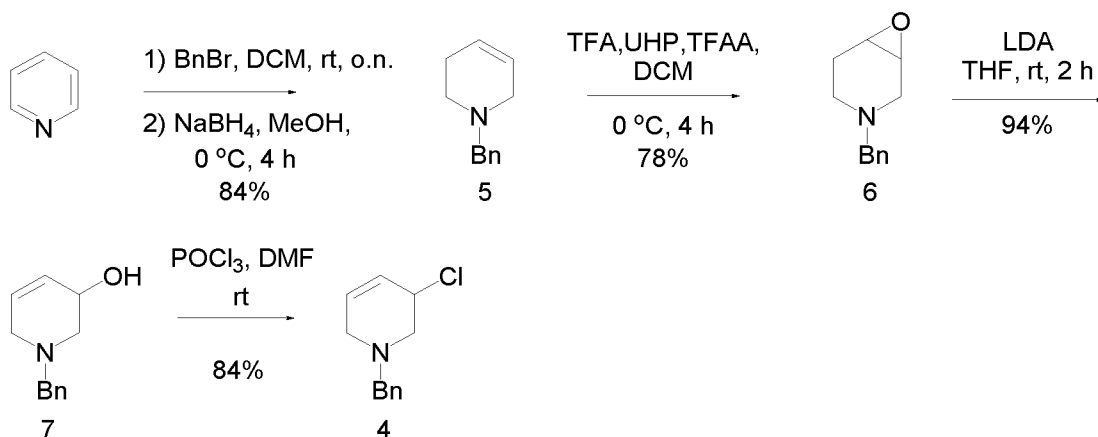
***N*-tert-Butoxycarbonyl-5-chloro-3-piperidene (3):**

A solution of *N*-tert-butoxycarbonyl-5-hydroxy-3-piperidene (**2**) prepared according to literature,³ (8.1 g, 41 mmol) in DMF (100 mL) was cooled down to 0 °C and under argon atmosphere POCl₃ (8.8 mL, 94 mmol) was added dropwise. The reaction mixture was left gradually warming up to room temperature and was stirred overnight. H₂O was carefully added at 0 °C. The reaction solution was extracted with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄, filtered, concentrated under vacuum and purified by flash column chromatography on silica gel (pentane/EtOAc (10/1 to 9/1)) to give *N*-tert-butoxycarbonyl-5-chloro-3-piperidene (**3**) in 85% yield (7.6 g, 35 mmol) as a yellow oil. ¹H NMR (400 MHz, CDCl₃, ppm) δ: 1.48 (s, 9H), 3.55-4.15 (rotameric m, 4H), 4.51 (s, 1H), 5.80-5.92 (m, 2H). Spectral data is in agreement with literature.⁴

1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine (4):

In a flame dried flask *N*-tert-butoxycarbonyl-5-chloro-3-piperidene (**3**) (3.5 g, 16 mmol) was dissolved in DCM (120 ml) and cooled to 0 °C. Trifluoroacetic acid (12 ml, 158 mmol) was added dropwise. Reaction was warmed to room temperature and monitored by TLC. Upon completion solvent was removed under vacuum. In a dried flask benzyl bromide (2.0 ml, 17 mmol) and EtOAc (25 ml) were mixed and cooled 0 °C. Crude material was dissolved in EtOAc (10 ml) and added to benzyl bromide solution dropwise. NaHCO₃ (20 g, 238 mmol) was added portionwise at 0 °C. The suspension was warmed up to room temperature and stirred overnight. The reaction was diluted with EtOAc and first washed with H₂O (x2) then with brine. Aqueous layers were back washed with EtOAc (x2). The combined organic phases were dried over MgSO₄, filtered, concentrated under vacuum and purified by flash column chromatography on silica gel (hexanes/EtOAc (9/1)) to give 1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine (**4**) in 75% yield (2.5 g, 12 mmol) as a colorless oil. *Note:* A decrease in yield was observed for trials in larger scale.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 2.73 (dd, *J* = 12.0, 6.0 Hz, 1H), 2.96 (ddd, *J* = 12.0, 4.6, 0.8 Hz, 1H), 2.99-3.12 (m, 2H), 3.62 (d, *J* = 13.2 Hz, 1H), 3.70 (d, *J* = 13.2 Hz, 1H), 4.57-4.61 (m, 1H), 5.82-5.89 (m, 2H), 7.25-7.29 (m, 1H), 7.31-7.38 (m, 4H); ¹³C NMR (101 MHz, CDCl₃, ppm) δ: 52.0, 53.7, 57.2, 61.8, 126.8, 127.3, 128.3, 128.98, 129.04, 137.5; ¹H NMR (400 MHz, C₆D₆, ppm) δ: 2.53-2.58 (m, 3H), 2.67 (dd, *J* = 12.0, 4.6 Hz, 1H), 3.21 (d, *J* = 13.2 Hz, 1H), 3.28 (d, *J* = 13.2 Hz, 1H), 4.30-4.35 (m, 1H), 5.35 (dtd, *J* = 9.8, 3.2, 1.2 Hz, 1H), 5.65 (bddd, *J* = 11.0, 5.2, 2.4 Hz, 1H), 7.08-7.12 (m, 1H), 7.16-7.19 (m, 2H), 7.26-7.28 (m, 2H); IR (ATR) ν (cm⁻¹) neat: 3030, 2802, 1493, 1453, 1144, 1071, 1026, 984, 911, 792, 731, 697; HRMS (ESI) *m/z* calcd for C₁₂H₁₅NCl⁺ [M+H]⁺ 208.08875, found 208.08884.

Method B:

5

1-benzyl-1,2,3,6-tetrahydropyridine (5):

In a dried 100 ml-round-bottom flask pyridine (4 ml, 48 mmol) and DCM (12 ml) were mixed and cooled to 0 °C. Benzyl bromide (5.7 ml, 48 mmol) was added dropwise. The reaction solution was stirred overnight gradually warming up to room temperature. Solvent was removed on rotary evaporator. Et₂O (10 ml) was added and evaporated off under vacuum affording pyridinium salt as off-white solid. Product was used in the next step without further purification.

Benzylpyridinium bromide was dissolved in MeOH (240 ml) and cooled to 0 °C. NaBH₄ (2.2 g, 56 mmol) was added portionwise and the reaction solution was stirred at 0 °C for 4 hours. Reaction was quenched with H₂O and concentrated under vacuum. EtOAc (100 ml) was added and the resultant solution was washed with brine, dried over MgSO₄, filtered, concentrated under vacuum and purified by flash column chromatography on silica gel (hexanes/EtOAc/Et₃N (4/1/0.05)) to give 1-benzyl-1,2,3,6-tetrahydropyridine (5) in 84% yield (7.0 g, 40 mmol) as a viscous yellow oil. ¹H NMR (400 MHz, CDCl₃, ppm) δ: 2.14-2.18 (m, 2H), 2.56 (t, *J* = 5.6 Hz, 2H), 2.96-2.99 (m, 2H), 3.58 (s, 2H), 5.64-5.69 (m, 1H), 5.73-5.77 (m, 1H), 7.23-7.27 (m, 1H), 7.29-7.37 (m, 4H). Spectral data is in agreement with literature.⁵

1-benzyl-3,4-epoxypiperidine (6):

In a dried flask urea hydrogen peroxide (UHP) (3.6 g, 38 mmol) and DCM (33 ml) were mixed and cooled 0 °C. A solution of trifluoroacetic anhydride (TFAA) (6.6 ml, 38 mmol) in DCM (20 ml) was added dropwise. The resultant suspension was stirred for 1 hour at 0 °C. Meanwhile TFA (2.8 ml, 35 mmol) was added dropwise into a solution of 1-benzyl-1,2,3,6-tetrahydropyridine (5) (4.7 g, 27 mmol) in DCM (20 ml) at 0 °C and stirred for 1 hour. Cold TFA/piperidine solution was added into UHP/TFAA solution dropwise and stirred for 4

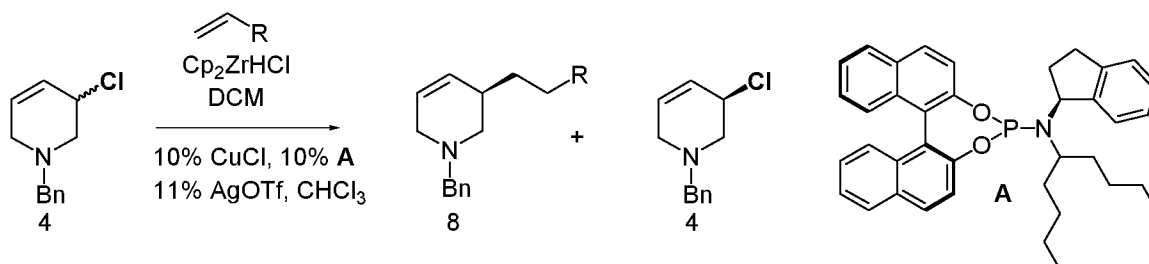
hours at 0 °C. After completion H₂O (50 ml) was added and biphasic solution was stirred for 15 minutes followed by addition of saturated Na₂SO₃ solution. Organic layer was separated and aqueous layer was neutralized by K₂CO₃ addition and washed with DCM (x2). The combined organic phases were washed with saturated NaHCO₃ (x2), dried over MgSO₄, filtered, concentrated under vacuum and purified by flash column chromatography on silica gel (hexanes/acetone (7/1)) to give 1-benzyl-3,4-epoxypiperidine (**6**) in 78% yield (4.0 g, 19 mmol) as a colorless oil. ¹H NMR (400 MHz, CDCl₃, ppm) δ: 1.94-2.08 (m, 2H), 2.20 (ddd, *J* = 11.4, 9.2, 4.2 Hz, 1H), 2.30-2.36 (m, 1H), 2.68 (d, *J* = 13.2 Hz, 1H), 3.03 (ddd, *J* = 13.6, 4.0, 1.2 Hz, 1H), 3.21-3.25 (m, 2H), 3.46 (s, 2H), 7.23-7.27 (m, 1H), 7.28-7.33 (m, 4H). Spectral data is in agreement with literature.⁶

1-benzyl-1,2,3,6-tetrahydropyridin-3-ol (7):

In a flame dried 250 ml-round-bottom flask THF (45 ml) and diisopropyl amine (2 ml, 14 mmol) were added and cooled 0 °C. 2.5 M n-butyllithium solution (5.7 ml, 14 mmol) was added dropwise and the resultant solution was stirred at 0 °C for 20-30 minutes. A solution of 1-benzyl-3,4-epoxypiperidine (**6**) (1.7 g, 9 mmol) in THF (20 ml) was added dropwise into the formed LDA solution, warmed up to room temperature and stirred for 2 hours. Reaction was quenched by addition of saturated NH₄Cl solution (40 ml) and extracted with DCM. The combined organic phases were washed with brine, dried over MgSO₄, filtered, concentrated under vacuum and purified by flash column chromatography on silica gel (hexanes/acetone (5/1)) to give 1-benzyl-1,2,3,6-tetrahydropyridin-3-ol (**7**) in 94% yield (1.6 g, 8.5 mmol) as a viscous yellow oil. ¹H NMR (400 MHz, CDCl₃, ppm) δ: 2.21 (bs, 1H (OH)), 2.51 (dd, *J* = 11.4, 3.2 Hz, 1H), 2.74-2.81 (m, 2H), 3.13 (dd, *J* = 17.0, 3.2 Hz, 1H), 3.61 (s, 2H), 4.05 (bd, *J* = 4.8 Hz, 1H), 5.82 (ddd, *J* = 10.0, 4.0, 2.4 Hz, 1H), 5.89-5.93 (m, 1H), 7.23-7.28 (m, 1H), 7.29-7.34 (m, 4H). Spectral data is in agreement with literature.⁶

1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine (4):

A solution of 1-benzyl-1,2,3,6-tetrahydropyridin-3-ol (**7**) (2.8 g, 14.7 mmol) in DMF (60 mL) was cooled down to 0 °C and under argon atmosphere POCl₃ (2.8 mL, 32.5 mmol) was added dropwise. The reaction mixture was left gradually warming up to room temperature and was stirred overnight. H₂O was carefully added at 0 °C. The reaction solution was extracted with EtOAc. Aqueous layer was neutralized by K₂CO₃ and washed with EtOAc (x3). The combined organic phases were washed with brine (x2), dried over MgSO₄, filtered, concentrated under vacuum and purified by flash column chromatography on silica gel (hexanes or pentane/EtOAc (9/1)) to give 1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine (**4**) in 84% yield (2.6 g, 12.5 mmol) as a colorless oil.

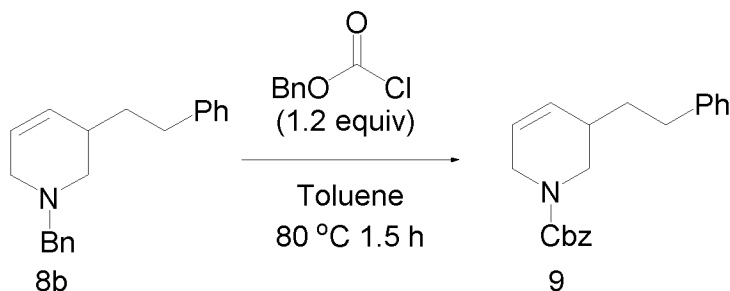
General Procedure 1: Cu-catalysed asymmetric allylic alkylations

- 5 A round-bottom flask with a stirbar was flame dried under vacuum and re-filled with Ar upon cooling. The flask was charged with CuCl (4 mg, 0.04 mmol) and ligand A (23 mg, 0.04 mmol), flushed with argon, sealed with septum and wrapped with aluminum foil. CHCl₃ (2 ml, freshly collected from SPS) was added and the resultant colorless solution was stirred at room temperature for 1 hour. Meanwhile a separate round-bottom flask with
- 10 a stirbar was flame dried under vacuum and re-filled with Ar upon cooling. The flask was charged with Cp₂ZrHCl (206 mg, 0.8 mmol), flushed with argon, sealed with septum and wrapped with aluminum foil. DCM (0.4 ml) and then corresponding alkene (1 mmol) were added and the resultant suspension was stirred at room temperature until the mixture became completely clear (times for hydrozirconation vary with different alkene derivatives).
- 15 After 1 hour fine crystalline Ag(OTf) (11.3 mg, 0.044 mmol) was quickly added to copper catalyst solution and stirred for 15 minutes until all the AgCl precipitated out. Suspension was filtered into alkylzirconocene solution using a syringe filter and the resultant black solution was cooled 0 °C. After 5 minutes neat 1-benzyl-3 chloro-1,2,3,6-tetrahydropyridine (**4**) (83 mg, 0.4 mmol) was added with a syringe at once. The reaction was stopped at the
- 20 specified time (predetermined via NMR screening experiments) by pouring into Et₂O (10 ml) in a separatory funnel. Remaining material in the flask was rinsed into Et₂O solution with EtOAc (2ml x2) and the resultant suspension was washed with saturated NaHCO₃ solution (5-7 ml x3). Aqueous phases were back washed with EtOAc (5-7 ml x2). The combined organic layers were dried over MgSO₄, filtered, concentrated under vacuum and
- 25 purified by flash column chromatography on silica gel. Yields in parenthesis were calculated with respect to consumed starting material. Enantiomeric excess of recovered (R)-1-benzyl-3 chloro-1,2,3,6-tetrahydropyridine (**4R**) were determined by HPLC [Chiralpak® ID; flow: 1.0 mL/min; hexane:IPA 99.3:0.7; λ = 210 nm]. Absolute stereochemistry of products were assigned according to literature.^{4,7}
- 30 *Note:* The heterogeneity of the solution was found to influence reaction results (rate, yield and ee). Ideally, Cu-catalysed reactions should be conducted in a round-bottom flask with an egg-shaped stirbar, magnetically stirring at a rate of 350 rpm. Brand new septa were used to seal reaction flasks to prevent solvent evaporation.

