Electronically varied quinazolinaps for asymmetric catalysis†

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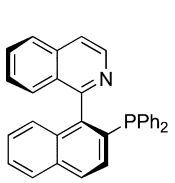
The synthesis and resolution of electronically varied axially chiral Quinazolinaps is reported. These ligands bear different aryl groups on the donor phosphorus atom and were synthesised as part of our investigations into electronic effects within this ligand class. A diastereomerically pure palladacycle of one ligand was characterised by X-ray crystallography. The application of these Quinazolinaps to the rhodium-catalysed hydroboration of vinylarenes resulted in enantioselectivities of up to 92%. Their application to the palladium-catalysed allylic alkylation of 1,3-diphenylprop-2-enyl acetate resulted in conversions of up to 99% and enantioselectivities of up to 94%.

Introduction

Much of the success in enantioselective homogeneous catalysis is dependent upon the application of specifically designed chiral ligands to important synthetic transformations. The development of atropisomeric diphosphines such as Binap has found widespread applicability in asymmetric hydrogenation, olefin isomerization, allylic alkylation, the Heck reaction and enantioselective hydroboration.[1–5] Subsequently, the development of axially chiral heterobidentate systems has become an active area of research, with the phosphinamine ligand class receiving 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.[6,7] Following on from work by Brown *et al.*,[8] who developed the first successful axially chiral phosphinamine Quinap **1**, we have designed a series of axially chiral phosphinamines termed Quinazolinaps. Previously, we have reported the synthesis and resolution of a steric series of these ligands **2a–f**, which have been applied to the rhodium-catalysed asymmetric hydroboration of vinylarenes where they induced excellent conversions, regioselectivities and enantioselectivities up to 99.5%.[9] We have also synthesised Quinazolinaps **2g–h**, as an investigation into the effect of having a hemilabile donor nitrogen atom on the 2-aryl substituent and applied them to the palladium-catalysed allylic alkylation of 1,3-diphenylpropenyl acetate with excellent conversions and enantioselectivities up to 81%.[10]

The majority of reports of ligand modification have followed from systematic variation of the spatial demands of the catalyst. However, research on substituent-controlled electronic tuning of chiral ligands has demonstrated that catalyst activity and selectivity can often be improved.[11] In order to gain further insights into electronic effects in our Quinazolinap series, we have commenced a study on electronic variations at the donor phosphorus atom, ligands **3a–b**, by including electron-donating and electron-withdrawing groups on the diarylphosphine unit. 2-*i*Pr-Quinazolinap **2e** was chosen as the parent ligand as it has consistently given the best results of the Quinazolinap family in the asymmetric transformations studied.[9] Herein we now wish to report the synthesis and resolution of ligands **3a–b** and their application in the rhodium-catalysed hydroboration of vinylarenes and palladium-catalysed allylic alkylation.



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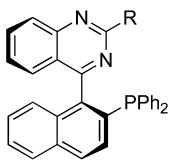
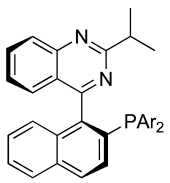


2a R = H; **2b** R = Me
2c R = Ph; **2d** R = Bn
2e R = *i*-Pr; **2f** R = *t*-Bu
2g R = 2-(2-pyridyl)
2h R = 2-(2-pyrazinyl)



3a Ar = 3,5-xylyl
3b Ar = 3,5-$F_2C_6H_3$

Results and discussion

Synthesis and resolution

Racemic Quinazolinaps **3a–b** were synthesised using a synthetic route originally developed for the preparation of an electronic series of Quinap ligands.[12] This involved the coupling of 1-(2-isopropyl-quinazolin-4-yl)-2-naphthyl(trifluoromethyl)sulfonate **4**, a late stage intermediate in the preparation of ligand **2e**[9e] with the diarylphosphine oxides **5a–b** (Scheme 1) in moderate to good yields (53–76%).[13–15] This was followed by reduction of the coupled phosphine oxide **6a–b** in 48–70% yields to afford the desired ligands **3a–b**.

