Supplementary Material (ESI) for Organic and Biomolecular Chemistry

A Sequential Enantioselective, Organocatalytic Route to Chiral 1,2-Oxazines and Chiral Pyridazines

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Electronic Supplementary Information

General Information

Solvents: Diethyl ether and tetrahydrofuran were distilled from sodium calcium hydride and lithium aluminium hydride (tetrahydrofuran using triphenylmethane as indicator); chloroform, dichloromethane, methanol and toluene from calcium hydride prior to use. Anhydrous dimethylsulfoxide was used as supplied. Petrol refers to petroleum ether b.p. 40-60 °C and ether to diethyl ether, which were distilled before use. **Reagents**: All reactions were performed under an argon atmosphere unless otherwise stated. Reagents were used as supplied or purified using standard procedures as necessary. **Chromatography**: Flash column chromatography was carried out using Silica Gel 60 (0.040-0.063 mm) 230-400 mesh under pressure unless otherwise indicated. Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F254) and visualised by ultraviolet radiation (254 nm), acidic ceric ammonium molybdate, or basic potassium permanganate solutions as appropriate. **Data Collection**: Melting points were performed on a Reichert hot-stage apparatus, and are uncorrected. Optical rotations were measured on a Perkin Elmer 343 digital polarimeter using a sodium lamp (589 nm) as the light source, $[\alpha]_D$ values are reported in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded as thin films on a Perkin Elmer Spectrum One FT-IR 1600

spectrometer fitted with an ATR sampling accessory. ^{1}H NMR spectra were recorded at 400, 500 and 600 MHz on Bruker DPX-400, Bruker Advance 500 (cryoprobe) and Bruker DPX-600 spectrometers, respectively with residual protic solvent $CDCl_3$ as the internal reference (δ_H = 7.26 ppm) and are reported as follows: chemical shift δ/ppm (number of protons, multiplicity, coupling constant *J*/Hz, assignment). ^{13}C NMR spectra were recorded at 100, 125 and 150 MHz on Bruker DPX-400, Bruker Advance 500 (cryoprobe) and Bruker DPX-600 spectrometers, respectively. The resonance of $CDCl_3$ (δ_C = 77.0 ppm, t) was used as an internal reference. ^{13}C DEPT-135 and two-dimensional (COSY, HMQC, HMBC and NOESY) NMR experiments were used where appropriate, to support the assignment of signals in the ^{1}H and ^{13}C spectra. Two-dimensional NOESY experiments were performed on a Bruker DPX-700 spectrometer at 700 MHz to assign through-space correlation where appropriate. NMR resolution enhancement was also used to assist coupling assignment in most ^{1}H NMR spectra. The ^{31}P NMR spectrum was recorded on a Bruker DPX-400 spectrometer at 162 MHz. Mass spectra and accurate mass data were obtained on an LCT Premier spectrometer by Waters using a Micromass MS software at the Department of Chemistry, University of Cambridge. The enantiomeric excesses (ee) were determined by high performance liquid chromatography (HPLC), performed on Hewlett-Packard Agilent 1100 chromatographs or by supercritical fluid chromatography (SFC) on a Berger Minigram using a Chiralpak AD (0.46 × 25 cm), Chiralpak AD-H (0.46 × 25 cm), Chiralcel OD (0.46 × 25 cm) or Chiralcel OD-H (0.46 × 25 cm) column as noted or gas chromatography (GC), performed on an Agilent 6890N chromatograph using an Astec Chiraldex column. The diastereomeric excesses (de) were determined by ^{1}H NMR spectroscopy of crude products. The racemic materials were prepared using DL-proline or a 50:50 mixture of (2*S*) and (2*R*)-5-pyrrolidin-2-yl-1*H*-tetrazoles as catalyst in the same procedure as their corresponding optically active compounds. In the experimental section, compounds are divided according to general reaction type, rather than table by table.

For full experimental data of compounds **3a-3j**, **9a** and **12a-12d** see[10a]: http://pubs3.acs.org/acs/journals/supporting_information.page?in_manuscript=ol051577u.

