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The Preparation, Resolution and Chemistry of 1-(3,6-Dimethylpyrazin-2-yl)(2-naphthyl)diphenylphosphine, an Axially Chiral Phosphinamine.#

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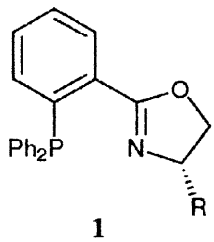
Abstract. A five step synthesis of the title compound in good yield is described. The biaryl linkage was formed in a Pd-catalysed coupling of 2-chloro-3,6-dimethylpyrazine **10** with 2-methoxy-1-naphthylboronic acid **9**. Demethylation of the product ether **11** afforded alcohol **12** which was converted into the corresponding triflate **13** by treatment with triflic anhydride. A Ni-catalysed phosphinylation gave the required phosphinamine ligand **7** as a racemate. Diastereomeric palladacycles **16**, formed from **7** and (+)-di-μ-chlorobis[(*R*)-dimethyl(1-(1-naphthyl)ethyl)aminato-C_2,N]dipalladium (II) **15** were separated, after considerable effort, to give diastereomerically pure **7**. Displacement of the resolving agent by reaction with 1,2-bis(diphenylphosphino)ethane gave enantiopure **7**. At ambient temperature this ligand was found to racemise.

Introduction.

Systematic changes in the ligand surrounding the metal template is one of the most studied variables in enantioselective metal-catalysed transformations.[1] Recently, interest in heterobidentate ligands, in particular, those ligands in which the donor atoms are phosphorous and nitrogen has increased.[2] The chirality of phosphinamine ligands may be due to an asymmetric phosphorus atom or, more commonly, to an asymmetric carbon centre on the backbone tethering the two donor atoms. The latter class of ligands may be classified into three groups, those possessing a chiral carbon centre, planar chirality, or axial chirality. The diphenylphosphinooxazolines **1** are typical examples of the first classification as they possess a chiral centre at position-4 which is readily varied as the oxazoline unit is synthesised from α-amino alcohols.[3] Phosphinamines possessing planar chirality were first prepared by Kumada and (S)-*N,N*-dimethyl-1-[(*R*)-2-(diphenylphosphino) ferrocenyl]ethylamine [(*S*)-(*R*)-PPFA] **2** is a typical example.[4] Many variations have subsequently been prepared and applied and this has been the subject of a recent excellent review.[5]



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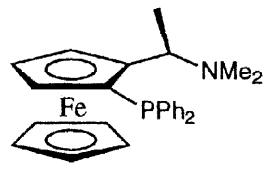
R = Bn, *i*-Pr, *t*-Bu, etc.



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#Dedicated with respect and admiration to my colleague and PhD supervisor Professor Dervilla Donnelly.

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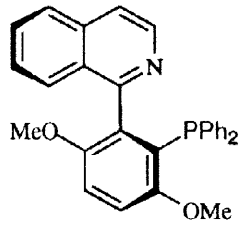
To date, surprisingly few axially chiral phosphinamine ligands have been reported and the group of Brown has been at the forefront in their design, preparation and application of their metal complexes in asymmetric catalysis. The initial example was 1-(2-diphenylphosphino-3,6-dimethoxyphenyl)isoquinoline **3** which was found to racemise with a half-life of 1 h at ambient temperature.[6]



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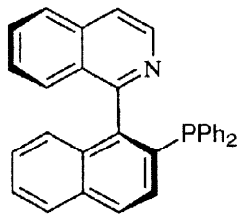

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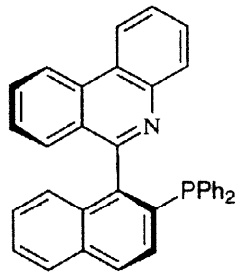

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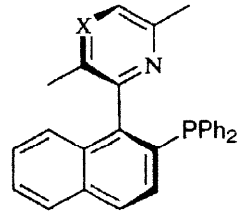


