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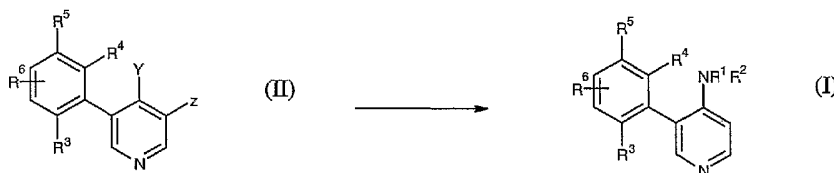
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(54) Title: PROCESS FOR THE PREPARATION OF ATROPISOMERIC ANALOGUES OF 4-AMINOPYRIDINE



(57) Abstract: The present invention relates to a process for the preparation of 3,4-disubstituted pyridines from commercially available starting materials. In particular, the invention relates to the process for the preparation for a compound of formula (I) wherein a compound of formula (II) undergoes an elimination reaction to remove the groups Z and Y, followed by the addition of a group H-NR¹R². The 3,4-disubstituted pyridines can be used commercially in acylative kinetic resolutions and asymmetric desymmetrisations.

PROCESS FOR THE PREPARATION OF ATROPISOMERIC ANALOGUES OF 4-AMINOPYRIDINE

5 The present invention relates to a process for the preparation of a class of chiral compounds. More specifically, the invention relates to a process for the preparation of atropisomeric analogues of 4-aminopyridine.

10 Commercially important compounds such as pharmaceuticals, agrochemicals, fragrances and flavourings are required in enantiomerically highly enriched forms and preferably as single enantiomers. The production of such optically pure compounds is particularly important for use in the medical or veterinary fields where the presence of an unwanted antipode may reduce or dilute the activity of the active enantiomer or may cause harmful or unwanted side effects.

15 The requirement for the synthesis of such enantiomerically enriched or pure compounds has resulted in investigations into suitable reagents or catalysts. Resolution of enantiomers can be carried out using enantioselective acylation to allow kinetic resolution or enantioselective desymmetrisation. Such enantioselective acylation is traditionally carried out using enzymes. However the natural specificity
20 of enzymes and the limited acceptable reaction conditions of enzymes results in a number of disadvantages.

Small organic molecules that catalyse enantioselective acyl transfer have therefore attracted great interest in the synthetic community in recent years. The use of such
25 reagents provides a number of advantages over the traditional use of enzymes, including the ability to work under more extreme thermal and physical conditions and the ability to be used with a wider range of substrates. Furthermore, such reagents can be made in both enantiomeric forms and the resolution reactions can be rendered irreversible. As a result, a number of chiral nucleophilic catalysts have been designed
30 that deliver useful levels of enantioselectivity in acylative kinetic resolutions (KRs), asymmetric desymmetrisations (ASDs) and related transformations. Examples of

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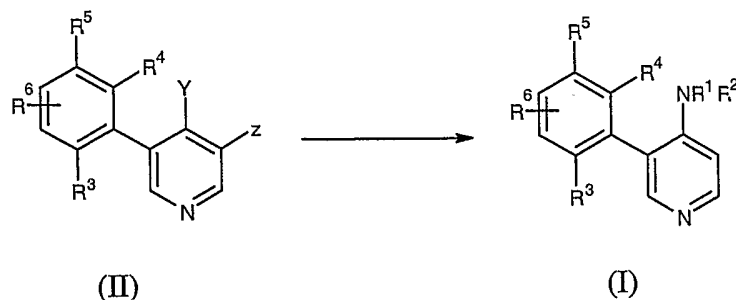
such catalysts include chiral bicyclic phosphines, proline-derived chiral diamines, a chiral 4-pyrrolidinopyridine derivative and N-alkylimidazole-functionalised peptides.

WO 01/39884 discloses a chiral catalyst comprising a 3,4-disubstituted pyridine and the use of such a catalyst for the kinetic resolutions of various aryl, alkyl *sec*-alcohols.

The preparation of the majority of the chiral nucleophilic catalysts involve multistep synthesis. In the case of the planar chiral 4-dimethylaminopyridine (DMAP) and axially chiral DMAP compounds, preparative-scale chiral stationary phase (CSP) HPLC is required to resolve the enantiomers. Such inaccessibility constitutes a significant disincentive to the widespread use of these catalysts and compromises their viability as practical enzyme-substitutes.

The present application provides an improved process for the synthesis of 3,4-disubstituted pyridines from commercially available starting materials. The 3,4-disubstituted pyridines can be used commercially in KRs and ASDs and related transformations. The provision of these compounds using the improved process of the invention allows the use of these compounds as commercially and/or industrially useful catalysts.

The first aspect of the invention relates to a process for the preparation of a compound of formula (I), comprising subjecting a compound of formula (II) to an elimination reaction to remove the groups Z and Y, followed by the addition of a group H-NR¹R²,



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wherein R^1 and R^2 are independently selected from C_{1-20} alkyl, C_{3-20} cyclo alkyl and/or C_{3-20} aryl, or NR^1R^2 form a cyclic amine; wherein R^1 and/or R^2 may optionally be substituted and/or include one or more heteroatoms;

R^3 is selected from C_{1-20} alkyl, C_{3-20} cyclo alkyl and/or C_{3-20} aryl, wherein R^3 may be optionally substituted and or include one or more hetero atoms,

R^4 is C_{1-20} alkyl, C_{3-20} cyclo alkyl and/or C_{3-20} aryl;

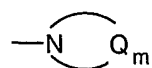
R^5 is hydrogen, or R^4 and R^5 together are a C_{3-20} fused cyclic or aromatic group wherein R^4 or R^4 and R^5 together may be optionally substituted or include one or more hetero atoms;

R^6 is one or more groups that improve or do not detract from performance of the compounds as catalyst;

wherein either Y or Z is independently a group which can be metallated to allow its replacement by hydrogen and Y and Z together allow the formation of a pyridyne intermediate wherein Y is preferably I, Br, Cl, F, OSO_2R^{11} or H, and Z is preferably I, Br, Cl, F, OSO_2R^{11} or H, or Y and Z may be together a group such as $-N=N-NH-$ which can be transformed into a pyridyne by methods known in the art (such as oxidation with for example $Pb(OAc)_4$) wherein R^{11} is C_{1-6} alkyl, C_{3-20} aryl, or C_{1-6} haloalkyl such as perfluoroalkyl preferably methyl, CF_3 .

Preferably each of R^1 independently are selected from: straight or branched chain lower (C_{1-5}) or higher (C_{6-20}) alkyl, more preferably methyl, ethyl, propyl, butyl, pentyl or hexyl, heptyl, octyl; or from C_{3-20} cyclo alkyl, preferably C_3 - C_{14} cyclo alkyl; or from C_{6-24} aryl, more preferably an unfused, optionally spiro 1, 2, 3, 4 or 5 ring alkyl or aryl structure; any of which are optionally substituted and/or include at least one heteroatom; or

R^1 and R^2 together form an optionally substituted cyclo amine, such as



wherein $m = 1-8$ and each Q is independently selected from $(CH_2)_nQ'_p$ wherein $n = 1-8$, $p = 0-4$ and the sum of n and p is at least 2, and each Q' is independently selected from NR^9 , O, S, P or Si,

preferably Q is $(\text{CH}_2)_n \cdot \text{Q}'$ wherein n' is 1 – 3 or the cyclic amine is pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl.

5 wherein R^9 is as hereinbefore defined for R^1 or forms a dimer or oligomer of a moiety of compounds of formula (I).

Preferably R^3 is selected from: straight or branched chain lower (C_{1-5}) or higher (C_{6-20}) alkyl, more preferably methyl, ethyl, propyl, butyl, pentyl or hexyl, heptyl, octyl;
10 or from C_{3-20} cyclo alkyl, preferably $\text{C}_3\text{-C}_{14}$ cyclo alkyl; or from C_{6-24} aryl, more preferably an unfused, optionally spiro 1, 2, 3, 4 or 5 ring alkyl or aryl structure; any of which are optionally substituted and/or include at least one heteroatom;

or R^3 comprises optionally substituted phenyl or biphenyl, such as optionally
15 substituted (3, 5-diphenyl)phenyl, such as [(3', 3'', 5', 5''-tetramethyl)-3, 5-diphenyl]phenyl.