General Procedure 2: Preparation of Racemic Products

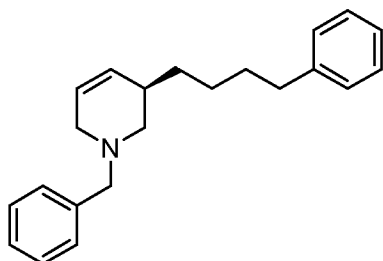
Racemic products were synthesized by *General Procedure 1* using racemic (3,5-dioxo-4-phosphacyclohepta[2,1-a:3,4-a']dinaphthalen-4-yl)dimethylamine (MonoPhos®). Reactions were stirred at room temperature overnight.

5 **General Procedure 3: Synthesis of Tetrahydropyridine Cbz-Carbamates for HPLC Analysis**



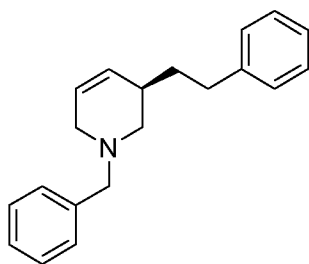
Literature procedure was followed.⁸ Representative procedure; in a vial charged with a stirbar was added 1-benzyl-3-phenethyl-1,2,3,6-tetrahydropyridine (**8b**) (44 mg, 0.16 mmol), followed by addition of 0.5 M benzyl chloroformate solution in toluene (0.4 ml). Vial was flushed with Ar, sealed with a cap, heated to 80 °C and stirred at this temperature for 1.5 hours. The reaction solution was filtered through silica gel with 9/1 heaxane/EtOAc mixture to remove nonpolar impurities and unreacted benzyl chloroformate. Benzyl 3-phenethyl-3,6-dihydropyridine-1(2*H*)-carboxylate (**9**) was obtained in 86% yield (42 mg, 0.14 mmol) as a colorless oil. ¹H NMR (400 MHz, CDCl₃, ppm) δ: 1.65-1.67 (m, 2H), 2.22 and 2.29 (rotameric bs), 2.60-2.72 (m, 2H), 3.26 and 3.36 (rotameric dd, *J* = 12.0, 6.6 and 4.8 Hz, 1H), 3.66 and 3.80 (rotameric bd, *J* = 10.8 and 9.6 Hz, 1H), 3.89-4.03 (m, 2H), 5.14-5.21 (rotameric m, 2H), 5.63-5.71 (m, 1H), 5.80 (bd, *J* = 8.8 Hz, 1H), 7.10-7.21 (m, 3H), 7.26-7.37 (m, 7H); ¹³C NMR (101 MHz, CDCl₃, ppm) δ: 33.1, 34.3 and 34.6 (rotameric), 34.7 and 34.9 (rotameric), 43.5 and 43.7 (rotameric), 45.19 and 45.27 (rotameric), 67.1, 123.5 and 124.1 (rotameric), 125.8, 127.9, 128.0, 128.39, 128.40, 128.5, 129.7 and 130.1 (rotameric), 136.9, 142.0 (m, rotameric), 155.5 and 155.7 (rotameric); IR (ν_{max}/cm⁻¹): 695, 732, 1112, 1231, 1426, 1495, 1697, 2855, 2922, 3029; HRMS (ESI) *m/z* calcd for C₂₁H₂₃O₂NNa⁺ [*M*+Na]⁺ 344.16210, found 344.16202.

25 **(*R*)-1-benzyl-3-(4-phenylbutyl)-1,2,3,6-tetrahydropyridine (8a):**



According to *General Procedure 1*; the reaction proceed for 2.5 hours at 0 °C. Flash column chromatography on silica gel (hexanes/EtOAc (15/1) + 0.5 % Et₃N) gave **4** in 64% yield (53 mg, 0.26 mmol, ee = 25%) and **8a** in 21% (58%) yield (26 mg, 0.08 mmol) as a yellow oil. Enantiomeric excess of 93% was determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; hexane:IPA 99:1; λ = 210 nm; major enantiomer t_R = 11.9 min; minor enantiomer t_R = 18.6 min]; [D]²⁵₅₈₉ = -30.5 (c 0.40 CHCl₃) for 93% ee; ¹H NMR (400 MHz, CDCl₃, ppm) δ: 1.27-1.41 (m, 4H), 1.56-1.63 (m, 2H), 2.08 (dd, J = 11.2, 7.6 Hz, 1H), 2.27 (bs, 1H), 2.59 (dd, J = 8.8, 6.8 Hz, 2H), 2.72 (dd, J = 11.2, 5.0 Hz, 1H), 2.79-2.87 (m, 1H), 2.99-3.06 (m, 1H), 3.54 (d, J = 13.2 Hz, 1H), 3.60 (d, J = 13.2 Hz, 1H), 5.62-5.69 (m, 2H), 6.96-7.19 (m, 3H), 7.23-7.26 (m, 7H); ¹³C NMR (101 MHz, CDCl₃, ppm) δ: 26.6, 31.7, 33.9, 35.89, 36.04, 53.1, 55.6, 62.8, 124.8, 125.6, 126.9, 128.2, 128.4, 129.0, 130.1, 138.5, 142.7; IR (ν_{max}/cm⁻¹): 695, 729, 908, 1026, 1133, 1360, 1454, 1494, 2855, 2926, 3026; HRMS (ESI) m/z calcd for C₂₂H₂₈N⁺ [M+H]⁺ 306.22163, found 306.22150.

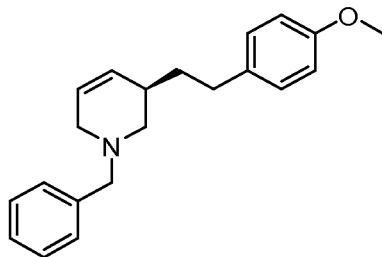
(R)-1-benzyl-3-phenethyl-1,2,3,6-tetrahydropyridine (8b):



According to *General Procedure 1*; the reaction proceed for 4 hours at 0 °C. Flash column chromatography on silica gel (hexanes/EtOAc (15/1) + 0.5 % Et₃N) gave **4** in 48% yield (40 mg, 0.19 mmol, ee = 54%) and **8b** in 42% (81%) yield (47 mg, 0.17 mmol) as a yellow oil. Enantiomeric excess (for corresponding Cbz carbamate) of 88% was determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; hexane:IPA 97.5:2.5; λ = 210 nm; major enantiomer t_R = 10.7 min; minor enantiomer t_R = 12.4 min]; [D]²⁵₅₈₉ = -58.8 (c 0.40 CHCl₃) for 88% ee; [D]²⁵₅₈₉ = -49.7 (c 0.50 CHCl₃) for 88% ee for Cbz carbamate; ¹H NMR (400 MHz, CDCl₃, ppm) δ: 1.59-1.72 (m, 2H), 2.18 (dd, J = 11.2, 7.2 Hz, 1H), 2.30-2.36 (m, 1H), 2.53-2.65 (m, 2H), 2.74 (dd, J = 11.2, 5.0 Hz, 1H), 2.87-2.91 (m, 1H), 3.04 (bd, J = 16.4 Hz, 1H), 3.54 (d, J = 13.2 Hz, 1H), 3.61 (d, J = 13.2 Hz, 1H), 5.67-5.73 (m, 2H), 7.12-7.20 (m, 3H), 7.23-7.28 (m, 3H), 7.30-7.37 (m, 4H); ¹H NMR (400 MHz, C₆D₆, ppm) δ: 1.55-1.66 (m, 2H), 2.17 (dd, J = 10.4, 6.4 Hz, 1H), 2.19-2.26 (m, 1H), 2.42 (d, J = 8.0 Hz, 1H), 2.44 (d, J = 8.0 Hz, 1H), 2.58 (dd, J = 10.4, 4.4 Hz, 1H), 2.78 (ddd, J = 16.2, 5.2, 2.6 Hz, 1H), 2.88 (ddd, J = 16.0, 4.8, 2.4 Hz, 1H), 3.35 (d, J = 13.2 Hz, 1H), 3.45 (d, J = 13.2 Hz, 1H), 5.54 (dtd, J = 9.8, 3.2, 2.0 Hz, 1H), 5.64 (bddd, J = 10.0, 5.0, 3.0 Hz, 1H), 7.02 (bd, J = 7.8 Hz, 2H), 7.05-7.14 (m, 3H), 7.16-7.22 (m, 3H), 7.37 (bd, J = 7.8 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃, ppm) δ: 33.3, 35.74, 35.79, 53.2, 55.3, 62.8, 125.2, 125.7, 127.0, 128.2, 128.3,

128.4, 129.1, 129.7, 136.6, 142.5; IR ($\nu_{\max}$ /cm⁻¹): 695, 730, 998, 1028, 1140, 1453, 1493, 2749, 2793, 2858, 2922, 3026; HRMS (ESI) m/z calcd for C₂₀H₂₄N⁺ [M+H]⁺ 278.19033, found 278.19022.

(R)-1-benzyl-3-(4-methoxyphenethyl)-1,2,3,6-tetrahydropyridine (8c):



5

According to *General Procedure 1*; the reaction proceed for 5 hours at 0 °C. Flash column chromatography on silica gel (hexanes/EtOAc (15/1 to 9/1) + 0.5 % Et₃N) gave **4** in 64% yield (40 mg, 0.19 mmol, ee = 37%) and **8c** in 33% (92%) yield (40 mg, 0.13 mmol) as a colorless oil. Enantiomeric excess (for corresponding Cbz carbamate) of 92% was

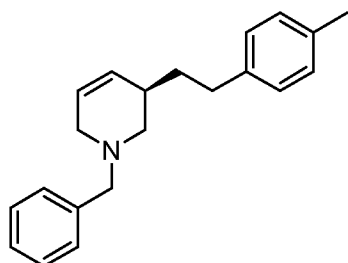
10 determined by HPLC [Chiralpak[®] IB; flow: 1.0 mL/min; hexane:IPA 97.5:2.5; λ = 210 nm; major enantiomer t_R = 13.4 min; minor enantiomer t_R = 16.6 min]; $[D]_{589}^{25}$ = -42.7 (c 0.125 CHCl₃) for 92% ee; ¹H NMR (400 MHz, CDCl₃, ppm) δ : 1.54-1.68 (m, 2H), 2.17 (dd, J = 10.8, 7.2 Hz, 1H), 2.23-2.32 (m, 1H), 2.47-2.59 (m, 2H), 2.73 (dd, J = 10.8, 4.8 Hz, 1H), 2.86-2.91 (m, 1H), 3.04 (bd, J = 16.4 Hz, 1H), 3.54 (d, J = 13.2 Hz, 1H), 3.60 (d, J = 13.2

15 Hz, 1H), 3.78 (s, 3H), 5.65-5.73 (m, 2H), 6.78-6.83 (m, 2H), 7.04 (bd, J = 8.8 Hz, 2H), 7.23-7.28 (m, 1H), 7.29-7.37 (m, 4H); ¹³C NMR (101 MHz, CDCl₃, ppm) δ : 32.3, 35.6, 35.9, 53.2, 55.26, 55.28, 62.8, 113.7, 125.1, 126.9, 128.2, 129.0, 129.2, 129.8, 134.5, 138.6, 157.7; IR ($\nu_{\max}$ /cm⁻¹): 698, 729, 824, 1036, 1141, 1245, 1456, 1511, 2750, 2793, 2857, 2926, 3027, 3732; HRMS (ESI) m/z calcd for C₂₂H₂₆ON⁺ [M+H]⁺ 308.20089, found

20 308.20071. For corresponding Cbz carbamate; ¹H NMR (400 MHz, CDCl₃, ppm) δ : 1.57-1.67 (m, 2H), 2.20 and 2.26 (rotameric s, 1H), 2.53-2.72 (m, 2H), 3.20-3.34 (m, 1H), 3.60-3.83 (m, 1H), 3.78 (s, 3H), 3.83-4.02 (m, 2H), 5.12-5.20 (rotameric m, 2H), 5.57-5.70 (m, 1H), 5.78 (bd, J = 8.4 Hz, 1H), 6.81 (bs, 2H), 7.03 and 7.10 (rotameric bd, J = 7.2 Hz, 2H), 7.29-7.38 (m, 5H).

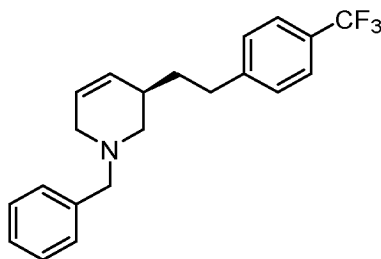
25

(R)-1-benzyl-3-(4-methylphenethyl)-1,2,3,6-tetrahydropyridine (8d):



- According to *General Procedure 1*; the reaction proceed for 3.5 hours at 0 °C. Flash column chromatography on silica gel (hexanes/EtOAc (15/1) + 0.5 % Et₃N) gave **4** in 71% yield (59 mg, 0.19 mmol, ee = 25%) and **8d** in 27% (93%) yield (32 mg, 0.11 mmol) as a yellow oil. Enantiomeric excess (for corresponding Cbz carbamate) of 93% was
- 5 determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; hexane:IPA 97.5:2.5; λ = 210 nm; major enantiomer t_R = 9.4 min; minor enantiomer t_R = 11.8 min]; [D]²⁵₅₈₉ = -58.3 (c 0.20 CHCl₃) for 93% ee; [D]²⁵₅₈₉ = -72.7 (c 0.50 CHCl₃) for 93% ee for Cbz carbamate; ¹H NMR (400 MHz, CDCl₃, ppm) δ: 1.56-1.69 (m, 2H), 2.17 (dd, J = 11.0, 7.4 Hz, 1H), 2.26-2.31 (m, 1H), 2.31 (s, 3H), 2.55 (ddd, J = 9.2, 6.8, 2.6 Hz, 2H), 2.74 (dd, J = 10.8, 4.8 Hz, 1H),
- 10 2.86-2.91 (m, 1H), 3.02-3.06 (m, 1H), 3.54 (d, J = 13.2 Hz, 1H), 3.61 (d, J = 13.2 Hz, 1H), 5.65-5.74 (m, 2H), 7.02 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 7.24-7.29 (m, 1H), 7.32-7.37 (m, 4H); ¹³C NMR (101 MHz, CDCl₃, ppm) δ: 21.0, 32.8, 35.7, 35.9, 53.2, 55.3, 62.8, 125.1, 127.0, 128.23, 128.25, 129.00, 129.07, 129.8, 135.1, 138.5, 139.4; IR (ν_{max}/cm⁻¹): 697, 729, 808, 1202, 1361, 1454, 1514, 2749, 2793, 2858, 2921, 3026, 3741;
- 15 HRMS (ESI) m/z calcd for C₂₁H₂₆N⁺ [M+H]⁺ 292.20598, found 292.20585. For corresponding Cbz carbamate; ¹H NMR (400 MHz, CDCl₃, ppm) δ: 1.57-1.70 (m, 2H), 2.21 and 2.26 (rotameric s, 1H), 2.31 (s, 3H), 2.53-2.72 (m, 2H), 3.19-3.35 (m, 1H), 3.73 (bdd, J = 16.0, 11.0 Hz, 1H), 3.87-4.02 (m, 2H), 5.12-5.19 (rotameric m, 2H), 5.62 and 5.68 (rotameric bd, J = 9.4 Hz, 1H), 5.79 (bd, J = 8.8 Hz, 1H), 6.97-7.13 (m, 4H), 7.28-7.37 (m,
- 20 5H).

