Remote Chiral Induction in Organocatalytic Hydrosilylation of Aromatic Ketones and Ketimines

Andrei V. Malkov,* Angus J. P. Stewart Liddon, Pedro Ramírez-López, Lada Bendová, David Haigh, and Pavel Kočovský*

Department of Chemistry, WestChem, Joseph Black Building, University of Glasgow, Glasgow G12 8QQ, U.K.
GlaxoSmithKline Pharmaceuticals, Medicines Research Centre, Stevenage SG1 2NY, U.K.

Experimental Section

General Methods

All reactions unless otherwise stated were run under an inert atmosphere in oven dried glassware. Room temperature refers to ambient room temperature (20-22°C), 0°C refers to an ice slush bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions were monitored by thin layer chromatography (TLC) using aluminium backed silica gel 60 (F254) plates, visualised using UV254 nm and potassium permanganate, phosphomolybdic acid or Dragendorf dips as appropriate. Flash chromatography was carried out routinely using 60 Å silica gel (Fischer). Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded at 25 °C unless otherwise indicated with an error of <±0.1. The \([\alpha]_D\) values are given in 10\(^{-1}\) deg cm\(^{-1}\) g\(^{-1}\). The NMR spectra were recorded in CDCl\(_3\), \(^1\)H at 400 MHz and \(^{13}\)C at 100.6 MHz with chloroform-d\(_1\) (\(\delta 7.26\), \(^1\)H; \(\delta 77.0\), \(^{13}\)C) as internal standard unless otherwise indicated. Coupling patterns are designated as follows: s - singlet, d - doublet, t - triplet, dd - doublet of doublets,ddd - doublet of doublet of doublets, tt - triplet of triplets, hept - heptet, m - multiplet, br - broad. 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, in a solid by the Golden Gate technique, or as a KBr disc. The mass spectra (EI and/or CI) were measured on a high resolution, dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. Enantiomeric excess was determined by GC (Supelco β-DEX\(^\text{TM}\) 120 fused capillary column, 30 m × 0.25 mm ×0.25 μm film thickness) or HPLC analysis as specified.

1. Materials

All solvents for the reactions were of reagent grade and were dried and distilled under argon or nitrogen immediately before use as follows: tetrahydrofuran, diethyl ether and toluene from sodium/benzophenone, dichloromethane from calcium hydride, chloroform from phosphorous pentoxide, methanol from magnesium turnings. Petroleum ether refers to the fraction boiling in the range 40-60 °C. 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 spectra. Imines 8a-f are known compounds and were prepared according to literature method.[81]
2. Reduction of Ketones

General Procedure for the Asymmetric Reduction of Ketones with Trichlorosilane.

Trichlorosilane (86 μL, 0.84 mmol, 2.1 eq) was slowly added dropwise to a solution of catalyst (21.9 mg, 0.08 mmol or 11.0 mg, 0.04 mmol) and the corresponding ketone (0.40 mmol, 1.0 eq) in CHCl₃ (2 mL) at –20 °C. The reaction mixture was stirred for 24 h at -20 °C, after which time saturated aqueous NaHCO₃ (1 mL) was added to quench the reaction. The mixture was extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic fractions were dried over MgSO₄. Concentration in vacuo followed by flash chromatography on silica gel (3 × 15 cm) with CH₂Cl₂ afforded sec-alcohols 3a-h.

(R)-(+)1-Phenylethanol (R)-(+)3a. [α]D +45.2 (c 0.93, CHCl₃, 80% ee), [lit.][S2] gives [α]D +49.0 (c 1.0, CHCl₃, 98% ee)]; ¹H NMR (400MHz, CDCl₃) δH 1.52 (d, J = 6.4 Hz, 3H), 2.21 (bd, 1H), 4.92 (q, J = 6.4 Hz, 1H), 7.28-7.50 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δC 25.2 (CH₃), 70.4 (CH), 125.4 (2 × CH), 127.5 (CH), 128.5 (2 × CH), 145.9 (C); Chiral GC (Supelco β-DEX), carrier gas: He (flow 2 mL/min), injection temp: 220 °C; column temp: initial temp, 80 °C for 2 min; rate, 1.5 °C/min; final temperature 160 °C (τR = 23.31 min; τS = 24.21 min).

