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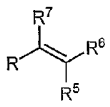
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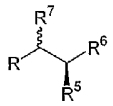
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(54) **Title:** PROCESS FOR THE MANUFACTURE OF SUBSTITUTED PROPIONIC ACIDS



(I)



(II)

(57) **Abstract:** The invention concerns a process for the manufacture of substituted propionic acids comprising providing a substrate of formula (I): And subjecting the substrate to enantioselective hydrogenation under enantioselective hydrogenation conditions in the presence of an enantioselective hydrogenation catalyst comprising a catalyst ligand having a metallocene group with a chiral phosphorus or arsenic substituent to provide in enantiomeric excess a product of formula (II): or its enantiomer or if applicable its diastereomer.

WO 2006/075177 A1

PROCESS FOR THE MANUFACTURE OF SUBSTITUTED PROPIONIC ACIDS

This invention relates to an enantioselective process for synthesising certain substituted propionic acids.

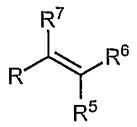
WO-A-2005/068477 discloses certain classes of ligand useful in chiral catalysis, and WO-A-2005/068478 discloses processes for making these and other ligands.

WO-A-2002/02500 discloses a stereoselective synthesis of (R)-2-alkyl-3-phenylpropionic acids comprising the addition of suitably substituted propionic acid esters to suitably substituted benzaldehydes to form corresponding substituted hydroxy propionic acid esters, followed by the conversion of the hydroxyl group to a leaving group, elimination of the leaving group, hydrolysis and then hydrogenation of the resulting intermediates.

Sturm et al disclose in Adv. Synth. Catal. 2003, 345, 160-164 a series of diphosphines of the Walphos ligand family and the use thereof in enantioselective hydrogenation.

WO-A-2005/030764 and *Organic Letters 2005, vol 7, pp1947* disclose processes for the preparation of chiral propionic acid derivatives.

According to the present invention, there is provided a process for the manufacture of substituted propionic acids comprising providing a substrate of formula (I):



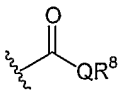
.....(I)

wherein:

R is selected from hydrogen, substituted and unsubstituted branched and straight-chain alkyl, alkoxy, alkylamino, substituted and unsubstituted cycloalkyl, substituted and unsubstituted cycloalkylamino, substituted and unsubstituted carbocyclic aryl, substituted and unsubstituted carbocylic aryloxy, substituted and unsubstituted heteroaryl, substituted and unsubstituted carbocylic arylamino and substituted and unsubstituted heteroarylamino, wherein the or each heteroatom is independently selected from sulphur, nitrogen and oxygen;

R^5 is the same as or different from R and is selected from hydrogen, substituted and unsubstituted branched and straight-chain alkyl, alkoxy, alkylamino, N-acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted cycloalkylamino, substituted and unsubstituted carbocyclic aryl, substituted and unsubstituted carbocylic aryloxy, substituted and unsubstituted heteroaryl, substituted and unsubstituted carbocylic arylamino and substituted and unsubstituted heteroarylamino, wherein the or each heteroatom is independently selected from sulphur, nitrogen and oxygen;

R^6 is selected from:



wherein:

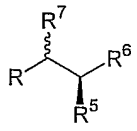
Q is selected from O or N; and

R^8 is selected from hydrogen, substituted and unsubstituted branched and straight-chain alkyl, amino, alkylamino, substituted and unsubstituted cycloalkyl, substituted and unsubstituted cycloalkylamino, substituted and unsubstituted carbocyclic aryl, substituted and, substituted and unsubstituted heteroaryl, substituted and unsubstituted carbocylic arylamino and substituted and unsubstituted heteroarylamino, wherein the or each heteroatom is independently selected from sulphur, nitrogen and oxygen;

R^7 is the same as or different from R and/or R^5 (except that if R and R^7 are the same then R^5 is not hydrogen) and is selected from hydrogen, substituted and unsubstituted branched and straight-chain alkyl, alkoxy, alkylamino, substituted and unsubstituted cycloalkyl, substituted and unsubstituted cycloalkylamino, substituted and unsubstituted carbocyclic aryl, substituted and unsubstituted carbocylic aryloxy, substituted and unsubstituted heteroaryl, substituted and unsubstituted carbocylic arylamino and substituted and unsubstituted heteroarylamino, wherein the or each heteroatom is independently selected from sulphur, nitrogen and oxygen; and

subjecting the substrate to enantioselective hydrogenation under enantioselective hydrogenation conditions in the presence of an enantioselective hydrogenation catalyst comprising a catalyst ligand having a

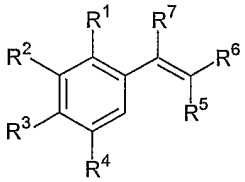
metallocene group with a chiral phosphorus or arsenic substituent to provide in enantiomeric excess a product of formula (II):



.....(II)

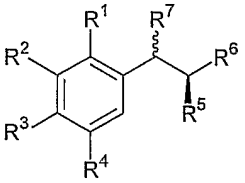
or its enantiomer or if applicable its diastereomer.

In one process according to the invention the substrate may be of formula (III):



.....(III)

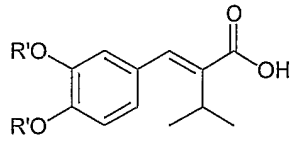
wherein R^1, R^2, R^3 and R^4 are the same or different and are independently selected from hydrogen, alkyl, haloalkyl, alkoxy, alkoxylated alkyl and alkoxylated alkoxy; the product of the process being of formula (IV):



.....(IV)

One particularly preferred process of the invention is for the manufacture of substituted arylpropionic acids, for example 2-substituted-3-arylpropionic acids, for example 2-alkyl-3-arylpropionic acids, such as 2-alkyl-3-phenylpropionic acids, particularly (R)-2-alkyl-3-phenylpropionic acids.

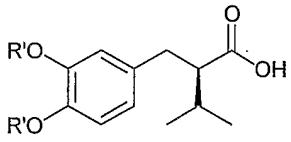
A preferred substrate for use in the process of the invention is a substrate of formula (V):



.....(V)

Wherein R'O is any suitable alkoxy or alkoxylated alkoxy group, and wherein each R'O may be the same or different.

Enantioselective hydrogenation if the formula (V) substrate in accordance with the invention yields a product of formula (VI):

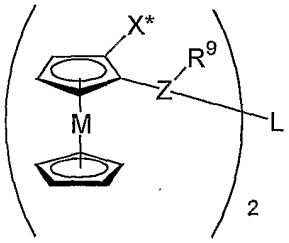


.....(VI)

The process of the invention has been found suitable for enantioselectively hydrogenating the formula (I) substrates, and the other substrates referred to herein with good yields and reactions rates and, importantly, with high enantiomeric excesses of the desired enantiomer. Certain characteristics of the catalyst are considered to be important in achieving good ee's. Thus, in some cases it is preferable that the metallocene group of the catalyst ligand comprise ortho to the chiral phosphorus or arsenic substituent a second chiral substituent group. It may also be desirable in some cases that the chiral phosphorus or arsenic substituent on the metallocene group be further connected via a linking moiety to a second chiral phosphorus or arsenic substituent on a second metallocene group in the catalyst ligand. In this case

it is also preferred that the chiral configuration of the chiral phosphorus or arsenic substituent is the same as the chiral configuration of the second chiral phosphorus or arsenic substituent. Still other catalyst characteristics may also be important and in some cases it has been found desirable that the catalyst ligand exhibit C_2 symmetry. Yet a further desirable characteristic of the catalyst ligand in some cases is that it be basic, for example as a result of the ability to donate one or more loan pairs from one or more nitrogen-containing substituents.

One preferred enantioselective hydrogenation catalyst ligand has the formula (VII):



.....(VII)

wherein:

M is a metal;

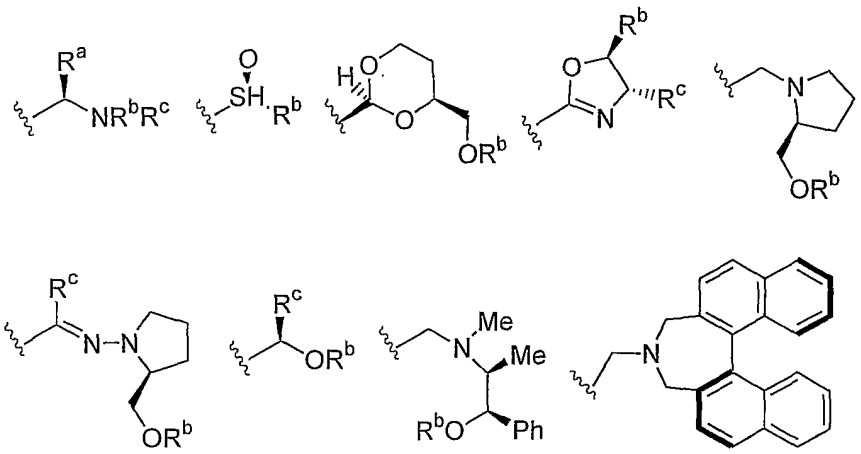
Z is P or As;

L is a suitable linker;

