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Electronically Varied Quinazolinaps for Asymmetric Catalysis

Aoife C. Maxwell,[a] Celine Franc,[a] Laurent Pouchain,[b] Helge Müller-Bunz[a] and Patrick J. Guiry[*, a]

[a] Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, UCD Conway Institute, University College Dublin, Belfield, Dublin 4, Ireland.
[b] Institut de Chimie, Université de RENNES 1, Campus de Beaulieu, 35042 Rennes Cedex, France.

*Email address for correspondence: p.guiry@ucd.ie

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 x 0.25 mm, 0.25 mm film) and a Chiralcel OD column (0.46 cm I.D. x 25 cm) respectively. Optical rotation values were measured on a Perkin Elmer 241 Polarimeter. $[\square]_D$ 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'.[1] 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.

Experimental procedures

Di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine oxide 6a. Di(3,5-xylyl)phosphine oxide (2.20 g, 8.5 mmol), 1-(2-isopropyl-quinazolin-4-yl)-2-naphthyl(trifluoromethyl)sulfonate (1.70 g, 3.80 mmol), palladium acetate (0.090 g, 0.40 mmol) and 1,2-bis(diphenylphosphino)butane (0.170 g, 0.40 mmol) were dissolved in anhydrous DMSO (15 mL) under nitrogen.[2] Diisopropylethylamine (15 mL) was added and the mixture was heated to 100ºC for twenty-four hours. The reaction mixture was cooled to room temperature and dichloromethane (30 mL) and saturated sodium bicarbonate solution (30 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (1 x 30 mL). The organic layers were combined and washed with brine (3 x 30 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo*. The brown oil obtained was dissolved in cyclohexane/ethyl acetate 1:1; after twelve hours' storage in the fridge the white crystals that precipitated were filtered to yield di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine oxide (1.11 g, 53%) as a white solid, m.p. 209–211ºC; ^1H NMR (500 MHz): δ ($CDCl_3$),

8.37 (1H, t, J = 8.8 Hz, H_4), 8.13 (1H, d, J = 8.5 Hz, H_3), 7.95 (1H, d, J = 8.3 Hz, H_8'), 7.77 (1H, d, J = 8.3, H_5), 7.61 (1H, t, J = 7.2 Hz, H_6), 7.53–7.49 (3H, m, $H_{7'}$, 2 Ar-H), 7.22 (1H, t, J = 7.7 Hz, H_6'), 7.15 (1H, t, J = 7.7 Hz, H_7), 7.09 (1H, s, Ar), 6.97 (1H, d, J = 8.3 Hz, H_8), 6.76 (1H, d, J = 8.5 Hz, H_5'), 6.59 (2H, d, J = 12.7 Hz, Ar), 6.43 (1H, s, Ar), 3.21 (1H, sept, J = 6.9 Hz, C<u>H</u>$(CH_3)_2$), 2.28 (6H, s, Ar-Me), 1.91 (6H, s, Ar-Me), 1.30 (6H, q, J = 6.9 Hz, CH(C<u>H</u>$_3)_2$); ^{13}C (125 MHz): δ ($CDCl_3$) 170.2 (4˚C), 167.6 (4˚C), 149.8 (4˚C), 139.2 (4˚C), 138.0 (4˚C), 137.9 (4˚C), 137.0 (4˚C), 134.8 (4˚C), 133.9 (CH), 133.3 (CH), 133.2 (CH), 132.1 (4˚C), 132.0 (4˚C), 131.6 (4˚C), 130.9 (4˚C), 130.7 (CH), 130.6 (CH), 130.1 (4˚C), 129.5 (CH), 129.4 (CH), 129.3 (CH), 129.2 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.3 (CH), 127.1 (CH), 126.9 (CH), 126.2 (CH), 123.6 (4˚C), 38.0 (<u>C</u>H$(CH_3)_3$), 22.0 (CH(<u>C</u>H$_3)_3$), 21.6 (Ar-CH_3), 21.5 (Ar-CH_3); ^{31}P NMR (121 MHz): δ ($CDCl_3$) 31.0 ppm; *m*/*z* (HRMS, ES) found: 554.2523, $C_{37}H_{35}N_2OP$ requires 554.2487.