(R)-(+)1-(2'-Methoxyphenyl)ethanol (R)-(+)3b. [α]D +15.3 (c 0.52, CHCl₃, 77% ee), [lit.][S3] gives [α]D +25.6 (c 1.94, CHCl₃, 96% ee)]; ¹H NMR (400 MHz, CDCl₃) δH 1.43 (d, J = 6.4 Hz, 3H), 2.45 (bs, 1H), 3.79 (s, 3H), 5.02 (q, J = 6.4 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.89 (td, J = 7.2, 0.8 Hz, 1H), 7.18 (td, 8.0, 2.0 Hz, 1H), 7.26 (dd, 7.6, 1.6 Hz, 1H), ¹³C NMR (100 MHz, CDCl₃) δC 22.9 (CH₃), 55.3 (CH₃), 66.5 (CH), 110.5 (CH), 120.8 (CH), 126.1 (CH), 128.3 (CH), 133.5 (C), 156.6 (C); Chiral GC (Supelco β-DEX), carrier gas: He (flow 2 mL/min), injection temp: 220 °C; column temp: initial temp 80 °C for 2 min, rate 1.5 °C/min, final temp 160 °C (τS = 38.03 min, τR = 38.87 min).
(R)-(+)-1-(2'-Fluorophenyl)ethanol (R)-(+)---3c. \([\alpha]_D^{+} 18.0\ (c\ 0.07,\ \text{CH}_2\text{Cl}_2,\ 68\%\ ee),\ \text{[lit.]}^{[S4]}\) gives \([\alpha]_D^{+} -44.5\ (c\ 0.782,\ \text{MeOH},\ 99\%\ ee\ of\ (S)\ enantiomer);\ \text{[1]H NMR}\ (400\ MHz,\ \text{CDCl}_3)\ \delta_{\text{H}} 1.46\ (d,\ J = 6.8\ \text{Hz},\ 3\text{H}),\ 1.67\ (bs,\ 1\text{H}),\ 5.14\ (q,\ J = 6.8\ \text{Hz},\ 1\text{H}),\ 6.95\ (ddd,\ J = 10.4,\ 8.0,\ 1.2\ \text{Hz},\ 1\text{H}),\ 7.08\ (td,\ J = 7.6,\ 1.2\ \text{Hz},\ 1\text{H}),\ 7.13-7.19\ (m,\ 1\text{H}),\ 7.42\ (td,\ J = 7.6,\ 1.6\ \text{Hz},\ 1\text{H});\ \text{[13]C NMR}\ (100\ MHz,\ \text{CDCl}_3)\ \delta_{\text{C}} 24.0\ (\text{CH}_3),\ 64.5\ (d,\ J_{\text{CF}} = 3.0\ \text{Hz},\ \text{CH}),\ 115.3\ (d,\ J_{\text{CF}} = 22.0\ \text{Hz},\ \text{CH}),\ 124.3\ (d,\ J_{\text{CF}} = 3.0\ \text{Hz},\ \text{CH}),\ 126.6\ (d,\ J_{\text{CF}} = 5.0\ \text{Hz},\ \text{CH}),\ 128.8\ (d,\ J_{\text{CF}} = 9.0\ \text{Hz},\ \text{CH}),\ 132.7\ (d,\ J_{\text{CF}} = 13.0\ \text{Hz},\ \text{C}),\ 159.8\ (d,\ J_{\text{CF}} = 244.0\ \text{Hz},\ \text{CF});\ \text{Chiral GC}\ \text{(Supelco}\ \beta-\text{DEX}^\text{TM}),\ \text{carrier gas: He}\ (\text{flow} 2\ \text{mL/min)},\ \text{injection temp: 220}^\circ\text{C};\ \text{column temp: initial temp} 80\ ^\circ\text{C for 2 min, rate, 1.5} ^\circ\text{C/min, final temp} 200\ ^\circ\text{C} (t_R = 23.48\ \text{min},\ t_S = 24.87\ \text{min}).

(R)-(+)-1-(4'-Methylphenyl)ethanol (R)-(+)---3d. \([\alpha]_D^{+} 41.2\ (c\ 0.63,\ \text{CHCl}_3,\ 80\%\ ee),\ \text{[lit.]}^{[S5]}\) gives \([\alpha]_D^{+} -44.5\ (c\ 1.0,\ \text{CHCl}_3,\ 76\%\ ee);\ \text{[1]H NMR}\ (400\ MHz,\ \text{CDCl}_3)\ \delta_{\text{H}} 1.42\ (d,\ J = 6.4\ \text{Hz},\ 3\text{H}),\ 1.66\ (bs,\ 1\text{H}),\ 2.28\ (s,\ 3\text{H}),\ 4.80\ (q,\ J = 6.4\ \text{Hz},\ 1\text{H}),\ 7.10\ (d,\ J = 8.0\ \text{Hz},\ 2\text{H}),\ 7.20\ (d,\ J = 9.2\ \text{Hz},\ 2\text{H});\ \text{[13]C NMR}\ (100\ MHz,\ \text{CDCl}_3)\ \delta_{\text{C}} 21.1\ (\text{CH}_3),\ 25.1\ (\text{CH}_2),\ 70.3\ (\text{CH}),\ 125.4\ (2\times\ \text{CH}),\ 129.2\ (2\times\ \text{CH}),\ 137.2\ (\text{C}),\ 142.9\ (\text{C});\ \text{Chiral GC}\ \text{(Supelco}\ \beta-\text{DEX}^\text{TM}),\ \text{carrier gas: He}\ (\text{flow} 2\ \text{mL/min)},\ \text{injection temp: 220}^\circ\text{C};\ \text{column temp: initial temp,} 100\ ^\circ\text{C, rate, 1} ^\circ\text{C/min, final temp,} 160\ ^\circ\text{C} (t_R = 18.15\ \text{min},\ t_S = 19.23\ \text{min}).

