A long-range chiral relay *via* tertiary amide group in asymmetric catalysis: new amino acid-derived *N,P*-ligands for copper-catalysed conjugate addition

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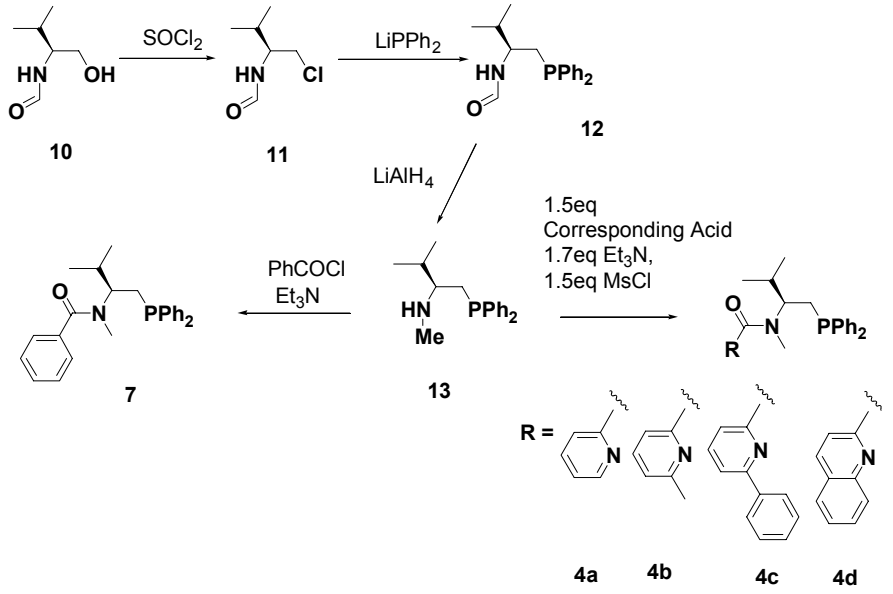
Experimental

General Methods. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded in $CHCl_3$ at 25 °C unless otherwise indicated, with an error of $<\pm 0.1$. The $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. The NMR spectra were recorded in $CDCl_3$, ^1H at 400 MHz and ^{13}C at 100.6 MHz, with chloroform-d_1 (δ 7.26, ^1H; δ 77.0, ^{13}C) as internal standard unless otherwise indicated. ^{31}P NMR spectra were recorded in $CDCl_3$ at 200 MHz on a WP 200 SY instrument, with 85% phosphoric acid as internal standard. Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded for a thin film between NaCl plates or for $CHCl_3$ solutions or in a solid by the Golden Gate technique. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. All reactions were performed under an atmosphere of dry, oxygen-free nitrogen (or argon where specified) in oven-dried glassware twice evacuated and filled with nitrogen. Solvents and solutions were transferred by syringe-septum and cannula techniques. All solvents for the reactions were of reagent grade and were dried and distilled immediately before use as follows: diethyl ether and tetrahydrofuran (THF) from sodium-benzophenone; dichloromethane from calcium hydride. All reagents were purchased from commercial suppliers and used as received. The actual concentration of commercial *n*-BuLi was determined by titration. Degassed silica gel columns were prepared by the following method: the silica gel slurry in petroleum ether was placed in a round bottom flask fitted with a reflux condenser under an argon atmosphere. The flask was brought to reflux several times and allowed to cool to room temperature before the column was packed with the slurry. The column was kept under an atmosphere of argon by attaching argon-filled balloons. Standard workup of an ethereal solution means washing 3 × with 5% HCl (aqueous), water, and 3 × with 5% $KHCO_3$ (aqueous) and drying with $MgSO_4$. Petroleum ether refers to the fraction boiling in the range of 40-60 ^oC. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behavior. The chiral GC and HPLC methods were calibrated with the corresponding racemic mixtures.

Scheme 2: Synthetic route to ligands **4a,b,c,d** and **7**



(*S*)-(–)-1-Chloro-2-formamido-3-methylbutane (*S*)-(–)-(11).

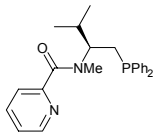
$SOCl_2$ (0.73 mL, 10.00 mmol) was added to a stirred solution of (*S*)-(–)-2-formamido-3-methylbutan-1-ol (*S*)-(–)-**10**[1] (1.31 g, 10.00 mmol) in dry CH_2Cl_2 (35 mL) at room temperature; no change of appearance was observed. The mixture was stirred at room temperature until completion (2.5 h), which was indicated by TLC. The mixture was then concentrated under vacuum to afford a crystalline solid, which was purified on a column of silica gel (65 g) with ethyl acetate. Evaporation of the corresponding fraction furnished (*S*)-(–)-**11** as fine white needles, (0.94 g, 63%): mp 66-68 ^oC (ethyl acetate); $[\alpha]_D$ –0.74 (*c* 1.33, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.89 (d, *J* = 7.0 Hz, 3H, Me_2CH), 0.93 (d, *J* = 6.6 Hz, 3H, Me_2CH), 1.83-1.92 (m, 1H, Me_2CH), 3.65 (dd, *J* = 11.5 and 3.7 Hz, 1H, CH_2Cl), 3.67 (dd, *J* = 11.5 and 3.7 Hz, 1H, CH_2Cl), 3.96-4.03 (m, 1H, C*H*), 5.58 (bs, 1H, N*H*), 8.19 (s, 1H, C*H*O); ^{13}C NMR ($CDCl_3$) δ 19.2 (CH_3), 19.6 (CH_3), 29.5 Me_2CH), 46.9 (CH_2Cl), 53.9 (*C*H), 161.2 (*C*HO); IR (NaCl disc) ν 3652(m) (NH), 1687(m) cm^{-1} (NHCO). Anal. Calcd for $C_6H_{12}ONCl$: C, 48.16; H, 8.03; N, 9.36; Cl, 23.75. Found: C, 48.21; H, 8.14; N, 9.27; Cl, 23.86.

(*S*)-2-Formamido-3-methylbut-1-yl-diphenylphosphine (*S*)-(12).