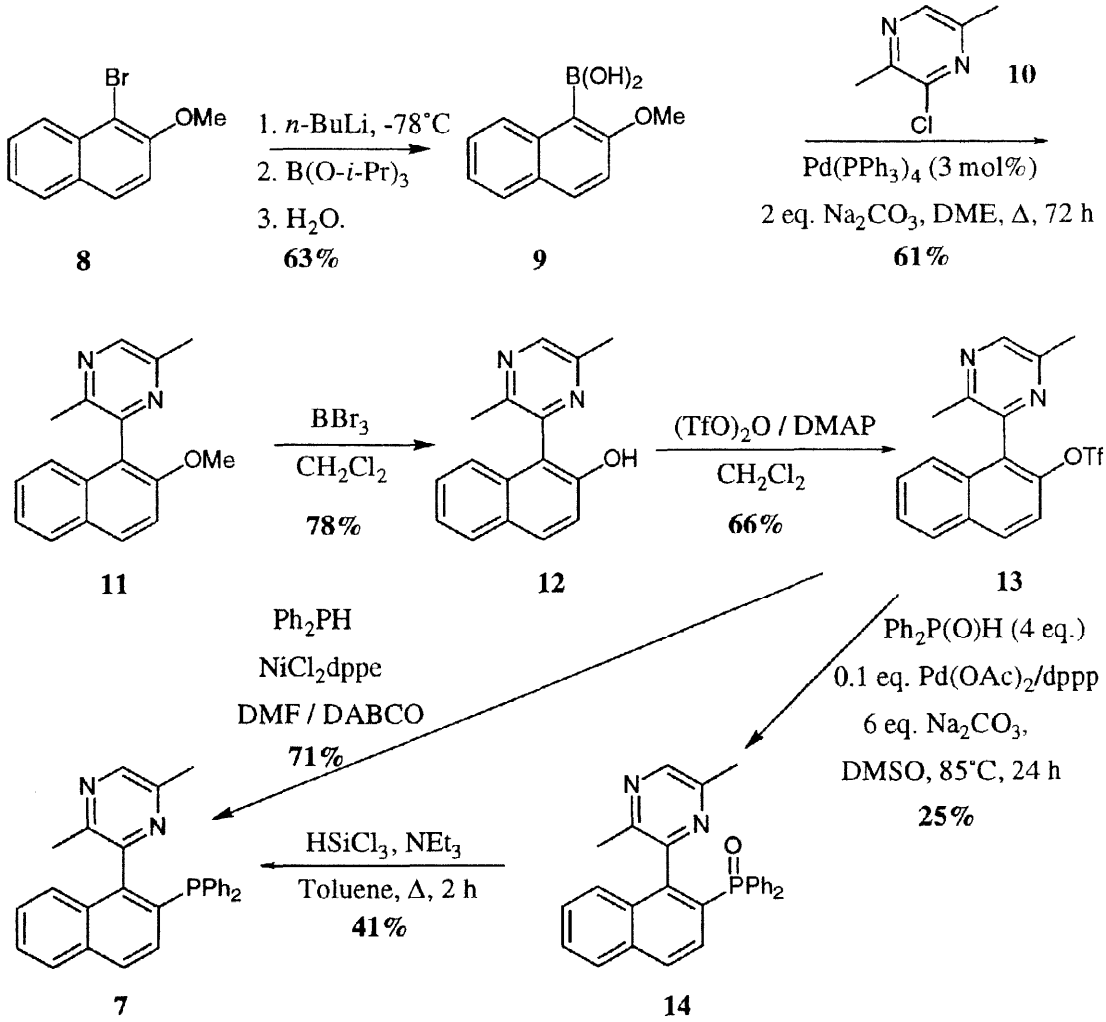
6: X = C; **7**: X = N.

Subsequently, Quinap **4** was prepared,[7] resolved[8] and applied with success in rhodium-catalysed hydroboration (up to 95% ee)[9] and palladium-catalysed allylic substitution (up to 98% ee).[10] It became apparent during a mechanistic investigation of the latter process, both from solution ^{1}H NMR and solid state studies, that the 3-H of the isoquinoline unit takes up a position in space leading to crucial ligand-reactant steric interactions which could be important for asymmetric induction. This observation led to the design principle behind the preparation of the vaulted analogue Phenap **5**, which in turn gave high enantioselectivities in rhodium-catalysed hydroboration[11] and palladium-catalysed allylic substitution (91 and 95%, respectively).[12] Systematic variation at this 3-position of the isoquinoline is possible but the preparation of 1-chloro-3-substituted isoquinolines is a limiting factor. We had encountered problems in accessing key chlorinated pyridine starting materials for ligand **6**.[13] For this reason we investigated the possibility of preparing axially chiral phosphinamine ligands composed of a naphthyldiphenylphosphine 'half' and a substituted pyrazine 'half', as chlorinated pyrazines are more accessible. The impetus to prepare the 3,6-dimethylpyrazine-containing ligand **7** was to determine the effect on enantioselection of the 6-methyl group and to investigate the enantiomeric stability given by the interaction of the naphthyl group and the 3-methyl group. In addition, the basicity of the nitrogen donor atom in **7** is considerably different to that of Quinap **4**. We now report the synthesis and resolution of **7** in addition to a preliminary investigation of its chemistry.[14]

Ligand Preparation.

The overall approach chosen for the preparation of **7** is similar to that previously reported for both Quinap and Phenap with the key steps being the metal-catalysed reactions of biaryl coupling and formation of the naphthyl-phosphorous bond. The nucleophilic component of the Pd-catalysed biaryl coupling, 2-methoxy-1-naphthylboronic acid **8**, was prepared from the organolithium reagent derived from 1-bromo-2-methoxynaphthalene **9**, and reaction with tri-*iso*-propylborate in THF at -78°C, Scheme 1. The use of tri-*iso*-propylborate was preferred to trimethylborate[10] giving a yield of 63% on a small scale (5 g) and up to 80% on a larger scale (20 g). Purification of the boronic acid, formed after aqueous work-up and standard extraction into diethyl ether, was aided by stirring the crude material in pentane for 2 h to remove impurities. The electrophilic component, 3-chloro-2,5-dimethylpyrazine **10**, was used as 2-chloropyrazines are known to undergo