(R)-(+)-1-Phenylpropanol (R)-(+)---3e. \([\alpha]_D^{+} 31.6\ (c\ 1.0,\ \text{CHCl}_3,\ 80\%\ ee),\ \text{[lit.]}^{[S2]}\) gives \([\alpha]_D^{+} 47.0\ (c\ 1.4,\ \text{CHCl}_3,\ 95\%\ ee);\ \text{[1]H NMR}\ (400\ MHz,\ \text{CDCl}_3)\ \delta_{\text{H}} 0.85\ (t,\ J = 7.6\ \text{Hz},\ 3\text{H}),\ 1.63-1.81\ (m,\ 3\text{H}),\ 4.53\ (dd,\ J = 6.8,\ 6.4\ \text{Hz},\ 1\text{H}),\ 7.18-7.34\ (m,\ 5\text{H});\ \text{[13]C NMR}\ (100\ MHz,\ \text{CDCl}_3)\ \delta_{\text{C}} 10.2\ (\text{CH}_3),\ 31.9\ (\text{CH}_2),\ 76.1\ (\text{CH}),\ 126.0\ (2\times\ \text{CH}),\ 127.5\ (\text{CH}),\ 128.4\ (2\times\ \text{CH}),\ 144.6\ (\text{C});\ \text{Chiral GC}\ \text{(Supelco}\ \beta-\text{DEX}^\text{TM}),\ \text{carrier gas: He}\ (\text{flow} 2\ \text{mL/min)},\ \text{injection temp: 220}^\circ\text{C};\ \text{column temp: initial temp,} 80\ ^\circ\text{C for 2 min; rate, 1.5} ^\circ\text{C/min, final temp,} 200\ ^\circ\text{C} (t_R = 26.29\ \text{min},\ t_S = 27.09\ \text{min}).
1-Cyclohexylethanol (±)-3f. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 0.84-1.25 (m, superimposed on a doublet at 1.09 [J = 6.4 Hz, 3H], total 10H), 1.56-1.80 (m, 5H), 3.48 (dq, $J$ = 6.4, 6.4 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$C 19.4 (CH$_3$), 25.1 (CH$_2$), 25.2 (CH$_2$), 25.5 (CH$_2$), 27.4 (CH$_2$), 27.7 (CH$_2$), 44.1 (CH), 71.2 (CH); Chiral GC (Supelco β-DEX$^{TM}$); carrier gas: He (flow 2 mL/min), injection temp: 220 °C; column temp: initial temperature, 80 °C for 2 min; rate, 1.5 °C/min; final temperature, 160 °C ($t_R = 16.72$ min, $t_S = 16.86$).$^{[S6]}

(R)-(+)1-(2-Naphthyl)ethanol (R)-(+)3g. $\left[\alpha\right]_D^{+}+25.2$ (c 1.0, MeOH, 83% ee), (lit.$^{[S7]}$ gives $\left[\alpha\right]_D^{+}+28.0$ (c 1.0, MeOH, 96% ee); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 1.51 (d, $J$ = 6.4 Hz, 3H), 1.79 (bs, 1H), 5.00 (q, $J$ = 6.4 Hz, 1H), 7.37-7.45 (m, 3H), 7.74-7.78 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$C 25.2 (CH$_3$), 70.6 (CH), 123.8 (2 × CH), 125.8 (CH), 126.2 (CH), 127.7 (CH), 128.0 (CH), 128.4 (CH), 133.0 (C), 133.4 (C), 143.2 (C); Chiral GC (Supelco β-DEX$^{TM}$), : He (flow 2 mL/min), injection temp: 220 °C; column temp: initial temp, 140 °C, rate, 0.5 °C/min, final temp, 200 °C ($t_R = 36.49$ min, $t_S = 37.27$ min).

(R)-(+)1-[(6'-Methyl)-2-Naphthyl]ethanol (R)-(+)3h. Mp 71-73 °C (CHCl$_3$); $\left[\alpha\right]_D^{+}+33.4$ (c 0.50, CHCl$_3$, 85% ee); IR (KBr) v 822, 888, (aromatic ring), 3241 (OH) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 1.50 (d, $J$ = 6.4 Hz, 3H), 1.83 (bs, 1H), 2.44 (s, 3H), 4.98 (q, $J$ = 6.4Hz, 1H), 7.25 (dd, $J$ = 8.4, 1.6Hz, 1H), 7.40 (dd, $J$ = 8.4, 2.0Hz, 1H), 7.52 (s, 1H), 7.65 (s, 1H), 7.67 (s, 1H), 7.69 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$C 21.7 (CH$_3$), 25.1 (CH$_3$), 70.6 (CH), 123.6 (CH), 123.9 (CH), 126.7 (CH), 127.7 (CH), 127.8 (CH), 128.5 (CH), 131.5 (C), 133. 2 (C), 135.5 (C), 142.3 (C); EI MS m/z (%) 186 (M$^+$, 50), 171 (55), 143 (100), 128 (45), 115 (25), 83 (65), 47 (12); HRMS (EI) 186.1044 (C$_{13}$H$_{14}$O requires 186.1045); Chiral GC (Supelco β-DEX$^{TM}$), : He (flow 2 mL/min), injection temp: 220 °C; column temp: initial temp, 140 °C, rate, 0.5 °C/min, final temp, 200 °C ($t_R = 46.44$ min, $t_S = 47.42$).
3. Reduction of Ketimines

General Procedure for the Asymmetric Reduction of Imines 2 with Trichlorosilane.
Trichlorosilane (82 μL, 0.80 mmol, 2.0 eq) was slowly added dropwise to a solution of catalyst (21.9 mg, 0.08 mmol) and the corresponding imine (0.40 mmol, 1.0 eq) in CHCl₃ (2 mL) at –20 °C. The reaction mixture was stirred for 24 h at -20 °C, after which time saturated aqueous NaHCO₃ (1 mL) was added to quench the reaction. The mixture was extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic fractions were dried over MgSO₄. Concentration in vacuo followed by flash chromatography on silica gel (3 × 15 cm) afforded imines 4a-f.

