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The preparation and resolution of 2-phenyl-Quinazolinap, a new atropisomeric phosphinamine ligand for asymmetric catalysis

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Abstract

The preparation and resolution of an axially chiral quinazoline-containing phosphinamine ligand is described. The biaryl linkage was formed in a Pd-catalysed coupling of 4-chloro-2-phenylquinazoline **10** with 2-methoxy-1-naphthylboronic acid **11**. Demethylation of the product ether **12** afforded alcohol **13** which was converted into the corresponding triflate **14** by treatment with trifluoromethanesulphonic anhydride. An Ni-catalysed phosphinylation gave the required phosphinamine ligand **9** as a racemate. Diastereomeric palladacycles **16**, formed from **9** and (+)-di-μ-chlorobis[(*R*)-dimethyl(1-(1-naphthyl)ethyl)aminato-C_2,*N*]dipalladium(II) **15** were separated to give diastereomerically pure materials. An X-ray crystal structure of the (*R*,*R*)-**16** palladacycle was determined and is discussed. Displacement of the resolving agent by reaction with 1,2-bis(diphenylphosphino)ethane gave enantiopure 2-phenyl-Quinazolinap **9**, a new atropisomeric phosphinamine ligand for asymmetric catalysis.

1. Introduction

Of the axially chiral ligands reported to date, the diphosphine BINAP has proven most successful in a wide range of enantioselective metal-catalysed transformations.[1] It is a C_2-symmetric ligand and a notable structural feature is that the free ligand possesses the conformational flexibility to accommodate a wide variety of transition metals by rotation about the binaphthyl C(1)–C(1′) pivot. Recently, interest in non-C_2-symmetric axially chiral phosphinamine bidentate ligands has increased.[2] The first axially chiral phosphinamine to be applied in asymmetric catalysis was Quinap **1** by Brown et al.[3] and more recent examples include the oxazoline-containing ligand **2** from Ikeda et al.[4] and Hayashi et al.[5] and MAP **3** from Kocovsky et al.[6] In an attempt to rationalise the effect of increasing the steric bulk at the phosphorus donor atom Brown have prepared a range of 1′-(2-diarylphosphino)-1-naphthyl)isoquinolines **4** and applied their rhodium complexes in enantioselective hydroboration.[7]

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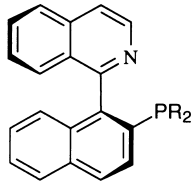
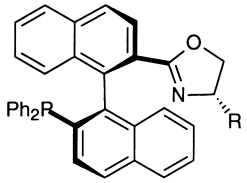
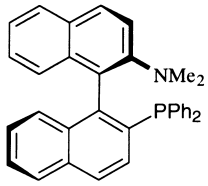


1 R = Ph
4 R = Ar



(*S*,*S*)-**2** R = *i*-Pr, *t*-Bu



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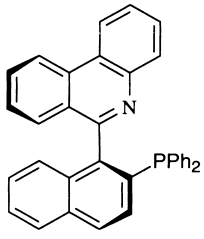
It became apparent during a mechanistic investigation of palladium-catalysed allylic substitution with Quinap **1**, that the 3-H of the isoquinoline unit takes up a position in space leading to ligand–reactant steric interactions which could be important for asymmetric induction.[8] This observation was the design principle behind the preparation of the vaulted analogue Phenap **5**, which in turn gave high enantioselectivities in rhodium-catalysed hydroboration[9] and palladium-catalysed allylic substitution (91 and 95%, respectively).[10] Subsequently, 1-methyl-2-diphenylphosphino-3-(1′-isoquinolyl)indole **6** was also synthesised but had an insufficient barrier to racemisation which precluded its application to enantioselective catalysis.[11]



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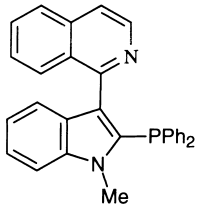

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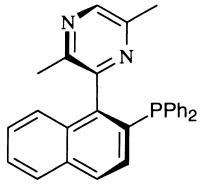

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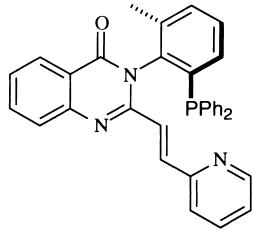

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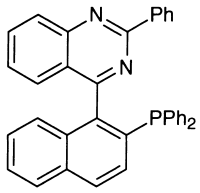
We also have an interest in the design and application in asymmetric catalysis of metal complexes of phosphinamine ligands[12] and recently reported the preparation and resolution of 1-(3,6-dimethylpyrazin-2-yl)(2-naphthyl)diphenylphosphine **7**.[13] In that study we wished to determine the effect on enantioselection of the 6-methyl group [equivalent to the 3-position of the isoquinoline ring of **1**] and to investigate the enantiomeric stability given by the interaction of the naphthyl group and the 3-methyl group. However, as with ligand **6**, this was found to racemise at room temperature indicating that a bulkier group than the 3-methyl was required. The quinazolinone unit has been incorporated in a range of atropisomeric monodentate phosphine[14] and phosphinamine ligands, e.g. ligand **8**, with the latter ligand affording up to 87% ee in palladium-catalysed allylic substitution.[15] These publications prompt us to report our preliminary work on incorporating the quinazoline unit into atropisomeric phosphinamines. The quinazoline unit itself is an important component of many biologically active compounds.[16] The target ligand is diphenyl[1-(2-phenylquinazolin-4-yl)(2-naphthyl)] phosphine **9**, which we refer to as 2-phenyl-Quinazolinap.[17] The 2-phenylquinazoline unit in particular was chosen as we expected that the naphthalene–quinazoline pivot would be essentially inert to racemisation and, once resolved, we could investigate the effect on enantioselection relative to Quinap and Phenap of the increased steric bulk at the 2-position. In addition, the donor nitrogen is substantially less basic than **1** (the pK_a of **1** is 5.1 whilst pK_a of **9** is 3.3).[18] Furthermore, the synthetic precursors of **9** were readily available. We now report the synthesis and resolution of the first quinazoline-containing atropisomeric phosphinamine ligand **9** for asymmmetric catalysis.



