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Synthesis and Post-Resolution Modification of New Axially Chiral Ligands for Asymmetric Catalysis

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Keywords: Ligand design / Chiral resolution / Chirality / Atropisomerism / Asymmetric synthesis / Palladium / Hydroboration

The synthesis of four new members of the Quinazolinap series of ligands is described. Three of these ligands were prepared by post-resolution modification of the known ligand (*R*)-7-chloro-2-isopropyl-Quinazolinap, a new approach which offers an expedient route to a range of enantiopure ligands as it precludes the need for resolution of each ligand prepared. The remaining ligand, 7-chloro-2-methyl-Quinazolinap, was prepared in a seven-step synthetic sequence incorporating palladium- and nickel-catalyzed transformations as the key steps. A diastereomerically pure palladacycle of this ligand was characterised by X-ray crystallography. (*R*)-7-Chloro-2-isopropyl-Quinazolinap was applied to the rhodium-catalyzed hydroboration of vinylarenes with regioselectivities of up to $> 99{:}1$ and *ee* values of up to 68 %. Each of the Quinazolinap ligands prepared were applied to the palladium-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate resulting in conversions of up to 100 % and *ee* values of up to 85 %. Solution-phase NMR studies on a palladium complex of one of the ligands provided a rationale for the sense of asymmetric induction.

Introduction

The theme of chirality has become central to contemporary organic synthesis due to its relevance in areas ranging from material to medical science. However, the synthesis of chiral molecules in one enantiomeric form is one of the most difficult challenges.[1] Since the outstanding success of Noyori's BINAP ligand,[2] and its subsequent applications in asymmetric transition metal catalysis,[3] the development of new atropisomeric ligands has become an area of intense interest.[4] Of particular relevance to our work is the development of chiral heterobidentate systems due to their ability to induce asymmetry in a variety of reactions. Of these the phosphinamine ligand class has received the most interest due to the combination of steric and electronic effects exerted on substrates at the coordination sphere of the transition metal to which they are bound.[5]

The first successful axially chiral phosphinamine ligand, Quinap **1**, was developed by Brown and incorporated a naphthalene-isoquinoline backbone with the necessary steric requirements to prevent free rotation about the biaryl linkage.[6] We subsequently developed the related Quinazolinap ligands (exemplified by **2a**–**j**).[7] This allowed for studies on the effects of altering the basicity of the donor nitrogen and for the facile introduction of steric bulk at the 2-position, which is believed to be important in the transfer of chiral information from catalyst to reaction product. Related atropisomeric axially chiral phosphinamine ligands from the groups of Knochel and Chan include PINAP **3** and Pyphos **4**, respectively, both of which have been successfully applied to rhodium-catalyzed hydroboration of vinylarenes.[8]

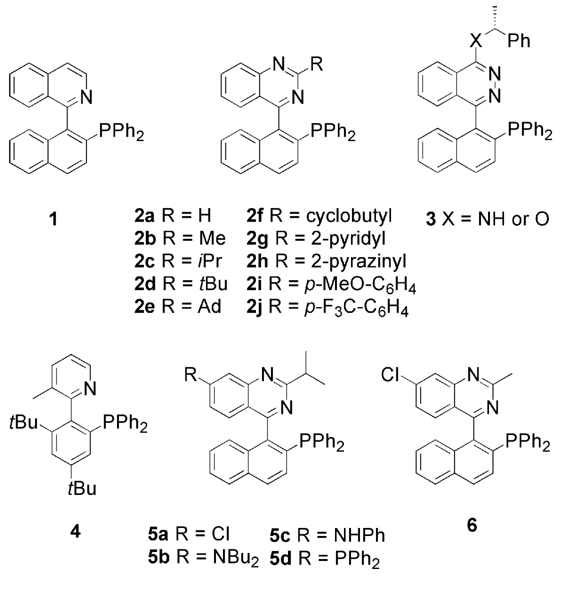

Figure 1. Quinap, Quinazolinap and related axially chiral P,N ligands.

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Recently we reported the synthesis and resolution of the Quinazolinap ligand **5a** which possesses a chlorine at the 7-position, which was incorporated to facilitate potential post-resolution modification at this position.[9] Ligand **5a** has previously been shown to be efficacious in the copper-catalyzed β-borylation of α, β-unsaturated esters[9] and we now wish to report the application of this ligand to the rhodium-catalyzed hydroboration of vinylarenes. We also wish to report the synthesis of ligands **5b–d**, via one step post-resolution modifications of **5a**, and the synthesis and resolution of 7-chloro-2-methyl-Quinazolinap (**6**) from commercially available starting materials (Figure 1).

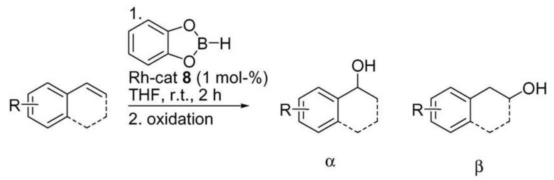
Results and Discussion

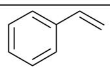
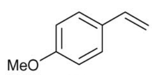
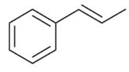
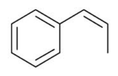
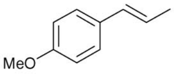
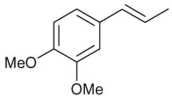
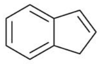
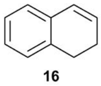
Rhodium-Catalyzed Hydroboration

The rhodium-catalyzed enantioselective hydroboration of olefins is a valuable synthetic transformation, typically employing a chiral catalyst and an achiral borane source. The ease of transformation of the organoboranes produced into various functional groups has made hydroboration a valuable synthetic technique in organic chemistry.[10] Previously, members of the Quinazolinap series of ligands have been shown to be effective for this transformation[7c,7f,7h,7i] and we now wish to report the application of the Quinazolinap ligand **5a** to this transformation.

Vinylarene derivatives **9–16** were tested as hydroboration substrates using in situ-prepared rhodium-Quinazolinap complex (*S*)-**8** as the active catalyst (Scheme 1). Reactions were carried out both at room temperature and at 0 °C and it was found that for all but one of the substrates the higher temperature gave superior results (Table 1). Styrene **9** was quantitatively converted to product, with an α: β ratio of 80:20 and an *ee* value of 65% (Table 1, entry 1). *p*-Methoxystyrene performed similarly, albeit with a lower regioselectivity of 68:32 (entry 2). The regioselectivity was increased when various β-methylstyrenes were used as substrates (entries 2–6) and *cis*-β-methylstyrene **12** was hydroborated with an α: β ratio of > 99:1. The presence of electron-donating substituents on the aryl ring was detrimental to conversion, regio- and enantioselectivity (entries 5 and 6). The cyclic substrates **15** and **16** gave excellent regioselectivities (entries 7 and 8) with moderate *ee* values of 55% and 64%, respectively. The effect of the 7-chloro substituent can be evaluated by comparison with the analogous unsubstituted ligand **2c**.[7c] As a general trend, the enantioselectivities were decreased by the inclusion of the 7-substituent, while the regioselectivities remained in the same range.