General procedure for the synthesis of 1,2-oxazines from aldehydes

To a stirred solution of the appropriate aldehyde (1.2 eq) in DMSO (5 ml/1 eq of nitrosobenzene) was added (2*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole (20 mol%). The resulting suspension was stirred vigorously for 1 min before addition of nitrosobenzene (1.0 eq). The bright green reaction mixture was stirred at room temperature until the reaction was determined to be complete by TLC and the disappearance of green colour, resulting in a yellow solution. The reaction mixture was then cooled to 0 °C and THF (1 ml/ml of DMSO) was added. Vinyltriphenylphosphonium bromide (1.5 eq) was added, followed by sodium hydride (2.0 eq). After stirring for 20 min at 0 °C, the reaction mixture was quenched using saturated aqueous NH_4Cl (2 ml/ml of reaction volume) and extracted with ether (3 × 2 ml/ml of reaction volume). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (solvents noted) to provide the title compounds.

(6*S*,2'*Z*)-6-(Pent-2'-enyl)-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (**10b**). Prepared according to the general procedure from *cis*-4-heptenal using (2*R*)-5-pyrrolidin-2-yl-1*H*-tetrazole catalyst to provide the title compound as a yellow oil (44%, 99% ee) after flash column chromatography (4:1, petrol/toluene). $[\alpha]_D^{25}$ +41.1 (*c* 0.37 in $CHCl_3$); HPLC (Chiralcel OD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(minor) 14.1 min, t_R(major) 14.6 min.

(6*S*)-6-Allyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (**10e**). Prepared according to the general procedure from 4-pentenal using (2*R*)-5-pyrrolidin-2-yl-1*H*-tetrazole catalyst to provide the title compound as a yellow oil (38%, 99% ee) after flash column chromatography (4:1, petrol/toluene). $[\alpha]_D^{25}$ +18.9 (*c* 0.44 in $CHCl_3$); HPLC

(Chiralcel OD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(minor) 15.7 min, t_R(major) 17.0 min.

(6*R*)-6-*tert*-Butyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (**10h**) Prepared according to the general procedure from 3,3-dimethylbutyraldehyde using (2*R*)-5-pyrrolidin-2-yl-1*H*-tetrazole catalyst to provide the title compound as a pale yellow solid (78%, 99% ee) after flash column chromatography (20:1, petrol/EtOAc). $[\alpha]_D^{25}$ -107.9 (*c* 0.43 in $CHCl_3$); HPLC (Chiralcel OD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(major) 10.1 min, t_R(minor) 14.6 min.

(6*S*)-6-(Benzyloxymethyl)-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (3l). Prepared according to the general procedure from 3-(benzyloxy)propanal (86 mg, 0.52 mmol) to provide the title compound as a pale yellow oil (9 mg, 7%, 98% ee) after flash column chromatography (10:1, petrol/EtOAc). R_f 0.52 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ -48.9 (*c* 0.18 in $CHCl_3$); ν_{max} (film) 2859, 2347, 1598, 1491, 1454, 1213, 1090, 755, 693 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.61 (1H, dd, *J* 10.6, 3.8, C*H*H'OCH$_2$Ph), 3.82-3.85 (3H, m, PhNC*H*$_2$CH=CHCHCH*H*'OCH$_2$Ph), 4.60 (1H, d, *J* 12.1, OC*H*H'Ph), 4.65 (1H, d, *J* 12.1, OCH*H*'Ph), 4.76-4.81 (1H, m, PhNCH$_2$CH=CHC*H*CH$_2$), 5.91 (1H, app ddt, *J* 10.1, 2.6, 2.1, PhNCH$_2$CH=C*H*), 6.03 (1H, app dtd, *J* 10.1, 3.4, 2.0, PhNCH$_2$C*H*=CH), 6.99 (1H, tt, *J* 7.3, 1.2, Ph*H*-para), 7.16 (2H, dd, *J* 8.7, 1.2, 2×Ph*H*-ortho), 7.31 (2H, dd, *J* 8.7, 7.3, 2×Ph*H*-meta), 7.33-7.37 (5H, m, 5×OCH$_2$Ph*H*); δ_C (100 MHz, $CDCl_3$) 51.4 (PhN*C*H$_2$CH=CH), 70.6 (*C*H$_2$OCH$_2$Ph), 73.4 (CH$_2$O*C*H$_2$Ph), 77.7 (PhNCH$_2$CH=CH*C*HCH$_2$), 115.7 (2×Ph*C*-ortho), 122.1 (Ph*C*-para), 124.8 (PhNCH$_2$*C*H=CH), 126.5 (PhNCH$_2$CH=*C*H), 127.6, 127.7, 128.4 (5×OCH$_2$Ph*C*), 128.7 (2×Ph*C*-meta), 138.2 (OCH$_2$Ph*C*-ipso), 150.4 (Ph*C*-N); *m/z* (ES) found 282.1497 ([M+H]$^+$ $C_{18}H_{20}NO_2$), requires 282.1494; HPLC (Chiralcel OD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(major) 36.3 min, t_R(minor) 46.1 min.

