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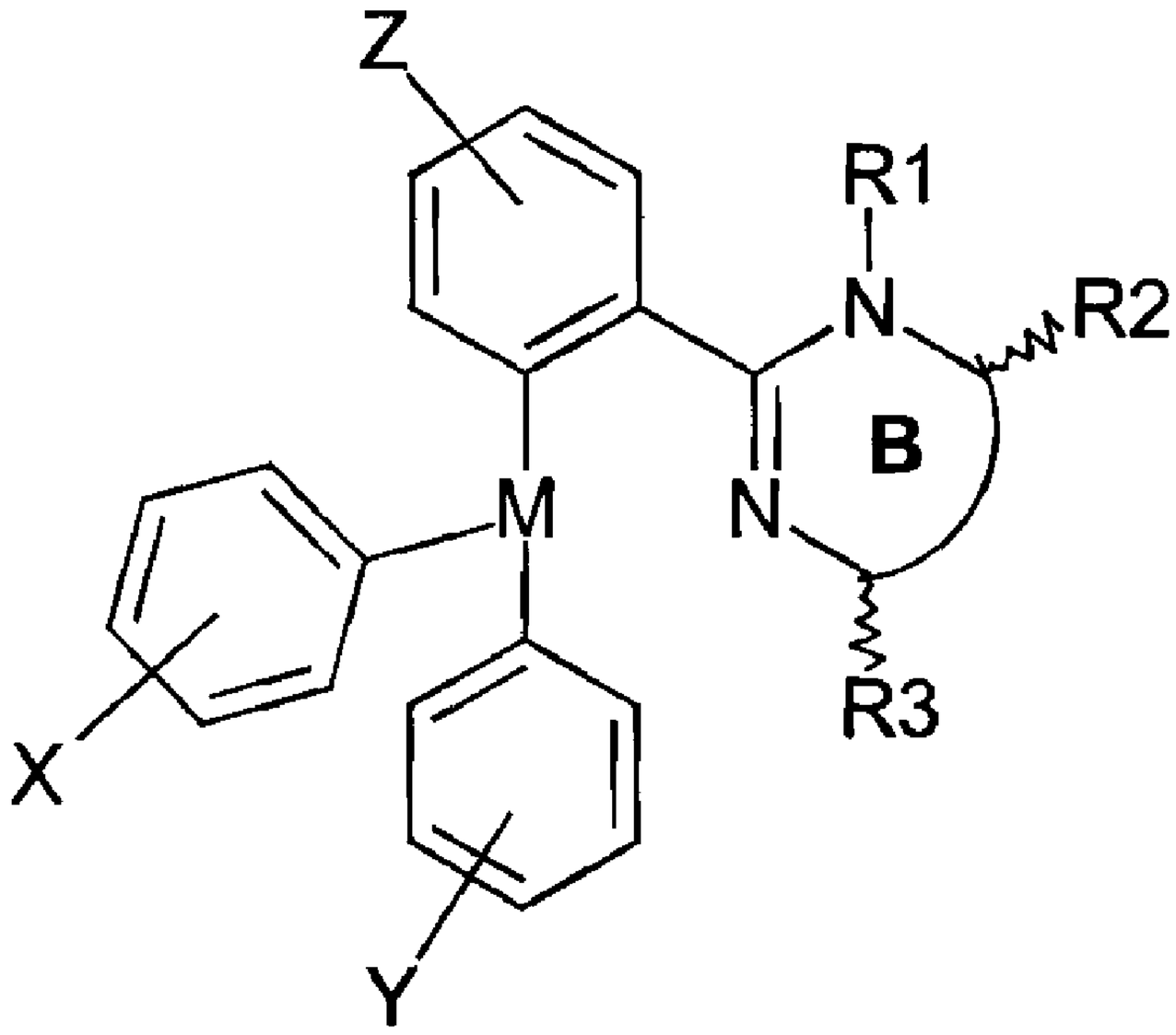
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(54) Titre : PREPARATION ELECTRONIQUE DE LIGANDS
(54) Title: ELECTRONICALLY TUNED LIGANDS



(1)

(57) Abrégé/Abstract:
A phosphino- or arsenoamidine of Formula (1) M is Phosphorus or Arsenic (P, As); X, Y, and Z can be independently selected from hydrogen, alkyl, aryl (pendant or fused), halogen, alkoxy (C1-C10), cyano, nitro, amino, alkylamino, dialkylamino, -CO_2H,

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(57) **Abrégé(suite)/Abstract(continued)**:
-CO(lower alkoxy), -CO(lower alkyl), -NCOH, -NCO(lower alkyl), NSO_2(alkyl), - NSO_2(aryl), hydroxy, alkyl, sulfonoxyalkyl, sulfonoxyaryl, or alkoxyalkyl; R1 is hydrogen, C1-C10 alkyl, branched alkyl or cycloalkyl; aryl, substituted aryl, heteroaryl or substituted heteroaryl where the heteroatoms may include atoms of nitrogen, oxygen, or sulfur, may be acyl, aroyl, substituted aroyl, heteroaroyl, or substituted heteroaroyl, or SO_2R4 where R4 is chosen from the group alkyl, aryl, heteroaryl, substituted aryl or substituted heteroaryl groups in direct attachment, with the provisos that R2 and R3 can be the same or different and are hydrogen, aryl or heteroaryl as defined above, substituted aryl or heteroaryl as defined (with substituents as defined below), alkyl, branched alkyl, cycloalkyl, benzyl, subtituted benzyl, with substituents as defined for aryl, or R2 and R3 together may form a fused carbocyclic ring, Ring B is an imidazoline ring or a tetrahydropyrimidine ring.

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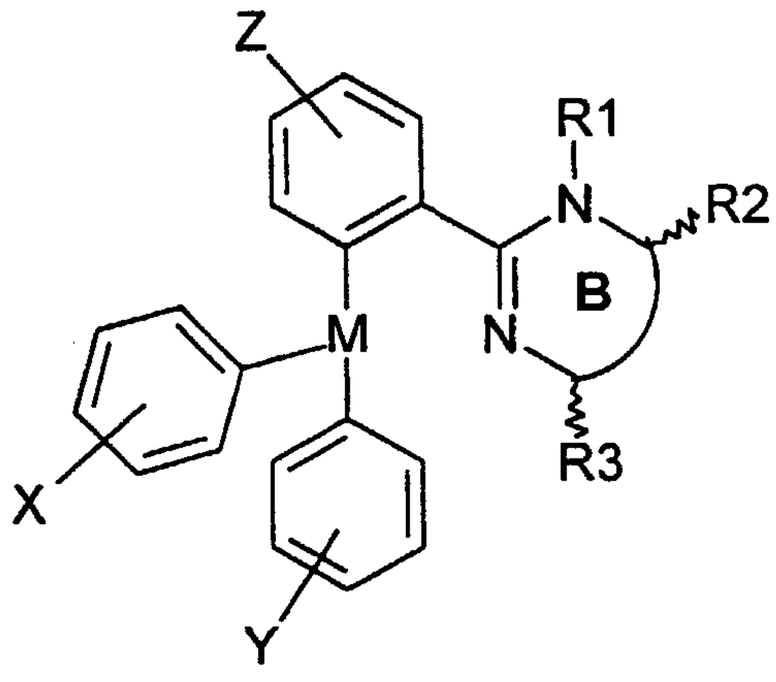
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(54) Title: ELECTRONICALLY TUNED LIGANDS



(1)

(57) Abstract: A phosphino- or arsenoamidine of Formula (1) M is Phosphorus or Arsenic (P, As); X, Y, and Z can be independently selected from hydrogen, alkyl, aryl (pendant or fused), halogen, alkoxy (C1-C10), cyano, nitro, amino, alkylamino, dialkylamino, -CO_2H, -CO(lower alkoxy), -CO(lower alkyl), -NCOH, -NCO(lower alkyl), NSO_2(alkyl), - NSO_2(aryl), hydroxy, alkyl, sulfonoxyalkyl, sulfonoxyaryl, or alkoxyalkyl; R1 is hydrogen, C1-C10 alkyl, branched alkyl or cycloalkyl; aryl, substituted aryl, heteroaryl or substituted heteroaryl where the heteroatoms may include atoms of nitrogen, oxygen, or sulfur, may be acyl, aroyl, substituted aroyl, heteroaroyl, or substituted heteroaroyl, or SO_2R4 where R4 is chosen from the group alkyl, aryl, heteroaryl, substituted aryl or substituted heteroaryl groups in direct attachment, with the provisos that R2 and R3 can be the same or different and are hydrogen, aryl or heteroaryl as defined above, substituted aryl or heteroaryl as defined (with substituents as defined below), alkyl, branched alkyl, cycloalkyl, benzyl, subtituted benzyl, with substituents as defined for aryl, or R2 and R3 together may form a fused carbocyclic ring, Ring B is an imidazoline ring or a tetrahydropyrimidine ring.