Table 1. Rhodium-catalyzed hydroboration of vinylarenes **9**–**16**.

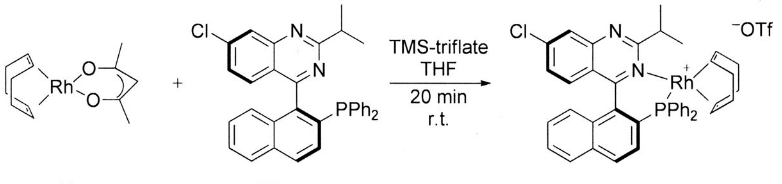


Entry[a]	Substrate	Conv. (%)[c]	α:β[c]	ee (%)[d]
1	 **9**	100	80:20	65 (*S*)
2	 **10**	100	68:32	60 (*S*)
3	 **11**	72	90:10	68 (*S*)
4	 **12**	94	>99:1	62 (*S*)
5[b]	 **13**	70	87:13	60 (*S*)
6	 **14**	55	83:17	54 (*S*)
7	 **15**	100	>99:1	55 (*S*)
8	 **16**	70	>99:1	64 (*S*)

[a] $T = 20$ °C. [b] $T = 0$ °C. [c] Conversion and α/β ratio determined by ^{1}H NMR spectroscopy. [d] *ee* determined by chiral HPLC or GC.[7c]

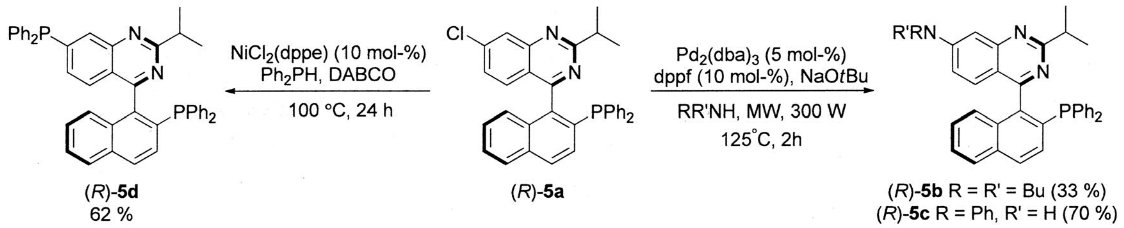
Post-Resolution Modification of (*R*)-5a

In the standard synthesis of previous members of the Quinazolinap ligand series, each ligand was prepared by a



7 (*S*)-**5a** **8**

Scheme 1. Formation of rhodium-Quinazolinap catalyst.



Scheme 2. Post-resolution modification of (*R*)-**5a**.

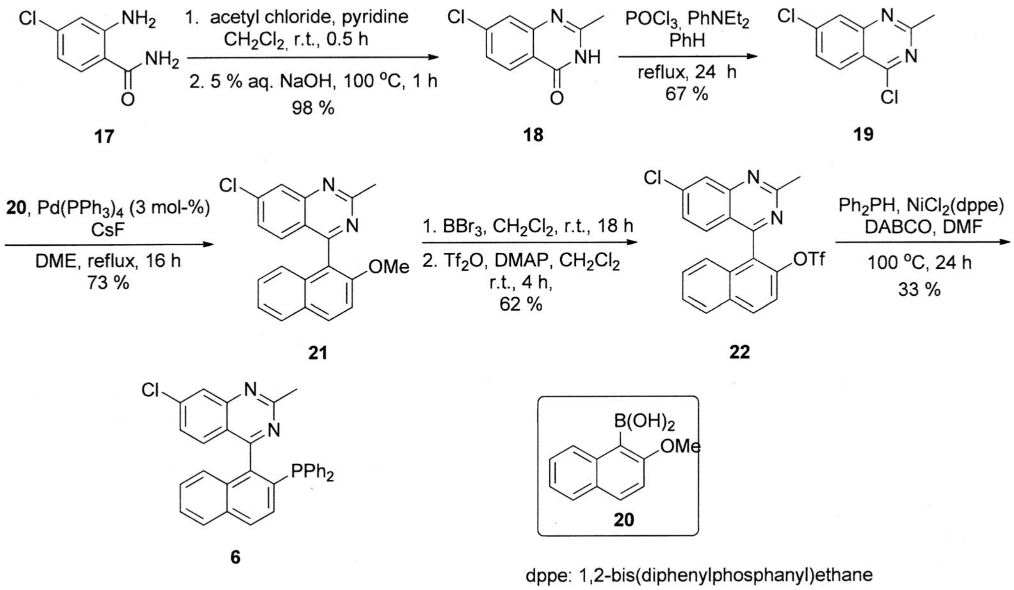
multi-step synthetic sequence from commercially available starting materials. As part of our ongoing investigations it was proposed that modification of resolved ligands could give access to a variety of enantiopure ligands. In contrast to BINAP and its analogues which are typically prepared from enantiopure BINOL, axially chiral P,N ligands are prepared racemically and then resolved.[4a] An important design feature of the ligands **5a** and **6** was the incorporation of a chlorine atom at the 7-position, as it was envisaged that this chlorine would not only act as an electronic modifier for the donor nitrogen but also as a functional handle for the diversification of these ligands at a late stage. Due to the availability of sufficient quantities of (*R*)-**5a** in our laboratory, this ligand was chosen for the post-resolution modifications in this study (Scheme 2).

We previously observed that oxidative addition occurred at the 7-position under the conditions of the Ni-catalyzed phosphanylation employed in the synthesis of **5a**.[9] With this in mind it was decided to subject (*R*)-**5a** to the same conditions which resulted in the formation of (*R*)-**5d** in a 62% yield. (*R*)-**5b** and (*R*)-**5c** were prepared in yields of 33% and 70%, respectively, by a Pd-dppf [dppf = 1,1′-bis(diphenylphosphanyl)ferrocene] mediated aryl amination under microwave conditions (initial power 300 W).