Di(3,5-difluorophenyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine oxide 6b. Di(3,5-difluorophenyl)phosphine oxide (1.53 g, 9.32 mmol), 1-(2-isopropyl-quinazolin-4-yl)-2-naphthyl(trifluoromethyl)sulfonate (1.60 g, 3.59 mmol), palladium acetate (0.157 g, 0.682 mmol) and 1,2-bis(diphenylphosphino)butane (0.245 g, 0.574 mmol) were dissolved in anhydrous DMSO (28 mL) under nitrogen.[9] Diisopropylethylamine (15 mL) was added and the mixture was heated to 110ºC for twenty-four hours. The reaction mixture was cooled to room temperature and dichloromethane (30 mL) and saturated sodium bicarbonate solution (30 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (1 x 30 mL). The organic layers were combined and washed with brine (3 x 30 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo*. The brown oil obtained was purified by column chromatography (silica, dichloromethane to dichloromethane/ethyl acetate 1:1) to yield di(3,5-difluorophenyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine oxide (1.56 g, 76%) as an off-white solid; ^{1}H NMR (500 MHz): δ ($CDCl_3$) 8.26–8.18 (2H, m, H_4, H_3), 8.00 (1H, d, J = 8.4 Hz, H_8'), 7.88 (1H, d, J = 8.4 Hz, H_5), 7.74 (1H, t, J = 7.3 Hz, H_6), 7.62–7.56 (3H, m, $H_{7'}$, 2 Ar-H), 7.34–7.26 (2H, m, $H_{7'}$, $H_{6'}$), 7.02 (1H, d, J = 8.7 Hz, $H_{5'}$), 6.99 (1H, t, J = 8.7 Hz, Ar), 6.87 (1H, d, J = 8.7 Hz, H_8), 6.52–6.49 (2H, m, 2 Ar-H), 6.40 (1H, t, J = 8.7 Hz, Ar), 3.28

(1H, quin., J = 7.0 Hz, C<u>H</u>$(CH_3)_2$), 1.35 (6H, q, J = 6.7 Hz, CH(C<u>H</u>$_3)_2$); ^{13}C NMR 170.6 (4˚C), 167.0 (4˚C), 164.2-163.9 (2C-F), 162.9–162.7 (2C-F), 162.1–161.9 (C-P), 160.9–160.7 (C-P), 150.1 (4˚C), 140.0 (4˚C), 135.8 (4˚C), 135.2 (4˚C), 134.5 (4˚C), 134.1 (CH), 132.1 (4˚C), 130.2 (CH), 129.0 (CH), 128.6 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.3 (CH), 126.9 (CH), 126.6 (CH), 123.5 (4˚C), 116.3-116.0 (2*o*-C), 114.4–114.1 (2*o*-C), 108.6–108.2 (*p*-C), 107.8–107.4 (*p*-C), 38.1 (<u>C</u>H$(CH_3)_2$), 21.9 (CH(<u>C</u>H$_3)_2$), 21.6 (CH(<u>C</u>H$_3)_2$); ^{31}P NMR (121 MHz): δ ($CDCl_3$) 27.5 ppm; *m*/*z* (HRMS, ES) found: 570.1512, $C_{33}H_{23}F_4N_2OP$ requires 570.1484.