The formation of diastereomeric complexes with enantiopure palladium amine complexes, followed by fractional crystallisation, is an important strategy in the resolution of phosphorus-containing ligands. In particular, the *ortho*-palladated derivatives of (*R*)-dimethyl(1-(1-naphthyl)ethyl)amine **7** have received significant attention;[16,17] it has been used as the resolving agent for the

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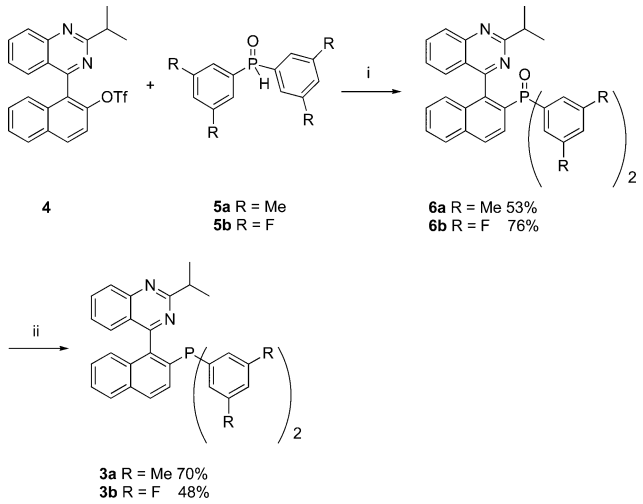
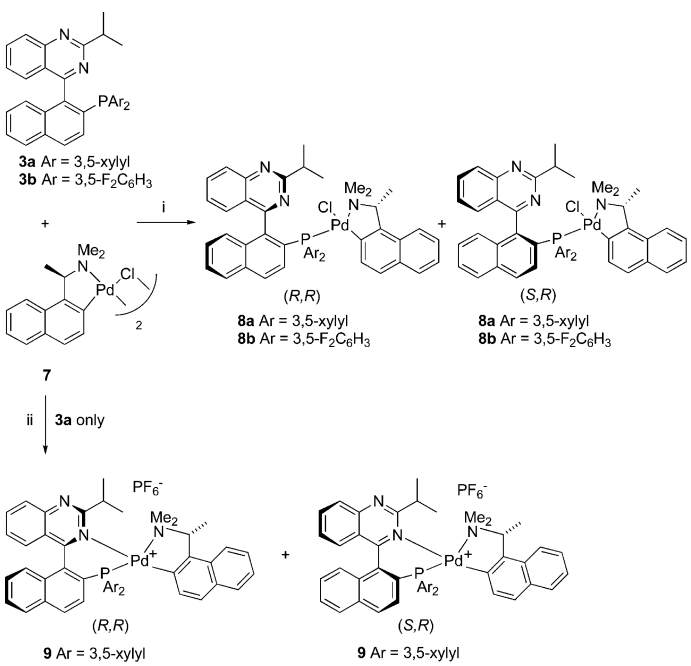
† Electronic supplementary information (ESI) available: Characterisation data for compounds **3a–b**, **6a–b**, **8–9**, **11a–b**, **6a–b**, details of the resolution of **3a–b**, and general procedures employed for asymmetric hydroboration and allylic alkylation. CCDC reference number 664580. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b810936b



Scheme 1 *Reagents and conditions:* (i) $Pd(OAc)_2$, dppb, DIPEA, DMSO, 110 °C, 24 h; (ii) $HSiCl_3$, Et_3N, toluene, 100 °C, 24 h.

resolution of Quinap, Phenap and previously synthesised members of the Quinazolinap ligand class.[8–10,18]

A mixture of monodentate palladacycles (*R*,*R*)-**8a** and (*S*,*R*)-**8a** were obtained by stirring ligand **3a** overnight in methanol with resolving agent **7** but all attempts at separation by fractional crystallisation were unsuccessful at this stage (Scheme 2). The mixture was redissolved in methanol, and after the addition of potassium hexafluorophosphate in water and stirring overnight, a creamy precipitate was obtained. This precipitate was a mixture of bidentate palladacycles (*R*,*R*)-**9** and (*S*,*R*)-**9**. Fractional crystallisation of this mixture, using hot chloroform and diethyl ether, yielded a precipitate that was determined by ^{1}H and ^{31}P NMR spectroscopy to be diastereomerically pure. Crystals suitable for X-ray crystallographic analysis were grown from deuterated chloroform and diethyl ether. The crystal structure obtained indicated that the isolated complex was (*S*,*R*)-di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine diastereomer (*S*,*R*)-**9** (Fig. 1).