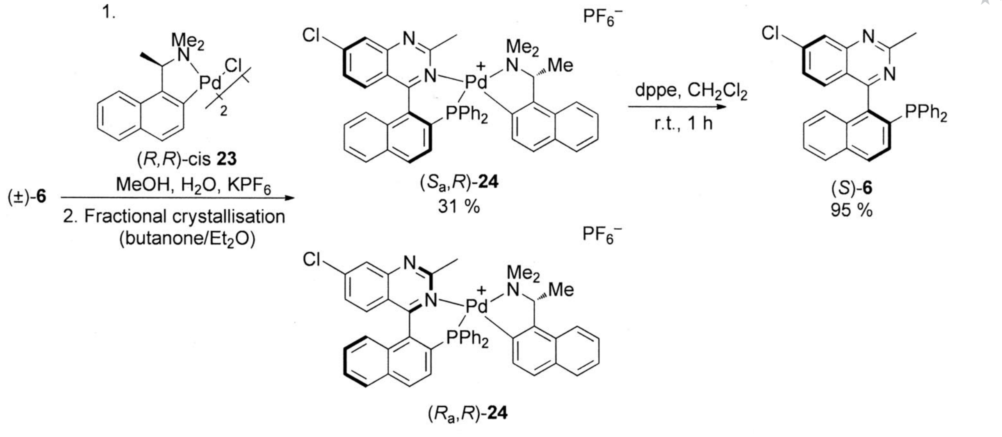
Synthesis and Resolution of 6

Racemic Quinazolinap **6** was prepared using the synthetic route previously employed for the synthesis of other members of this class of ligand.[7] Acylation of the commercially available 7-chloroanthranilamide **17** followed by a cyclocondensation furnished the quinazoline **18** in almost quantitative yield over the 2 steps. $POCl_3$-mediated chlorination of **18** yielded the chloro-quinazoline **19** in 67% yield after column chromatography. The Suzuki–Miyaura cross-coupling of **19** with aryl boronic acid **20** gave the biaryl **21** in moderate yield (73%). Removal of the methyl ether with BBr_3 and triflation of the resulting naphthol led to the formation of **22** in a 62% yield over the 2 steps. The final step in the ligand synthesis was the nickel-catalyzed cross-coupling between the triflate **22** and diphenylphosphane in the presence of $NiCl_2$(dppe)/DABCO following the protocol of Cai[11] which gave the desired phosphne **6** in a low yield of 33% (Scheme 3).[12]

The resolution of atropisomeric P-N ligands is typically carried out by the formation of diastereomers using enantiopure palladacycles derived from palladium amine complexes, followed by fractional crystallisation to yield a diastereomerically pure complex (Scheme 4). The palladium



Scheme 3. Synthesis of racemic ligand **6**.



Scheme 4. Resolution of ligand **6**.

complex (*R*,*R*)-cis-**23** was used in the resolution of Quinap **1** and previously prepared members of the Quinazolinap family. This method was employed in the present study via the formation of the diastereomeric palladacycles (S_a,*R*)-**24** and (R_a,*R*)-**24**. The racemic phosphane **6** was stirred in MeOH with the chloro-bridged resolving agent (*R*,*R*)-cis-**23** and subsequent addition of KPF_6 in water formed the diastereomeric palladacycles in a 1:1 ratio. Crystallisation from hot butanone/Et_2O precipitated (S_a,*R*)-**24** whose purity was determined to be $> 99\%$ by ^1H and ^{31}P NMR spectroscopy. The absolute configuration of the precipitated diastereomer was determined by single-crystal X-ray analysis, Figure 2. Decomplexation of the enantiopure ligand from palladium was achieved in a 95% yield by stirring the palladacycle (S_a,*R*)-**24** with dppe in dichloromethane.

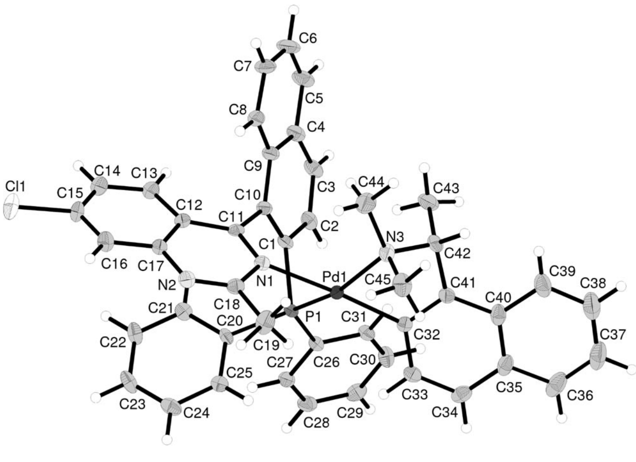
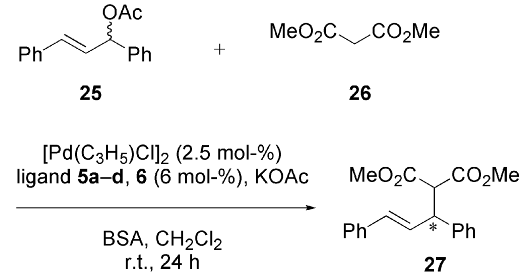


Figure 2. Single crystal X-ray structure of (S_a,*R*)-**24**,[13] counterion and hydrogens omitted for clarity. Selected bond lengths (Å): N1–Pd1 2.177(2), P1–C1 1.822(2), Cl–C 1.722(4) and P–Pd 2.2422(9). Selected bond angles: P1–Pd1–N1 81.27(8)°, C1–P1–Pd1 91.7(1)° and N1–Pd–N2 100.5(1)°.

Palladium-Catalyzed Allylic Alkylation

Allylic alkylation is an important reaction for forming different types of carbon-carbon and carbon-heteroatom bonds.[14] The reaction involves the nucleophilic displacement of an allylic leaving group and is catalyzed by a variety of transition metal catalysts, although palladium remains the most widely used. Quinazolinaps (*S*)-**5a** and **6** and (*R*)-**5b–d** were applied to the palladium-catalyzed asymmetric allylic alkylation involving the reaction of 1,3-diphenylprop-2-enyl acetate **25** and dimethyl malonate **26**, Table 2. In the present study conditions were optimised for ligand (*S*)-**5a** and these conditions were employed for reactions involving each of the remaining ligands **5b–e**.[15]

Table 2. Palladium-catalyzed allylic alkylation.



Entry[a]	Ligand	Conversion (%)	*ee* (%)[b]
1	(*S*)-**5a**	100	78 (*R*)
2	(*R*)-**5b**	100	51 (*S*)
3	(*R*)-**5c**	100	64 (*S*)
4	(*R*)-**5d**	100	58 (*S*)
5	(*S*)-**6**	100	85 (*R*)

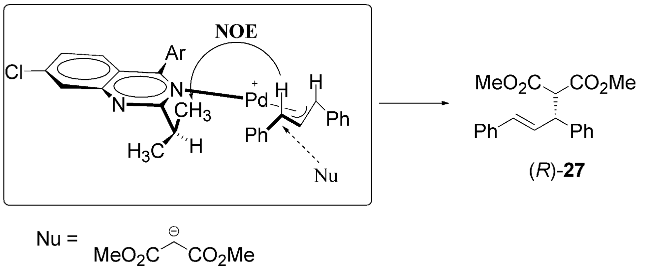
[a] Conversion determined by ^1H NMR spectroscopy. [b] *ee* values determined by chiral HPLC [OD, 99:1 hexane/2-propanol, 0.2 mL/min, R_T (*R*) = 46.2 min, R_T (*S*) 49.1 min].