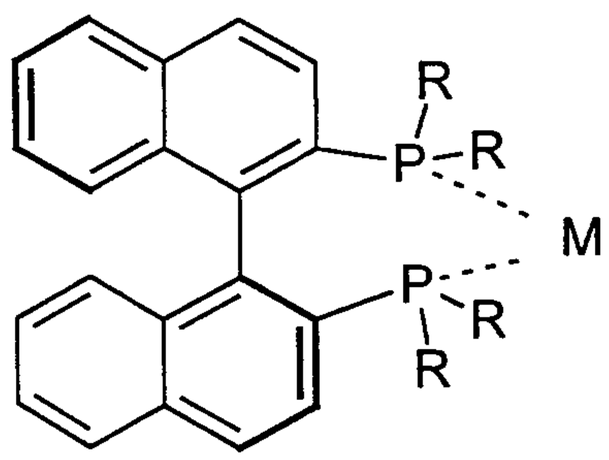
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ELECTRONICALLY TUNED LIGANDS

BACKGROUND OF THE INVENTION

Asymmetric synthesis is becoming more and more important in the pharmaceutical industry. There is growing regulatory pressure to approve only those enantiomers of drugs that have the desired biological activity. For safety reasons and to demonstrate efficacy, regulatory agencies are taking the position that only those enantiomers with pharmaceutical action should be administered, apart from the enantiomers with little or no action or even adverse or toxic effect. The total market for enantiomerically pure pharmaceuticals is projected to be ninety billion U.S. dollars by 2000. To prepare such large quantities of drug only *via* resolution will often be cost prohibitive. Chiral catalysis will no doubt complement traditional methods such as resolution or chiral separation.

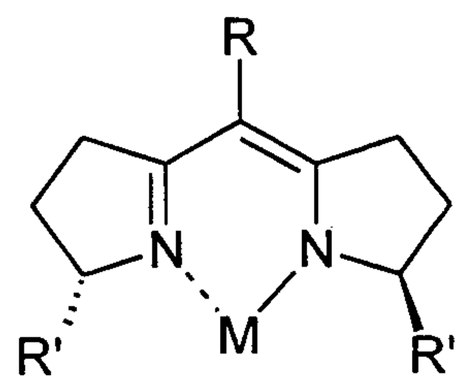
Many asymmetric syntheses involve use of catalysts, and typically employ chiral ligands and late transition metals. Bidentate ligands play a central role in catalyst design for asymmetric synthesis. Ligands that have been used successfully in asymmetric synthesis include the BINAP family of catalysts for asymmetric reductions and isomerizations (For example, see *Asymmetric Catalysis in Organic Synthesis*, Noyori, R., Ed.; John Wiley and Sons: New York, **1994**, p.16-121).



BINAP's

M is Pd, Rh, Ru or Ir;
R is phenyl, substituted phenyl or alkyl

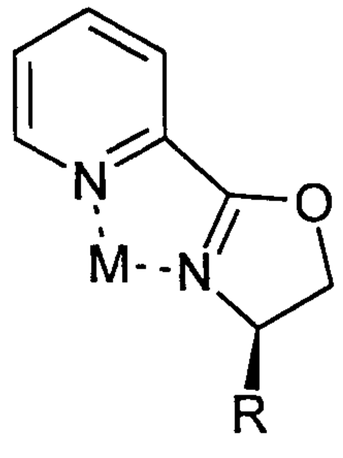
Bisoxazolines for asymmetric cyclopropanation and cycloadditions have been reported (For a review, see Ghosh, A.K.; Mathivanan, P.; and Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1-45).



Bisoxazolines

M is Cu, Mg, Fe, Ni, Co, Ru or Pd
R is CN or alkyl;
R' is alkyl, aryl, substituted alkyl, benzyl,

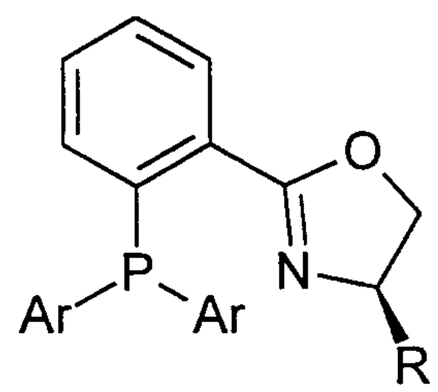
Pyridyloxazolines for asymmetric hydrosilations have also been described (Brunner, H.; Obermann, U. *Chem. Ber*. **1989**, *122*, 499).



Pyridyloxazolines

M is Rh;
R is i-Pr, t-Bu, aryl, benzyl,
or substituted alkyl.

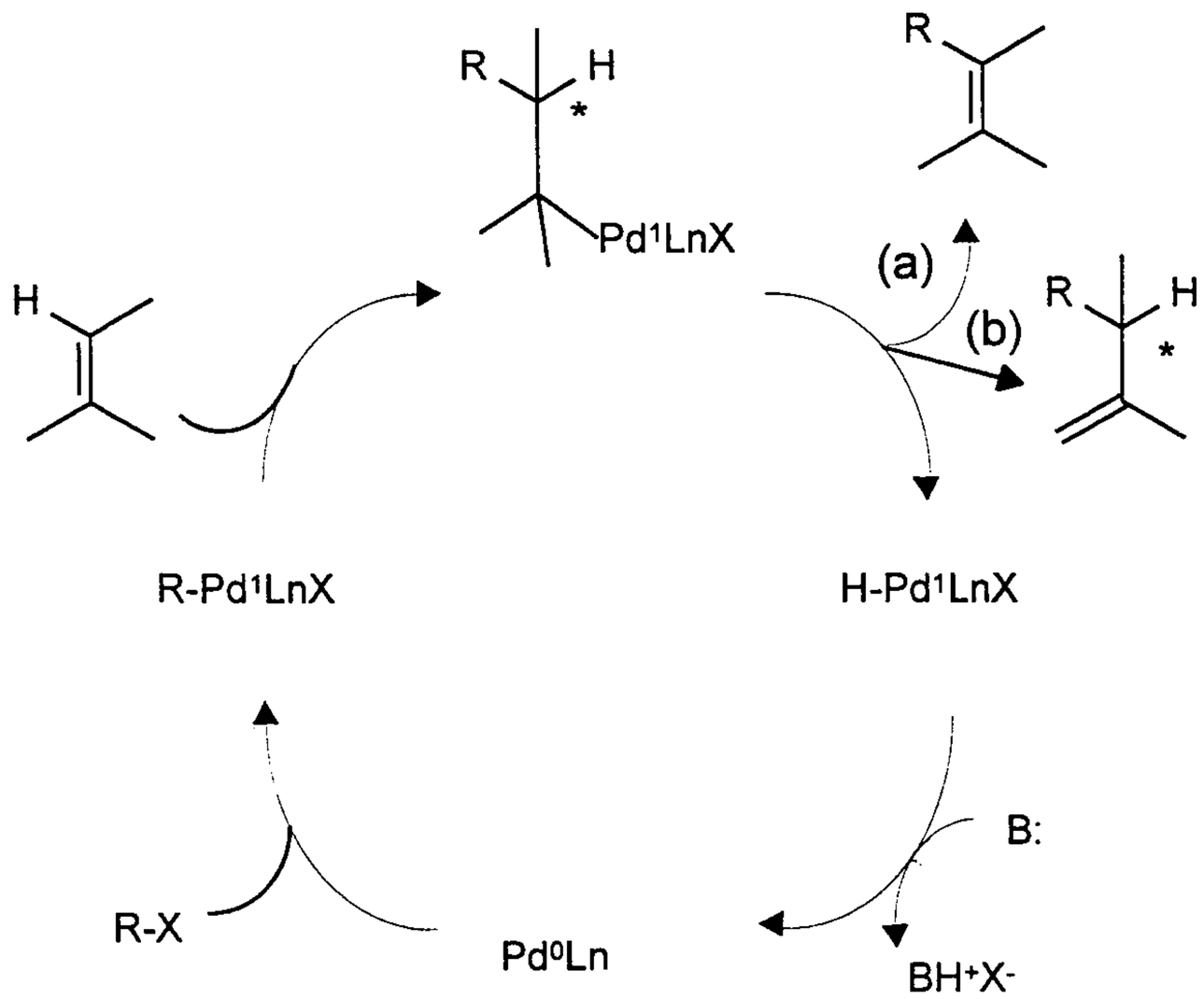
Even more recently, electronically "mixed" bidentate ligands with two different ligating heteroatons (N-O, P-N, P-O) have emerged. Such ligands have been shown empirically to outperform P-P bidentate ligands in a number of synthetically important transformations. Such "mixed" ligands are the phosphino-oxazolines described by Pfaltz et al. (*Synthesis*, **1997**, 1338), Helmchen et al. (*Angew. Chem. Int. Ed. Eng.*, **1997**, *36* (19) 2108), and Williams et al., (*Tetrahedron*, **1994**, *50*, 9).