The compounds of formulae (I) or (II) as hereinbefore defined may be further substituted or unsubstituted in the pyridine 2- and/or 6- positions and/or on the 3-
20 phenyl ring with one or more R^6 group, wherein R^6 is selected from the example C_{1-20} alkyl or C_{3-20} aryl, either being optionally substituted or including one or more heteroatoms, halide, hydroxy, amino, alkoxy or cycloalkyl, such as hereinbefore preferably defined for R^1 , R^2 or R^3 .

25 Any optional substituents of R^1 , R^2 , R^3 , R^4 , R^5 or R^6 as hereinbefore defined may be independently selected from any groups that improve or do not detract from performance of the compounds as catalyst.

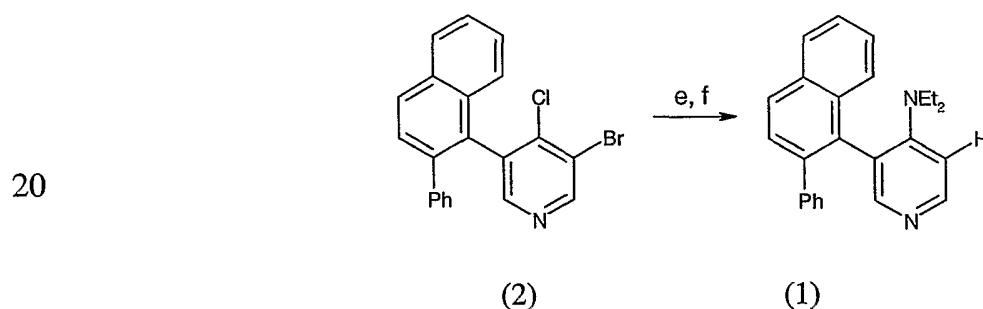
Suitable substituents include halide, hydroxy, amino, alkoxy, alkyl, cycloalkyl aryl,
30 such as hereinbefore preferably defined for R^1 , R^2 or R^3 .

Heteroatoms as hereinbefore defined include optionally substituted N, O, S, P, Si.

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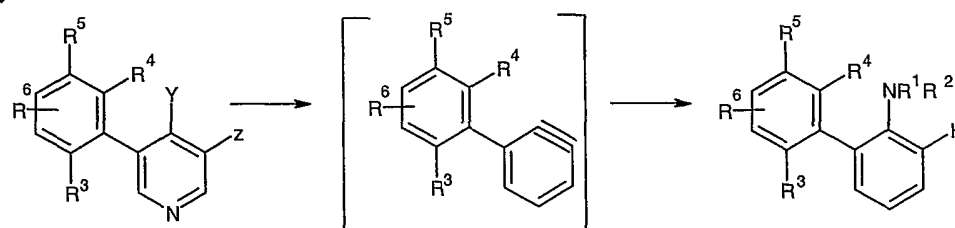
More preferably, there is provided a compound of formula (I) in which: R^1 and R^2 are methyl, ethyl, propyl, or butyl; or R^1 and R^2 together form a pyrrolidinyl-, piperidinyl-, or morpholinyl ring; and R^3 comprises a phenyl, 4'-biphenyl, (3, 5-diphenyl)phenyl, or [(3', 3'', 5', 5''-tetramethyl)-3, 5-diphenyl]phenyl.

In a particularly preferred feature of the first aspect, there is provided a process comprising the treatment of a compound of formula (II), preferably compound (2) with $i\text{PrMgCl}$ then water to effect 3-dehalogenation. Addition of the group $\text{H-NR}^1\text{R}^2$, can be achieved by refluxing HNR^1R^2 , and phenyllithium in a solvent such as THF for 16 h. In a preferred feature of the first aspect the elimination-addition pathway was carried out on the dihalopyridine 2 to give the clean formation of a readily separable 1:2 mixture of the desired 4-diethylamino product ($\pm$)-1 (30% isolated yield) and its 3-diethylamino isomer (65% isolated yield). Compound 1 can be prepared in three steps from commercially available 3,5-dibromo-4-chloropyridine in 24% overall yield.



25 e) $i\text{PrMgCl}$, then H_2O , 99%, f) PhLi , Et_2NH , THF, 67°C , 16h, 30% [$\pm$ 3-diethylamino isomer, 65%].

Without being bound by scientific theory, the process of the first aspect of the invention is believed to proceed via a pyridyne intermediate, wherein the group Z is initially metallated by a group M, followed by an elimination reaction to form pyridyne intermediate.



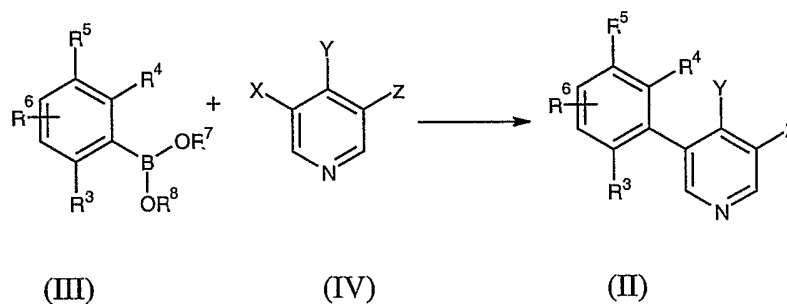
(II)

(I)

5 For the purpose of this invention, the groups Y and Z are therefore any groups which favour or allow the formation of the pyridyne intermediate.

The second aspect of the invention relates to a process for the production of a compound of formula (II),

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comprising reacting a compound of formula (III), with a compound of formula (IV), in the presence of a transition metal catalyst wherein, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , Y and Z are as defined for the first aspect,

R^7 , R^8 are independently a branched or unbranched C_{1-10} alkyl, preferably methyl, ethyl, propyl or butyl. More preferably R^8 and R^7 together form a group $-C(CH_3)_2-C(CH_3)_2-$.

25

and X is a group which can undergo oxidative insertion of a metal M, preferably selected from F, Cl, Br, I, OSO_2R^{12} , N_2^+ , SAr wherein R^{12} is alkyl, aryl or haloalkyl, preferably methyl, ethyl, phenyl or trifluoromethyl.

Preferably X and Z are bromide and Y is chloride.

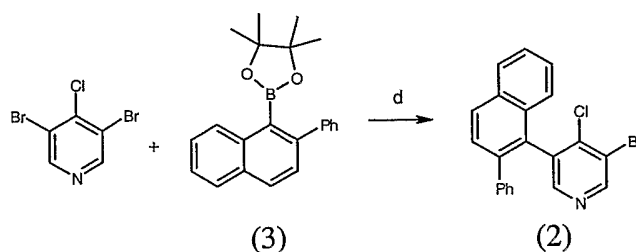
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The coupling of a compound of formula (III) with a compound of formula (IV) is preferably catalysed by a palladium or nickel catalyst. More preferably the reaction is catalysed by palladium (0). It will be appreciated that the compound of formula (II)

can be produced by a Suzuki cross-coupling protocol in accordance with for example H. Chaumeil et al, *Tetrahedron*, 2000, **56**, 9655.

5 In a preferred aspect of this invention the second aspect provides a process for the preparation of a compound of compound 2 via Suzuki reaction between 3,5-dibromo-4-chloropyridine and pinacolato-boronic ester (3). The compound (2) is produced reproducibly in 80% yield on a multi-gram scale.

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15 d) Ag_2CO_3 , $\text{Pd}(\text{PPh}_3)_4$ (5mol%), PhH, 80°C , 96h, 80%.

The use of a boronic ester (such as that illustrated in compound 3) as opposed to the corresponding boronic acid is advantageous as the boronic ester is easier to prepare and purify.