A 1.44M solution of *n*-butyllithium in hexanes (7.22 mL, 10.43 mmol) was added to a solution of Ph_2PH (1.81 mL, 10.43 mmol) in dry THF (25 mL) at 0 ^oC with constant stirring under an argon atmosphere; a persistent orange coloration was observed. A solution of (*S*)-(–)-**11** (1.20 g, 8.03 mmol) in dry THF (25 mL) was then added dropwise at 0 ^oC; the mixture changed to a pale yellow colour upon completion of the addition. The mixture was stirred at 0 ^oC until TLC indicated completion of the reaction (3 h). The mixture was concentrated under vacuum and the crude (*S*)-**12** (~2.50 g) thus obtained was used in the next step without further purification.

(*S*)-(+)-2-Methylamino-3-methylbut-1-yl-diphenylphosphine (*S*)-(+)-(13).

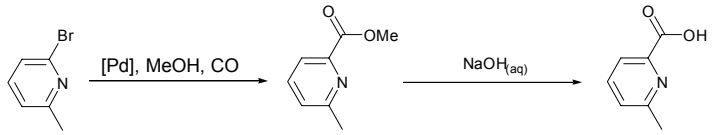
A solution of crude (*S*)-**12** (8.03 mmol - asuming 100 % yield in the formation of **12** from **11**) in dry THF (25 mL) was added dropwise to a stirred solution of $LiAlH_4$ (620 mg, 16.34 mmol) in dry THF (25 mL) at 0 ^oC under an argon atmosphere; an olive-green coloration was observed. The reaction mixture was allowed to warm to an ambient temperature and then heated at reflux for 18 h. The mixture was cooled to 0 ^oC, the excess of $LiAlH_4$ was decomposed by a slow addition of $Na_2SO_4.10H_2O$ crystals. The mixture was filtered through a pad of Celite, the pad was washed with Et_2O (30 mL) and the filtrate was concentrated under vacuum. The crude product was purified on a degassed column of silica gel (65 g) with mixture of petroleum ether and ethyl acetate (2:1) to remove less polar byproducts, followed by methanol to afford (*S*)-(+)-**13** as a viscous oil (880 mg, 39% overall from **11**): $[\alpha]^{19}_D$ +88.0 (*c* 1.33; $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.76 (d, *J* = 7.2 Hz, 3H, *Me*$_2$CH), 0.82 (d, *J* = 6.8 Hz, 3H, *Me*$_2$CH), 1.86-1.96 (m, 1H), 2.09-2.25 (2 × m, 2 × 1H), 2.27 (s, 3H, N*Me*), 2.74 (bs, 2H), 7.22-7.51 (m, 10H, Ar); ^{31}P NMR ($CDCl_3$) δ –21.27; IR (NaCl discs) ν 3388 (NH), 1436 (P-Ph) cm^{-1}; HRMS (FAB) 286.1724 ($C_{18}H_{25}NP$ requires 286.1725).



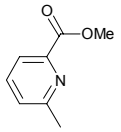
(*S*)-(+)-*N*-Methyl-*N*-(1-diphenylphosphino-3-methylbut-1-yl)-2-pyridine-carboxamide (*S*)-(+)-(4a).

Methyl chloroformate (0.12 mL, 1.58 mmol) was slowly added to a solution of 2-picolinic acid (194 mg, 1.58 mmol) and Et_3N (0.25 mL, 1.79 mmol) in dry THF (25 mL) at 0 ^oC while stirring under an argon atmosphere and the resulting mixture was stirred in an ice bath for 30 min. The white precipitate of triethylammonium chloride was removed by filtration. A clear solution of the mixed anhydride thus obtained (25.00 mL; 1.58 mmol, 1.5 equiv) was added slowly to a solution of (*S*)-(+)-**13** (300 mg, 1.58 mmol) in dry THF (20 mL) and Et_3N (0.22 mL, 1.58 mmol) while stirring at room temperature. The reaction mixture was observed to have a clear yellow color. After 3.5 h TLC (petroleum ether – AcOEt, 1:2; ninhydrin developing agent) indicated that the starting material **13** had disappeared. The mixture was concentrated under vacuum to afford a viscous yellow oil, which was purified by chromatography on a column of degassed silica gel (65 g) with a petroleum ether – ethyl acetate mixture (1:1) to give pure (*S*)-(+)-**4a** as a viscous oil (388 mg, 95%): $[\alpha]_D$ +0.4 (*c* 1.33, $CHCl_3$); ^1H NMR ($CDCl_3$) indicated a mixture of rotamers were present in approximately 1:1 ratio, δ 0.89 (d, *J* = 6.4 Hz, 6H, *Me*$_2$CH), 0.96 (d, *J* = 6.8 Hz, 6H, *Me*$_2$CH), 1.79-1.88 (m, 1H) 1.88-1.97 (m, 1H), 1.97-2.05 (m, 1H), 2.15-2.35 (m, 1H), 2.43-2.54 (m, 2 × 1H), 2.73 (s, 3H, NMe), 2.85 (s, 3H, NMe), 3.85-3.93 (m, 1H, C**H*) 4.12-4.35 (m, 1H, C**H*), 6.93-7.02 (m, 1H, py), 7.17-7.29 (m, 19H), 7.35-7.40 (m, 2H), 7.42-7.47 (m, 4H), 7.68 (td, *J* = 8.0 and *J* = 2.0 Hz, 1H), 8.12 (dt, *J* = 4.8 and 1.2 Hz, 1H), 8.52-8.54 (m, 1H); ^{31}P NMR ($CDCl_3$) δ -24.47, -22.14; IR (NaCl plates) ν 1636 (NCO) cm^{-1}; HRMS (EI) 374.1546 ($C_{23}H_{23}ON_2P$ requires 374.1548).

Scheme 3: Synthesis of 6-methyl-pyridine-2-carboxylic acid.

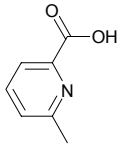


14 **15** **16**



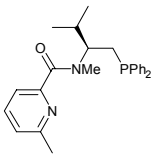
6-methyl-pyridine-2-carboxylic acid methyl ester (15).