Phosphino-oxazolines

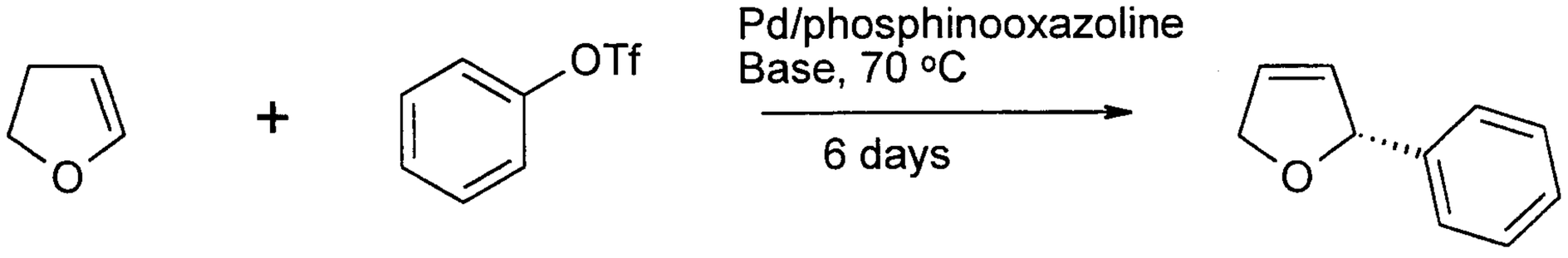
R is aryl, i-Pr, t-Bu, or benzyl.

The Heck reaction is one of the most versatile catalytic methods for C-C bond formation. In this reaction, an aryl or alkenyl halide or triflate is coupled with an alkene, as shown in the following scheme:



Scheme 1

The catalytic cycle starts with an oxidative addition of organic halide or triflate to a Pd (0) complex, followed by insertion of an alkene. The resulting Pd (II) alkyl complex then undergoes ß-hydride elimination. Several isomeric products can be formed, depending upon the structure of the substrate. In path (a), the C-C double bond is restored in the original position and a stereogenic center is not created. However, if ß-hydride elimination takes path (b), the stereogenic C atom introduced in the insertion step is retained. For path (b), the use of chiral palladium complexes makes it possible to perform such reactions in an enantioselective manner. Pfaltz et al. showed that chiral phosphino-oxazolines are very efficient ligands for enantioselective Heck reactions (*Synthesis* **1997**, 1338). For example, asymmetric Heck arylation, using Pd/phosphino-oxazolines, produces substituted dihydrofuran in 90% yield and 92% ee, as shown below:



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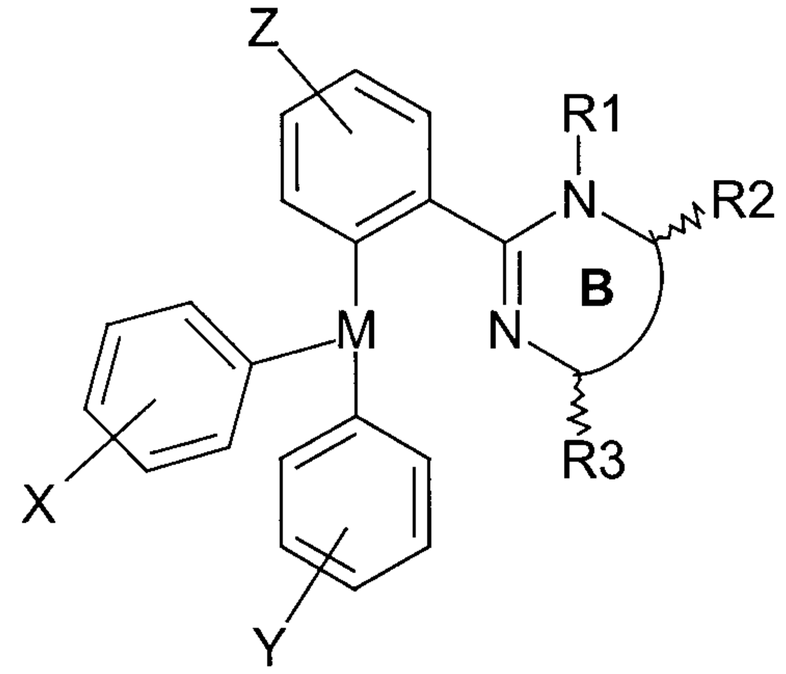
The phosphino-oxazolines described and taught by Pfaltz et al., Helmchen et al. and Williams et al. are superior to BINAP catalysts in the Heck reaction in that: (a) such ligands are insensitive to the nature of the added base; (b) have more ability to suppress side products; and (c) have very high enantioselectivity. However, such phosphino-oxazolines have a major deficiency. The above Heck arylation required six (6) days, an extremely long reaction time. It appears that the R substituent of the phosphino-oxazolines is not in conjugation with the ligating atoms, and therefore functions solely in a steric role. From the long reaction time or the low turnover of these catalysts, it is clear that the donicity of the bidentate ligand is not optimized.

THE INVENTION

A new class of chiral bidentate ligands to transition metals has been discovered. Such ligands can be electronically tuned at will for optimum performance. (For an example of electronic tuning in asymmetric catalysis using a different ligand class see: E.N. Jacobsen et al., *J. Am. Chem. Soc.* **1991**, *113*, pp. 6703 - 6704). Additionally, such ligands can be used to prepare chiral compounds of high optical purity. This new class of chiral ligands to transition metals can be easily tuned electronically by the replacement of a single substituent.

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According to one aspect of the present invention, there is provided a compound of Formula (1)



(1)

wherein: M is Phosphorous or Arsenic; X, Y and Z are independently selected from hydrogen, alkyl, aryl wherein the aryl is pendant or fused, halogen, C_{1-10}-alkoxy, cyano, nitro, amino, alkylamino, dialkylamino, $-CO_2H$, -CO(lower alkoxy), -CO(lower alkyl), -NCOH, -NCO(lower alkyl), NSO_2(alkyl), $-NSO_2$(aryl), hydroxy, sulfonoxyalkyl, sulfonoxyaryl, and alkoxyalkyl; R1 is hydrogen, C_{1-10}-alkyl, branched alkyl, cycloalkyl; phenyl, naphthyl, substituted phenyl or naphthyl, wherein the substituents are as defined below for aryl; heteroaryl or substituted heteroaryl comprising one or more heteroatoms independently selected from nitrogen, oxygen and sulfur; acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, or SO_2R4 where R4 is selected from the group consisting of alkyl, aryl, heteroaryl, substituted aryl and substituted heteroaryl groups in direct attachment; R2 and R3 are the same or different and are hydrogen, aryl as defined above for X, Y and Z or heteroaryl as defined above for R1; substituted aryl or heteroaryl as defined below; alkyl, branched alkyl,

cycloalkyl, benzyl or substituted benzyl, with substituents as defined for aryl below, or R2 and R3 together form a fused carbocyclic ring; Ring B is an imidazoline ring or a tetrahydropyrimidine ring; and at least one, or both, of R2 and R3 must be attached to a chiral carbon, of either (R) or (S) absolute configuration; wherein aryl, heteroaryl, aroyl and heteroaroyl groups are optionally substituted by one or more substituent independently selected from the group consisting of alkyl, halogen, alkoxy, acyl, phenoxy, cyano, nitro, hydroxy, amino, alkylamino, dialkylamino, carboalkoxy, keto, amido, and sulfoxy.

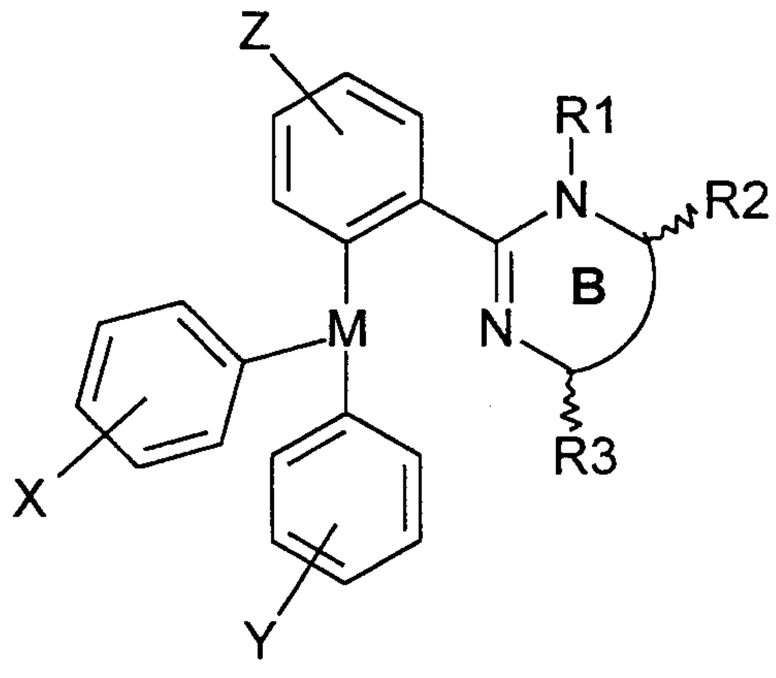
According to another aspect of the present invention, the compound described herein may be used to isolate a specific enantiomer from a group of enantiomers when the compound is complexed with a transition metal.