(R)-N-Phenyl-N-(1-phenylethyl)amine (R)-4a. Eluted from silica gel using a 75:1 petroleum ether/ethyl acetate mixture. [α]D -16.5 (c 0.4, MeOH) [lit. gives [α]D -12.5, (c 1.3, MeOH, 72% ee)]; ¹H-NMR (400 MHz, CDCl₃) δH 1.44 (d, J = 6.8 Hz, 3H), 3.98 (bs, 1H), 4.41 (q, J = 6.8 Hz, 1H), 6.44 (m, 2H), 6.57 (m, 1H), 7.01 (m, 2H), 7.15 (m, 1H), 7.22-7.31 (m, 4H) in agreement with literature data; chiral HPLC (Chiralcel OD-H, hexane/2-propanol 99:1, 0.9 mL/min) showed 87% ee (tR = 14.1 min, tS = 16.7 min).

(R)-N-(4-Methoxyphenyl)-N-(1-phenylethyl)amine (R)-4b. Eluted from silica gel using a 4:1 chloroform/petroleum ether mixture. [α]D +4.0 (c 0.4, CHCl₃) [lit. gives [α]D +2.4, (c 1.6, CHCl₃, 74% ee)]; ¹H-NMR (400 MHz, CDCl₃) δH 1.43 (d, J = 6.8 Hz, 3H), 3.62 (s, 3H), 3.72 (bs, 1H), 4.34 (q, J = 6.8 Hz, 1H), 6.40 (m, 2H), 6.62 (m, 2H), 7.15 (m, 1H), 7.22-7.30 (m, 4H) in agreement with literature data; chiral HPLC (Chiralcel OD-H, hexane/2-propanol 98:2, 0.6 mL/min) showed 85% ee (tR = 23.9 min, tS = 27.2 min).
(R)-N-[1-(2-Naphthyl)ethyl]-N-phenylamine (R)-4c. Eluted from silica gel using a 90:1 petroleum ether/ethyl acetate mixture. [α]D +12.5 (c 1.0, CHCl3); 1H-NMR (400 MHz, CDCl3) δH 1.52 (d, J = 6.8 Hz, 3H), 4.07 (bs, 1H), 4.57 (q, J = 6.8 Hz, 1H), 6.48 (m, 2H), 6.56 (m, 1H), 7.00 (m, 2H), 7.34-7.44 (m, 3H), 7.71-7.75 (m, 4H) in agreement with literature data;[8] chiral HPLC (Chiralcel AD, hexane/2-propanol 98:2, 0.6 mL/min) showed 87% ee (tR = 16.1 min, tS = 18.9 min).

(R)-N-(4-Methoxyphenyl)-N-[1-(2-Naphthyl)ethyl]amine (R)-4d. Eluted from silica gel using a 25:1 petroleum ether/ethyl acetate mixture. [α]D +22.7 (c 1.0, CHCl3) [lit.8 gives [α]D +23.0, (c 1.4, CHCl3, 94% ee)]; 1H-NMR (400 MHz, CDCl3) δH 1.50 (d, J = 6.8 Hz, 3H), 3.60 (s, 3H), 3.84 (bs, 1H), 4.50 (q, J = 6.8 Hz, 1H), 6.44 (m, 2H), 6.60 (m, 2H), 7.34-7.44 (m, 3H), 7.71-7.75 (m, 4H) in agreement with literature data;[8] chiral HPLC (Chiralcel OD-H, hexane/2-propanol 99:1, 0.9 mL/min) showed 86% ee (tR = 28.6 min, tS = 35.4 min).

(R)-N-(4-Methoxyphenyl)-N-[1-(4-methoxyphenyl)ethyl]amine (R)-4e. Eluted from silica gel using chloroform/petroleum ether 4:1 as eluent. [α]D +14.9 (c 0.65, CHCl3); 1H-NMR (400 MHz, CDCl3) δH 1.40 (d, J = 6.8 Hz, 3H), 3.63 (s, 3H), 3.71 (s, 3H), 4.30 (q, J = 6.8 Hz, 1H), 6.40 (m, 2H), 6.62 (m, 2H), 6.78 (m, 2H), 7.20 (m, 2H) in agreement with literature data;[8] chiral HPLC (Chiralcel OD-H, hexane/2-propanol 98:2, 0.6 mL/min) showed 87% ee (tR = 32.9 min, tS = 38.5 min).
(R)-N-(4-Methoxyphenyl)-N-[1-(4-trifluoromethylphenyl)ethyl]amine (R)-4f. Eluted from silica gel using a 10:1 petroleum ether/ethyl acetate mixture. [$\alpha$]$_D$ +6.5 (c 2.3, CHCl$_3$); $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$H 1.43 (d, $J$ = 6.8 Hz, 3H), 3.62 (s, 3H), 4.38 (q, $J$ = 6.8 Hz, 1H), 6.36 (m, 2H), 6.62 (m, 2H), 7.41 (d, $J$ = 8.2 Hz, 2H), 7.50 (d, $J$ = 8.2 Hz, 2H) in agreement with literature data;$^{[88]}$ chiral HPLC (Chiralcel OD-H, hexane/2-propanol 95:5, 0.9 mL/min) showed 87% ee ($t_R$ = 14.7 min, $t_S$ = 19.6 min).