In a dry schlenk tube 2-Bromo-6-methyl pyridine **14** (1.32 mL, 11.61 mmol) and Et_3N (3.33 mL, 23.91 mmol) were added to dry methanol (4 mL). The reaction mixture was degassed by vigorously bubbling argon through the liquid (5 min). A CO filled balloon was attached to the Schlenk tube and the reaction mixture was stirred vigorously under the CO atmosphere (15 min). $Pd(OAc)_2$ (80 mg, 0.36 mmol), [1,1'-Bis(diphenylphosphino)ferrocene] palladium(II) chloride 1:1 complex with dichloromethane (310 mg, 0.42 mmol), and dppf (250 mg, 0.34 mmol) were quickly added subsequently as solids. The Schlenk tube was sealed with a glass stopper secured with NESCO film and the reaction mixture was refluxed at 65 ^{o}C overnight. The reaction was monitored by TLC (petroleum ether – AcOEt 1:5; potassium permanganate developing agent). The reaction mixture was partitioned between brine (20 mL) and dichloromethane (20 mL) and the aqueous layer was extracted with dichloromethane (4 × 20 mL). The combined organics were dried over magnesium sulfate and the solvent was removed in vacuo to afford 6-methyl-pyridine-2-carboxylic acid methyl ester **15** as a brown partially crystalline mixture (1.06 g, 60%), the product was used in the next step without further purification.^{1}H NMR ($CDCl_3$) δ 2.66 (s, 3H, *Me*), 4.00 (s, 3H, O*Me*), 7.34 (d, J = 8.2 Hz, 1H, py), 7.73 (t, J = 4.0 Hz, 1H, py), 7.95 (d, J = 7.7 Hz, 1H, py); ^{13}C NMR ($CDCl_3$) δ 25.0 (CH_3), 53.3 (OCH_3), 122.8 (CH), 127.3 (CH), 137.5 (CH), 147.8 (C), 159.4 (C), 166.4 (C).



6-methyl-pyridine-2-carboxylic acid (16).

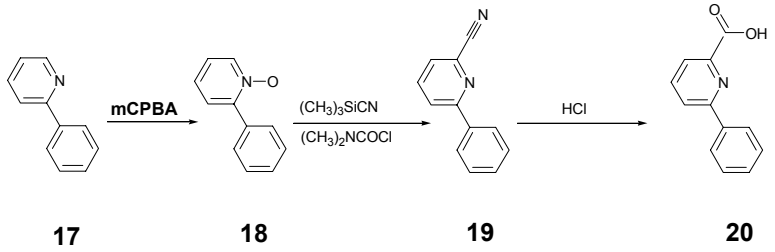
Aqueous 5M NaOH (15 mL) was added to a solution of 6-methyl-pyridine-2-carboxylic acid methyl ester **15** (1.06 g, 7.01 mmol) in ethanol (3 mL) in a 100 mL round bottom flask. Two boiling stones were added to the reaction mixture before it was warmed to reflux (25 min). The reaction mixture was allowed to cool to an ambient temperature and then acidified to pH 1 with HCl, at which point a white solid precipitated out of solution. The white solid was filtered at the pump before being washed with acetone (30 mL) and then MeOH (30 mL). The product 6-methyl-pyridine-2-carboxylic acid was furnished as a white flaky solid (0.91 g, 95%) and was used in the next step without further purification. ^{1}H NMR (d_6-DMSO) δ 2.59 (s, 3H, Me), 7.60 (d, J = 4.0 Hz, 1H, py), 7.92 (d, J = 7.2 Hz, 1H, py), 8.00 (t, J = 7.7 Hz, 1H, py). Consistent with the literature.[2]



(*S*)-6-Methyl-pyridine-2-carboxylic acid {1-[(diphenylphosphanyl)-methyl]-2-methyl-propyl}-methyl-amide. (*S*)-(–)-(4b)

Methyl chloroformate (0.065 mL, 0.85 mmol) was slowly added to a solution of 6-methyl-pyridine-2-carboxylic acid (117 mg, 0.85 mmol) and Et_3N (0.13 mL, 0.96 mmol) in dry THF (35 mL) at 0 ^oC while stirring under an argon atmosphere and the mixture was stirred in an ice bath for 30 minutes. Not all of the acid appeared to have been dissolved, the reaction mixture was warmed to 45 ^oC for 65 minutes. The white precipitate of triethylammonium chloride was removed by filtration. A clear solution of the mixed anhydride thus obtained (35 mL; 0.85 mmol, 1.5 equiv) was added slowly to a solution of (*S*)-(+)-**13** (162 mg, 0.567 mmol) in dry THF (25 mL) and Et_3N (0.106 mL, 0.85 mmol) while stirring at room temperature. The reaction mixture was stirred under argon for 18 h. TLC (petroleum ether – AcOEt, 1:2; Iodoplatinate developing agent) indicated that the reaction was finished. The mixture was concentrated under vacuum to furnish the crude product as a clear oil. The product was purified by chromatography on a column of degassed silica gel (65 g) with a petroleum ether – AcOEt mixture (1:2) to afford pure (*S*)-(–)-**4b** as a viscous clear oil (24 mg, 10%).$[\alpha]^{22}_D$ –3.90 (*c* 1.0; $CHCl_3$); ^1H NMR ($CDCl_3$) δ ^1H NMR ($CDCl_3$) indicates a mixture of rotamers were present in approximately 1.5:1 ratio, δ 0.86 (d, *J* = 7.4 Hz, 3H, *Me*$_2$CH), 0.93 (d, *J* = 7.4 Hz, 3H, *Me*$_2$CH), 0.94 (d, *J* = 7.4 Hz, 3H, *Me*$_2$CH), 0.99 (d, *J* = 7.4 Hz, 3H, *Me*$_2$CH), 1.79-1.88 (m, 1H), 1.88-1.98 (m, 1H), 1.98-2.05 (m, 1H), 2.29 (s, 3H, N*Me*), 2.36-2.43 (m, 1H), 2.48 (s, 3H, N*Me*), 2.69 (s, 3H, O*Me*), 2.83 (s, 3H, O*Me*), 3.97-4.04 (m, 1H, CH_2), 4.10-4.35 (m, 1H, CH_2), 6.90 (d, *J* = 7.6 Hz, 1H, py), 7.04-7.16 (m, 6H, Ar), 7.19-7.35 (m, 14H, Ar), 7.39-7.46 (m, 4H, py).

Scheme 4: Synthesis of 6-phenyl-pyridine-2-carboxylic acid **20**.



2-Phenyl-pyridine *N*-oxide (18).