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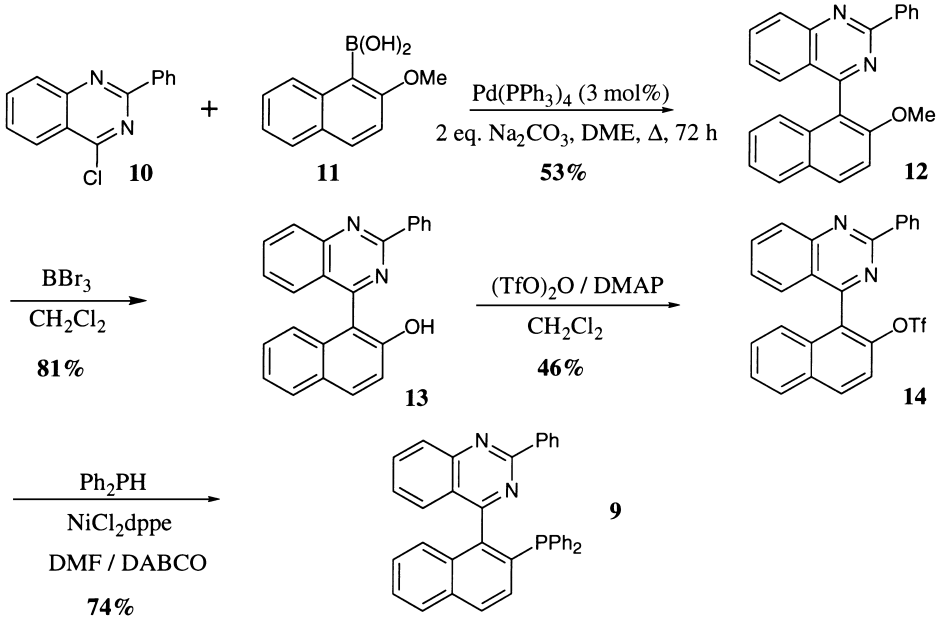
2. Ligand preparation

The synthetic approach chosen for the preparation of **9** is similar to that previously reported for ligands **1**, **5** and **7** in which the two key steps are the metal catalysed reactions of biaryl coupling and formation of the naphthyl–phosphorus bond (Scheme 1). The introduction of the phosphine in the final step is preferred as it allows facile handling of the intermediate compounds.



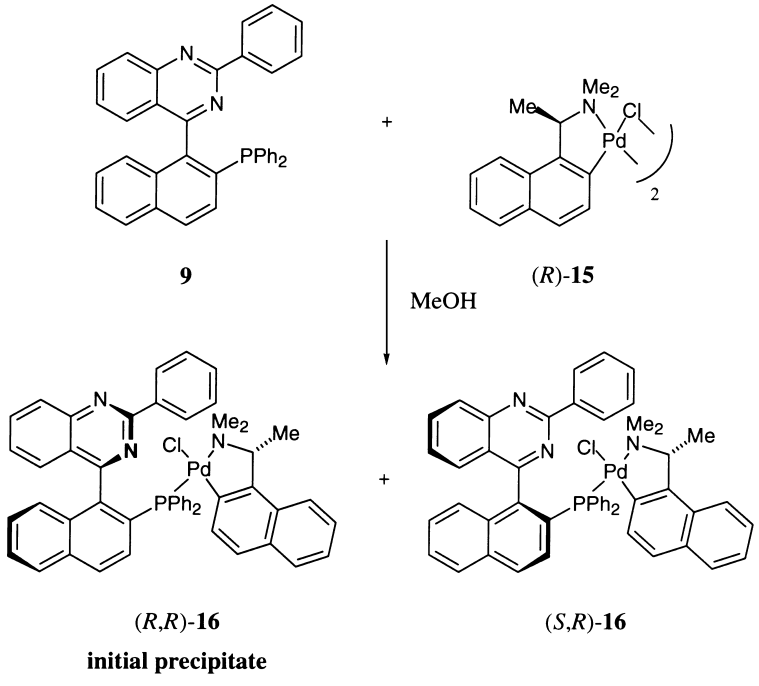
Scheme 1.