Here, and throughout this application unless otherwise specified, the term "alkyl" refers to a saturated aliphatic radical containing from one to ten carbon atoms. "Alkyl" refers to both branched and unbranched alkyl groups. Preferred alkyl groups are straight chain alkyl groups containing from one to eight carbon atoms and branched alkyl groups containing from three to eight carbon atoms. More preferred alkyl groups are straight chain alkyl groups containing from one to six carbon atoms and branched alkyl groups containing from three to six carbon atoms. "Alkyl", as used herein, includes unsubstituted alkyl radicals, those radicals that are partially or fully halogenated and those radicals substituted with one to four, preferably one or two, substituents selected

from halo, amino, cyano, nitro, methoxy, ethoxy, hydroxy, keto, carboalkoxy, or amido. The term "cycloalkyl" refers to the cyclic analog of an alkyl group, as defined above. Preferred cycloalkyl groups are saturated cycloalkyl groups containing from three to eight carbon atoms, and more preferably three to six carbon atoms. "Alkyl" and "cycloalkyl", as used herein, include unsubstituted alkyl and cycloalkyl radicals, those radicals that are partially or fully halogenated and those radicals substituted with one to four, preferably one or two, substituents selected from halo, amino, cyano, nitro, methoxy, ethoxy, hydroxy, keto, carboalkoxy, or amido. It should be understood that any combination term using an "alk" or "alkyl" prefix refers to analogs according to the above definition of "alkyl". For example, terms such as "alkoxy", "alkylthio" refer to alkyl groups linked to a second group *via* an oxygen or sulfur atom.

The term "halo" or "halogen" refers to a halogen selected from fluoro, chloro, bromo, or iodo.

The new chiral bidentate ligands can be represented by Formula (1) below:



(1)

wherein

M is Phosphorus or Arsenic (P, As)

X, Y and Z can be independently selected from hydrogen, aryl (pendant or fused), halogen, alkyl, alkoxy, cyano, nitro, amino, alkylamino, dialkylamino, $-CO_2H$, $-CO(C_{1-6}$ alkoxy), $-CO(C_{1-6}$alkyl), -NCOH, $-NCO(C_{1-6}$alkyl), NSO_2(alkyl), $-NSO_2$(aryl), hydroxy, sulfonoxyalkyl, sulfonoxyaryl, or alkoxyalkyl.

R1 is selected from the group consisting of hydrogen, alkyl, branched alkyl, cycloalkyl, aryl selected from the group phenyl and naphthyl, which may optionally be substituted with one or more alkyl, halogen, alkoxy, acyl, phenoxy, cyano, nitro, hydroxy, amino, alkylamino, dialkylamino, carboalkoxy, amido, or sulfoxy group; heteroaryl selected from the group 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 2-benzofuryl, 3-benzofuryl, 2-thiophenyl, 3-thiophenyl, 2-benzothiophenyl, 3-benzothiophenyl, 2-pyrrolyl, 3-pyrrolyl, 2-indolyl, 3-indolyl, benzimidazolyl, imidazolyl, quinolinyl, isoquinolinyl, oxazolyl, benzoxazolyl, thiazolyl, and pyrimidinolyl, which may be optionally substituted with one or more alkyl, halogen, alkoxy, acyl, phenoxy, cyano, nitro, hydroxy, amino, alkylamino, dialkylamino, carboalkoxy, amido, or sulfoxy group; C_{2-6}acyl, aroyl selected from the group benzoyl and napthoyl, optionally substituted one or more group as described above for aryl; heteroaroyl selected from the group 2-furoyl, 3-furoyl, 2-pyridoyl, 3-pyridoyl, 4-pyridoyl, 2-benzofuranoyl, 3-benzofuranoyl, 2-thiophenoyl, 3-thiophenoyl, 2-benzothiophenoyl, 3-benzothiophenoyl, 2-pyrroyl, 3-pyrroyl, 2-indoloyl, 3-indoloyl, benzimidazoyl, imidazoyl, quinolinoyl, isoquinolinoyl, oxazoyl, benzoxazoyl, thiazoyl, and pyrimidoyl, optionally substituted with one or more group as defined above for heteroaryl; SO_2R4 where R4 is chosen from the group alkyl, aryl and heteroaryl, which may be optionally substituted as described above.

R2 and R3 can be the same or different and can be selected from hydrogen, aryl or heteroaryl as defined above, substituted aryl or heteroaryl as defined above, (with substituents as defined above), alkyl, branched alkyl, cycloalkyl, benzyl, substituted

benzyl, with substituents as defined for aryl, or R2 and R3 together may form a fused carbocyclic ring.

The amidine portion must be constrained to form a ring (ring B), and said ring must be either 5- or 6- membered. For example, B may be an imidazoline or tetrahydropyrimidine ring.

At least one, or both, of R2 and R3 must be attached to a chiral carbon, of either (R) or (S) absolute configuration.

The compounds of the present invention are particularly useful in Heck reactions. In such instances, preferred X,Y, and Z would be H, alkyl, aryl as described above, halogen, alkoxy, cyano, nitro, amino, alkylamino, and dialkylamino. Preferred R1 would be H, alkyl, benzyl, aryl, substituted aryl as described above, heteroaryl and substituted heteroaryl as described above, C_{2-6} acyl, and aroyl selected from the group of benzoyl, naphthoyl, and pyridoyl, optionally substituted with one or more groups as described above for aryl. Preferred R2,R3 would be H, alkyl, cycloalkyl, aryl and substituted aryl as described above, and heteroaryl and substituted heteroaryl as described above. Preferred B ring size might be five membered, that is, an imidazoline ring.

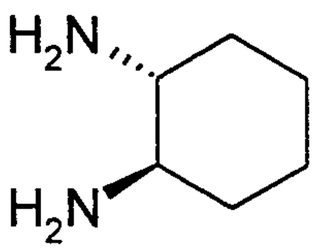
Solvent effects can be quite important in asymmetric synthesis. For the asymmetric Heck reaction in particular, the ligands of Formula (1) are most effective when used in a non-polar solvent. If a polar solvent is used, disappointing yields can be obtained that may render use of the ligands of the present invention not commercially feasible.

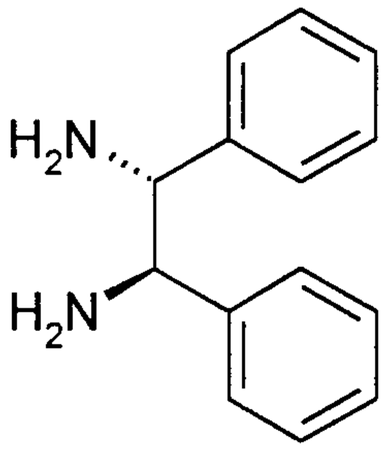
The phosphino- and arsenoamidines of Formula (1) are electronically tunable. By varying the R1 substituent from electron withdrawing groups (e.g., acyl, benzoyl) to electron donating groups (e.g., alkyl, phenyl, benzyl), the basicity and donicity of the ligand can be easily modified and altered to suit the requirements of any given asymmetric synthesis.

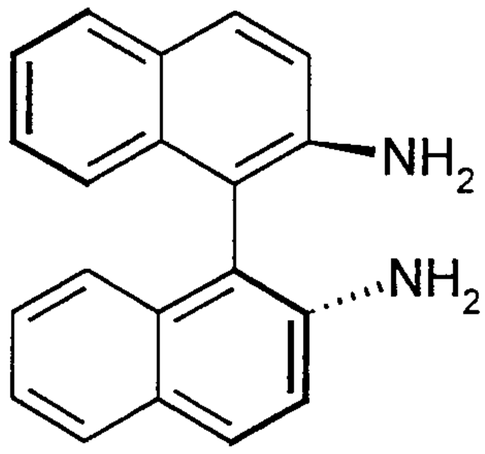
To practice the instant invention, a complex is prepared between a ligand of Formula (1) and a transition metal, such as palladium. Other transition metals such as rhodium, ruthenium, iridium, nickel or platinum can be employed for catalyzed asymmetric hydrogenations. For catalyzed, enantioselective isomerization of allyl species, rhodium or cobalt would be employed. For catalyzed asymmetric cyclopropanations, rhodium, palladium or copper would be used. For catalyzed asymmetric hydroformylations of olefins, cobalt, rhodium, platinum or palladium would be used. Rhodium would also be used for catalyzed, asymmetric hydrosilylations of ketones. Rhodium or palladium would be used in catalyzed asymmetric hydrosilylation of olefins. However, this provides only a brief list of catalyzed, asymmetric reactions where the ligands of the instant invention could be successfully used.