MCPBA (4.00g, 23.20 mmol) was slowly added to a solution of 2-phenylpyridine **17** (3.0 g, 19.33 mmol) in dichloromethane (10 mL) at 0 ^oC under an atmosphere of argon while stirring. The reaction mixture was allowed to warm to room temperature and was stirred overnight, a pale yellow colour developed. TLC (petroleum ether – AcOEt, 1:5; $KMnO_4$ developing agent) indicated the reaction was complete. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (50 mL) and dichloromethane (50 mL) and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over magnesium sulfate and the solvent was removed in vacuo to afford crude 2-phenylpyridine *N*-oxide **18**. The product was recrystallised from ethyl acetate to afford fine white crystals (1.95 g, 59%); ^1H NMR ($CDCl_3$) δ 7.16 (ddd, *J* = 8.8, 7.6 and 2.4 Hz, 1H), 7.23 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.34-

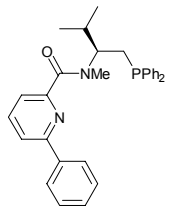
7.44 (m, 4H), 7.72-7.77 (m, 2H), 8.62 (dd, J = 6.5 and 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$); δ 124.9 (CH), 126.0 (CH), 127.8 (CH), 128.7 (CH), 129.7 (CH), 130.0 (CH), 133.0 (CH), 138.5 (C), 140.9 (C); IR (NaCl plates) ν 1242 (N-O) cm^{-1}; HRMS (EI+) 171.0684 ($C_{11}H_9ON$ requires 171.0684). Anal. Calcd for $C_{11}H_9ON$: C, 77.19; H, 5.26; N, 8.19. Found: C, 77.13; H, 5.24; N, 8.22.

6-Phenyl-pyridine-2-carbonitrile (19).[3]

A solution of 2-phenyl-pyridine *N*-oxide (1.67 g, 9.80 mmol) in dichloromethane (20 mL) was added to trimethylsilyl cyanide (1.66 mL, 12.40 mmol) at room temperature with constant stirring. A solution of dimethylcarbamoyl chloride (0.79 mL, 12.40 mmol) in dichloromethane (10 mL) was then added dropwise with stirring to the reaction mixture over a 30 min period and the reaction mixture was stirred at room temperature for 4 days. TLC (petroleum ether – AcOEt, 1:3; Dragendorf - nitrite overspray developing agent) indicated the reaction was complete. A solution of 10% aqueous potassium carbonate (50 mL) was added dropwise, and the stirring was continued for 10 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×50 mL) The combined organics were dried over magnesium sulfate and the solvent was removed in vacuo to afford the crude product as a brown crystalline solid. The product was purified by chromatography on a column of silica gel (45 g) with a petroleum ether – ethyl acetate mixture (1:3) to afford pure **19** as a pale yellow crystalline solid (1.17 g, 66%). ^{1}H NMR ($CDCl_3$) δ 7.38-7.43 (m, 3H), 7.52 (dd, J = 7.6 and 1.2 Hz, 1H), 7.79 (t, J = 8.4 Hz, 1H), 7.85 (dd, J = 8.4 and 1.2 Hz, 1H), 7.91-7.95 (m, 2H).

6-Phenyl-pyridine-2-carboxylic acid (20)

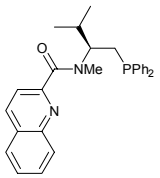
Aqueous HCl (5 mL, 10N, 37% w/w basis) was added to 6-phenyl-pyridine-2-carbonitrile **19** (1.14 g, 6.30 mmol) and the reaction mixture was refluxed at 90 ^{o}C for 2 days. TLC (petroleum ether – AcOEt, 1:3; Dragendorf - nitrite overspray developing agent) indicated the reaction was complete. The reaction mixture was allowed to cool to an ambient temperature and the product was extracted into dichloromethane (3 × 25 mL). The combined organics were dried over magnesium sulfate and the solvent was removed in vacuo to afford crude 6-phenyl-pyridine-2-carboxylic acid **20** (1.20 g, 95%): ^{1}H NMR ($CDCl_3$) δ 7.41-7.49 (m, 3H), 7.90-7.98 (m, 5H), 8.11 (dd, J = 6.8 and 2.0 Hz, 1H); IR (NaCl plates) ν 1720 (C=O) cm^{-1}. The product was used in the next step without further purification



(*S*)-6-Phenyl-pyridine-2-carboxylic acid {1-[(diphenylphosphanyl)-methyl]-2-methyl-propyl}-methyl-amide. (*S*)-(4c)

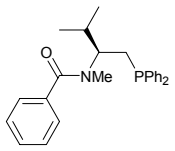
Methyl chloroformate (0.08 mL, 1.05 mmol) was slowly added to a solution of 6-Phenyl-pyridine-2-carboxylic acid **20** (210 mg, 1.05 mmol) and Et_3N (0.167 mL, 1.19 mmol) in dry THF (20 mL) at 0 ^{o}C while stirring under an argon atmosphere and the mixture was stirred in an ice bath for 30 min. The white precipitate of triethylammonium chloride was removed by filtration.

A clear solution of the mixed anhydride thus obtained (20 mL; 1.05 mmol, 1.5 equiv) was added slowly to a solution of (*S*)-(+)-**13** (200 mg, 0.70 mmol) in dry THF (25 mL) (first filtered through cotton wool) and Et_3N (0.167 mL, 1.19 mmol) while stirring at room temperature and the reaction mixture was stirred overnight. TLC (petroleum ether – AcOEt, 1:1); iodoplatinate developing agent) indicated that reaction was complete. The mixture was concentrated under vacuum to furnish a viscous yellow oil, which was purified by chromatography on a column of degassed silica gel (65 g) with a petroleum ether – ethyl acetate mixture (1:1) to afford **4d** as a viscous clear oil (271 mg, 83%): ^{1}H NMR ($CDCl_3$) indicated a 1:1 mixture of two rotamers δ 0.85 (d, *J* = 6.4 Hz, 3H, *Me*$_2$CH), 0.96 (d, *J* = 6.4 Hz, 3H, *Me*$_2$CH), 0.97 (d, *J* = 6.8 Hz, 3H, *Me*$_2$CH), 1.06 (d, *J* = 6.8 Hz, 3H, *Me*$_2$CH), 1.82-1.91 (m, 2H), 1.97-2.01 (m, 2H), 2.21-2.37 (m, 1H), 2.40 (apparent dt, *J* = 14.4 and 3.8 Hz, 1H), 2.51 (apparent dt, *J* = 14.0 and 3.8 Hz, 1H), 2.77 (s, 3H, NMe), 2.86 (s, 3H, NMe), 4.15-4.31 (m, 2H), 7.01-7.08 (m, 4H), 7.18-7.50 (m, 26H), 7.67-7.76 (m, 2H, py), 7.82-7.86 (m, 2H, py), 7.97-8.00 (m, 2H, py); ^{31}P NMR ($CDCl_3$) δ –25.0 (P(III)), -21.7 (P(III)), 28.7 (P(V), minor); IR (NaCl plates) ν 1631 (C=O) cm^{-1}; HRMS (EI+) 466.2176 ($C_{30}H_{31}ON_2P$ requires 466.2174).