Complete conversions were obtained with all the Quinazolinap ligands tested using the optimised conditions (Table 2, entries 1–5). Each of the ligands derived from (*R*)-**5a** gave a lower *ee* value than the parent 7-chloro analogue, entries 1–4. For each of these ligands there is a possibility of some monodentate binding to palladium through the phosphorus at the 7-position of **5d** and the nitrogen at the 7-position of **5b** and **5c**, although it appears that this is not the case as this would most likely have led to much lower *ee* values. It is clear that substitution at the 7-position has an effect on the enantioselectivity, although it is difficult to make a correlation between the nature of the substituent and the enantioselectivity induced. The nitrogen and phosphorus containing substituents are both electron-donating by resonance, although chlorine is net electron-withdrawing. Increasing the pK_a of nitrogen may decrease the effect of the *trans*-influence of phosphorus, which could be deleterious to enantioinduction. Ligand **6** was the best performing ligand in the present study (entry 5), with complete conversion with a good *ee* of 85%.

Solution-Phase ^{1}H NMR Studies on the Palladium Allyl Complex of 7-Chloro-2-isopropyl-Quinazolinap (S_a)-5a

A detailed solution-phase ^{1}H NMR study on the cationic palladium(II) 1,3-diphenyl-η^3-allyl intermediate **29** derived from ligand (*S*)-**5a** was carried out to gain insight in the enantioselection process. The procedure involved identifying the diastereomeric complexes formed by ^{1}H NMR spectroscopy and measuring the ratio of diastereomers by integration. The coupling between the allyl protons was confirmed by ^{1}H-^{1}H correlation spectroscopy (COSY), and insight into the relative positions of the allyl and ligand protons was gained by 2-D nuclear Overhauser effect spectroscopy (NOESY). The Quinazolinap-allyl complexes were prepared by the reaction of the Quinazolinap ligand (*S*)-**5a** with the palladium allyl dimer **28** in the presence of an excess of sodium tetrafluoroborate. The two possible diastereomeric complexes *exo*- and *endo*-**29** are shown, Scheme 5.[16]

In the ^{1}H NMR spectrum taken at –20 °C both diastereomeric complexes were present in a ratio of 87:13, which was confirmed by the ^{31}P NMR spectrum which showed two peaks at δ = 29.4 ppm (most abundant) and 32.1 ppm.[17] In the major diastereomeric intermediate the central allyl proton showed up as a triplet at δ = 6.42 ppm with a coupling constant of 11.2 Hz. The other allyl protons of the major diastereomer were identified by ^{1}H-^{1}H COSY and appeared at 5.58 (dd, J = 11.2, 9.9 Hz, *trans* to phosphorus) and 3.86 (d, J = 11.2 Hz, *trans* to nitrogen). In the 2D NOESY spectrum, a cross-peak between the isopropyl unit, specifically one of the two diastereotopic methyl groups of the Quinazolinap ligand, and the major allyl proton *trans* to phosphorus indicates that under these conditions the major diastereomer formed was *endo*-**29**, Scheme 6.

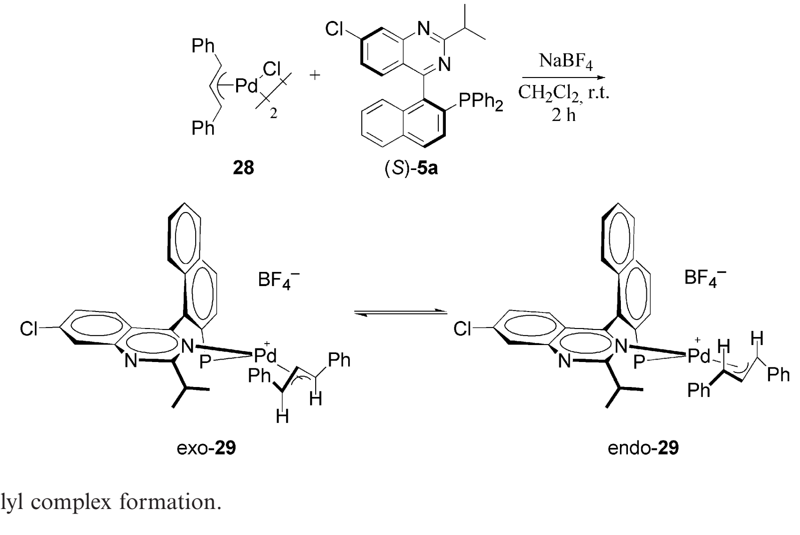


Scheme 6. NOE interactions.

Experimentally, the use of ligand (*S*)-**5a** gives the (*R*)-enantiomer of **27** as the major product (78% *ee*). This can be explained by considering nucleophilic attack occurring *trans* to phosphorus in a late transition state model, Scheme 6. In this model, as the nucleophile approaches, the allyl phenyl group is free to roll upwards without any steric interaction with the quinazoline moiety to give the η^2-palladium olefin complex, leading to the (*R*)-product. In contrast, attack *trans* to the phosphorus of the *exo*-diastereomer is disfavoured as the allylphenyl group would be required to roll downwards causing an unwanted (and high energy) steric clash with the isopropyl unit.[18] This suggests that ligands possessing (*S*)-chirality favour the formation of the (*R*)-product.

Conclusions

The synthesis of four new enantiopure Quinazolinap ligands is presented; three of these ligands **5b–d** were prepared by post-resolution modification of (*R*)-7-chloro-2-isopropyl-Quinazolinap **5a** and the remaining ligand **6** was prepared by a 7-step synthetic sequence followed by resolu-



Scheme 5. Quinazolinap-allyl complex formation.

tion. Post-resolution modification is a new approach which offers an expedient route to a range of enantiopure ligands as it precludes the need for resolution of each ligand prepared. Ligand **5a** was applied to the rhodium-catalyzed hydroboration of a range of vinylarenes with *ee* values of up to 68% and regioselectivities of up to > 99:1. Each of the ligands were applied to the palladium-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate with complete conversions and *ee* values of up to 85%. Solution phase NMR studies on the 1,3-diphenylallyl palladium complex of ligand (*S*)-**5a** provided a rationale for the sense of asymmetric induction.