The complex formed using the ligands of the present invention could be isolated or could be allowed to form *in situ* prior to addition of the substrate molecule. In general, the reaction would be allowed to proceed under the influence of the catalyst produced by the novel ligand until completion, the product then being isolated and optical purity measured.

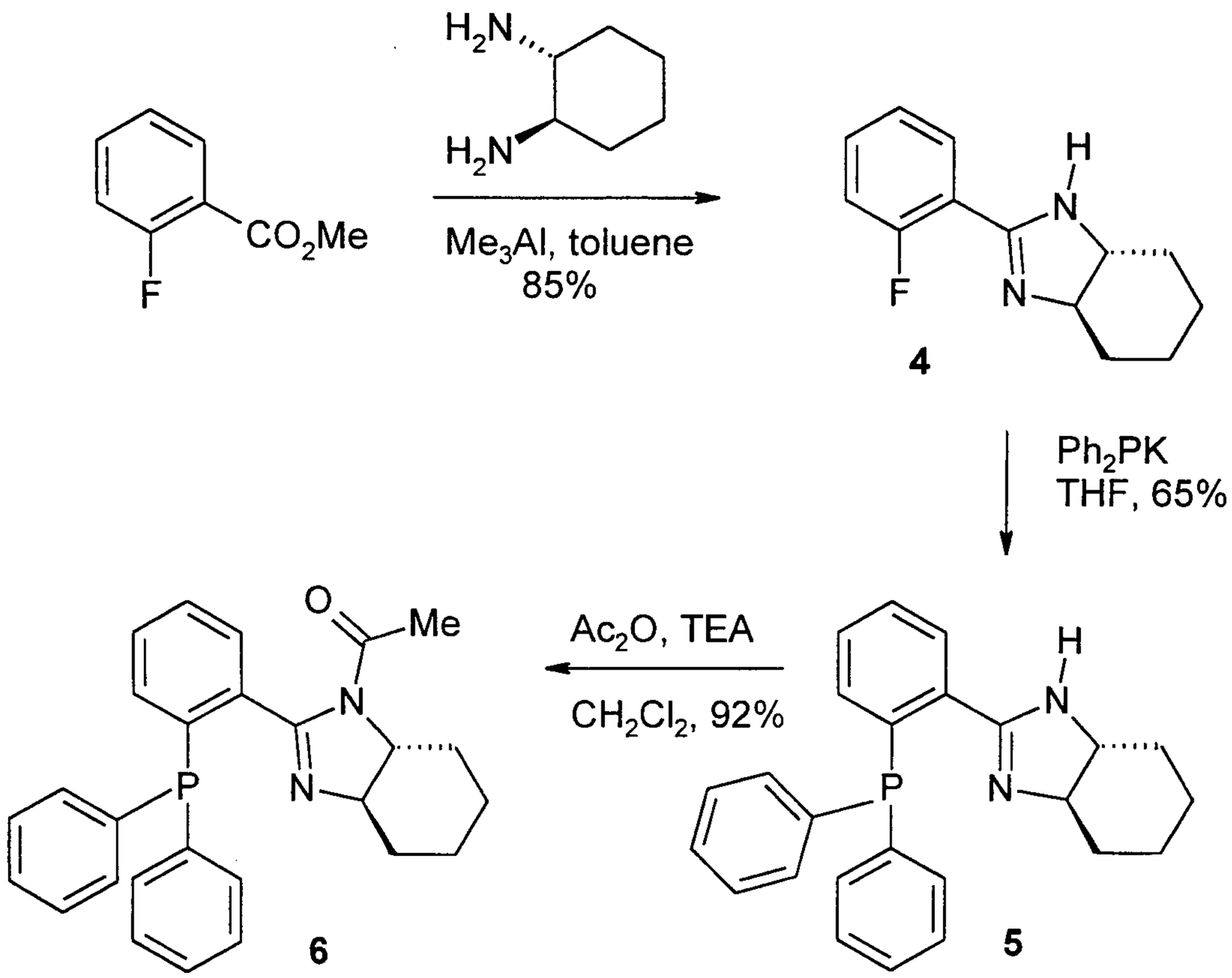
The phosphino- and arsenoamidines of Formula (1) can be readily prepared from commercially available chiral amines or chiral amines which are themselves independently synthesized by methods known to those skilled in the art. Examples of such amines are the following:







The new ligands are readily prepared, as shown in Schemes 2 and 3. As shown below (Scheme 2) condensation of the trimethylaluminum complex of (R,R)-cyclohexanediamine with 2-fluoromethylbenzoate produced the fluoroimidazoline **4** in 85% yield. Fluoride displacement with commercially available Ph_2PK in refluxing THF provided the phosphinoimidazoline **5** of Formula (1), where X, Y and Z are H, M is P, R1 is H and R2 and R3 form a fused cyclohexyl ring in 65 % yield without chromotography.



m.p. 158-160 °C

^{31}P- 10.5 ppm

m.p. 178-179 °C

^{31}P- 8.6 ppm

Scheme 2

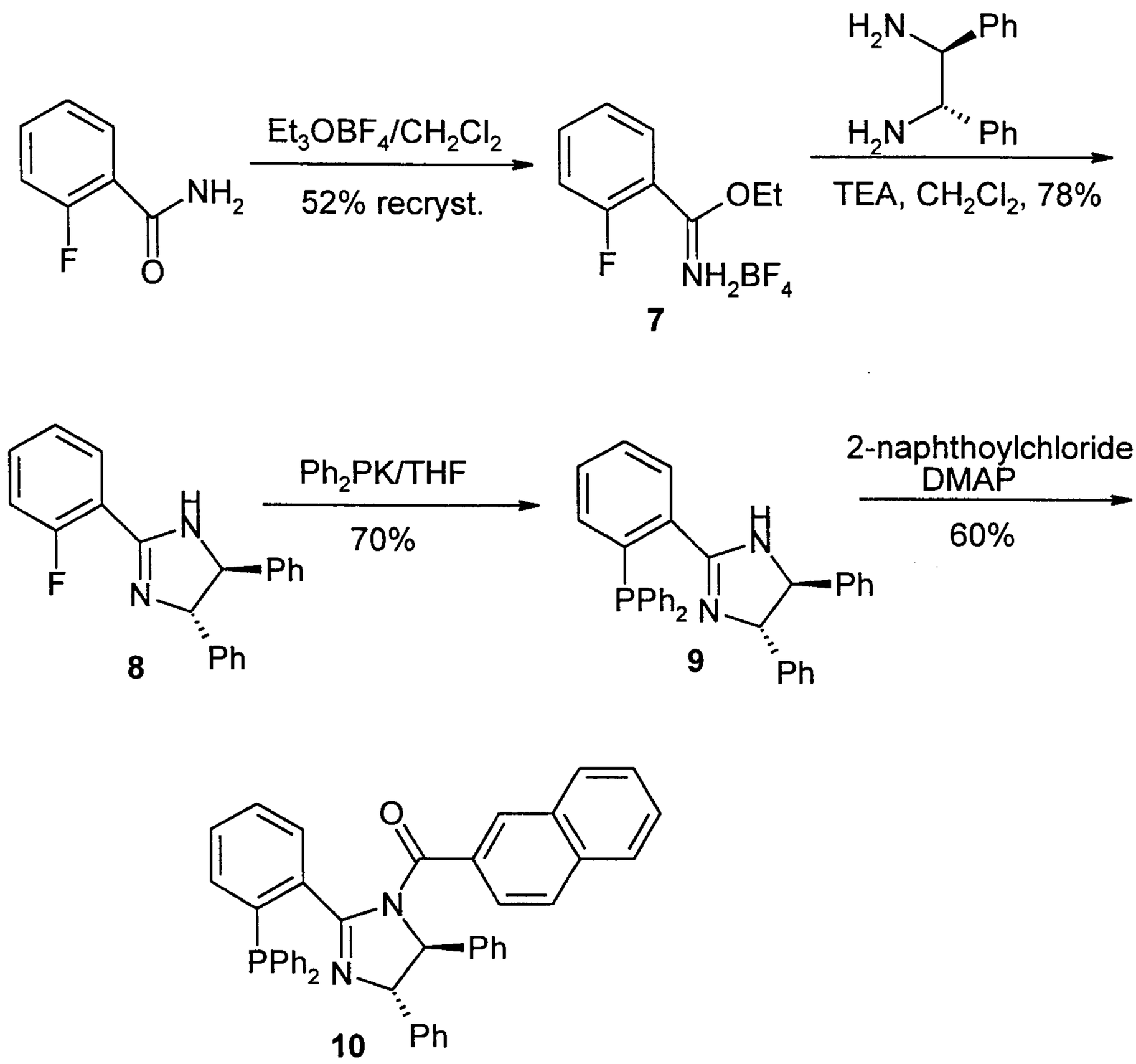
Acylation of **5** produced in high yield the phosphinoimidazoline **6** of Formula (1), where R1 is acetyl and X, Y, Z, M, R2 and R3 are as described for **5**.