(*S*)-(–)-*N*-Methyl-*N*-(1-diphenylphosphino-3-methylbut-1-yl)-2-quinoline-carboxamide (*S*)-(–)-(4d).

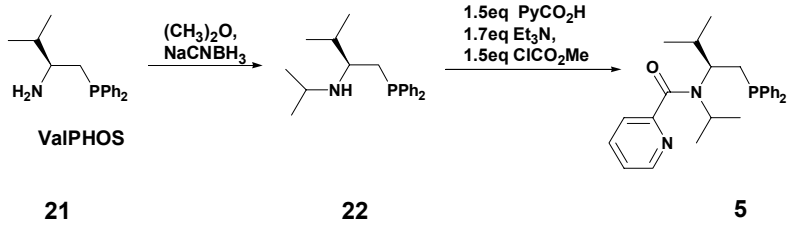
Methyl chloroformate (0.06 mL, 0.79 mmol) was slowly added to a solution of quinoline-2-carboxylic acid (136 mg, 0.79 mmol) and Et_3N (0.12 mL, 0.89 mmol) in dry THF (35 mL) at 0 ^{o}C while stirring under an argon atmosphere and the mixture was stirred in an ice bath for 30 minutes. The white precipitate of triethylammonium chloride was removed by filtration. A clear solution of the mixed anhydride thus obtained (35 mL; 0.79 mmol, 1.5 equiv) was added slowly to a solution of (*S*)-(+)-**13** (150 mg, 0.52 mmol) in dry THF (25 mL) (first filtered through cotton wool) and Et_3N (0.11 mL, 7.88 mmol) while stirring at room temperature. The reaction mixture was observed to have a clear yellow colour. After 1 h TLC (petroleum ether – AcOEt, 1:2; iodoplatinate developing agent) indicated that the starting material (*S*)-(+)-**13** had disappeared. The mixture was concentrated under vacuum to furnish a viscous yellow oil, which was purified by chromatography on a column of degassed silica gel (65 g) with a petroleum ether – ethyl acetate mixture (1:1) to afford pure (*S*)-(–)-**4c** as a clear viscous oil (147 mg, 63%): $[\alpha]^{20}_D$ –35.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) indicated a 1.5:1 mixture of two rotamers, δ 0.88 (d, *J* = 6.4 Hz, 3H, *Me*$_2$CH), 0.97 (d, *J* = 6.8 Hz, 3H, *Me*$_2$CH), 0.99 (d, *J* = 6.8 Hz, 3H, *Me*$_2$CH), 1.10 (d, *J* = 6.8 Hz, 3H, *Me*$_2$CH), 1.83-1.93 (m, 2H), 2.00-2.01 (m, 2H), 2.39 (apparent dt, *J* = 14.6 and 3.8 Hz, 1H), 2.53 (apparent dt, *J* = 14.2 and 3.9 Hz, 1H), 2.72 (s, 3H, NMe), 2.90 (s, 3H, NMe), 4.23-4.31 (m, 2H), 6.83-6.87 (m, 2H), 6.92-6.96 (m, 4H), 7.18-7.39 (m, 10H), 7.41-7.45 (m, 2H), 7.46-7.50 (m, 4H), 7.55-7.60 (m, 4H), 7.63-7.69 (m, 2H), 7.72-7.77 (m, 2H), 8.04 (d, *J* = 8.4 Hz, 1H), 8.14 and 8.24 (2 × d, *J* = 8.4 Hz, 2 ×1H); ^{31}P NMR ($CDCl_3$): δ –24.4 (P(III)), -21.9 (P(III)), 28.8 (P(V), minor); IR (NaCl plates) 1627 cm^{-1}.

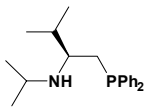


(*S*)-*N*-{1-[(Diphenylphosphanyl)-methyl]-2-methyl-propyl}-*N*-methyl-benzamide (*S*)-(+)-(7).

Et_3N (0.059 mL, 0.42 mmol) was added to a solution of (*S*)-(+)-**13** (100 mg, 0.35 mmol) in dry THF (5 mL) at 0 °C while stirring under an argon atmosphere. Benzoyl chloride (0.041 mL, 0.35 mmol) wasn then slowly added to the solution with constant stirring. After 2 h the TLC (petroleum ether – AcOEt, 1:2; ninhydrin developing agent) indicated that the reaction was complete. The mixture was concentrated under vacuum to furnish a viscous yellow oil, which was purified by chromatography on a column of degassed silica gel (40 g) with a petroleum ether – ethyl acetate mixture (1:1) to afford pure (*S*)-(–)-**7** as a white solid (139 mg, 100%): ^{1}H NMR ($CDCl_3$) indicated a 2:1 mixture of two rotamers δ 0.77 (d, *J* = 6.5 Hz, 3H, *Me*$_2$CH), 0.78 (d, *J* = 6.6 Hz, 3H, *Me*$_2$CH), 0.76 (d, *J* = 6.6 Hz, 3H, *Me*$_2$CH), 0.91 (d, *J* = 6.6 Hz, 3H, *Me*$_2$CH), 1.72 apparent ddd, *J* = 15.6, 13.2 and 6.8 Hz, 1H), 1.78-1.95 (bm, 1H), 2.02 (dd, *J* = 14.8 and 11.2 Hz, 1H), 2.12-2.30 (bm, 1H), 2.41-2.52 (m, 2H), 2.65 (s, 3H, NMe), 2.71 (s, 3H, NMe), 3.45-3.52 (m, 1H), 4.07-4.30 (bm, 1H), 7.01-7.43 (m, 30 H); ^{31}P NMR ($CDCl_3$): δ –25.1 (P(III)), -22.6 (P(III)), 28.7 (P(V), minor); IR (NaCl plates) ν 1632 (C=O) cm^{-1}; HRMS (EI+) 389.1910 ($C_{25}H_{28}ONP$ requires 389.1909).