20

The compound of formula (II) prepared according to the second aspect of the invention can be used to prepare a compound of formula (I) in accordance with the first aspect of the invention.

25 Accordingly, the third aspect of the invention provides a process for the production of a compound of formula (I), comprising preparing a compound of formula (II) according to the second aspect of the invention, and converting said compound of formula (II) to a compound of formula (I) according to the first aspect of the invention.

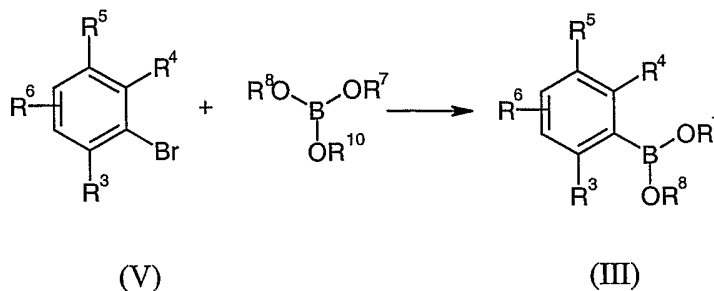
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The fourth aspect of the invention relates to a process for the production of a compound of formula (III) comprising reacting a compound of formula (V) with $(R^{10}O)-B(OR^7)-(OR^8)$

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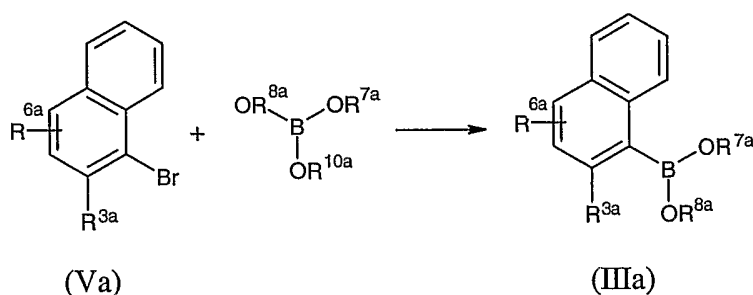
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wherein R^3 , R^4 , R^5 and R^6 are as defined for the first aspect of the invention, R^7 , R^8 and R^{10} are independently hydrogen or a branched or unbranched C_{1-10} alkyl, preferably methyl, ethyl, propyl or butyl. More preferably R^8 and R^7 together form a group $-C(CH_3)_2-C(CH_3)_2-$ and R^{10} is *i*-propyl.

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In a preferred feature, the fourth aspect provides a process for the production of a compound of formula (IIIa)

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comprising reacting a compound of formula (Va) with $R^{10a}O-B(OR^{7a})-(OR^{8a})$ wherein R^{6a} is as defined for R^6 in the first aspect of the invention.

R^{3a} is C_{3-20} aryl, preferably phenyl or naphthyl R^{8a} , R^{7a} and R^{10a} are independently hydrogen or a branched or unbranched C_{1-10} alkyl, preferably, methyl, ethyl, *n*-propyl or *i*-propyl, or R^{8a} and R^{7a} form a five or six-membered ring with the O-B-O motif, said five or six-membered ring being optionally substituted with one or more methyl

or ethyl groups, more preferably wherein R⁸ and R⁷ together form a group –C(CH₃)₂–C(CH₃)₂– or –CH₂–CH₂–CH₂–.

5 The compound of formula (III) prepared according to the fourth aspect of the invention can be used to prepare a compound of formula (II) in accordance with the second aspect of the invention.

10 Accordingly, the fifth aspect of the invention provides a process for the production of a compound of formula (I), comprising preparing a compound of formula (III) according to the fifth aspect of the invention, converting said compound of formula (III) to a compound of formula (II) according to the second aspect of the invention, and converting said compound of formula (II) into a compound of formula (I) in accordance with the first aspect of the invention.

15 The sixth aspect of the invention relates to a process for the resolution of the compound of formula (I), comprising crystallization of the diastereomeric salt of the compound of formula (I) with an appropriate homochiral acid. Preferably, the compound of formula (I), more preferably compound (1) ((±)-diethyl-[3-(2-phenyl-naphthalen-1-yl)-pyridin-4-yl]-amine) is crystallised with the homochiral acid *N*-Boc-*O*-benzyl-(*S*)-tyrosine.

20

Identification of suitable optimal acid partners can be carried out using automated salt synthesis between the compounds of the invention and an array of commercially available homochiral acids using a robot, followed by differential scanning

25 calorimetry (DSC) screening to identify eutectic crystals, trial crystallizations, and then optimization of the crystallization conditions with the aid of the software package 'Resolution Companion' as disclosed in WO 01/39884. In a preferred feature of the sixth aspect, a 1:1 mixture of compound (1) and *N*-Boc-*O*-benzyl-(*S*)-tyrosine is crystallised from ⁱPrOH, followed by two recrystallisations from ⁱPrOH.

30 The resulting salt is isolated in 34% yield with >99.8% de (determined by CSP-HPLC). Enantiomerically pure compound (1) is obtained by passing a solution of the salt in CH₂Cl₂/Et₂N (10:1) through a short plug of silica and removing the solvents *in*

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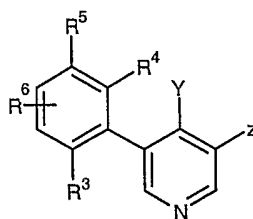
vacuo. The other enantiomer of the catalyst may also be obtained enantiomerically pure by recrystallisation of the combined mother liquers of the above experiment with *N*-Boc-*O*-benzyl-*(R)*-tyrosine

5 The seventh aspect of the invention relates to a compound as produced by the process set out in the first, second, third, fourth, fifth and sixth aspects of the invention. The seventh aspect further relates to a chiral catalyst comprising the compound as produced by the processes described herein.

10 The eighth aspect of the invention relates to a process for stereoselective reaction of a compound of formula (I), comprising reaction with an optically inactive substrate to provide one or both enantiomers of a derivative thereof, with simultaneous or subsequent recovery of the catalyst. The eighth aspect further relates to a process comprising the enantioselective acylation by means of kinetic resolution of a
15 compound such as a secondary or tertiary alcohol or a primary, or a secondary amine, or aniline.

In a preferred feature of the eighth aspect, compound (I) catalyzes the acylative kinetic resolution of a range of aryl alkyl *sec*-alcohols with $(^i\text{PrCO})_2\text{O}$ giving
20 enantioselectivities (*s*) in the range 8-29 for formation of the *R* configured esters. The compounds of formula (I) as produced by the process of the present application can be used to carry out kinetic resolutions.

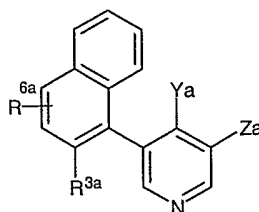
25 The ninth aspect of the invention relates to a compound of formula II,



(II)

30 wherein the groups R³, R⁴, R⁵, R⁶, Y and Z are as defined in the first aspect of the invention. In particular, the ninth aspect relates to a compound of formula IIa.

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(IIa)

wherein R^{6a} is as defined for R^6 in the first aspect, preferably hydrogen or methyl

R^{3a} is C_{3-20} aryl, preferably phenyl or naphthyl

Y^a and Z^a are independently Br, I or Cl, preferably Y^a is Cl and Z^a is Br.

All preferred features of the aspects of the invention relate to all other preferred features *mutandis mutandi*.

The present invention will now be further illustrated by reference to one or more of the non-limiting examples.

Examples

General Procedures.