Alternatively, a typical ligand can be prepared as shown in Scheme 3, below. Formation of imidate **7** from 2-fluorobenzamide is accomplished with triethyloxonium tetrafluoroborate. Condensation of the imidate with a chiral diamine such as (S,S)-1,2-diphenylethylenediamine then readily furnished fluoroimidazoline **8**. Displacement of the fluoride with potassium diphenylphosphide, followed by acylation with 2-naphthoyl chloride then furnished ligand **10**, of Formula (1), where R1 is 2-naphthoyl, X, Y, and Z are hydrogen, M is P, and R2 and R3 are both (S)-phenyl.

Other ligands of Formula (1) can be prepared by methods analogous to those described above.

EXPERIMENTAL SECTION

Synthesis of a typical ligand, **10** (See Scheme 3):



Scheme 3

2-Fluoro-ethylbenzimidate tetrafluoroborate (7):

To 13.6g 2-fluorobenzamide (98 mmol, 1 eq.) was added 100ml 1M triethyloxonium terafluoroborate/methylene chloride solution (100 mmol, 1.02 eq.) via canula under N_2. After stirring 18h at ambient temperature, the reaction mixture was filtered, and the resultant solid recrystallized from 100ml ethyl acetate to give 13.0g of 2-fluoro-ethylbenzimidate tetrafluoroborate 7 (52% recrystallized) as a colorless solid. M.p. 128-131°C; ^{19}F NMR (DMSO) δ: -113.8, -154.2 ppm.

2-(2'-Fluorophenyl)- (4S,5S)-diphenyl-4,5-dihydroimidazole (8):

To a 100ml flask was charged 5.00g imidate **7** (19.6 mmol, 1 eq.), 4.16g (S,S)-1,2-diphenylethylenediamine (19.6 mmol, 1 eq.), 50ml dichloromethane, and 6.3ml triethylamine (45.3 mmol, 2.3 eq.) in the order given. After stirring 4 hours at ambient temperature, the reaction mixture was poured into 50ml water, the phases separated, and the aq. phase reextracted with dichloromethane. The combined methylene chloride layers were washed with 2% aq. ammonium chloride, dried with magnesium sulfate, filtered, and the filtrate evaporated in vacuo to give an oil. This oil was dissolved in 25ml boiling hexane, cooled to 0^{o}, filtered and air dried to give 4.80g of 2-(2'-fluorophenyl)-(4S,5S)-diphenyl-4,5-dihydroimidazole **8** (78%) as a colorless solid. M.p. 122-124^{0}C; MS (ES+): MH+ 317; ^{19}F NMR ($CDCl_3$) δ: -113.6 ppm.

2-(2'-Diphenylphosphinophenyl)- (4S,5S)-diphenyl-4,5-dihydroimidazole (9):

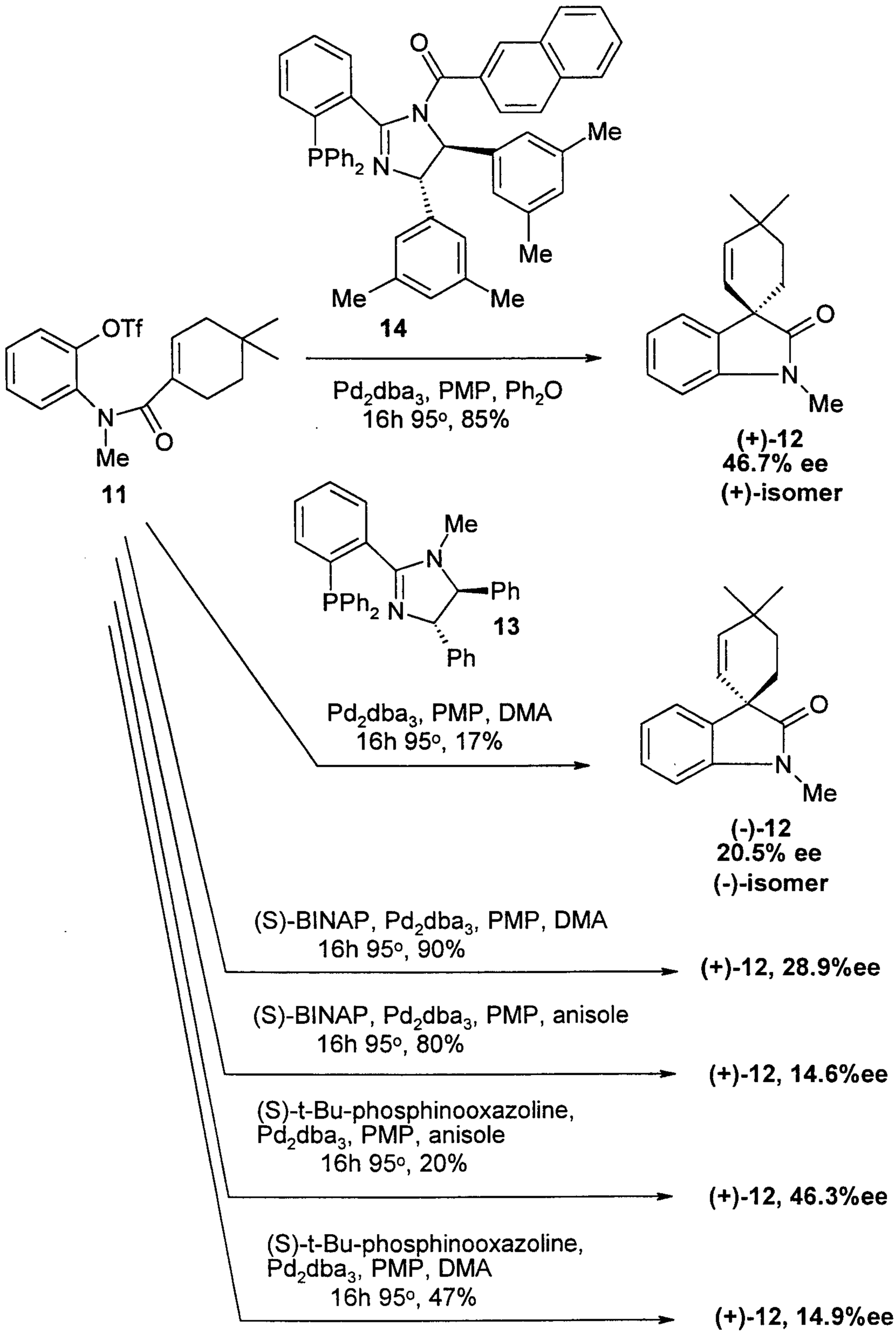
13.9ml of 0.5M potassium diphenylphosphide/THF (6.95 mmol, 1.1 eq.) was heated to 60^{o} in a thermostated oil bath. To this warm solution was then added a solution of 2.00g fluoride **8** (6.32 mmol, 1 eq.) in 5ml THF via syringe over 2 minutes. The resulting solution was then heated at reflux for 1 hour, cooled to room temperature and quenched by the addition of 10ml water. The resulting mixture was extracted with methylene chloride (2 X 25ml), dried ($MgSO_4$), and the solvents removed in vacuo to give an oil. This oil was then chromatographed on C18 silica gel eluting with 5:1 acetonitrile:water to give, after drying under high vacuum, 2.13g (70%) of 2-(2'-diphenylphosphinophenyl)- (4S,5S)-diphenyl-4,5-dihydroimidazole **9** as a colorless, amorphous foam. MS (ES+): MH+ 483; ^{31}P NMR ($CDCl_3$) δ: -9.6 ppm.

2-(2'-Diphenylphosphinophenyl)-3-(2''-naphthoyl)-(4S,5S)-diphenyl-4,5-dihydroimidazole (10):

A 10ml round bottom flask was charged with 150mg dihydroimidazole **9** (0.311 mmol, 1 eq.), 76mg p-dimethylaminopyridine (0.622 mmol, 2 eq.), 1.5ml of 1,2-dichloroethane, and 89mg 2-naphthoyl chloride (0.467 mmol, 1.5 eq.) in the order given. After 1 hour,

the volatiles were removed in vacuo and the residue chromatographed on silica gel eluting with 2% methanol/dichloromethane to give 117mg of the ligand, 2-(2'-diphenylphosphinophenyl)-3-(2''-naphthoyl)-(4S,5S)-diphenyl-4,5-dihydroimidazole **(10)** (60%) as a colorless foam. MS (ES+): MH+ 637; ^{31}P NMR ($CDCl_3$) δ: -11.0 ppm.

