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(71) Applicant: **THE UNIVERSITY OF LIVERPOOL** [GB/GB]; Foundation Building, 765 Brownlow Hill, Liverpool L69 7ZX (GB).

(72) Inventors: **XIAO, Jianliang**; University of Liverpool, Department of Chemistry, Crown Street, Liverpool L69 7ZD (GB). **WU, Jianjun**; 99 Newsham Drive, Liverpool L6 7UH (GB).

(74) Agents: **WELLS, Andrew** et al.; HGF Limited, 4th Floor, Merchant Exchange, 17-19 Whitworth Street West, Manchester, M1 5WG (GB).

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(54) Title: SYNTHETIC PROCESS

(57) Abstract: The present invention relates to a process for preparing substituted piperidine compounds and especially chiral substituted piperidine compounds. The process involves reacting a substituted pyridinium ion with an amine as defined herein, in the presence of a hydrogen donor, a catalysts and a suitable solvent.

Synthetic process

[0001] This invention relates to a process for synthesising substituted piperidine compounds. More particularly, but not exclusively, the present invention relates to a process for synthesising chiral substituted piperidine compounds. Substituted piperidine compounds are useful for a variety of important commercial applications, especially in the pharmaceutical, biotechnology and agrochemical fields.

BACKGROUND

[0002] Piperidine and its derivatives are ubiquitous building blocks in the synthesis of many naturally occurring products, pharmaceuticals and fine chemicals. In 2008, there were twenty one piperidine-containing drugs in Top 200 Selling Drugs, which showed sales of $11.2 billion (USD), with $ 2.5 billion for OxyContin (Purdue Pharma), $ 1.1 billion for the Concerta (Johnson & Johnson) and $0.31 billion for the Focalin XR (Novartis). In addition, Paxil (GSK), a chiral piperidine drug, had attributed total sales of $11.7 billion (USD) in 1997-2006.

[0003] Apart from the significant drug market, chiral piperidine compounds have also been studied extensively in both academic institutions and R&D sectors of pharmaceutical and biotechnology companies, due to their abundant presence as naturally occurring products which often have unique bioactivities, such as anopterine, pergoline, scopolamine and morphine, coniine, pipecoline, anabasine and anatabine, β-conhydrine, pipecolic acid, sedamine, indolizidine alkaloids and aza-sugars. As a result, the market for the chiral-piperidine based fine chemicals, which serve as building blocks for drug discovery and development, is of great significance and increasingly expanding due to the increasing demand mainly from pharmaceutical companies and generic drug producers.

[0004] While small chiral, cyclic amines such as piperidines are privileged chemical scaffolds, present in many natural products and pharmaceutical compounds[1], approaches for the effective, atom economic synthesis of such compounds from simple starting materials are rare.

[0005] One attractive approach is the catalytic reduction of the parent heterocycles using hydrogen (H_2) or another hydrogen source. Although much progress has been made in the asymmetric reduction of the more reactive benzofused heterocycles, direct synthesis of chiral piperidines by reduction of simple pyridine derivatives remains extremely challenging.[2]

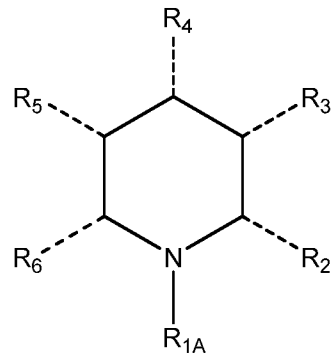
[0006] It is the aromatic nature of pyridine (resonance energy 27 kcal/mol), coupled with the tendency of pyridines to poison metal catalysts by coordination through the basic nitrogen atom, that makes the reduction of pyridines a particularly challenging task, typically requiring heterogeneous catalysts and forcing reaction conditions. As a result, the great advances made in homogeneous asymmetric hydrogenation have not been brought to bear, and a simple cost-effective asymmetric reduction of pyridines remains unrealised.[2]

[0007] It is therefore an objective of the present application to provide a facile process for the formation of substituted piperidines.

[0008] It is a further objective to provide a facile process for the formation of chiral piperidines by the hydrogenation of pyridines.

BRIEF SUMMARY OF THE DISCLOSURE

[0009] In a first aspect, the present invention provides a process for the preparation of a substituted piperidine compound of formula I:



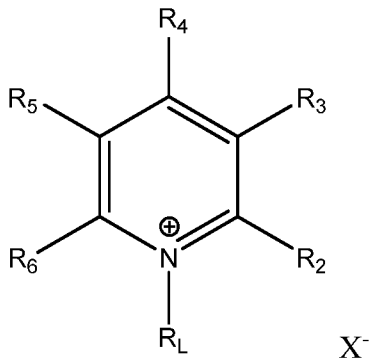
I

wherein:

R_{1A} is a substituent group as defined herein;

R_2, R_3, R_4, R_5, and R_6 are each independently selected from hydrogen or a substituent group as defined herein, with the proviso that at least one of R_2, R_3, R_4, R_5, and R_6 is a substituent group as defined herein;

the process comprising reacting, in the presence of a suitable solvent, a pyridinium salt of the formula:



wherein:

X^- is a counter ion,

R_L is a substituent group as defined herein,

and R_2, R_3, R_4, R_5, and R_6 are as defined above;

with an amine of the formula:

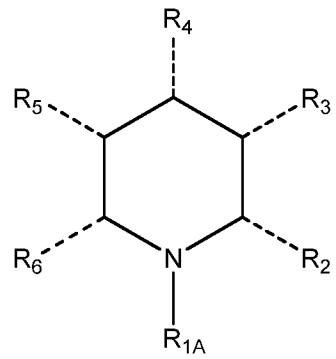
$$H_2N\text{-}R_{1A}$$

wherein:

R_{1A} is a substituent group as defined above;

in the presence of a hydrogen donor and a catalyst that is capable of generating hydride from the hydrogen donor.

[0010] In a particular aspect, the present invention provides a process for the preparation of a chiral substituted piperidine compound of formula I:

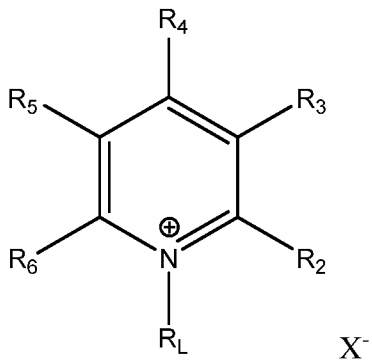


I

wherein:

R_{1A}, R_2, R_3, R_4, R_5, and R_6 are each as defined herein, with the proviso that at least one of R_2, R_3, R_4, R_5, and R_6 is a substituent group as defined herein and the carbon atom to which the group is attached is present in the (R) or (S) stereochemical configuration;

the process comprising reacting, in the presence of a suitable solvent, a pyridinium salt of the formula:



wherein:

X^-, R_L, R_2, R_3, R_4, R_5, and R_6 are as defined above;

with a chiral amine of the formula:

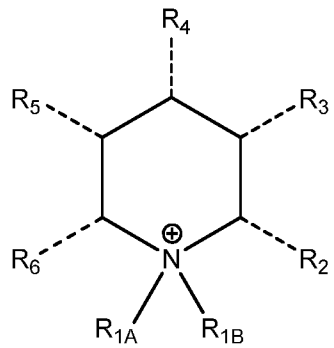
$$H_2N\text{-}R_{1A}$$

wherein:

R_{1A} is a substituent group as defined above;

in the presence of a hydrogen donor and a catalyst that is capable of generating hydride from the hydrogen donor.

[0011] In a further aspect, the present invention provides a process for the preparation of a substituted piperidine compound of formula II:



II

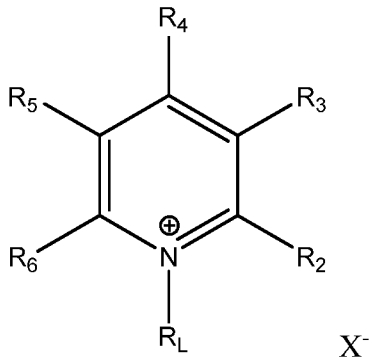
wherein:

R_{1A} is a substituent group as defined herein;

R_{1B} is a substituent group as defined herein;

R_2, R_3, R_4, R_5, and R_6 are each independently selected from hydrogen or a substituent group as defined herein, with the proviso that at least one of R_2, R_3, R_4, R_5, and R_6 is a substituent group as defined herein;

the process comprising reacting, in the presence of a suitable solvent, a pyridinium salt of the formula:



wherein:

X^-, R_L, R_2, R_3, R_4, R_5, and R_6 are as defined above;

with an amine of the formula:

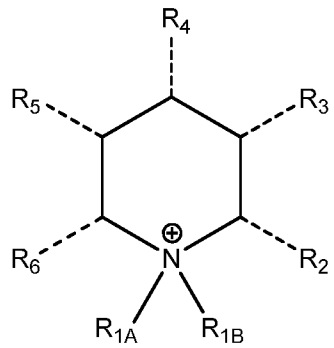
$$HNR_{1A}R_{1B}$$

wherein:

R_{1A} and R_{1B} are as defined above;

in the presence of a hydrogen donor and a catalyst capable of generating hydride from the hydrogen donor.

[0012] In a particular aspect, the present invention provides a process for the preparation of a chiral substituted piperidine compound of formula II above:



II

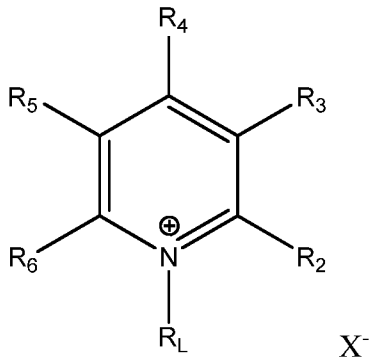
wherein:

R_{1A} is a substituent group as defined herein;

R_{1B} is a substituent group as defined herein;

R_2, R_3, R_4, R_5, and R_6 are each independently selected from hydrogen or a substituent group as defined herein, with the proviso that at least one of R_2, R_3, R_4, R_5, and R_6 is a substituent group as defined herein and the carbon atom to which the group is attached is present in the (R) or (S) stereochemical configuration;

the process comprising reacting, in the presence of a suitable solvent, a pyridinium salt of the formula:



wherein:

X^- is a counter ion,

R_L is a substituent group as defined herein,

and R_2, R_3, R_4, R_5, and R_6 are as defined above;

with a chiral amine of the formula:

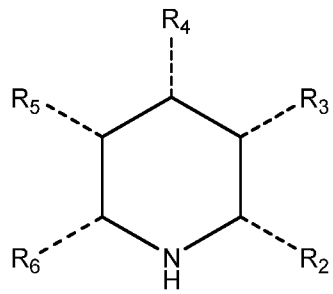
$$HNR_{1A}R_{1B}$$

wherein:

R_{1A} and R_{1B} are as defined above;

in the presence of a hydrogen donor and a catalyst capable of generating hydride from the hydrogen donor.

[0013] In a further aspect, the present invention relates to the formation of a substituted piperidine of formula III below



III

wherein:

R_2, R_3, R_4, R_5, and R_6 are as defined herein;

the process comprising:

forming a compound of formula I as defined above and deprotecting the compound of formula I to remove the group R_{1A}.

[0014] The hashed bonds are used herein in Formulae I, II and III to indicate that the carbon atom of the piperidine ring to which the R group is attached may be chiral and in either the (S) or the (R) stereochemical configuration.

[0015] In a further aspect, the present invention relates to certain novel piperidine compounds of formula I, II or III described herein (including any compounds exemplified in the example section below).

[0016] It has surprisingly been found that the processes of the present invention enable substituted piperidine compounds of formula I, II and III to be prepared by facile processes. In particular, the processes for forming compounds of formula I or II can be carried out in one pot . The resultant end products can be attained in good yields.

[0017] One particular advantage of the processes of the present invention is that the use of a chiral amine of the formula H_2NR_{1A} or $HNR_{1A}R_{1B}$ enables chiral substituted piperidines of formula I, II or III to be prepared with good yields and with high enantiomeric purity. The chirality of the amine used in the reaction directly dictates the chirality of the carbon atoms to which the substituent groups R_2, R_3, R_4, R_5 and R_6 are attached. The ability to control the chirality of the resultant piperidine in this way (i.e. by the selection of a suitable chiral amine) and in such a facile reaction process represents a major advance in this field.