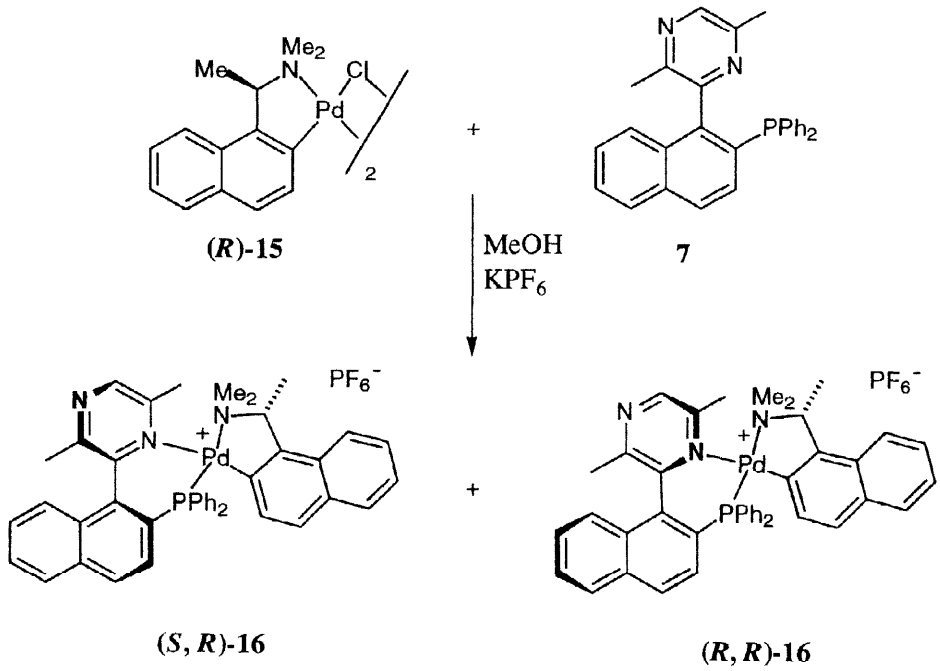
palladium-catalysed cross-coupling reactions.[15] The coupling was catalysed by 3 mol % of tetrakis(triphenylphosphine)palladium in dimethoxyethane at reflux in the presence of aqueous 2 M sodium carbonate and gave the pyrazinyl ether **11** in 61% yield. Boron tribromide promoted demethylation in dichloromethane afforded the pyrazinyl alcohol **12** in 78% yield. Treatment of this alcohol with trifluoromethanesulfonic anhydride in the presence of 4-dimethylaminopyridine gave in 66% yield the pyrazinyltrifluoromethanesulfonate **13**, the key electrophilic component for the final coupling for C-P bond formation. Few procedures exist for this transformation and our initial attempts looked at the established reaction of diphenylphosphine oxide with aryl trifluoromethanesulfonates catalysed by palladium acetate and 1,2-bis(diphenylphosphino)propane in dimethyl sulfoxide in the presence of base.[16] After refluxing for 24 h the aryldiphenylphosphine oxide **14** was formed in a low yield of 25%. Subsequent reduction used the standard conditions of refluxing **14** with trichlorosilane and triethylamine in toluene for 2 h gave the required pyrazinyldiphenylphosphine **7** in a disappointing 41% yield. Prior to this study an alternative nickel-catalysed procedure to convert aryl trifluoromethanesulfonates directly into aryl diphenylphosphines was reported by Cai.[17] Application of this protocol allowed us to access **7** directly from **13** in a more favourable 71% yield.



Scheme 1.

Ligand Resolution.

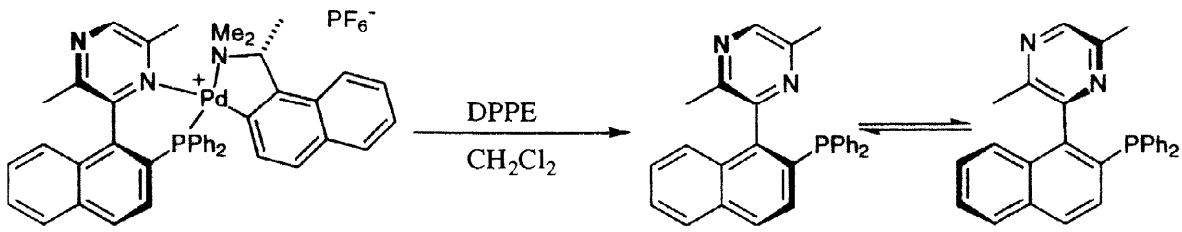
The resolution of bidentate ligands has been widely studied and *ortho*-palladated derivatives of (*R*)-dimethyl(1-phenylethyl)amine[18] and, more recently and with wider applicability, (*R*)-dimethyl(1-(1-naphthyl)ethyl)amine[19] have proved to be useful resolving agents. Since phosphinamine **7** was structurally related to Quinap **4** and Phenap **5**, our initial resolution attempts focused on the preparation and separation of diastereomeric complexes derived from **7** and (+)-di-μ-chlorobis[(*R*)-dimethyl(1-(1-naphthyl)ethyl)aminato-C_2,N]dipalladium (II) **15**, the latter being a successful resolving agent in the resolution of **4** and **5**, Scheme 2.



Scheme 2.

In the present study the phosphinamine **7** was stirred in methanol for 4 h and the diastereomeric products (*S*,*R*)-**16** and (*R*,*R*)-**16** were precipitated by the addition of KPF_6. A pale yellow solid was isolated after filtration and was shown by ^1H NMR to be a 1:1 mixture of diastereomers. The key resonances which confirm this are associated with the benzylic methines which for one diastereomer appear as a quintet at 4.46 ppm and for the other at 4.16 ppm. The ^{31}P NMR spectrum shows two peaks, one at 37.3 ppm and the other at 39.5 ppm, again integrating for a 1:1 mixture. The separation of this diastereomeric pair was attempted by fractional crystallisation. A series of solvents and solvent mixtures were investigated and two fractional crystallisations from propan-2-ol (entry 8) gave diastereomerically pure (*S*,*R*)-**16**, the more stable diastereomer in very small amounts from the filtrate (typically 5-10 % yield).