The electrophilic component of the palladium catalysed cross-coupling, Scheme 1, was 4-chloro-2-phenyl-quinazoline **10**,[19] while the nucleophilic component was 2-methoxy-1-naphthylboronic acid **11**, which was readily prepared from 1-bromo-2-methoxynaphthalene. The coupling was catalysed by 3 mol% of tetrakis(triphenylphosphine)palladium(0) in dimethoxyethane at reflux in the presence of aqueous 2 M sodium carbonate and gave 2-methyloxy-1-(2-phenylquinazolin-4-yl)naphthalene **12** in 53% yield as a white solid after precipitation from diethyl ether. The next two steps involved the conversion of the ether into the more reactive electrophilic component for the carbon–phosphorus bond forming reaction by first converting it into 1-(2-phenylquinazolin-4-yl)naphthalen-2-ol **13** in 81% yield by reaction with boron tribromide in dichloromethane.[20] This alcohol **13** was converted into the triflate by reaction with trifluoromethanesulfonic anhydride in the presence of 4-dimethylaminopyridine to give 1-(2-phenylquinazolin-4-yl)-2-naphthyl(trifluoromethyl)sulfonate **14** in 46% yield after pu-

rification by silica gel chromatography. The conversion of **14** into 2-phenyl-Quinazolinap **9** was carried out in one step, rather than the two steps required by Morgan's method.[21] Thus, [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) catalysed the coupling with diphenylphosphine using dimethyl formamide as solvent in the presence of DABCO as base, as reported by Cai et al.[22] to access 2-phenyl-Quinazolinap **9** in 74% yield.

3. Ligand resolution

Since phosphinamine **9** was structurally related to Quinap **1** and Phenap **5**, our initial resolution attempts focused on the preparation and separation of diastereomeric complexes derived from **9** 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 a wide range of phosphorus-containing ligands including **1** and **5**.[23] In contrast to the resolution of Quinap **1** which required several crystallisations,[3b] the resolution of Phenap **5** proved more facile. On mixing **5** with palladium dimer **15** in a 2:1 molar ratio in methanol at ambient temperature, a precipitate of the (*R*,*R*)-diastereomer occurred which was isolated after stirring overnight. KPF_6 was added to the residual solution causing the (*S*,*R*)-diastereomer to precipitate.[10] Because the steric demand of 2-phenyl-Quinazolinap **9** resembles Phenap **5** rather than Quinap **1**, the resolution of **9** was suspected to follow a similar pattern to that of **5**. Therefore, racemic **9** and palladium dimer **15** were stirred in a 2:1 molar ratio in methanol at ambient temperature, Scheme 2.



Scheme 2.

A white precipitate formed after 15 minutes and the suspension was stirred overnight after which time the solid was filtered. ^{1}H NMR spectroscopy showed that this corresponded to one of the diastereomers. The key resonances include a quintet at 4.10 ppm corresponding to the benzylic methine. This multiplicity is due to vicinal coupling and a smaller ^{31}P-coupling. This confirms that the nitrogen donor atom from the resolving agent **15** and the phosphorus atom from the ligand **9** are *trans* to each other. The

nitrogen bonded methyl groups occur as a doublet (small ^{31}P coupling) and a singlet at 2.8 and 1.94 ppm, respectively, and the other methyl occurs as a doublet at 1.97 ppm. The ^{31}P spectrum shows a singlet at 40.0 ppm. The specific rotation of this diastereomer was found to be $[\alpha]_D^{23}$ +94.2 (*c* 0.6, $CHCl_3$).

This material was recrystallised from chloroform/pentane by isothermal diffusion. X-Ray crystallography showed that the diastereomer is the (*R*,*R*)-**16** diastereomer and that the ligand is monodentate through its phosphorus atom, Fig. 1. The structure exhibits several interesting features (Table 1) in particular a distorted square planar coordination of the Pd atom [P–Pd–N1 166.9(1)°] caused in part by the close approach of the quinazoline moiety [Pd lies 3.35(2) Å from the mean plane of the group]. Whether this is caused by the steric requirements of the phosphine ligand or a weak interaction of the quinazoline group with the metal is difficult to say. The Pd–P–C angle at the naphthylene group [111.5(1)°] is certainly only slightly larger than that to one of the two phenyl groups [107.7(1)°] and significantly smaller than that to the other [126.3(1)°]. In any case, there appears to be some charge transfer to the extremities of the complex since chloroform molecules in the crystal form hydrogen bonds to not only the Cl atom but also to N1′ in the quinazoline group.