Di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine 3a. Di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine oxide (1.00 g, 1.8 mmol) was dissolved in dry toluene (20 mL) under nitrogen. Triethylamine (1.20 g, 1.7 mL, 12.20 mmol) was added.[12] The reaction mixture was cooled to 0ºC and trichlorosilane (2.44 g, 1.8 mL, 18.00 mmol) added slowly. The yellow suspension was then heated to 100ºC for twenty-four hours. The mixture was cooled to room temperature and dichloromethane (25 mL) was added, followed by saturated sodium bicarbonate solution (50 mL) added carefully; a yellow precipitate was seen, the mixture was stirred vigorously for thirty minutes and then filtered over celite. The precipitate was washed with saturated sodium bicarbonate solution (25 mL) and dichloromethane (15 mL). The filtrate was transferred to a separating funnel, the layers separated and the aqueous layer extracted with dichloromethane. The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The yellow oil obtained was purified by column chromatography (silica, cyclohexane/ethyl acetate 1:4) to yield di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine (0.678 g, 70%) as a white solid, R_f 0.37, m.p. 186–188 ºC; ν_{max} (KBr) 2960 (C-H), 2917 (C-H), 1733 (C=N), 1563 (Ar-H), 1496 (P-Ar), 1124 (Ar) and 690 (Ar-H) cm^{-1}; ^{1}H NMR (500 MHz): δ ($CDCl_3$) 8.09 (1H, d, J = 8.5 Hz, H_8'), 7.92 (2H, t, J = 8.8 Hz, H_4, H_5), 7.79 (1H, t, J = 6.6 Hz, H_7'), 7.52–7.49 (2H, m, H_3, H_6), 7.32–7.27 (3H, m, H_7, H_6', H_5'), 7.11 (1H, d, J = 8.5 Hz, H_8), 6.92 (3H, d, J = 8.5 Hz, Ar), 6.86 (1H, s, Ar), 6.77 (2H, d, J = 7.9 Hz, Ar), 3.37 (1H, sept, J = 6.9, C<u>H</u>$(CH_3)_2$), 2.24 (6H, s, Ar-Me), 2.19 (6H, s, Ar-Me), 1.38 (6H, q, J = 6.9 Hz, CH(C<u>H</u>$_3)_2$); ^{13}C (125 MHz): δ ($CDCl_3$) 171.4 (4˚C), 169.6 (4˚C), 169.5 (4˚C),

150.8 (4˚C), 137.2 (4˚C), 137.1 (4˚C), 136.6 (4˚C), 135.7 (4˚C), 135.6 (4˚C), 133.7 (4˚C), 133.5 (CH), 132.2 (4˚C), 132.1 (4˚C), 131.8 (CH), 131.6 (CH), 131.5 (CH), 131.4 (CH), 130.5 (CH), 130.4 (CH), 129.1 (CH), 128.5 (CH), 128.3 (CH), 127.2 (CH), 127.0 (CH), 126.9 (CH), 126.5 (CH), 126.4 (CH), 124.1 (4˚C), 124.0 (4˚C), 38.2 ($\underline{C}H(CH_3)_3$), 22.0 ($CH(\underline{C}H_3)_3$), 21.5 (Ar-CH_3), 21.4 (Ar-CH_3); ^{31}P NMR (121 MHz): δ ($CDCl_3$) -13.17 ppm; *m*/*z* (HRMS, ES) found: 538.2494, $C_{37}H_{35}N_2P$ requires 538.2538.

Di(3,5-difluorophenyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine 3b. Di(3,5-difluorophenyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine oxide (1.55 g, 2.73 mmol) was dissolved in dry toluene (40 mL) under nitrogen. Triethylamine (3.29 g, 4.5 mL, 32.49 mmol) was added.[2] The reaction mixture was cooled to 0ºC and trichlorosilane (3.62g, 2.7 mL, 26.75 mmol) added slowly. The yellow suspension was then heated to 100ºC for twenty-four hours. The mixture was cooled to room temperature and saturated sodium bicarbonate solution (50 mL) was added carefully; a yellow precipitate was seen and the mixture was stirred for one hour and then filtered over celite. The filtrate was transferred to a separating funnel, the layers separated and the aqueous layer extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The yellow oil obtained was purified by column chromatography (silica, dichloromethane) to yield di(3,5-difluorophenyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine (0.704 g, 48%) as a white solid, R_f 0.25, m.p. 180–182ºC; ν_{max} (KBr) 2966 (C-H), 1783 (C=N), 1573 (Ar-H), 1417 (P-Ar), 1282 (Ar-F), 1112 (Ar) and 696 (Ar-H) cm^{-1}; ^{1}H NMR (500 MHz): δ ($CDCl_3$) 8.10 (1H, d, J = 8.6 Hz, H_8'), 7.99 (1H, d, J = 8.6 Hz, H_4), 7.95 (1H, d, J = 8.1 Hz, H_5), 7.84 (1H, dt, J = 7.58, 1.5 Hz, H_7'), 7.57 (1H, dt, J = 7.6, 1.0 Hz, H_6), 7.38–7.27 (4H, m, H_5', H_6', H_7, H_3), 7.14 (1H, dd, J = 8.6, 0.5 Hz, H_8), 6.79–6.72 (4H, m, Ar) 6.67–6.62 (2H, m, Ar), 3.21 (1H, q, J = 7.0 Hz, $C\underline{H}(CH_3)_2$), 1.30 (6H, d, J = 7.0 Hz, $CH(C\underline{H}_3)_2$); ^{13}C (125 MHz): δ ($CDCl_3$) 171.7 (4˚C), 168.7 (4˚C), 164.3–164.1 (2C-F), 162.2–162.1 (2C-F), 150.9 (4˚C), 143.7 (4˚C), 143.4 (4˚C), 141.4–141.2 (C-P), 140.6–140.3 (C-P), 134.0 (CH), 132.1 (4˚C), 131.7 (4˚C), 130.1 (CH), 129.5 (CH), 128.9 (CH), 128.5 (CH), 128.0 (CH), 127.7 (CH), 127.2 (CH), 126.7 (CH), 126.6 (CH), 123.8 (4˚C), 116.2–115.8 (4*o*-C), 105.1–104.1 (2*p*-C), 38.2 ($\underline{C}H(CH_3)_3$), 22.0 ($CH(\underline{C}H_3)_3$), 21.3 ($CH(\underline{C}H_3)_3$); ^{31}P NMR