Once resolved, the free (*S*)-**7** ligand was generated by the adding 1,2-bis(diphenylphosphino)ethane to (*S*,*R*)-**16** in dichloromethane at room temperature over 2 h, Scheme 3. The optical activity of the free ligand was found to be $[\alpha]_D^{23}$ -97.3 (*c* 1.35, chloroform) but this decreased to zero on standing in solution. Attempts to carry out detailed racemisation studies were hampered by low yields of diastereomerically pure material and a study to obtain an accurate half-life (estimated at between 2 and 7 days) is in progress.



(*S*, *R*)-**16** (*S*)-**7** (*R*)-**7**

Scheme 3.

The difficulty in isolating diastereomerically pure (*S*,*R*)-**16** in workable quantities and the demonstrated racemisation of ligand **7** means that it is of little use in asymmetric catalysis. This suggests that the 3-methyl group is insufficiently large to prevent racemisation. However, it is itself of interest to determine the required size of substituents in this series to prevent racemisation. A related series of pyridinylphenols **17** and **18** have been recently prepared by the group of Chan and found to be optically stable and applicable in asymmetric catalysis.[20] In the former compound the clash is between a methyl and a *t*-butyl group whilst in the latter the clash is between two methyl groups, Fig. 2.

17 **18**

Fig. 2.

In conclusion, we have prepared a new axially chiral phosphinamine ligand in good yield using metal-catalysed transformations in the two key steps. It was resolved *via* fractional crystallisation of its diastereomeric palladium salts. Its application in asymmetric catalysis is precluded as it was found to racemise at room temperature. Further work will be disclosed on the preparation of related axially chiral ligands which have been successfully applied in asymmetric catalysis.[21]

Acknowledgements.

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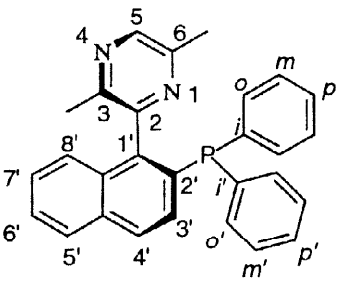
Experimental

General. NMR spectra were recorded on a Jeol 270 MHz or a Varian Unity 500 MHz spectrometer. ^{1}H chemical shifts are reported in δ ppm relative to $CHCl_3$ (7.27 ppm), ^{13}C chemical shifts are reported relative to

the central peak of $CDCl_3$ (77.0 ppm), and ^{31}P chemical shifts are reported relative to 85% aqueous phosphoric acid (0.0 ppm). Elemental microanalyses were carried out in house using a Carlo Erba 1106 elemental analyser. Electron impact mass spectra were determined on a VG Analytical 770 mass spectrometer with attached INCOS 2400 data system in the EI mode unless otherwise stated. Electrospray mass spectra were recorded on a VG (Micromass) Quattro with electrospray probe. IR spectra were recorded on a Perkin Elmer Paragon 1000 FT spectrometer. Optical rotations were recorded on a Perkin Elmer 241 polarimeter. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected.

Solvents were dried immediately before use by distillation from standard drying agents and subjected to degassing by three freeze-thaw cycles. Tri-*iso*-propylborate, 3-chloro-2,5-dimethylpyrazine, boron tribromide, diphenylphosphine, 1,2-bis(diphenylphosphino)propane, trichlorosilane and [1,2-bis(diphenylphosphino) ethane]dichloronickel(II) were commercially available (Aldrich Chemical Co.) and were used as purchased. *n*-Butyllithium was used as a 1.6M solution in hexane. Pd salts were obtained on loan from Johnson Matthey. 1-Bromo-2-methoxynaphthalene,[22] (*R*)-dimethyl(1-(1-naphthyl)ethyl)amine,[23] and diphenylphosphine oxide[24] were prepared by literature procedures. Separations by column chromatography was performed using Merck Kieselgel 60 (Art. 7734). For ease of interpretation of NMR data the following numbering scheme is used for ligand **7** and related compounds are numbered similarly.



1-(3,6-Dimethylpyrazin-2-yl)-2-methyloxynaphthalene (11)