R^9 is selected from substituted and unsubstituted, branched- and straight-chain alkyl, alkoxy, alkylamino, substituted and unsubstituted cycloalkyl, substituted and unsubstituted cycloalkoxy, substituted and unsubstituted cycloalkylamino, substituted and unsubstituted carbocyclic aryl, substituted and unsubstituted carbocyclic aryloxy, substituted and unsubstituted

heteroaryl, substituted and unsubstituted heteroaryloxy, substituted and unsubstituted carbocyclic arylamino and substituted and unsubstituted heteroarylamino, wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen;

X* is selected from:

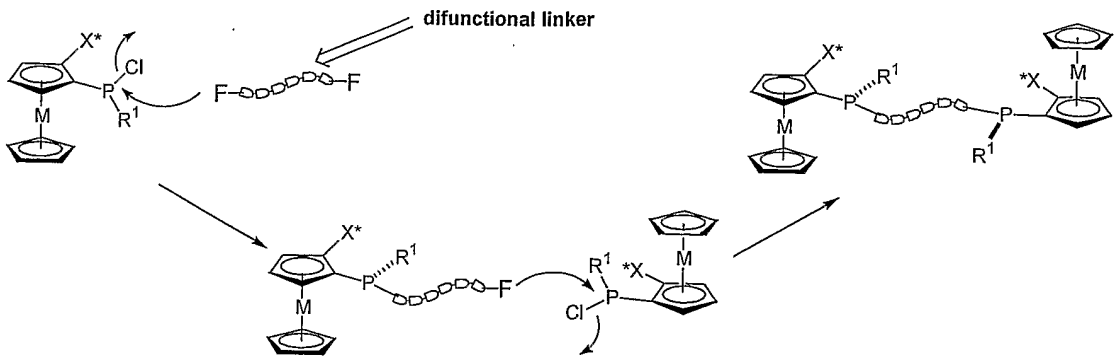


wherein R^a, R^b and R^c are independently selected from substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen.

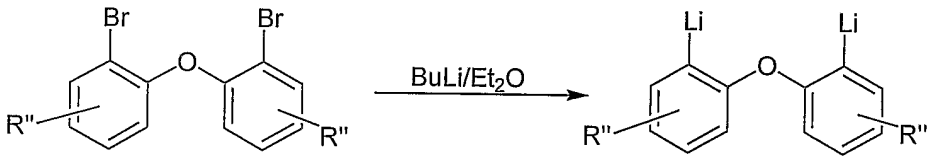
In the first of the structures defining X*, R^b and R^c may form, together with the nitrogen to which they are attached, an optionally substituted hetero-ring, such as morpholine, pyrollidine, piperidine, and derivatives thereof.

L preferably comprises a difunctional moiety having the capability at each functionality to bind to phosphorus or arsenic, as the case may be. Generally the linker (L) will be derived from a difunctional compound, in particular a

compound having at least two functional groups capable of binding to phosphorus or arsenic, as the case may be. The difunctional compound may conveniently comprise a compound which can be di-lithiated or reacted to form a di-Grignard reagent, or otherwise treated, to form a dianionic reactive species which can then be combined directly with phosphorus or arsenic, in a diastereoselective manner to form a chiral phosphorus or arsenic as the case may be. In this case, a first anionic component of the dianionic reactive species may combine with a phosphorus (or arsenic) substituent in a first ligand precusor of the ligand according to the invention, and a second anionic component of the dianionic reactive species may combine again in a diastereoselective manner with a phosphorus (or arsenic) substituent in a second ligand precursor of the ligand again to form a chiral phosphorus (or arsenic) centre according to the invention (the first and second ligand precursors being the same as each other) to connect the first and second ligand precursors together via the linker. Usually a leaving group such as a halide will be provided on the phosphorus (or arsenic) substituents of the first and second ligand precursors, which leaving group departs on combination of the anionic component with the phosphorus (or arsenic) substituent. The following scheme is illustrative of this process:

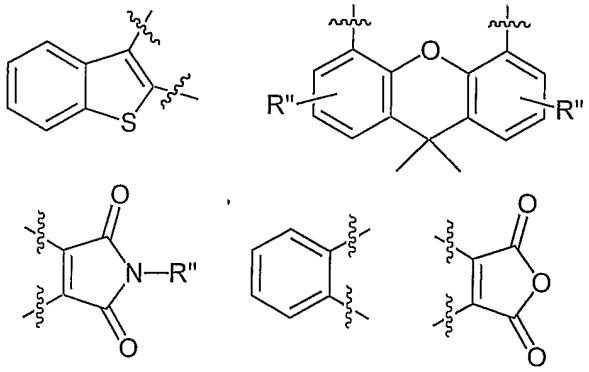


For example, L may be selected from ferrocene and other metallocenes, diphenyl ethers, xanthenes, 2,3-benzothiophene, 1,2-benzene, succinimides, cyclic anhydides and many others. Conveniently, although not necessarily such dianionic linkers may be made from a corresponding di-halo precursor, eg:



di-lithio diphenyl ether

where R" represents any suitable number of suitable substituent groups. Certain suitable dianionic linkers (wherein again R" is simply any suitable number of any suitable substituent(s)) may be represented as follows:



However, ferrocene is a preferred linker in accordance with the invention.

Preferably M is Fe, although Ru may be another preferred M in some cases.

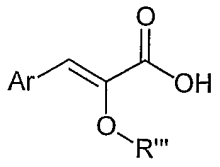
Preferred R^9 include phenyl, methyl, cyclohexyl and t-butyl groups.

Preferred R^b and R^c include, independently, methyl, ethyl, isopropyl and t-butyl groups. Also, R^b and R^c may form, together with the nitrogen to which they are attached, an optionally substituted hetero-ring such as morpholine, pyrollidine, piperidine, and derivatives thereof.

With very many known ligands for asymmetric hydrogenation of substrates of formula (V) enantoselectivities of 80% are achieved (*Adv. Synth. Catal.* 2003, **345**, 160). In the same paper Sturm and in WO 02/02500 A1 Herold disclose that certain ligands of the Walphos family can furnish enantioselectivites of 95% for substrates of formula (V). It has been surprisingly found that certain ligands described here of general formula (VII) are especially useful for the enantioselective hydrogenation of substrates of formula (V) and can furnish with industrially useful reaction rates enantioselectivites of up to 99 % or more. This improvement can offer significant cost savings during industrial manufacture of compounds of formula (VI) or their enantiomers.

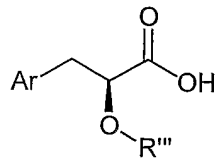
Similarly certain of the ligands described here are also suitable as catalysts in combination with an appropriate metal for the enantioselective hydrogenation

of substrates (in which R''' is any suitable substituents such as substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl, wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen, for example) of formula (VIII).



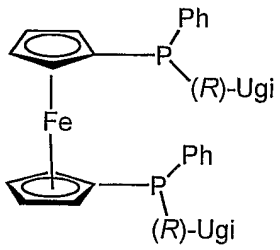
.....(VIII)

Thus compounds such as formula (IX) are also accessible in high enantioselectivity using the ligands and processes described here.

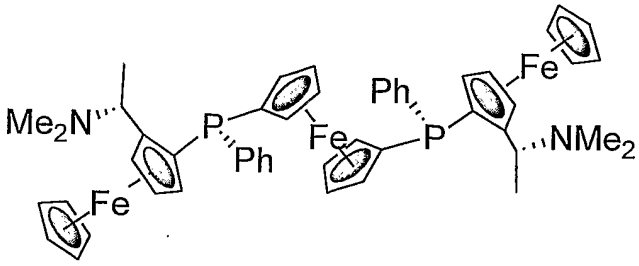


.....(IX)

Certain ligands useful in the process of the invention are derived from Ugi's amine and one preferred ligand for use in accordance with the process of the invention (wherein the dianionic linker is ferrocene) may be represented as:



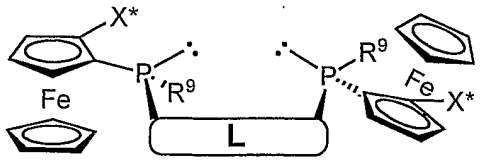
The same preferred ligand, with the Ugi amine groups fully represented may be shown as:



The ligand above has three chiral elements; *carbon centred chirality*, *phosphorus centred chirality* and *planar chirality* with two examples of each type present in the ligand. Due to its symmetry (C_2 symmetric) these elements are in two identical groups 2(S_P,R_C,S_{Fe}) where the labels R or S have their usual meaning and where S_P refers to phosphorus centred, R_C carbon centred and S_{Fe} planar chirality .

The invention also relates to the use of enantiomers and diastereomers of the ligands described above in the process of the invention.