(121 MHz): δ ($CDCl_3$) -10.3 ppm; found: C, 71.3%; H, 4.15%; F, 14.1%; N, 4.9%; P, 5.8%; $C_{33}H_{23}F_4N_2P$ requires: C, 71.5%; H, 4.2%; F, 13.7%; N, 5.05%; P, 5.6%.

Resolution of di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine 9. A solution of di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine (2.15 g, 4.98 mmol) and (+)-di-μ-chlorobis[(*R*)-dimethyl(1-(1-naphthyl)ethyl)aminato-C_2,N] dipalladium(II) (0.959 g, 2.49 mmol) in dry, degassed methanol (150 mL) was stirred for eighteen hours under an atmosphere of nitrogen. A yellowy cream precipitate was observed after this time. On filtration, both the precipitate and the filtrate were found to be an equal mixture of (*R,R*) and (*S,R*)-*cis*-[dimethyl(1-(1-naphthyl)ethyl)aminato-C^2,N]-[1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)di(3,5-xylyl)]palladium(II)chloride. The precipitate and filtrate were combined but all attempts to resolve the diastereomers by fractional crystallisation at this stage were unsuccessful. Thus (*R,R*) and (*S,R*)-*cis*-[dimethyl(1-(1-naphthyl)ethyl)aminato-C^2,N]-[1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)di(3,5-xylyl)]palladium(II)chloride (4.163 g, 4.74 mmol) was dissolved in dry, degassed methanol (100 mL). Potassium hexafluorophosphate (0.872 g, 4.74 mmol) in distilled water (100 mL) was added to this solution. A creamy precipitate was seen and this was stirred overnight. This precipitate was a mixture of the diastereomeric cationic palladium complexes. Recrystallisation of this mixture using hot chloroform and ether yielded a precipitate that was diastereomerically pure. Further fractional crystallisation of the subsequent filtrates increased the yield of (*S,R*)-*cis*-[dimethyl(1-(1-naphthyl)ethyl)aminato-C^2,N]-[1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)di(3,5-xylyl)phosphine]palladium(II) hexafluorophosphate, m.p. 189–191ºC; $[\alpha]^{20}_D$ = -174 (c = 0. 41, $CHCl_3$); ^{1}H NMR (300 MHz): δ ($CDCl_3$) 8.20 (1H, d, J = 8.5 Hz), 8.11 (1H, d, J = 8.3 Hz), 7.92 (2H, d, J = 3.6 Hz), 7.67 (3H, m), 7.51 (1H, t, J = 7.5 Hz), 7.40 (4H, m), 7.23–7.03 (4H, m), 6.97 (1H, d, J = 8.5 Hz), 6.71 (2H, t, J = 8.1 Hz), 6.37 (1H, d, J = 10.4 Hz), 6.26 (2H, d, J = 12.7 Hz), 4.32 (1H, q, J = 6.3 Hz, C<u>H</u>(Me)), 3.48 (1H, q, J = 7.0 Hz, C<u>H</u>$(CH_3)_2$), 2.71 (3H, s, NMe), 2.46 (3H, s, NMe), 1.86 (6H, s, (xylyl)CH_3), 1.78 (3H, d, J = 6.6 Hz, CH(<u>Me</u>)), 1.60 (6H, d, J = 5.9 Hz, (xylyl)CH_3), 1.30 (6H, d, J = 6.3 Hz, $CH(CH_3)_2$); ^{13}C NMR (75 MHz): δ ($CDCl_3$) 169.1 (4˚C), 150.9 (4˚C), 150.8 (4˚C), 148.6 (4˚C), 138.6 (4˚C), 138.4 (4˚C), 138.2 (4˚C), 137.0 (4˚C), 136.9 (4˚C), 136.7 (4˚C), 136.5