3-Chloro-2,5-dimethylpyrazine (2.80 g, 19.7 mmol) was added *via* syringe to a solution of tetrakis (triphenylphosphine)palladium (0.68 g, 0.59 mmol) in DME (40 ml) and stirred for 10 min under nitrogen. 2-Methoxy-1-naphthylboronic acid (3.97 g, 19.7 mmol), dissolved in the minimum amount of ethanol, was added. Sodium carbonate solution (19.7 ml, 2 M) was added and the solution was refluxed for 48 h. The solution was allowed to cool and the solid filtered off. The solid was washed with dichloromethane and the solvent was removed to give a brown oil which was dissolved in dichloromethane (30 ml), washed with saturated brine (2 x 15 ml), and dried with sodium sulfate. Removal of the solvent *in vacuo* gave a brown oil which was purified by silica gel column chromatography (petroleum ether / ethyl acetate 2:1) yielding 1-(3,6-dimethylpyrazin-2-yl)-2-methyloxynaphthalene (3.14 g, 61 %), as a yellow solid, m.p. 118-119°C. ^1H NMR (500 MHz): δ ($CDCl_3$) 8.40 (s, 1H, $H_{5'}$), 7.92 (d, 1H, J = 8.8 Hz, H_4), 7.82 (m, 1H, H_7), 7.35-7.32 (m, 3H, H_3 + H_6 + H_8), 7.12 (m, 1H, H_5), 3.83 (s, 3H, OCH_3), 2.60 (s, 3H, CH_3), and 2.26 (s, 3H, CH_3); ^{13}C NMR (125.7 MHz): δ ($CDCl_3$) 154.2 (C_2), 151.1 (4°C), 150.4 (4°C), 150.2 (4°C), 142.2 ($C_{5'}$), 132.9 (C_9), 130.6 (C_4), 129.2 (C_{10}), 128.2 (C_7), 127.0 (C_8), 124.0 (C_5), 123.7 (C_6), 121.1 (C_1), 113.1 (C_3), 56.3 (OCH_3), 21.2 (CH_3), and 21.1 (CH_3); ν_{max} (KBr) 1622 (m) (Ar-H), 1604 (m) (Ar-H), 1509 (m) (Ar-H), 1276 (s) (C-O), 1253 (s) (C-O), 839 (m) (Ar-H), and 768 (m) (Ar-H) cm^{-1}; m/z (eims 70eV) 264 (M^+, 100 %), 263 (74), 233 (22) and 206 (13); HRMS (eims 70eV): M^+, found 264.1250. $C_{17}H_{16}N_2O$ requires 264.1263.

1-(3,6-Dimethylpyrazin-2-yl)naphthalen-2-ol (12)

Boron tribromide (2.60 g, 10.35 mmol) was added slowly *via* syringe to a solution of 1-(3,6-dimethylpyrazin-2-yl)-2-methyloxynaphthalene (1.37 g, 5.18 mmol) in dry dichloromethane (22 ml). The initial yellow-coloured solution turned dark purple and was allowed to stir at room temperature overnight. Water (11 ml) was added cautiously, white fumes were evolved and a yellow precipitate formed. The mixture was stirred for 1 h, then the solid was collected by filtration. The aqueous layer was neutralised with sodium hydroxide solution and extracted with dichloromethane. Aqueous hydrochloric acid (10%) was stirred with the dichloromethane extracts. The dichloromethane extracts were reduced *in vacuo* giving a yellow oil. The yellow oil and solid were stirred with dichloromethane (5 ml) and sodium carbonate solution (2 ml, 2 M) to give a pale pink solution. The organic phase was separated, and the aqueous phase washed with more dichloromethane (10 ml). The combined organic extracts were reduced *in vacuo* leaving a solid which was recrystallised from chloroform to give 1-(3,6-dimethylpyrazin-2-yl)naphthalen-2-ol (1.25 g, 78 %) as a white solid, m.p. 198-200°C. ^{1}H NMR (500 MHz): δ ($CDCl_3$) 8.39 (s, 1H, $H_{5'}$), 7.78 (d, 1H, J = 8.0 Hz, H_7), 7.65 (d, 1H, J = 8.83 Hz, H_4), 7.38-7.31 (m, 2H, H_6 + H_8), 7.12 (d, 1H, J = 8.21 Hz, H_5), 6.98 (d, 1H, J = 8.84 Hz, H_3), 2.54 (s, 3H, CH_3), and 2.26 (s, 3H, CH_3); ^{13}C NMR (125.7 MHz): δ ($CDCl_3$) 152.4 (C_2), 151.7 (4°C), 150.3 (4°C), 149.6 (4°C), 142.5 ($C_{5'}$), 132.3 (C_9), 130.9 (C_4), 128.9 (C_{10}), 128.4 (C_7), 127.0 (C_8), 123.7 (C_5), 123.6 (C_6), 118.9 (C_3), 117.1 (C_1), 21.7 (CH_3), and 20.9 (CH_3); ν_{max} (KBr) 3560 (br.) (O-H), 1621 (m) (Ar-H), 1596 (m) (Ar-H), 1515 (m) (Ar-H), and 883 (m) (Ar-H) cm^{-1}; m/z (eims, 70eV) 250 (M^+, 76%), 249 (100), 235 (60), 152 (7), 88 (2), and 76 (6); HRMS (eims 70eV): M^+, found 250.1155. $C_{16}H_{14}N_2O$ requires 250.1106.

1-(3,6-Dimethylpyrazin-2-yl)-2-naphthyl(trifluoromethyl)sulfonate (13)