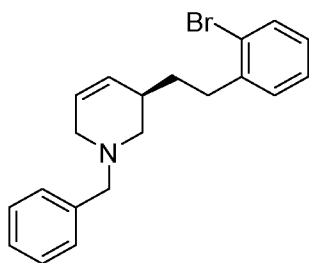
(R)-1-benzyl-3-(4-(trifluoromethyl)phenethyl)-1,2,3,6-tetrahydropyridine (8e):



- According to *General Procedure 1*; the reaction proceed for 13 hours at 0 °C. Flash column chromatography on silica gel (hexanes/EtOAc (15/1) + 0.5 % Et₃N) gave **4** in 69% yield (57 mg, 0.27 mmol, ee = 30%) and **8e** in 22% (71%) yield (30 mg, 0.09 mmol) as a white solid. Enantiomeric excess (for corresponding Cbz carbamate) of 91% was
- 25 determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; hexane:IPA 99.3:0.7; λ = 210 nm; major enantiomer t_R = 22.7 min; minor enantiomer t_R = 24.8 min]; [D]²⁵₅₈₉ = -56.4 (c 1.08 CHCl₃) for 91% ee for Cbz carbamate; ¹H NMR (400 MHz, CDCl₃, ppm) δ: 1.56-1.73 (m, 2H), 2.19 (dd, J = 10.8, 7.0 Hz, 1H), 2.25-2.33 (m, 1H), 2.57-2.67 (m, 2H), 2.71 (dd, J = 10.8, 4.8 Hz, 1H), 2.92 (dd, J = 16.0, 2.8 Hz, 1H), 3.05 (bd, J = 16.0 Hz, 1H), 3.55 (d, J = 13.2 Hz, 1H), 3.61 (d, J = 12.8 Hz, 1H), 5.68-5.73 (m, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.25-
- 30

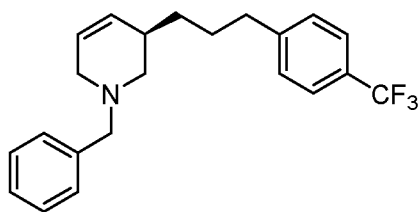
- 7.29 (m, 1H), 7.31-7.37 (m, 4H), 7.51 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3 , ppm) δ : 33.1, 35.4, 35.6, 53.2, 54.9, 62.7, 125.2 (q, $J = 3.8$ Hz, 1C), 125.5, 128.2 (2C), 128.6, 129.0 (2C), 129.3, 138.5, 146.6; IR (ν_{max} /cm $^{-1}$): 698, 732, 842, 1067, 1117, 1161, 1323, 1456, 2797, 2966, 2926, 3032; HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{23}\text{NF}_3^+$ $[\text{M}+\text{H}]^+$ 346.17771, found 346.17737. For corresponding Cbz carbamate; ^1H NMR (400 MHz, CDCl_3 , ppm) δ : 1.65 (bs, 2H), 2.20 and 2.26 (rotameric s, 1H), 2.58-2.88 (m, 2H), 3.29-3.44 (m, 1H), 3.55-3.77 (m, 1H), 3.97 (bs, 2H), 5.11-5.21 (rotameric m, 2H), 5.61-5.72 (m, 1H), 5.78 (bd, $J = 9.6$ Hz, 1H), 7.15-7.22 (m, 1H), 7.26-7.36 (m, 6H), 7.45-7.60 (m, 2H).

10 **(R)-1-benzyl-3-(2-bromophenethyl)-1,2,3,6-tetrahydropyridine (8f):**



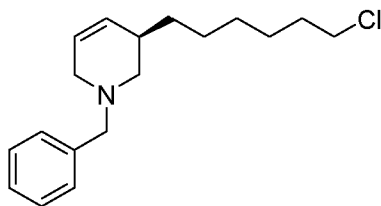
- According to *General Procedure 1*; the reaction proceed for 4 hours at 0 °C. Flash column chromatography on silica gel (hexanes/EtOAc (15/1) + 0.5 % Et_3N) gave **4** in 41% yield (34 mg, 0.16 mmol, ee = 71%) and **8f** in 44% (75%) yield (63 mg, 0.17 mmol) as a viscous colorless oil. Enantiomeric excess (for corresponding Cbz carbamate) of 88% was determined by HPLC [Chiralpak[®] IB; flow: 1.0 mL/min; hexane:IPA 99:1; $\lambda = 210$ nm; major enantiomer $t_R = 15.9$ min; minor enantiomer $t_R = 18.1$ min]; $[\text{D}]^{25}_{589} = -55.1$ (c 0.70 CHCl_3) for 88% ee; ^1H NMR (400 MHz, CDCl_3 , ppm) δ : 1.65 (dd, $J = 15.2, 7.6$ Hz, 2H), 2.23 (dd, $J = 11.2, 7.6$ Hz, 1H), 2.37 (bs, 1H), 2.70 (dd, $J = 13.2, 8.0$ Hz, 1H), 2.76 (dd, $J = 13.6, 7.6$ Hz, 1H), 2.81 (dd, $J = 11.2, 5.2$ Hz, 1H), 2.89 (bd, $J = 16.4$ Hz, 1H), 3.05 (bd, $J = 16.0$ Hz, 1H), 3.48-3.69 (m, 2H), 5.62-5.86 (m, 2H), 7.0 (bt, $J = 7.4$ Hz, 1H), 7.15-7.23 (m, 2H), 7.25-7.29 (m, 1H), 7.32-7.39 (m, 4H), 7.51 (bd, $J = 8.0$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3 , ppm) δ : 33.6, 34.1, 35.9, 53.1, 55.3, 62.9, 124.4, 125.3, 127.0, 127.44, 127.50, 128.2, 129.1, 129.6, 130.3, 132.8, 138.5, 141.8; IR (ν_{max} /cm $^{-1}$): 696, 728, 748, 1069, 1142, 1202, 1492, 2749, 2794, 2861, 2966, 2921, 3027; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{23}\text{BrN}^+$ $[\text{M}+\text{H}]^+$ 356.10084, found 356.10046. For corresponding Cbz carbamate; ^1H NMR (400 MHz, CDCl_3 , ppm) δ : 1.48-1.65 (m, 2H), 2.26 and 2.33 (rotameric bs, 1H), 2.75-2.81 (m, 2H), 3.20-3.39 (m, 1H), 3.62-4.05 (m, 3H), 5.13-5.21 (rotameric m, 2H), 5.66 and 5.71 (rotameric bd, $J = 9.4$ Hz, 1H), 5.82 (bs, 1H), 7.02-7.07 (m, 1H), 7.10-7.21 (m, 2H), 7.27-7.36 (m, 5H), 7.51 (d, $J = 7.6$ Hz, 1H).

(R)-1-benzyl-3-(3-(4-(trifluoromethyl)phenyl)propyl)-1,2,3,6-tetrahydropyridine (8g):



According to *General Procedure 1*; the reaction proceed for 4 hours at 0 °C. Flash column chromatography on silica gel (hexanes/EtOAc (10/1) + 0.5 % Et₃N) gave **4** in 70% yield (58 mg, 0.28 mmol, ee = 23%) and **8g** in 24% (80%) yield (34 mg, 0.09 mmol) as a colorless oil. Enantiomeric excess (for corresponding Cbz carbamate) of 83% was determined by HPLC [Chiralpak® ID; flow: 1.0 mL/min; hexane:IPA 90:10; λ = 210 nm; minor enantiomer t_R = 8.9 min; major enantiomer t_R = 9.4 min]; [D]²⁵₅₈₉ = -40.0 (c 1.08 CHCl₃) for 83% ee; ¹H NMR (400 MHz, CDCl₃, ppm) δ: 1.31-1.41 (m, 2H), 1.53-1.70 (m, 2H), 2.10 (dd, J = 10.8, 7.2 Hz, 1H), 2.25-2.32 (m, 1H), 2.63 (dd, J = 8.0, 7.6 Hz, 2H), 2.70 (dd, J = 11.2, 5.2 Hz, 1H), 2.85 (dd, J = 16.4, 3.2 Hz, 1H), 3.03 (bd, J = 16.0 Hz, 1H), 3.53 (d, J = 12.8 Hz, 1H), 3.59 (dd, J = 13.2 Hz, 1H), 5.63-5.69 (m, 2H), 7.24 (d, J = 8.4 Hz, 2H) 7.23-7.27 (m, 1H), 7.29-7.36 (m, 4H), 7.5 (d, J = 8.0 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃, ppm) δ: 28.5, 33.4, 35.92, 35.96, 53.1, 55.3, 62.8, 125.1, 125.2 (q, J = 3.8 Hz, 1C), 128.2 (2C), 128.7, 129.0 (2C), 129.7, 138.5, 146.6; IR (ν_{max}/cm⁻¹): 696, 730, 841, 1066, 1116, 1161, 1323, 2795, 2859, 2929, 3028; HRMS (ESI) m/z calcd for C₂₂H₂₅NF₃⁺ [M+H]⁺ 360.19336, found 360.19302. For corresponding Cbz carbamate; ¹H NMR (400 MHz, CDCl₃, ppm) δ: 1.30-1.43 (m, 2H), 1.60-1.79 (m, 2H), 2.19 and 2.25 (rotameric bs, 1H), 2.64 (dt, J = 25.6, 7.2 Hz, 2H), 3.10-3.30 (m, 1H), 3.59-3.79 (m, 1H), 3.84-4.02 (m, 2H), 5.10-5.19 (rotameric m, 2H), 5.56-5.68 (m, 1H), 5.73 (ddd, J = 10.4, 5.2, 2.0 Hz, 1H), 7.19-7.36 (m, 7H), 7.51 (bs, 2H).

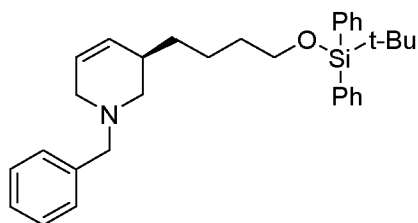
(R)-1-benzyl-3-(6-chlorohexyl)-1,2,3,6-tetrahydropyridine (8h):



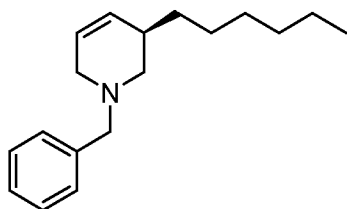
According to *General Procedure 1*; the reaction proceed for 2 hours at room temperature. Flash column chromatography on silica gel (hexanes/EtOAc (15/1) + 0.5 % Et₃N) gave **4** in 46% yield (38 mg, 0.18 mmol, ee = 43%) and **8h** in 37% (68%) yield (43 mg, 0.15 mmol) as a colorless oil. Enantiomeric excess (for corresponding Cbz carbamate) of 86% was determined by HPLC [Chiralpak® ID; flow: 1.0 mL/min; hexane:IPA 90:10; λ = 210 nm; minor enantiomer t_R = 10.8 min; major enantiomer t_R = 11.2 min]; [D]²⁵₅₈₉ = -35.2 (c 1.25 CHCl₃) for 86% ee; ¹H NMR (400 MHz, CDCl₃, ppm) δ: 1.25-1.34 (m, 6H), 1.37-1.46 (m,

2H), 1.74 (p, $J = 7.2$ Hz, 2H), 2.08 (dd, $J = 11.2, 7.6$ Hz, 1H), 2.25 (bs, 1H), 2.72 (dd, $J = 11.2, 5.2$ Hz, 1H), 2.82-2.86 (m, 1H), 3.01-3.07 (m, 1H), 3.52 (t, $J = 6.8$ Hz, 2H), 3.53 (d, $J = 14.0$ Hz, 1H), 3.60 (d, $J = 13.2$ Hz, 1H), 5.62-5.68 (m, 2H), 7.22-7.27 (m, 1H), 7.29-7.36 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3 , ppm) δ : 26.73, 26.80, 29.0, 32.6, 33.8, 36.0, 45.1, 53.1, 55.6, 62.8, 124.8, 126.9, 128.1, 129.0, 130.1, 138.5; IR (ν_{max} /cm $^{-1}$): 697, 728, 997, 1130, 1393, 1455, 2749, 2793, 2855, 2926, 3027, 3742; HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{27}\text{ClN}^+$ $[\text{M}+\text{H}]^+$ 292.18265, found 292.18242. For corresponding Cbz carbamate; ^1H NMR (400 MHz, CDCl_3 , ppm) δ : 1.19-1.43 (m, 8H), 1.75 (bs, 2H), 2.16 and 2.22 (rotameric bs, 1H), 3.08 and 3.24 (rotameric dd, $J = 12.4, 6.6$ Hz, 1H), 3.52 (bs, 2H), 3.60-3.78 (m, 1H), 3.87-4.03 (m, 2H), 5.11-5.20 (rotameric m, 2H), 5.60 and 5.66 (rotameric bd, $J = 5.2$ Hz, 1H), 5.75 (bd, $J = 10.4$ Hz, 1H), 7.02-7.63 (m, 5H).

(R)-1-benzyl-3-(4-((tert-butyldiphenylsilyl)oxy)butyl)-1,2,3,6-tetrahydropyridine (8i):



According to *General Procedure 1*; the reaction proceed for 30 minutes at room temperature. Flash column chromatography on silica gel (hexanes/EtOAc (10/1) + 0.5 % Et $_3$ N) gave **4** in 43% yield (36 mg, 0.17 mmol, ee = 55%) and **8i** in 44% (77%) yield (85 mg, 0.18 mmol) as a yellow oil. Enantiomeric excess (for corresponding Cbz carbamate) of 80% was determined by HPLC [Chiralpak $^{\text{®}}$ IC; flow: 1.0 mL/min; hexane:IPA 99:1; $\lambda = 210$ nm; major enantiomer $t_R = 20.7$ min; minor enantiomer $t_R = 21.9$ min]; $[\text{D}]_{\text{D}}^{25} = -22.6$ (c 0.80 CHCl_3) for 80% ee; ^1H NMR (400 MHz, CDCl_3 , ppm) δ : 1.04 (s, 9H), 1.22-1.43 (m, 4H), 1.54 (p, $J = 6.8$ Hz, 2H), 2.05 (dd, $J = 10.8, 7.6$ Hz, 1H), 2.25 (bs, 1H), 2.73 (dd, $J = 10.8, 4.8$ Hz, 1H), 2.83 (bdd, $J = 16.4, 3.2$ Hz, 1H), 3.05 (bd, $J = 16.4$ Hz, 1H), 3.55 (d, $J = 12.8$ Hz, 1H), 3.60 (d, $J = 13.2$ Hz, 1H), 3.64 (t, $J = 6.4$ Hz, 2H), 5.61-5.67 (m, 2H), 7.21-7.43 (m, 11H), 7.64-7.67 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3 , ppm) δ : 19.2, 23.1, 26.9, 32.7, 33.6, 36.0, 53.1, 55.7, 62.8, 63.8, 124.7, 127.0, 127.6, 128.2, 129.0, 129.5, 130.1, 134.1, 135.6, 138.5; IR (ν_{max} /cm $^{-1}$): 699, 733, 822, 1107, 1457, 2796, 2930, 3027; HRMS (ESI) m/z calcd for $\text{C}_{32}\text{H}_{42}\text{ONSi}^+$ $[\text{M}+\text{H}]^+$ 484.30302, found 484.30231. For corresponding Cbz carbamate; ^1H NMR (400 MHz, CDCl_3 , ppm) δ : 1.05 (s, 9H), 1.20-1.59 (m, 8H), 2.15 and 2.22 (rotameric bs, 1H), 3.01-3.20 (m, 1H), 3.56-4.10 (m, 1H), 3.65 (bs, 2H), 3.81-4.04 (m, 2H), 5.11-5.19 (rotameric m, 2H), 5.54-5.66 (m, 1H), 5.74 (bd, $J = 10.0$ Hz, 1H), 7.10-7.61 (m, 11 H), 7.64 (bd, $J = 10.4$ Hz, 4H).