(CH), 136.2 (CH), 133.8 (CH), 133.2 (CH), 132.5 (CH), 132.4 (CH), 132.0 (CH), 129.6 (CH), 129.3 (CH), 129.0 (CH), 128.5 (CH), 128.4 (CH), 127.4 (CH), 126.0 (CH), 125.0 (CH), 125.0 (CH), 123.4 (4˚C), 122.8 (4˚C), 73.7 (CHMe), 51.4 (NMe), 48.1 (NMe), 38.2 ($\underline{C}H(CH_3)_2$), 23.1 (CH$\underline{Me}$), 22.1 ($CH(\underline{C}H_3)_2$), 21.0 ((xylyl)CH_3); ^{31}P NMR (121 MHz): δ ($CDCl_3$) 33.3, -144.4 (sept., J = 737.6 Hz) ppm.

Crystal data for (*S*,*R*)-9

Crystal data were collected at 100K using a Bruker SMART APEX CCD area detector diffractometer. A full sphere of reciprocal space was scanned by phi-omega scans. Pseudo-empirical absorption correction based on redundant reflections was performed by the program SADABS.[3] The structures were solved by direct methods using SHELXS-97 [4] and refined by full matrix least-squares on F^2 for all data using SHELXL-97.[5] Hydrogen atoms were added at calculated positions and refined using a riding model. Their isotropic temperature factors were fixed to 1.2 times (1.5 times for methyl groups) the equivalent isotropic displacement parameters of its parent carbon atom. Anisotropic thermal displacement parameters were used for all non-hydrogen atoms. CCDC- 664580 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.

Resolution of di(3,5-diflurophenyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine 8b. A solution of di(3,5-diflurophenyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine (0.495 g, 0.91 mmol) and (+)-di-μ-chlorobis[(*R*)-dimethyl(1-(1-naphthyl)ethyl)aminato-C_2,N]dipalladium(II) (0.45 g, 0.45mmol) in dry, degassed dichloromethane (65 mL) was stirred for eighteen hours under an atmosphere of nitrogen. The clear yellow solution was reduced *in vacuo* and dried on a vacuum line to yield (*R,R*) and (*S*,*R*)-*cis*-[dimethyl(1-(1-naphthyl)ethyl)aminato-C^2,N]-[1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)di(3,5-diflurophenyl)]palladium(II)chloride as a light yellow solid (0.92g, 97%). Recrystallisation of the mixture from hot chloroform/diethyl ether gave (*S*,*R*)-*cis*-[dimethyl(1-(1-naphthyl)ethyl)aminato-C^2,N]-[1-(2-isopropyl-quinazolin-4-yl)(2-