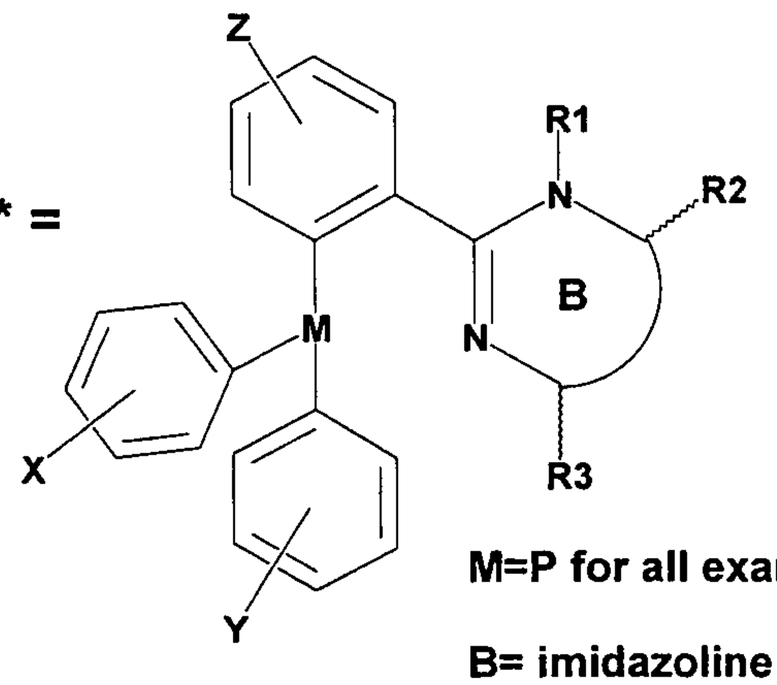
Typical use of the invention in asymmetric synthesis (See Scheme 4):


PPh2
N
O
N
Me
Me
Me
Me
14
OTf
N
O
Me
11
Pd2dba3, PMP, Ph2O
16h 95°, 85%
(+)-12
46.7% ee
(+)-isomer
Me
N
PPh2
N
Ph
13
Ph
Pd2dba3, PMP, DMA
16h 95°, 17%
(-)-12
20.5% ee
(-)-isomer
(S)-BINAP, Pd2dba3, PMP, DMA
16h 95°, 90%
(+)-12, 28.9%ee
(S)-BINAP, Pd2dba3, PMP, anisole
16h 95°, 80%
(+)-12, 14.6%ee
(S)-t-Bu-phosphinooxazoline,
Pd2dba3, PMP, anisole
16h 95°, 20%
(+)-12, 46.3%ee
(S)-t-Bu-phosphinooxazoline,
Pd2dba3, PMP, DMA
16h 95°, 47%
(+)-12, 14.9%ee

Scheme 4

A 10ml headspace vial was charged with 11.4mg Pd_2dba_3 (0.0125 mmol, 0.05 eq.), 19.1mg ligand **14** (0.0275 mmol, 0.11 eq.) and 1.5ml Ph_2O. The resulting solution was evacuated/filled with Ar (3X), then placed in a preequilibrated 50° oil bath for 1 hour. To the resulting solution was then added a solution of triflate **11** (98mg, 0.25 mmol, 1 eq.), pentamethylpiperidine (PMP, 181 microliters, 1.00 mmol, 4 eq.) and 1.0 ml Ph_2O via syringe, at once. The resulting solution was heated 16h at 95°, cooled, and chromatographed directly on silica gel eluting with 4:1 hexane:ethyl acetate to give 51mg of spirolactam **12** (85% yield). Analysis of this material by chiral HPLC using a Chiracel OD column, 250mm X 4.6mm, using 99:1 Hexane:IPA at a flow rate of 1.0 ml/minute, revealed the enantiomeric excess of the product to be 46.7%, that is, 46.7%ee. The enantiomer obtained with this ligand, where R1 was an electron withdrawing group, was the (+)-isomer. When the reaction was repeated with ligand **13**, where R1= methyl, an electron donating group, *the opposite enantiomer*, the (-)-isomer, was obtained, in 20.5%ee. Although this initial method is not yet fully optimized, the concept of controlling enantioselectivity by electronic tuning of the R1 substituent is clearly validated. When commercial (S)-BINAP was examined for this transformation, the product obtained, (+)-**12**, using Ph_2O as solvent, was formed in 90% yield, yet only 14.6%ee, while in dimethylacetamide as solvent, the yield was 80%, and the observed enantiomeric excess was only 28.9%ee. When the (S)-t-butyl phosphinooxazoline of Pfaltz/Helmchen/Williams was used in anisole, the isolated yield of (+)-**12** was only 20%, and the observed enantiomeric excess was 46.3%ee. When that ligand was used in dimethylacetamide, the isolated yield was higher, 47%, yet the enantiomeric excess was only 14.9%ee. Table 1, shows results for 18 of the new ligands when evaluated in the asymmetric Heck reaction.

L_2^* =



M=P for all examples

B= imidazoline for all examples

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Table 1. Ligands Evaluated for the Asymmetric Heck Reaction.

Entry	R1	R2,R3	X,Y,Z	Solvent	Yield	%ee	MI*
1	Acetyl	(S,S)-diphenyl	X=Y=Z=H	Anisole	68%	31.2	1, (+)
2	Benzoyl	(S,S)-diphenyl	X=Y=Z=H	Anisole	60%	36.0	1, (+)
3	Benzoyl	(S,S)-diphenyl	X=Y=Z=H	Ph_2O	76%	42.2	1, (+)
4	Benzoyl	(S,S)-diphenyl	X=Y=Z=H	p-Dioxane	66%	47.1	1, (+)
5	p-phenyl-benzoyl	(S,S)-diphenyl	X=Y=Z=H	Ph_2O	73%	40.5	1, (+)
6	Methyl	(S,S)-diphenyl	X=Y=Z=H	DMA	17%	20.5	2, (-)
7	p-methoxybenzoyl	(S,S)-diphenyl	X=Y=Z=H	Anisole	60%	33.4	1, (+)
8	p-methoxybenzoyl	(S,S)-diphenyl	X=Y=Z=H	Ph_2O	27%	47.6	1, (+)
9	p-cyanobenzoyl	(S,S)-diphenyl	X=Y=Z=H	Ph_2O	83%	36.6	1, (+)
10	1-napthoyl	(S,S)-diphenyl	X=Y=Z=H	Ph_2O	85%	40.6	1, (+)
11	2-napthoyl	(S,S)-diphenyl	X=Y=Z=H	Ph_2O	68%	44.6	1, (+)
12	t-butoxycarbonyl (BOC)	(S,S)-diphenyl	X=Y=Z=H	Ph_2O	92%	32.5	1, (+)
13	p-methoxybenzoyl	(S,S)-di-(m-xylyl)	X=Y=Z=H	Ph_2O	88%	41.8	1, (+)
14	2-napthoyl	(S,S)-di-(m-xylyl)	X=Y=Z=H	Ph_2O	85%	46.7	1, (+)
15	p-methoxybenzoyl	(S,S)-diphenyl	X=Y=H; Z=benzo fused (napthalene)	Ph_2O	8%	35.3	1, (+)

16	**p-methoxybenzoyl**	**(R,R)-di-(p-methoxyphenyl)**	**X=Y=Z=H**	**Ph_2O**	**20%**	**33.4**	**2, (-)**
17	**p-dimethylamino benzoyl**	**(R,R)-diphenyl**	**X=Y=Z=H**	**Ph_2O**	**25%**	**37.0**	**2, (-)**
18	**Acetyl**	**(R,R)-cyclohexyl**	**X=Y=Z=H**	**Anisole**	**10%**	**29.2**	**1, (+)**

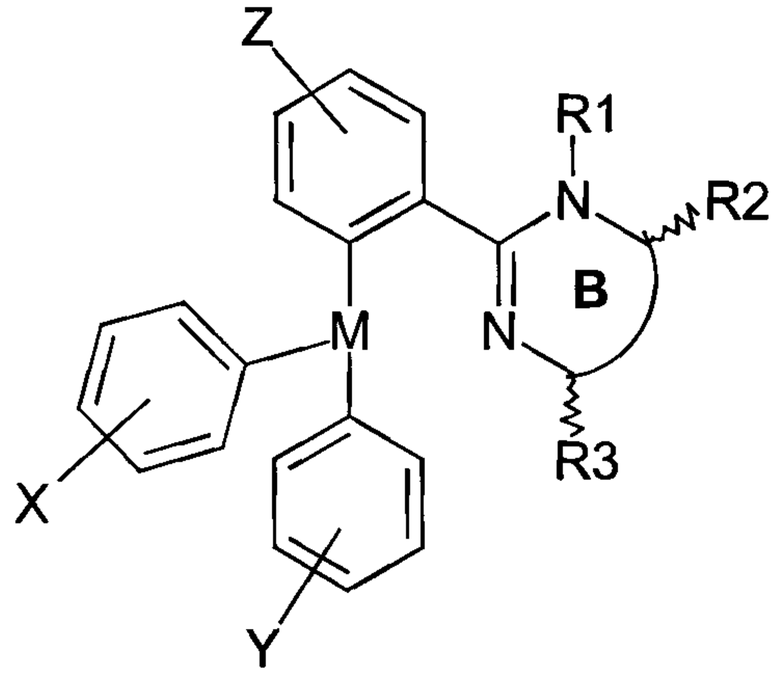
*MI= Major Isomer: 1= first eluted, (+)-isomer; 2= second eluted, (-)-isomer.
Notes: 1) All reactions at 100°C unless otherwise noted. 2) All ee's determined by chiral HPLC (see "Typical use of the invention in asymmetric synthesis" (Scheme 4) section). 3) M=P for all ligands. 4) B ring = imidazoline (5 membered ring) for all ligands 5) X=Y=H for all ligands 6) Z=H for all ligands except entry 15 where Z= fused benzo ring (naphthalene) 7) All yields are for isolated, chromatographically pure 12.