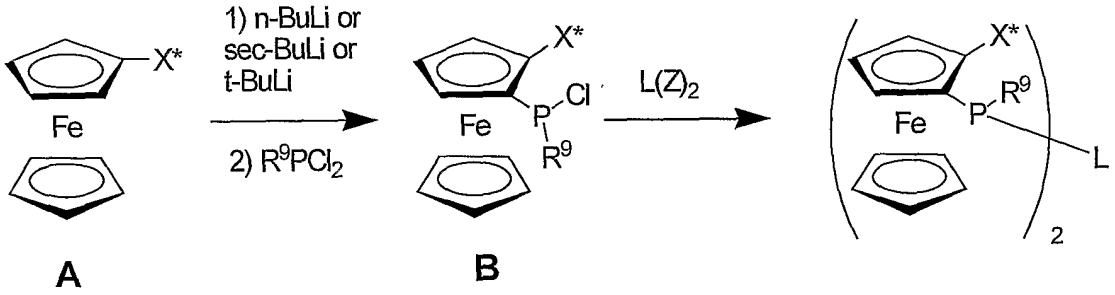
Ligands used in the process of the invention may also be represented as: follows:



Wherein M, L, R^9 and X* are as previously defined.

Also provided in accordance with the invention is the use in the process of the invention of a transition metal complex comprising at least one transition metal coordinated to the aforementioned ligand. The metal is preferably a Group VIb or a Group VIII metal, especially rhodium, ruthenium, iridium, palladium, platinum and nickel.

Synthesis of ferrocene-based phosphorus chiral phosphines may be effected in accordance with the following scheme:



Scheme 1.0 *General synthetic scheme for the preparation of ligands disclosed herein*

wherein L is a linker derived from an organolithium species or Grignard reagent $L(Z)_2$ and wherein X* and R^9 are as previously defined. The organodilithium or di-Grignard reagent (the linker $L(Z)_2$ in the above scheme) adds to the chlorophosphine intermediate **B** to generate a phosphorus chiral centre with very good diastereoselectivity as is shown in WO2005/068478 A1. Other reactions used in the synthesis of these ligands are known or are analogous to known reactions. The same synthetic scheme is generally applicable to other chiral metallocene-based ligands for use in accordance with the invention.

The metal complexes used as catalysts can be prepared and isolated separately and then added to the reaction or they can be prepared in-situ before the reaction (not isolated) and then mixed with the material to be hydrogenated. It has been unexpectedly found that with the ligands described here there is no need to pre-form (either in-situ or separately with isolation) the catalyst by mixing a solution of the ligand and metal source when carrying out enantioselective hydrogenations of the acid substrates described here. Thus conveniently, all the solid materials (ligand, metal source and substrate) required for reaction can be placed in the vessel, the solvent is transferred, the vessel placed under the required temperature and pressure and the reaction commenced. In this way it is convenient to add extra ligand, other ligands and/or other additives to the reaction. Additives such as protic acids and quaternary ammonium halides can be used as co-catalysts.

The enantioselective hydrogenation reaction can be carried out at any suitable temperature, for example temperatures of from about 0 to about 120 °C, or from about 20 to about 80 °C for example.

The enantioselective hydrogenation reaction can be carried out at any suitable pressure, for example at hydrogen pressures of 5-200 bar.

The enantioselective hydrogenation reaction can be carried out using any suitable substrate to catalyst ration, for example with catalyst present in the reaction mixture in an amount of from about 0.0001 to about 10 mol% (with 100 mol% being the amount of material to be hydrogenated). The range 0.001

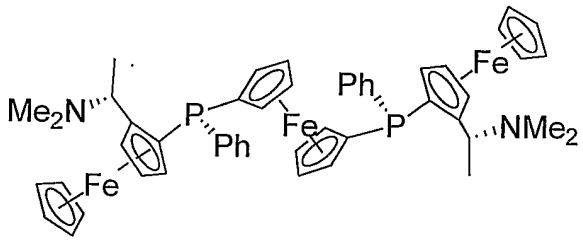
to 5 mol% is preferred with the range 0.01 to 1 mol% being particularly preferred.

The enantioselective hydrogenation reaction can be carried out with or without the use of a solvent. When a solvent is used it is preferably at least substantially inert with respect to the substrate and/or the catalyst. The solvent when present may comprise for example one or more of: alcohols (such as methanol, ethanol, propanol, butanol, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, diethylene glycol monomethyl ether), aliphatic, cycloaliphatic and aromatic hydrocarbons (pentane, hexane, petroleum ether, cyclohexane, methylcyclohexane, benzene, toluene, xylene), aliphatic halogenated hydrocarbons (dichloromethane, chloroform, diandtetrachloroethane), nitriles (acetonitrile, propionitrile, benzonitrile), ketones (acetone, methyl isobutyl ketone), carbonic esters and lactones (ethyl or methyl acetate,valerolactone), N-substituted lactams (N-methylpyrrolidone), carboxamides(dimethylamide, dimethylformamide), acyclic ureas (dimethylimidazoline), and sulfoxides and sulfones (dimethyl sulfoxide, dimethyl sulfone, tetramethylene sulfoxide, tetramethylene sulfone), water, and suitable mixtures of two or more thereof.

The invention will now be more particularly illustrated with reference to the following Examples. In these examples the synthesised substrates are in many cases themselves novel compounds. According to the present invention there is provided a novel compound having the structure indicated

below in one or more of the following examples, and derivatives and close variants thereof.

Example 1



L1

***1,1' bis-[(S_P,R_C,S_{Fe})(1-N,N-Dimethylamino)ethylferrocenyl)phenylphosphino] ferrocene* L1**

To a solution of (R)-N,N-dimethyl-1-ferrocenylethylamine [(R)-Ugi's amine] (3.09 g, 12 mmol) in Et_2O (20 ml) was added 1.5 M t-BuLi solution in pentane (8.0 ml, 12.0 mmol) at –78 °C. After addition was completed, the mixture was warmed to room temperature, and stirred for 1.5 h at room temperature. The mixture was then cooled to –78 °C again, and dichlorophenylphosphine (1.63 ml, 12.0 mmol) was added in one portion. After stirring for 20 min at –78 °C, the mixture was slowly warmed to room temperature, and stirred for 1.5 h at room temperature. The mixture was then cooled to –78 °C again, and a suspension of 1,1' dilithioferrocene [prepared from 1,1' dibromoferrocene (1.72 g, 5.0 mmol) and 1.5 M t-BuLi solution in pentane (14.0 ml, 21.0 mmol) in Et_2O (20 ml) at –78 °C] was added slowly via a cannula. The mixture was warmed to room temperature and allowed to stir for 12 h. The reaction was quenched by the addition of saturated $NaHCO_3$ solution (20 ml). The organic

layer was separated and dried over $MgSO_4$ and the solvent removed under reduced pressure. The filtrate was concentrated. The residue was purified by chromatography (SiO_2, hexane-EtOAc-Et_3N = 85:10:5) to afford an orange solid (3.88 g, 85%) as a mixture of 95% *bis*-(S_P,R_C,S_{Fe}) title compound **L1** and 5% (R_P,R_C,S_{Fe}-S_P,R_C,S_{Fe}) *meso* compound. The *meso* compound can be removed by further careful purification using chromatography (SiO_2, hexane-EtOAc-Et_3N = 85:10:5). Orange/yellow crystalline solid m.p. 190-192 °C. $[\alpha]_D$ = -427 ° (c=0.005 (g/ml), toluene); ^1H NMR ($CDCl_3$, 400.13 MHz): δ 1.14 (d, 6H,J = 6.7 Hz), 1.50 (s, 12H); 3.43 (m; 2H); 3.83 (m, 2H); 3.87 (m, 2H); 4.01 (s, 10H), 4.09 (t, 2H, J = 2.4 Hz); 4.11 (m, 2H); 4.20 (m, 2H); 4.28 (m, 2H); 4.61 (m, 2H); 4.42 (d, 2H, J = 5.3 Hz); 7.18 (m, 6H); 7.42(m, 4H) ppm. ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ 38.28, 57.40 (d, J = 5.6 Hz); 67.02, 69.04 (d, J = 4.0 Hz); 69.16 (d, J = 51.6 Hz); 69.66, 71.60 (d, J = 4.8 Hz), 71.91 (d, J = 7.2 Hz), 72.18 (d, J = 5.6 Hz), 75.96 (d, J = 35.7 Hz), 79.96 (d, J = 6.4 Hz), 95.73 (d, J = 19.1 Hz), 127.32 (d, J = 7.9 Hz), 127.62, 133.12 (d, J = 21.4 Hz), 139.73 (d, J = 4.0 Hz). ^{31}P NMR ($CDCl_3$, 162 MHz): δ –34.88 (s). Found: C, 65.53; H, 5.92; N 3.01 Calculated for $C_{50}H_{54}Fe_3N_2P_2$; C, 65.81; H, 5.97; N, 3.07. HRMS (10eV, ES+): Calcd for $C_{50}H_{55}Fe_3N_2P_2$ $[M+H]^+$: 913.1889; Found: 913.1952.

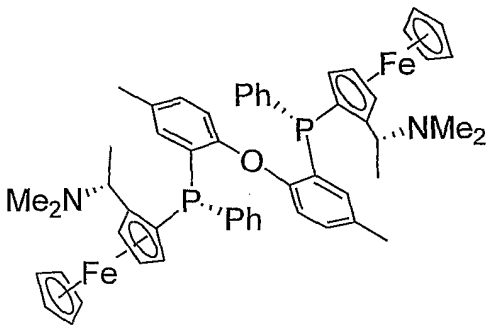
The label S_P refers to S configuration at phosphorus, R_C refers to R configuration at carbon (or other auxiliary) and S_{Fe} refers to S configuration at the planar chiral element.