Experimental Section

General: All reactions were performed under anhydrous conditions and an inert atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise indicated. Reagents were used as obtained from commercial sources or purified according to the guidelines of Perrin and Armarego.[19] Evaporation in vacuo refers to the removal of volatiles on a Büchi rotary evaporator with an integrated vacuum pump. Flash chromatography was carried out using Merck Kiesegel 60 F254 (230–400 mesh) silica gel following the method of Still et al.[20] Thin-layer chromatography (TLC) was performed on Merck DC-Alufolien plates pre-coated with silica gel 60 F254. They were visualised either by quenching of ultraviolet fluorescence, or by charring with an acidic vanillin solution (vanillin, H_2SO_4 and acetic acid in MeOH). The Microanalytical Laboratory, University College Dublin, performed elemental analyses. Electrospray mass spectra were recorded on a Micromass Quattro with electrospray probe. Exact mass ESI mass spectra (HRMS) were measured on a micromass LCT orthogonal time of flight mass spectrometer with leucine enkephalin (Tyr-Gly-Phe-Leu) as an internal lock mass. ^{1}H NMR spectra were recorded on a 300 MHz Varian-Inova spectrometer, a 400 MHz Varian-Inova spectrometer, a 500 MHz Varian-Inova spectrometer or a 600 MHz Varian-Inova spectrometer. Chemical shifts are quoted in ppm relative to tetramethylsilane and coupling constants (J) are quoted in Hz and are uncorrected. $CDCl_3$ was used as the solvent for all NMR spectra unless otherwise stated. 75.4 MHz ^{13}C NMR spectra were recorded on a 300 MHz Varian-Inova spectrometer, 101 MHz ^{13}C NMR spectra on a 400 MHz Varian-Inova spectrometer and 125 ^{13}C NMR spectra on a 500 MHz Varian-Inova spectrometer. Tetramethylsilane was used as the internal standard in all ^{13}C NMR spectra recorded. All ^{13}C NMR spectra are ^{1}H decoupled unless otherwise stated. 121.4 MHz ^{31}P NMR spectra were recorded on a 300 MHz Varian-Inova spectrometer and 162 MHz ^{31}P NMR spectra on a 400 MHz Varian-Inova spectrometer. ^{31}P Chemical shifts are reported relative to 85% aqueous phosphoric acid (δ =0.0 ppm). All ^{31}P NMR spectra are ^{1}H decoupled unless otherwise stated. All reaction solvents were obtained from a PureSolv-300–3-MD dry solvent dispenser and used without further purification unless otherwise stated. Melting points (m.p.) are quoted to the nearest 0.5 °C. HPLC analysis was carried out on a Shimadzu LC 2010A using a Supelco 2-4304 β-Dex® 120 column (30 m × 0.25 mm, 0.25 mm film). GC analysis was carried out on a Shimadzu GC 2010 using a Chiralcel OD column (0.46 cm I.D. × 25 cm). Optical rotation values were measured on a Perkin–Elmer 241 Polarimeter. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}.

Preparation of Ligands 5b–d

Post-Resolution Modification of 5a

(*R*$_a$)-*N*,*N*-Dibutyl-4-[2-(diphenylphosphanyl)naphthalen-1-yl]-2-isopropylquinazolin-7-amine (5b): A Schlenk tube was charged with tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3, 5.5 mg, 0.006 mmol), (diphenylphosphanyl)ferrocene (dppf, 6.7 mg, 0.012 mmol) and dry, degassed toluene (1.5 mL) and stirred at room temperature for 30 min. The resulting dark solution was transferred via syringe to a 10 mL microwave vial containing (*R*$_a$)-7-chloro-4-[2-(diphenylphosphanyl)naphthalen-1-yl]-2-isopropylquinazoline (30 mg, 0.06 mmol) and sodium *tert*-butoxide (7.0 mg, 0.072 mmol) and to this was added dibutylamine (9.3 mg, 12.2 µL, 0.072 mmol). The vial was placed in a CEM Discoverer microwave with an initial power setting of 300 W and heated to 125 °C for 2 h. The toluene was removed in vacuo to yield a brown oil. Column chromatography (silica gel, pentane/EtOAc, 2:1) yielded the title compound (13 mg, 33% yield) as a yellow oil, $[\alpha]_D^{20}$ = +15 (c = 0.25, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.79 (m, 3 H), 7.65–7.54 (m, 2 H), 7.48 (t, J = 7.6 Hz, 2 H), 7.40–7.10 (m, 7 H), 7.02 (d, J = 9.3 Hz, 1 H), 6.97 (dd, J = 8.3, 1.6 Hz, 2 H), 6.83 (dd, J = 9.5, 2.3 Hz, 1 H), 6.69 (dd, J = 9.3, 2.3 Hz, 1 H), 3.47–3.29 (m, 4 H), 3.15 (sept, J = 6.5 Hz, 1 H), 1.71–1.50 (m, 4 H), 1.54–1.11 (m, 8 H), 1.02–0.90 (m, 6 H), 0.88 (t, J = 7.0 Hz, 2 H) ppm. ^{13}C NMR (101 MHz $CDCl_3$): δ = 152.8, 151.8, 133.8, 133.5, 133.5, 133.3, 130.1, 129.1, 128.6, 128.3, 128.2, 128.1, 128.1, 127.9, 127.9, 127.5, 126.8, 126.6, 126.5, 126.3, 126.1, 126.0, 126.0, 125.0, 50.9, 38.2, 38.0, 21.8, 21.2, 20.3, 13.5 ppm, C-P couplings not assigned (2 peaks obscured). ^{31}P NMR (121 MHz, $CDCl_3$): δ = –13.7 ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 2957, 1612, 1550, 1497, 1368 cm^{-1}. HRMS $C_{41}H_{45}N_3P$ calcd. 610.3351, found 610.3334.