Scheme 5: Synthetic route to (*S*)-(+)-(**5**)

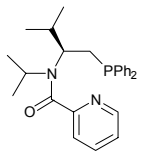




(*S*)-(+)-N-*iso*-Propyl-2-amino-3-methylbutyl-1-diphenylphosphine (*S*)-(+)-(22).[4]

Sodium cyanoborohydride (377 mg, 6.00 mmol) was added to a solution of crude (*S*)-(+)-ValPHOS **21**[5] (979 mg, 1.5 mmol) in methanol (10 mL) and acetone (0.16 mL, 2.25 mmol) and the mixture was allowed to stir overnight at room temperature. Volatiles were removed in vacuo and the residue was partitioned between water (20 mL) and dichloromethane (20 mL) and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organics were washed with brine (75 mL), dried over magnesium sulfate, and the solvent was removed in vacuo. The product was purified by passing through a column of degassed silica gel (65 g) (petroleum ether with 2% Et_3N) to yield (*S*)-(+)-**22** as a clear oil (209 mg, 34%): ^{1}H NMR ($CDCl_3$): δ 0.74 (d, *J* = 6.8 Hz, 3H, CH*Me*$_2$), 0.80 (d, *J* = 6.8 Hz, 3H, CH*Me*$_2$), 0.83 (d, *J* = 6.4 Hz, 3H, NCH*Me*$_2$), 0.84 (d, *J* = 6.4 Hz, 3H, NCH*Me*$_2$), 1.18-1.93 (bs, 1H, N*H*), 1.82-1.93 (m, 1H, C*H*Me$_2$), 1.82-1.93 (m, 1H, C**H*), 2.13 (ddd, *J* = 13.6 Hz, *J* = 4.8 Hz, *J* = 2.0 Hz, 1H, C*H*$_2$),

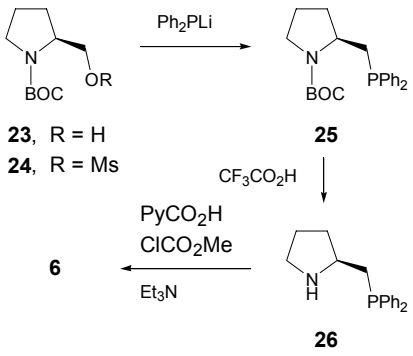
2.36-2.42 (m, 1H, CH_2), 2.68 (apparent septet, J = 6.4 Hz, 1H, NCHMe$_2$), 7.18-7.42 (m, 10H, Ph). Consistent with the literature.[4]

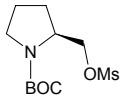


(*S*)-*N*-isopropyl-*N*-(1-diphenylphosphino-3-methylbut-1-yl)-2-pyridine-carboxamide (*S*)-(+)-(5).

Methyl chloroformate (0.058 mL, 0.76 mmol) was slowly added to a solution of 2-picolinic acid (93 mg, 0.76 mmol) and Et_3N (0.12 mL, 0.86 mmol) in dry THF (35 mL) at 0 ^oC while stirring under an argon atmosphere and the mixture was stirred in an ice bath for 30 minutes. The white precipitate of triethylammonium chloride was removed by filtration. A clear solution of the mixed anhydride thus obtained (35 mL; 0.76 mmol, 1.5 equiv) was added slowly to a solution of (*S*)-(+)-**22** (209 mg, 0.506 mmol) in dry THF (25 mL) and Et_3N (0.106 mL, 0.76 mmol) while stirring at room temperature. The mixture was observed to be clear yellow during the reaction. After 5 h TLC (petroleum ether – AcOEt, 1:2; iodoplatinate developing agent) indicated that the starting material had disappeared. The mixture was concentrated under vacuum to furnish the crude product as a clear yellow oil. The product was purified by chromatography on a column of degassed silica gel (65 g) with a petroleum ether – AcOEt mixture (3:1, 1:1, and then 1:2) to afford pure (*S*)-(+)-**5** as a viscous clear oil (220 mg, 100%): $[\alpha]_D^{18}$ +13.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) indicates a mixture of rotamers were present in approximately 1.5:1 ratio, δ 0.86 (d, J = 6.7 Hz, 3H, *Me*$_2$CH), 0.93 (d, J = 6.7 Hz, 3H, *Me*$_2$CH), 0.98 (d, J = 6.5 Hz, 3H, *Me*$_2$CH), 1.03 (d, J = 6.5 Hz, 3H, *Me*$_2$CH), 1.58 (d, J = 6.6 Hz, 6H, *Me*$_2$CHN), 1.68 (d, J = 6.7 Hz, 6H, *Me*$_2$CHN), 1.92 (apparent sextet, J = 6.9 Hz, 1H, Me$_2$C*H*), 2.05 (m, 1H, Me$_2$C*H*), 2.44 (dt, J = 14.9 Hz, J = 4.1 Hz, 1H, CH_2), 2.59 (bm, 1H, CH_2), 2.89 (bm, 1H, CH_2), 3.56 (hept, J = 6.8 Hz, 1H, Me$_2$C*H*N), 3.67 (m, 1H, CH_2), 3.72 (apparent hept, J = 6.8 Hz, 1H, Me$_2$C*H*N), 6.95 (apparent q, J = 4.5 Hz, 1H, Ar), 7.11-7.38 (m, 25H, Ar), 7.65 (apparent t, J = 7.7 Hz, 1H, py), 7.99 (d, J = 4.6 Hz, 1H, py), 8.50 (d, J = 4.0 Hz, 1H, py); ^{31}P NMR ($CDCl_3$) δ –24.07 (s, P(III), major peak), -18.54 (s, P(V), minor peak); IR (NaCl discs) ν 1630 cm^{-1} (NCO); HRMS (EI) 418.2175 ($C_{26}H_{31}N_2OP$ requires 418.2174).

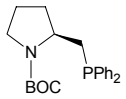
Scheme 6: Synthetic route to (S)-(**6**)





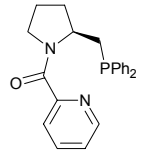
(S)-*N*-Boc-2-{[(methylsulphonyl)oxy]methyl}pyrrolidine (*S*)-(24).[6]

A solution of methanesulfonyl chloride (0.1 mL, 1.26 mmol) in dry THF (10 mL) was added dropwise to a solution of (*S*)-(+)-**23** (2-hydroxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester) (230 mg, 1.14 mmol) and Et_3N (0.18 mL 1.26 mmol) in dry THF (25 mL) was at -15 ^oC with constant stirring under an argon atmosphere. The mixture was then allowed to warm to an ambient temperature. The reaction was monitored by TLC (1:1 petroleum ether – AcOEt, 1:1; Dragendorf and nitrite over spray developing agents) until completion (1.5 h). Saturated aqueous Na_2CO_3 was added to the reaction mixture and the product was extracted into CH_2Cl_2 (3 × 20 mL), the organic extract was dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford (*S*)-**24** as a viscous oil (0.33 g, 98%): ^1H NMR ($CDCl_3$) δ 1.36 (s, 9H, *t*-Bu), 1.80-1.98 (m, 4H), 2.94 (s, 3H, Me), 3.28-3.38 (m, 2H), 3.96 (m,1H), 4.23 (m, 1H).