naphthyl)di(3,5-diflurophenyl)]palladium(II)chloride as yellow crystals after slow crystallisation, m.p. 210–212ºC; $[\alpha]^{20}_{D}$ = -121 (c = 0.85, $CHCl_3$); ^{1}H NMR (400 MHz): δ ($CDCl_3$) 8.52 (1H, S), 8.11 (1H, d, J = 7.9 Hz), 7.98 (1H, d, J = 8.0 Hz), 7.87 (1H, d, J = 8.4 Hz), 7.64 (4H, m), 7.50–7.10 (8H, m), 6.97 (2H, d, J = 8.4 Hz), 6.87 (1H, t, J = 8.0 Hz), 6.70 (1H, d, J = 8.5 Hz), 6.54 (1H, t, J = 5.4 Hz), 6.33 (1H, t, J = 5.2 Hz), 4.22 (1H, t, J = 5.9 Hz, C<u>H</u>(Me)), 3.15 (1H, sept., J = 6.8 Hz, C<u>H</u>(CH_3)$_2$), 2.84 (3H, s, NMe), 2.45 (3H, s, NMe), 1.88 (3H, d, J = 5.7 Hz, CH(<u>Me</u>)), 1.28 (6H, d, J = 6.9 Hz, CH(CH_3)$_2$); ^{13}C NMR (100 MHz): δ ($CDCl_3$) 166. 8 (4˚C), 163.5 (4˚C), 163.4 (4˚C), 162.1 (4˚C), 161.0 (4˚C), 159.9 (4˚C), 159.6 (4˚C), 150.4 (4˚C), 149.3 (4˚C), 140.4 (4˚C), 135.2 (CH), 135.1 (CH), 134.6 (4˚C), 134.0 (CH), 133.4 (4˚C), 132.9 (4˚C), 132.8 (4˚C), 131.4 (4˚C), 129.5 (CH), 129.3 (CH), 128.9 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127.8 (CH), 127.7 (4˚C), 127.2 (CH), 126.6 (CH), 126.1 (CH), 125.7 (4˚C), 125.2 (4˚C), 124.9 (CH), 124.8 (CH), 124.6 (CH), 123.5 (CH), 118.2 (CH), 106.8 (CH), 106.2 (CH), 73.8 (<u>C</u>HMe), 51.2 (NMe), 48.9 (NMe), 38.0 (<u>C</u>H(CH_3)$_2$), 23.7 (CH<u>Me</u>), 21.6 (CH(<u>C</u>H_3)$_2$); ^{31}P NMR (161 MHz): δ ($CDCl_3$) 44.7 ppm.

(*S*)-Di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine (*S*)-3a. (*S*,*R*)-*cis*-[dimethyl(1-(1-naphthyl)ethyl)aminato-C^2,N]-[1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)di(3,5-xylyl)]palladium(II)chloride (0.292 g, 0.285 mmol) and 1,2-bis(diphenylphosphino)ethane (0.114 g, 0.285 mmol) were dissolved in dry, degassed dichloromethane (15 mL). The pale yellow solution was stirred for three hours at room temperature under an atmosphere of nitrogen. The dichloromethane was removed *in vacuo* and purified by column chromatography (silica, pentane/ethyl acetate, 4:1) to give (*S*)-Di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine as a white solid (0.138 g, 89%), R_f 0.4, $[\alpha]^{20}_{D}$ = -64 (c = 0.25, $CHCl_3$), identical in all other respects to the previously prepared racemic sample.

(*S*)-Di(3,5-diflurophenyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine (*S*)-3b. (*S*,*R*)-*cis*-[dimethyl(1-(1-naphthyl)ethyl)aminato-C^2,N]-[1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)di(3,5-diflurophenyl)]palladium(II)chloride (0.090 g, 0.10 mmol) and 1,2-bis(diphenylphosphino)ethane (0.041 g, 0.10 mmol) were dissolved in dry, degassed

dichloromethane (10 mL). The pale yellow solution was stirred for three hours at room temperature under an atmosphere of nitrogen. The dichloromethane was removed *in vacuo* and purified by column chromatography (silica, dichloromethane) to give (*S*)-di(3,5-diflurophenyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine as a white solid (0.044 g, 93%), R_f 0.25, $[\alpha]^{20}_D$ = -256 (c = 0.25, $CHCl_3$), identical in all other respects to the previously prepared racemic sample.