Note: To maintain consistency in all of this work when assigning configuration at phosphorus we have given the Ugi amine (1-N,N-dimethylamino)ethylferrocenyl) fragment a priority of 1, the incoming lithium or

Grignard nucleophile (in the above example lithioferrocene) a priority of 2 and the remaining group a priority of 3. This method will not always be consistent with the rigorous approach. These assignations and the proposed phosphorus configurations have been checked using single crystal x-ray crystallography.

Example 2

2,2' bis-[(S_P,R_C,S_{Fe})(1-N,N-Dimethylamino)ethylferrocenyl)phenylphosphino]-4-tolylether **L2**



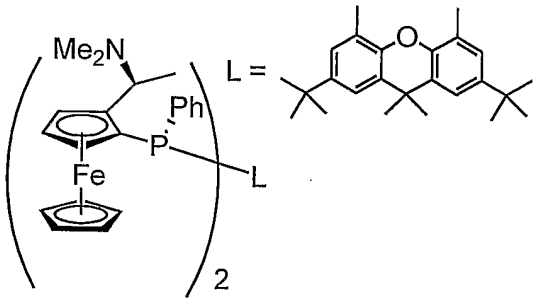
L2

Using a similar procedure to that described above with the exception that a suspension of 2,2' dilithio-4-tolylether [prepared by known procedures from 2,2' dibromo-4-tolylether (1.78 g, 5.0 mmol) and 1.5 M t-BuLi solution in pentane (14.0 ml, 21.0 mmol) in Et_2O (20 ml) at –78 °C] was used as the linker reagent rather than 1,1' dilithioferrocene.

Yellow crystalline solid $[\alpha]_D$ = -105 ° (c=0.005 (g/ml), toluene); ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.23 (d, 6H), 1.72 (s, 12H); 2.28 (s, 6H); 4.11 (s, 10H); 4.12 (m, 2H overlapping); 4.28 (m, 2H); 4.31 (m, 4H); 4.35 (m, 2H, overlapping); 7.00-7.30 (m, 14H) ppm. ^{31}P NMR ($CDCl_3$, 162 MHz): δ –40.69 (br s) ppm.

Example 3

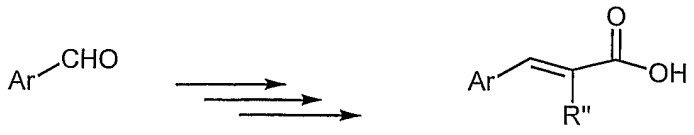
2,7-di-tert-butyl-4,5-bis-[(S_P,R_C,S_{Fe})(1-N,N-Dimethylamino)ethylferrocenyl)phenylphosphino]-9,9-dimethyl-9H-xanthene



L3

Using a similar procedure to that described above with the exception that a suspension of 2,7-di-tert-butyl-4,5-dilithio-9,9-dimethyl-9H-xanthene [prepared by known procedures from 2,7-di-tert-butyl-4,5-dibromo-9,9-dimethyl-9H-xanthene and 1.5 M t-BuLi solution in pentane in Et_2O at –78 °C] was used as the linker reagent rather than 1,1' dilithioferrocene.

Orange/yellow crystalline solid; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 1.12 (s, 18H); 1.13 (m, 6 H overlapping); 1.78 (s, 6H); 1.98 (s, 12H); 3.99 (m, 2H); 4.15 (s, 10H overlapping); 4.32 (m, 2H); 4.41 (m, 4H); 7.00-7.40 (m, 14H) ppm. ^{31}P NMR ($CDCl_3$, 162 MHz): δ –41.78 (br s) ppm. HRMS (10eV, ES+): Calcd for $C_{63}H_{75}Fe_2N_2OP_2$ $[M+H]^+$: 1049.4053; Found: 1049.4222



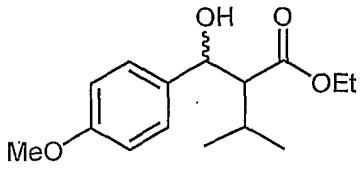
Scheme 2.0 *Route for the synthesis of substrates of formula (III) (R" being any suitable substituent group).*

Example 4

(E)-2-(4-methoxybenzylidine)-3-methylbutanoic acid

Step 1

Ethyl-2-hydroxy (4-methoxyphenyl)-methyl-3-methylbutanoate

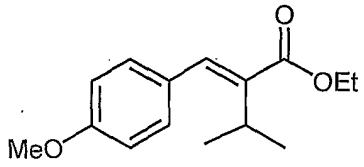


A solution of diisopropylamine (66 ml, 467 mmol) and anhydrous THF (394 ml) was cooled to (-30 °C). To this was added drop-wise n-butyl lithium (1.6 M, 292 ml) using syringe over a period of (20 min) and under stream of nitrogen. After addition of the n-BuLi, the reaction mixture was stirred at -30 °C for 10 min. Ethylisovalarate (55.8 ml, 428 mmol) in THF (250 ml) was added drop-wise over a period of (10 min). The reaction mixture was stirred for a further of 15 min then a solution of 4-methoxybenzaldehyde (34g, 250 mmol) in THF (250 ml) was added over a period of 30 min at (maintaining temperature at -30 °C).The reaction mixture was stirred for 2h at -30 °C and then saturated ammonium chloride (325 ml) was added drop-wise over a period of 30 min. The product was then extracted with EtOAc (200 ml), washed with brine and dried over sodium sulphate. Evaporation of the solvent under reduced pressure afforded a colourless oil 66.5g (93%) which gave only one spot by TLC. m/z = [(ES) 289 $(M+Na)^+$, 555 $(2M + Na)^+$, calculated for $C_{15}H_{22}O_4Na$ 289.1428, found 289.1426]. ^1H NMR (250 MHz, $CDCl_3$) δ 7.33-7.24 (2H, m, Ar), 6.92-6.84 (2H, m, Ar), 4.93 (1H, d), 3.93 (2H, q, $\underline{CH_2}CH_3$), 3.89 (3H, s, OCH_3), 2.73 (1H, m), 2.44 (1H, m, CH), 2.40 (1H, m, OH) , 1.19

(3H, t, $CH_2\underline{CH_3}$), 1.17 (3H, d, CH $\underline{CH_3}$), 1.15 (3H, d, CH_3), 1.13 (3H, d, CH $\underline{CH_3}$).

Step 2

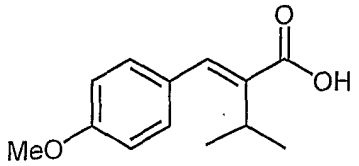
(E)-ethyl 2-(4-methoxybenzylidene)-3-methylbutanoate



A solution of (31.56 g, 118 mol) of ethyl-2-hydroxy(4-methoxyphenyl)-methyl-3-methylbutanoate and dimethylaminopyridine (DMAP) (0.72 g, 5.9 mmol) in anhydrous THF (200 ml) were cooled to 0 °C using an ice bath. To this mixture was added acetic anhydride (12.3 ml, 12.5 mmol) drop-wise and then the reaction mixture was left stirring at 0 °C for 2h. Potassium-t-butoxide (34.5g, 350 mol) in 265 ml of THF was then added drop-wise using syringe. The reaction mixture was then stirred for two hours at 0 °C and overnight at room temperature. The mixture was then cooled to 0 °C and treated with water (150 ml). The mixture was extracted with TBME (100 ml), washed with brine and dried over sodium sulphate. Evaporation of the solvent under reduced pressure afforded a colourless light oil 18.52g (63 %).

Step 3

(E)-*2- (4-methoxybenzylidine)-3-methylbutanoic acid*

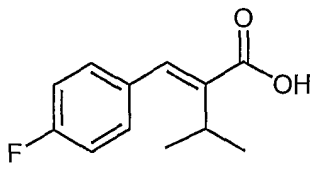


The oil from above (2-(4-methoxybenzylidine)-3-methoxyethylbutanoate) (16 g, 64.5 mmol) was dissolved in methanol (150 ml). To this was then added anhydrous lithium hydroxide (10g, 417 mmol) at room temperature and the mixture was refluxed under a plug of nitrogen on oil bath for 12 h. The mixture was then cooled to 0-10 °C and quenched with water (100 ml). The basic solution was washed with EtOAc (3 x 50 ml) and then acidified with HCl (2 molar) and the precipitated product was extracted with EtOAc (3 x 50ml), washed with brine and dried over sodium sulphate. Evaporation of solvent under reduced pressure afforded a solid residue this was then re-crystallised from EtOAc/hexane to afford 6.8g (48%) of the title compound as white fine crystals, m.p. 137-138°C. H NMR (250 MHz, $CDCl_3$) δ ppm: 11.50 (1H, br s, COOH), 7.71 (1H, s, CH=C), 7.34-7.38 (2H, m, Ar), 6.87-6.97 (2H, m, Ar), 3.81 (3H, s, OCH_3), 3.21 (1H, m, $CH(CH_3)_2$), 1.26 (6H, d, $CH(CH_3)_2$). M/z [(CI) 221 (M+H)+ 45%, 238 (M+NH4) 100%].