While in the foregoing description the detailed embodiments of the present invention have been set forth, it will be understood by those skilled in the art that considerable variation may be made in such detail without departing from the spirit of the invention.

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CLAIMS:

1. A compound of Formula (1)



(1)

wherein:

M is Phosphorous or Arsenic;

X, Y and Z are independently selected from hydrogen, alkyl, aryl wherein the aryl is pendant or fused, halogen, C_{1-10}-alkoxy, cyano, nitro, amino, alkylamino, dialkylamino, $-CO_2H$, -CO(lower alkoxy), -CO(lower alkyl), -NCOH, -NCO(lower alkyl), NSO_2(alkyl), $-NSO_2$(aryl), hydroxy, sulfonoxyalkyl, sulfonoxyaryl, and alkoxyalkyl;

R1 is hydrogen, C_{1-10}-alkyl, branched alkyl, cycloalkyl; phenyl, naphthyl, substituted phenyl or naphthyl, wherein the substituents are as defined below for aryl; heteroaryl or substituted heteroaryl comprising one or more heteroatoms independently selected from nitrogen, oxygen and sulfur; acyl, aroyl, substituted aroyl,

heteroaroyl, substituted heteroaroyl, or SO_2R4 where R4 is selected from the group consisting of alkyl, aryl, heteroaryl, substituted aryl and substituted heteroaryl groups in direct attachment;

R2 and R3 are the same or different and are hydrogen, aryl as defined above for X, Y and Z or heteroaryl as defined above for R1; substituted aryl or heteroaryl as defined below; alkyl, branched alkyl, cycloalkyl, benzyl or substituted benzyl, with substituents as defined for aryl below, or R2 and R3 together form a fused carbocyclic ring;

Ring B is an imidazoline ring or a tetrahydropyrimidine ring;

and at least one, or both, of R2 and R3 must be attached to a chiral carbon, of either (R) or (S) absolute configuration;

wherein aryl, heteroaryl, aroyl and heteroaroyl groups are optionally substituted by one or more substituent independently selected from the group consisting of alkyl, halogen, alkoxy, acyl, phenoxy, cyano, nitro, hydroxy, amino, alkylamino, dialkylamino, carboalkoxy, keto, amido, and sulfoxy.

2. The compound of claim 1, wherein the aryl, heteroaryl, aroyl and heteroaroyl groups are optionally substituted by one or more substituent independently selected from the group consisting of alkyl, halogen, alkoxy, phenoxy, cyano, nitro, hydroxy, amino, alkylamino, dialkylamino, carboalkoxy, keto, amido, and sulfoxy.

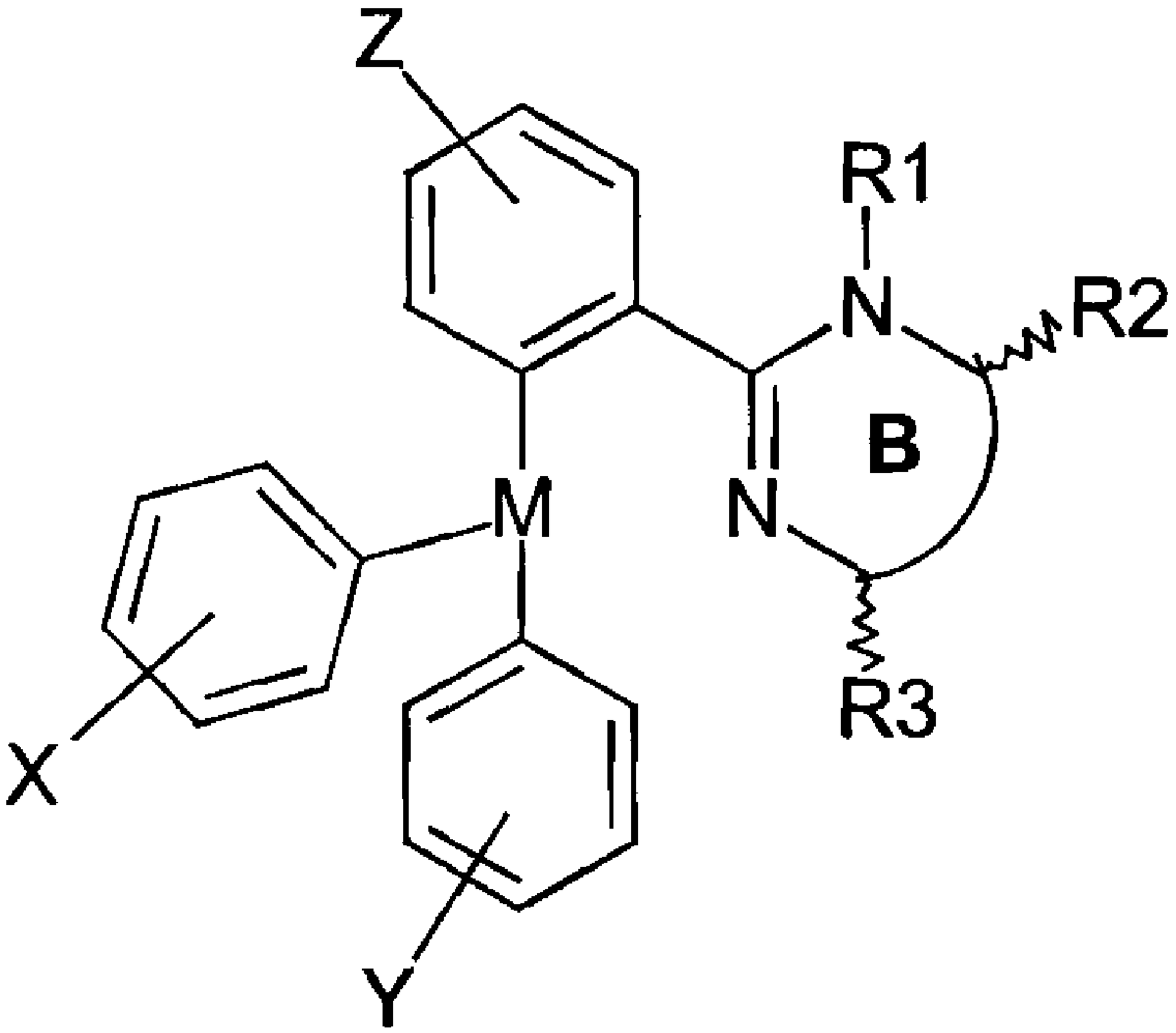
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3. The compound of claim 1, wherein R1 is heteroaryl selected from the group consisting of 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 2-benzofuryl, 3-benzofuryl, 2-thiophenyl, 3-thiophenyl, 2-benzothiophenyl, 3-benzothiophenyl, 2-pyrrolyl, 3-pyrrolyl, 2-indolyl, 3-indolyl, benzimidazolyl, imidazolyl, quinolinyl, isoquinolinyl, oxazolyl, benzoxazolyl, thiazolyl, and pyrimidinolyl, which is optionally substituted with one or more substituents independently selected from alkyl, halogen, alkoxy, acyl, phenoxy, cyano, nitro, hydroxy, amino, alkylamino, dialkylamino, carboalkoxy, amido, and sulfoxy.

4. The compound of claim 1, wherein R1 is aroyl selected from benzoyl and napthoyl, optionally substituted with one or more substituents as defined in claim 1.

5. The compound of claim 1, wherein R1 is heteroaroyl selected from the group consisting of 2-furoyl, 3-furoyl, 2-pyridoyl, 3-pyridoyl, 4-pyridoyl, 2-benzofuranoyl, 3-benzofuranoyl, 2-thiophenoyl, 3-thiophenoyl, 2-benzothiophenoyl, 3-benzothiophenoyl, 2-pyrroyl, 3-pyrroyl, 2-indoloyl, 3-indoloyl, benzimidazoyl, imidazoyl, quinolinoyl, isoquinolinoyl, oxazoyl, benzoxazoyl, thiazoyl, and pyrimidoyl optionally substituted with one or more substituents selected from the group of substituents defined in claim 3.

6. Use of a compound as defined in any one of claims 1 to 5, wherein the compound is complexed with a transition metal, in isolating a specific enantiomer from a mixture of enantiomers.



(1)