**Synthesis of Organocatalysts**

1. AcCl, MeOH, 0 °C to rt (69%)
2. NH$_3$, H$_2$O, MeOH, -5 °C (90%)
3. MsCl, Et$_3$N, DCM, 0 °C to rt (95%)
4. ClCO$_2$Me, 8, Et$_3$N, THF, 0 °C to rt (89%)
5. NaOMe, MeOH
6. ClCO$_2$Me, 8, Et$_3$N, THF, 0 °C to rt (95%)
7. HO
8. R$_n$N
9. R$_n$N
10. R$_n$N
11. R$_n$N
12. R$_n$N
13. R$_n$N
14. R$_n$N
15. R$_n$N
16. R$_n$N
17. R$_n$N

(S)-(–)-2-(4-Phenyl-4,5-dihydro-oxazol-2-yl)pyridine (S)-(–)-5. Following the protocol of Brunner,$^{[89]}$ methyl pyridine-2-carboxyimidate 13 (350 mg, 2.57 mmol, 1.0 eq) was added to a solution of (S)-phenylglycinol (352 mg, 2.57 mmol, 1.0 eq) in chlorobenzene (5 mL). A drop
of conc. HCl was added and the reaction mixture was stirred at 80 °C overnight with argon bubbling through the solvent. The solvent was then removed and purification via flash chromatography on silica gel (hexane-ethyl acetate, 1:1) afforded pyridine-oxazoline 5 (322 mg, 56%) as a clear oil: [α]D –42.0 (c 1.0, CHCl3); IR (KBr) v 1640 (C=N), 2899 (CH/CH2), 3029 (Ar-H) cm–1; 1H NMR (400 MHz, CDCl3) δH 4.33 (t, J = 8.5 Hz, 1H), 4.83 (dd, J = 10.2, 8.6 Hz, 1H), 5.39 (dd, J = 10.2, 8.6 Hz, 1H), 7.46-7.24 (m, 6H), 7.73(td, J = 7.6, 2.0 Hz, 1H), 8.10 (dt, J = 7.6, 1.2 Hz, 1H), 8.67 (ddd, J = 4.8, 2.0, 1.2 Hz, 1H); 13C NMR (100 MHz, CDCl3) δC 70.75 (CH), 75.70 (CH2), 124.64 (CH), 126.14 (CH), 127.20 (2×CH), 128.13 (CH), 129.19 (2×CH), 137.07 (CH), 142.20 (C), 147.10 (C), 150.16 (CH), 164.26 (C); EI MS m/z (%) 224 (M*+, 90), 194 (100), 193 (35), 167 (20), 118 (65), 89 (35), 78 (30), 51 (10); HRMS (EI) 224.0949 (C14H12N2O requires 224.0950).

(S)-(+)-2-(5-Phenyl-4,5-dihydro-oxazo-2-yl)-pyridine (S)-(+)–6. Following the protocol of Brunner,[29] methyl pyridine-2-carboxyimidate 13 (427 mg, 3.14 mmol, 1.0 eq) was added to a solution of (S)-2-amino-1-phenylethanol 12 (431 mg, 3.14 mmol, 1.0 eq) in chlorobenzene (5 mL). A drop of conc. HCl was added and the reaction mixture was stirred at 60 °C overnight with argon bubbled through the solvent. The solvent was then removed and purification via column chromatography on silica gel (methanol-ethyl acetate, 1:25) followed by recrystallization from ether afforded 6 (540 mg, 76%) as crystalline solid: mp 84-86 °C (Et2O); [α]D +106.5 (c 0.5, CHCl3); IR (KBr) v 1641 (C=N), 2869, 2933 (CH/CH2), 3058 (Ar-H) cm–1; 1H NMR (CDCl3) δ 4.02 (dd, J = 15.2, 8.2 Hz, 1H), 4.48 (dd, J = 15.2, 10.2 Hz, 1H), 5.68 (dd, J = 10.2, 8.2 Hz, 1H), 7.24-7.37 (m, 6H), 7.73 (dt, J = 8.0, 1.6Hz, 1H), 8.01 (d, J = 7.9 Hz, 1H), 8.67 (ddd, J = 4.8, 1.6, 0.9 Hz, 1H); 13C NMR δC 62.20 (CH2), 80.86 (CH), 122.89 (CH), 124.61 (CH), 124.99 (2×CH), 127.41 (CH), 127.78 (2×CH), 135.67 (CH), 139.49 (C), 145.66 (C), 148.89 (CH), 162.17 (C); EI MS m/z (%) 224 (M*+, 45), 118 (100), 85(35), 78 (75), 51 (10); HRMS (EI) 224.0949 (C14H12N2O requires 224.0950).