(*R*$_a$)-4-[2-(Diphenylphosphanyl)naphthalen-1-yl]-2-isopropyl-*N*-phenylquinazolin-7-amine (3c): A Schlenk tube was charged with tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3, 5.5 mg, 0.006 mmol), diphenylphosphanylferrocene (dppf, 6.7 mg, 0.012 mmol) and dry, degassed toluene (1.5 mL) and stirred at room temperature for 30 min. The resulting dark solution was transferred via syringe to a 10 mL microwave vile containing (*R*$_a$)-7-chloro-4-[2-(diphenylphosphanyl)naphthalen-1-yl]-2-isopropylquinazoline (30 mg, 0.06 mmol) and sodium *tert*-butoxide (7.0 mg, 0.072 mmol) and to this was added aniline (6.5 mg, 6.5 µL, 0.072 mmol). The vial was placed in a CEM Discoverer microwave with an initial power setting of 300 W and heated to 125 °C for 2 h. The toluene was removed in vacuo to yield the title compound as a brown oil. Preparative TLC (silica gel, pentane/EtOAc, 2:1) yielded the title compound (24 mg, 70% yield) as an orange powder, m.p. 150–152 °C, $[\alpha]_D^{20}$ = +30 (c = 0.2, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (br. s, 1 H), 7.99–7.78 (m, 4 H), 7.46 (t, J = 6.5 Hz, 2 H), 7.35–7.02 (m, 15 H), 7.01–6.88 (m, 3 H), 3.55 (sept., J = 6.1 Hz, 1 H), 1.17 (d, J = 6.1 Hz, 6 H) ppm. ^{13}C{^{31}P} NMR (101 MHz $CDCl_3$): δ = 138.5, 136.0 (d, J = 11.2 Hz), 133.6 (d, J = 20.2 Hz), 133.3, 133.2 (d, J = 18.8 Hz), 131.3 (d, J = 7.7 Hz), 130.0, 129.8, 129.4, 129.0, 128.9, 128.5 (d, J = 6.6 Hz), 128.5, 128.3 (d, J = 11.2 Hz), 128.3, 127.4, 127.3, 125.5 (d, J = 6.9 Hz), 125.2, 122.4, 34.9, 20.9, 20.6 ppm, 3 C signals obscured. ^{31}P NMR (121 MHz, $CDCl_3$): δ = –13.6 ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 3055, 2087, 1265, 909, 735 cm^{-1}. HRMS $C_{39}H_{33}N_3P$ calcd. 574.2412, found 574.2414.

(*R*)-7-(Diphenylphosphanyl)-4-[2-(diphenylphosphanyl)naphthalen-1-yl]-2-isopropylquinazoline (3d): To a solution of $NiCl_2$(dppe) [5.2 mg, 0.01 mmol; dppe: 1,2-bis(diphenylphosphane)ethane] in DMF (1 mL) was added Ph_2PH (14 mg, 0.075 mmol), and the mixture was stirred at 100 °C for 30 min. A solution of (*R*$_a$)-7-chloro-4-[2-(diphenylphosphanyl)naphthalen-1-yl]-2-isopropylquinazoline

(51.7 mg, 0.1 mmol) and DABCO (44 mg, 0.4 mmol) in DMF (1 mL) was added via syringe to form a dark brown solution. After 1 h a second portion of Ph_2PH (14 mg, 0.075 mmol) was added and stirring continued for 24 h, after which the solution was cooled to room temperature and filtered through Celite®. The residue was reduced in vacuo and taken up in dichloromethane (10 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), and concentrated in vacuo to give a brown oil. Flash column chromatography (silica gel, pentane/EtOAc, 4:1) gave the title compound as a white solid (41 mg, 62%). $[\alpha]_D^{20} = +20$ (c = 0.25, $CDCl_3$), identical physical data to previously prepared racemic sample.

Procedures for the Synthesis and Resolution of Ligand 3e

7-Chloro-2-methylquinazolin-4(3*H*)-one (15): 2-Amino-4-chlorobenzamide **14** (25.0 g, 147 mmol) was suspended in dichloromethane (250 mL) and to this pyridine (13.0 mL, 161 mmol) was added. Acetyl chloride (11.4 mL, 161 mmol) was added slowly and the precipitate dissolved. Stirring was continued at room temperature for 2 h during which time a precipitate formed. The solvent was reduced in vacuo and a small sample of the acylated product was purified by column chromatography (pentane/ethyl acetate, 1:1), m.p. 205.5–208.0 °C. ^{1}H NMR (400 MHz, DMSO [D_6]): δ = 11.73 (s, 1 H), 8.52 (d, J = 2.1 Hz, 1 H), 8.30 (br. s, 1 H), 7.79 (d, J = 8.4 Hz, 2 H), 7.16 (dd, J = 8.4, 2.1 Hz, 1 H), 2.06 (s, 3 H) ppm. ^{13}C (101 MHz, DMSO [D_6]): δ = 170.6, 169.4, 141.6, 137.3, 131.0, 122.7, 120.0, 118.7, 25.7 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1764, 1642, 1599, 1049, 779 cm^{-1}. To the remaining residue was added to 5% aqueous NaOH (350 mL) and the solution was heated at reflux until all solid had dissolved (ca. 15 mins). 1 M HCl was added until the pH was about 7, the white precipitate which formed was filtered, washed with water (200 mL) and dried by applying pump vaccum. **5** (27.1 g, 98%) was isolated as white fibrous crystals, m.p. 264–266 °C. ^{1}H NMR (300 MHz, DMSO): δ = 12.30 (br. s, 1 H), 8.05 (d, J = 8.5 Hz, 1 H), 7.60 (d, J = 1.5 Hz, 1 H), 7.46 (dd, J = 6.5, 2 Hz, 1 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 161.8, 156.8, 150.8, 139.5, 128.5, 126.8, 126.4, 120.2, 22.2 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3023, 1679, 1600 and 1340 cm^{-1}. m/z (EIMS 70 eV) 193 (M^+ 100%), 195 (36%). $C_9H_7ClN_2O$ (194.62): calcd. C 55.54, H 3.63, N 14.39, Cl 18.22; found C 55.35, H 3.49, N 14.17, Cl 18.47.

4,7-Dichloro-2-methyl-3,4-dihydroquinazoline (16): A solution of 7-chloro-2-methylquinazolin-4(3*H*)-one **15** (5.0 g, 25.7 mmol) and *N*,*N*-diethylanailine (5.6 mL, 38.5 mmol) in benzene (60 mL) was azeotropically dried using a Dean–Stark trap. Phosphorus oxychloride (1.56 mL, 16.9 mmol) was added and refluxed for 16 h giving a brick-red solution. The mixture was cooled to room temperature, diluted with ethyl acetate (40 mL) and washed sequentially with water (2 × 40 mL), HCl (1 M, 2 × 40 mL), water (40 mL), $NaHCO_3$ (40 mL), water (40 mL) and brine (40 mL). The solution was dried ($MgSO_4$) and volatiles reduced in vacuo to give a yellow solid. This was purified by column chromatography (silica gel, pentane/EtOAc, 4:1) to yield **6** (3.67 g, 67%) as a white solid, m.p. 95–96 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (d, J = 9.0 Hz, 1 H), 7.96 (d, J = 2.1 Hz, 1 H), 7.60 (dd, J = 9.0, 2.1 Hz, 1 H), 2.85 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.0, 162.2, 152.2, 141.6, 129.4, 127.4, 127.3, 120.5, 26.3 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 760, 1463, 1583, 1360 cm^{-1}. m/z (EIMS 70 eV) 212.9 [(M – H)$^+$ 100%], 215.0 [(M^+ – H) 68%], 216.0 [(M^+ – H) 10%]. $C_9H_6Cl_2N_2$ (213.92): calcd. C 50.73, H 2.84, N 13.15; found C 50.75, H 2.93, N 13.04.