Trifluoromethane sulphonic anhydride (4.7 g, 16.7 mmol) was added dropwise from a glass syringe with stirring to a solution of 1-(3,6-dimethylpyrazin-2-yl)naphthalen-2-ol (3.8 g, 15.2 mmol) and 4-dimethylamino pyridine (5.56 g, 45.6 mmol) in dry dichloromethane (60 ml). The resulting black solution was left stirring overnight. The solution was washed with 1 M hydrochloric acid (3 x 70 ml), water (2 x 70 ml) and saturated brine (2 x 70 ml). The organic layer was dried with magnesium sulfate, the solvent removed *in vacuo* leaving crude 1-(3,6-dimethylpyrazin-2-yl)-2-naphthyl(trifluoromethyl)sulfonate as a black oil. This was purified by column chromatography on silica gel (petroleum ether / ethyl acetate 1:1) to afford 1-(3,6-dimethylpyrazin-2-yl)-2-naphthyl(trifluoromethyl)sulfonate as an orange oil which crystallised on standing (3.82 g, 66%), m.p. 68-70°C. Found: C, 53.5; H, 3.4; N, 7.2. $C_{17}H_{13}N_2O_3SF_3$ requires C, 53.4; H, 3.5; N, 7.2 %; ^{1}H NMR (500 MHz): δ ($CDCl_3$) 8.52 (s, 1H, $H_{5'}$), 8.04 (d, 1H, J = 9.2 Hz, H_4), 7.97 (d, 1H, J = 8.4 Hz, H_8), 7.60 (dt, 1H, J = 7.0 Hz, H_6), 7.53 (d, 1H, J = 9.2 Hz, H_3), 7.52 (dt, 1H, J = 7.0 Hz, H_7),7.35 (d, 1H, J = 8.4 Hz, H_5), 2.63 (s, 3H, CH_3), and 2.29 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz): δ ($CDCl_3$) 151.1 (4°C), 150.7 (4°C), 146.5 (4°C), 144.5 (4°C), 143.7 ($C_{5'}$), 132.6 ($C_{9'}$), 132.0 ($C_{10'}$), 131.4 (C_4), 128.7 (C_1), 128.5 (C_8), 128.2 (C_7), 127.3 (C_6), 125.6 (C_5), 119.6 (C_3), 117.0 (4°C), 21.2 (CH_3), and 21.0 (CH_3); ν_{max} (KBr) 2964 (w) (Ar-H), 1511 (w) (Ar-H), 1415 (s) (-SO_3-), 1210 (s) (-SO_3-), 1137 (s) (C-O), 945 (s) (Ar-H), 839 (s) (Ar-H), 810 (s) (Ar-H), and 750 (s) (Ar-H) cm^{-1}; m/z (eims, 70eV) 382 (M^+, 36%), 313 (2), 249 (100), 233 (5), 221 (19), 206 (3), 194 (20), 150 (10), and 76 (12).

[1-(3,6-Dimethylpyrazin-2-yl)(2-naphthyl)]diphenylphosphino-1-one (14)

1-(3,6-Dimethylpyrazin-2-yl)-2-naphthyl (trifluoromethyl)sulfonate (0.400 g, 1.05 mmol), diphenylphosphine oxide (0.883 g, 4.37 mmol), 1,2-bis(diphenylphosphino)propane (0.045 g, 0.109 mmol), palladium acetate (0.025 g, 0.109 mmol) and sodium carbonate (0.55 g, 6.55 mmol) were added as solids to a Schlenk tube against a nitrogen counterflow . Dimethly sulfoxide (4.4 ml) was added *via syringe*. The flask was heated for

24 h at 85°C, and a precipitate formed. The suspension was allowed to cool to room temperature, added to dichloromethane (25 ml), washed with water (2 x 25 ml), [the precipitate dissolved on addition of water], saturated sodium carbonate solution (25 ml), water (2 x 25 ml) and saturated brine (25 ml). The organic layer was dried with magnesium sulfate and the solvent removed *in vacuo* to give a white solid. A short silica column was run to remove impurities, the required product remained on the baseline which was then eluted to give after solvent removal [1-(3,6-dimethylpyrazin-2-yl)(2-naphthyl)]diphenylphosphino-1-one as a white crystalline solid (0.112 g, 25%), m.p. 174-176°C. ^{1}H NMR (500 MHz): δ ($CDCl_3$) 8.19 (s, 1H, $H_{5'}$), 7.96-7.91 (m, 2H, H_4 + H_8), 7.81-7.75 (m, 2H, *o*-Ph), 7.68 (dd, 1H, $J_{H,H}$ = 8.8 Hz, $J_{P,H}$ = 11.4 Hz, H_3), 7.58 (t, 1H, J = 7.5 Hz, *p*-Ph), 7.54 (t, 1H, J = 7.5 Hz, H_6), 7.49-7.39 (m, 6H, *m*+*o*+*p*-Ph, H_7), 7.31 (dt, 2H, $J_{H,H}$ = 7.7 Hz, $J_{P,H}$ = 2.9 Hz, *m*-Ph), 7.11 (d, 1H, J = 8.4 Hz, H_5), 2.21 (s, 3H, CH_3), and 2.16 (s, 3H, CH_3); ^{31}P NMR (101.3 MHz): δ ($CDCl_3$) 29.6; ν_{max} (KBr) 1629 (w) (Ar-H), 1438 (w) (PPh), 1138 (m) (P=O), 750 (m) (Ar-H), 723 (m) (Ar-H), and 693 (m) (Ar-H) cm^{-1}; m/z (eims, 70eV) 434 (M^+, 27%), 433 (51), 233 (12), 126 (3), and 77 (26); HRMS (eims 70eV): M^+, found 434.1541. $C_{28}H_{23}N_2OP$ requires 434.1548.