(R)-1-benzyl-3-hexyl-1,2,3,6-tetrahydropyridine (8j):

According to *General Procedure 1*; the reaction proceed for 40 minutes at room

temperature. Flash column chromatography on silica gel (CHCl_3 to hexanes/EtOAc (10/1)

5 + 0.5 % Et_3N) gave **4** in 46% yield (38 mg, 0.18 mmol, ee = 68%) and **8j** in 47% (87%)

yield (48 mg, 0.18 mmol) as a yellow oil. Enantiomeric excess (for corresponding Cbz

carbamate) of 87% was determined by HPLC [Chiralpak[®] IC; flow: 1.0 mL/min; hexane:IPA

97:3; λ = 210 nm; major enantiomer t_R = 13.6 min; minor enantiomer t_R = 14.3 min]; $[\text{D}]^{25}_{589}$

= -42.1 (c 0.30 CHCl_3) for 87% ee; **¹H NMR (400 MHz, CDCl_3 , ppm) δ :** 0.87 (t, J = 6.8 Hz,

10 3H), 1.25-1.35 (m, 10H), 2.08 (dd, J = 10.8, 8.0 Hz, 1H), 2.27 (bs, 1H), 2.74 (dd, J = 10.8,

4.8 Hz, 1H), 2.83 (bd, J = 15.6 Hz, 1H), 3.04 (bd, J = 16.4 Hz, 1H), 3.54 (d, J = 13.2 Hz,

1H), 3.61 (d, J = 12.8 Hz, 1H), 5.61-5.69 (m, 2H), 7.23-7.27 (m, 1H), 7.29-7.36 (m, 4H);

¹³C NMR (101 MHz, CDCl_3 , ppm) δ : 14.1, 22.6, 26.8, 29.5, 31.8, 33.9, 36.1, 53.1, 55.7,

62.8, 124.6, 126.9, 128.1, 129.0, 130.3, 138.5; **IR** (ν_{max} /cm⁻¹): 695, 727, 998, 1071, 1126,

15 1492, 2854, 2923, 2955, 3028; **HRMS** (ESI) m/z calcd for $\text{C}_{18}\text{H}_{28}\text{N}^+$ $[\text{M}+\text{H}]^+$ 258.22163,

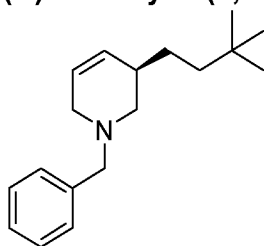
found 258.22156; For corresponding Cbz carbamate; **¹H NMR (400 MHz, CDCl_3 , ppm) δ :**

0.88 (t, J = 7.2 Hz, 3H), 1.25-1.30 (m, 10H), 2.16 and 2.23 (rotameric bs, 1H), 3.01-3.25

(m, 1H), 3.63-4.05 (m, 3H), 5.11-5.20 (rotameric m, 2H), 5.59 and 5.65 (rotameric bd, J =

9.4 Hz, 1H), 5.75 (dd, J = 10.2, 1.4 Hz, 1H), 7.04-7.64 (m, 5H).

20 **(R)-1-benzyl-3-(3,3-dimethylbutyl)-1,2,3,6-tetrahydropyridine (8k):**



According to *General Procedure 1*; the reaction proceed for 30 minutes at room

temperature. Flash column chromatography on silica gel (CHCl_3 to hexanes/EtOAc (9/1) +

25 0.5 % Et_3N) gave **4** in 64% yield (53 mg, 0.25 mmol, ee = 30%) and **8k** in 31% (86%) yield

(32 mg, 0.12 mmol) as a colorless oil. Enantiomeric excess (for corresponding Cbz

carbamate) of 88% was determined by HPLC [Chiralpak[®] ID; flow: 1.0 mL/min; hexane:IPA

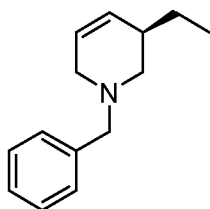
90:10; λ = 210 nm; minor enantiomer t_R = 6.5 min major enantiomer t_R = 7.5 min]; $[\text{D}]^{25}_{589}$ =

-50.7 (c 0.80 CHCl_3) for 88% ee; **¹H NMR (400 MHz, CDCl_3 , ppm) δ :** 0.86 (s, 9H), 1.09-

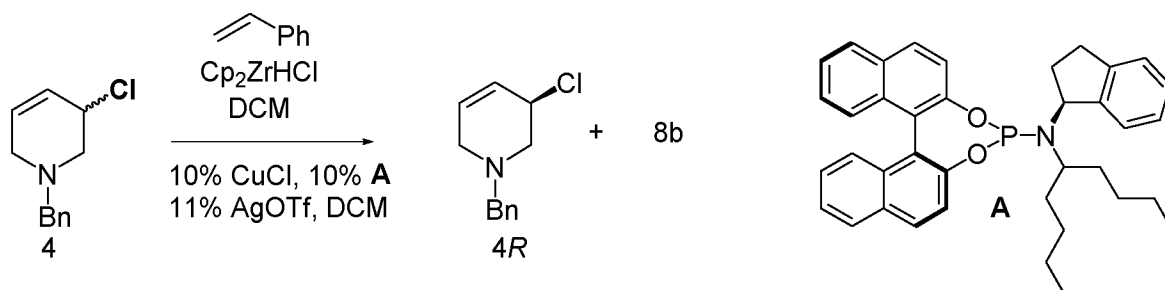
30 1.22 (m, 2H), 1.23-1.32 (m, 2H), 1.12 (dd, J = 10.8, 7.6 Hz, 1H), 2.14-2.26 (m, 1H), 2.73

(dd, $J = 10.8, 4.8$, Hz, 1H), 2.84-2.89 (m, 1H), 3.06 (dd, $J = 16.4, 2.8$ Hz, 1H), 3.54 (d, $J = 13.2$ Hz, 1H), 3.62 (d, $J = 13.2$ Hz, 1H), 5.64-5.72 (m, 2H), 7.24-7.28 (m, 1H), 7.31-7.38 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3 , ppm) δ : 28.7, 29.3, 30.2, 36.8, 41.3, 53.2, 55.5, 62.8, 124.6, 126.9, 128.2, 129.0, 130.4, 138.6; IR (ν_{max} /cm $^{-1}$): 694, 726, 995, 1137, 1393, 1456, 2863, 2952; HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{28}\text{N}^+$ $[\text{M}+\text{H}]^+$ 258.22163, found 258.22183. For corresponding Cbz carbamate; ^1H NMR (400 MHz, CDCl_3 , ppm) δ : 0.85 (rotameric s, 9H), 1.19-1.33 (m, 4H), 2.09 and 2.16 (rotameric bs, 1H), 2.98-3.27 (m, 1H), 3.59-4.06 (m, 3H), 5.15 (bs, 2H), 5.60 and 5.65 (rotameric bd, $J = 9.2$ Hz, 1H), 5.76 (ddd, $J = 10.4, 5.2, 2.4$ Hz, 1H), 7.28-7.38 (m, 5H).

(R)-1-benzyl-3-ethyl-1,2,3,6-tetrahydropyridine (8I):



According to *General Procedure 1*; the reaction proceed for 30 minutes at room temperature, under 1 atm of ethylene gas. Flash column chromatography on silica gel (CHCl_3 to hexanes/EtOAc (9/1) + 0.5 % Et_3N) gave **4** in 63% yield (52 mg, 0.25 mmol, ee = 34%) and **8I** in 25% (68%) yield (20 mg, 0.10 mmol) as a colorless oil. Enantiomeric excess (for corresponding Cbz carbamate) of 90% was determined by HPLC [Chiralpak[®] IC; flow: 1.0 mL/min; hexane:IPA 97:3; $\lambda = 210$ nm; major enantiomer $t_R = 16.0$ min; minor enantiomer $t_R = 16.9$ min]; $[\text{D}]_{589}^{25} = -39.2$ (c 0.75 CHCl_3) for 90% ee for Cbz carbamate; ^1H NMR (400 MHz, CDCl_3 , ppm) δ : 0.89 (t, $J = 7.6$ Hz, 3H), 1.29-1.41 (m, 2H), 2.09 (dd, $J = 10.8, 8.0$ Hz, 1H), 2.16-2.25 (m, 1H), 2.76 (dd, $J = 10.8, 5.2$ Hz, 1H), 2.81-2.87 (m, 1H), 3.06 (bd, $J = 16.8$ Hz, 1H), 3.56 (d, $J = 13.2$ Hz, 1H), 3.61 (d, $J = 12.8$ Hz, 1H), 5.64-5.71 (m, 2H), 7.23-7.27 (m, 1H), 7.30-7.37 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3 , ppm) δ : 11.4, 26.7, 37.7, 53.1, 55.4, 62.9, 124.8, 126.9, 128.2, 129.0, 130.0, 138.6; IR (ν_{max} /cm $^{-1}$): 697, 727, 750, 978, 1151, 1492, 2748, 2793, 2923, 2960, 3027; HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_{20}\text{N}^+$ $[\text{M}+\text{H}]^+$ 202.15903, found 202.15894. Spectral data is in agreement with literature.⁹ For corresponding Cbz carbamate; ^1H NMR (400 MHz, CDCl_3 , ppm) δ : 0.92-0.94 (rotameric m, 3H), 1.25-1.43 (m, 2H), 2.10 and 2.16 (rotameric bs, 1H), 3.04-3.24 (m, 1H), 3.66-4.04 (m, 3H), 5.11-5.19 (rotameric m, 2H), 5.60 and 5.66 (rotameric bd, $J = 10.0$ Hz, 1H), 5.76 (bdd, $J = 10.0, 1.8$ Hz, 1H), 7.07-7.50 (m, 5H).

General Procedure 4: Resolution of 1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine (4):

A round-bottom flask with a stirbar was flame dried under vacuum and re-filled with Ar upon cooling. The flask was charged with CuCl (4 mg, 0.04 mmol) and ligand **A** (23 mg, 0.04 mmol), flushed with argon and wrapped with aluminum foil. DCM (2 ml, freshly collected from SPS) was added and the resultant colorless solution was stirred at room temperature for 1 hour. Meanwhile a separate round-bottom flask with a stirbar was flame dried under vacuum and re-filled with Ar upon cooling. The flask was charged with Cp_2ZrHCl (206 mg, 0.8 mmol), flushed with argon and wrapped with aluminum foil. DCM (0.4 ml) and then styrene (0.12 ml, 1.0 mmol) were added and the resultant suspension was stirred at room temperature until the mixture became completely clear. After 1 hour fine crystalline $\text{Ag}(\text{OTf})$ (12 mg, 0.044 mmol) was quickly added to copper catalyst solution and stirred for 15 minutes until all the AgCl precipitated out. Suspension was filtered into alkylzirconocene solution using a syringe filter and the resultant black solution was cooled 0 °C and more DCM (5.6 ml) was added for dilution. After 5 minutes neat 1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine (**4**) (83 mg, 0.4 mmol) was added with a syringe and solution was stirred for 18 hours at 0 °C. The reaction was stopped by pouring into Et_2O (10 ml) in a separatory funnel. Remaining material in the reaction flask was rinsed into Et_2O solution with EtOAc (2 ml x2) and the resultant suspension was washed with saturated NaHCO_3 solution (5-7 ml x3). Aqueous phases were back washed with EtOAc (5-7 ml x2). The combined organic layers were dried over MgSO_4 , filtered, concentrated under vacuum and purified by flash column chromatography on silica gel (hexanes/ EtOAc (19/1)) to give **4R** in 30% yield (25 mg, 0.12 mmol) as a yellow oil. Enantiomeric excess of 99% was determined by HPLC [Chiralpak® ID; flow: 1.0 mL/min; hexane:IPA 99.3:0.7; λ = 210 nm, minor enantiomer t_R = 6.0 min, major enantiomer t_R = 6.6 min]; $[\text{D}]^{25}_{589} = +154.9$ (c 1 CHCl_3) for 99% ee.

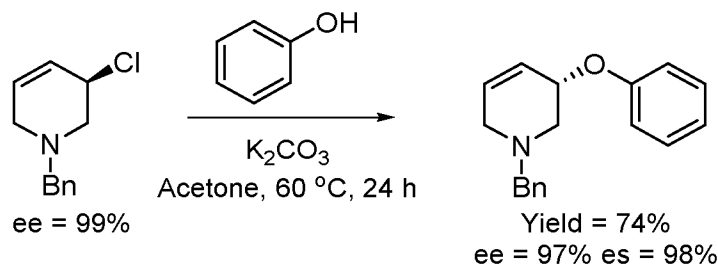
Procedure for resolution of 4 in larger scale:

Above mentioned procedure was followed with 831 mg (4.00 mmol) **4**, 1.2 ml (10.0 mmol) styrene, 40 mg (0.4 mmol) CuCl , 230 mg (0.4 mmol) ligand **A**, 120 mg (0.44 mmol) AgOTf and 2.0 g (8.0 mmol) Cp_2ZrHCl . The reaction was run in 80 ml DCM (8 ml of DCM was used in hydrozirconation step and 52 ml of DCM was added for dilution) for 2 hours at 0

°C. Resolved **4R** was obtained in 37% yield (309 mg, 1.5 mmol). Enantiomeric excess of 92% was determined by HPLC [Chiralpak® ID; flow: 1.0 mL/min; hexane:IPA 99.3:0.7; λ = 210 nm, minor enantiomer t_R = 5.7 min major enantiomer t_R = 6.2 min].