DETAILED DESCRIPTION

Definitions

[0018] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

[0019] The term "hydrocarbyl" as used herein includes reference to moieties consisting exclusively of hydrogen and carbon atoms; such a moiety is an aliphatic moiety. The moiety may, for example, comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms. Examples of hydrocarbyl groups include C_{1-6} alkyl (e.g. C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl); alkenyl (e.g. 2-butenyl); and alkynyl (e.g. 2-butynyl) and the like.

[0020] 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.

[0021] The term "(m-nC)" or "(m-nC) group" used alone or as a prefix, refers to any group having m to n carbon atoms.

[0022] The term "carbocyclyl" as used herein includes reference to a saturated (e.g. cycloalkyl) or unsaturated (e.g. aryl) ring moiety having 3, 4, 5, 6, 7, 8, 9 or 10 ring carbon atoms. In particular, carbocyclyl includes a 3- to 10-membered ring or ring system and, in particular, a 6-membered ring, which may be saturated or unsaturated. A carbocyclic moiety is, for example, selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, bicyclo[2.2.2]octyl, phenyl, naphthyl, and the like.

[0023] "(3-8C)cycloalkyl" means a hydrocarbon ring containing from 3 to 8 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicycle[2.2.2]octane, bicycle[2.1.1]hexane, bicycle[1.1.1]pentane and bicyclo[2.2.1]heptyl.

[0024] The term "(1-8C)heteroalkyl" refers to an alkyl chain comprising 1-8 carbon atoms which additionally comprises one, two or three heteroatoms present within the alkyl chain which are selected from the group consisting of N, O, or S.

[0025] The term "halo" refers to fluoro, chloro, bromo and iodo.

[0026] 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, azetidinyl, 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 SO_2 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 azetidinyl, 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.

[0027] By "bridged ring systems" is meant ring systems in which two rings share more than two atoms, see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience, pages 131-133, 1992. Examples of bridged heterocyclyl ring systems include, aza-bicyclo[2.2.1]heptane, 2-oxa-5-azabicyclo[2.2.1]heptane, aza-bicyclo[2.2.2]octane, aza-bicyclo[3.2.1]octane and quinuclidine.

[0028] By "spiro bi-cyclic ring systems" we mean that the two ring systems share one common spiro carbon atom, i.e. the heterocyclic ring is linked to a further carbocyclic or heterocyclic ring through a single common spiro carbon atom. Examples of spiro ring systems include 6-azaspiro[3.4]octane, 2-oxa-6-azaspiro[3.4]octane, 2-azaspiro[3.3]heptanes, 2-oxa-6-azaspiro[3.3]heptanes, 7-oxa-2-azaspiro[3.5]nonane, 6-oxa-2-azaspiro[3.4]octane, 2-oxa-7-azaspiro[3.5]nonane and 2-oxa-6-azaspiro[3.5]nonane.

[0029] "Heterocyclyl(m-nC)alkyl" means a heterocyclyl group covalently attached to a (m-nC)alkylene group, both of which are defined herein.

[0030] 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. 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.

[0031] 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, quinoxalinyl, cinnolinyl, pteridinyl, naphthyridinyl, carbazolyl, phenazinyl, benzisoquinolinyl, pyridopyrazinyl, thieno[2,3-b]furanyl, 2H-furo[3,2-b]-pyranyl, 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, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 2-oxo-1,2,3,4-tetrahydroquinolinyl, 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, indolinyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl, 1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazinyl and 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl.

[0032] "Heteroaryl(m-nC)alkyl" means a heteroaryl group covalently attached to a (m-nC)alkylene group, both of which are defined herein. Examples of heteroaralkyl groups include pyridin-3-ylmethyl, 3-(benzofuran-2-yl)propyl, and the like.

[0033] 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 and the like. In particular embodiment, an aryl is phenyl.

[0034] The term "aryl(m-nC)alkyl" means an aryl group covalently attached to a (m-nC)alkylene group, both of which are defined herein. Examples of aryl-(m-nC)alkyl groups include benzyl, phenylethyl, and the like.

[0035] This specification also makes use of several composite terms to describe groups comprising more than one functionality. Such terms will be understood by a person skilled in the art. For example heterocyclyl(m-nC)alkyl comprises (m-nC)alkyl substituted by heterocyclyl.

[0036] The term "optionally substituted" refers to either groups, structures, or molecules that are substituted and those that are not substituted.

[0037] Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

[0038] It will, of course, be understood that substituents are only at positions where they are chemically possible, the person skilled in the art being able to decide (either experimentally or

theoretically) without inappropriate effort whether a particular substitution is possible. For example, amino or hydroxy groups with free hydrogen may be unstable if bound to carbon atoms with unsaturated (e.g. olefinic) bonds. Additionally, it will of course be understood that the substituents described herein may themselves be substituted by any substituent, subject to the aforementioned restriction to appropriate substitutions as recognised by the skilled man.

[0039] The present invention also encompasses the formation of compounds of the invention as defined herein which comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H(D), and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; and N may be in any isotopic form, including ^{15}N and the like.

[0040] The phrase "compound of the invention" means those compounds which are disclosed herein, both generically and specifically.

Substituted piperidine compounds

[0041] As stated above, the present invention provides processes for the formation of compounds of formulae I, II and III defined above.

[0042] In the compounds of formulae I, II and III above, 1, 2, 3, 4, or 5 of the groups R_2, R_3, R_4, R_5 and R_6 are a substituent group and the remaining groups are hydrogen.

[0043] In an embodiment, 1, 2 or 3 of the groups R_2, R_3, R_4, R_5 and R_6 are a substituent group and the remaining groups are hydrogen.

[0044] In a further embodiment, 1 or 2 of the groups R_2, R_3, R_4, R_5 and R_6 are a substituent group and the remaining groups are hydrogen.

[0045] In another embodiment, one of the groups R_2, R_3, R_4, R_5 and R_6 is a substituent group and the remaining groups are all hydrogen.

[0046] In yet another embodiment, R_2 is a substituent group and R_3, R_4, R_5 and R_6 are all hydrogen.

[0047] The R_2, R_3, R_4, R_5 and R_6 groups may be selected from any substituent group. The precise nature of the groups is not critical, but they are preferably carbon-linked substituent groups (i.e. the substituent group is linked to the piperidine ring via a carbon atom).

[0048] Suitable R_2, R_3, R_4, R_5 and R_6 substituent groups include groups containing up to 50 atoms selected from C, N, O, S and H. Examples of suitable substituent groups include (1-10C)alkyl, (2-10C)alkenyl, (2-10C)alkynyl, (3-12C)cycloalkyl, (3-12C)cycloalkyl(1-6C)alkyl, (3-12C)cycloalkenyl, (3-12C)cycloalkenyl(1-6C)alkyl, aryl, aryl(1-6C)alkyl, heteroaryl, heteroaryl(1-6C)alkyl, heterocyclyl, heterocyclyl(1-6C)alkyl, each of which is optionally further substituted by

one or more groups Q_1. Suitably, the heteroaryl and heterocyclyl groups are carbon-linked.

[0049] In an embodiment, R_2, R_3, R_4, R_5 and R_6 are selected from hydrogen or a substituent group selected from (1-10C)alkyl, (2-10C)alkenyl, (2-10C)alkynyl, (3-12C)cycloalkyl, (3-12C)cycloalkyl(1-6C)alkyl, (3-12C)cycloalkenyl, (3-12C)cycloalkenyl(1-6C)alkyl, aryl, aryl(1-6C)alkyl, heteroaryl, heteroaryl(1-6C)alkyl, heterocyclyl, heterocyclyl(1-6C)alkyl, each of which is optionally further substituted by one or more groups Q_1 as defined herein.

[0050] In a further embodiment, R_2, R_3, R_4, R_5 and R_6 are selected from hydrogen or a substituent group selected from (1-10C)alkyl, (3-12C)cycloalkyl, (3-12C)cycloalkyl(1-6C)alkyl, aryl, aryl(1-6C)alkyl, heteroaryl, heteroaryl(1-6C)alkyl, heterocyclyl, heterocyclyl(1-6C)alkyl, each of which is optionally further substituted by one or more groups Q_1 as defined herein.

[0051] In a further embodiment, R_2, R_3, R_4, R_5 and R_6 are selected from hydrogen or a substituent group selected from (1-10C)alkyl, aryl, aryl(1-6C)alkyl, heteroaryl, heteroaryl(1-6C)alkyl, heterocyclyl, heterocyclyl(1-6C)alkyl, each of which is optionally further substituted by one or more groups Q_1 as defined herein.

[0052] Suitably, the Q_1 substituent groups are each independently selected from halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, ureido, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl,

or Q_1 is a group of the formula:

$$-L^1\text{-}L^2\text{-}R_A$$

wherein

L^1 is absent or a linker group of the formula $-[CR_bR_c]_n-$ in which n is an integer selected from 1, 2, 3 or 4, and R_b and R_c are each independently selected from hydrogen or (1-4C)alkyl;

L^2 is absent or is selected from O, S, SO, SO_2, $N(R_d)$, C(O), C(O)O, OC(O), $CH(OR_d)$, $C(O)N(R_d)$, $N(R_d)C(O)$, $N(R_d)C(O)N(R_e)$, $S(O)_2N(R_d)$, or $N(R_d)SO_2$, wherein R_d and R_e are each independently selected from hydrogen or (1-4C)alkyl; and

R_A is (1-6C)alkyl, aryl, aryl-(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-4C)alkyl, heteroaryl, heteroaryl-(1-4C)alkyl, heterocyclyl, heterocyclyl-(1-4C)alkyl,

and wherein R_A is optionally further substituted by one or more substituent groups independently selected from oxo, halo, cyano, nitro, hydroxy, NR_fR_g, (1-4C)alkoxy, (1-4C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-3C)alkyl, (1-5C)alkanoyl, (1-5C)alkylsulphonyl, heterocyclyl, heterocyclyl-(1-2C)alkyl, heteroaryl, heteroaryl-(1-2C)alkyl,

$CONR_fR_g$, and $SO_2NR_fR_g$; wherein R_f and R_g are each independently selected from hydrogen, (1-4C)alkyl or (3-6C)cycloalkyl or (3-6C)cycloalkyl(1-2C)alkyl; or R_f and R_g can be linked such that, together with the nitrogen atom to which they are attached, they form a 4-6 membered heterocyclic ring;

and wherein when said substituent group comprises an alkyl, cycloalkyl, heterocyclyl or heteroaryl moiety then said moiety is optionally further substituted by hydroxy, fluoro, chloro, cyano, CF_3, OCF_3, (1-2C)alkyl, (1-2C)alkoxy, SO_2(1-2C)alkyl or NR_hR_i (where R_h and R_i are each independently selected from hydrogen, (1-3C)alkyl, (3-6C)cycloalkyl, or (3-6C)cycloalkyl(1-2C)alkyl);

or R_A is a group having the formula:

$$-L^3-L^4-R_B$$

wherein

L^3 is absent or a linker group of the formula $–[CR_jR_k]_n-$ in which n is an integer selected from 1, 2, 3 or 4, and R_j and R_k are each independently selected from hydrogen or (1-4C)alkyl;

L^4 is absent or is selected from O, S, SO, SO_2, $N(R_l)$, C(O), C(O)O, OC(O), $CH(OR_l)$, $C(O)N(R_l)$, $N(R_l)C(O)$, $N(R_l)C(O)N(R_m)$, $S(O)_2N(R_l)$, or $N(R_l)SO_2$, wherein R_l and R_m are each independently selected from hydrogen or (1-4C)alkyl; and

R_B is (1-6C)alkyl, aryl, aryl-(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-4C)alkyl, heteroaryl, heteroaryl-(1-4C)alkyl, heterocyclyl, heterocyclyl-(1-4C)alkyl.

[0053] In an embodiment, each Q_1 substituent group is independently selected from halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, ureido, (1-6C)alkyl, or Q_1 is a group of the formula:

$$-L^1-L^2-R_A$$

wherein

L^1 is absent or a linker group of the formula $–[CR_bR_c]_n-$ in which n is an integer selected from 1, 2, 3 or 4, and R_b and R_c are each independently selected from hydrogen or (1-4C)alkyl;

L^2 is absent or is selected from O, S, SO, SO_2, $N(R_d)$, C(O), C(O)O, OC(O), $CH(OR_d)$, $C(O)N(R_d)$, $N(R_d)C(O)$, $N(R_d)C(O)N(R_e)$, $S(O)_2N(R_d)$, or $N(R_d)SO_2$, wherein R_d and R_e are each independently selected from hydrogen or (1-4C)alkyl; and

R_A is (1-6C)alkyl, aryl, aryl-(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-4C)alkyl, heteroaryl, heteroaryl-(1-4C)alkyl, heterocyclyl, heterocyclyl-(1-4C)alkyl,

and wherein R_A is optionally further substituted by one or more substituent groups independently selected from oxo, halo, cyano, nitro, hydroxy, NR_fR_g, (1-4C)alkoxy, (1-4C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-3C)alkyl, (1-5C)alkanoyl, (1-5C)alkylsulphonyl, heterocyclyl, heterocyclyl-(1-2C)alkyl, heteroaryl, heteroaryl-(1-2C)alkyl, $CONR_fR_g$, and $SO_2NR_fR_g$; wherein R_f and R_g are each independently selected from hydrogen, (1-4C)alkyl or (3-6C)cycloalkyl or (3-6C)cycloalkyl(1-2C)alkyl; or R_f and R_g can be linked such that, together with the nitrogen atom to which they are attached, they form a 4-6 membered heterocyclic ring.