Using a similar procedure to that described above the following compounds were prepared:

Example 5

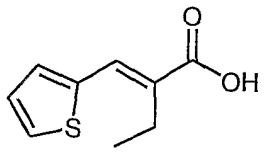
(E)-2-(4-Fluorobenzylidine)-3-methylbutanoic acid



White crystalline solid. ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 12.44 (1H, br s, COOH), 7.68 (1H, s, CH=C), 7.19-7.25 (2H, m, Ar), 6.99-719 (2H, m, Ar), 3.01-3.19 (1H, m, $\underline{CH}(CH3)_2$) , 1.33 (6H, d, $CH(CH_3)_2$).

Example 6

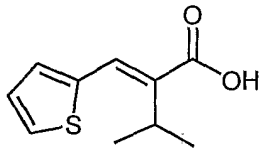
(E)-2-((thiophen-2-yl)methylene)butanoic acid



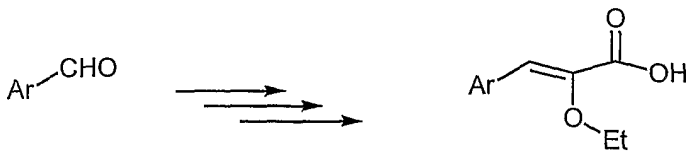
White crystalline solid M.p. 116-117 °C.; H NMR (250 MHz, $CDCl_3$) δ ppm: 12.46 (1H, br s, COOH), 7.92 (1H, s, CH=C), 7.47 (1H, m, Ar), 7.24 (1H, m, Ar), 7.08 (1H, m, Ar), 2.69 (2H, q, CH_2) and 1.25 (3H, s, CH_3) ppm.

Example 7

(E)-3-methyl-2-((thiophen-2-yl)methylene)butanoic acid



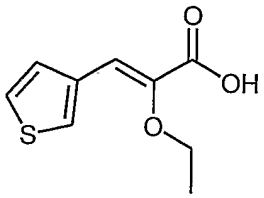
Beige crystalline solid. M.p. 116-117 °C.; H NMR (250 MHz, $CDCl_3$) δ ppm: 12.57 (1H, br s, COOH), 7.87 (1H, s, CH=C), 7.52 (1H, d, Ar), 7.26 (1H, d, Ar), 7.09 (1H, dd, Ar), 3.40-3.59 (1H, m, CH), 1.33 (6H, d, $CH(CH_3)_2$). M/z [(CI) 196 $(M)^+$ 10%, 197 $(M+H)^+$ 30%, 214 $(M+NH4)^+$ 100%].



Scheme 1.0 Route for the synthesis of substrates of formula (VI)

Example 8

(Z)-2-Ethoxy-3-(thiophen-3-yl) acrylic acid

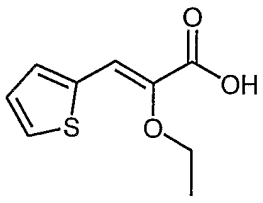


Ethyl chloroacetate (44.8 ml, 421 mmol) and anhydrous ethanol (30 ml) were cooled to 10-12 °C. A solution of sodium ethoxide in ethanol (21% w/w, 165 ml) was added over 25 min at 12-16 °C under N_2. After addition was complete the reaction mixture was warmed to 25°C and stirred for 1h. The mixture was then cooled to 10 °C and solid NaOEt (33.3 g, 488 mmol) was then added portion-wise over 0.5 h at 10-14 °C. Ethanol (20 ml) was then added followed by the addition of diethyl carbonate (31 ml, 256 mmol). The slurry was then cooled to 0-5 °C and then 3-thiophene carboxaldehyde (20.2 g, 179.5 mmol) was added over a period of 1 h. After addition was complete the mixture was stirred at 40 °C in an oil bath for 15 h. The slurry was then cooled to 10-15 °C and then water (40 ml) was added followed by the addition of aqueous NaOH (55 ml of a 10 M solution). The resulting slurry was then stirred at pH 14 for 3 h at 20 °C. The mixture was then diluted with water (60 ml) and then placed under reduced pressure at 45 °C to remove most of the ethanol and some water. The resulting thick slurry was then cooled to 4 °C in an ice-bath and then treated with conc. HCl (115 ml) drop-wise. The resulting slurry was then stirred at room temperature for 1.5 h and then extracted with EtOAc (2 x 200 ml) and the organic layer washed with water, brine and then dried (sodium sulphate). Evaporation of the solvent under reduced pressure afforded a deep-brown residue. This was dissolved in 5 M NaOH (250 ml)

and this solution was washed with EtOAc (100 ml). The basic aqueous was then cooled to 4 °C and acidified with conc. HCl (11 M) to pH 4-6. The product was extracted with diethyl ether (3 x 200 ml), washed with brine, dried (sodium sulphate) and the solvent removed under reduced pressure. The residue was then filtered through a pad of silica (eluent hexane:EtOAc 90:10). The solvent was removed under reduced pressure and then the residue recrystallised from Et_2O/hexane to afford the title compound as yellow crystals (79%). M.p. 88-89 °C. ^{1}H NMR ($CDCl_3$, 250MHz) δ 11.16 (1H, br s, COOH), 7.73-7.75(1H, dd, j= 0.5 Hz, Ar), 7.44-7.47 (1H, dd, J= 1Hz, Ar), 7.25-7.28 (1H, m, Ar), 7.18 (1H, s, CH=C), 3.96-4.05 (2H, q, J= 7Hz, $\underline{CH_2}CH_3$), 1.35 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$),). Found: C, 54.64; H, 5.08; Calculated for $C_9H_{10}SO_3$ C, 54.54; H, 5.08. M/z [(CI) 222 $(M)^+$ 30%, 223 (M+H)+ 50%, 240 $(M+NH_4)^+$ 100%; Found: 223.09705; required for $C_{12}H15O_4$ 223.09155]. M/z [(CI) 198 $(M)^+$ 22%, 199 $(M+H)^+$ 50%, 216 $(M+NH_4)^+$ 100%].

Using a similar procedure to that described above the following compounds were prepared:

Example 9



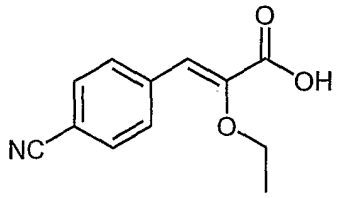
(Z)-2-ethoxy-3-(thiophen-2-yl)acrylic acid

Pink crystalline solid (77%). M.p. 103-104°C. ^{1}H NMR ($CDCl_3$, 250MHz) δ 12.15 (1H, br s, COOH), 7.48(1H, s CH=C), 7.40 (1H, m, Ar), 7.29 ((1H, m,

Ar), 7.08 (1H, m, Ar), 4.11 (2H, q, J= 7Hz, $\underline{CH_2}CH_3$), 1.48 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$). Found: C, 54.82; H, 5.11, S, 16.00 Calculated for $C_9H_{10}SO_3$ C, 54.54; H, 5.08; S, 16.16]. M/z [(CI) 222 $(M)^+$ 30%, 223 (M+H)+ 50%, 240 $(M+NH_4)^+$ 100%; Found: 223.09705; required for $C_{12}H15O_4$ 223.09155. M/z [(CI) 198 $(M)^+$ 22%, 199 $(M+H)^+$ 50%, 216 $(M+NH_4)^+$ 100%].

Example 10

(Z)-3-(4-Cyanophenyl)-2-ethoxy acrylic acid

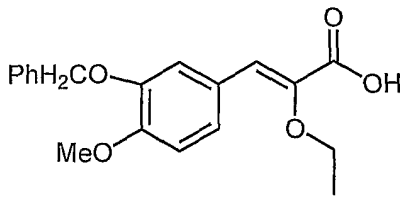


Following the procedure of (Vol. 8, No. 6, 2004, Organic Research & Development) with modification, this compound was synthesised as follows: Ethyl chloroacetate (44.5 ml, 421 mmol) and anhydrous ethanol (30 ml) were mixed and the solution cooled to 10-12 °C and treated slowly with NaOEt (21% w/w in EtOH, 165 ml, 421 mmol) over a period of 30 minutes. After the addition was complete, the reaction mixture was warmed to 25°C and stirred for 1h then cooled to 10°C. To this mixture was then added portion wise solid sodium ethoxide (33.5g, 488 mmol) over a period of 0.5 h at 10-12°C followed by addition ethanol (10 ml) and diethyl carbonate (31 ml, 256 mmol). The mixture was then cooled to 5-8°C and then treated very slowly with 4-cyanobenzaldehyde (16.75 ml, 175 mmol) over a period of 1h. After the addition of the reagent was complete, the reaction mixture was stirred on oil bath at 35°C for 15 h. The slurry was then cooled to 15 °C and water (38 ml) was then added followed by the addition of sodium hydroxide (10 M, 55 ml, 55

mmol).The basic slurry at (pH 14) was stirred at 20 °C for 2.5 h. The mixture was diluted with water (120 ml) and most of the alcohol and some water was removed on rotary evaporator at 45 °C. The resulting thick slurry was then diluted with water (105 ml) and cooled to 10-12 °C on ice bath. The slurry was then treated portion wise with dilute HCl (0.5 M, until pH 7) for a period of 1h. The slightly acidic solution was then extracted with EtOAc (2 x 200 ml) washed with water, and then dried over sodium sulphate. After evaporation of the solvent the title compound was afforded as a solid and was re-crystallised from EtOAc-hexane to afford 21g (54%) as fine white crystals M.p. 171-172 °C. ^{1}H NMR ($CDCl_3$, 250MHz) δ 10.75 (1H, br s, COOH), 7.87 (2H, m, Ar), 7.67 (2H, m, Ar), 7.07 (1H, s, CH=C), 4.09-4.12 (2H, q, $\underline{CH_2}CH3$), 1.38 (3H, t, J= 5 and 7.5Hz, $CH_2\underline{CH_3}$). Found: C, 66.28: H, 5.12; N, 6.42. Calculated for $C_{12}H_{11}NO_3$ C, 66.36; H, 5.09; NS, 6.45]. M/z [(CI) 217 $(M)^+$ 250%, 218 $(M+H)^+$ 200%, 235 $(M+NH_4)^+$ 100%.