(±)-[1-(3,6-Dimethylpyrazin-2-yl)(2-naphthyl)]diphenylphosphine (7)

[1-(3,6-Dimethylpyrazin-2-yl)(2-naphthyl)]diphenylphosphino-1-one (0.200 g, 0.46 mmol) was dissolved in toluene (18 ml) in a Schlenk tube under a nitrogen atmosphere. Trichlorosilane (0.494 ml, 4.89 mmol) was added to the yellow solution, followed by triethylamine (0.61 ml, 4.36 mmol) and white fumes were evolved. The solution was refluxed for 2 h. The solution was then cooled to 0°C and 2 N sodium hydroxide solution (20 ml) was added cautiously with vigorous stirring. The layers were separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried with magnesium sulfate and the solvent removed *in vacuo* to give a brown oil which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 2:1) to give (±)-[1-(3,6-dimethylpyrazin-2-yl)(2-naphthyl)]diphenylphosphine as a white solid (0.078 g, 41%), m.p. 163-164°C. ^{1}H NMR (500 MHz): δ ($CDCl_3$) 8.38 (s, 1H, $H_{5'}$), 7.84 (d, 1H, J = 7.9 Hz, H_4), 7.81 (d, 1H, J = 8.2 Hz, H_8), 7.48 (dt, 1H, $J_{P,H}$ = 1.22 Hz, $J_{H,H}$ = 7.0 Hz, *o*-Ph), 7.37 (dt, 1H, $J_{P,H}$ = 1.22 Hz, $J_{H,H}$ = 8.5 Hz, *o*-Ph), 7.32-7.21 (m, 11H, Ar-H), 7.17 (d, 1H, J = 8.5 Hz, H_5), 2.35 (s, 3H, CH_3), and 2.20 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz): δ ($CDCl_3$) 152.5 (d, $J_{P,C}$ = 6.2 Hz, $C_{2'}$), 150.26 ($C_{3'}$), 150.2 ($C_{6'}$), 150.1 (4°C), 142.9 (d, $J_{P,C}$ = 32 Hz, C_2), 142.5 ($C_{5'}$), 136.8 (d, $J_{P,C}$ = 39 Hz, *i*), 136.7 (d, $J_{P,C}$ = 38 Hz, *i'*), 134.5 (d, $J_{P,C}$ = 13 Hz, C_1), 133.83 (d, $J_{P,C}$ = 19.5 Hz, C_3), 133.8-133.6 (m, *o*-C + *o'*-C + 4°C), 131.6 (d, $J_{P,C}$ = 7 Hz, C_9), 129.7 (C_7), 128.7 (C_8), 128.6 (d, $J_{P,C}$ = 6.2 Hz, *m*-C), 128.4 (C_6), 128.3 (d, $J_{P,C}$ = 4.0 Hz, C_4), 127.0 (*p*-C), 126.9 (*p'*-C), 125.5 (C_5), 21.5 (CH_3), and 20.9 (CH_3); ^{31}P NMR (101.3 MHz): δ ($CDCl_3$) -12.4; ν_{max} (KBr) 3049 (w) (Ar-H), 1616 (w) (Ar-H), 1583 (w) (Ar-H), 1563 (w) (Ar-H), 1472 (m) (P-Ph), 741 (s) (Ar-H), and 696 (s) (Ar-H) cm^{-1}; m/z (eims, 70eV) 418 (M^+, 56%), 403 (100), 341 (43), 264 (4), and 233 (4); HRMS (eims 70eV): M^+, found 418.1587. $C_{28}H_{23}N_2P$ requires 418.1599.

(±)-[1-(3,6-Dimethylpyrazin-2-yl)(2-naphthyl)]diphenylphosphine (7)

To a solution of $NiCl_2$dppe (0.276 g, 0.523 mmol), in DMF (8 ml) was added diphenylphosphine (0.523 ml, 3.01 mmol) at room temperature, and the resulting solution was heated at 100°C. After heating at 100°C for 30 min, a solution of 1-(3,6-dimethylpyrazin-2-yl)-2-naphthyl (trifluoromethyl)sulfonate (1.60 g, 4.19 mmol) and DABCO (2.35 g, 20.9 mmol) in DMF (12 ml) was added at once. The resulting dark green solution was kept at 100°C and an additional portion of diphenylphosphine (0.523 ml, 3.01 mmol) was added after 1 h. The reaction was kept at 100°C for 4 days. After this time the solution was cooled down to 0-5°C in an ice bath. A yellow precipitate formed which was isolated by filtration. The filtrate was reduced *in vacuo* and was purified by column chromatography on silica gel (petroleum ether / ethyl acetate 2:1) to afford (±)-[1-(3,6-

dimethylpyrazin-2-yl)(2-naphthyl)]diphenylphosphine as a white solid (1.24 g, 71 %), identical in all respects to a previously prepared sample.

(*S*,*R*) and (*R*,*R*)-*cis*-[Dimethyl(1-(1-naphthyl)ethyl)aminato-C^2,N]-[[1-(3,6-dimethylpyrazin-2-yl)(2-naphthyl)]diphenylphosphine]palladium(II) hexafluorophosphate (16)