Scheme 2 *Reagents and conditions:* (i) CH_2Cl_2–MeOH, RT, 18 h; (ii) MeOH, KPF_6, H_2O, RT, 18 h.

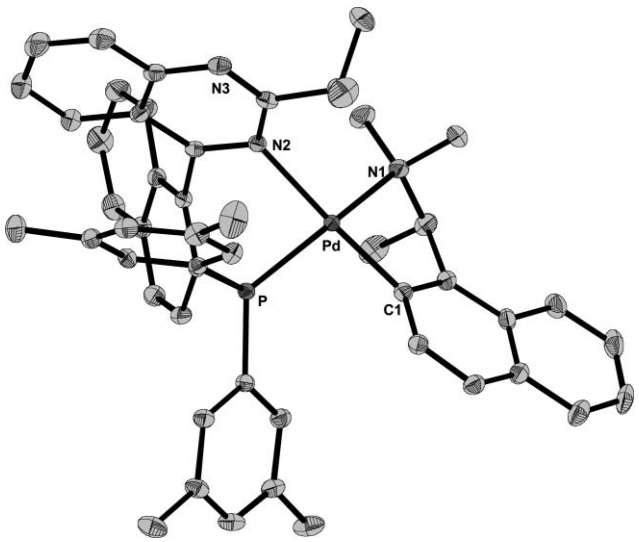
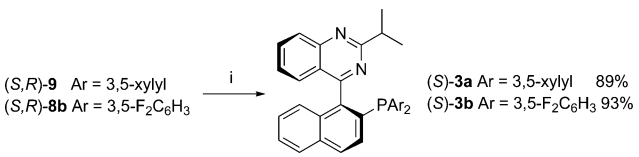


Fig. 1 ORTEP representation of (*S*,*R*)-**9** (hydrogen atoms and counter ion omitted for clarity).

Using a similar approach, a mixture of monodentate palladacycles (*R*,*R*)-**8b** and (*S*,*R*)-**8b** were obtained by stirring ligand **3b** overnight in dichloromethane with resolving agent **7** (Scheme 2). After stirring overnight, a creamy yellow-coloured precipitate had formed. The precipitate and filtrate were combined and recrystallised from hot chloroform and ether. A long crystallisation period of three weeks eventually resulted in yellow crystals which, by ^{1}H and ^{31}P NMR spectroscopy, were found to be diastereomerically pure. To date no X-ray crystallographic analysis of this complex has been obtained; however, the isolated diastereomeric complex has been assigned the configuration (*S*,*R*)-**8b** based on comparing the optical rotation of the free ligand to previously investigated members of the Quinazolinap ligand class and the sense of induction obtained in asymmetric catalysis (*vide infra*).

Enantiomerically pure (*S*)-di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine **3a** and (*S*)-di(3,5-difluorophenyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine **3b** were readily obtained by decomplexation of the resolved diastereomers (*S*,*R*)-**9** and (*S*,*R*)-**8b**, respectively, with 1,2-bis(diphenylphosphino)ethane in dichloromethane (Scheme 3).



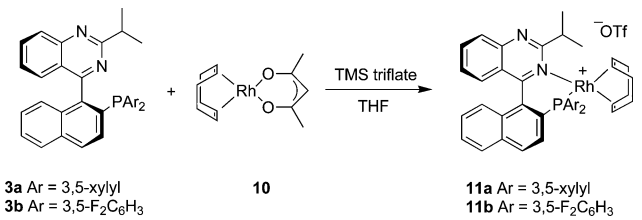
Scheme 3 *Reagents and conditions:* (i) DPPE, CH_2Cl_2, RT, 3 h.