(R)-(–)-2-(5-phenyl-4,5-dihydro-1,3-oxazol-2-yl)quinoline (R)-(–)–7. Following the protocol of Brunner,[29] methyl quinoline-2-carboxyimidate 14 (300 mg, 1.6 mmol, 1.0 eq) was added to a solution of (R)-2-amino-1-phenylethanol 12 (221 mg, 1.6 mmol, 1.0 eq) in chlorobenzene (5 mL). A drop of conc. HCl was added and the reaction mixture was stirred at 80 °C overnight with argon bubbled through the solvent. The solvent was then removed and purification via column chromatography on silica gel (cyclohexane-ethyl acetate, 1:1) afforded 5 (297 mg,
67%) as pale yellow crystalline solid: mp 75-77 °C (CH₂Cl₂); [α]D -199.0 (c 0.5, CHCl₃); IR (KBr) v 1638 (C=燃), 2879, 2946 (CH/CH₂), 3031 (aryl-H) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δH 4.16 (dd, J = 15.4, 8.4 Hz, 1H), 4.63 (dd, J = 15.4, 10.4 Hz, 1H), 5.85 (dd, J = 10.4, 8.4 Hz, 1H), 7.33-7.45 (m, 5H), 7.62 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 7.77 (ddd, J = 8.4, 6.8, 1.2 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.33 (bd, J = 8.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δC 63.4 (CH₂), 82.2 (CH), 120.7 (CH), 126.1 (2 × CH), 127.6 (CH), 128.0 (CH), 128.5 (C), 128.8 (2 × CH), 130.1 (CH), 130.5 (CH), 136.9 (CH), 140.6 (C), 146.7 (C), 147.8 (C), 163.6 (C); EI MS m/z (%) 274 (M⁺, 70), 168 (65), 128 (100), 118 (13), 101 (13), 77 (10), 51 (5); HRMS (EI) 274.1105 (C₁₈H₁₄N₂O requires 274.1106).

(R)-(−)-3-(5-phenyl-4,5-dihydro-1,3-oxazol-2-yl)isoquinoline (R)-(−)-8. Following the protocol of Brunner,[⁹] methyl isoquinoline-3-carboxyimidate 15 (242 mg, 1.30 mmol, 1.0 eq) was added to a solution of (R)-2-amino-1-phenylethanol 12 (178 mg, 1.30 mmol, 1.0 eq) in chlorobenzene (3 mL). A drop of conc. HCl was added and the reaction mixture was stirred at 80 °C overnight with argon bubbled through the solvent. The solvent was then removed and purification via column chromatography on silica gel (ethyl acetate-methanol-triethylamine 50:1:0.5) afforded 8 (181 mg, 51%) as a white solid: mp 108-110 °C (CH₂Cl₂); [α]D -184.4 (c 0.5, CHCl₃); IR (KBr) ν 1646 (C=N), 2882, 2951 (CH/CH₂), 3032 (aryl-H) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δH 4.06 (dd, J = 15.2, 8.0 Hz, 1H), 4.53 (dd, J = 15.2, 10.0 Hz, 1H), 5.71 (dd, J = 10.0, 8.0 Hz, 1H), 7.24-7.36 (m, 5H), 7.61-7.71 (m, 2H), 7.84 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 8.34 (s, 1H), 9.28 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δC 63.4 (CH₂), 81.9 (CH), 121.8 (CH), 126.1 (2 × CH), 127.3 (CH), 127.8 (CH), 128.5 (CH), 128.9 (2 × CH), 128.9 (CH), 129.4 (C), 131.1 (CH), 135.6 (C), 140.1 (C), 140.8 (C), 152.9 (CH), 163.6 (C); EI MS m/z (%) 274 (M⁺, 65), 168 (100), 128 (80), 101 (10), 82 (35), 77 (15), 51 (5); HRMS (EI) 274.1105 (C₁₈H₁₄N₂O requires 274.1106).

(S)-(+)–1-(5-phenyl-4,5-dihydro-1,3-oxazol-2-yl)isoquinoline (S)-(+)–9. Triethylamine (2.5 mL, 17.78 mmol, 5.2 equiv) was added to a solution of (R)-17 (1.00 g, 3.42 mmol, 1.0 equiv) in CH₂Cl₂ (65 mL). The reaction was then cooled to 0 °C and mesyl chloride (0.62 mL, 7.87 mmol, 2.3 equiv) in CH₂Cl₂ (10 mL) was added dropwise over 15 min. The reaction vessel was then allowed to attain room temperature and stirred overnight. The reaction mixture was
washed with water (3 × 40 mL) and the organic layer was dried over MgSO\(_4\). Concentration \textit{in vacuo} afforded a residue which was purified via column chromatography on silica gel (petroleum ether-ethyl acetate, 1:1) to give 9 (0.89 g, 95%) as a white solid: mp 78-80 °C (CH\(_2\)Cl\(_2\)); \([\alpha]_D\) +83.5 (c 0.5, CHCl\(_3\)); IR (KBr) 700, 759, 838 (aryl), 1645 (C=N), 2866, 2931 (CH/CH\(_2\)), 3064 (aryl-H) cm\(^{-1}\); \(\text{H NMR} (400 MHz, CDCl}_3\) \(\delta\) 4.29 (dd, \(J = 15.2, 8.0\) Hz, 1H), 4.74 (dd, \(J = 15.2, 10.4\) Hz, 1H), 5.84 (dd, \(J = 10.4, 8.0\) Hz, 1H), 7.35-7.55 (m, 5H), 7.71-7.80 (m, 2H), 7.83 (d, \(J = 5.6\) Hz, 1H), 7.92 (d, \(J = 7.6\) Hz, 1H), 8.71 (d, \(J = 5.6\) Hz, 1H), 9.28 (d, \(J = 8.8\) Hz, 1H); \(^{13}\text{C NMR} (100 MHz, CDCl}_3\) \(\delta\) 63.9 (CH\(_2\)), 80.7 (CH), 123.5 (CH), 126.1 (2× CH), 127.2 (CH), 127.3 (CH), 127.4 (C), 128.4 (CH), 128.6 (CH), 128.9 (2× CH), 130.5 (CH), 136.8 (C), 140.7 (C), 141.9 (CH), 146.3 (C), 162.7 (C); EI MS \(m/z\) (%) 274 (M\(^+\)•, 65), 168 (70), 128 (100), 101 (15), 82 (35), 77 (10), 47 (5); HRMS (EI) 274.1105 (C\(_{18}\)H\(_{14}\)N\(_2\)O requires 274.1106).