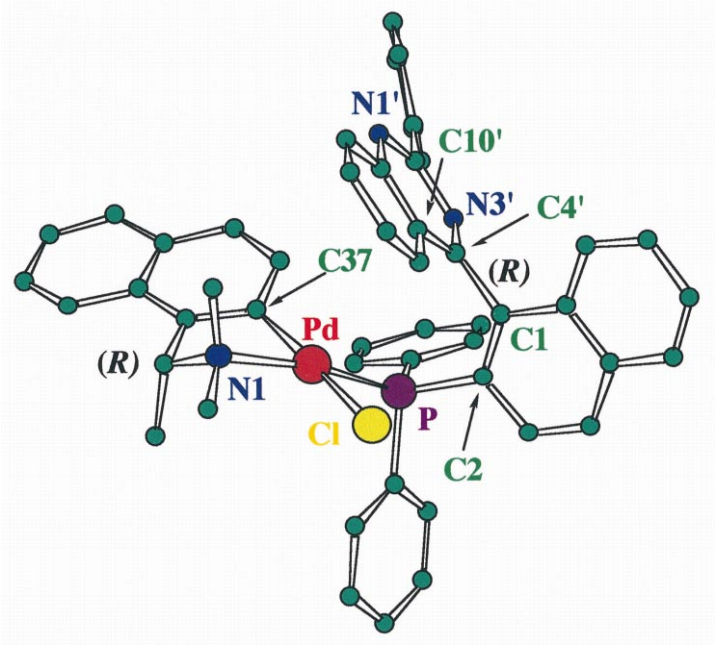


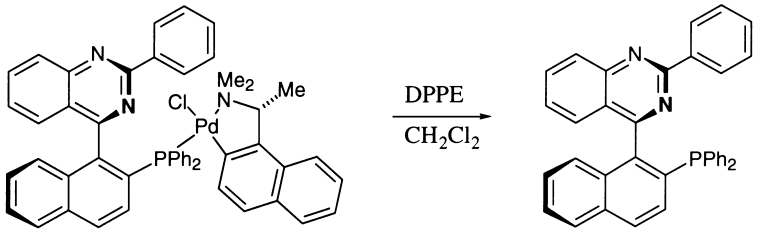
Figure 1. Crystal structure of (*R*,*R*)-**16**. (Hydrogen atoms and chloroform solvate omitted for clarity)

Table 1

Selected Bond Lengths (Å)		Selected Angles (°)	
Pd-P	2.263(1)	P-Pd-N1	166.9(6)
Pd-N1	2.144(2)	P-Pd-Cl	88.77(2)
Pd-Cl	2.432(1)	P-Pd-C37	97.7(1)
Pd-C37	1.993(2)	N1-Pd-Cl	94.3(1)
Pd-N3'	4.185(2)	N1-Pd-C37	79.8(1)
Pd-C4'	3.658(2)	Cl-Pd-C37	173.3(1)
Pd-C10'	3.496(3)	C2-C1-C4'-C10'	108.1(5)

The filtrate was reduced in vacuo and precipitated from butanone/diethyl ether. ^{1}H NMR shows that this product corresponds to the other diastereomer, namely (*S*,*R*)-**16** (assuming monodentate binding as before). Again the benzylic methine appears as a quintet but now at 4.20 ppm showing that the nitrogen donor atom from resolving agent **15** and the phosphorus atom from ligand **9** are again *trans* to each other as they are in the (*R*,*R*)-**16** diastereomer. The nitrogen bonded methyl groups occur as a doublet (small ^{31}P coupling) and a singlet at 2.87 and 2.55 ppm and the other methyl appears as a doublet at 1.75 ppm. The ^{31}P spectrum shows a singlet at 45.1 ppm. The optical rotation of this diastereomer was found to be $[\alpha]_D^{23}$ −96.8 (*c* 1.4, $CHCl_3$). All attempts to date to obtain X-ray quality crystals of complex (*S*,*R*)-**16** failed.

Enantiopure ligand was easily generated after decomplexation of the appropriate diastereomer by the addition of 1,2-bis(diphenylphosphino)ethane in dichloromethane at ambient temperature followed by separation on a short silica column, Scheme 3. The (*R*)-enantiomer of **9** was found to have a specific rotation of $[\alpha]_D^{23}$ −25.0 (*c* 0.9, $CHCl_3$), while the (*S*)-enantiomer was found to have a value of $[\alpha]_D^{23}$ +24.6 (*c* 0.9, $CHCl_3$).



(*R*,*R*)-**16** (*R*)-**9**

Scheme 3.

The optical stability of (*R*)-2-phenyl-Quinazolinap **9** was then tested by heating its toluene solution to reflux under nitrogen and after 7 days the optical rotation was not found to change. An isolated sample was then recomplexed to (*R*)-**15** following previous protocol and ^{1}H NMR of the product showed the presence of only (*R*,*R*)-**16**.

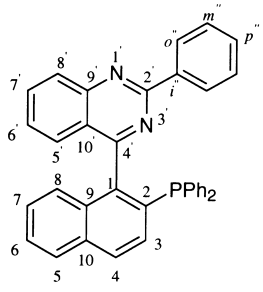
In conclusion, the effective synthesis of 2-phenyl-Quinazolinap **9** and its successful resolution has been described. Both diastereomers were isolated in good yield. The structure of (*R*,*R*)-**16** was determined by X-ray crystallography. Enantiopure ligand was obtained after decomplexation by the addition of 1,2-bis(diphenylphosphino)ethane. Both hands of enantiopure 2-phenyl-Quinazolinap **9** had therefore been accessed. The application of transition metal complexes of this ligand in catalytic asymmetric synthesis will be described in future publications from these laboratories.

4. Experimental

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 an 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. 4-Chloro-2-phenylquinazoline, boron tribromide, diphenylphosphine, 1,2-bis(diphenylphosphino)propane, [1,2-bis(diphenylphosphino)ethane]dichloronickel(II), DABCO, KPF_6, trifluoromethanesulphonic anhydride and 4-dimethylaminopyridine were commercially available (Aldrich Chemical Co.) and were used as purchased. Pd salts were obtained on loan from Johnson Matthey. (*R*)-Dimethyl(1-(1-naphthyl)ethyl)amine[24] and tetrakis(triphenylphosphine)palladium(0)[25] were prepared by literature procedures. Separations by column chromatography were performed using Merck Kieselgel 60 (Art. 7734). For ease of interpretation of NMR data the following numbering scheme was used for ligand **9** and related compounds are numbered similarly.