7-Chloro-4-(2-methoxynaphthalen-1-yl)-2-methylquinazoline (17): 4,7-Dichloro-2-methyl-3,4-dihydroquinazoline (**16**) (3.5 g, 16.4 mmol) and $Pd(PPh_3)_4$ (0.57 g, 0.05 mmol) were dissolved in anhydrous dimethoxyethane (DME, 100 mL) and stirred at room temperature for 10 min. 2-(Methoxynaphthalen-1-yl)boronic acid (3.3 g, 16.4 mmol) and caesium fluoride (4.98 g, 32.8 mmol) were added under a flow of nitrogen. The yellow solution was stirred at 85 °C for 16 h (TLC). After cooling to room temperature water (60 mL) and dichloromethane (60 mL) were added and the layers separated. Extraction was completed with further portions of dichloromethane (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$) and reduced in vacuo to give the crude product as a yellow solid. Purification by column chromatography (silica gel, pentane/EtOAc, 3:1) gave **7** (4.0 g, 73%) as a white solid, m.p. 140–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.4 (dd, J = 9.2, 2.0 Hz, 2 H), 7.87 (dd, J = 7.2, 3.2 Hz, 1 H), 7.41 (app t, J = 9.2 Hz, 2 H), 7.35–7.36 (m, 1 H), 7.32–7.33 (m, 1 H), 7.29–7.31 (m, 1 H), 7.06–7.08 (m, 1 H), 3.80 (s, 3 H), 2.99 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.7, 165.7, 154.8, 151.6, 140.2, 133.1, 131.7, 129.2, 128.7, 128.3, 128.1, 127.6, 127.3, 124.3, 124.2, 122.0, 119.1, 113.2, 56.6, 27.0 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3061, 1601, 6504, 800 cm^{-1}. $C_{20}H_{15}ClN_2O$ (338.58): calcd. C 71.75, H 4.52, N 8.37, Cl 10.59; found C 71.64, H 4.45, N 8.26, Cl 10.55.

1-(7-Chloro-2-methylquinazolin-4-yl)naphthalen-2-yl Trifluoromethanesulfonate (18): 7-Chloro-4-(2-methoxynaphthalen-1-yl)-2-methylquinazoline (8.0 g, 23.9 mmol) was dissolved in dry dichloromethane (120 mL). Boron tribromide (1 M in DCM, 47.8 mL, 47.8 mmol) was added carefully and the dark red/black solution was stirred for 18 h.[6a] Water (100 mL) was added carefully and stirring continued for 1 h, after which time an orange precipitate formed, which was filtered and thoroughly dried under vacuum. The orange solid was taken up in dichloromethane (120 mL) and to this was added *N*,*N*-dimethylaminopyridine (8.8 g, 71.7 mmol). Trifluoromethanesulfonic anhydride (7.4 g, 4.45 mL, 26.3 mmol) was added and the resulting black solution stirred at room temperature for 4 h. The solution was washed with HCl (1 M, 100 mL) and extraction completed with further portions of dichloromethane (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$) and solvent removed in vacuo. Purification by column chromatography (silica gel, pentane/EtOAc, 3:1) yielded the title compound (6.4 g, 62% over 2 steps) as a white solid, m.p. 133.0–135.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, J = 9.1 Hz, 1 H), 8.09 (d, J = 1.7 Hz, 1 H), 8.01 (d, J = 8.3 Hz, 1 H), 7.62–7.59 (m, 2 H), 7.46 (t, J = 7.2 Hz, 1 H), 7.39–7.31 (m, 2 H), 7.24 (m, 1 H), 2.99 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 265.8, 163.4, 151.8, 144.9, 141.0, 132.6, 132.4, 132.4, 128.8, 128.7, 128.7, 128.0, 127.8, 127.7, 126.9, 126.1, 121.4, 119.8, 119.8, 26.7 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3063, 1557, 1415, 1215 cm^{-1}. LRMS 453.0, 455.0 (2:1). $C_{20}H_{12}ClF_3N_2O_3S$ (452.61): calcd. C 53.05, H 2.67, N 6.19, Cl 7.83, S 7.08; found C 53.00, H 2.70, N 6.06, Cl 8.21, S 7.58.

7-Chloro-4-[2-(diphenylphosphanyl)naphthalen-1-yl]-2-methylquinazoline (3e): To a solution of $NiCl_2$(dppe) [116 mg, 0.22 mmol; dppe: 1,2-bis(diphenylphosphane)-ethane] in DMF (4 mL) was added Ph_2PH (305 mg, 3.3 mmol), and the mixture was stirred at 100 °C for 30 min. A solution of **8** (1.0 g, 2.2 mmol) and DABCO (1.6 g, 8.8 mmol) in DMF (4 mL) was added via cannula to give initially a pale green transparent solution which over the course of 1 h became a dark brown solution. After 1 h a second portion of Ph_2PH (305 mg, 3.3 mmol) was added. After 24 h at 100 °C the solution was cooled to room temperature and filtered through Celite® the residue was reduced in vacuo and taken up in dichloromethane (10 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a brown oil. **3e** (355 mg, 33%) was isolated by column chromatography (silica gel, pentane/EtOAc, 20:1 to 9:1) as a white solid, m.p. 94–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ =

8.03 (d, J = 8.5 Hz, 1 H), 7.90, (t, J = 8.3 Hz, 2 H), 7.80 (ddd, J = 8.4, 6.8, 1.5 Hz, 1 H), 7.50 (t, J = 7.5 Hz, 1 H), 7.40 (dd, J = 8.5, 3.2 Hz, 1 H), 7.36–7.19 (m, 10 H), 7.16 (dd, J = 10.7, 4.4 Hz, 2 H), 7.10 (d, J = 8.5 Hz, 1 H), 2.79 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.2 (d, J_{cp} = 6.7 Hz), 163.9, 150.6, 136.8 (d, J_{cp} = 11.4 Hz), 136.7 (d, J_{cp} = 10.7 Hz), 134.7 (d, J_{cp} = 15.5 Hz), 133.8 (d, J_{cp} = 4.2 Hz), 133.7 (d, J_{cp} = 12.5 Hz), 133.5 (d, J_{cp} = 7.2 Hz), 131.8 (d, J_{cp} = 7.4 Hz), 129.8, 129.1, 128.6, 128.6, 128.4, 128.3, 128.0, 128.0, 127.0, 126.9, 126.9, 126.6, 126.1, 26.4 ppm. (2 peaks obscured). ^{31}P NMR (121 MHz, $CDCl_3$): δ = –13.4 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2360, 1555, 1478, 1461 cm^{-1}. HRMS calcd. for $C_{31}H_{22}ClN_2P$ 489.1287, found 489.1273.