[0054] In a further embodiment, each Q_1 substituent group is independently selected from halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, ureido, (1-6C)alkyl, or Q_1 is a group of the formula:

$$-L^1-L^2-R_A$$

wherein

L^1 is absent or a linker group of the formula $–[CR_bR_c]_n-$ in which n is an integer selected from 1, 2, 3 or 4, and R_b and R_c are each independently selected from hydrogen or (1-4C)alkyl;

L^2 is absent or is selected from O, S, SO, SO_2, $N(R_d)$, C(O), C(O)O, OC(O), $CH(OR_d)$, $C(O)N(R_d)$, $N(R_d)C(O)$, $N(R_d)C(O)N(R_e)$, $S(O)_2N(R_d)$, or $N(R_d)SO_2$, wherein R_d and R_e are each independently selected from hydrogen or (1-4C)alkyl; and

R_A is (1-6C)alkyl, aryl, aryl-(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-4C)alkyl, heteroaryl, heteroaryl-(1-4C)alkyl, heterocyclyl, heterocyclyl-(1-4C)alkyl,

and wherein R_A is optionally further substituted by one or more substituent groups independently selected from oxo, halo, cyano, nitro, hydroxy, NR_fR_g, (1-4C)alkoxy, (1-4C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-3C)alkyl, (1-5C)alkanoyl, (1-5C)alkylsulphonyl,

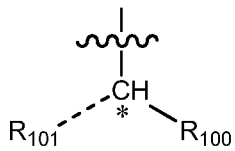
heterocyclyl, heterocyclyl-(1-2C)alkyl, heteroaryl, heteroaryl-(1-2C)alkyl, $CONR_fR_g$, and $SO_2NR_fR_g$; wherein R_f and R_g are each independently selected from hydrogen, (1-4C)alkyl or (3-6C)cycloalkyl or (3-6C)cycloalkyl(1-2C)alkyl; or R_f and R_g can be linked such that, together with the nitrogen atom to which they are attached, they form a 4-6 membered heterocyclic ring.

[0055] The R_{1A} group may be any suitable substituent group and is optionally a substituent group as defined above for R_2, R_3, R_4, R_5 and R_6. Suitably, R_{1A} is a substituent group selected from (1-10C)alkyl, (3-12C)cycloalkyl, (3-12C)cycloalkyl(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl or heterocyclyl(1-6C)alkyl, each of which is optionally substituted with a group Q_1 as defined above. Most suitably, R_{1A} is (1-10C)alkyl or aryl(1-6C)alkyl, each of which is optionally substituted with a group Q_1 as defined above.

[0056] In an embodiment, R_{1A} is an aliphatic group, such as a (1-10C)alkyl group.

[0057] Suitably, R_{1A} is a chiral group comprising a chiral carbon atom within the group.

[0058] In an embodiment, R_{1A} has the formula X:



X

wherein ~~~ represents the point of attachment to the N atom of the piperidine ring and * represents a chiral carbon atom; and

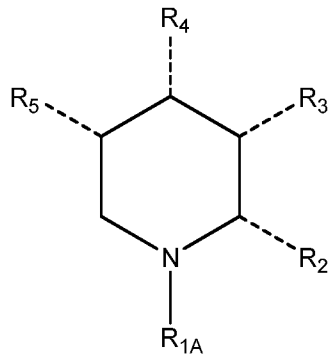
R_{100} and R_{101} are different substituent groups that, together with the carbon atom to which they are attached, form a substituent group R_{1A} selected from any one of the options set out above.

[0059] Suitably, R_{101} is (1-6C)alkyl, for example methyl or ethyl, and R_{100} is a group selected from a (1-8C)alkyl, aryl or aryl(1-6C)alkyl, heteroaryl or heteroaryl(1-6C)alkyl each of which is optionally substituted by a group Q_1 as defined herein.

[0060] The R_{1B} group may be any suitable substituent group and is optionally a substituent group as defined above for R_2, R_3, R_4, R_5 and R_6. Suitably, R_{1B} is a substituent group selected from (1-10C)alkyl, (3-12C)cycloalkyl, (3-12C)cycloalkyl(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl or heterocyclyl(1-6C)alkyl, each of which is optionally substituted with a group Q_1 as defined above. Most suitably, it is (1-10C)alkyl or aryl(1-6C)alkyl, each of which is optionally substituted with a group Q_1 as defined above.

[0061] In a particular embodiment, R_{1B} is (1-10C)alkyl.

[0062] In an embodiment, the compounds of formula I have the structural formula IA shown below (i.e. R_6 is H):

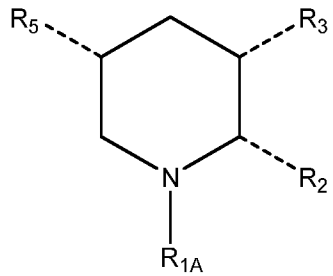


IA

wherein:

R_{1A}, R_2, R_3, R_4 and R_5 each have any one of the definitions set out herein.

[0063] In an embodiment, the compounds of formula I have the structural formula IB shown below (i.e. R_4 and R_6 are H):

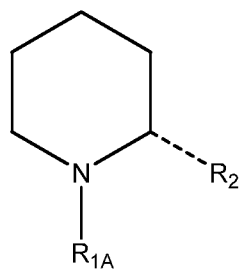


IB

wherein:

R_{1A}, R_2, R_3 and R_5 each have any one of the definitions set out herein.

[0064] In an embodiment, the compounds of formula I have the structural formula IC shown below (i.e. R_3, R_4, R_5 and R_6 are H):

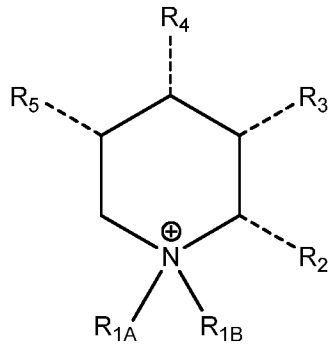


IC

wherein:

R_{1A} and R_2 each have any one of the definitions set out herein.

[0065] In an embodiment, the compounds of formula II have the structural formula IIA shown below (i.e. R_6 is H):

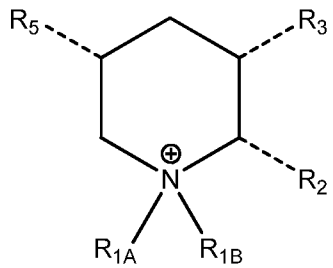


IIA

wherein:

R_{1A}, R_{1B}, R_2, R_3, R_4 and R_5 each have any one of the definitions set out herein.

[0066] In an embodiment, the compounds of formula II have the structural formula IIB shown below (i.e. R_4 and R_6 are H):

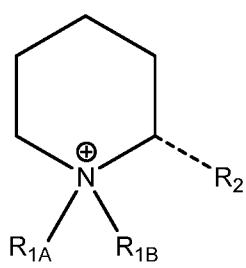


IIB

wherein:

R_{1A}, R_{1B}, R_2, R_3 and R_5 each have any one of the definitions set out herein.

[0067] In an embodiment, the compounds of formula I have the structural formula IIC shown below (i.e. R_3, R_4, R_5 and R_6 are H):

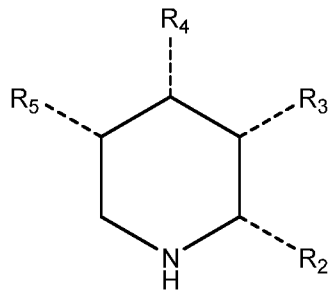


IIC

wherein:

R_{1A}, R_{1B} and R_2 each have any one of the definitions set out herein.

[0068] In an embodiment, the compounds of formula III have the structural formula IIIA shown below (i.e. R_6 is H):

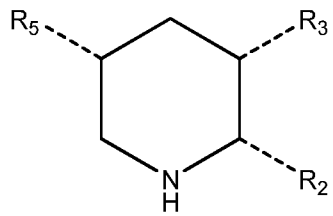


IIIA

wherein:

R_2, R_3, R_4 and R_5 each have any one of the definitions set out herein.

[0069] In an embodiment, the compounds of formula III have the structural formula IIIB shown below (i.e. R_4 and R_6 are H):

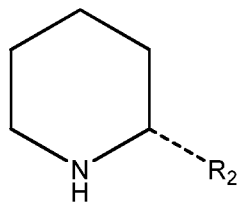


IIIB

wherein:

R_2, R_3 and R_5 each have any one of the definitions set out herein.

[0070] In an embodiment, the compounds of formula III have the structural formula IIIC shown below (i.e. R_3, R_4, R_5 and R_6 are H):



IIIC

wherein:

R_2 has any one of the definitions set out herein.

[0071] Particular examples of compounds of the formula I are provided in the accompanying examples.

The pyridinium salt

[0072] In the pyridinium salt used as the starting material in the process of the present invention, R_2, R_3, R_4, R_5 and R_6 each have any one of the definitions set out above in relation to the compounds of formulae I, II or III.

[0073] Suitably R_L is any substituent group that can be bound the pyridine nitrogen to form a pyridinium salt or hydrogen formed *in situ* by protonation with an acid. Exemplary R_L groups include (1-10C)alkyl, (2-10C)alkenyl, (2-10C)alkynyl, (3-12C)cycloalkyl, (3-12C)cycloalkyl(1-6C)alkyl, (3-12C)cycloalkenyl(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, or heterocyclyl(1-6C)alkyl, each of which is optionally further substituted by one or more groups Q_1 as defined hereinbefore. Suitably, the heteroaryl and heterocyclyl groups are carbon-linked.

[0074] In an embodiment, R_L is selected from (1-10C)alkyl, (2-10C)alkenyl, (2-10C)alkynyl, (3-12C)cycloalkyl(1-6C)alkyl, or aryl(1-6C)alkyl, each of which is optionally further substituted by one or more groups Q_1 as defined herein.

[0075] In a particular embodiment, R_L is (1-10C)alkyl, e.g. ethyl.

[0076] The counter ion, X^-, may be any suitable counter ion. In an embodiment, X^- is a halide. Suitably, X^- is bromo or iodo. Most suitably, X^- is iodo.

The amine

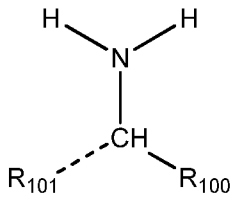
[0077] The amine used in the processes of the present invention may be any primary amine (H_2NR_{1A}) or any secondary amine ($HNR_{1A}R_{1B}$).

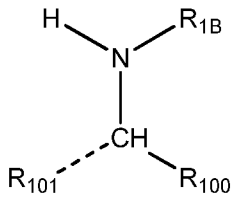
[0078] Suitably, the amine is any primary amine (i.e. H_2NR_{1A}).

[0079] The amine may be chiral, i.e. R_{1A} or R_{1B} comprise one or more chiral carbon atoms.

[0080] Suitably, R_{1A} comprises one or more chiral atoms. Most suitably, the carbon atom directly attached to the N atom of the amine is chiral.

[0081] In an embodiment, R_{1A} has the structural formula X defined above. This means that the amine may have one of the structural formulae shown below:





wherein R_{1B}, R_{100} and R_{101} are each as defined hereinbefore.

[0082] The amount of amine will depend on the amount of pyridinium ion present. The amine may be present in amounts of 1 molar equivalent or higher. For example, there may be between 1 and 20 molar equivalents of amine relative to the pyridinium ion. Suitably, between 1 and 10 molar equivalents of the amine are used. Any unused/excess amine may be optionally recycled and used again in the process.

The hydrogen donor

[0083] Any suitable hydrogen donor may be used in the process of the present invention.