4.1. 2-Methyloxy-1-(2-phenylquinazolin-4-yl)naphthalene **12**

4-Chloro-2-phenylquinazoline (2.30 g, 9.4 mmol) was added as a solid to a solution of tetrakis(triphenylphosphine)palladium(0) (0.33 g, 0.28 mmol) in DME (20 ml) and stirred for 10 min under a nitrogen atmosphere. 2-Methoxy-1-naphthylboronic acid (1.89 g, 9.4 mmol), dissolved in the minimum amount of ethanol, was added. Sodium carbonate solution (9.5 ml, 2 M) was added and the solution was refluxed for 48 h under nitrogen. The solution was allowed to cool and the solid filtered off. The solid was washed with dichloromethane until it was white. The solvent was removed from the dark red filtrate to give a brown oil which was dissolved in dichloromethane (30 ml), washed with saturated brine (2×15 ml), dried with sodium sulfate and the solvent removed in vacuo to give a brown oil. The oil was stirred overnight in diethyl ether after which time a white solid had formed. The solid was collected by filtration to give 2-methyloxy-1-(2-phenylquinazolin-4-yl)naphthalene (3.41 g, 53%), m.p. 188–189°C. Found: C, 83.0; H, 5.0; N, 7.6. $C_{25}H_{18}N_2O$ requires: C, 82.9; H, 5.0; N, 7.7%; ^{1}H NMR (500 MHz): δ ($CDCl_3$) 8.68 (dd, 2H, J_1=8.3 Hz, J_2=1.96 Hz, *o*-Ph), 8.21 (d, 1H, J=8.8 Hz, H_8), 8.07 (d, 1H, J=9.3 Hz, H_4), 7.91 (d, 1H, J=7.3 Hz, $H_{5'}$), 7.87 (t, 1H, J=7.6 Hz, H_7), 7.53–7.48 (m, 4H, *m*+*p*-Ph, $H_{8'}$), 7.46 (d, 1H, J=8.8 Hz, H_3), 7.40 (t, 1H, J=7.4 Hz, H_6), 7.38 (t, 1H, J=7.1 Hz, $H_{6'}$), 7.32 (t, 1H, J=7.3 Hz, $H_{7'}$), 7.26 (d, 1H, J=7.8 Hz, H_5) and 3.80 (s, 3H, OCH_3); ^{13}C NMR (125.7 MHz): δ ($CDCl_3$) 167.5 (4°C), 161.0 (4°C), 154.8 (C_2), 151.3 (4°C), 138.6 (C_9), 133.8 (C_7), 133.2 ($C_{9'}$), 131.2 (C_4), 130.4 (CH), 129.2 (4°C), 129.0 (C_8), 128.9 (*o*-Ph), 128.9 (*o*-Ph), 128.6 (CH), 128.5 (CH), 128.1 ($C_{5'}$), 127.2 ($C_{7'}$), 127.1 (CH), 127.0 (C_6), 124.7 (C_5), 124.2 (4°C), 124.1 ($C_{6'}$), 120.4 (4°C), 113.6 (C_3) and 56.8 (OCH_3); ν_{max} (KBr): 1615 (m) (Ar-H), 1560 (m) (Ar-H), 1537 (m) (Ar-H), 1279 (s) (C-O), 1250 (s) (C-O), 813 (m) (Ar-H), 777 (m) (Ar-H) and 732 (m) (Ar-H) cm^{-1}; *m/z* (EIMS 70 eV) 362 (M^+, 25%), 347 (15), 331 (7), 319 (7), 102 (9), 77 (15) and 76 (13).

4.2. 1-(2-Phenylquinazolin-4-yl)naphthalen-2-ol **13**

Boron tribromide (4.90 g, 19.6 mmol) was added slowly via syringe to a solution of 2-methyloxy-1-(2-phenylquinazolin-4-yl)naphthalene (3.55 g, 9.79 mmol) in dry dichloromethane (70 ml). The yellow solution turned dark red in colour and was allowed to stir at room temperature overnight. Water (36 ml) was added cautiously, [white fumes were evolved] and a bright orange precipitate formed which dissolved when more dichloromethane was added. The organic layer was isolated, dried with magnesium sulfate and reduced in vacuo to give 1-(2-phenylquinazolin-4-yl)naphthalen-2-ol as an orange solid (2.75 g, 81%). The product was pure enough to be used in subsequent reactions; a sample was recrystallised from dichloromethane for characterisation. M.p. 183–185°C. ^{1}H NMR (500 MHz): δ ($CDCl_3$) 8.65 (dd, 2H, J_1=7.8 Hz, J_2=1.96 Hz, *o*-Ph), 8.19 (d, 1H, J=8.3 Hz, H_8), 7.98 (d, 1H, J=8.8 Hz, H_4), 7.89 (dt, 1H, J_1=8.3 Hz, J_2=1.5 Hz, H_7), 7.88 (d, 1H, J=7.8 Hz, $H_{5'}$), 7.60 (d, 1H, J=8.8 Hz, $H_{8'}$), 7.57–7.54 (m, 3H, *m*+*p*-Ph), 7.40 (d, 1H, J=8.8 Hz, H_3) and 7.38–7.27 (m, 4H, H_5+H_6+$H_{6'}$+$H_{7'}$); ^{13}C NMR (125.7 MHz): δ ($CDCl_3$) 166.1 (4°C), 159.8 (4°C), 154.6 (4°C), 152.4 (C_2), 137.4 (C_9), 134.5 (C_7), 132.7 (CH), 132.6 ($C_{9'}$), 131.1 (C_4), 129.4 (C_8), 128.9 (*o*-Ph), 128.9 (*o*-Ph), 128.7 (CH), 128.6 (CH), 128.6 (4°C), 128.5 (CH), 128.1 (CH), 127.1 (CH), 126.9 (CH), 125.1 (CH), 123.8 (CH), 122.8 (4°C), 119.2 (C_3) and 114.9 (C_1); ν_{max} (CH_2Cl_2): 3031 (Ar-H), 1605 (m) (Ar-H), 1253 (s) (C-O), 892 (m) (Ar-H) and 842 (m) (Ar-H) cm^{-1}; HRMS calcd for $C_{24}H_{16}N_2O$: 348.403, found: 348.404.