All reactions were performed under anhydrous conditions and under an atmosphere of nitrogen in oven-dried glassware. Yields refer to chromatographically and spectroscopically (1H NMR) homogenous materials. Reagents were used as obtained from commercial sources or purified according to known procedures. Flash chromatography was carried out using Merck Kieselgel 60 F₂₅₄ (230-400 mesh) silica gel. Only distilled solvents were used as eluents. Thin layer chromatography (TLC) was performed on Merck DC-Alufolien or glass plates pre-coated with silica gel 60 F₂₅₄ which were visualised either by quenching of ultraviolet fluorescence ($\lambda_{max} = 254$ nm) or by charring with 10% $KMnO_4$ in 0.1 M NaOH. All reaction solvents were distilled before use and stored over activated 4 Å molecular sieves, unless otherwise indicated. Anhydrous CH_2Cl_2 was obtained by refluxing over calcium hydride. Petrol refers to the fraction of light petroleum boiling between 40-60 °C. High Resolution Mass Spectrometry (HRMS) measurements are valid to ± 5 ppm.

Experimental Procedures.

4,4,5,5-Tetramethyl-2-(2-phenyl-naphthalen-1-yl)-[1,3,2]dioxaborolane 3. To a solution of 1-bromo-2-naphthol (3g, 13.4mmol) in pyridine at 0 °C was added trifluoromethanesulfonic anhydride (2.70ml, 16.1mmol). The mixture was stirred at 0 °C for 1 h then allowed to warm to RT and stirred for a further 3 h. The resulting mixture was partitioned between 2M HCl (aq) and Et₂O, the organic layer was washed with two further portions of acid then filtered through a thin pad of silica gel. The solvent was removed *in vacuo* to give 1-bromo-2-naphthyl triflate (4.60g, 97%) as a yellow oil which was used without further purification.

To a solution of 1-bromo-2-naphthyl triflate (4.60g, 13.0mmol) in Et₂O (16ml) was added Pd₂(dba)₃ (180mg, 0.195mmol), 1,3-bis(diphenylphosphino)propane (161mg, 0.39mmol) and LiBr (1.13g, 13.0mmol). The resulting mixture was stirred at RT for 5 min, then a solution of PhMgBr in Et₂O (3.0M, 5.2ml, 15.5mmol) was added using a water bath to cool down the mildly exothermic reaction. The mixture was then stirred at RT for 7 h, before quenching with methanol (1.5ml) and filtering through a plug of silica gel with Et₂O and the solvent removed *in vacuo* to give 1-bromo-2-phenylnaphthalene as a yellow oil (3.68g, 100%) which was used without further purification.

To a solution of 1-bromo-2-phenylnaphthalene (3.68g, 13.0mmol) in Et₂O (35ml) at -78 °C, was added a solution of *n*-BuLi in hexanes (2.5M, 5.7ml, 14.3mmol) dropwise. After 15min at -78 °C, 2-isopropoxy-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (2.66g, 14.3mmol) was added in one portion. After 1 h at -78 °C, the mixture was allowed to warm to RT and stirred for a further 2 h. The resulting mixture was quenched with HCl in Et₂O (1.0M, 13.0ml, 13.0mmol) and stirred for 45 min at RT. The solvent was removed *in vacuo* to give an off white semi-solid. Purification by flash chromatography (petrol/CH₂Cl₂, 2:1) gave the boronic ester **3** as a colourless solid (4.04g, 94%): mp 52-53 °C; R_f 0.56 (petrol/CH₂Cl₂, 1:1); ¹H NMR (300MHz,

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CDCl₃) δ 1.31 (s, 12H), 7.36-7.70 (8H), 7.92 (m, 2H), 8.17 (d, $J=8.0$ Hz, 1H); ¹³C NMR (75.5MHz, CDCl₃) δ 25.1 (4q), 84.1 (2s), 125.5 (d), 126.4 (d), 127.1 (d), 127.3 (d), 127.9 (d), 128.1 (d), 128.3 (d), 129.3 (d), 129.4 (d), 132.0 (s), 136.2 (s), 143.9 (s), 145.4 (s); FTIR (neat) $\nu_{\max}$ 3056, 2978, 1312, 1134 cm⁻¹; MS(EI⁺) m/z (rel intensity) 330 (67%, M⁺), 214 (100%); HRMS(EI⁺) calcd. for C₂₂H₂₃BO₂ 330.1791 found 330.1786.

(±)-3-Bromo-4-chloro-5-(2-phenyl-naphthalen-1-yl)-pyridine 2. To a solution of 3,5-dibromo-4-chloropyridine (A.C.Spivey, T. Fekner, S. E. Spey, *J. Org. Chem.* **2000**, 65, 3154-3159) (3.90g, 14.3mmol) and 4,4,5,5-tetramethyl-2-(2-phenyl-naphthalen-1-yl)-[1,3,2]dioxaborolane **3** (6.13g, 18.6mmol) in benzene (100ml) was added silver(I) carbonate (5.13g, 18.6mmol) and Pd(PPh₃)₄ (0.826g, 0.72mmol) and the resulting mixture heated to reflux for 96 h. The reaction mixture was filtered, washed with water, dried (MgSO₄) and then the solvent removed *in vacuo* to give the crude product. Purification by flash chromatography (petrol – EtOAc/petrol, 1:20) gave dihalopyridine **2** as an off white solid (5.64g, 80%): mp 118-119 °C; R_f 0.25 (EtOAc/petrol, 1:20); ¹H NMR (270MHz, CDCl₃) δ 7.16-7.25 (5H), 7.32 (1H, d, $J=8.5$ Hz), 7.46 (m, 1H), 7.54 (m, 1H), 7.60 (d, $J=8.5$ Hz, 1H), 7.96 (d, $J=8.5$ Hz, 1H), 8.02 (d, $J=8.5$ Hz, 1H) 8.24 (s, 1H), 8.68 (s, 1H); ¹³C NMR (125.7MHz, CDCl₃) δ 121.4 (s), 125.3 (d), 126.2 (d), 127.1 (d), 127.2 (d), 127.9 (d), 128.0 (2d), 128.3 (d), 129.1 (2d), 129.3 (d), 130.4 (s), 131.6 (s), 132.5 (s), 136.1 (s), 139.8 (s), 140.7 (s), 144.5 (s), 151.2 (d), 151.3 (d); FTIR (neat) $\nu_{\max}$ 3057, 1494, 1395, 1200 cm⁻¹; MS(EI⁺) m/z (rel intensity) 397 (25%, M⁺(⁸¹Br³⁷Cl)), 395 (100%, M⁺(⁸¹Br³⁵Cl or ⁷⁹Br³⁷Cl)), 393 (77%, M⁺(⁷⁹Br³⁵Cl)); HRMS(EI⁺) calcd. for C₂₁H₁₃N⁸¹Br³⁵Cl 394.9899 found 394.9904.

4-Chloro-3-(2-phenyl-naphthalen-1-yl)-pyridine. To a solution of (±)-3-bromo-4-chloro-5-(2-phenyl-naphthalen-1-yl)-pyridine **2** (1.50g, 3.8mmol) in THF (10ml) was added dropwise at RT a solution of ⁱPrMgCl in THF (2.0M, 2.28ml, 4.56mmol). After stirring at RT for 2 h the resulting brown solution was treated with water (10ml). The mixture was partitioned between water and CH₂Cl₂, the organic layer dried (MgSO₄) and the solvent removed *in vacuo* to give the crude product as a pale yellow solid.

Purification by flash chromatography (EtOAc/petrol, 1:10) gave the 4-chloro-3-(2-phenyl-naphthalen-1-yl)-pyridine as an off white solid (1.18g, 99%). mp 161-162 °C; R_f 0.10 (EtOAc/petrol, 1:20); ^1H NMR (270MHz, CDCl_3) δ 7.13-7.28 (5H), 7.30-7.70 (5H), 7.95 (d, $J=8.0\text{Hz}$, 1H), 8.00 (d, $J=8.5\text{Hz}$, 1H), 8.37 (s, 1H), 8.43 (d, $J=8.5\text{Hz}$, 1H); ^{13}C NMR (125.7MHz, CDCl_3) δ 124.1 (d), 125.5 (d), 126.0 (d), 126.9 (2d), 127.9 (2d), 128.0 (d), 128.2 (d), 129.0 (d), 129.3 (2d), 130.6 (s), 131.9 (s), 132.5 (s), 134.4 (s), 139.9 (s), 140.9 (s), 144.6 (s), 149.2 (d), 153.1 (d); FTIR (neat) ν_{max} 3056, 1547, 1495, 1085 cm^{-1} ; MS(EI^+) m/z (rel intensity) 317 (33%, $\text{M}^+(\text{}^{37}\text{Cl})$), 315 (100%, $\text{M}^+(\text{}^{35}\text{Cl})$); HRMS(EI^+) calcd. for $\text{C}_{21}\text{H}_{14}\text{N}^{35}\text{Cl}$ 315.0815 found 315.0813.