\[
\text{(R)-(–)-2-Hydroxy-2-phenyl-acetimide (R)-(–)-11. Following the protocol of Brunner,}^{[59]}\hfill
\]
acetyl chloride (1.5 mL) was added to a solution of (R)-mandelic acid 10 (4.0g, 26.0 mmol, 1.0 eq) in methanol (100 mL) at 0 °C. The reaction was then allowed to attain room temperature and stirred overnight. Concentration \textit{in vacuo} yielded a solid residue which was dissolved in a mixture of methanol (75 mL) and aqueous ammonium hydroxide (28%, 185 mL) and stored in the fridge overnight. The solvent was then evaporated to give the crude product, which was recrystallised from ethanol to give pure amide 11 (4.4g, 90%) as a white solid: \([\alpha]_D\) –69.4 (c 1.0, MeOH); mp 102-104 °C; IR \(\nu\) 1682 (C=O), 2843 (C-H), 2926 (Ar-H), 3187, 3357 (N-H) cm\(^{-1}\); \(\text{H NMR} (400 MHz, CDCl}_3\) \(\delta\) 2.19 (bs, 1H), 5.11 (s, 1H), 5.59 (bs, 1H), 6.02 (bs, 1H), 7.36-7.47 (m, 5H); \(^{13}\text{C NMR} (100 MHz, CDCl}_3\) \(\delta\) 74.1 (CH), 126.6 (2× CH), 128.9 (C), 139.1 (C), 146.3 (C), 162.7 (C); EI MS \(m/z\) (%) 151 (M\(^+\), 10), 107 (100), 105 (10), 79 (75) 77 (50), 51 (12); HRMS (EI) 151.0631 (C\(_8\)H\(_9\)NO requires 151.0633).

\[
\text{(R)-(–)-2-Amino-1-phenyl-ethanol (R)-(–)-12. A solution of 1M lithium aluminium hydride}^{[58]}\hfill
\]
in THF (100 mL, 100 mmol, 3.8 equiv) was diluted with THF (250 mL), a solution of (R)-11 (3.95 g, 26.1 mmol, 1.0 eq) in THF (100 mL) was then slowly added and the mixture was stirred at reflux overnight. The reaction was quenched with Na\(_2\)SO\(_4\)·10H\(_2\)O, the resulting suspension was filtered through celite eluting with diethyl ether and the residue washed with ether (100 mL). The filtrate was dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo} to give (R)-(–)-12 as a yellow oil (3.01g, 84%); \([\alpha]_D\) -60.6 (c 0.5, CHCl\(_3\)); \(\text{H NMR} (400 MHz, CDCl}_3\) \(\delta\) 1.78 (bs, 3H), 2.74 (dd, \(J = 12.8, 7.8\) Hz, 1H), 2.93 (dd, \(J = 12.8, 4.0\) Hz, 1H), 4.56 (dd, \(J = 7.8, 4.0\) Hz, 1H), 7.19-7.36 (m, 5H) in accordance with the literature.\(^{[58]}\)
Methyl pyridine-2-carboximidate 13. Following the protocol Schaefer,[510] sodium methoxide (675 mg, 12.5 mmol, 0.1 eq) was added to a solution of 2-cyanopyridine (13.0 g, 125 mmol, 1.0 equiv) in methanol (110 mL) at 0 °C. The mixture was stirred for 15 h at room temperature and the reaction was quenched by the dropwise addition of glacial acetic acid (1 mL). After concentration in vacuo, the crude product was distilled in vacuum to yield methyl pyridine-2-carboximidate 13 (13.3 g, 78%) as a clear oil: (bp 108-111 °C, 23 mmHg); \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta_\text{H} 4.03\) (s, 3H), 7.39 (ddd, \(J = 7.2, 4.8, 1.2\) Hz, 1H), 7.80 (dt, \(J = 7.6, 1.6, 1.2\) Hz, 1H), 7.86 (dt, \(J = 7.6, 1.2\) Hz, 1H), 8.67 (ddd, \(J = 4.8, 1.6, 0.8\) Hz, 1H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta_\text{C} 53.9\) (CH\(_3\)), 121.0 (CH), 125.4 (CH), 137.3 (CH), 147.5 (C), 149.2 (CH), 166.9 (C); EI MS \(m/z\) (%) 136 (M\(^+\), 5), 122 (20), 105(30), 79 (100), 78 (50), 51 (20), 50 (10); HRMS (EI) 136.0636 (C\(_7\)H\(_8\)N\(_2\)O requires 136.0637).