(*S*)-Di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)]phosphine rhodium(1,5-cyclooctadiene)trifluoromethanesulfonate 11a. (1,5-Cyclooctadiene)(2,4-pentanedionato)rhodium (3.2 mg, 0.01 mmol) and (*S*)-di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)]phosphine (5.3 mg, 0.01 mmol) were dissolved in dry THF (2 mL) under an atmosphere of nitrogen to give a clear yellow solution. Trimethylsilyltrifluoromethanesulfonate (2 μL, 1.11 equiv) was added via syringe and a bright yellow colour developed. The reaction mixture was allowed to stir for twenty minutes and the volume was then reduced *in vacuo* to 0.5 mL. Pentane (10 mL) was added via syringe to produce a bright yellow precipitate. This was allowed to stir for five minutes before the pentane was removed via syringe. The precipitate was washed twice more with pentane (2 x 10 mL), which was syringed from the Schlenk tube to leave (*S*)-di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)]phosphine rhodium(1,5-cyclooctadiene)trifluoromethanesulfonate as a light yellow powder. ^{1}H NMR (400 MHz): δ ($CDCl_3$) = 8.42 (1H, d, J = 8.7 Hz), 8.15 (1H, d, J = 8.2 Hz), 7.84–7.74 (3H, m), 7.69 (1H, t, J = 7.6 Hz), 7.48–7.39 (3H, m), 7.16 (1H, d, J = 8.5 Hz), 7.11 (1H, s), 6.97 (2H, d, J = 11.2 Hz), 6.56 (2H, d, J = 12.2 Hz), 6.40 (1H, s), 5.20 (1H, br. s, C<u>H</u>=CH), 4.80 (1H, sept., J = 6.6, C<u>H</u>(CH_3)$_2$), 4.28 (1H, br. s, C<u>H</u>=CH), 4.17 (1H, br. s, C<u>H</u>=CH), 3.98 (1H, br. s, C<u>H</u>=CH), 2.97 (2H, m, CH_2), 2.61 (2H, m, CH_2), 2.27 (6H, s, Ar-Me), 2.18 (2H, m, CH_2), 1.71 (6H, s, Ar-Me), 1.46 (6H, d, J = 6.5 Hz, CH(CH_3)$_2$), 0.63 (2H, m, CH_2); ^{13}P NMR (162 MHz): δ ($CDCl_3$) 24.93 (d, J = 132.0 Hz) ppm. The product was dried under vacuum for forty-five minutes before use in Rh-catalysed hydroboration. Dry THF (4 mL) was added to the Schlenk tube and 2 mL portions of the catalyst precursor (1 mol%) were transferred to two oven-dried Schlenk tubes under nitrogen.

(*S*)-Di(3,5-difluorophenyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)]phosphine rhodium(1,5-cyclooctadiene)trifluoromethanesulfonate 11b. (1,5-Cyclooctadiene)(2,4-pentanedionato)rhodium (3.2 mg, 0.01 mmol) and (*S*)-di(3,5-difluorophenyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)]phosphine (5.5 mg, 0.01 mmol) were dissolved in dry THF (2 mL) under an atmosphere of nitrogen to give a clear yellow solution. Trimethylsilyltrifluoromethanesulfonate (2 μL, 1.11 equiv) was added via syringe and a bright yellow colour developed. The reaction mixture was allowed to stir for twenty minutes and the volume was then reduced *in vacuo* to 0.5 mL. Pentane (10 mL) was added via syringe and to produce a bright yellow precipitate. This was allowed to stir for five minutes before the pentane was removed via syringe. The precipitate was washed twice more with pentane (2 x 10 mL), which was syringed from the Schlenk tube to leave (*S*)-di(3,5-difluorophenyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)]phosphine rhodium(1,5-cyclooctadiene)trifluoromethanesulfonate as a light yellow powder. ^{1}H NMR (400 MHz): δ ($CDCl_3$) = 8.46 (1H, d, J = 8.5 Hz), 8.15 (1H, d, J = 8.2 Hz), 7.84 (3H, m), 7.70 (1H, t, J = 7.5 Hz), 7.46 (2H, m), 7.35 (1H, d, J = 7.8 Hz), 6.96 (4H, m), 6.68 (2H, t, J = 8.1 Hz), 6.28 (1H, s); ^{13}P NMR (162 MHz): δ ($CDCl_3$) 26.8 (d, J = 138.0 Hz) ppm. The product was dried under vacuum for forty-five minutes before use in Rh-catalysed hydroboration. Dry THF (4 mL) was added to the Schlenk tube and 2 mL portions of the catalyst precursor (1 mol%) were transferred to two oven-dried Schlenk tubes under nitrogen.