***(*S)-(–)-*N*-tert-Butoxycarbonyl-2-(diphenylphosphinomethyl)pyrrolidine (*S*)-(–)-25.**

A solution of Ph_2PH (1.17 mL, 6.74 mmol) in dry THF (25 mL) was cooled to 0 ^oC with constant stirring under a nitrogen atmosphere. *n*-BuLi (4.21 mL, 1.6 M, 6.74 mmol) was added to the reaction mixture at which point a persistent red coloration was observed. A solution of (*S*)-**24** (750 mg, 2.70 mmol) in dry THF (10 mL) was added dropwise to the reaction mixture; no change in colouration was observed. The reaction was monitored by TLC (*n*-hexane – AcOEt, 9:1; iodoplatinate developing agent) which indicated that the reaction was complete after 1 h. The red mixture was quickly filtered through a Celite pad and the pad was washed with dry THF (30 mL) to afford a clear yellow filtrate. Removal of the solvent under vacuum afforded a viscous yellow oil, which was purified on a degassed silica gel column (*n*-hexane – AcOEt, 9:1). Concentration of the product solution under vacuum afforded the product, (*S*)-(–)-**25** as a translucent white oil (370 mg, 50%): ^1H NMR ($CDCl_3$) indicated the presence two amide isomers: δ 1.34 (s, 9H, *t*Bu), 1.71-1.97 (bm, 5H), 2.62 (bm, 1H), 3.25 (bm, 2H, NCH_2), 3.79 (bm, 1H, NCH), 7.19-7.34 (bm, 10H, Ar).



(*S*)-(–)-*N*-2-Picolinoyl-2-(diphenylphosphinomethyl)pyrrolidine (*S*)-(–)-(6).

Neat trifluoroacetic acid (5 mL) was degassed by bubbling nitrogen through the liquid (3 min) and then added to a solution of (*S*)-(–)-**25** (2.31 g, 6.25 mmol) and the reaction flask was swirled. TLC (petroleum ether – Et_2O, 9:2; iodoplatinate and nitrite over spray developing agents) indicated that the reaction was complete after 40 min (migration of the spot towards the baseline). The bulk of the acid was removed by rotary evaporation, dry toluene (25 mL) was then added and evaporated in vacuum to remove the remaining traces of acid. Saturated aqueous Na_2CO_3 (30 mL) was added to the residue and the product was extracted into dichloromethane (3 × 30 mL) and the organic phase was dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded (*S*)-(–)-**26** as a clear viscous oil (340 mg, 1.28 mmol): ^1H NMR ($CDCl_3$) δ

1.30-1.37 (m, 1H), 1.83-1.97 (m, 2H), 2.12-2.17 (m, 2H), 2.25-2.30 (m, 2H), 2.71-2.78 (m, 1H), 2.92-3.01 (m, 2H), 7.19-7.38 (m, 10H, Ar).

A solution of 2-picolinc acid (240 mg, 1.91 mmol) and Et_3N (0.3 mL, 2.17 mmol) in dry THF (25 mL) was cooled to 0 °C with constant stirring under an argon atmosphere. Methyl chloroformate (0.18 mL, 1.92 mmol) was slowly added and the resulting mixture was stirred for 0.5 h and then was filtered to afford a clear filtrate. A solution of (*S*)-(–)-**26** (340 mg, 1.28 mmol) in dry THF (25 mL) was filtered through cotton wool and Et_3N (0.27 mL, 1.94 mmol) was added to the filtrate. The solution of (*S*)-(–)-**26** was slowly added to the mixed anhydride filtrate under an argon atmosphere and stirred continuously for 0.5 h of stirring at 0 °C, after which period the TLC (petroleum ether – AcOEt, 1:1; iodoplatinate developing agent) indicated that the reaction was complete. The reaction mixture was concentrated under vacuum to afford a viscous oil, which was purified by column chromatography on degassed silica gel (65 g) with a petroleum ether – Et_2O mixture (1:3). The solvent was removed under reduced pressure to afford (*S*)-(–)-**6** as a viscous translucent white oil (360 mg, 69%): ^{1}H NMR indicated a mixture of two *N*-methylamide isomers: ^{1}H NMR ($CDCl_3$) taken in a mixture with minor isomer δ 1.65-1.73 (m 1H), 1.88-2.12 (bm, 4H), 3.16-3.21 (m, 1H), 3.52-3.58 (m, 1H), 3.52-3.95 (bm, 1H), 4.30-4.32 (m, 1H), 7.14-7.36 (bm, 10H, Ar), 7.64-7.70 (m, 3H), 4.50-4.51 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 25.5, 31.1, 32.9, 49.9, 56.9, 124.1-148.4 (14 × CH, Ar); IR (NaCl discs) ν 1636 cm^{-1} (NCO); HRMS (EI) 374.1546, M^+ for $C_{23}H_{23}ON_2P$ requires 374.1548, consistent with the literature.[7]