Rhodium-catalysed hydroboration

The rhodium-catalysed 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.[19] The steric series of Quinazolinaps **2a–f** have been successfully applied to the asymmetric rhodium-catalysed hydroboration[9e] and we now wish to report the application of the novel Quinazolinaps **3a–b** to this transformation.

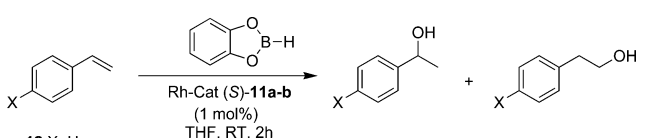
Styrene and two vinylarene derivatives **12–14** were tested as hydroboration substrates using *in situ*-prepared rhodium-Quinazolinap complexes (*S*)-**11a–b** as the active catalysts (Scheme 4).[9e] Reactions were carried out both at room temperature and at 0 °C and it was found that reactions at the higher temperature always gave superior results so it is these results that are reported (Table 1).



Scheme 4 Formation of rhodium-Quinazolinap catalysts.

The application of catalyst complexes (*S*)-**11a–b** to the hydroboration of substrates **12–14** gave both significantly decreased enantioselectivities and conversions compared to those observed with the catalyst derived from parent 2-isopropyl-Quinazolinap **2e**.[9e] However, the regioselectivities obtained with (*S*)-**11a–b** were generally high, in particular complex (*S*)-**11b**, containing the 3,5-difluorophenylphosphine moiety, gave consistently higher regioselectivities than 2-isopropyl-Quinazolinap (typically in the range 77 : 23 to 81 : 19). The best result with these substrates (entry 4–76% conversion, 92% ee and 86 : 14 regioselectivity) was obtained using catalyst (*S*)-**11b** in the hydroboration of *p*-methoxystyrene (entry 4). By comparison, the application of the catalyst based on 2-*i*Pr-Quinazolinap ligand **2e** under the same conditions also resulted in 92% ee combined with 76 : 24 regioselectivity. There was a marked reduction in enantioselectivities when changing from an electron-releasing to an electron-withdrawing substituent in the substrate vinylarenes (compare entries 5,6 with 1–4). An analysis

Table 1 Rhodium-catalysed hydroboration of substituted styrenes



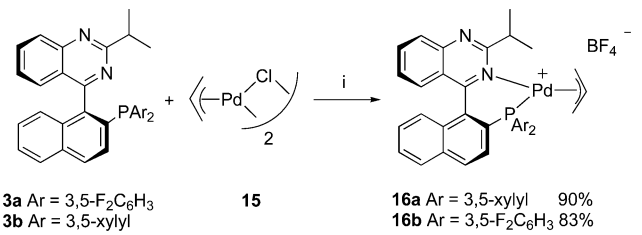
Entry	Catalyst	Substrate	Conversion (%)[a]	α : β[a]	Ee (%)[b]
1	(*S*)-**11a**	**12**	89	81 : 19	68 (*S*)
2	(*S*)-**11b**	**12**	55	85 : 15	72 (*S*)
3	(*S*)-**11a**	**13**	93	68 : 32	80 (*S*)
4	(*S*)-**11b**	**13**	76	86 : 14	92 (*S*)
5	(*S*)-**11a**	**14**	69	81 : 19	44 (*S*)
6	(*S*)-**11b**	**14**	56	85 : 15	58 (*S*)

[a] Conversions and regioselectivities determined by ^{1}H NMR spectroscopy. [b] Enantiomeric excesses determined by chiral GC.

of the results obtained with rhodium complexes of ligands **3a** and **3b** shows that substitution at the *m*-positions with fluorine rather than methyl groups, results in better regio- and enantioselectivities, although the conversions tend to be somewhat lower.