4.3. 1-(2-Phenylquinazolin-4-yl)-2-naphthyl (trifluoromethyl)sulfonate **14**

Trifluoromethanesulphonic anhydride (2.45 g, 8.69 mmol) was added dropwise from a glass syringe with stirring to a solution of 1-(2-phenylquinazolin-4-yl)naphthalen-2-ol (2.75 g, 7.9 mmol) and 4-dimethylaminopyridine (2.89 g, 23.7 mmol) in dry dichloromethane (40 ml). The resulting yellow solution was stirred overnight. The solution was then washed with 1 M hydrochloric acid (3×70 ml), water (2×70 ml) and saturated brine (2×70 ml) and dried with magnesium sulfate. Removal of the solvent in vacuo gave a yellow solid which was purified by silica gel column chromatography (petroleum ether:ethyl acetate 2:1) yielding 1-(2-phenylquinazolin-4-yl)-2-naphthyl (trifluoromethyl)sulfonate (1.73 g, 45.5%), as a yellow solid, m.p. 144–145°C. Found: C, 62.2; H, 3.2; N, 5.6. $C_{25}H_{15}N_2O_3SF_3$ requires: C, 62.5; H, 3.2; N, 5.8%; ^{1}H NMR (500 MHz): δ ($CDCl_3$) 8.68 (dd, 2H, J_1=7.8 Hz, J_2=1.95 Hz, *o*-Ph), 8.25 (d, 1H, J=8.3 Hz, H_8), 8.17 (d, 1H, J=9.3 Hz, H_4), 8.04 (d, 1H, J=8.3 Hz, $H_{5'}$), 7.93 (dt, 1H, J_1=6.8 Hz, J_2=1.5 Hz, H_7), 7.66 (d, 1H, J=9.8 Hz, H_3), 7.61 (t, 1H, J=7.32 Hz, $H_{6'}$), 7.55–7.51 (m, 3H, *m*+*p*-Ph), 7.47–7.44 (m, 2H, $H_{7'}$+$H_{8'}$), 7.42 (d, 1H, J=8.3 Hz, H_6) and 7.37 (d, 1H, J=8.3 Hz, H_5); ^{13}C NMR (125.7 MHz): δ ($CDCl_3$) 163.4 (4°C), 160.8 (4°C), 151.5 (C_2), 144.8 (4°C), 137.9 (C_9), 134.4 (C_7), 132.6 (4°C), 132.5 (4°C), 131.9 (C_4), 130.8 (CH), 129.4 (C_8), 129.0 (*o*-Ph), 129.0 (*o*-Ph), 128.7 (CH), 128.6 (CH), 128.5 ($C_{5'}$), 128.3 (CH), 127.6 (CH), 127.5 ($C_{6'}$), 126.4 (C_6), 126.3 (C_5), 123.5 (4°C), 119.6 (C_3), 119.5 (4°C) and 117.0 (4°C); ν_{max} (CH_2Cl_2): 3049 (Ar-H), 1614 (m) (Ar-H), 1565 (m) (Ar-H), 1543 (m) (Ar-H), 1427 (s) (-SO_3-), 1220 (s) (-SO_3-), 1139 (s) (C-O) and 832 (s) (Ar-H) cm^{-1}; *m/z* (EIMS 70 eV) 480 (M^+, 12%), 347 (100), 319 (37), 189 (21), 205 (18) and 77 (48).

4.4. (R,S) Diphenyl[1-(2-phenylquinazolin-4-yl)(2-naphthyl)]phosphine **9**

To a solution of [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) (0.098 g, 0.185 mmol), in DMF (5 ml) was added diphenylphosphine (0.185 ml, 1.06 mmol) at room temperature, and the resulting solution was heated at 100°C. After 30 min a solution of 1-(2-phenylquinazolin-4-yl)-2-naphthyl (trifluoromethyl)sulfonate (0.888 g, 1.85 mmol) and 1,4-diazabicyclo[2.2.2.]octane (DABCO)