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 1M 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 1M 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.[6]

[(*S*)-Di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine-[π-allyl]palladium]tetrafluoroborate 16a. Di-μ-chloro-bis(π-allyl)dipalladium (0.012 g, 0.033 mmol), (*S*)-di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine (0.035 g, 0.066 mmol) and sodium tetrafluoroborate (0.014 g, 0.132 mmol) were placed in a Schlenk tube under nitrogen. Dry degassed dichloromethane (2 mL) was added via syringe to give a pale yellow suspension, which was stirred overnight. The white solid was removed by filtration. The filtrate was reduced *in vacuo* to 0.5 mL and pentane added to precipitate a light yellow solid, which was filtered to give [(*S*)-di(3,5-xylyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine-[π-allyl]-palladium]tetrafluoroborate (0.023 g, 90%), ^{1}H NMR (500 MHz): δ ($CDCl_3$) *Diastereomer 1*: 8.01–6.67 (m, Ar), 5.49 (1H, br. s, H_3), 4.52 (1H, br. s, H_2), 3.58 (1H, br. s, H_1), 3.19 (1H, m, C<u>H</u>$(CH_3)_2$), 2.97 (1H, br. s, H_5), 2.81 (1H, m, H_4), 2.19 (12H, s, (xylyl)CH_3), 1.31 (6H, d, J = 6.8 Hz, CH(C<u>H</u>$_3)_2$); *Diastereomer 2*: 8.01–6.67 (m, Ar), 5.21 (1H, br. s, $H_{3'}$), 4.39 (1H, br. s, $H_{2'}$), 3.23 (1H, br. s, $H_{1'}$), 3.19 (1H, m, C<u>H</u>$(CH_3)_2$), 2.81 (1H, m, $H_{5'}$), 2.58 (1H, m, $H_{4'}$), 2.08 (12H, s, (xylyl)CH_3), 1.21 (6H, d, J = 5.3 Hz, CH(C<u>H</u>$_3)_2$); ^{31}P NMR (121 MHz): δ ($CDCl_3$) = 24.6 and 24.7 ppm.

[(S)-Di(3,5-difluorophenyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine-[π-allyl]palladium]tetrafluoroborate 16b. Di-μ-chloro-bis(π-allyl)dipalladium (0.005 g, 0.013 mmol), (*S*)-di(3,5-diflurophenyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine (0.014 g, 0.025 mmol) and sodium tetrafluoroborate (0.005 g, 0.052 mmol) were placed in a Schlenk tube under nitrogen. Dry degassed dichloromethane (2 mL) was added via syringe to give a pale yellow suspension, which was stirred overnight. The white solid was removed by filtration. The filtrate was reduced *in vacuo* to 0.5 mL

and pentane added to precipitate a light yellow solid, which was filtered to give [(*S*)-di(3,5-difluorophenyl)(1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)phosphine-[π-allyl]-palladium]tetrafluoroborate (0.09 g, 83%), ^{1}H NMR (500 MHz): δ ($CDCl_3$) *Diastereomer 1*: 8.07–6.69 (m, Ar), 5.30 (1H, br. s, H_3), 4.47 (1H, br. s, H_2), 4.28 (1H, br. s, H_1), 3.13 (1H, m, C<u>H</u>(CH_3)$_2$), 2.91 (1H, br. s, H_5), 2.79 (1H, app d, J = 11.8 Hz, H_4), 1.27 (6H, d, J = 7.2 Hz, CH(C<u>H</u>$_3$)$_2$); *Diastereomer 2*: 8.07–6.69 (m, Ar), 4.85 (1H, br. s, $H_{4'}$), 4.11 (1H, m, $H_{2'}$), 3.51 (1H, br. s, $H_{1'}$), 3.13 (1H, m C<u>H</u>(CH_3)$_2$), 3.09 (1H, br. s, $H_{5'}$), 2.79 (1H, app d, J = 11.8 Hz, $H_{4'}$), 1.17 (6H, d, J = 6.9 Hz, CH(C<u>H</u>$_3$)$_2$); ^{31}P NMR (121 MHz): δ ($CDCl_3$) = 25.8 and 26.1 ppm.

Allylic Alkylation Procedures

Malonate Ion Procedure. Sodium dimethyl malonate (0.042g, 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, C<u>H</u>(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. x 25 cm], hexane/isopropanol 99:1, 0.3 mL/min, 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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