Palladium-catalysed allylic alkylation

Allylic alkylation is an important reaction for forming different types of carbon–carbon and carbon–heteroatom bonds.[20,21] The reaction involves the nucleophilic displacement of an allylic leaving group and is catalysed by a variety of transition-metal catalysts, although palladium remains the most widely used. Quinazolinaps (*S*)-**3a–b** were applied to the palladium-catalysed asymmetric allylic alkylation involving the addition of the dimethyl malonate anion to 1,3-diphenylprop-2-enyl acetate **17**. As the active palladium(0) species for allylic alkylation are not isolable, an air-stable form of the ligand complexes was prepared. The reaction of (*S*)-**3a–b**, with di-μ-chloro-bis(π-allyl)dipalladium **15** and sodium tetrafluoroborate in dichloromethane gave the η^3-palladium-allyl complexes (*S*)-**16a–b** in high yields of 83–90% (Scheme 5).



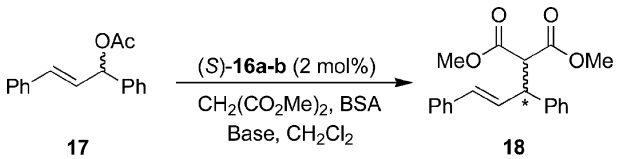
Scheme 5 *Reagents and conditions:* (i) $NaBF_4$, CH_2Cl_2, RT, 18 h.

The two standard methods employed for the reaction between dimethyl malonate and 1,3-diphenylprop-2-enyl acetate are the bis-trimethylsilylacetamide (BSA) procedure, in which the nucleophile is generated *in situ* upon addition of a base; and the malonate procedure, in which the nucleophile is pre-formed as its sodium salt. Both methods were applied in the current study. Although dimethylformamide, tetrahydrofuran and acetonitrile were also screened as solvents, dichloromethane gave superior results in all cases. When using the malonate method, a selection of bases (KOAc, NaOAc, LiOAc and $CsCO_3$) was also screened. Reactions were carried out at room temperature, 40 °C and 0 °C and the results for each method is presented (Tables 2 and 3).

The application of catalysts (*S*)-**16a–b** in the palladium-catalysed allylic alkylation of 1,3-diphenylprop-2-enyl acetate **17** using the BSA method resulted in good to excellent enantiomeric excesses of 80–94% (Table 2). In particular, catalyst (*S*)-**16a** gave consistently high enantioselectivities; the highest obtained was 94% after 120 h at 0 °C when using NaOAc as the base (entry 6). By comparison, the application of the catalyst derived from 2-*i*Pr-Quinazolinap ligand **2e** resulted in a maximum enantioselectivity of 91% at 0 °C when using KOAc as the base.[22] The maximum enantioselectivity achieved with catalyst (*S*)-**16b** was 84% (entry 8).

The use of the malonate method, in which the nucleophile is used as its sodium salt, resulted in a lowering of conversion in all cases. It resulted in increased enantioselectivity, however, in the case of catalyst (*S*)-**16a**. Under all conditions, enantioselectivities of over 90% were obtained using this catalyst system (Table 2, entries 1–4). This catalyst gave the highest ee (94%) obtained to date within the Quinazolinap series. Enantioselectivities obtained

Table 2 Palladium-catalysed allylic alkylation, BSA procedure

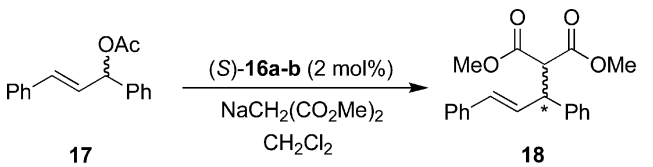


17 18

Entry	Catalyst	Base	Temperature	Time	Conversion (%)[a]	Ee (%)[b]
1	(*S*)-**16a**	KOAc	RT	24 h	83	86 (*R*)
2	(*S*)-**16a**	NaOAc	RT	24 h	94	88 (*R*)
3	(*S*)-**16a**	KOAc	40 °C	16 h	100	92 (*R*)
4	(*S*)-**16a**	NaOAc	40 °C	16 h	61	90 (*R*)
5	(*S*)-**16a**	KOAc	0 °C	5 d	94	92 (*R*)
6	(*S*)-**16a**	NaOAc	0 °C	5 d	76	94 (*R*)
7	(*S*)-**16b**	KOAc	RT	48 h	100	84 (*R*)
8	(*S*)-**16b**	LiOAc	RT	48 h	96	84 (*R*)
9	(*S*)-**16b**	KOAc	40 °C	16 h	35	80 (*R*)

[a] Conversions determined by ^{1}H NMR spectroscopy. [b] Enantiomeric excesses determined by chiral HPLC.