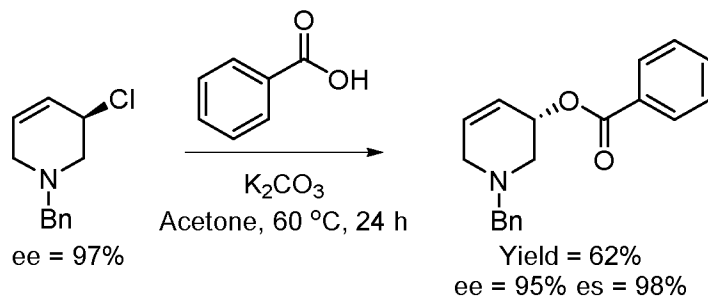
5 Nucleophilic Substitution Reactions with **4R**

(S)-1-benzyl-3-phenoxy-1,2,3,6-tetrahydropyridine (**10**):



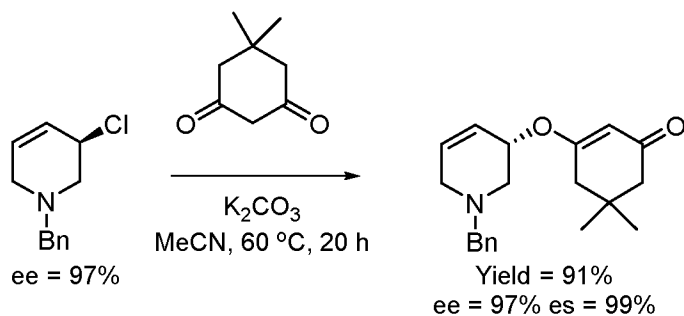
In a flame dried vial with a stirbar were added phenol (21 mg, 0.22 mmol) and K_2CO_3 (111 mg, 0.80 mmol) followed by a solution of (*R*)-1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine (**4R**) (42 mg, 0.20 mmol) in acetone (1.5 ml). The vial was sealed with a cap and resulting suspension was stirred at 60 °C for 24 hours. The reaction mixture was cooled to room temperature, transferred to a round-bottom flask and the reaction vial was rinsed with EtOAc (1 ml x 3). Flash column chromatography on silica gel (hexanes/EtOAc (19/1 to 9/1)) gave **10** in 74% yield (39 mg, 0.15 mmol) as off-white solid. Enantiomeric excess of 97% was determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; hexane:IPA 90:10; λ = 210 nm; major enantiomer t_R = 5.6 min; minor enantiomer t_R = 6.7 min]; $[D]^{25}_{589} = +70.2$ (c 0.85 $CHCl_3$) for 97% ee; 1H NMR (400 MHz, $CDCl_3$, ppm) δ : 2.70 (dd, J = 11.2, 6.0 Hz, 1H), 2.97 (dd, J = 11.2, 4.8 Hz, 1H), 3.07 (bs, 2H), 3.66 (d, J = 12.8 Hz, 1H), 3.71 (d, J = 13.2 Hz, 1H), 4.91-4.94 (m, 1H), 5.94-6.01 (m, 2H), 6.91-6.97 (m, 3H), 7.25-7.38 (m, 7H); 1H NMR (400 MHz, C_6D_6 , ppm) δ : 2.56 (dd, J = 10.8, 7.0 Hz, 1H), 2.61 (ddd, J = 16.8, 5.2, 2.8 Hz, 1H), 2.76-2.82 (m, 1H), 2.94 (bdd, J = 11.0, 5.0 Hz, 1H), 3.31 (d, J = 13.2 Hz, 1H), 3.36 (d, J = 13.2 Hz, 1H), 4.84-4.89 (m, 1H), 5.52-5.56 (m, 1H), 5.85-5.88 (m, 1H), 6.78-6.82 (m, 1H), 6.85-6.88 (m, 2H), 7.05-7.12 (m, 3H), 7.15-7.19 (m, 2H), 7.28-7.30 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ : 52.4, 54.0, 62.2, 70.7, 115.8, 120.9, 124.9, 127.2, 128.3, 129.0, 129.5, 129.8, 137.6, 157.7; IR (ν_{max} / cm^{-1}): 692, 751, 773, 1032, 1238, 1490, 1591; HRMS (ESI) m/z calcd for $C_{18}H_{20}ON^+$ $[M+H]^+$ 266.15394, found 266.15396. Spectral data is in agreement with literature.⁹

(S)-1-benzyl-1,2,3,6-tetrahydropyridin-3-yl benzoate (**11**):



In a flame dried vial with a stirbar were added benzoic acid (32 mg, 0.26 mmol) and K_2CO_3 (100 mg, 0.72 mmol) followed by a solution of (*R*)-1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine (**4R**) (50 mg, 0.24 mmol) in acetone (2.5 ml). The vial was sealed with a cap and resulting suspension was stirred at 60 °C for 24 hours. The reaction mixture was cooled to room temperature, transferred to a round-bottom flask and the reaction vial was rinsed with EtOAc (1 ml x 3). Flash column chromatography on silica gel (hexanes/EtOAc (19/1 to 9/1) + 0.5% Et_3N) gave **11** in 62% yield (43 mg, 0.15 mmol) as white solid. Enantiomeric excess of 95% was determined by HPLC [Chiralpak® ID; flow: 1.0 mL/min; hexane:IPA 90:10; λ = 210 nm; minor enantiomer t_R = 6.6 min; major enantiomer t_R = 7.7 min]; $[\text{D}]^{25}_{589}$ = +175.4 (c 0.83 CHCl_3) for 95% ee; $^1\text{H NMR}$ (400 MHz, CDCl_3 , ppm) δ : 2.76-2.84 (m, 2H), 2.96 (ddd, J = 16.8, 2.4, 2.0 Hz, 1H), 3.14 (ddt, J = 16.8, 3.2, 2.0 Hz, 1H), 3.58 (d, J = 13.6 Hz, 1H), 3.72 (d, J = 13.6 Hz, 1H), 5.49-5.50 (bm, 1H), 5.91 (ddt, J = 10.0, 3.6, 2.0 Hz, 1H), 6.01 (dtd, J = 10.0, 3.2, 0.8 Hz, 1H), 7.18-7.29 (m, 3H), 7.34-7.37 (m, 2H), 7.38-7.43 (m, 2H), 7.50-7.54 (m, 1H), 8.01-8.05 (m, 2H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3 , ppm) δ : 52.3, 53.9, 61.9, 68.2, 124.0, 127.2, 128.28, 128.29, 128.8, 129.7, 130.4, 131.1, 132.9, 137.8, 166.3; IR (ν_{max} /cm $^{-1}$): 705, 731, 1070, 1265, 1711; HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{20}\text{O}_2\text{N}^+$ $[\text{M}+\text{H}]^+$ 294.14886, found 294.14865.

(S)-3-((1-benzyl-1,2,3,6-tetrahydropyridin-3-yl)oxy)-5,5-dimethylcyclohex-2-en-1-one (12):



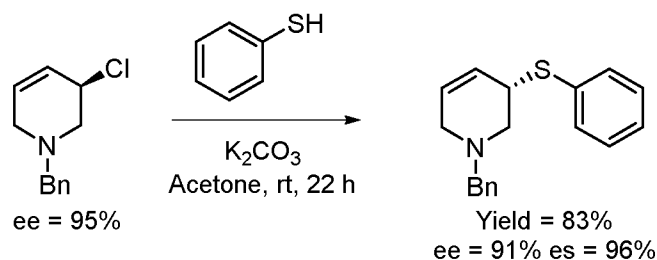
In a flame dried vial with a stirbar were added dimedone (67 mg, 0.48 mmol) and K_2CO_3 (116 mg, 0.84 mmol) followed by a solution of (*R*)-1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine (**4R**) (50 mg, 0.24 mmol) in acetonitrile (2.5 ml). The vial was sealed with a cap and resulting suspension was stirred at 60 °C for 20 hours. The reaction mixture

was cooled to room temperature, transferred to a round-bottom flask and the reaction vial was rinsed with EtOAc (1 ml x 3). Flash column chromatography on silica gel (hexanes/EtOAc (1/1)) gave **12** in 91% yield (68 mg, 0.22 mmol) as white solid.

Enantiomeric excess of 96% was determined by HPLC [Chiralpak® ID; flow: 1.0 mL/min;

- 5 hexane:IPA 90:10; λ = 210 nm; major enantiomer t_R = 18.2 min; minor enantiomer t_R = 19.4 min]; $[D]^{25}_{589}$ = +29.0 (c 0.84 CHCl₃) for 96% ee; **¹H NMR (400 MHz, CDCl₃, ppm) δ** : 1.02 (s, 3H), 1.05 (s, 3H), 2.15 (d, J = 18.0 Hz, 1H), 2.19 (d, J = 16.8 Hz, 1H), 2.23 (d, J = 17.2 Hz, 1H), 2.29 (d, J = 17.6 Hz, 1H), 2.68 (dd, J = 12.0, 3.6 Hz, 1H), 2.77 (dd, J = 12.0, 4.8 Hz, 1H), 2.96 (bdd, J = 17.0, 1.8 Hz, 1H), 3.15 (bddt J = 16.8, 3.2, 1.6 Hz, 1H), 3.55 (d, J = 13.2 Hz, 1H), 3.72 (d, J = 13.2 Hz, 1H), 4.70 (bs, 1H), 5.33 (s, 1H), 5.85 (ddt, J = 10.0, 3.4, 2.2 Hz, 1H), 6.03 (dtd, J = 10.0, 3.2, 2.0 Hz, 1H), 7.22-7.27 (m, 1H), 7.28-7.34 (m, 4H); **¹³C NMR (101 MHz, CDCl₃, ppm) δ** : 28.22, 28.34, 32.4, 43.2, 50.7, 52.4, 52.9, 61.9, 70.9, 101.9, 122.6, 127.3, 128.3, 129.0, 131.7, 137.4, 174.9, 199.5; **IR** (ν_{max} /cm⁻¹): 729, 1042, 1144, 1219, 1378, 1589, 1638, 2965, 3749; **HRMS** (ESI) m/z calcd for C₂₆H₂₂O₂N⁺ [M+H]⁺
- 10 312.19581, found 312.19556.
- 15

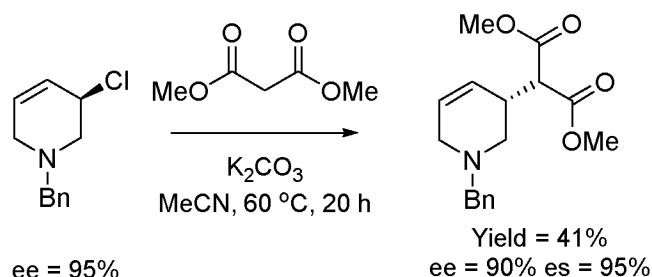
(S)-1-benzyl-3-(phenylthio)-1,2,3,6-tetrahydropyridine (13):



- 20 In a flame dried vial with a stirbar were added K₂CO₃ (166 mg, 1.2 mmol) and a solution of (R)-1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine (**4R**) (50 mg, 0.24 mmol) in acetone (2.5 ml) followed by the addition of thiophenol (0.06 ml, 0.48 mmol). The vial was sealed with a cap and resulting suspension was stirred at room temperature for 22 hours. The reaction mixture was diluted with H₂O and extracted with Et₂O (x3). Combined organic layers were
- 25 washed with brine, dried over MgSO₄, filtered, concentrated under vacuum and purified by flash column chromatography on silica gel (hexanes/EtOAc (19/1 to 9/1)) to give **13** in 83% yield (56 mg, 0.20 mmol) as a yellow oil. Enantiomeric excess (for corresponding Cbz carbamate) of 91% was determined by HPLC [Chiralpak® ID; flow: 1.0 mL/min; hexane:IPA 90:10; λ = 210 nm; minor enantiomer t_R = 17.1 min; major enantiomer t_R = 18.9 min];
- 30 $[D]^{25}_{589}$ = -45.8 (c 0.72 CHCl₃) for 91% ee; **¹H NMR (400 MHz, CDCl₃, ppm) δ** : 2.65 (dd, J = 11.6, 5.6 Hz, 1H), 2.81 (dd, J = 11.6, 4.4 Hz, 1H), 2.96-3.01 (m, 1H), 3.07 (ddd, J = 16.8, 4.8, 2.4 Hz, 1H), 3.52 (d, J = 13.2 Hz, 1H), 3.72 (d, J = 13.2 Hz, 1H), 3.83-3.87 (m, 1H), 5.78-5.82 (m, 1H), 5.83-5.87 (m, 1H), 7.17-7.38 (m, 10H); **¹³C NMR (101 MHz, CDCl₃,**

ppm) δ : 44.7, 52.5, 54.7, 62.2, 125.8, 126.9, 127.1, 128.0, 128.2, 128.8, 129.1, 132.0, 135.1, 137.8; IR ($\nu_{\max}$ /cm⁻¹): 695, 736, 758, 1026, 1134, 2756, 3710; HRMS (ESI) m/z calcd for C₁₈H₂₀SN⁺ [M+H]⁺ 282.13110, found 282.13092. For corresponding Cbz carbamate; ¹H NMR (400 MHz, CDCl₃, ppm) δ : 3.60-3.71 (m, 1H), 3.77 (bs, 2H), 3.86 and 3.91 (rotameric bs, 1H), 4.03 and 4.14 (rotameric bd, J = 19.0 Hz, 1H), 5.12-5.19 (rotameric m, 2H), 5.76 and 5.84 (rotameric bd, J = 10.0 Hz, 1H), 5.93 (bs, 1H), 7.10-7.36 (m, 9H), 7.54 (d, J = 6.4 Hz, 1H).

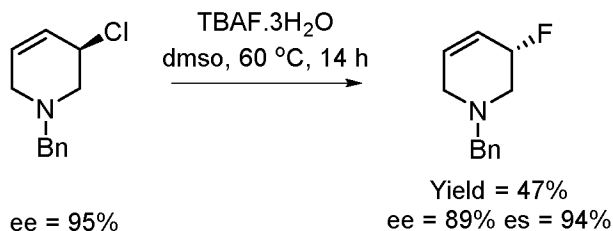
Dimethyl (*R*)-2-(1-benzyl-1,2,3,6-tetrahydropyridin-3-yl)malonate (14**):**



In a flame dried vial with a stirbar were added K₂CO₃ (166 mg, 1.2 mmol) and a solution of (*R*)-1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine (**4R**) (50 mg, 0.24 mmol) in acetone (2.5 ml) followed by the addition of dimethyl malonate (0.05 ml, 0.36 mmol). The vial was sealed with a cap and resulting suspension was stirred at 60 °C for 24 hours. The reaction mixture was diluted with H₂O and extracted with EtOAc (x3). Combined organic layers were washed with brine, dried over MgSO₄, filtered, concentrated under vacuum and purified by flash column chromatography on silica gel (hexanes/EtOAc (19/1)) to give **14** in 41% yield (30 mg, 0.10 mmol) as a yellow oil. Enantiomeric excess (for corresponding Cbz carbamate) of 90% was determined by HPLC [Chiralpak[®] IB; flow: 1.0 mL/min; hexane:IPA 85:15; λ = 210 nm; minor enantiomer t_R = 8.5 min; major enantiomer t_R = 9.1 min]; [D]₅₈₉²⁵ = +127.4 (c 0.27 CHCl₃) for 90% ee; [D]₅₈₉²⁵ = +84.9 (c 0.90 CHCl₃) for 91% ee for Cbz carbamate; ¹H NMR (400 MHz, CDCl₃, ppm) δ : 2.49 (d, J = 4.0 Hz, 2H), 2.84 (ddd, J = 16.8, 4.8, 2.4 Hz, 1H), 2.90-2.98 (m, 1H), 3.11 (ddt, J = 16.4, 3.6, 2.0 Hz, 1H), 3.44 (d, J = 12.8 Hz, 1H), 3.57 (s, 3H), 3.62 (d, J = 12.8 Hz, 1H), 3.66 (d, J = 10.0 Hz, 1H), 3.73 (s, 3H), 5.64 (ddt, J = 10.0, 4.0, 2.0 Hz, 1H), 5.77 (dtd, J = 10.0, 2.4, 1.2 Hz, 1H), 7.21-7.26 (m, 1H), 7.27-7.36 (m, 4H); ¹³C NMR (101 MHz, CDCl₃, ppm) δ : 36.2, 52.46, 52.48, 52.56, 53.3, 55.3, 62.5, 125.5, 127.1, 128.3, 128.5, 129.2, 138.4, 168.97, 169.06; IR ($\nu_{\max}$ /cm⁻¹): 700, 735, 1020, 1148, 1241, 1492, 1733, 2801, 2953, 3749; HRMS (ESI) m/z calcd for C₁₇H₂₂O₄N⁺ [M+H]⁺ 304.15433, found 304.15439. Spectral data is in agreement with literature.⁹ For corresponding Cbz carbamate; ¹H NMR (400 MHz, CDCl₃, ppm) δ : 2.99 and 3.03 (rotameric bs, 1H), 3.38 (bd, J = 9.2 Hz, 1H), 3.45-3.52 (rotameric m, 2H), 3.69-3.83 (rotameric m, 6H), 3.88-4.17 (rotameric m, 2H), 5.12 (bs, 2H), 5.67-5.83 (m, 2H),

7.30-7.37 (m, 5H). Spectral data is in agreement with and absolute stereochemistry was determined according to literature.¹⁰

(S)-1-benzyl-3-fluoro-1,2,3,6-tetrahydropyridine (15):

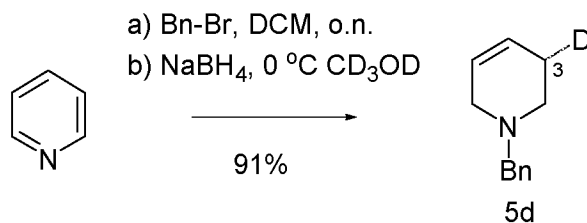


In a flame dried vial with a stirbar were added TBAF·3H₂O (152 mg, 0.48 mmol) and a solution of (*R*)-1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine (**4R**) (50 mg, 0.24 mmol) in dmsO (2.5 ml). The vial was sealed with a cap and resulting solution was stirred at 60 °C for 14 hours. The reaction mixture was diluted with H₂O and extracted with Et₂O (x3).