Example 11

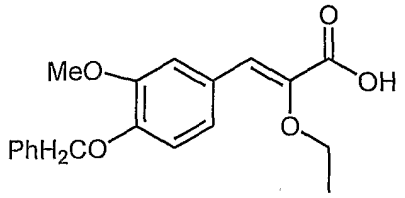
(Z)-3-(3-(benzyloxy)-4-methoxyphenyl)-2-ethoxyacrylic acid



Pink crystalline solid. M.p. 147-148°C. ^{1}H NMR ($CDCl_3$, 250MHz) δ 11.82 (1H, br s, COOH), 7.66 (1H, s CH=C), 7.24-7.57 (8H, m, Ar), 5.17 (2H, s, CH_2O), 3.83-3.99 (2H, q, $\underline{CH_2}CH_3$), 3.94 (3H, s, OCH_3), 1.22-1.29 (3H, t, $CH_2\underline{CH_3}$). Found: C, 69.40; H, 6.18, Calculated for $C_{19}H_{20}O_5$; C, 69.51; H, 6.15. M/z [(CI) 328 $(M)^+$ 20%, 329 $(M+H)^+$ 45%, 346 $(M+NH_4)^+$ 100%.

Example 12

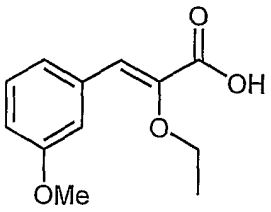
(Z)-3-(4-(benzyloxy)-3-methoxyphenyl)-2-ethoxyacrylic acid



Pink crystalline solid. M.p. 148-149°C. ^{1}H NMR ($CDCl_3$, 250MHz) δ 9.62 (1H, br s, COOH), 7.66 (1H, s, Ar), 7.11 (1H, s, (CH=C)), 7.10-7.45 (5H, m, Ar), 6.88 (2H, d, Ar), 4.17 (2H, q, $CH_3\underline{CH_2}$), 3.94 (3H, s, OCH_3), 1.40 (3H, t, J = 7 Hz,& J= 5 Hz $CH_2\underline{CH_3}$). Found: C, 69.27; H, 6.11: Calculated $C_{19}H_{20}O_5$; C, 69.51; H, 6.15. M/z [(CI), 328 $(M)^+$ 25%, 329 $(M+H)^+$ 35%, 346 $(M+NH_4)^+$ 100%.

Example 13

(Z)-2-ethoxy-3-(3-methoxyphenyl)acrylic acid



White crystalline solid. M.p. 99-100°C. ^{1}H NMR ($CDCl_3$, 250MHz) δ 12.07 (1H, br s, COOH), 7.56 (1H, br s, Ar), 7.29 (2H, m, Ar), 7.15 (1H, s, CH=C), 6.92 (1H, m, Ar), 4.07 (2H, q, J= 7.5Hz, CH_2), 3.83 (3H, s, OCH_3), and 1.37 (3H, t, J= 7 Hz). Found: C, 65.13; H, 6.37, Calculated for $C_{12}H_{14}O_4$; C, 64.86; H, 6.35. M/z [(CI) 222 $(M)^+$ 30%, 223 (M+H)+ 50%, 240 $(M+NH_4)^+$ 100%; [Found: 223.09705; required for $C_{12}H15O_4$; 223.09155].

Example 14

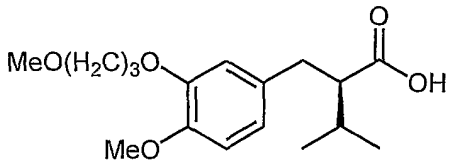
General hydrogenation screening method:

Into a 45 ml autoclave was placed ligand (3.25×10^{-3} mM) and the vessel placed under vacuum/Ar cycles. The vessel was then flushed with Argon. A degassed solution of $[(COD)_2Rh]BF_4$ in MeOH (5 ml of a 0.64 mM solution) was then added by syringe/needle and a rubber bung placed over the vessel to maintain an inert atmosphere. This mixture was stirred for 10 min to give a clear yellow solution. A degassed solution of starting material in MeOH was then added by syringe/needle while carefully attempting to maintain an inert atmosphere. The autoclave was then connected to a Parr 3000 multi-vessel reactor system and then placed under Ar (5 bar) and vented while stirring, this process was repeated 3 times. After the final vent the mixture was placed

under H_2 (50 bar) and again vented carefully. The mixture was then placed under H_2 (50 bar), sealed and heated to the desired temperature for the required time. After this time the reaction mixture was cooled and the vessel vented. An aliquot of 0.5-1.0 ml was then taken for analysis.

Example 15

(S)-2-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-methylbutanoic acid



Into a 45 ml autoclave was placed *1,1' bis-[(R_P,S_C,R_{Fe})* **L1** (0.0063 g,0.0069 mmol), $[(COD)_2Rh]BF_4$ (0.0025 g, 0.0061 mmol) and (*E*)-2-(3-(3-methoxypropoxy)-4-methoxybenzylidene)-3-methylbutanoic acid (2 g, 6.49 mmol). The vessel was then placed under vacuum/Ar cycles. The vessel was then flushed with Argon and a rubber bung placed over the vessel to maintain an inert atmosphere. Degassed MeOH (10 ml) was then added by cannula taking care to maintain an inert atmosphere in the vessel. The vessel was then sealed and stirring commenced. The vessel was then placed under Ar (5 bar) and vented, this process was repeated three times. The autoclave was then placed under H_2 (50 bar) and again vented carefully. The mixture was then placed under H_2 (50 bar), sealed and heated to 40 °C for 12 h. After this time the reaction mixture was cooled and the vessel vented. An aliquot of 0.5-1.0 ml was then taken for analysis. Conversion >98%, e.e >98.5 % (major enantiomer second running peak).

^{1}H NMR ($CDCl_3$, 250.13 MHz): δ 1.01 (m, 6H), 1.95 (m, 1H); 2.05 (m, 2H); 2.45 (m, 1H); 2.78 (m, 2H); 3.35 (s, 3H), 3.55 (m, 2H); 3.83 (s, 3H); 4.10 (m, 2H); 6.65-6.80 (m, 3H).

HPLC method for e.e. determination of 2-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-methylbutanoic acid

Chiralpak-AD column (250 mm x 4.6 mm), 94 % Hexane, 3 % 2-methyl-2-propanol and 3 % t-amyl alcohol, flow: 1 ml/min, 230 nm. S-acid 13.15 min (largest peak with bis-[(R_P,S_C,R_{Fe})] ***1***), R-acid 14.01 min, starting material 42.73 min.

HPLC method for e.e. determination of 2-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-methylbutanoic acid (methyl ester) - diazomethane derivatization

Into a 10 ml vial was placed a stirring bar and a 1ml aliquot of the crude hydrogenation reaction mixture. With vigorous stirring trimethylsilyl diazomethane in hexane (2 M) was added drop-wise into the reaction mixture and the good yellow colour of the diazomethane solution disappeared along with good gas evolution. This drop-wise process was continued until the reaction mixture became a yellow colour and gas evolution ceased. Neat acetic acid (15-30 μl, - Caution too much acetic acid and excessive gas evolution occurs) was then added upon which the mixture became very pale yellow. Approximately 1/3 of this mixture was then filtered through a small pad of wetted silica in a Pasteur pipette washing with a little hexane/IPA (80:20). The resulting solution was then analysed using HPLC: Chiralpak-AD

column (250 mm x 4.6 mm), 95 % Hexane, 5 % i-Propyl alcohol, flow: 1 ml/min, 230 nm. Product enantiomers; 9-10 min, Starting material; 14-16 min. Note: the order of elution of the enantiomers is reversed relative to analysis on the non-derivatized acids.