[0084] Examples of suitable hydrogen donors include hydrogen gas (H_2) or hydrogen donors used for transfer hydrogenation processes, such as, for example, formic acid or isopropanol.

[0085] In an embodiment, the hydrogen donor is hydrogen gas.

[0086] In another embodiment, the hydrogen donor is formic acid or isopropanol.

[0087] In a particular embodiment, the hydrogen donor is formic acid.

[0088] The amount of hydrogen donor present relative to the amine may be within the range 1:1 to 10:1 (molar equivalents of hydrogen donor to amine).

[0089] Suitably, the ratio of hydrogen donor to amine is between 1:1 to 3:1, and more suitably it is between 2:1 and 2.6:1 (molar equivalents of hydrogen donor to amine).

The solvent

[0090] Any suitable solvent may be used for the present reaction.

[0091] Suitably, the solvent comprises water as a co-solvent. Suitably, the solvent comprises between 1 and 50% by volume of water. More suitably, the solvent comprises between 3 and 15% by volume of water. Most suitably, the solvent comprises between 4 and 8% by volume of water. Even more suitably, the solvent comprises between 6 and 7% by volume of water.

[0092] Examples of suitable solvents include dichloromethane (DCM), dichloroethane (DCE), chloroform, ethanol, tetrahydrofuran (THF), ethyl acetate and dimethylformamide (DMF).

The catalyst

[0093] Any catalyst that is capable of forming hydride from the hydrogen donor may be used in the process of the present invention. A person skilled in the art will understand how to select suitable catalysts capable of performing this function for the particular hydrogen donor that is used.

[0094] Transition metal catalysts are suitable candidates, especially catalysts based on rhodium (Rh), iridium (Ir) and ruthenium (Ru). Catalysts comprising Cp* (pentamethylcyclopentadienyl) or cymene and halides coordinated on the transition metal atom are generally preferred.

[0095] Examples of suitable catalysts include those of the formula:

$$[ArMX_2]_2$$

where Ar is pentamethylcyclopentadienyl, benzene or cymene; M is a transition metal (e.g. Rh, Ir and Ru); and X is a halide, such as chloro, bromo or iodo

[0096] In an embodiment, Ar is pentamethylcyclopentadienyl or cymene. In a further embodiment, Ar is pentamethylcyclopentadienyl.

[0097] Suitably, M is Rh.

[0098] Suitable X is chloro or iodo.

[0099] Particular examples of suitable catalysts include $[Cp^*RhCl_2]_2$, $[Cp^*IrCl_2]_2$ and $[Cp^*RhI_2]_2$.

[00100] The catalyst may be present in an amount of 0.1 to 5 mol.%. Suitably, the catalyst is present in an amount of 0.2 to 2 mol.%. More suitably, the catalyst is present in an amount of 0.5 to 1.5 mol.%, e.g. at about 1 mol.%.

Reaction conditions

[00101] The reaction is performed by mixing the pyridinium salt, the amine, the hydrogen donor and the catalyst in a suitable vessel in the presence of the solvent. The components may be added in a particular order or all at the same time. It may be necessary to control the temperature as the components are mixed.

[00102] In an embodiment, the amine and the hydrogen donor are mixed together first and then the pyridinium salt and catalysts are added to the reaction mixture.

[00103] In a further embodiment, the pyridinium salt is placed in a vessel and the amine is then

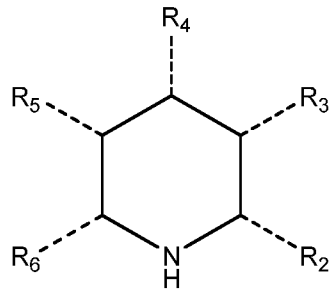
added followed by the hydrogen donor (e.g. formic acid), and the catalyst (e.g. $[Cp^*RhCl_2]_2$). The solvent is then added followed by the co-solvent (water). The temperature may be controlled by cooling the vessel during the addition of the hydrogen donor.

[00104] The reaction suitably proceeds at an elevated temperature for a period of time. A person skilled in the art will appreciate that the temperature and reaction time may be varied. Suitably, the reaction proceeds at a temperature of 25-100 °C, optionally over a period of 2 to 48 hours. More suitably, the reaction proceeds at a temperature of 30-50 °C, optionally over a time period of 15 - 24 hours. Even more suitably, the reaction proceeds at a temperature of 35-45 °C (e.g. around 40 °C), optionally over a time period of 15 - 24 hours.

[00105] The reaction vessel may be pressurised if hydrogen gas is used as the hydrogen donor.

[00106] If another hydrogen donor is used (such as those used for transfer hydrogenation reactions), then no pressurisation will be necessary.

[00107] As indicated above, the present invention also relates to the formation of a substituted piperidine of formula III below



III

wherein:

R_2, R_3, R_4, R_5, and R_6 are as defined herein;

the process comprising:

forming a compound of formula I as defined herein and reacting the compound of formula I to remove the group R_{1A}.]

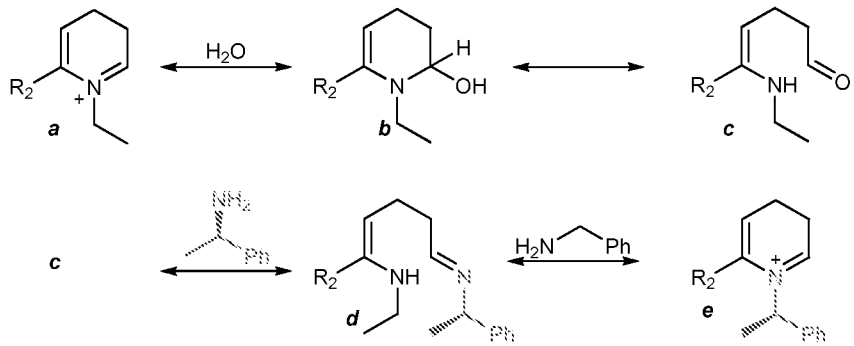
[00108] A person skilled in the art will understand how to remove the group R_{1A} from the piperidine compound of formula I using standard techniques. For example, the group R_{1A} may be removed by using a catalytic amount of Pd/C under 1-30 atm hydrogen pressure in ethanol (with or without aqueous HCl).

[00109] The compound of formula III may then be protected in the 1-position by the addition of a suitable protecting group, such as BOC, benzyl, FMOC etc. In a particular embodiment, the

protecting group BOC may be added *in situ* during the deprotection process.

Reaction mechanism

[00110] Without wishing to be bound by any particular theory, it is believed that the reaction between the pyridinium ion and the amine proceeds by the following mechanism:



Applications

[00111] As indicated above, the process of the present invention makes substituted piperidines, and in particular chiral substituted piperidines readily accessible.

[00112] Substituted piperidines have a wide range of uses, especially in the pharmaceutical, biotechnology, agrochemical and fine chemical supply fields. As such, it is envisaged that the process of the present invention will find broad ranging applications in the pharmaceutical, agrochemical, biotech and fine chemical supply industries.

Particular examples of piperidine compounds that could be prepared by the process of the present invention include:, (S) or (R)-1-N-Boc-2-methylpiperidine, (S)-1-N-Boc-2-(hydroxymethyl)piperidine, (S) or (R)-1-N-Boc-2-(hydroxymethyl)piperidine (S) or (R)-2-phenylpiperidine, (S) or (R)1-N-Boc-2-phenylpiperidine, (S) or (R)-2-(3,4-dimethylphenyl)piperidine, (S) or (R)-tert-butyl (piperidin-2-ylmethyl)carbamate, (S) or (R)-benzyl (piperidin-2-ylmethyl)carbamate hydrochloride, (S) or (R)-Coniine HCl,

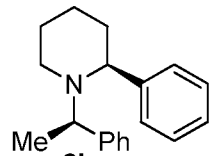
EXAMPLES

Materials

[00113] Unless otherwise specified, the chemicals were obtained commercially from Aldrich, Alfa Aesar, Apollo Scientific or TCI and used without further purification. Silica gel plates (GF_{254}) were used for TLC monitoring and silica gel (230-400 mesh) was used for running column chromatography. NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer

with TMS as the internal standard. The mass spectra were obtained by chemical ionization (CI) or electrospray ionization (ESI).

Example 1 – the preparation of (S)-2-phenyl-1-((R)-1-phenylethyl)piperidine (2b)



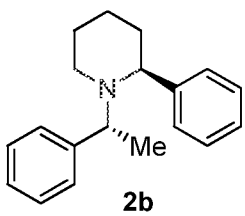
2b

[00114] To a carousel reaction tube containing a magnetic stirring bar and (R)-(+)-α-methylbenzylamine (615 mg, 5 mmol) was added formic acid (564 mg, 12 mmol) dropwise at room temperature. After stirring the amine/acid mixture for 10 min, a pyridinium salt, N-ethyl-2-phenylpyridinium iodide (157 mg, 0.5 mmol), $[Cp^*RhCl_2]_2$ (3.1 mg, 5 μmol), 3.75 mL of CH_2Cl_2 and 0.25 mL of distilled H_2O were introduced into the mixture. The reaction system was placed in a carousel reactor. The mixture was stirred at 40 °C for 22 h, cooled to room temperature and then basified with an aqueous solution of KOH. The resulting mixture was extracted with ethyl acetate (3×10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane) to give the desired product **2b** in 86% yield.

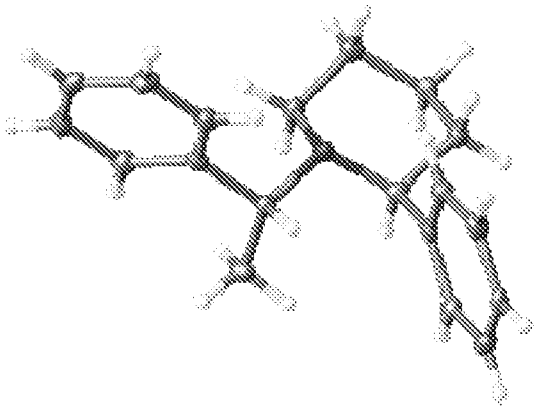
Analytic data:

[00115] ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.49-7.42 (m, 4H), 7.35-7.18 (m, 6H), 3.83 (q, J = 6.8 Hz, 1H), 3.50 (dd, J = 10.0, 2.8 Hz, 1H), 2.56 (dt, J = 11.6, 2.6 Hz, 1H), 2.22 (td, J = 11.0, 3.0 Hz, 1H), 1.80-1.26 (m, 6H), 1.18 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.4, 144.9, 128.6, 127.9, 126.68, 127.65, 127.0, 126.2, 65.7, 55.1, 45.2, 37.3, 26.4, 25.8, 8.2; HRMS for $C_{19}H_{24}N$ $[M+H]^+$: m/z calcd 266.1903, found 266.1906.

Crystallographic data for compound 2b:



2b

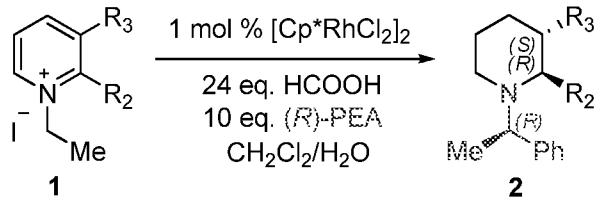


$C_{19}H_{23}N$, M = 265.38, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 7.8158(6) Å, b = 10.3447(7) Å, c = 18.8075(14) Å, V = 1520.63(19) $Å^3$, Z = 4, T = 100.0 K, μ(Mo kα) = 0.499 mm-1, Dcalc = 1.159 g/mm3, 13955 reflections measured (9.4 ≤ 2Θ ≤ 149.24), 3073 unique (Rint = 0.0281) which were used in all calculations. The final R1 was 0.0305 (>2sigma(I)) and wR2 was 0.0776 (all data).