Combined organic layers were washed with brine, dried over MgSO₄, filtered, concentrated under vacuum and purified by flash column chromatography on silica gel (hexanes/EtOAc (19/1)) to give **15** in 47% yield (21 mg, 0.11 mmol) as a yellow oil. Enantiomeric excess of 89% was determined by HPLC [Chiralpak[®] IC; flow: 1.0 mL/min; hexane:IPA 99:1; λ = 210 nm; minor enantiomer t_R = 7.1 min; major enantiomer t_R = 7.7 min]; [D]_D²⁵₅₈₉ = +44.7 (c 0.27 CHCl₃) for 89% ee; ¹H NMR (400 MHz, CDCl₃, ppm) δ: 2.70 (dddd, J = 22.4, 12.2, 4.0, 1.2 Hz, 1H), 2.82-2.93 (m, 2H), 3.09-3.16 (m, 1H), 3.62 (d, J = 13.2 Hz, 1H), 3.68 (d, J = 13.2 Hz, 1H), 5.0 (dm, J_{HF} = 49.6 Hz, 1H), 5.84-5.93 (m, 1H), 6.03 (bddd, J = 10.0, 3.2, 2.8 Hz, 1H), 7.24-7.28 (m, 1H), 7.30-7.36 (m, 4H); ¹³C NMR (101 MHz, CDCl₃, ppm) δ: 52.1 (d, ⁴J = 3.23 Hz), 54.5 (d, ²J = 22.5 Hz), 62.0, 84.7 (d, ¹J = 166.9 Hz), 123.6 (d, ²J = 18.3 Hz), 127.2, 128.3, 129.0, 132.1 (d, ³J = 9.6 Hz), 137.5; ¹⁹F NMR (376 MHz, CDCl₃, ppm) δ: -171.35 (m); IR (ν_{max}/cm⁻¹): 697, 736, 998, 1147, 1493, 2759, 2804, 2922; HRMS (ESI) m/z calcd for C₁₂H₁₅FN⁺ [M+H]⁺ 192.11830, found 192.11801.

Preparation of 1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine-5-d (4d)

1-benzyl-1,2,3,6-tetrahydropyridine-3-d (5d):



Benzylpyridinium bromide (2 g, 8 mmol) was dissolved in MeOH-d₄ (10 ml) and cooled to 0 °C. NaBH₄ (360 mg, 9.5 mmol) was added portionwise and the reaction solution was stirred at 0 °C for 4 hours. Reaction was quenched with H₂O and washed with EtOAc (x3).

Combined organic layers were washed with brine, dried over MgSO_4 , filtered, concentrated under vacuum and purified by flash column chromatography on silica gel

(hexanes/EtOAc/ Et_3N (4/1/0.05)) to give 1-benzyl-1,2,3,6-tetrahydropyridine-3-*d* (**5d**) in

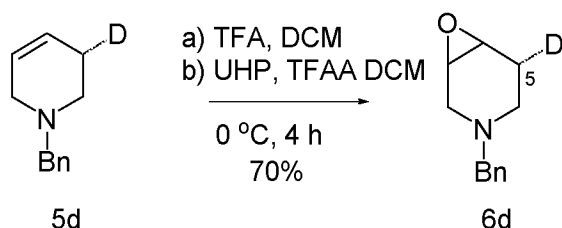
91% yield (1.27 g, 7.29 mmol) as a viscous yellow oil. ^1H NMR (400 MHz, CDCl_3 , ppm) δ :

2.13-2.18 (m, 1H, CD-3 H), 2.55 (d, J = 5.6 Hz, 2H, C-2 H), 2.97 (dd, J = 5.2, 2.8 Hz, 2H, C-6 H), 3.58 (s, 2H, benzylic), 5.66 (dtd, J = 10.0, 3.2, 2.0 Hz, 1H, vinylic), 5.75 (ddt, J = 10.0, 3.2, 2.2 Hz, 1H, vinylic), 7.23-7.27 (m, 1H, aromatic), 7.29-7.37 (m, 4H, aromatic);

^{13}C NMR (101 MHz, CDCl_3 , ppm) δ : 25.8 (t, CDH), 49.6, 52.8, 63.0, 125.2, 125.5, 127.0, 128.2, 129.2, 138.4; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{15}\text{DN}^+$ [$\text{M}+\text{H}$] $^+$ 175.13400, found

175.13403.

3-benzyl-7-oxa-3-azabicyclo[4.1.0]heptane-5-*d* (**6d**):



In a dried flask urea hydrogen peroxide (UHP) (2.7 g, 28 mmol) and DCM (24 ml) were

mixed and cooled 0 °C. A solution of trifluoroacetic anhydride (TFAA) (4.8 ml, 28 mmol) in DCM (15 ml) was added dropwise. The resultant suspension was stirred for 1 hour at 0 °C.

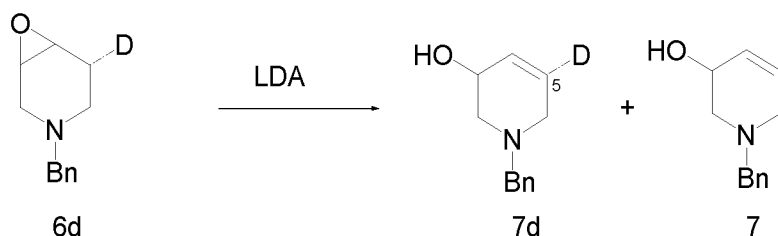
Meanwhile TFA (2.2 ml, 27.5 mmol) was added dropwise into a solution of **5d** (3.4 g, 19 mmol) in DCM (15 ml) at 0 °C and stirred for 1 hour. Cold TFA/piperidine solution was added into UHP/TFAA solution dropwise and stirred for 4 hours at 0 °C. After completion

H_2O (40 ml) was added and biphasic solution was stirred for 15 minutes followed by addition of saturated Na_2SO_3 solution. Organic layer was separated and aqueous layer was neutralized by K_2CO_3 and washed with DCM (x2). The combined organic phases were washed with saturated NaHCO_3 (x2), dried over MgSO_4 , filtered, concentrated under vacuum and purified by flash column chromatography on silica gel (hexanes/acetone (7/1))

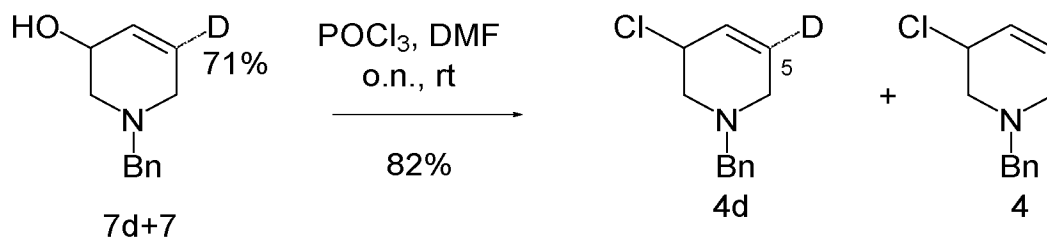
to give 1-benzyl-3,4-epoxypiperidine-5-*d* (**6d**) in 70% yield (2.6 g, 13 mmol) as a colorless oil. ^1H NMR (400 MHz, CDCl_3 , ppm) δ : 1.94-2.03 (m, 1H, CD-5 H), 2.16-2.23 (m, 1H, C-6 H), 2.33 (dd, J = 11.6, 4.4 Hz, 1H, C-6 H), 2.68 (d, J = 13.6 Hz, 1H, C-2 H), 3.02 (bdd, J = 13.6, 4.2 Hz, 1H, C-2 H), 3.20-3.24 (m, 2H, C-3, C-4 H), 3.46 (s, 2H, benzylic), 7.22-7.29 (m, 1H, aromatic), 7.30-7.33 (m, 4H, aromatic); ^{13}C NMR (101 MHz, CDCl_3 , ppm) δ : 25.4

(t, CDH), 45.9 (m), 50.8 (m), 51.4 (d, J = 3.7 Hz), 52.5, 62.5, 127.2, 128.4, 129.2, 138.0;

HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{15}\text{DON}^+$ [$\text{M}+\text{H}$] $^+$ 191.12892, found 191.12885.

1-benzyl-1,2,3,6-tetrahydropyridin-5-*d*-3-ol (7d):

In a flame dried 100 ml-round-bottom flask THF (20 ml) and diisopropyl amine (0.3 ml, 2.2 mmol) were added and cooled 0 °C. 2.5 M *n*-butyllithium solution (0.9 ml, 2.2 mmol) was added dropwise and the resultant solution was stirred at 0 °C for 20-30 minutes. A solution of 1-benzyl-3,4-epoxypiperidine-5-*d* (6d) (850 mg, 4.5 mmol) in THF (10 ml) was added dropwise into the formed LDA solution, warmed up to room temperature and stirred for 2 hours. Reaction was quenched by addition of saturated NH₄Cl solution (20 ml) and extracted with DCM. The combined organic phases were washed with brine, dried over MgSO₄, filtered, concentrated under vacuum and purified by flash column chromatography on silica gel (hexanes/acetone (5/1)) to give (7d+7) in 31% yield (265 mg, 1.4 mmol, n_D/n_H = 2.85/1) as a viscous yellow oil. ¹H NMR (400 MHz, CDCl₃, ppm) δ : 2.19 (bs, 1H (OH)), 2.52 (ddd, *J* = 11.4, 3.2, 1.0 Hz, 1H, C-2 H), 2.73-2.81 (m, 2H, C-2 H and C-6 H), 3.12 (d, *J* = 16.8 Hz, 1H, C-6 H), 3.61 (s, 2H, benzylic), 4.05 (bs, 1H, C-3 H), 5.88-5.93 (m, 1H, C-4 H), 7.23-7.29 (m, 1H), 7.29-7.34 (m, 4H); ¹³C NMR (101 MHz, CDCl₃, ppm) δ : 52.7 (d, *J* = 9.7 Hz, C-6), 57.6, 62.5, 64.6 (d, *J* = 1.7 Hz, C-3), 127.2, 127.8 (d, *J* = 13.0 Hz, C-4), 128.3, 128.8 (m, CD-5), 129.0, 137.9; HRMS (ESI) *m/z* calcd for C₁₂H₁₅DO⁺ [M+H]⁺ 191.12892, found 191.12871.

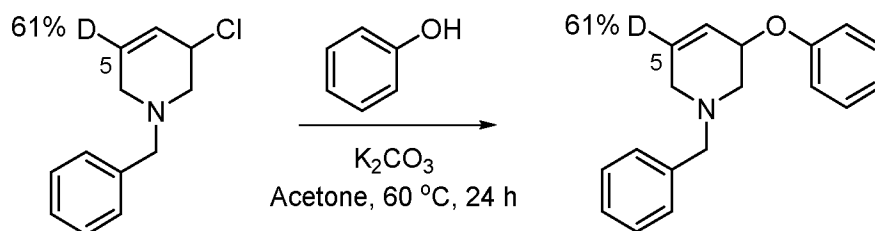
1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine-5-*d* (4d):

A solution of (7d+7 n_D/n_H = 2.45/1) (312 mg, 1.6 mmol) in DMF (7 mL) was cooled down to 0 °C and under argon atmosphere POCl₃ (0.3 mL, 3.5 mmol) was added dropwise. The reaction mixture was left gradually warming up to room temperature and was stirred overnight. H₂O was carefully added at 0 °C. The reaction solution was extracted with EtOAc. Aqueous layer was neutralized by K₂CO₃ and washed with EtOAc (x3). The combined organic phases were washed with brine (x2), dried over MgSO₄, filtered, concentrated under vacuum and purified by flash column chromatography on silica gel (hexanes or pentane/EtOAc (9/1)) to give (4d+4) in 82% yield (280 mg, 1.3 mmol, n_D/n_H =

1.56/1) as a colorless oil. ¹H NMR (400 MHz, C₆D₆, ppm) δ: 2.53-2.58 (m, 3H, C-2 H and C-6 H), 2.67 (dd, *J* = 11.6, 4.8 Hz, 1H, C-2 H), 3.21 (d, *J* = 13.2 Hz, 1H, benzylic), 3.28 (d, *J* = 13.2 Hz, 1H, benzylic), 4.30-4.35 (m, 1H, C-3 H), 5.63-5.67 (m, 1H, C-4 H), 7.08-7.12 (m, 1H, aromatic), 7.16-7.19 (m, 2H, aromatic), 7.26-7.28 (m, 2H, aromatic); ¹³C NMR (101 MHz, CDCl₃, ppm) δ: 52.0 (d, *J* = 9.3 Hz, C-6), 53.7 (C-3), 57.2, 61.8, 126.8, 126.7 (d, *J* = 12.5 Hz, C-4), 127.3, 128.3, 128.9, 129.14 (m, C-5), 137.5; HRMS (ESI) *m/z* calcd for C₁₂H₁₄DONCl⁺ [M+H]⁺ 209.09503, found 209.09515.

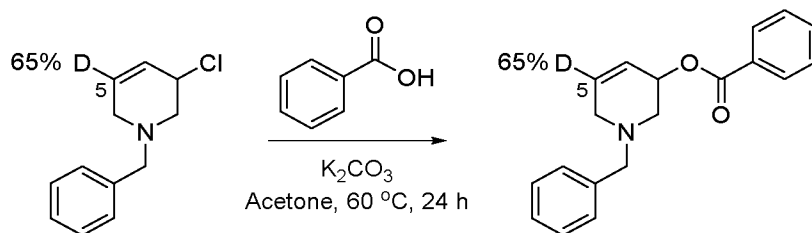
Nucleophilic Substitution Reactions with 4d

1-benzyl-3-phenoxy-1,2,3,6-tetrahydropyridine-5-*d* (10d):



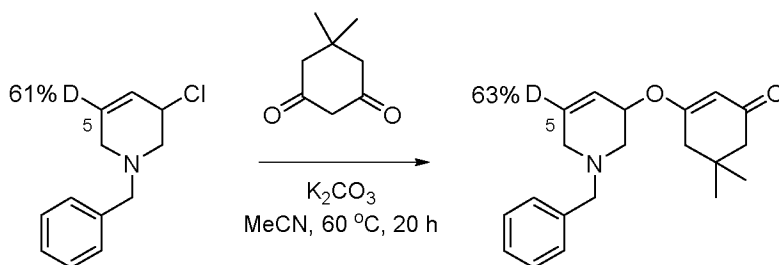
¹H NMR (400 MHz, C₆D₆, ppm) δ: 2.56 (dd, *J* = 10.8, 6.8 Hz, 1H, C-2 H), 2.58-2.64 (m, 1H, C-6 H), 2.76-2.82 (m, 1H, C-6 H), 2.94 (dd, *J* = 10.8, 5.2 Hz, 1H, C-2 H), 3.31 (d, *J* = 13.2 Hz, 1H, benzylic), 3.36 (d, *J* = 13.2 Hz, 1H, benzylic), 4.84-4.89 (m, 1H, C-3 H), 5.85-5.88 (m, 1H, C-4 H), 6.76-6.82 (m, 1H, aromatic), 6.85-6.88 (m, 2H, aromatic), 7.05-7.11 (m, 3H, aromatic), 7.15-7.19 (m, 2H, aromatic), 7.28-7.30 (m, 2H, aromatic); ¹³C NMR (101 MHz, CDCl₃, ppm) δ: 52.4 (d, *J* = 9.2 Hz, C-6), 54.0, 62.2, 70.7, 115.8, 120.9, 124.9 (d, *J* = 13.1 Hz, C-4), 127.2, 128.3, 129.0, 129.5, 129.8 (m, C-5), 137.6, 157.7; HRMS (ESI) *m/z* calcd for C₁₈H₁₉DON⁺ [M+H]⁺ 267.16022, found 267.15994.