(0.830 g, 7.4 mmol) in DMF (6 ml) was added. The resulting black solution was kept at 100°C and an additional portion of diphenylphosphine (0.185 ml, 1.06 mmol) was added after 1 h. The reaction was kept at 100°C under nitrogen for 3 days. The solvent was removed in vacuo (40°C on a vacuum line). The product was purified by silica gel flash column chromatography (hexane:ethyl acetate 2:1) to give (*R*,*S*) diphenyl[1-(2-phenylquinazolin-4-yl)(2-naphthyl)]phosphine (0.710 g, 74.4%) as a white solid, m.p. 218–219°C. Found: C, 83.3; H, 4.9; N, 5.4. $C_{36}H_{25}N_2P$ requires: C, 83.7; H, 4.9; N, 5.4%; ^{1}H NMR (500 MHz): δ ($CDCl_3$) 8.19 (m, 3H, H_8+*o*-Ph), 7.96 (d, 1H, J=8.8 Hz, H_4), 7.93 (d, 1H, J=8.3 Hz, $H_{5'}$), 7.87 (dt, 1H, J_1=6.8 Hz, J_2=1.95 Hz, H_7), 7.51 (dt, 1H, J_1=6.8 Hz, J_2=1.5 Hz, $H_{6'}$), 7.42 (dd, 1H, $J_{H,H}$=8.8 Hz, $J_{P,H}$=2.9 Hz, H_3), 7.40–7.39 (m, 2H, Ar-H), 7.36–7.32 (m, 3H, *m*-Ph, H_6), 7.32–7.25 (m, 9H, H_7+Ar-H) and 7.21–7.15 (m, 3H, $H_{8'}$+$H_{5'}$+Ar-H); ^{13}C NMR (125.7 MHz): δ ($CDCl_3$) 169.3 (d, $J_{P,C}$=6.6 Hz, $C_{4'}$), 160.5 (4°C), 151.2 (4°C), 142.1 (d, $J_{P,C}$=32 Hz, C_2), 138.2 (4°C), 137.6–136.7 (m, *i*+*i*′), 134.8 (d, $J_{P,C}$=15.3 Hz, C_1), 133.8 (CH), 133.8 (CH), 133.7 (C_7), 133.7–133.5 (CH), 132.0 (d, $J_{P,C}$=7.1 Hz, C_9), 130.2 (d, $J_{P,C}$=13.7 Hz, C_3), 129.2 (d, $J_{P,C}$=10.7 Hz, C_4), 128.9 (C_8+*o*-Ph), 128.5–128.3 (CH), 128.2 ($C_{5'}$), 127.1 (CH), 127.0 (CH), 126.9 ($C_{6'}$), 126.5 (C_5), 126.5 (CH), 124.1 (4°C) and 124.0 (4°C); ^{31}P NMR (101.3 MHz): δ ($CDCl_3$) −12.4; ν_{max} (KBr): 3054 (w) (Ar-H), 1614 (m) (Ar-H), 1584 (m) (Ar-H), 1568 (m) (Ar-H), 1435 (m) (P-Ph), 711 (s) (Ar-H) and 697 (s) (Ar-H) cm^{-1}; *m/z* (EIMS 70 eV) 516 (M^+, 62%), 439 (100), 362 (5) and 77 (15).

4.5. *Resolution of diphenyl[1-(2-phenylquinazolin-4-yl)(2-naphthyl)]phosphine*

A mixture of diphenyl[1-(2-phenylquinazolin-4-yl)(2-naphthyl)]phosphine (0.616 g, 1.19 mmol) and (+)di-μ-chlorobis[(*R*)-dimethyl(1-(1-naphthyl)ethyl)aminato-C_2,*N*]dipalladium(II) (0.406 g, 0.597 mmol) in methanol (35 ml) was stirred at room temperature overnight. The reagents slowly dissolved, but after 15 min a white solid precipitated from the solution. The solid was filtered off, washed with methanol (10 ml) and dried, to give a white solid. The solution was concentrated to dryness. To the residue was added methanol (8 ml) and the mixture was stirred for 1 h. The solid was filtered off, washed with methanol (20 ml), and dried to give more white solid. The solids were combined to give (*R*,*R*)-**16** (0.414 g, 81%), as its chloride salt. The filtrate was reduced in vacuo, butanone (5 ml) and diethyl ether (10 ml) were added and a solid precipitated upon standing (2 days). The solid was filtered off, washed with diethyl ether (10 ml) to give (*S*,*S*)-**16** (0.318 g, 62%).

Complex (*R*,*R*)-**16**, m.p. 211–212°C; $[\alpha]_D^{21}$ 94.2 (*c* 0.6, $CHCl_3$). Found: C, 69.9; H, 4.7; N, 4.85; Cl, 4.0. $C_{50}H_{41}N_3ClPPd$ requires: C, 70.0; H, 4.8; N, 4.9; Cl, 4.1%; ^{1}H NMR (500 MHz): δ ($CDCl_3$) 8.45 (d, 2H, J=7.33 Hz), 7.96 (d, 1H, J=8.3 Hz), 7.92 (d, 1H, J=7.8 Hz), 7.89 (d, 1H, J=8.3 Hz), 7.86–7.82 (m, 2H), 7.73 (dt, 1H), 7.57 (d, 1H, J=8.3 Hz), 7.53–7.19 (m, 15H), 6.97 (br, 2H), 6.77 (d, 1H, J=8.8 Hz), 6.13 (br, 1H), 5.99 (dd, 1H, J_1=8.8 Hz, J_2=2.44 Hz), 4.11 (quin, 1H, J=6.4 Hz, C*H*Me), 2.83 (d, 3H, J=2.9 Hz, NCH_3), 1.97 (d, 3H, J=5.9 Hz, CH*Me*) and 1.94 (s, 3H, NCH_3); ^{13}C NMR (125.7 MHz): δ ($CDCl_3$) 168.2, 160.0, 151.1, 148.3, 138.3, 138.2, 136.0, 135.9, 135.8, 133.8, 133.6, 132.5, 131.2, 130.5–128.3, 128.2, 128.0, 127.9, 127.3, 127.1, 127.0, 126.9, 126.8, 126.5, 125.2, 124.4, 123.7, 123.1, 72.9 (CH), 50.4 (NCH_3), 48.6 (NCH_3) and 23.5 (CCH_3); ^{31}P NMR (101.3MHz): δ ($CDCl_3$) 40.0 ppm; ν_{max} (CH_2Cl_2): 3049 (Ar-H), 1614 (m) (Ar-H), 1565 (m) (Ar-H), 1543 (m) (Ar-H), 1436 (P-Ph) and 812 (Ar-H) cm^{-1}; *m/z* (ESI/pos in CH_3OH) cation 821=M−Cl.