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(±)-Diethyl-[3-(2-phenyl-naphthalen-1-yl)-pyridin-4-yl]-amine 1 (A.C.Spivey, T. Fekner, S. E. Spey, *J. Org. Chem.* **2000**, 65, 3154-3159) and **diethyl-[5-(2-phenyl-naphthalen-1-yl)-pyridin-3-yl]-amine**. To a solution of 4-chloro-3-(2-phenyl-naphthalen-1-yl)-pyridine (50mg, 0.16mmol) in THF (1ml) was added diethylamine (165 μl , 1.6mmol) and a solution of PhLi in cyclohexane/ Et_2O (7:3)(2M, 100 μl , 0.19mmol). The mixture was heated at reflux for 16 h then the solvent removed *in vacuo*. Purification by flash chromatography (EtOAc), gave:

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(±)-Diethyl-[3-(2-phenyl-naphthalen-1-yl)-pyridin-4-yl]-amine 1 (A.C.Spivey, T. Fekner, S. E. Spey, *J. Org. Chem.* **2000**, 65, 3154-3159) (17mg, 30%): R_f 0.25 (EtOAc); mp 124-125 °C (*cf.* Lit mp 124-125 °C); ^1H NMR (300MHz, CDCl_3) δ 0.53 (t, $J=6.0\text{Hz}$, 6H), 2.73 (m, 4H), 6.51 (d, $J=6.0\text{Hz}$, 1H), 7.05-7.23 (5H), 7.42-7.60.

25

Diethyl-[5-(2-phenyl-naphthalen-1-yl)-pyridin-3-yl]-amine (36mg, 65%): R_f 0.80 (EtOAc); ^1H NMR (300MHz, CDCl_3) δ 1.01 (t, $J=7.0\text{Hz}$, 6H), 3.25 (m, 4H), 6.67 (s, 1H), 7.12-7.27 (5H), 7.50 (m, 2H), 7.61 (d, $J=8.5\text{Hz}$, 1H), 7.78 (d, $J=8.0\text{Hz}$, 1H), 7.88 (s, 1H), 7.91-8.05 (4H); ^{13}C NMR (75.5MHz, CDCl_3) δ 12.1 (2q), 44.2 (2t), 121.5 (d), 125.8 (d), 126.4 (2d), 126.5 (d), 127.8 (2d), 127.9 (d), 128.0 (d), 128.2 (d), 129.9 (2d), 130.2 (s), 132.6 (s), 132.7 (s), 132.8 (d), 134.6 (s), 138.9 (d), 141.6 (s), 142.9 (s); FTIR (neat) ν_{max} 3054, 2970, 1586 cm^{-1} ; MS(EI^+) m/z (rel intensity) 352 (10, M^+), 337 (22), 281 (100), 154 (50), 94 (30); HRMS (EI^+) calcd. for $\text{C}_{25}\text{H}_{24}\text{N}_2$ (M^+) 352.1939, found 352.1930.

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Optical resolution of DMAP

- 5 A suspension of ($\pm$)-DMAP **1** (500mg, 1.42mmol) and *N*-Boc-*O*-benzyl-(*S*)-tyrosine (527.5mg, 1.42mmol) in IPA (4.95ml) was heated to 75 °C for 0.5 h to furnish a clear solution. Heating was removed and the solution allowed to cool to RT naturally. After 14 h the precipitated solid collected by suction and washed with the minimum of cold IPA (*ca.* 20-30 ml at 5-10 °C). The resulting solid was dried in a vacuum oven at
- 10 40 °C for 14 h to yield the salt **4** (594mg, 58%, 63% *de* by CSP-HPLC). Recrystallization of 500mg of this salt from hot IPA (2.4ml) and isolation as above gave the salt **4** (350mg, 70%, 96% *de* by CSP-HPLC). Recrystallization of 238mg of this salt from hot IPA (1.14ml) and isolation as above gave the pure salt **4** (196mg, 83%, >99.8% *de* by CSP-HPLC). This salt was dissolved in CH₂Cl₂/Et₃N (10:1, 3ml),
- 15 stirred for 14 h, concentrated *in vacuo* and passed through a plug of silica eluting with EtOAc to give (-)-DMAP **1** (95mg, 34% from racemate, >99.8% *ee* by CSP-HPLC).

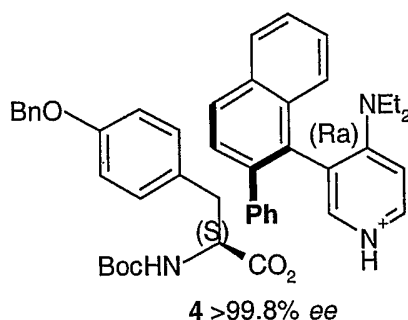
- CSP HPLC Assay Conditions:** Both salt **4** and DMAP **1** were analyzed using the same conditions and gave the same retention times. In the case of salt **4** the *N*-Boc-*O*-
- 20 benzyl-(*S*)-tyrosine is retained on the column under these conditions:

Chiralcel OD 1.0*25cm; hexane/EtOAc/Et₃N (80:19.6:0.4); 4.0ml/min; temp=30 °C; UV detection 254nm ($\pm$ 10), Ref to 525nm ($\pm$ 50); retention time: 9.6min (-), 15.0min (+).

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Single-crystal X-ray data for salt **4** [from *N*-Boc-*O*-benzyl-(*S*)-tyrosine].

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Crystal data for $C_{46}H_{49}N_3O_5$; $M = 723.88$; crystallises from CH_2Cl_2/Et_3N as colourless prisms; crystal dimensions $0.32 \times 0.12 \times 0.12 \text{ mm}^3$. Triclinic, $a = 8.356(3)$, $b = 10.294(4)$, $c = 12.232(5) \text{ \AA}$, $\alpha = 73.599(9)^\circ$, $\beta = 85.683(8)^\circ$, $\gamma = 77.564(8)^\circ$, $U = 985.5(7) \text{ \AA}^3$, $Z = 1$, $D_c = 1.220 \text{ Mg/m}^3$, space group $P1 (C_i^1, \text{No. } 1)$, Mo- $K\alpha$ radiation ($\bar{\lambda} = 0.71073 \text{ \AA}$), $\mu(\text{Mo-}K\alpha) = 0.079 \text{ mm}^{-1}$, $F(000) = 386$. Data collected were measured on a Bruker Smart CCD area detector with Oxford Cryosystems low temperature system. Cell parameters were refined from the setting angles of 666 reflections (θ range $1.74 < 28.32^\circ$).

Reflections were measured from a hemisphere of data collected of frames each covering 0.3 degrees in omega. Of the 6278 reflections measured, all of which were corrected for Lorentz and polarisation effects and for absorption by semi empirical methods based on symmetry-equivalent and repeated reflections (minimum and maximum transmission coefficients 0.9751 and 0.9906), 2822 independent reflections exceeded the significance level $|F|/\sigma(|F|) > 4.0$. The structure was solved by direct methods and refined by full matrix least squares methods on F^2 . Hydrogen atoms were placed geometrically and refined with a riding model (including torsional freedom for methyl groups) and with U_{iso} constrained to be 1.2 (1.5 for methyl groups) times U_{eq} of the carrier atom. Refinement converged at a final $R = 0.0948$ ($wR_2 = 0.2507$, for all 5159 data, 497 parameters, mean and maximum δ/σ_1) with allowance for the thermal anisotropy of all non-hydrogen atoms. Minimum and maximum final electron density -0.599 and $0.680 \text{ e.\AA}^{-3}$. A weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.1075 * P)^2 + 0.00 * P]$ where $P = (F_o^2 + 2 * F_c^2)/3$ was used in the latter stages of refinement. Complex scattering factors were taken from the program package SHELXTL as implemented on a Viglen Pentium computer.