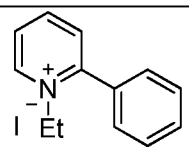
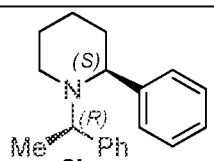
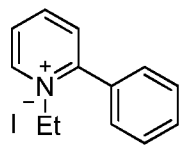
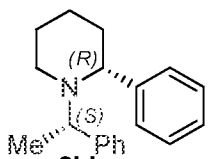
Examples 2 - 23

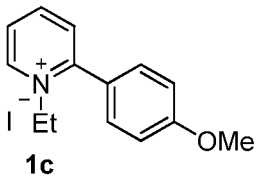
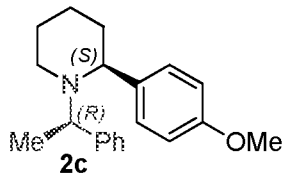
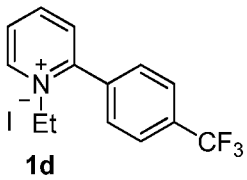
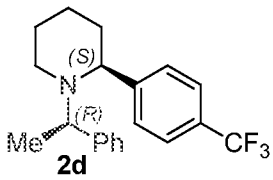
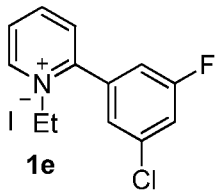
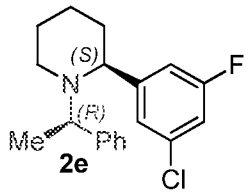
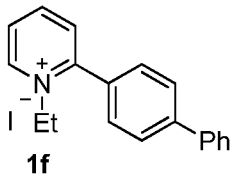
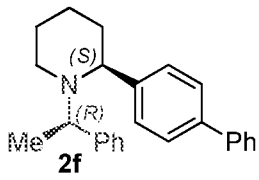
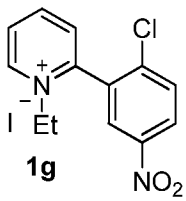
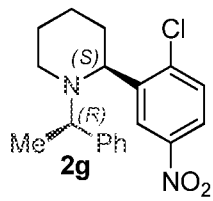
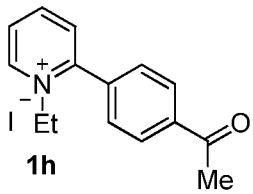
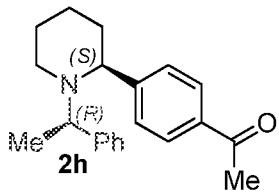
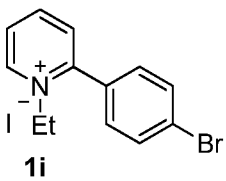
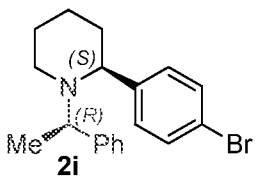
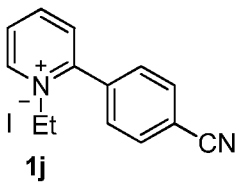
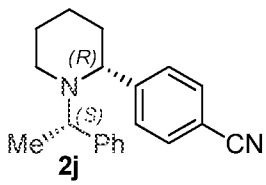
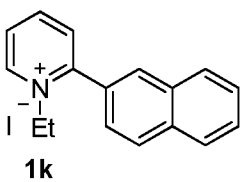
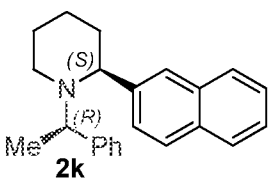
[00116] Using the procedure outlined in Example 1 above and the appropriate amine, the following compounds were prepared:

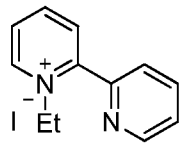
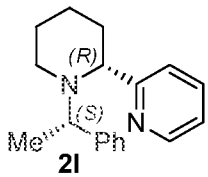
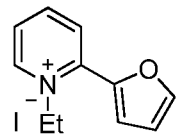
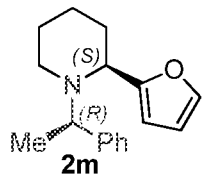
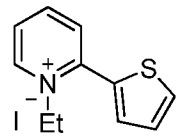
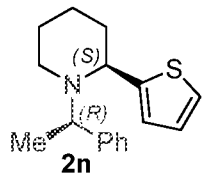
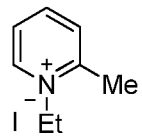
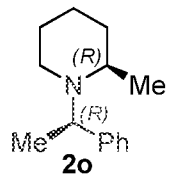
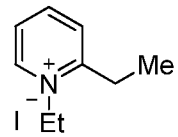
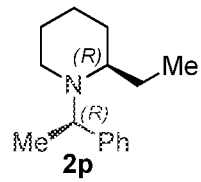
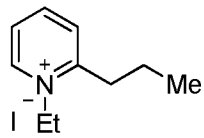
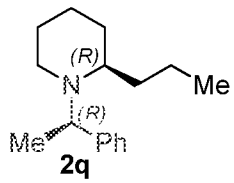
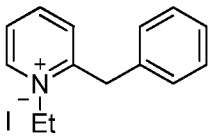
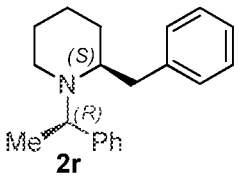
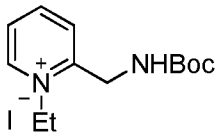
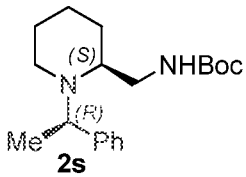
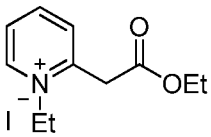
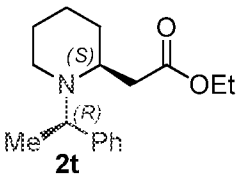
Table 1. Transamination of 2-substituted pyridiniums to piperidines.[a]

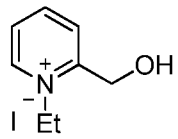
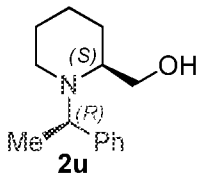
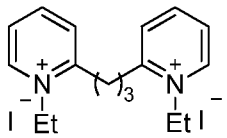
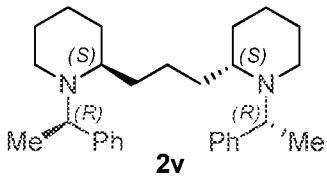
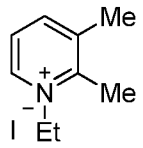
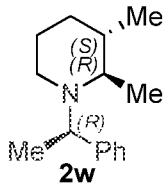
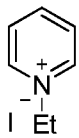
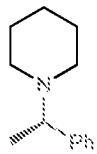


1 2

Example	Substrate	Product	Yield [%][b]
1	 1b	 2b	86
2	 1b	 2b'	83[c]

3	 **1c**	 **2c**	82
4	 **1d**	 **2d**	80
5	 **1e**	 **2e**	58
6	 **1f**	 **2f**	87
7	 **1g**	 **2g**	33
8	 **1h**	 **2h**	43
9	 **1i**	 **2i**	86
10	 **1j**	 **2j**	70[c],[d]
11	 **1k**	 **2k**	85

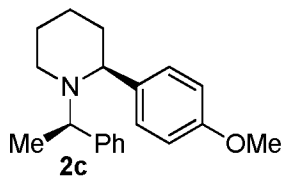
12	 **1l**	 **2l**	54[c]
13	 **1m**	 **2m**	71
14	 **1n**	 **2n**	48
15	 **1o**	 **2o**	88
16	 **1p**	 **2p**	84
17	 **1q**	 **2q**	82
18	 **1r**	 **2r**	55
19	 **1s**	 **2s**	82
20	 **1t**	 **2t**	68

21	 **1u**	 **2u**	83
22[e]	 **1v**	 **2v**	75
23	 **1w**	 **2w**	56
24		 **2x**	38

[a] All reactions were carried out under the standard conditions: **1** (0.5 mmol), $[Cp^*RhCl_2]_2$ (5 µmol), HCOOH (12 mmol), (*R*)-PEA (5 mmol), $[Cp^*RhCl_2]_2$ (5 µmol), CH_2Cl_2/H_2O (3.75/0.25 mL), 40 °C, 22 h, in air. [b] Isolated yields. [c] (*S*)-PEA was used. [d] The reaction was carried out in 2.5 mmol scale. [e] Reaction conditions were the same as standard conditions except for using HCOOH (24 mmol), (R)-PEA (10 mmol), $[Cp^*RhCl_2]_2$ (10 µmol), CH_2Cl_2/H_2O (7.5/0.5 mL).

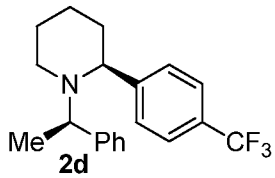
[00117] Notably the isolated yields approached 90% in some cases, which would be the maximum theoretical yield of the desired product if the transamination reaction had reached equilibrium, assuming a 10:1 ration of starting material and PEA.

Analytical data of sample products :


2c

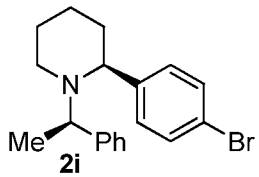
[00118] **(S)-1-((R)-1-Phenylethyl)-2-(4-(trifluoromethyl)phenyl)piperidine** (**2c**, unknown compound): ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.43 (d, J = 7.6 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 7.6 Hz, 2H), 7.17 (d, J = 7.4 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 3.83 (q, J = 6.8 Hz, 1H), 3.76 (s, 3H), 3.45 (dd, J = 10.8, 2.8 Hz, 1H), 2.55 (d, J = 11.6 Hz, 1H), 2.20 (td, J = 11.4, 2.6 Hz, 1H), 1.78-1.26 (m, 6H), 1.17 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 158.6, 145.0, 137.5, 128.6, 127.9,

127.6, 126.1, 114.0, 65.0, 55.4, 54.9, 45.3, 37.4, 26.6, 25.8, 8.2; HRMS for $C_{20}H_{26}NO$ $[M+H]^+$: m/z calcd 296.2009, found 296.2005.



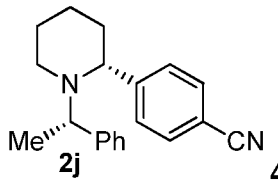
2d

[00119] **(S)-1-((R)-1-phenylethyl)-2-(4-(trifluoromethyl)phenyl)piperidine** (**2d**, unknown compound): ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.58 (s, 4H), 7.43 (d, J = 7.8 Hz, 2H), 7.29 (t, J = 7.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 1H), 3.75 (q, J = 6.8 Hz, 1H), 3.58 (dd, J = 10.3, 2.8 Hz, 1H), 2.58 (dt, J = 12.0, 2.8 Hz, 1H), 2.23 (td, J = 11.0, 2.8 Hz, 1H), 1.81-1.31 (m, 6H), 1.19 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 149.6, 144.3, 128.0, 127.9, 127.5, 126.4, 125.7 (q, J_{CF} = 3.7 Hz), 122.2, 65.3, 55.4, 45.1, 37.3, 26.2, 25.5, 8.3; HRMS for $C_{20}H_{23}NF_3$ $[M+H]^+$: m/z calcd 334.1778, found 334.1779.



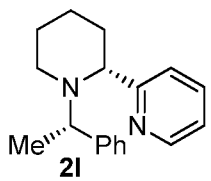
2i

[00120] **(S)-2-(4-Bromophenyl)-1-((R)-1-phenylethyl)piperidine** (**2i**, unknown compound): ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.46-7.34 (m, 6H), 7.29 (t, J = 7.4 Hz, 2H), 7.19 (d, J = 7.2 Hz, 2H), 3.78 (q, J = 6.8 Hz, 1H), 3.48 (dd, J = 10.8, 2.6 Hz, 1H), 2.55 (d, J = 11.6 Hz, 1H), 2.21 (td, J = 11.6, 2.4 Hz, 1H), 1.79-1.72 (m, 2H), 1.66-1.28 (m, 4H), 1.18 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 144.47, 144.46, 131.8, 129.4, 128.0, 127.6, 126.3, 120.5, 65.0, 55.1, 45.1, 37.3, 26.3, 25.6, 8.3; HRMS for $C_{19}H_{23}BrN$ $[M+H]^+$: m/z calcd 346.0988, 344.1009, found 346.0987, 344.0995.



2j

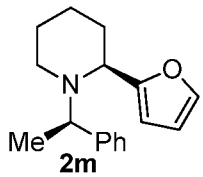
[00121] **4-((R)-1-((S)-1-Phenylethyl)piperidin-2-yl)benzonitrile** (**2j**, unknown compound): ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.65-7.57 (m, 4H), 7.41 (d, J = 12.8 Hz, 2H), 7.34-7.18 (m, 3H), 3.71 (q, J = 10.8 Hz, 1H), 3.59 (dd, J = 16.8, 4.8 Hz, 1H), 2.58 (d, J = 19.0 Hz, 1H), 2.23 (td, J = 18.0, 4.6 Hz, 1H), 1.83-1.72 (m, 4H), 1.67-1.28 (m, 4H), 1.20 (d, J = 10.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 151.2, 144.0, 132.6, 128.3, 128.1, 127.4, 126.5, 119.1, 110.8, 65.3, 55.6, 44.9, 37.2, 26.1, 25.4, 8.5; HRMS for $C_{20}H_{23}N_2$ $[M+H]^+$: m/z calcd 291.1856, found 291.1854.