1,1' bis-[(S_P,R_C,S_{Fe})] **L1** yields *(R)-2-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-methylbutanoic acid*

1,1' bis-[(R_P,S_C,R_{Fe})] **L1** yields *(S)-2-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-methylbutanoic acid*

Example 16

Table 1.0 Results of enantioselective hydrogenations on (E)-2-(3-(3-methoxypropoxy)-4-methoxybenzylidene)-3-methylbutanoic acid with bis-[(S_P,R_C,S_{Fe})] **L1** at 50 bar H_2 pressure.

entry	s/c ratio	T (°C)	Substrate [M]	Conversion (%)	e.e. (%)
1	500:1	40	0.16	>95	99.6[1]
2	500:1	50	0.16	>95	99.6[2]
3	500:1	65	0.16	>95	99.3[2]
4	1000:1	40	0.55	72	98.5[3]
5	2000:1	40	0.55	72	98.3[3]

1 Reactions carried out in MeOH for 20 h
2 Reactions carried out in MeOH for 5 h
3 Reactions carried out in MeOH for 14 h

Example 17

Table 2.0 Results of enantioselective hydrogenations on (E)-2-(3-(3-methoxypropoxy)-4-methoxybenzylidene)-3-methylbutanoic acid with bis-[(S_P,R_C,S_{Fe})] **L1** at 50 bar H_2 pressure.

entry	s/c ratio	T (°C)	Substrate [M]	Solvent MeOH:1-BuOH	e.e. (%)
1	1000:1	40	0.65	8.75:1	98.7
2	1000:1	50	0.65	8.75:1	98.2
3	1000:1	65	0.65	8.75:1	96.6

Example 18

Table 3.0 Results of enantioselective hydrogenations on (E)-2-(3-(3-methoxypropoxy)-4-methoxybenzylidene)-3-methylbutanoic acid with bis-[(S_P,R_C,S_{Fe})] **L1** at 50 bar H_2 pressure (using solid addition method*)

entry	Time (h)	T (°C)	Substrate [M]	s/c ratio	e.e. (%)
1	4	50	0.55	1000:1	98.6
2	4	60	0.55	2000:1	98.4
3	4	60 for 1 h then 50	0.55	1000:1	98.2

Note: in all cases >98 % conversion was observed
* All solids (substrate, ligand and metal source) placed in vessel then solvent added

Example 19

It has been found to be preferable for very high enantioselectivity that the *meso* impurity (R_P,R_C,S_{Fe}-S_P,R_C,S_{Fe})- **L1** present in the ligand should be minimised .

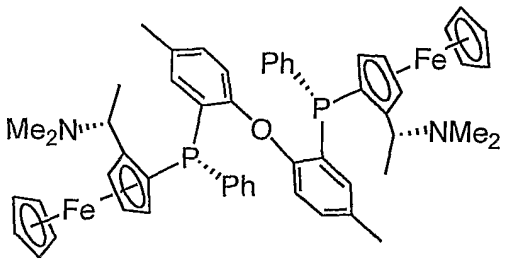
Table 4.0 Results of enantioselective hydrogenations on (E)-2-(3-(3-methoxypropoxy)-4-methoxybenzylidene)-3-methylbutanoic acid with bis-[(S_P,R_C,S_{Fe})] **L1** contaminated with *meso* impurity at 50 bar H_2 pressure.

entry	*meso* present (%)	T (°C)	Time (h)	Solvent MeOH:1-BuOH	Conversion (%)	e.e. (%)
1	~2	45	5	8.75:1	53	98.5
2	~2	55	5	8.75:1	92	98.2
3	~2	45	5	1:1.7	25	96.4
4	6-8	45	5	8.75:1	74	95.1
5	6-8	55	5	8.75:1	>99	94.5
6	6-8	45	5	1:1.7	40	90.2

All reactions carried out at s/c ratio of 1000:1

Example 20

Ligands containing flexible linker units have been found to be most preferable, for the enantioselective hydrogenation of the acid substrates described, eg



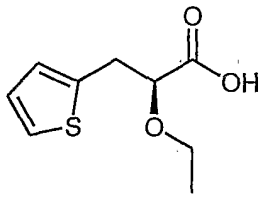
L2

Table 5.0 Results of enantioselective hydrogenations on (E)-2-(3-(3-methoxypropoxy)-4-methoxybenzylidene)-3-methylbutanoic acid with ligands **L1-L3** at 50 bar H_2 pressure in MeOH.

entry	**Ligand**	T (°C)	Time (h)	S/C ratio	Conversion (%)	e.e. (%)
1	L1	40	12	1000:1	83	>99
2	L2	40	12	1000:1	52	90.8

Example 21

HPLC method for e.e. determination for (S)-2-ethoxy-3-(thiophen-2-yl)propanoic acid (as methyl ester)

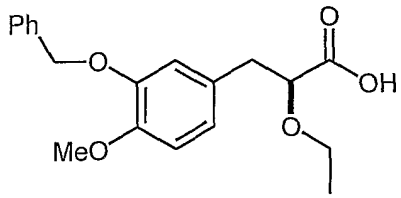


After derivatization:

Chiralpak-AD column (250 mm x 4.6 mm), 95 % Hexane, 2.5 % 2-methyl-2-propanol and 2.5 % t-amyl alcohol, flow: 1 ml/min, 236 nm. Enantiomers 5.44 and 5.81 min (largest peak with bis-[(S_P,R_C,S_{Fe})] ***1***).

Example 22

HPLC method for e.e. determination for (S)-3-(3-(benzyloxy)-4-methoxyphenyl)-2-ethoxypropanoic acid



Chiralpak-AD column (250 mm x 4.6 mm), 93 % Hexane, 7 % i-Propyl alcohol, flow: 1.2 ml/min, 235 nm. Enantiomers 11.71 min, 13.33 min (largest peak with bis-[(R_P,S_C,R_{Fe})] ***1***), starting material 36.68 min.

Example 23

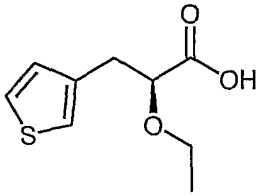
Table 6.0 Results of enantioselective hydrogenations on (Z)-[-(3-Benzyloxy-4-methoxyphenyl)]-2-ethoxyacrylic acid with bis-[(S_P,R_C,S_{Fe})] ***1*** at 48 bar H_2 pressure for 12 h.

entry	s/c ratio	T (°C)	Substrate [M]	e.e. (%)
1	2000:1	50	0.40	96.2
2	2000:1	50	0.83	93.4
3	250:1	55	0.25	97.1
4	500:1	55	0.5	97.6
5	1000:1	55	1.0	94.9
6	1500:1	55	1.5	90.9
7	1000:1	80	1	81.2

All reactions carried out in MeOH
All reactions achieved >98% conversion

Example 24

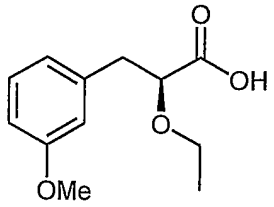
HPLC method for e.e. determination for (S)-2-ethoxy-3-(thiophen-3-yl)propanoic acid



Chiralpak-AD column (250 mm x 4.6 mm), 99 % Hexane, 1 % i-Propyl alcohol, flow: 0.7 ml/min, Integrated 235-239 nm. Enantiomers 9.71 min, 10.88 min (largest peak with bis-[(R_P,S_C,R_{Fe})] ***1***), starting material16.35 min.

Example 25

HPLC method for e.e. determination for (S)-2-ethoxy-3-(3-methoxyphenyl)propanoic acid (as methyl ester)



After derivatization:

Chiralpak-AD column (250 mm x 4.6 mm), 95 % Hexane, 2.5 % 2-methyl-2-propanol and 2.5 % t-amyl alcohol, flow: 1 ml/min, Integrated 280-290 nm. Enantiomers 7.49 and 10.00 min (largest peak with bis-[(S_P,R_C,S_{Fe})] ***1***).

Example 26

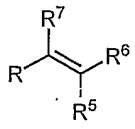
Table 7.0 Screening results of enantioselective hydrogenations on various (Z)-substituted 3-aryl-2-ethoxyacrylic acid substrates with bis-[(S_P,R_C,S_{Fe})] ***1*** at 50 bar H_2 pressure.

entry	s/c ratio	T (°C)	Substrate [M]	Substituted aryl	e.e. (%)
1	500:1	40	0.41	3-OMe	95.2
2	1000:1	40	0.82	3-OMe	94.6
3	500:1	35	0.50	4-CN	98.0
4	500:1	55	0.50	4-CN	96.5
5	500:1	50	0.41	2-thienyl	95.0
6	1000:1	55	0.41	3-thienyl	96.5

All reactions carried out in MeOH

CLAIMS

1. A process for the manufacture of substituted propionic acids comprising providing a substrate of formula (I):



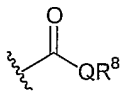
.....(I)

wherein:

R is selected from hydrogen, substituted and unsubstituted branched and straight-chain alkyl, alkoxy, alkylamino, substituted and unsubstituted cycloalkyl, substituted and unsubstituted cycloalkylamino, substituted and unsubstituted carbocyclic aryl, substituted and unsubstituted carbocylic aryloxy, substituted and unsubstituted heteroaryl, substituted and unsubstituted carbocylic arylamino and substituted and unsubstituted heteroarylamino, wherein the or each heteroatom is independently selected from sulphur, nitrogen and oxygen;