General Procedure for Analytical-Scale Catalytic Acylative Kinetic Resolution/Asymmetric Desymmetrization. (Table 1)

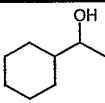
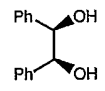
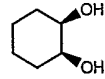
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A solution of ($\pm$)-alcohol (1.00 mmol), Et₃N (104 μ L, 0.75 mmol), and (-)-DMAP **1** (3.5 mg, 10 μ mol, >99.8% ee) in toluene (2.0 mL) was cooled to -78 °C. During vigorous stirring, (iPrCO)₂O (331 μ L, 2.00 mmol) was added dropwise over 3 min. After 9.0 h, the reaction mixture was quenched by dropwise addition of MeOH (5.0 mL) over 2 min. After 15 min at -78 °C and 15 min at RT, the solvents were evaporated *in vacuo*. For entries 1-8 (i.e. KR_s) the alcohol and ester were separated by flash chromatography and the enantiomeric excess for the unreacted alcohols and esters were established by analytical CSP HPLC. For entries 9 and 10 (i.e. ASD_s) the enantiomeric excess for the product ester was established directly by either analytical CSP HPLC or GC:

Using the optimised conditions we now report the performance of (-)-DMAP **1**, prepared as described above, for the KR and ASD of a range of more structurally diverse *sec*-alcohols (Table 1).

Table 1

Entry	Substrate	%ee _A	%ee _E	%C	s ^[19]	Product enantiomer
1 X=CN		8.2	67.2	11.0	5.5	(-) 1R,2S ^a
2 X=NO ₂		85.3	39.1	69.0	5.7	(-) 1R,2S
3 X=NMe ₂		17.9	86.4	18.0	16.1	(-) 1R,2S
4 X=H		97.7	64.8	64.0	19.7	(+) 1S,2R
5		75.4	72.8	51.0	14.2	(+) 1R,2S ^b
6		61.4	52.8	54.0	5.9	(-) 1R,2R
7		14.3	78.0	16.0	9.3	(-) 1R,2S

8		37.0	71.0	34.0	8.4	(+) <i>R</i>
9		-	44.6	26.0 (yield)	-	(+) <i>1S,2R</i> ^c
10		-	77.5	20.0 (yield)	-	(-) <i>1R,2S</i>

^a Tentative assignment assuming the 4-CN benzoate has the same sense of rotation as the other benzoates in this series (i.e. *cf.* entries 2-4). ^b Tentative assignment assuming the benzoate has same sense of rotation as the corresponding 4-NMe₂ benzoate. ^c Tentative assignment assuming the isobutyrate has the same sense of rotation as the corresponding acetate.

HPLC analysis of chiral esters and recovered alcohols from Table 1

Entry 1. *cis*-4-cyano-benzoic acid 2-hydroxy-cyclohexyl ester: Chiralcel AD

0.46*25cm; hexane/IPA (90:10); flow=1.0ml/min; temp=20 °C; UV detection 210nm (±8), Ref to 360nm (±100); retention time: 21.7min (-), 26.0min [(+), enriched]; ***cis*-4-cyano-benzoic acid 2-isobutyryloxy-cyclohexyl ester:** Chiralcel AD 0.46*25cm; hexane/IPA (98:2); flow=0.8ml/min; temp=20 °C; UV detection 210nm (±8), Ref to 360nm (±100); retention time: 26.1min [(-), enriched], 34.3min (+).

Entry 2. *cis*-4-nitro-benzoic acid 2-hydroxy-cyclohexyl ester: Chiralcel AD

0.46*25cm; hexane/IPA (90:10); 1.0ml/min; temp=20 °C; UV detection 250nm (±10), Ref to 360nm (±100); retention time: 21.4min [(+), enriched], 28.6min (-); ***cis*-4-nitro-benzoic acid 2-isobutyryloxy-cyclohexyl ester:** Chiralcel AD 0.46*25cm; hexane/IPA (98:2); 0.8ml/min; temp=20 °C; UV detection 250nm (±10), Ref to 360nm (±100); retention time: 20.8min (+), 23.55min [(-), enriched].

Entry 3. *cis*-4-dimethylamino-benzoic acid 2-hydroxy-cyclohexyl ester: Chiralcel

AD 0.46*25cm; hexane/IPA (90:10); 1.0ml/min; temp=20 °C; UV detection 220nm (±10), Ref to 360nm (±100); retention time: 31.8min (-), 39.8min [(+), enriched]; ***cis*-4-dimethylamino-benzoic acid 2-isobutyryloxy-cyclohexyl ester:** Chiralcel AD 0.46*25cm; hexane/IPA (92:8); 1.0ml/min; temp=30 °C; UV detection 220nm (±10), Ref to 360nm (±100); retention time: 20.4min [(-), enriched], 30.3min (+).

Entry 4. *cis*-benzoic acid 2-hydroxy-cyclohexyl ester: Chiralcel OD 0.46*25cm; hexane/IPA (99:1); 1.0ml/min; temp=20 °C; UV detection 220nm (±10), Ref to

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360nm (± 100); retention time: 28.3min (+), 30.9min [(-), enriched]; **cis-benzoic acid 2-isobutyryloxy-cyclohexyl ester**: Chiralcel AD 0.46*25cm; hexane/IPA (99:1); 0.5ml/min; temp=20 °C; UV detection 210nm (± 8), Ref to 360nm (± 100); retention time: 32.1min [(+), enriched], 34.8min (-).

- 5 **Entry 5. cis-benzoic acid 2-hydroxy-cyclopentyl ester**: Chiralcel AD 0.46*25cm; hexane/IPA (96:4); 1.0ml/min; temp=20 °C; UV detection 210nm (± 8), Ref to 360nm (± 100); retention time: 18.6min (+), 20.6min [(-), enriched]; **cis-benzoic acid 2-isobutyryloxy-cyclopentyl ester**: Chiralcel AD 0.46*25cm; hexane/IPA (98:2); 0.8ml/min; temp=20 °C; UV detection 210nm (± 8), Ref to 360nm (± 100); retention time: 16.4min [(+), enriched], 24.2min (-).

- 10 **Entry 6. trans-2-bromo-cyclohexanol**: Chiralcel OD 0.46*25cm; hexane/IPA (99:1); 0.5ml/min; temp=20 °C; UV detection 210nm (± 8), Ref to 360nm (± 100); retention time: 20.4min [(+), enriched], 21.5min (-); **trans-isobutyric acid 2-bromo-cyclohexyl ester**: Chiralcel OD 0.46*25cm; hexane/IPA (99:1); 0.5ml/min; temp=20 °C; UV detection 210nm (± 8), Ref to 360nm (± 100); retention time: 7.4min (+), 7.7min [(-), enriched].

- 20 **Entry 7. trans-2-phenyl-cyclohexanol**: Chiralcel OD 0.46*25cm; hexane/IPA (96:4); 1.0ml/min; temp=30 °C; UV detection 220nm (± 10), Ref to 360nm (± 100); retention time: 7.3min [(+), enriched], 8.1min (-); **trans-isobutyric acid 2-phenyl-cyclohexyl ester**: hydrolysed to give starting alcohol. Chiralcel OD 0.46*25cm; hexane/IPA (96:4); 0.5ml/min; temp=30 °C; UV detection 210nm (± 8), Ref to 360nm (± 100); retention time: 7.2min (+), 7.8min [(-), enriched].