(+)-Di-μ-chlorobis[(*R*)-dimethyl(1-(1-naphthyl)ethyl)aminato-C^2,N]dipalladium(II) (0.16 g, 0.24 mmol) and (*R*,*S*)-[1-(3,6-dimethylpyrazin-2-yl)(2-naphthyl)]diphenylphosphine (0.20 g, 0.48 mmol) were placed in a Schlenk tube under nitrogen. Dry, degassed methanol (14 ml) was added *via* syringe and the solution was stirred for 4 h. Potassium hexafluorophosphate (0.097 g, 0.53 mmol) was added in water (14 ml) with vigorous stirring and a cream precipitate occurred. A further 34 ml of water was added. The precipitated solid was collected by filtration and washed with diethyl ether to give a 50: 50 mixture of two diastereomers (*R*,*S*) and (*R*,*R*)-*cis*-[dimethyl(1-(1-naphthyl)ethyl)aminato-C^2,N]-[[1-(3,6-dimethylpyrazin-2-yl)(2-naphthyl)]diphenyl phosphine]palladium(II) hexafluorophosphate (0.320g, 77%). Found: (mixture) C, 58.4; H, 4.9; N, 4.8. $C_{42}H_{39}F_6N_3P_2Pd$ requires C, 58.1; H, 4.6; N, 4.8%; ν_{max} (KBr) (mixture) 1607 (w) (Ar-H), 1573 (w) (Ar-H), 1501 (w) (Ar-H), 1411 (m) (P-Ph) and 846 (vs) (P-F) cm^{-1}; m/z (ES$^+$) (mixture) 724 (M$^+$, 40%) and 523 (100). Fractional crystallisation of the racemic mixture from propan-2-ol gave (*S*,*R*)-*cis*-[dimethyl(1-(1-naphthyl)ethyl)aminato-C^2,N]-[[1-(3,6-dimethylpyrazin-2-yl)(2-naphthyl)]diphenylphosphine]palladium(II) hexafluorophosphate which was recovered from the filtrate. ^{1}H NMR (500 MHz): δ ($CDCl_3$) : (*S*,*R*)-**16** 8.45 (s, 1H, $H_{5'}$), 8.02 (d, 1H, J = 9.3 Hz, H_8), 7.8 (dd, 1H, J_1 = 6.4 Hz, J_2 = 14.7 Hz, *o*-Ph), 7.75-7.61 (m, 4H, H_7 + Ar-H), 7.61-7.48 (m, 4H, Ar-H), 7.48-7.32 (m, 2H, Ar-H), 7.32-7.19 (m, 4H, H_6 + Ar-H), 7.18-7.12 (t, 2H, *m*-H), 7.05 (d, 1H, J = 8.6 Hz, H_b), 6.82 (d, 1H, J = 7.33 Hz, H_5), 6.77 (d, 1H, J = 7.1 Hz, H_4), 6.56 (dd, 1H, J_1 = 6.2 Hz, J_2 = 8.4 Hz, H_a), 4.16 (quin, 1H, J = 5.9 Hz, C<u>H</u>CH_3), 3.3 (s, 3H, CH_3), 2.70 (d, 3H, J = 2.4 Hz, NMe), 2.4 (d, 3H, J = 3.7 Hz, NMe), 1.83 (s, 3H, CH_3) and 1.22 (d, 3H, J = 8.1 Hz, CH<u>CH_3</u>); ^{31}P NMR (101.3 MHz): δ ($CDCl_3$) (*S*,*R*)-**16**: 37.3; $[\alpha]_D^{21}$ -95.5 (*c* 0.75, $CHCl_3$).

NMR data for (*R*,*R*)-**16** was determined by subtraction. (*R*,*R*)-**16**: 8.45 (s, 1H, $H_{5'}$), 8.04 (d, 1H, J = 8.8 Hz, H_4), 7.71-7.60 (m, 4H, Ar-H), 7.60-7.32 (m, 8H, H_3 + Ar-H), 7.3-7.18 (m, 7H, Ar-H), 6.9 (d, 1H, J = 8.8 Hz, H_b), 6.57 (dd, 1H, J_1 = 6.4 Hz, J_2 = 8.6 Hz, H_a), 4.46 (quin, 1H, J = 6.4 Hz, C<u>H</u>CH_3), 3.42 (s, 3H, CH_3), 2.65 (d, 3H, J = 4.4 Hz, NMe), 2.4 (s, 3H, NMe), 2.17 (s, 3H, CH_3) and 1.66 (d, 3H, J = 6.4 Hz, CH<u>CH_3</u>); ^{31}P NMR (101.3 MHz): δ ($CDCl_3$) (*R*,*R*)-**16**: 39.5.

(*S*)-[1-(3,6-Dimethylpyrazin-2-yl)(2-naphthyl)]diphenylphosphine (7)

1,2-Bis(diphenylphosphino)ethane (0.06 g, 0.15 mmol) was added to a solution of (*S*,*R*)-*cis*-[dimethyl(1-(1-naphthyl)ethyl)aminato-C^2,N]-[[1-(3,6-dimethylpyrazin-2-yl)(2-naphthyl)]diphenylphosphine]palladium(II) hexafluorophosphate (0.13 g, 0.15 mmol) in dichloromethane (5 ml) and the resulting solution was stirred for 2 h. Toluene (10 ml) was added and the solvent was removed *in vacuo* to give a white solid. Toluene (10 ml) was then added and the suspension was stirred for 30 min. The solid (dppe-Pd complex) was removed by filtration. The solvent was removed *in vacuo* and the residue was purified by filtration over a short silica column with dichloromethane to give (*S*)-[1-(3,6-dimethylpyrazin-2-yl)(2-naphthyl)]diphenylphosphine as a white solid. $[\alpha]_D^{21}$ -97.3 (*c* 1.35, $CHCl_3$), identical in all other respects to a previously prepared racemic sample.

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