2l

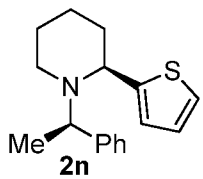
[00122] **2-((R)-1-((S)-1-phenylethyl)piperidin-2-yl)pyridine** (**2l**, unknown compound): ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.53 (d, J = 4.8 Hz, 1H), 7.67-7.61

(m, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 7.6 Hz, 2H), 7.19 (t, J = 7.4 Hz, 1H), 7.13 (ddd, J = 7.2, 5.0, 1.8 Hz, 1H), 3.78 (dd, J = 10.8, 2.8 Hz, 1H), 3.72 (q, J = 6.8 Hz, 1H), 2.59 (d, J = 11.2 Hz, 1H), 2.28 (td, J = 11.2, 2.8 Hz, 1H), 1.91-1.86 (m, 1H), 1.81-1.77 (m, 1H), 1.70-1.33 (m, 4H), 1.26 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 164.9, 149.0, 144.5, 136.7, 128.0, 127.6, 126.3, 122.0, 121.9, 67.2, 56.0, 44.9, 35.8, 26.2, 25.2, 8.8; HRMS for $C_{18}H_{23}N_2$ $[M+H]^+$: m/z calcd 267.1856, found 267.1863.



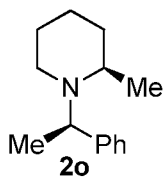
2m

[00123] **(S)-2-(Furan-2-yl)-1-((R)-1-phenylethyl)piperidine** (**2m**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.39 (t, J = 7.6 Hz, 3H), 7.27 (d, J = 7.6 Hz, 2H), 7.18 (t, J = 7.2 Hz, 1H), 6.31 (dd, J = 3.0, 1.8 Hz, 1H), 6.25 (d, J = 3.2 Hz, 1H), 3.79 (dd, J = 9.2, 3.2 Hz, 1H), 3.66 (q, J = 6.8 Hz, 1H), 2.52 (dt, J = 11.2, 4.0 Hz, 1H), 2.55 (td, J = 10.4, 2.8 Hz, 1H), 1.97-1.72 (m, 3H), 1.54-1.30 (m, 3H), 1.26 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 157.2, 145.0, 141.3, 128.0, 127.8, 126.3, 110.0, 106.8, 57.3, 57.1, 45.4, 32.7, 26.0, 24.3, 11.2; HRMS for $C_{17}H_{22}NO$ $[M+H]^+$: m/z calcd 256.1696, found 256.1689.



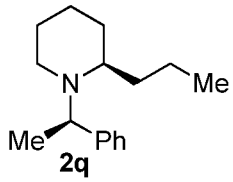
2n

[00124] **(S)-1-((R)-1-phenylethyl)-2-(thiophen-2-yl)piperidine** (**2n**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.42 (t, J = 4.8 Hz, 3H), 7.48-7.15 (m, 6H), 6.93-6.83 (m, 2H), 3.92-3.75 (m, 2H), 2.62 (dt, J = 7.0, 2.5 Hz, 1H), 2.18 (td, J = 6.5, 1.8 Hz, 1H), 1.88-1.27 (m, 6H), 1.20 (d, J = 4.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 149.5, 144.7, 127.9, 127.7, 126.3, 126.0, 124.4, 60.1, 55.4, 45.1, 37.9, 26.0, 25.3, 9.0; HRMS for $C_{17}H_{22}NS$ $[M+H]^+$: m/z calcd 272.1467, found 272.1463.



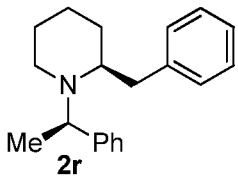
2o

[00125] **(R)-2-Methyl-1-((R)-1-phenylethyl)piperidine (2o):** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.42 (d, J = 7.2 Hz, 2H), 7.29 (t, J = 7.2 Hz, 2H), 7.19 (t, J = 7.6 Hz, 1H), 4.04 (q, J = 6.8 Hz, 1H), 2.84-2.77 (m, 1H), 2.36-2.31 (m, 1H), 2.15-2.09 (m, 1H), 1.72-1.56 (m, 2H), 1.43-1.28 (m, 4H), 1.25 (d, J = 6.8 Hz, 3H), 1.12 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.9, 128.0, 127.8, 126.3, 56.7, 52.1, 45.0, 34.8, 26.5, 23.5, 17.2, 12.6; HRMS for $C_{14}H_{22}N$ $[M+H]^+$: m/z calcd 204.1747, found 204.1747.



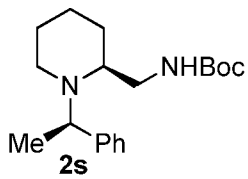
2q

[00126] **(R)-1-((R)-1-Phenylethyl)-2-propylpiperidine (2q):** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.41 (d, J = 7.6 Hz, 2H), 7.28 (t, J = 7.6 Hz, 2H), 7.19 (t, J = 7.4 Hz, 1H), 4.01 (q, J = 6.6 Hz, 1H), 2.72 (brs, 1H), 2.36 (ddd, J = 11.2, 8.0, 3.2 Hz, 1H), 2.23-2.18 (m, 1H), 1.69-1.28 (m, 10H), 1.25 (d, J = 6.4 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 146.4, 128.1, 127.6, 126.3, 56.9, 55.8, 45.2, 31.1, 29.7, 25.9, 22.8, 19.0, 14.9, 14.7; HRMS for $C_{16}H_{26}N$ $[M+H]^+$: m/z calcd 232.2060, found 232.2057.



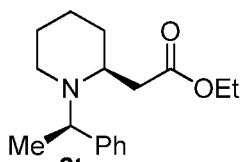
2r

[00127] **(S)-2-Benzyl-1-((R)-1-phenylethyl)piperidine** (**2r**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.40 (d, J = 7.2 Hz, 2H), 7.32-7.17 (m, 8H), 4.02 (q, J = 6.8 Hz, 1H), 3.19-3.14 (m, 1H), 3.01 (dd, J = 13.2, 3.6 Hz, 1H), 2.75 (dd, J = 13.0, 10.6 Hz, 1H), 2.46-2.32 (m, 2H), 1.64-1.40 (m, 6H), 1.37 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 146.7, 141.0, 129.4, 128.4, 128.3, 127.5, 126.6, 125.8, 58.9, 57.0, 45.2, 32.8, 28.3, 25.9, 21.3, 17.8; HRMS for $C_{20}H_{26}N$ $[M+H]^+$: m/z calcd 280.2060, found 280.2062.



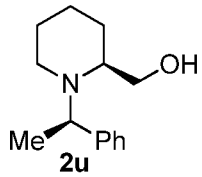
2s

[00128] **tert-butyl (((S)-1-((R)-1-Phenylethyl)piperidin-2-yl)methyl)carbamate** (**2s**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.38 (d, J = 7.2 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 4.98 (s, 1H), 4.12 (q, J = 6.8 Hz, 1H), 3.40-3.35 (m, 1H), 3.29-3.23 (m, 1H), 2.72 (brs, 1H), 2.54-2.49 (m, 1H), 2.34 (ddd, J = 12.0, 8.8, 2.8 Hz, 1H), 1.71-1.64 (m, 3H), 1.44 (s, 10H), 1.38-1.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 156.5, 145.1, 128.3, 127.6, 126.7, 79.1, 56.0, 55.2, 44.1, 41.1, 28.6, 28.2, 24.7, 23.3, 13.4; HRMS for $C_{19}H_{31}N_2O_2$ $[M+H]^+$: m/z calcd 319.2380, found 319.2396.



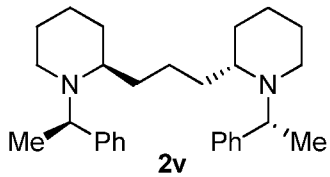
2t

[00129] **Ethyl 2-((S)-1-((R)-1-phenylethyl)piperidin-2-yl)acetate (2t)**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.35-7.21 (m, 5H), 4.18 (q, J = 7.2 Hz, 2H), 3.86 (q, J = 6.4 Hz, 1H), 2.84-2.80 (m, 1H), 2.76-2.73 (m, 1H), 1.90-1.83 (m, 1H), 1.68-1.43 (m, 6H), 1.32-1.26 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 174.7, 146.6, 128.5, 126.9, 126.8, 60.1, 55.1, 53.5, 44.6, 30.0, 25.7, 24.8, 23.4, 23.0, 14.5; HRMS for $C_{17}H_{26}NO_2$ $[M+H]^+$: m/z calcd 276.1958, found 276.1965.



2u

[00130] **((S)-1-((R)-1-Phenylethyl)piperidin-2-yl)methanol (2u)**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.38-7.19 (m, 5H), 4.25 (q, J = 6.8 Hz, 1H), 3.62 (d, J = 6.8 Hz, 2H), 2.78-2.68 (m, 1H), 2.66-2.54 (m, 2H), 1.79-1.40 (m, 5H), 1.35 (d, J = 5.5 Hz, 3H), 1.31-1.19 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 144.9, 128.4, 127.6, 126.9, 61.2, 56.4, 56.2, 42.9, 25.6, 23.2, 22.7, 15.4; HRMS for $C_{14}H_{22}NO$ $[M+H]^+$: m/z calcd 220.1696, found 220.1692.



2v

[00131] **1,3-bis((S)-1-((R)-1-Phenylethyl)piperidin-2-yl)propane** (**2v**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.41 (d, J = 11.2 Hz, 4H), 7.29 (t, J = 11.2 Hz, 4H), 7.23-7.15 (m, 2H), 4.00 (q, J = 10.8 Hz, 2H), 2.73-2.70 (m, 18H), 2.41-2.33 (m, 2H), 2.25-2.15 (m, 2H), 1.65-1.30 (m, 2H), 1.24 (d, J = 10.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 146.3, 128.1, 127.6, 126.6, 57.0, 56.1, 45.1, 29.7, 29.4, 25.9, 22.8, 22.0, 14.8; HRMS for $C_{19}H_{43}N_2$ $[M+H]^+$: m/z calcd 419.3421, found 419.3419.

Discussion

[00132] Under the optimised conditions, the reaction proceeds smoothly with *N*-ethylpyridium salts bearing a variety of 2-aryl and alkyl substituents, affording the corresponding *N*-(1-phenylethyl)piperidines in good yields and almost uniformly high diastereoselectivities (>49:1) (see Table 1 above).

[00133] In contrast to heterogeneous catalytic methods, the reduction of the pyridinium ring occurred selectively in the presence of other potentially reducible functional groups, including, aryl bromides, esters and cyano, nitro and carbonyl groups (Table 1, Examples 7-10 and 20).

[00134] Heterocyclic substituents, such as pyridine, thiophene and furan, were also well tolerated albeit in diminished yields (Table 1, Examples 12-14).

[00135] The presence of other groups including protected amines and free alcohols did not inhibit the reaction (Table 1, Examples 19 and 21).

[00136] It is worth to note that 2,3-disubstituted piperidines could be obtained in excellent d.r. and moderate yield (Table 1, Example 23). Thus, this method allows for a broad range of chiral piperidines to be accessed with excellent diastereoselectivities in a single step from simple precursors.

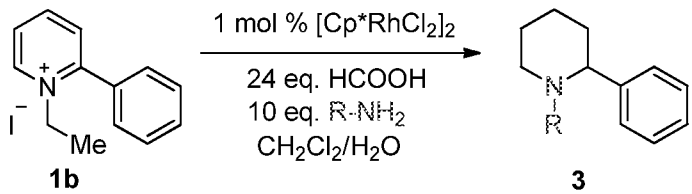
[00137] In some cases, naturally occurring alkaloids such as coniine, previously always by multistep synthesis starting from complex materials, could be directly obtained by a simple

debenzylation (Table 1, Example 17). Chiral *bis*-piperidines could also be produced by this method (Table 1, Example 22), which may find use in asymmetric catalysis as chiral diamine ligands.