1-benzyl-1,2,3,6-tetrahydropyridin-3-yl benzoate-5-*d* (11d):



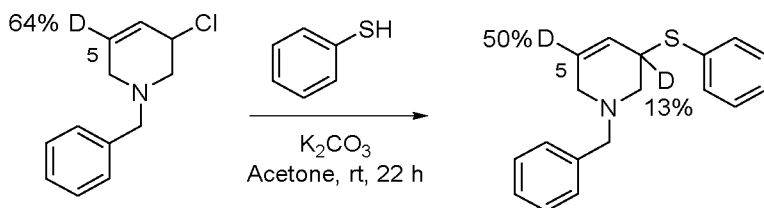
¹H NMR (400 MHz, CDCl₃, ppm) δ: 2.79-2.87 (m, 2H, C-2 H), 2.98 (bdt, *J* = 17.2, 2.0 Hz, 1H, C-6 H), 3.16 (bdt, *J* = 16.8, 2.0 Hz, 1H, C-6 H), 3.61 (d, *J* = 13.2 Hz, 1H, benzylic), 3.72 (d, *J* = 13.2 Hz, 1H, benzylic), 5.50-5.54 (m, 1H, C-3 H), 5.91-5.96 (m, 1H, C-4 H), 7.20-7.31 (m, 3H), 7.37-7.39 (m, 2H), 7.42-7.45 (m, 2H), 7.53-7.58 (m, 1H), 8.04-8.07 (m, 2H); ¹³C NMR (101 MHz, CDCl₃, ppm) δ: 52.2 (d, *J* = 9.3 Hz, C-6), 53.9, 61.9, 68.2, 123.9 (d, *J* = 13.1 Hz, C-4), 127.2, 128.27, 128.28, 128.8, 129.7, 130.4, 131.1 (m, C-5), 132.8, 137.8, 166.3; HRMS (ESI) *m/z* calcd for C₁₉H₁₉DO₂N⁺ [M+H]⁺ 295.15513, found 295.15475.

3-((1-benzyl-1,2,3,6-tetrahydropyridin-3-yl-5-*d*)oxy)-5,5-dimethylcyclohex-2-en-1-one (12d):

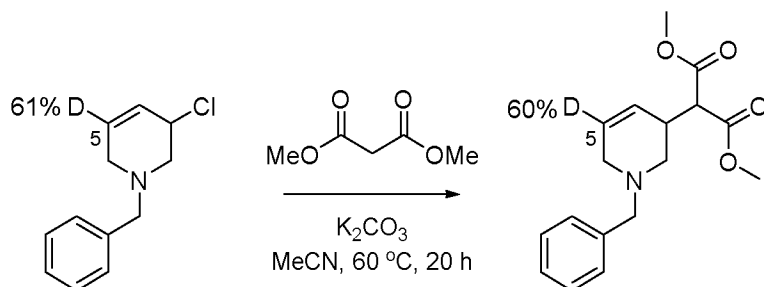


- 5 **¹H NMR (400 MHz, CDCl₃, ppm) δ:** 1.02 (s, 3H), 1.05 (s, 3H), 2.15 (d, *J* = 17.6 Hz, 1H), 2.19 (d, *J* = 16.8 Hz, 1H), 2.23 (d, *J* = 17.2 Hz, 1H), 2.29 (d, *J* = 17.2 Hz, 1H), 2.69 (dd, *J* = 12.0, 4.4 Hz, 1H, C-2 H), 2.77 (dd, *J* = 12.0, 4.4 Hz, 1H, C-2 H), 2.96 (bd, *J* = 16.8 Hz, 1H, C-6 H), 3.14 (bd *J* = 17.2 Hz, 1H, C-6 H), 3.55 (d, *J* = 13.2 Hz, 1H, benzylic), 3.72 (d, *J* = 13.2 Hz, 1H, benzylic), 4.70-4.71 (m, 1H, C-3 H), 5.33 (s, 1H), 5.83-5.86 (m, 1H, C-4 H),
 10 7.22-7.27 (m, 1H), 7.28-7.34 (m, 4H); **¹³C NMR (101 MHz, CDCl₃, ppm) δ:** 28.21, 28.33, 32.4, 43.2, 50.7, 52.3 (d, *J* = 9.6 Hz, C-6), 52.9, 61.9, 70.9, 101.9, 122.6 (d, *J* = 13.2 Hz, C-4), 127.3, 128.3, 128.9, 131.7 (m, C-5), 137.4, 174.9, 199.4; **HRMS (ESI) *m/z* calcd for C₂₀H₂₅DO₂N⁺ [M+H]⁺ 313.20208, found 313.20153.**

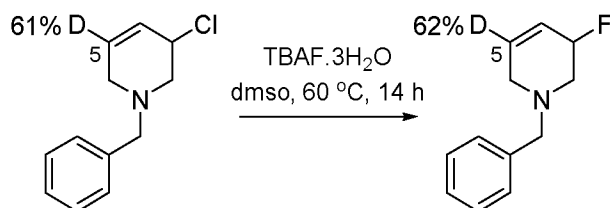
15 **1-benzyl-3-(phenylthio)-1,2,3,6-tetrahydropyridine-5-*d* (13d):**



- ¹H NMR (400 MHz, CDCl₃, ppm) δ:** 2.64 (dd, *J* = 11.8, 5.8 Hz, 1H, C-2 H), 2.81 (dd, *J* = 11.6, 4.8 Hz, 1H, C-2 H), 2.95-3.00 (m, 1H, C-6 H), 3.04-3.09 (m, 1H, C-2 H), 3.52 (d, *J* = 13.2 Hz, 1H, benzylic), 3.71 (d, *J* = 13.2 Hz, 1H, benzylic), 3.83-3.87 (m, 1H, C-3 H), 5.83-
 20 5.87 (m, 1H, C-4 H), 7.17-7.28 (m, 4H), 7.29-7.37 (m, 6H); **¹³C NMR (101 MHz, CDCl₃, ppm) δ:** 44.7 (d, *J* = 2.5 Hz, C-3), 52.5 (d, *J* = 9.4 Hz, C-6), 54.7 (d, *J* = 10.3 Hz, C-2), 62.2, 125.8 (m, C-4), 126.9, 127.1, 128.0 (d, *J* = 5.9 Hz, C-5), 128.2, 128.8, 129.1, 131.9, 135.1, 137.9; **HRMS (ESI) *m/z* calcd for C₁₈H₁₉DNS⁺ [M+H]⁺ 283.13737, found 283.13702.**

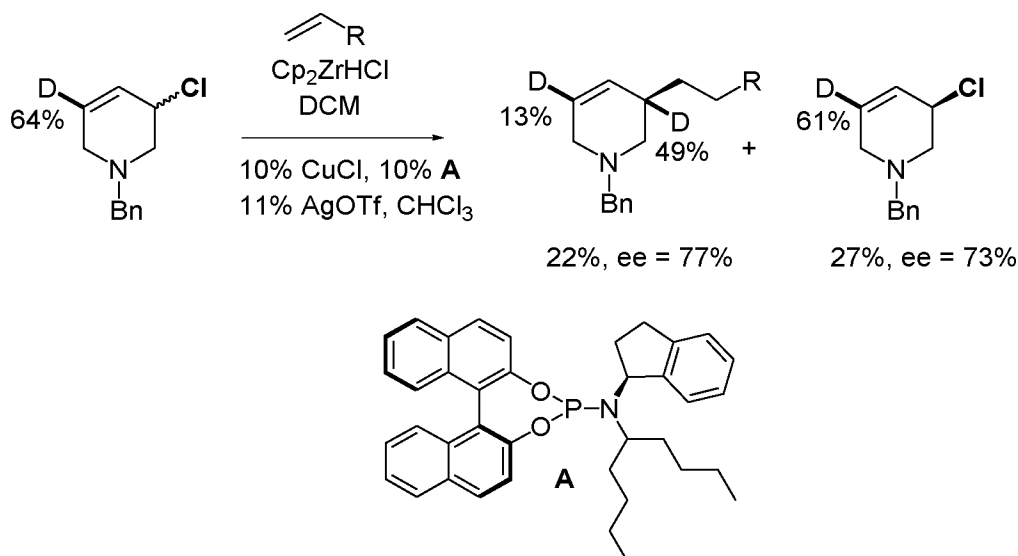
Dimethyl 2-(1-benzyl-1,2,3,6-tetrahydropyridin-3-yl-5-*d*)malonate (14d):

¹H NMR (400 MHz, CDCl₃, ppm) δ: 2.50 (d, *J* = 4.0 Hz, 2H, C-2 H), 2.84 (dt, *J* = 16.4, 2.4 Hz, 1H, C-6 H), 2.91-2.98 (m, 1H, C-3 H), 3.10 (dt, *J* = 16.4, 1.8 Hz, 1H, C-6 H), 3.44 (d, *J* = 12.8 Hz, 1H, benzylic), 3.57 (s, 3H, CH₃), 3.62 (d, *J* = 12.8 Hz, 1H, benzylic), 3.66 (d, *J* = 10.0 Hz, 1H, CH(CO₂CH₃)₂), 3.73 (s, 3H, CH₃), 5.62-5.66 (m, 1H, C-4 H), 7.21-7.26 (m, 1H), 7.27-7.36 (m, 4H); **¹³C NMR (101 MHz, CDCl₃, ppm) δ:** 36.0, 52.3 (2C), 52.4, 53.1 (d, *J* = 9.5 Hz, C-6), 55.2, 62.4, 125.3 (d, *J* = 13.7 Hz, C-4), 127.0, 128.2, 128.3 (m, C-5), 129.0, 138.3, 168.85, 169.93; **HRMS (ESI) *m/z* calcd for C₁₇H₂₁DO₄N⁺ [M+H]⁺ 305.16061, found 305.16040.**

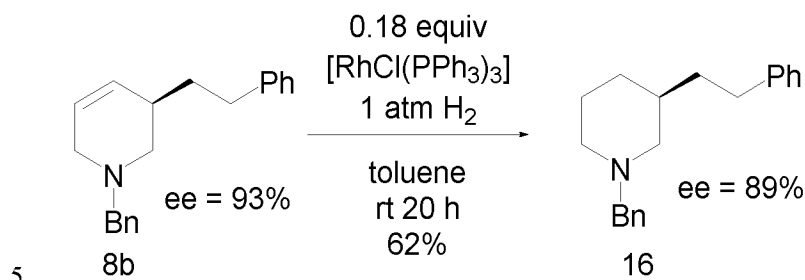
1-benzyl-3-fluoro-1,2,3,6-tetrahydropyridine-5-*d* (15d):

¹H NMR (400 MHz, CDCl₃, ppm) δ: 2.70 (dddd, *J* = 22.8, 12.4, 4.0, 1.2 Hz, 1H, C-2 H), 2.83-2.93 (m, 2H, C-2 and C-6 H), 3.12 (bdd, *J* = 17.0, 9.4 Hz, 1H, C-6 H), 3.62 (d, *J* = 13.2 Hz, 1H, benzylic), 3.68 (d, *J* = 13.2 Hz, 1H, benzylic), 5.0 (dm, *J*_{HF} = 49.2 Hz, 1H, C-3 H), 5.87-5.93 (m, 1H, C-4 H), 7.24-7.28 (m, 1H), 7.30-7.36 (m, 4H); **¹³C NMR (101 MHz, CDCl₃, ppm) δ:** 52.1 (dd, ⁴*J* = 3.28, *J* = 9.4 Hz, C-6), 54.5 (d, ²*J* = 22.4 Hz, C-2), 62.0, 84.7 (d, ¹*J* = 166.8 Hz, C-3), 123.5 (bd, ²*J* = 18.3 Hz, C-4), 127.2, 128.3, 129.0, 132.2 (m, C-5), 137.5; **HRMS (ESI) *m/z* calcd for C₁₂H₁₄DNF⁺ [M+H]⁺ 193.12458, found 193.1246.**

General Procedure 1 performed with 4d:



Synthesis of (R)-1-benzyl-3-phenethylpiperidine (16)



A solution of (*R*)-1-benzyl-3-phenethyl-1,2,3,6-tetrahydropyridine (**8b**) (40 mg, 0.14 mmol), [RhCl(PPh₃)₃] (24 mg, 0.026 mmol) in toluene (2 mL) was first flushed with argon and after with H₂. The mixture was then stirred for 20 h at room temperature under H₂ atmosphere (1 atm). The resulting mixture was concentrated *in vacuo*. Purification by column

chromatography (pentane/EtOAc (9/1)) gave **16** in 62% yield (25 mg, 0.09 mmol) as a colourless oil. Enantiomeric excess (for corresponding Cbz carbamate) of 89% was determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; hexane:IPA 97.5:2.5; λ = 210 nm; major enantiomer t_R = 9.6 min; minor enantiomer t_R = 12.3 min]; $[D]_{589}^{25}$ = -6.5 (c 1.0 CHCl₃) for 89% ee; **¹H NMR (400 MHz, CDCl₃, ppm) δ** : 1.43-1.71 (m, 7H), 1.78-1.82 (m, 1H), 1.92 (td, J = 11.2, 2.8 Hz, 1H), 2.52-2.64 (m, 2H), 2.78 (bd, J = 10.8 Hz, 1H), 2.84 (bd, J = 10.4 Hz, 1H), 3.46 (d, J = 13.2 Hz, 1H), 3.51 (d, J = 13.2 Hz, 1H), 7.12-7.17 (m, 3H), 7.23-7.27 (m, 3H), 7.28-7.33 (m, 4H); **¹³C NMR (101 MHz, CDCl₃, ppm) δ** : 25.3, 30.9, 33.2, 35.7, 36.4, 54.3, 60.2, 63.6, 125.6, 126.8, 128.1, 128.2, 128.3, 129.1, 142.7 (2C); **IR** (ν_{max} /cm⁻¹): 698, 739, 1029, 1075, 1107, 1157, 1452, 1494, 2337, 2361, 2794, 2852, 2927, 3026; **HRMS** (ESI) m/z calcd for C₂₀H₂₆N⁺ [M+H]⁺ 280.20598, found 280.20590. For Cbz carbamate **¹H NMR (400 MHz, CDCl₃, ppm) δ** : 1.25-1.33 (m, 4H), 1.45-1.54 (m, 3H), 1.66 (bd, J = 9.2 Hz, 1H), 1.88 (bd, J = 13.6 Hz, 1H rotameric), 2.63 (bs, 1H rotameric), 2.86 (td,

$J = 11.6, 2.8$ Hz, 1H), 3.48-3.53 (m, 1H), 4.00 (dt, $J = 13.2, 4.0$ Hz, 1H rotameric), 5.13 (bs, 2H), 7.16-7.19 (m, 3H), 7.24-7.28 (m, 2H), 7.29-7.37 (m, 5H).