AgOTf•(*S*)-3a

(*S*)-3a (12.5 mg, 0.033 mmol) was added to a vial containing $CDCl_3$ (0.45 mL) and AgOTf (57.6 mg, 0.224 mmol). The mixture was gently warmed until the $CDCl_3$ started to boil, the AgOTf did not completely dissolve. The solution was allowed to cool to an ambient temperature before being filtered through cotton wool and submitted for NMR analysis.^{1}H NMR ($CDCl_3$) δ 0.90 (d, *J* = 6.8 Hz, 3H, *Me*$_2$CH), 0.91 (d, *J* = 6.8 Hz, 3H, *Me*$_2$CH), 1.92 (apparent sextet, *J* = 6.4 Hz, 1H, Me$_2$C*H*), 2.60-2.75 (bm, 1H, C*H*$_2$), 3.10 (apparent dd, *J* = 14.4 and 12.4 Hz, 1H, C*H*$_2$), 4.09 (m, 1H, C**H*), 7.24 (dd, *J* = 6.8 and 5.2 Hz, 1H, Ar), 7.31-7.37 (m, 5H, Ar), 7.42-7.46 (m, 2H, Ar), 7.58 (m, 1H, Py), 7.80 (d, *J* = 7.2 Hz, 1H, Ar), 7.83 (d, *J* = 7.2 Hz, 1H, Ar), 7.91 (td, *J* = 8.0 and 1.6 Hz, 1H, Py), 8.45 (d, *J* = 8.0 Hz, 1H, Py), 8.51 (d, *J* = 4.4 Hz, 1H, Py), 9.33 (d, *J* = 9.2 Hz, 1H, NH); ^{31}P NMR spectra were recorded at room temperature, chemical shifts were calculated from 85% H_3PO_4 external standard; ^{31}P{^{1}H} NMR ($CDCl_3$) δ 3.39 (d, $J_{31P\text{-}109Ag}$ = 789 Hz, $J_{31P\text{-}107Ag}$ = 685 Hz); IR (NaCl plates) ν 1664 (NCO) cm^{-1}.

AgOTf•(*S*)-4a

(*S*)-(4a) (12.9 mg, 0.033 mmol) was added to a vial containing $CDCl_3$ (0.45 mL) and AgOTf (57.6 mg, 0.224 mmol). The mixture was gently warmed until the $CDCl_3$ started to boil, the AgOTf did not completely dissolve. The solution was allowed to cool to an ambient temperature before being filtered through cotton wool and submitted for NMR analysis. ^{1}H NMR ($CDCl_3$) δ 0.89 (d, *J* = 6.8 Hz, 3H, *Me*$_2$CH), 0.96 (d, *J* = 6.4 Hz, 3H, *Me*$_2$CH), 1.93 (bs, 1H), 2.41 (bs, 1H), 2.76 (s, 3H, *N*-Me), 2.78 (bs, 1H), 4.29 (bs, 1H), 7.40-7.44 (m, 4H), 7.46-7.51 (m, 4H), 7.59 (bs, 4H), 7.90 (td, *J* = 8.0 and 1.6 Hz, 1H, Py), 8.88 (d, *J* = 5.1 Hz, 1H, Py); ^{31}P{^{1}H} NMR ($CDCl_3$) δ –1.0 (bs); IR (NaCl plates) ν 1635 (NCO) cm^{-1}.

General procedure for the asymmetric addition of diethylzinc catalyzed by Cu/L* (Scheme 1 and Table 1).

A mixture of chiral ligand **L*** (40 μmol) and copper salt (30 μmol) in dry solvent (4 mL) was stirred at room temperature for 30 min under an argon atmosphere to produce a green coloured solution. A solution of enone (1.50 mmol) in dry solvent (4 mL) was then added and the resulting mixture was stirred at room temperature for 15 minutes. The mixture was then cooled and maintained at the temperature indicated and a 1M solution of Et_2Zn in hexanes (300 mol%) was added; decolourisation of the mixture occurred. The reaction mixture was stirred overnight at the indicated temperature; the reaction was monitored by TLC (for chalcone: 4:1 *n*-hexane–Et_2O; for 2-cyclohexen-1-one and 2-cyclohepten-1-one 5:1 petroleum ether–AcOEt; $KMnO_4$ was used as a developing agent). The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and the mixture was extracted with CH_2Cl_2 (5 × 20 mL). The organic extracts were combined and dried over Na_2SO_4, and the solvent was removed under reduced pressure to afford the oily product, which was purified by chromatography on a column of silica gel (65 g) with a 4:1 *n*-hexane–Et_2O mixture (for chalcone), or neat petroleum ether (for 2-cyclohexen-1-one and 2-cyclohepten-1-one) (30 g silica gel).

(*S*)-(–)-3-Ethyl-cyclohexanone (2a): ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7.4 Hz, 3H), 1.01-1.32 (m, 3H), 1.48 (bs, 1H), 1.59-1.63 (m, 2H), 1.89-1.97 (m, 1H), 2.17-2.23 (ddd, J = 12.2, 6.1, and 1.1 Hz, 1H), 2.34-2.38 (m, 1H); chiral GC on a SUPELCO β-DEX 120 column, 60 °C, 5 min, 1 °C/min (t_S = 39.84 min (major), t_R = 37.18 min (minor)). The absolute configuration assigned according to literature data.[8] $[\alpha]_D^{22}$ –0.3 (*c* 0.9, $CHCl_3$) for a 7% ee sample. A negative sign of optical rotation corresponds to the (*S*)-enantiomer.

(–)-3-Ethyl-cycloheptanone (2b): ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7.6 Hz, 3H, CH_3), 1.18-1.35 (m, 4H), 1.45-1.60 (m, 2H), 1.77-1.88 (m, 3H), 2.28-2.42 (m, 4H), consistent with the literature;[9] chiral GC on a SUPELCO β-DEX 120 column, 80 °C, 5 min, 1 °C/min (t_{major} = 30.45 min, t_{minor} = 31.83 min); $[\alpha]_D^{17}$ –35.7 (*c* 2.1, $CHCl_3$) for 68% ee sample. No correlation between optical rotation and absolute configuration has been documented in the literature.

(*R*)-(–)-1,3-Diphenyl-pentan-1-one (2c): ^{1}H NMR δ 0.69 (t, J = 6.7 Hz, 3H, CH_3), 1.47-1.56 (m, 1H, CH_3CH_2CH), 1.62-1.72 (m, 1H, CH_3CH_2CH), 3.09-3.17 (m, 3H, CH_2COPh and PhC*H*), 7.01-7.20 (m, 5H, Ar), 7.25-7.29 (m, 2H, Ar), 7.34-7.39 (m, 1H, Ar), 7.76-7.77 (m, 2H, Ar), consistent with the literature.[10] Chiral HPLC on a Chiralpak AD column with a 99.2:0.8 mixture of *n*-hexane and 2-propanol, flow rate 0.75 mL/min, UV detection at 220 nm (t_S = 9.48 min (minor), t_R = 12.43 min (major)). $[\alpha]_D^{22}$ –0.6 (*c* 1.0, $CHCl_3$) for a 41% ee sample. A negative sign of optical rotation corresponds to the (*R*)-enantiomer.

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