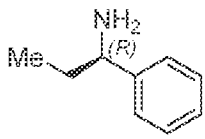
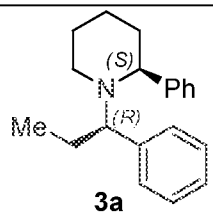
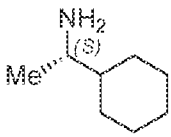
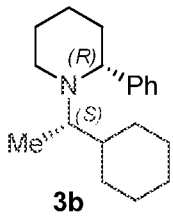
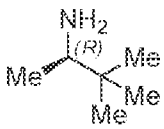
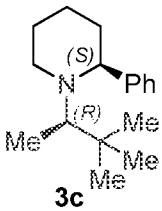
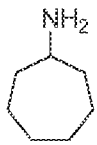
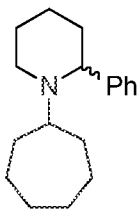
Examples 25 - 37

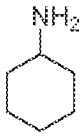
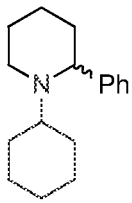
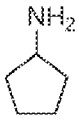
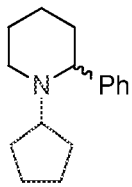
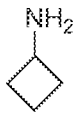
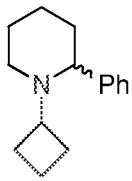
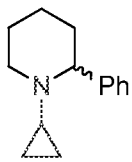
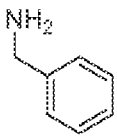
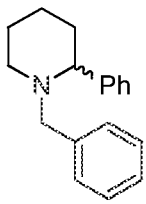
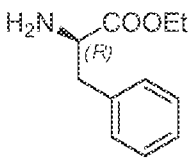
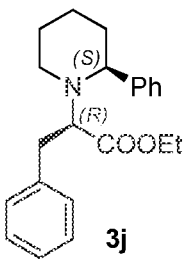
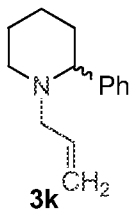
[00138] Compounds prepared from other amines are shown in Table 2:

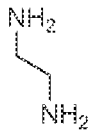
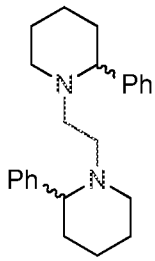
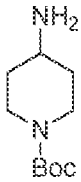
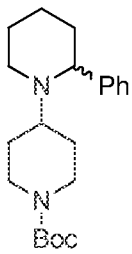
Table 2. Transamination of 2-phenylpyridiniums with various primary amines.[a]



1b **3**

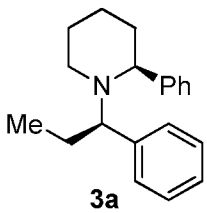
Example	Amine	Product	Yield [%][b]
25		 **3a**	78
26		 **3b**	88
27		 **3c**	77
28		 **3d**	77

29		 **3e**	88
30		 **3f**	64
31		 **3g**	72
32		 **3h**	64
33		 **3i**	83
34		 **3j**	48(d.r. = 8:1)
35		 **3k**	55

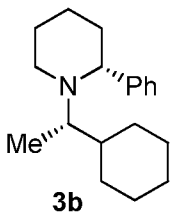
36		 **3l**	37[c]
37		 **3m**	68[d]

[a] Reactions were carried out under the standard conditions given in Table 2 except for using different amines. [b] Isolated yield. [c] 5.0 equivalent of amines were used. [d] Reaction conditions: **1b** (0.5 mmol), HCOOH (6.0 mmol), 1-Boc-4-aminopiperidine (0.5 mmol), Et_3N (2.0 mmol), $[Cp^*RhCl_2]_2$ (5 μmol) and CH_2Cl_2/H_2O (3.75/0.25 mL), 40 °C, 22 h.

Analytical data of sample products:

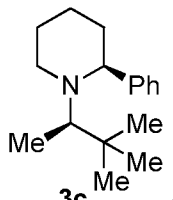

3a

[00139] **(S)-2-Phenyl-1-((R)-1-phenylpropyl)piperidine (3a**, unknown compound): ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.54 (d, J = 7.6 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.36-7.29 (m, 5H), 7.25 (t, J = 6.4 Hz, 1H), 3.62 (d, J = 10.4 Hz, 1H), 3.51 (dd, J = 9.6, 3.4 Hz, 1H), 2.78 (d, J = 11.6 Hz, 1H), 2.32 (t, J = 11.2 Hz, 1H), 1.93-1.30 (m, 8H), 0.68 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.3, 142.2, 128.9, 128.6, 128.0, 127.8, 127.1, 126.4, 65.8, 63.1, 45.5, 36.7, 26.4, 25.6, 15.3, 12.1; HRMS for $C_{20}H_{26}N$ $[M+H]^+$: m/z calcd 280.2060, found 280.2060.


3b

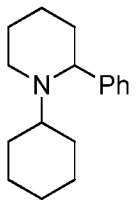
[00140] **(R)-1-((S)-1-Cyclohexylethyl)-2-phenylpiperidine (3b**, unknown compound): ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.30-7.16 (m, 5H), 3.32 (dd, J = 10.8, 2.8 Hz, 1H), 2.78 (d, J = 11.6 Hz, 1H), 2.25-2.09 (m, 3H), 1.76-1.49 (m, 9H), 1.35-1.00 (m, 5H), 0.73 (d,

J = 6.4 Hz, 3H), 0.69-0.62 (m, 1H), 0.58-0.48 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.7, 128.2, 128.1, 126.6, 65.7, 57.5, 44.9, 41.1, 37.6, 31.2, 30.6, 26.9, 26.8, 26.6, 25.8, 8.4; HRMS for $C_{19}H_{30}N$ [M+H]$^+$: m/z calcd 272.2373, found 272.2378.



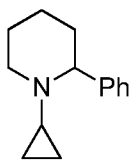
3c

[00141] **(S)-1-((R)-3,3-Dimethylbutan-2-yl)-2-phenylpiperidine** (**3c**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.23-7.10 (m, 5H), 3.19-3.16 (m, 1H), 2.89 (d, J = 11.2 Hz, 1H), 2.20-2.11 (m, 2H), 1.69-1.47 (m, 5H), 1.27-1.16 (m, 1H), 0.73-0.71 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.8, 128.5, 128.1, 126.8, 67.3, 60.2, 48.4, 37.2, 35.2, 28.9, 26.6, 25.9, 5.6; HRMS for $C_{17}H_{28}N$ [M+H]$^+$: m/z calcd 246.2216, found 246.2209.



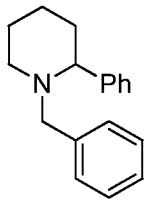
3e

[00142] **1-Cyclohexyl-2-phenylpiperidine** (**3e**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.32-7.19 (m, 5H), 3.41 (dd, J = 10.8, 2.8 Hz, 1H), 3.02 (d, J = 11.2 Hz, 1H), 2.32-2.25 (m, 2H), 1.77-1.25 (m, 12H), 1.14-0.73 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.6, 128.4, 127.5, 126.7, 65.7, 58.2, 46.4, 37.3, 31.8, 26.72, 26.68, 26.64, 26.0, 25.6, 23.8; HRMS for $C_{17}H_{26}N$ [M+H]$^+$: m/z calcd 244.2060, found 244.2063.



3h

[00143] **1-Cyclopropyl-2-phenylpiperidine** (**3h**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.31-7.21 (m, 5H), 3.17 (d, J = 11.6 Hz, 1H), 3.09 (dd, J = 10.4, 3.2 Hz, 1H), 2.25 (td, J = 11.8, 3.0 Hz, 1H), 1.85-1.51 (m, 5H), 1.45-1.26 (m, 2H), 0.28-0.13 (m, 2H), -0.01--0.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 144.4, 128.7, 127.9, 127.0, 71.3, 56.1, 39.1, 34.6, 26.1, 24.9, 9.6, 4.0; HRMS for $C_{14}H_{20}N$ [M+H]$^+$: m/z calcd 202.1590, found 202.1595.



3i

[00144] **1-Benzyl-2-phenylpiperidine (3i):** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.46 (d, J = 7.2 Hz, 2H), 7.31 (t, J = 7.8 Hz, 2H), 7.28 (d, J = 4.4 Hz, 4H), 7.25-7.18 (m, 2H), 3.76 (d, J = 13.6 Hz, 1H), 3.11 (dd, J = 11.0, 2.6 Hz, 1H), 2.96 (d, J = 11.6 Hz, 1H), 2.81 (d, J = 13.2 Hz, 1H), 1.98-1.89 (m, 1H), 1.81-1.74 (m, 2H), 1.67-1.53 (m, 3H), 1.42-1.31 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.9, 140.0, 128.8, 128.6, 128.1, 127.6, 127.0, 126.6, 69.3, 59.9, 53.5, 37.2, 26.1, 25.4; HRMS for $C_{18}H_{22}N$ $[M+H]^+$: m/z calcd 252.1752, found 252.1748.

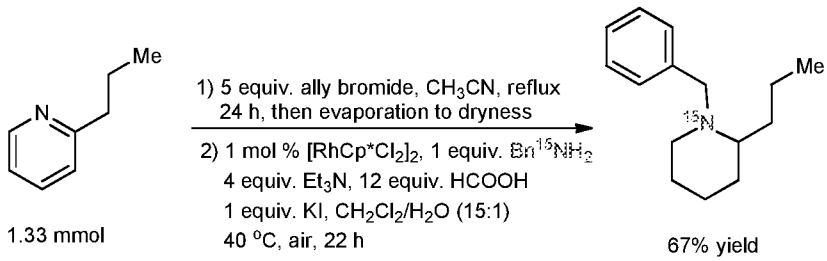
Discussion:

[00145] Although the *in situ* incorporation of a PEA auxiliary and subsequent reduction to give chiral piperidines is the most immediate use of this transamination-reduction reaction, it can also be used to furnish the alkylation of piperidines, starting from pyridinium precursors, using amines as the alkylating agent, as shown in Table 2. This offers an advantage in cases where an effective alkylating agent is not available due to its instability or lack of reactivity. For instance, *N*-cyclopropylpiperidine **3h**, which is not obtainable by alkylation or reductive amination, was obtained in a yield of 64% using cheap reagents. In addition, due to the retention of the nitrogen atom in the reactant amine, the stereochemistry of this unit is completely conserved. Using this method, a variety of *N*-alkyl piperidines **3a-m** bearing cyclic and acyclic alkyl groups were synthesised in a single step, including those bearing optically active *N*-alkyl groups **3a-c, 3j** (Table 2, Examples 24-26 and 33).

Example 41 – preparation of ^{15}N-labled-benzyl Coniine

[00146] The nitrogen atom in the product was shown to be derived from the added amine, and not the parent pyridinium salt by the use of ^{15}N labelled benzylamine. Subsequent deprotection, e.g. de-benzylation by hydrogenolysis, allows for a convenient, traceless, method for the ^{15}N labelling of piperidine derivatives.

[00147] The effectiveness of this method was demonstrated in a one-pot, two-step synthesis of a ^{15}N labelled alkaloid, a coniine derivative, directly from a neutral pyridine



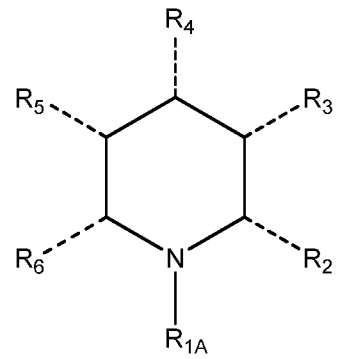
References

1. (a) D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435; (b) S. Laschat, T. Dickner, *Synthesis* **2000**, 1781; (c) P. M. Weintraub, J. S. Sabol, J. M. Kane, D. R. Borcherding, *Tetrahedron* **2003**, *59*, 2953; (d) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701; (e) P. Merino, T. Tejero, G. Greco, E. Marca, I. Delso, A. Gomez-SanJuan, R. Matute, *Heterocycles* **2012**, *84*, 75.

2. (a) F. Glorius, *Org. Biomol. Chem.* **2005**, *3*, 4171; (b) D. S. Wang, Q. A. Chen, S. M. Lu, Y. G. Zhou, *Chem. Rev.* **2012**, *112*, 2557; (c) Z. Yu, W. Jin, Q. Jiang, *Angew. Chem. Int. Ed.* **2012**, *51*, 6060.