- 25 **Entry 8. 1-cyclohexyl-ethanol**: Supelco GC α -DEX (30m); isocratic, temp=65 °C, run time 30mins; He pressure=24 psi; retention time: 21.8min (+), 22.6min [(-), enriched]; **isobutyric acid 1-cyclohexyl-ethyl ester**: Supelco GC α -DEX (30m); isocratic, temp=65 °C, run time 30mins; He pressure=24 psi; retention time: 22.6min (-), 23.7min [(+), enriched].

- 30 **Entry 9. cis-isobutyric acid 2-hydroxy-1,2-diphenyl-ethyl ester**: Chiralcel OD 0.46*25cm; hexane/IPA (90:10); 1.0ml/min; temp=30 °C; UV detection 210nm (± 8), Ref to 360nm (± 100); retention time: 7.7min (-), 9.2min [(+), enriched].

Entry 10. *cis*-isobutyric acid 2-hydroxy-cyclohexyl ester: Chiralcel OD

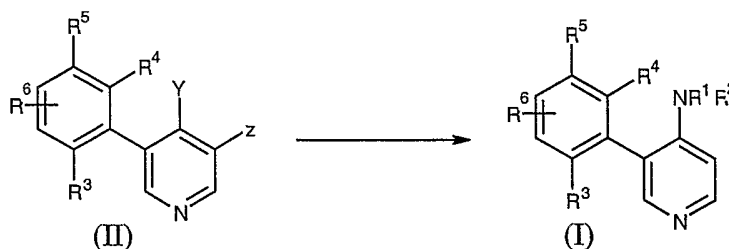
0.46*25cm; hexane/IPA (99:1); 1.0ml/min; temp=30 °C; UV detection 210nm (± 8),

Ref to 360nm (± 100); retention time: 12.4min [(-), enriched], 13.0min (+).

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CLAIMS

1. A process for the preparation of a compound of formula (I), comprising
 5 subjecting a compound of formula (II) to an elimination reaction to remove the groups
 Z and Y, followed by the addition of a group $\text{H-NR}^1\text{R}^2$,



10

wherein R^1 and R^2 are independently selected from C_{1-20} alkyl, C_{3-20} cyclo alkyl and/or C_{3-20} aryl, or NR^1R^2 form a cyclic amine; wherein R^1 and/or R^2 may optionally be substituted and/or include one or more heteroatoms;

15

R^3 is selected from C_{1-20} alkyl, C_{3-20} cyclo alkyl and/or C_{3-20} aryl, wherein R^3 may be optionally substituted and or include one or more hetero atoms,

R^4 is C_{1-20} alkyl, C_{3-20} cyclo alkyl and/or C_{3-20} aryl;

R^5 is hydrogen, or R^4 and R^5 together are a C_{3-20} fused cyclic or aromatic group wherein R^4 or R^4 and R^5 together may be optionally substituted or include one or more hetero atoms;

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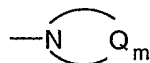
R^6 is one or more groups that improve or do not detract from performance of the compounds as catalyst, wherein any of R^1 , R^2 , R^3 , R^4 , R^5 or R^6 may optionally be substituted with one or more of halide, hydroxy, amino, alkoxy, alkyl, cycoalkyl aryl and/or include one or more heteroatoms selected from N, O, S, P, Si;

25

wherein either Y or Z is independently a group which can be metallated to allow its replacement by hydrogen, and Y and Z together allow the formation of a pyridyne intermediate wherein Y is preferably I, Br, Cl, F, $\text{OSO}_2\text{R}^{11}$ or H, and Z is preferably I, Br, Cl, F, $\text{OSO}_2\text{R}^{11}$, or H wherein R^{11} is C_{1-6} alkyl, C_{3-20} aryl or C_{1-6} haloalkyl or Y and Z may together be a group which can be transformed into a pyridyne.

2. A process as claimed in claim 1 wherein R^1 is selected from: straight or branched chain lower (C_{1-5}) or higher (C_{6-20}) alkyl, C_{3-20} cyclo alkyl, C_{6-24} aryl, or wherein R^1 and R^2 together form an optionally substituted cyclo amine

5



wherein $m = 1-8$ and each Q is independently selected from $(CH_2)_n Q'$,
 wherein $n = 1-8$, $p = 0-4$ and the sum of n and p is at least 2, and each Q' is

independently selected from NR^9 , O, S, P or Si,

10 wherein R^9 is as hereinbefore defined for R^1 or forms a dimer or oligomer of a moiety of compounds of formula (I).

3. The process as claimed in claim 1 or claim 2 wherein R^3 is selected from:
 15 straight or branched chain lower (C_{1-5}) or higher (C_{6-20}) alkyl, C_{3-20} cyclo alkyl, C_{6-24} aryl.

4. The process as claimed in any one of claims 1 to 3 wherein R^1 and R^2 are
 methyl, ethyl, propyl, or butyl; or R^1 and R^2 together form a pyrrolidinyl-, piperidinyl-,
 or morpholinyl ring; and R^3 comprises a phenyl, 4'-biphenyl, (3, 5-diphenyl)phenyl,
 20 or [(3', 3'', 5', 5''-tetramethyl)-3, 5-diphenyl]phenyl.

5. A process as claimed in any one of claims 1 to 4 wherein R^6 is selected from
 C_{1-20} alkyl or C_{3-20} aryl, either being optionally substituted or including one or more
 heteroatoms.

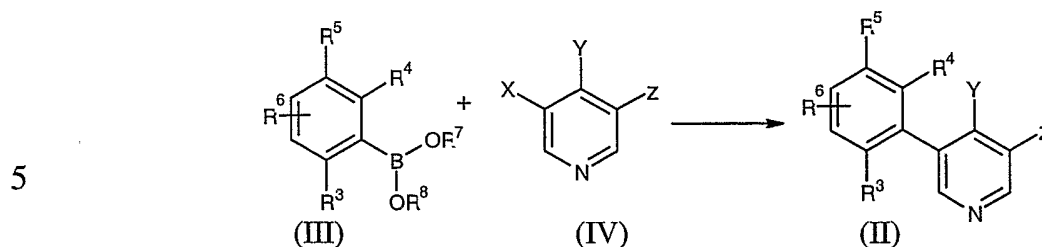
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6. The process as claimed in any one of claims 1 to 5 comprising treatment of a
 compound of formula (II) with iPrMgCl then water to effect 3-dehalogenation,
 followed by addition of the group $H-NR^1R^2$, by refluxing HNR^1R^2 , and phenyllithium
 in a solvent .

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7. A process for the production of a compound of formula (II),



comprising reacting a compound of formula (III), with a compound of formula (IV),
in the presence of a transition metal catalyst wherein, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , Y and Z
10 are defined in any one of claims 1 to 4,

R^7 , R^8 are independently a branched or unbranched C_{1-10} alkyl, or R^8 and R^7 together
form a group $-C(CH_3)_2-C(CH_3)_2-$.

and X is a group which can undergo oxidative insertion of a metal M .

15 8. The process as claimed in claim 7 wherein X is F , Cl , Br , I , OSO_2R^{12} , SAr , or N_2^+ wherein R^{12} is C_{1-6} alkyl, C_{6-12} aryl, or C_{1-6} haloalkyl.

9. The process as claimed in claim 7 or claim 8 wherein X and Z are bromide and
 Y is chloride.

20

10 The process as claimed in any one of claims 6 to 9 wherein the coupling of a
compound of formula (III) with a compound of formula (IV) is catalysed by a
palladium or nickel catalyst.

25 11 The process as claimed in any one of claims 6 to 10 wherein the coupling of a
compound of formula (III) with a compound of formula (IV) is catalysed by
palladium (0).