Resolution of 3e: (+)-Di-μ-chlorobis{(*R*)-dimethyl[1-(1-naphthyl)-ethyl]aminato-*C*^{2},*N*}dipalladium(II) (41.6 mg, 0.065 mmol) and (*R*,*S*)-7-chloro-4-[2-(diphenylphosphanyl)naphthalen-1-yl]-2-methylquinazoline (60 mg, 0.12 mmol) were dissolved in MeOH (5 mL) and stirred for 16 h to give a yellow solution. To this was added KPF_6 (22 mg, 0.12 mmol) in water (1 mL), upon which a yellow precipitate formed. Stirring was continued for 10 min and filtered to yield a yellow powder which was shown to be a 1:1 mixture of the (R_a,*R*) and (S_a,*R*) bidentate complexes (^{31}P NMR showed two peaks of equal intensity at δ = 37.6 and 40.8 ppm). Fractional crystallisation from butanone/diethyl ether gave a single diastereomer (S_a, *R*)-**3e** (35 mg, 31%), m.p. 226–227 °C. $[\alpha]_D^{20}$ = –201 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, J = 8.3 Hz, 1 H), 8.08 (d, J = 8.3 Hz, 1 H), 7.89–7.13 (m, 11 H), 7.09 (d, J = 8.7 Hz, 1 H), 6.97–6.74 (m, 9 H), 6.70 (t, J = 6.2 Hz, 1 H), 6.61 (dd, J = 8.3, 6.5 Hz, 1 H), 4.26 (t, J = 7.9 Hz, 1 H), 3.55 (s, 3 H), 2.75 (s, 3 H), 2.52 (d, J = 3.3 Hz, 3 H), 1.29 (d, J = 6.3 Hz, 3 H) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = 37.6, 143.5 (sept, J = 712 Hz) ppm. HRMS calcd. for $C_{45}H_{38}ClN_3PPd$ 792.1527, found 792.1498. Absolute configuration was determined by X-ray crystallography, crystals were grown by slow diffusion of pentane into a solution of the complex in $CDCl_3$.

Decomplexation: The (S_a,*R*)-palladium complex (30 mg, 0.03 mmol) was dissolved in dichloromethane (2 mL) and to this was added 1,2-bis(diphenylphosphane)ethane (11 mg, 0.03 mmol) and the resulting solution was stirred for 3 h at room temperature. Solvent was removed in vacuo and the resulting solid was purified by column chromatography (silica gel, CH_2Cl_2) to give (S_a)-7-chloro-4-[2-(diphenylphosphanyl)naphthalen-1-yl]-2-methylquinazoline as a white solid (95%). $[\alpha]_D^{20}$ = –61 (c = 1, $CHCl_3$). Identical physical data to a previously prepared racemic sample.

Asymmetric Hydroboration Procedure: The required Quinazolinaprhodium(1,5-cyclooctadiene)trifluoromethanesulfonate catalyst (5 μmol) in THF (2 mL) was placed under nitrogen in a Schlenk tube. Freshly distilled catecholborane (53 μL, 0.5 mmol) was added via microlitre syringe and the light brown solution was allowed to stir for five minutes at the required temperature. The substrate olefin (0.5 mmol) was injected and the reaction mixture was stirred for either two hours or twenty-four hours at room temperature or at 0 °C. The reaction was then cooled to 0 °C; ethanol (1 mL) was added; followed by 1 M NaOH (3 mL) and H_2O_2 (3 mL). The ice bath was removed and the solution was stirred for one h at room temperature. The reaction mixture was transferred to a separatory funnel and diethyl ether (10 mL) was added. The organic layer was washed with 1 M NaOH (10 mL), brine (10 mL) and dried with $MgSO_4$. The solution was filtered and the solvent was removed in vacuo to give the hydroborated product as an oil. Conversion and regioselectivity were determined by ^{1}H NMR spectroscopy. The *ee* value was calculated by chiral GC or HPLC analysis as previously reported.[7c]

Asymmetric Allylic Alkylation Procedure: Ligand **3a**–**e** (9.1μmol, 6.0 mol-%) and $[Pd(C_3H_5)Cl]_2$ (1,4 mg, 3.8 μmol, 2.5 mol-%) were stirred in dichloromethane (1.5 mL) for 20 min to give a pale yellow solution. To this was added (*E*)-1,3-diphenylallyl acetate (37.8 mg, 0.15 mmol) and the resulting solution stirred for an additional 5 min. Dimethyl malonate (51 μL, 0.45 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 111 μL, 0.45 mmol) and base (ca. 1 mg) were added. The resulting mixture was stirred at room temperature for 24 h. The solvent was reduced in vacuo to give a yellow oil which was purified by column chromatography (pentane/ethyl acetate, 10:1) to give the product as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 10 H), 6.47 (d, J = 15.8 Hz, 1 H), 6.34 (dd, J = 15.8, 8.4 Hz, 1 H), 4.27 (dd, J = 10.8, 8.5 Hz, 1 H), 3.95 (d, J = 10.8 Hz 1 H), 3.70 (s, 3 H), 3.52 (s, 3 H) ppm. The% conversion was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. The *ee* values were determined by chiral HPLC Diacel's Chiralpak® OD, 1 cm × 25 cm; hexanes/isopropyl alcohol (99:1), 0.2 mL min^{-1}; 25 °C; 254 nm; R_T 46.2 min (*R*), 49.1 min (*S*). Absolute configuration was assigned by comparison of the optical rotation of enantio-enriched product with the literature data.[21]

Supporting Information (see also the footnote on the first page of this article): Relevant ^{1}H, ^{13}C, NMR spectra for compounds **5b**–**d**, **6**, **21**–**22**, and spectra relating to the NMR studies of allylic alkylation.

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[13] Crystal data and structure refinement for (S_a,R)-**24**: empirical formula $C_{91}H_{78}N_6F_{12}P_4Cl_4Pd_2$, formula weight 1962.07, T = 100(2) K, crystal system: triclinic, space group $P1$(#1), unit cell dimensions: a = 9.4963(7) Å, α = 103.099(2)°, b = 15.2678(11) Å, β = 94.973(2)°, c = 15.3460(11) Å, γ = 99.163(2)°, volume 2121.9(3) Å^3, Z = 1, density (calcd.): 1.535 Mg/m^3, reflections collected: 43701, independent reflections: 20950 [R(int) = 0.0338]. CCDC-745826 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from: The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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