Claims

1. A process for the preparation of a substituted piperidine compound of formula I:



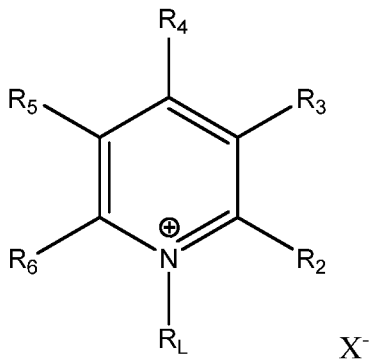
I

wherein:

R_{1A} is a substituent group;

R_2, R_3, R_4, R_5, and R_6 are each independently selected from hydrogen or a substituent group, with the proviso that at least one of R_2, R_3, R_4, R_5, and R_6 is a substituent group;

the process comprising reacting, in the presence of a suitable solvent, a pyridinium salt of the formula:



wherein:

X^- is a counter ion,

R_L is a substituent group,

and R_2, R_3, R_4, R_5, and R_6 are as defined above;

with an amine of the formula:

$H_2N\text{-}R_{1A}$

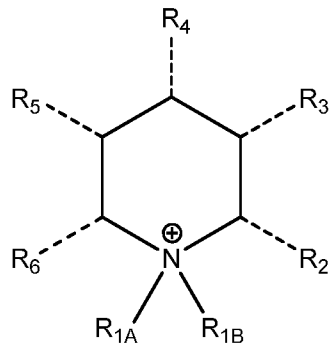
wherein:

R_{1A} is a substituent group as defined above and the nitrogen is ^{14}N or ^{15}N;

in the presence of a hydrogen donor and a catalyst that is capable of generating hydride from the hydrogen donor.

2. A process according to claim 1, wherein one or more of R_2, R_3, R_4, R_5, and R_6 is a substituent group and the carbon atom of the piperidine ring to which the substituent group is attached is chiral and the group R_{1A} comprises a chiral carbon atom.

3. A process for the preparation of a substituted piperidine compound of formula II:



II

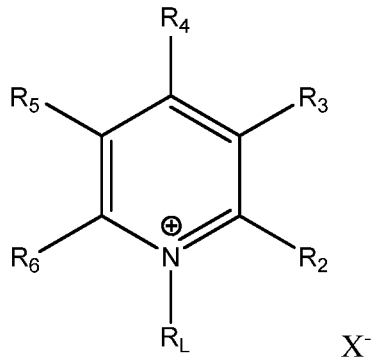
wherein:

R_{1A} is a substituent group;

R_{1B} is a substituent group;

R_2, R_3, R_4, R_5, and R_6 are each independently selected from hydrogen or a substituent group, with the proviso that at least one of R_2, R_3, R_4, R_5, and R_6 is a substituent group;

the process comprising reacting, in the presence of a suitable solvent, a pyridinium salt of the formula:



wherein:

X^-, R_L, R_2, R_3, R_4, R_5, and R_6 are as defined above;

with an amine of the formula:

$$HNR_{1A}R_{1B}$$

wherein:

R_{1A} and R_{1B} are as defined above;

in the presence of a hydrogen donor and a catalyst capable of generating hydride from the hydrogen donor.

4. A process according to claim 3, wherein one or more of R_2, R_3, R_4, R_5, and R_6 is a substituent group and the carbon atom of the piperidine ring to which the substituent group is attached is chiral and the group R_{1A} comprises a chiral carbon atom.

5. A process according to any one of the preceding claims, wherein 1, 2 or 3 of the groups R_2, R_3, R_4, R_5 and R_6 are a substituent group and the remaining groups are hydrogen.

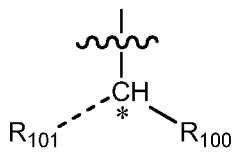
6. A process according to claim 5, wherein 1 or 2 of the groups R_2, R_3, R_4, R_5 and R_6 are a substituent group and the remaining groups are hydrogen.

7. A process according to any one of the preceding claims, wherein R_2, R_3, R_4, R_5 and R_6 are selected from hydrogen or a substituent group selected from (1-10C)alkyl, (2-10C)alkenyl, (2-10C)alkynyl, (3-12C)cycloalkyl, (3-12C)cycloalkyl(1-6C)alkyl, (3-12C)cycloalkenyl, (3-12C)cycloalkenyl(1-6C)alkyl, aryl, aryl(1-6C)alkyl, heteroaryl, heteroaryl(1-6C)alkyl, heterocyclyl, heterocyclyl(1-6C)alkyl, each of which is optionally further substituted by one or more groups Q_1.

8. A process according to any one of the preceding claims, wherein R_{1A} is a substituent group selected from (1-10C)alkyl, (2-10C)alkenyl, (2-10C)alkynyl, (3-12C)cycloalkyl, (3-12C)cycloalkyl(1-6C)alkyl, (3-12C)cycloalkenyl, (3-12C)cycloalkenyl(1-6C)alkyl, aryl, aryl(1-6C)alkyl, heteroaryl, heteroaryl(1-6C)alkyl, heterocyclyl, heterocyclyl(1-6C)alkyl, each of which is optionally further substituted by one or more groups Q_1.

9. A process according the any one of the preceding claims, wherein R_{1A} comprises a chiral carbon atom.

10. A process according the any one of the preceding claims, wherein R_{1A} has the formula X:



X

wherein

~~~ represents the point of attachment to the N atom of the piperidine ring,

* represents a chiral carbon atom; and

R_{100} and R_{101} are different substituent groups that, together with the carbon atom to which they are attached, form a substituent group R_{1A} as defined in claim 8 above.

11. A process according to any one of claims 3 to 10, wherein R_{1B} is a substituent group selected from (1-10C)alkyl, (2-10C)alkenyl, (2-10C)alkynyl, (3-12C)cycloalkyl, (3-12C)cycloalkyl(1-6C)alkyl, (3-12C)cycloalkenyl, (3-12C)cycloalkenyl(1-6C)alkyl, aryl, aryl(1-6C)alkyl, heteroaryl, heteroaryl(1-6C)alkyl, heterocyclyl, heterocyclyl(1-6C)alkyl, each of which is optionally further substituted by one or more groups Q_1.

12. A process according to any one of claims 7 to 11, wherein Q_1 is selected from halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, ureido, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl,

or Q_1 is a group of the formula:
~~~

$-L^1-L^2-R_A$

wherein

L^1 is absent or a linker group of the formula $–[CR_bR_c]_n-$ in which n is an integer selected from 1, 2, 3 or 4, and R_b and R_c are each independently selected from hydrogen or (1-4C)alkyl;

L^2 is absent or is selected from O, S, SO, SO_2, $N(R_d)$, C(O), C(O)O, OC(O), $CH(OR_d)$, $C(O)N(R_d)$, $N(R_d)C(O)$, $N(R_d)C(O)N(R_e)$, $S(O)_2N(R_d)$, or $N(R_d)SO_2$, wherein R_d and R_e are each independently selected from hydrogen or (1-4C)alkyl; and

R_A is (1-6C)alkyl, aryl, aryl-(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-4C)alkyl, heteroaryl, heteroaryl-(1-4C)alkyl, heterocyclyl, heterocyclyl-(1-4C)alkyl,

and wherein R_A is optionally further substituted by one or more substituent groups independently selected from oxo, halo, cyano, nitro, hydroxy, NR_fR_g, (1-4C)alkoxy, (1-4C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-3C)alkyl, (1-5C)alkanoyl, (1-5C)alkylsulphonyl, heterocyclyl, heterocyclyl-(1-2C)alkyl, heteroaryl, heteroaryl-(1-2C)alkyl, $CONR_fR_g$, and $SO_2NR_fR_g$; wherein R_f and R_g are each independently selected from hydrogen, (1-4C)alkyl or (3-6C)cycloalkyl or (3-6C)cycloalkyl(1-2C)alkyl; or R_f and R_g can be linked such that, together with the nitrogen atom to which they are attached, they form a 4-6 membered heterocyclic ring;

and wherein when said substituent group comprises an alkyl, cycloalkyl, heterocyclyl or heteroaryl moiety then said moiety is optionally further substituted by hydroxy, fluoro, chloro, cyano, CF_3, OCF_3, (1-2C)alkyl, (1-2C)alkoxy, SO_2(1-2C)alkyl or NR_hR_i (where R_h and R_i are each independently selected from hydrogen, (1-3C)alkyl, (3-6C)cycloalkyl, or (3-6C)cycloalkyl(1-2C)alkyl);

or R_A is a group having the formula:

$-L^3-L^4-R_B$

wherein

L^3 is absent or a linker group of the formula $–[CR_jR_k]_n-$ in which n is an integer selected from 1, 2, 3 or 4, and R_j and R_k are each independently selected from hydrogen or (1-4C)alkyl;

L^4 is absent or is selected from O, S, SO, SO_2, $N(R_l)$, C(O), C(O)O, OC(O), $CH(OR_l)$, $C(O)N(R_l)$, $N(R_l)C(O)$, $N(R_l)C(O)N(R_m)$, $S(O)_2N(R_l)$, or $N(R_l)SO_2$, wherein R_l and R_m are each independently selected from hydrogen or (1-4C)alkyl; and

R_B is (1-6C)alkyl, aryl, aryl-(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-4C)alkyl, heteroaryl, heteroaryl-(1-4C)alkyl, heterocyclyl, heterocyclyl-(1-4C)alkyl.

13. A process according to any one of the preceding claims, wherein X^- is bromo or iodo.

14. A process according to any one of the preceding claims, wherein H_2NR_{1A} is any primary amine.

15. A process according to any one of the preceding claims, wherein the amine is present in an amount of 1 and 20 molar equivalents of amine relative to the pyridinium ion are present.

16. A process according to any one of the preceding claims, wherein the hydrogen donor is selected from hydrogen gas, formic acid or isopropanol.

17. A process according to any one of the preceding claims, wherein the ratio of hydrogen donor to amine is between 1:1 and 10:1 (molar equivalents of hydrogen donor to amine).

18. A process according to any one of the preceding claims, wherein the solvent comprises between 1 and 50% by volume of water as a co-solvent.

19. A process according to any one of the preceding claims, wherein the catalyst is a metal complex that reacts with hydrogen gas or formic acid to form a metal hydride.

20. A process according to any one of the preceding claims, wherein the catalyst has the formula

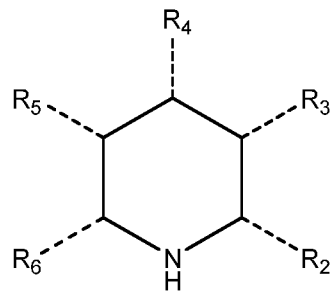
$$[ArMX_2]_2$$

where Ar is pentamethylcyclopentadienyl or an arene, such as cymene; M is a transition metal (e.g. Rh, Ir and Ru); and X is a halide, such as chloro, bromo or iodo.

21. A process according to any one of the preceding claims, wherein the catalyst is present in an amount of 0.1 to 5 mol.%.

22. A process according to any one of the preceding claims, wherein the reaction proceeds at a temperature of 25-100 °C, optionally over a period of 2 to 48 hours.

23. A process of preparing a substituted piperidine of formula III below



III

wherein:

R_2, R_3, R_4, R_5, and R_6 are as defined in any one of claims 1 to ;

the process comprising:

forming a compound of formula I according to claim 1 and deprotecting the compound of formula I to remove the group R_{1A}.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2015/050883

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/02 C07D211/14
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.
Y	TH. ZINCKE ET AL: "Ueber Dinitrophenylpyridiniumchlorid und dessen Umwandlungsproducte. Ueber die Einwirkung aliphatischer Amine auf Dinitrophenylpyridiniumchlorid", JUSTUS LIEBIGS ANNALEN DER CHEMIE, vol. 341, no. 3, 1 January 1905 (1905-01-01), pages 365-379, XP55189057, ISSN: 0075-4617, DOI: 10.1002/jlac.19053410305	1-9, 11-22
A	page 365, first paragraph	10

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[X] 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

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"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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 2015	27/05/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gutke, Hans-Jürgen

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2015/050883

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HANS LETTRÉ ET AL: "Zur Darstellung von Derivaten des Nicotinsäureamids", JUSTUS LIEBIGS ANNALEN DER CHEMIE, vol. 579, no. 2, 18 February 1953 (1953-02-18), pages 123-132, XP055189061, ISSN: 0075-4617, DOI: 10.1002/jlac.19535790207	1-9, 11-22
A	page 125, reaction scheme pages 130-132, 3-rd to 11-th preparation	10

X	ZHI-SHI YE ET AL: "Iridium-Catalyzed Asymmetric Hydrogenation of Pyridinium Salts", ANGEWANDTE CHEMIE INTERNATIONAL EDITION, vol. 51, no. 40, 1 October 2012 (2012-10-01), pages 10181-10184, XP055188720, ISSN: 1433-7851, DOI: 10.1002/anie.201205187	23
Y	page 10183, scheme 2	1-9, 11-22
A		10