R^5 is the same as or different from R and is selected from hydrogen, substituted and unsubstituted branched and straight-chain alkyl, alkoxy, alkylamino, N-acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted cycloalkylamino, substituted and unsubstituted carbocyclic aryl, substituted and unsubstituted carbocylic aryloxy, substituted and unsubstituted heteroaryl, substituted and unsubstituted carbocylic arylamino and substituted and unsubstituted heteroarylamino, wherein the or each heteroatom is independently selected from sulphur, nitrogen and oxygen;

R^6 is selected from:



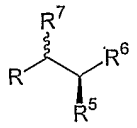
wherein:

Q is selected from O or N; and

R^8 is selected from hydrogen, substituted and unsubstituted branched and straight-chain alkyl, amino, alkylamino, substituted and unsubstituted cycloalkyl, substituted and unsubstituted cycloalkylamino, substituted and unsubstituted carbocyclic aryl, substituted and, substituted and unsubstituted heteroaryl, substituted and unsubstituted carbocylic arylamino and substituted and unsubstituted heteroarylamino, wherein the or each heteroatom is independently selected from sulphur, nitrogen and oxygen;

R^7 is the same as or different from R and/or R^5 (except that if R and R^7 are the same then R^5 is not hydrogen) and is selected from hydrogen, substituted and unsubstituted branched and straight-chain alkyl, alkoxy, alkylamino, substituted and unsubstituted cycloalkyl, substituted and unsubstituted cycloalkylamino, substituted and unsubstituted carbocyclic aryl, substituted and unsubstituted carbocylic aryloxy, substituted and unsubstituted heteroaryl, substituted and unsubstituted carbocylic arylamino and substituted and unsubstituted heteroarylamino, wherein the or each heteroatom is independently selected from sulphur, nitrogen and oxygen; and

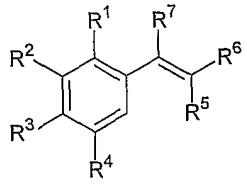
subjecting the substrate to enantioselective hydrogenation under enantioselective hydrogenation conditions in the presence of an enantioselective hydrogenation catalyst comprising a catalyst ligand having a metallocene group with a chiral phosphorus or arsenic substituent to provide in enantiomeric excess a product of formula (II):



.....(II)

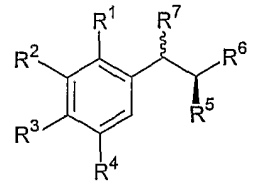
or its enantiomer or if applicable its diastereomer.

2. A process according to claim 1 wherein the substrate is of formula (III):



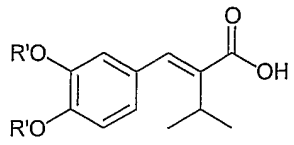
.....(III)

wherein R^1, R^2, R^3 and R^4 are the same or different and are independently selected from hydrogen, alkyl, haloalkyl, alkoxy, alkoxylated alkyl and alkoxylated alkoxy; the product of the process being of formula (IV):



.....(IV)

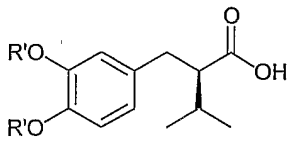
3. A process according to claim 2 wherein the substrate is a substrate of formula (V):



.....(V)

Wherein R'O is any suitable alkoxy or alkoxylated alkoxy group, and wherein each R'O may be the same or different.

4. A process according to claim 3 wherein the product is a product of formula (VI):



.....(VI)

5. A process according to any one of claims 1 to 4 wherein the metallocene group comprises ortho to the chiral phosphorus or arsenic substituent a second chiral substituent group.

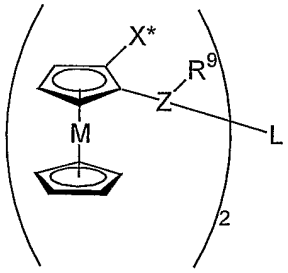
6. A process according to any one of claims 1 to 5 wherein the chiral phosphorus or arsenic substituent on the metallocene group is further connected via a linking moiety to a second chiral phosphorus or arsenic substituent on a second metallocene group.

7. A process according to claim 6 wherein the configuration of the chiral phosphorus or arsenic substituent is the same as the configuration of the second chiral phosphorus or arsenic substituent.

8. A process according to any one of claims 1 to 7 wherein the catalyst ligand exhibits C_2 symmetry.

9. A process according to any one of claims 1 to 8 wherein the catalyst ligand is basic.

10. A process according to any one of claims 1 to 9 wherein the catalyst ligand has the formula (VII):



.....(VII)

wherein:

M is a metal;

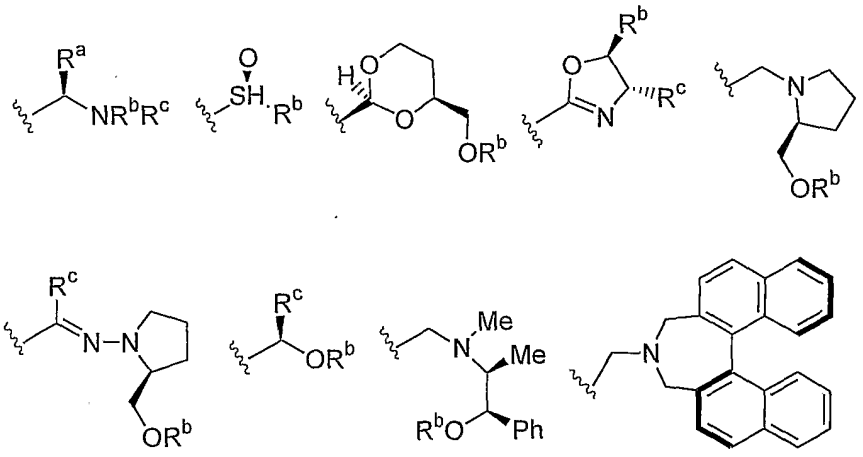
Z is P or As;

L is a suitable linker;

R^9 is selected from substituted and unsubstituted, branched- and straight-chain alkyl, alkoxy, alkylamino, substituted and unsubstituted cycloalkyl, substituted and unsubstituted cycloalkoxy, substituted and unsubstituted cycloalkylamino, substituted and unsubstituted carbocyclic aryl, substituted and unsubstituted carbocyclic aryloxy, substituted and unsubstituted heteroaryl, substituted and unsubstituted heteroaryloxy, substituted and unsubstituted carbocyclic arylamino and substituted and unsubstituted

heteroarylamino, wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen;

X* is selected from:



wherein R^a, R^b and R^c are independently selected from substituted and unsubstituted, branched- and straight-chain alkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted carbocyclic aryl, and substituted and unsubstituted heteroaryl wherein the or each heteroatom is independently selected from sulphur, nitrogen, and oxygen.

11. A process according to claim 10 wherein R^b and R^c form, together with the nitrogen to which they are attached, an optionally substituted hetero-ring.

12. A process according to claim 10 or claim 11 wherein L the linker is derived from a dianionic reactive species.

13. A process according to any one of claims 10 to 12 wherein L is selected from metallocenes, diphenyl ethers, xanthenes, 2,3-benzothiophenes, 1,2-benzenes, cyclic anhydrides and succinimides.

14. A process according to claim 13 wherein the linker comprises ferrocene.

15. A process according to any one of claims 10 to 14 wherein the enantioselective hydrogenation catalyst comprises the enantiomer or diastereomer of a ligand having the formula (VII).

16. A process for the preparation of substituted propionic alcohols comprising preparing a substituted propionic acid by the process of any one of claims 1 to 15, and then hydrogenating the acid.

17. A process for the preparation of substituted propionic halides comprising preparing a substituted propionic alcohol by the process of claim 16 and halogenating the alcohol.

18. A process for the preparation of substituted lactic acid comprising preparing by a process of any one of claims 1 to 15 a substituted propionic acid of formula (II) wherein R^5 is alkoxy and converting the alkoxy group to a hydroxy group.

19. A process according to any one of claims 1 to 18 wherein the enantioselective hydrogenation catalyst comprises a transition metal coordinated to the catalyst ligand.

20. A process according to claim 19 wherein coordination between the transition metal and the catalyst ligand takes place *in situ* in the presence of the substrate.

21. A process according to claim 19 wherein the transition metal and the catalyst ligand are pre-coordinated before contact with the substrate.

22. A process according to any one of claims 19 to 21 wherein the transition metal is a Group VIb or a Group VIII metal.

23. A process according to claim 22 wherein the transition metal is selected from rhodium, ruthenium, iridium, palladium, platinum or nickel.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/000129

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C51/36 C07C253/30 C07D333/24 C07C59/64 C07C59/70
ADD. C07C255/57

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)
C07C 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, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/068477 A (STYLACATS LIMITED; CHEN, WEI-PING; WHITTALL, JOHN) 28 July 2005 (2005-07-28) Page 1, lines 4-10; page 86, lines 9-20; examples 39-41,60-63	1,5,8,9, 19,21-23

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

"E" earlier 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)

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"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
20 April 2006	08/05/2006

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, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Cooper, S

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2006/000129

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