Table 3 Palladium-catalysed allylic alkylation, malonate procedure



17 18

Entry	Catalyst	Temperature	Time	Conversion (%)[a]	Ee (%)[b]
1	(*S*)-**16a**	RT	120 h	57%	92 (*R*)
2[c]	(*S*)-**16a**	RT	120 h	33%	94 (*R*)
3	(*S*)-**16a**	40 °C	16 h	47%	90 (*R*)
4	(*S*)-**16a**	0 °C	5 d	50%	92 (*R*)
6	(*S*)-**16b**	RT	48 h	10%	70 (*R*)
7	(*S*)-**16b**	40 °C	24 h	27%	70 (*R*)
8[c]	(*S*)-**16b**	40 °C	24 h	22%	56 (*R*)

[a] Conversions determined by ^{1}H NMR. [b] Enantiomeric excesses determined by chiral HPLC. [c] 15-crown-5 added.

with catalyst (*S*)-**16b** using this method reached a maximum of 70% (entries 6 and 7) although with poor conversions.

Conclusions

Two new axially chiral Quinazolinaps have been synthesised, resolved and applied in rhodium-catalysed hydroboration and palladium-catalysed allylic alkylation with ees of up to 92% and 94%, respectively. As well as expanding the range of Quinazolinaps available for asymmetric catalysis, these ligands were synthesised in order to study potential electronic effects within the series. When they were applied in the hydroboration of substituted styrenes, it was Quinazolinap (*S*)-**3b**, containing a 3,5-difluorophenylphosphine moiety that performed the better of the two ligands. Comparison of the results obtained with ligands (*S*)-**3a–b** to those obtained using 2-isopropyl-Quinazolinap **2e** show that both electronically modified Quinazolinaps seemed to demonstrate a decrease in activity and selectivity which may be attributed to the steric effect of the substitution on the aryl rings. In the screening of Quinazolinaps (*S*)-**3a–b** in palladium-catalysed allylic alkylation, it was (*S*)-**3a**, rather than (*S*)-**3b**, which gave superior results. Indeed, the use of (*S*)-**3b** has led to the highest ee observed in this reaction to date using the Quinazolinap series.

The difference in activity observed in the two catalytic applications demonstrates the practicality of optimising ligands for specific reactions. Work continues on the expansion of the range of electronically-varied Quinazolinaps and the results will be reported in due course from these laboratories.

Experimental details

General experimental

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 infrared FT spectrometer. 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 and ^{1}H-^{1}H COSY spectra were recorded on a 300 MHz Varian-Unity spectrometer, a 400 MHz Varian-Unity spectrometer or a 500 MHz Varian-Unity 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 spectra were recorded on a 300 MHz Varian-Unity spectrometer and 100 MHz ^{13}C spectra on a 400 MHz Varian-Unity spectrometer. Tetramethylsilane was used as the internal standard in all ^{13}C spectra recorded. 121.4 MHz ^{31}P spectra were recorded on a 300 MHz Varian-Unity spectrometer and 162 MHz ^{31}P spectra on a 400 MHz Varian-Unity spectrometer. ^{31}P Chemical shifts are reported relative to 85% aqueous phosphoric acid (0.0 ppm). Flash chromatography was performed using Merck Kieselgel 60 (Art. 9385). Merck precoated Kieselgel 60F_{254} was used for thin layer chromatography. GC and HPLC analysis was carried out using a Supelco 2-4304 beta-Dex® 120 (30 × 0.25 mm, 0.25 mm film) and a Chiralcel OD column (0.46 cm I.D. × 25 cm) respectively. Optical

rotation values were measured on a Perkin-Elmer 241 polarimeter. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. All commercially available solvents were purified and dried before use. Tetrahydrofuran was distilled from sodium–benzophenone and dichloromethane was distilled from calcium hydride. Where necessary, other solvents and reagents used were purified according to the procedures in 'Purification of Laboratory Chemicals'.[23] Pd salts were obtained on loan from Johnson Matthey. Solvents were degassed using three freeze–thaw cycles. Oxygen-free nitrogen was obtained from BOC gases.