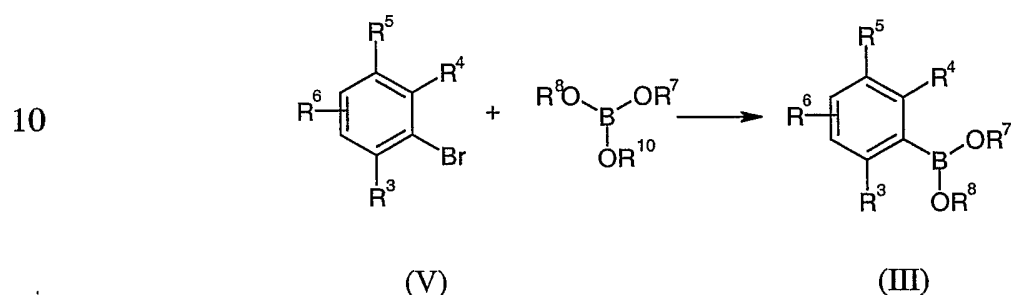
30 12 The process as claimed in any one of claims 6 to 11 wherein the coupling of a
compound of formula (III) with a compound of formula (IV) is carried out under the
conditions of a Suzuki cross-coupling.

24

13 A process for the preparation of a compound of formula (I) comprising producing a compound of formula (II) by the process as claimed in any one of claims 7 to 12, followed by the conversion of the compound of formula (II) to a compound of formula (I) by the process as claimed in any one of claims 1 to 6.

5

14 A process for the production of a compound of formula (III) comprising reacting a compound of formula (V) with $(R^{10}O)-B(OR^7)-(OR^8)$

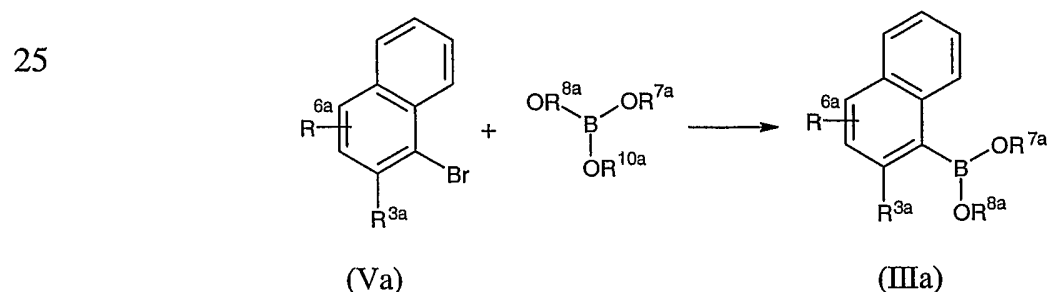


15 wherein R^3 , R^4 , R^5 and R^6 are defined as in claims 1 to 6, R^7 , R^8 and R^{10} are independently a branched or unbranched C_{1-10} alkyl, preferably methyl, ethyl, propyl or butyl.

15 A process as claimed in claim 14 wherein R^8 and R^7 together form a group – $C(CH_3)_2-C(CH_3)_2-$ and R^{10} is *i*-propyl.

20

16 A process as claimed in claim 14 or claim 15 comprising reacting a compound of formula (Va) with $R^{10a}O-B(OR^{7a})-(OR^{8a})$ to form a compound of formula (IIIa);



30

wherein R^{6a} is as defined for R^6 in claims 1 to 6,
 R^{3a} is C_{3-20} aryl

25

R^{8a} , R^{7a} and R^{10a} are independently hydrogen or a branched or unbranched C_{1-10} alkyl group or R^{8a} and R^{7a} form a five or six-membered ring with the O-B-O motif, said five or six-membered ring being optionally substituted with one or more methyl or ethyl group.

5

17 A process for the production of a compound of formula (I) comprising producing a compound of formula (III) by the process as claimed in claim 14 or claim 15, converting said compound of formula (III) into a compound of formula (II) by the process claimed in any one of claims 7 to 13, and converting said compound of
10 formula (II) into a compound of formula (I) by the process claimed in any one of claims 1 to 6.

18 A process for the resolution of the compound of formula (I) prepared according to any one of claims 1 to 6, 13 or 17, comprising crystallization of the
15 diastereomeric salt of the compound of formula (I) with an appropriate homochiral acid.

19 A process as claimed in claim 18, wherein compound (I) is resolved by crystallisation of the diastereomeric salt of compound (I) with *N*-Boc-*O*-benzyl-(*S*)-
20 tyrosine.

20 A product as produced by any one of claims 1 to 6, 13, 17, 18 or 19.

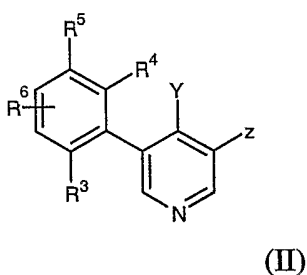
21 A chiral catalyst comprising a product as claimed in claim 20.
25

22. Process for stereoselective reaction of a compound of formula (I) as prepared according to claim 1, comprising reaction with an optically inactive substrate to provide one or both enantiomers of a derivative thereof, with simultaneous or subsequent recovery of the catalyst.
30

26

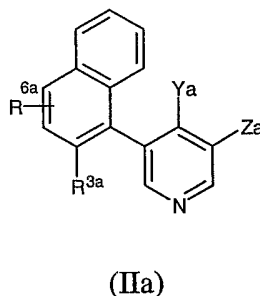
23. Process as claimed in claim 22 comprising the enantioselective acylation by means of kinetic resolution of a compound such as a secondary or tertiary alcohol or a primary, or a secondary amine, or aniline.

5 24. A compound of formula II,



wherein the groups R^3 , R^4 , R^5 , R^6 , Y and Z are as defined in any one of claims 1 to 6.

15 25. A compound as claimed in claim 24 wherein



wherein R^{6a} is as defined for R^6 in any one of claims 1 to 6
 R^{3a} is C_{3-20} aryl and Y^a and Z^a are independently Cl, Br, or I.

25

26. A process as hereinbefore described with reference to one or more of the examples.

27. A compound as hereinbefore described with reference to one or more of the
 30 examples.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB2004/002375

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07F5/04 C07D213/61 C07D213/74

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)

IPC 7 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 practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/39884 A (SPIVEY ALAN CHRISTOPHER ; UNIV SHEFFIELD (GB); FEKNER TOMASZ (US)) 7 June 2001 (2001-06-07) cited in the application the whole document in particular claim 20	1,7,13, 17
X,P	A.C. SPIVEY ET AL.: "Concise Synthesis, Preparative Resolution, Absolute Configuration Determination, and Applications of an Atropisomeric Biaryl Catalyst for Asymmetric Acylation" JOURNAL OF ORGANIC CHEMISTRY, vol. 68, October 2003 (2003-10), pages 7379-7385, XP002294362 the whole document	1,7,13, 17

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

"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

30 August 2004

Date of mailing of the international search report

25.10.04

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB2004/002375

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A.O. ALIPRANTIS ET AL.: "Observation of Catalytic Intermediates in the Suzuki Reaction by Electrospray Mass Spectrometry" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 116, 1994, pages 6985-6986, XP002294363 figure 1 -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2004/002375

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6, 7-12 (part), 13, 17-19, 24-26 (part)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6, 7-12(part), 13, 17-19, 24-26(part)

Process according to present claim 1 for the preparation of compounds of formula I, process according to present claim 7 for the preparation of novel compounds of formula II, novel compounds of formula II (i.e. compounds for which X and Y are halogen or OSOR₂ as defined in present claim 1).

2. claims: 7-12(part), 24-26(part)

Process according to present claim 7 for the synthesis of known compounds of formula II.

3. claims: 14-16, 26 (part)

Process according to present claim 14 for the preparation of compounds of formula III.

4. claims: 20, 21, 27

Compounds of formula I.

5. claims: 22, 23

Use of compounds of formula I as stereoselective catalysts.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/002375

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0139884	A	07-06-2001	AT 265887 T 15-05-2004
		AU 2186801 A	12-06-2001
		DE 60010506 D1	09-06-2004
		DE 60010506 T2	14-10-2004
		EP 1233828 A2	28-08-2002
		WO 0139884 A2	07-06-2001
		US 2003017942 A1	23-01-2003
		US 2004127740 A1	01-07-2004