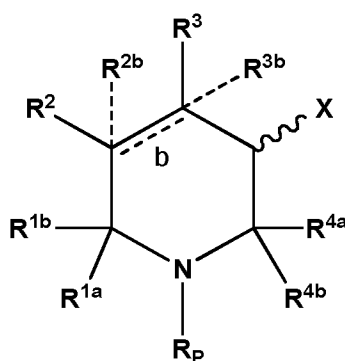
References to Experimental Details and Spectral Data

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Claims

1. A compound according to Formula (I) or a salt, hydrate or solvate thereof, as shown below, with an enantiomeric excess of at least 20%:

5



Formula (I)

10 wherein:

bond **b** is independently selected from a single bond or double bond;

X is a leaving group;

15

R_P is a protecting group, hydrogen, (1-8C)alkyl, (3-10C)cycloalkyl or aryl;

wherein R^{1a} and R^{1b} are identical and R^{4a} and R^{4b} are identical; and R^{1a}, R^{1b}, R^{4a} and R^{4b} are selected from hydrogen, carbonyl, (1-8C)alkyl, (3-10C)cycloalkyl, (3-10C)cycloalkenyl, aryl, heteroaryl and heterocyclyl; wherein R^{1a}, R^{1b}, R^{4a} and R^{4b} are optionally further substituted by one or more substituent groups independently selected from halo, (1-4C)alkyl and (1-4C)haloalkyl;

when bond **b** is a double bond, R^{2b} and R^{3b} are absent, R² is selected from hydrogen, halo, (1-8C)alkyl, (3-10C)cycloalkyl, alkoxy, hydroxyl and R³ is selected from hydrogen, halo (1-8C)alkyl, (3-10C)cycloalkyl, (3-10C)cycloalkenyl, (1-8C)alkoxy, hydroxyl, epoxide and aryl; or

when bond **b** is a single bond, R² and R^{2b} are identical and are selected from hydrogen, halo, (1-8C)alkyl and (3-10C)cycloalkyl; and R³ and R^{3b} are identical and

selected from hydrogen, halo, (1-8C)alkyl, (3-10C)cycloalkyl, (3-10C)cycloalkenyl, (1-8C)alkoxy, hydroxyl, epoxide and aryl; and

wherein R^2 , R^3 and, if present R^{2b} and R^{3b} are optionally substituted by one or more substituent groups independently selected from halo, (1-4C)alkyl and (1-4C)haloalkyl.

5

2. A compound according to claim 1, wherein X is selected from alkoxy, halo, tosylate, mesylate and perfluoroalkylsulfonates.

10

3. A compound according to any preceding claim, wherein X is halo, for example chloro.

15

4. A compound according to any preceding claim, wherein R_P is a protecting group selected from acyl, arylmethyl (e.g. benzyl), arylmethoxycarbonyl (e.g. benzyloxycarbonyl) and alkoxycarbonyl, or R_P is hydrogen, (1-8C)alkyl, (3-10C)cycloalkyl.

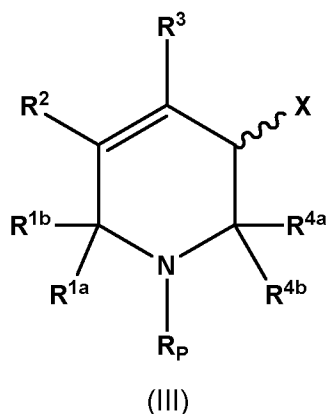
20

5. A compound according to claim 4, wherein R_P is benzyl or benzyloxycarbonyl.

6. A compound according to any preceding claim, wherein R^{1a} and R^{1b} are hydrogen or (1-4C)alkyl.

7. A compound according to any preceding claim, wherein R^{4a} and R^{4b} are hydrogen or (1-4C)alkyl.

8. A compound according to claim 1, which has the formula (IIa) below:



25

wherein X, R^{1a} , R^{1b} , R^2 , R^3 , R^{4a} , R^{4b} and R_P are as defined in any of the preceding claims.

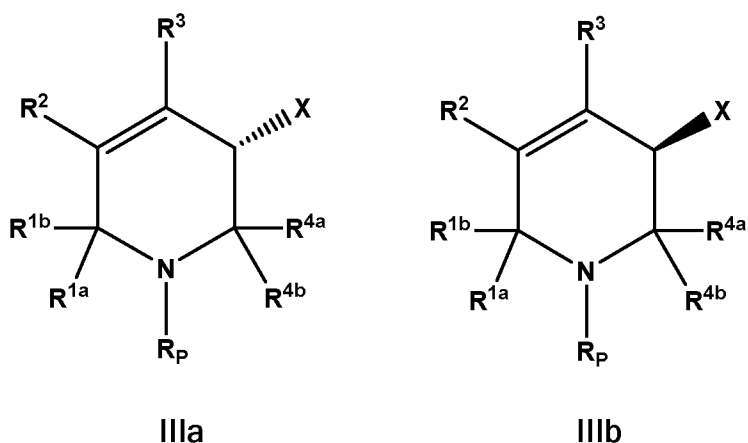
30

9. A compound according to claim 8, wherein R^2 is selected from hydrogen, halo or (1-8C)alkyl.

10. A compound according to claim 8 or 9, wherein R^3 is selected from hydrogen, halo, (1-8C)alkyl, or aryl.

11. A compound according to any one of claims 8 to 10, wherein each of R^{1a} , R^{1b} , R^2 , R^3 , R^{4a} , R^{4b} are hydrogen.

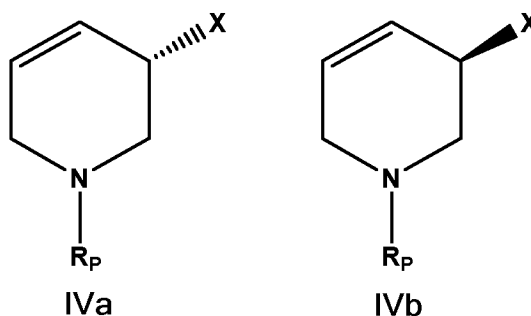
12. A compound according to any preceding claim, having the formula (IIIa) or (IIIb), shown below:



10 wherein each of X, R^{1a} , R^{1b} , R^2 , R^3 , R^{4a} , R^{4b} and R_P are as defined in any of the preceding claims.

13. A compound according to any preceding claim, having the formula (IIIa) or (IIIb), shown below:

15



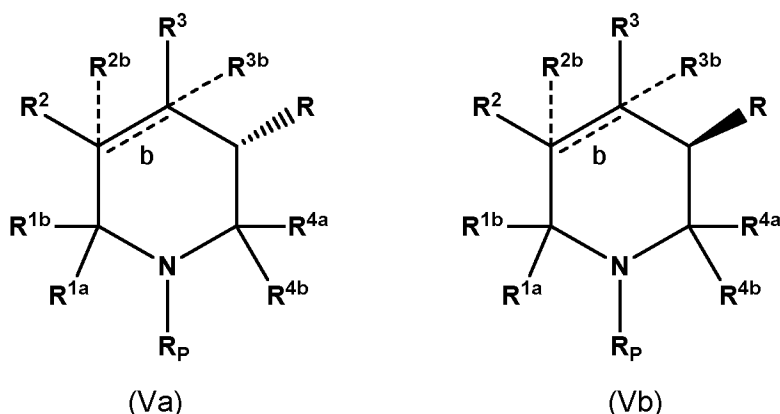
wherein X and R_P are as defined in any of the preceding claims.

14. A compound according to any preceding claim, with an enantiomeric excess of at least 20%, optionally at least 40%.

15. A compound according to any preceding claim, with an enantiomeric excess of at least 90%.

16. The use of a compound according to any of claims 1 to 15, in stereospecific reactions.

5 17. A method of producing a compound having the formula (Va) or (Vb):



wherein R is a substituent group; and

10 bond **b**, R^{1a}, R^{1b}, R², R^{2b}, R³, R^{3b}, R^{4a}, R^{4b} and R_P are as defined in any one of claims 1 to 15, and wherein the compound of formula (Va) or (Vb) has an enantiomeric excess of at least 20%;

wherein the process comprises reacting a compound as defined in any one of claims 1 to 15, with a nucleophilic compound comprising and the R group, so that the X-
15 group in the compound according to any one of claims 1 to 15 is replaced by the R group to form a compound of formula (Va) or (Vb).

18. A method according to claim 17, wherein the nucleophilic compound comprising an R group is a compound of the formula:



wherein L_G is a displaceable group; or the nucleophilic compound comprising an R group is an alkene.

19. The method according to claim 17 or 18, wherein the compound of formula (Va) or
25 (Vb) has an enantiomeric excess of at least 40%, preferably at least 60%.

20. The method according to any one of claims 17 to 19, further comprising the step of removing any protecting groups present on the compound of formula (Va) or (Vb).

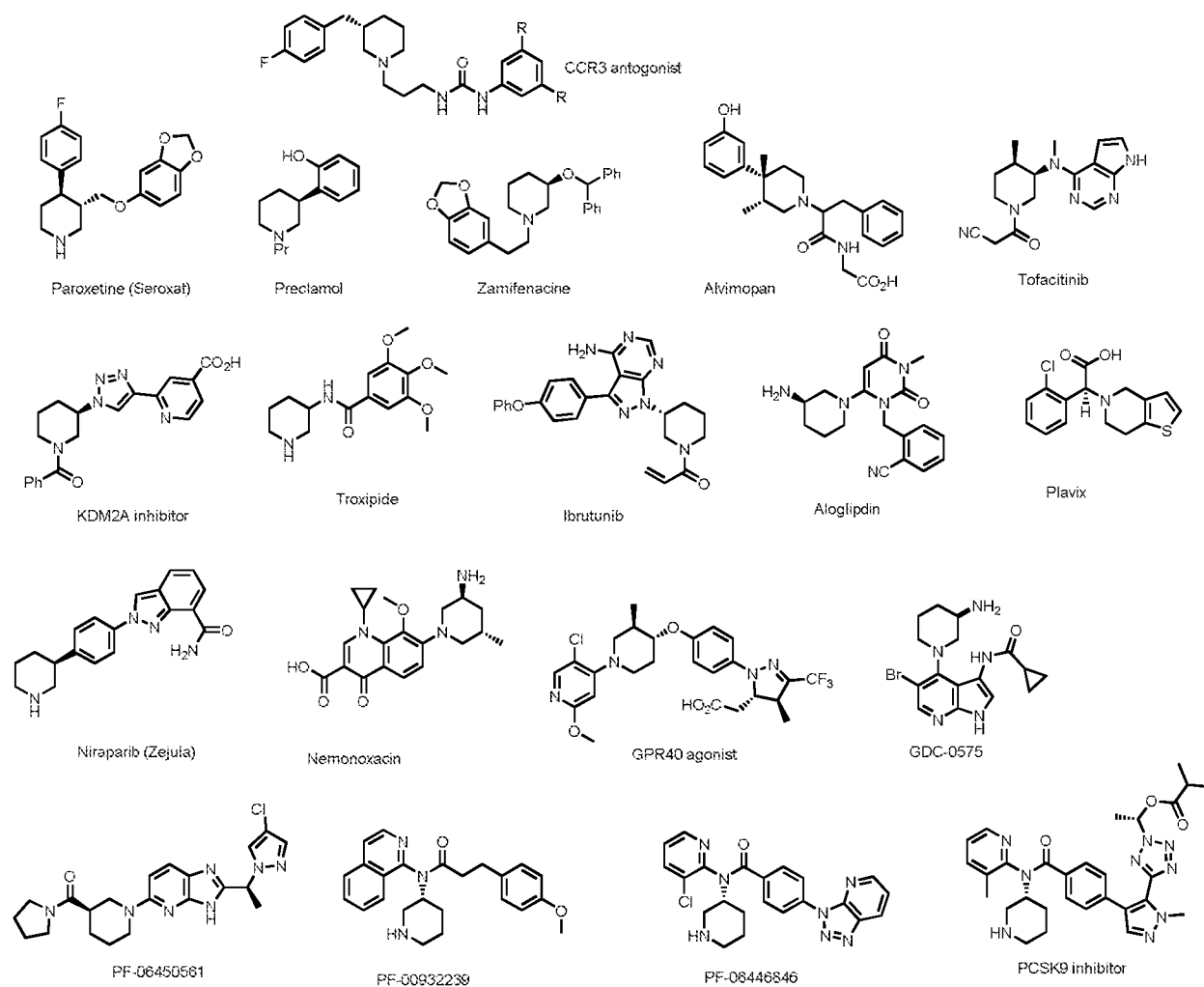


FIGURE 1

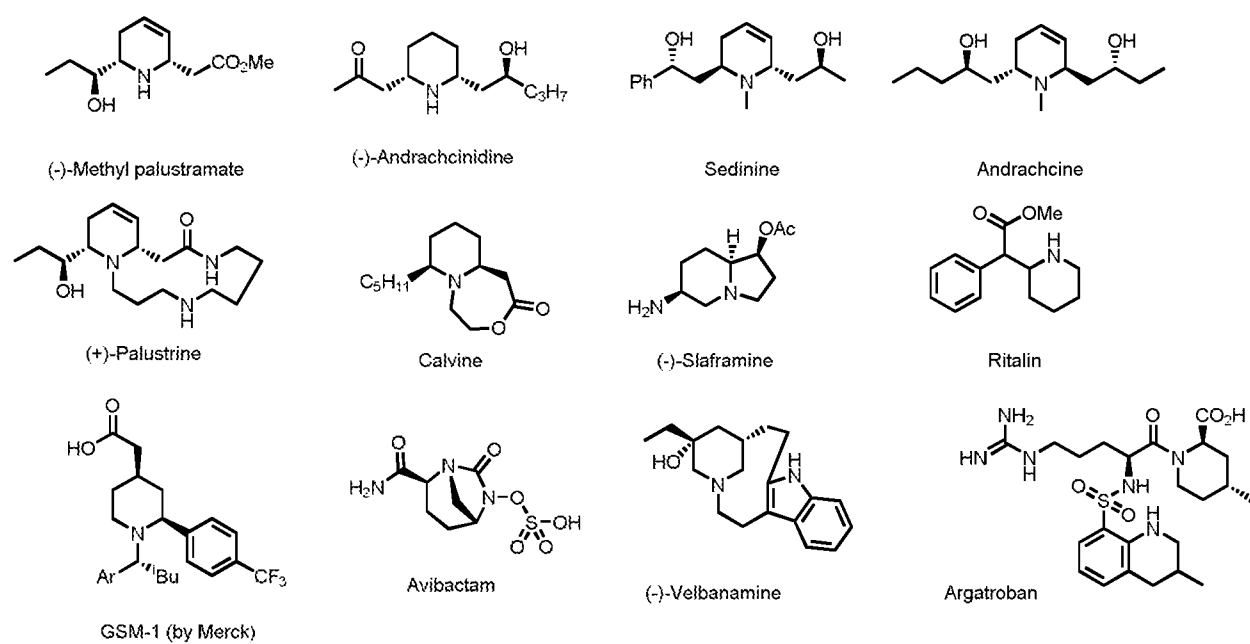


FIGURE 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2019/052581

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/70 C07D211/72 C07D211/74
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HIDEKI SAKAGAMI ET AL: "Lipase-Mediated Synthesis of Enantiopure N-Carbobenzoxy-3-hydroxy-1,2,3,4-tetrahydro- and N-Carbobenzoxy-3-hydroxy-1,2,3,6-tetrahydro pyridines from 3-Hydroxypyridine", SYNTHESIS, vol. 2000, no. 04, 1 January 2000 (2000-01-01), pages 521-524, XP055631649, STUTTGART, DE. ISSN: 0039-7881, DOI: 10.1055/s-2000-6363 scheme 5; page 523; compounds (R)-2, (S)-2, (S)-14 ----- -/-	1,5-16



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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