Methyl quinoline-2-carboximidate 14. Following the protocol Schaefer,[510] sodium methoxide (15 mg, 0.26 mmol, 0.1 eq) was added to a solution of 2-quinoline carbonitrile (400 mg, 2.6 mmol, 1.0 eq) in methanol (10 mL). The reaction mixture was stirred overnight at room temperature and then quenched with glacial acetic acid (1.0 mL). The mixture was concentrated by evaporation in vacuo, the crude product was purified via flash chromatography on silica gel (cyclohexane-ethyl acetate, 1:1) to give methyl quinoline-2-carboximidate 14 (440 mg, 91%) as a white crystalline solid: mp 78-80 °C (CH\(_2\)Cl\(_2\)); IR (KBr) v 765, 841 (aryl ring), 1650 (C=O), 2945 (OMe), 3298 (NH) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta_\text{H} 4.16\) (s, 3H), 7.65 (ddd, \(J = 8.4, 7.2, 1.2\) Hz, 1H), 7.81 (ddd, \(J = 8.4, 6.8, 1.2\) Hz, 1H), 7.90 (d, \(J = 8.4\) Hz, 1H), 8.00 (d, \(J = 8.4\) Hz, 1H), 8.20 (d, \(J = 8.8\) Hz, 1H), 8.31 (d, \(J = 8.8\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta_\text{C} 54.2\) (CH\(_3\)), 118.2 (CH), 127.6 (CH), 128.7 (C), 130.0 (CH), 130.1 (CH), 137.5 (CH), 147.4 (C), 147.4 (C), 167.0 (C); EI MS \(m/z\) (%) 186 (M\(^+\), 45), 155 (60), 129 (100), 128 (50), 75 (10), 51 (5); HRMS (EI) 186.0795 (C\(_{11}\)H\(_{10}\)NO\(_2\) requires 186.0795).
Methyl isooquinoline-3-carboxyimidate 15. Following the protocol Schaefer, sodium methoxide (15 mg, 0.28 mmol, 0.1 eq) was added to a solution of 3-isoquinoline carbonitrile (430 mg, 2.8 mmol, 1.0 eq.) in methanol (10 mL). The reaction mixture was stirred overnight at room temperature and then quenched with glacial acetic acid (1.0 mL). The mixture was concentrated by evaporation in vacuo, the crude product was purified via flash chromatography on silica gel (cyclohexane-ethyl acetate, 1:1) to give methyl isooquinoline-3-carboxyimidate 15 (372 mg, 72%) as a white crystalline solid: mp 77-79 °C (CH₂Cl₂); IR (KBr) ν 762, 874 (aryl ring), 1643 (C=N), 2943 (OMe), 3013, 3037 (aryl-H), 3294 (NH) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.14 (s, 3H), 7.74 (dd, J = 8.4, 6.8, 1.2 Hz, 1H), 7.80 (dd, J = 8.0, 6.8, 1.2 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 7.6 Hz, 1H), 9.28 (s, 1H), 9.32 (s, 1H); ¹³C NMR (100MHz, CDCl₃) δ 54.0 (CH₃), 118.7 (CH), 127.7 (CH), 127.9 (CH), 128.8 (CH), 129.3 (C), 131.0 (CH), 136.0 (C), 141.1 (C), 152.0 (CH), 167.4 (C); EI MS m/z (%) 186 (M⁺, 45), 155 (100), 129 (95), 128 (55), 101 (20), 83 (30), 77 (20), 46 (10); HRMS (EI) 186.0795 (C₁₁H₁₀NO₂ requires 186.0793).

(R)-(−)-N-(2-hydroxy-2-phenylethyl)isoquinoline-1-carboxamide (R)-(−)-17. Methylchloroformate (1.56mL, 19.82 mmol, 1.2 equiv) was added dropwise to a stirred solution of 1-isoquinoline carboxylic acid 16 (2.86 g, 16.52 mmol, 1.0 equiv) and triethylamine (2.76 mL, 19.82 mmol, 1.2 equiv) in anhydrous THF (80 mL) at 0 °C under an argon atmosphere and the solution was stirred at that temperature for 2 h. The precipitate was removed by filtration in vacuo and the filtrate was added dropwise to a solution of (R)-12 (2.72 g, 19.82 mmol, 1.2 equiv) and triethylamine (2.76 mL, 19.82 mmol, 1.2 equiv) in anhydrous THF (80 mL) at 0 °C under an argon atmosphere and the mixture was allowed to attain room temperature and stirred overnight. The solvent was removed under reduced pressure and the residue was purified via column chromatography on silica gel (petroleum ether-ethyl acetate, 1:1) to afford 17 (4.30 g, 89%) as a white solid: mp 104-106 °C (CH₂Cl₂); [α]D -55.1 (c 0.5, CHCl₃); IR (KBr) 749, 838 (aryl ring), 1525, 1633 (C=O), 2868, 2924, 2968 (CH/CH₂/CH₃), 3340, 3464 (NH) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.63-3.70 (m, 2H), 3.97 (ddd, J = 14.0, 7.2, 3.2 Hz, 1H), 5.08 (dd, J = 8.0, 3.2 Hz, 1H), 7.32-7.42 (m, 3H), 7.50 (d, J = 7.2 Hz, 1H), 7.69-7.77 (m, 2H), 7.81 (d, J = 5.6 Hz, 2H), 7.87 (d, J = 7.6 Hz, 1H), 8.43 (d, J = 5.6 Hz, 1H), 8.67 (bs, 1H), 9.55 (d, J = 8.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δₖ 47.9 (CH₃), 74.0 (CH), 124.6 (CH), 126.0 (2 × CH), 126.9 (CH), 127.0 (C), 127.7 (CH), 127.9 (CH), 128.6 (2 × CH), 128.8 (CH), 130.7 (CH), 137.4 (C), 140.1 (CH), 142.0 (C), 1478.0 (C), 167.3 (C); CI MS m/z
(%) 293 ([M+H]+, 100), 275 (15), 186 (7), 173 (5), 123 (4), 107 (5), 71 (9); HRMS (CI) 293.1288 (C18H17N2O2 requires 293.1290).

References