Complex (*S*,*S*)-**16**, m.p. 199–200°C; $[\alpha]_D^{21}$ −96.8 (*c* 1.4, $CHCl_3$). Found: C, 69.9; H, 4.8; N, 4.8; Cl, 4.0. $C_{50}H_{41}N_3ClPPd$ requires: C, 70.0; H, 4.8; N, 4.9; Cl, 4.1%; ^{1}H NMR (500 MHz): δ ($CDCl_3$) 8.32 (t, 1H), 8.17 (d, 2H, J=8.5 Hz), 8.02 (d, 1H, J=8.5 Hz), 7.90 (t, 3H), 7.78 (br t, 3H), 7.72 (t, 1H), 7.62 (d, 1H, J=8.6 Hz), 7.54 (d, 1H, J=7.9 Hz), 7.49–7.24 (m, 11H), 7.16 (t, 1H), 6.79 (d, 1H, J=8.54 Hz), 6.72 (d, 1H, J=8.8 Hz), 6.68 (br d, 1H, J=7.0 Hz), 6.56 (br t, 2H), 6.45 (br, 1H), 4.20 (quin, 1H, J=6.1 Hz, C*H*Me),

2.87 (d, 3H, J=3.1 Hz, NCH_3), 2.55 (s, 3H, NCH_3) and 1.75 (d, 3H, J=6.1 Hz, CH*Me*); ^{13}C NMR (125.7 MHz): δ ($CDCl_3$) 167.5, 160.0, 150.7, 150.6, 149.0, 139.4, 138.2, 137.1, 137.0, 136.3, 136.2, 135.9, 135.8, 134.1, 133.7, 133.4, 133.2, 132.6, 131.0, 130.7–128.0, 127.9, 127.6, 127.1, 127.0, 126.9, 126.4, 125.6, 124.3, 124.0, 123.3, 73.2 (CH), 50.9 (NCH_3), 48.5 (NCH_3) and 23.4 (CCH_3); ^{31}P NMR (101.3 MHz): δ ($CDCl_3$) 45.1 ppm; ν_{max} (CH_2Cl_2): 3049 (Ar-H), 1614 (m) (Ar-H), 1570 (m) (Ar-H), 1542 (m) (Ar-H), 1436 (P-Ph) and 811 (Ar-H) cm^{-1}; *m/z* (ESI/pos in CH_3OH) cation 821=M−Cl.

*4.6. (*R*)-Diphenyl[1-(2-phenylquinazolin-4-yl)(2-naphthyl)]phosphine (*R*)-**9***

1,2-Bis(diphenylphosphino)ethane (0.174 g, 0.437 mmol) was added to a solution of palladium bound (*R*)-diphenyl[1-(2-phenylquinazolin-4-yl)(2-naphthyl)]phosphine (0.374 g, 0.437 mmol) in dichloromethane (15 ml) and the resulting solution was stirred for 2 h. The solvent was almost all removed to leave a yellow oil which was purified by filtration over a short silica column with dichloromethane to give (*R*)-diphenyl[1-(2-phenylquinazolin-4-yl)(2-naphthyl)]phosphine as a white solid, $[\alpha]_D^{21}$ −25.0 (*c* 0.9, $CHCl_3$) identical in all respects to a previously prepared sample. (*S*)-Diphenyl[1-(2-phenylquinazolin-4-yl)(2-naphthyl)]phosphine was isolated in an identical manner, $[\alpha]_D^{21}$ 24.6 (*c* 0.9, $CHCl_3$).

*4.7. X-Ray analysis of (*R,R*)-**16***

$C_{50}H_{41}ClN_3PPd\cdot 3(CHCl_3)$, M_r=1214.78 g mol^{-1}, yellow-green, crystal size 0.12×0.42×0.50 mm, *a*=10.3705(3), *b*=12.1069(3), *c*=21.0159(6) Å, *U*=2638.5(2) Å^3, *T*=100 K, monoclinic, $P2_1$ [No. 4], *Z*=2, d_{cal}=1.53 g cm^{-3}, μ=0.92 mm^{-1}, Siemens SMART diffractometer, λ=0.71073 Å, 22823 reflections, 14226 independent, 13263 with $I>\sigma(I)$ (gt), θ*max*=33.82°, analytical absorption correction (T_{min}=0.63466, T_{max}=0.89718), direct methods,[26] least-squares refinement (on F_o^2),[27] H riding, 613 refined parameters, *R*=0.029 (gt), R_w=0.076 (Chebyshev weights), final shift/error 0.001, Flack parameter −0.03(1), residual electron density +0.744 eÅ^{-3}. Structural data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; CSD-127393.

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