Procedures for the preparation of **6a–b**, **3a–b**, **11a–b**, **16a–b**, the resolution of **3a–b**, details of the X-ray analysis of (*S*)-**9** are described and physical data for **6a–b**, **3a–b**, (*S*)-**9**, **11a–b**, **16a–b**, are available in the ESI.† The general procedures employed for the asymmetric hydroboration and allylic alkylation are described below.

Asymmetric hydroboration general procedure. The required Quinazolinap-rhodium(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 hour 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 was calculated by chiral GC or HPLC analysis. Conditions for chiral GC and HPLC analysis as previously reported.[9e]

Allylic alkylation procedures

Malonate ion procedure. Sodium dimethyl malonate (0.042 g, 0.275 mmol) and the required catalyst (0.005 mmol, 2 mol%) were placed in a Schlenk tube under an atmosphere of nitrogen. Dry degassed solvent (0.2 mL) and 15-crown-5 (if required) (55 μL, 0.275 mmol) were added, followed by (*E*)-1,3-diphenylprop-2-enyl-acetate (0.063 g, 0.25 mmol) in dry degassed solvent (0.3 mL). The suspension was stirred for the required time under an atmosphere of nitrogen and the progress was monitored by TLC (pentane–diethyl ether, 2 : 1). The reaction was quenched by the addition of acetic acid (0.1 mL). The solvent was removed *in vacuo* and water (25 mL) was added to the reaction mixture before transfer to a separatory funnel. The suspension was then extracted with diethyl ether (25 mL); the organic layer was washed with water (25 mL), brine (25 mL) and dried over anhydrous $MgSO_4$. The solution was filtered and reduced *in vacuo* to leave a clear yellow oil. ^{1}H NMR of the crude product gave the % conversion. The product was purified using preparative silica plates (2 : 1 pentane–diethyl ether) to afford (*R*) or (*S*)-methyl-2-carbomethoxy-3,5-diphenylpent-4-enoate as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.34–7.20 (10H, m, Ar-H), 6.47 (1H, d, J = 15.8 Hz, H_3), 6.34 (1H, dd, J = 15.8, 8.4, H_2), 4.27 (1H, dd, J = 10.8, 8.5 Hz, H_1), 3.95 (1H, d, J = 10.8 Hz, $CH(CO_2Me)_2$), 3.70 (3H, s, OMe) and 3.52 (3H, s, OMe). The % conversion could also be determined by filtering the quenched reaction mixture over silica to remove catalyst. The % conversion and enantiomeric excess were then determined by chiral HPLC [Daicel (Chiracel OD) column, 0.46 cm I.D. × 25 cm], hexane–isopropanol 99 : 1, 0.3 mL min^{-1}, R_t = starting material 26 min and 30 min, (*R*)-product—34 min, (*S*)-product—37 min.

BSA procedure. Base (0.05 mmol) and the corresponding catalyst (0.005 mmol, 2 mol%) were added to a Schlenk tube under an atmosphere of nitrogen. Dry degassed solvent (0.2 mL) was added, followed by (*E*)-1,3-diphenylprop-2-enyl-acetate (0.063 g, 0.25 mmol) in dry degassed solvent (0.3 mL). Dimethyl malonate (31.5 μL, 0.275 mmol) and N,O-bis(trimethylsilyl)acetamide (BSA) (68 μL, 0.275 mmol) were then added *via* syringe. The reaction was stirred under nitrogen at the required temperature and the reaction progress was monitored by TLC (pentane–diethyl ether, 2 : 1). The work-up was the same as described above for the malonate procedure.

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