(6*R*)-6-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (3m). Prepared according to the general procedure from 4-(*tert*-

butyldimethylsilyloxy)butanal (0.12 g, 0.59 mmol) to provide the title compound as a yellow oil (50 mg, 31%, 98% ee) after flash column chromatography (1:1, petrol/CH_2Cl_2). R_f 0.81 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ +28.5 (*c* 0.80 in $CHCl_3$); ν_{max} (film) 2953, 2928, 2857, 1599, 1491, 1472, 1434, 1388, 1361, 1253, 1211, 1092, 1004, 952, 832, 774, 753, 712, 689 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.08 (3H, s, Si(C*H*$_3$)(CH'$_3$)), 0.09 (3H, s, Si(CH$_3$)(C*H*'$_3$)), 0.91 (9H, s, 3H, s, SiC(C*H*$_3$)$_3$), 1.79-1.87 (1H, m, C*H*H'CH$_2$OSi), 1.93-2.01 (1H, m, CH*H*'CH$_2$OSi), 3.75-3.91 (4H, m, PhNC*H*$_2$CH=CHCHCH$_2$C*H*$_2$O), 4.74-4.79 (1H, m, PhNCH$_2$CH=CHC*H*CH$_2$), 5.93 (2H, m, PhNCH$_2$C*H*=C*H*), 6.98 (1H, tt, *J* 7.3, 1.1, Ph*H*-para), 7.11 (2H, dd, *J* 8.8, 1.1, 2×Ph*H*-ortho), 7.30 (2H, dd, *J* 8.8, 7.3, 2×Ph*H*-meta); δ_C (100 MHz, $CDCl_3$) -5.3 (Si(*C*H$_3$)$_2$), 18.3 (Si*C*(CH$_3$)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 36.6 (*C*H$_2$CH$_2$OSi), 51.8 (PhN*C*H$_2$CH=CH), 59.5 (CH$_2$*C*H$_2$OSi), 74.8 (PhNCH$_2$CH=CH*C*H), 115.4 (2×Ph*C*-ortho), 121.9 (Ph*C*-para), 122.8 (PhNCH$_2$*C*H=CH), 128.7 (2×Ph*C*-meta), 130.1 (PhNCH$_2$CH=*C*H), 150.7 (Ph*C*-N); *m/z* (ES) found 320.2035 ($[M+H]^+$ $C_{18}H_{30}NO_2Si$), requires 320.2046; HPLC (Chiralcel OD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(major) 8.6 min, t_R(minor) 10.2 min.

(6*R*)-6-(2-(Benzyloxy)ethyl)-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (3n). Prepared according to the general procedure from 4-(benzyloxy)butanal (0.22 g, 1.21 mmol) to provide the title compound as a yellow oil (94 mg, 32%, 99% ee) after flash column chromatography (20:1, petrol/EtOAc). R_f 0.58 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ +43.6 (*c* 0.39 in $CHCl_3$); ν_{max} (film) 2859, 1598, 1491, 1454, 1363, 1212, 1093, 1029, 1005, 888, 753, 690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.96 (1H, dddd, *J* 14.3, 8.2, 6.3, 4.3, C*H*H'CH$_2$OCH$_2$Ph), 2.05 (1H, app ddt, *J* 14.3, 8.9, 5.2, CH*H*'CH$_2$OCH$_2$Ph), 3.65 (1H, ddd, *J* 9.4, 6.3, 5.2, CH$_2$C*H*H'OCH$_2$Ph), 3.72-3.88 (3H, m, PhNC*H*$_2$CH=CHCHCH$_2$CH*H*'O), 4.55 (1H, d, *J* 12.0, OC*H*H'Ph), 4.58 (1H, d, *J* 12.0, OCH*H*'Ph), 4.76-4.82 (1H, m, PhNCH$_2$CH=CHC*H*CH$_2$), 5.89-5.97 (2H, m, PhNCH$_2$C*H*=C*H*), 6.97 (1H, tt, *J* 7.3, 1.2, Ph*H*-para), 7.06 (2H, dd, *J* 8.8, 1.2, 2×Ph*H*-ortho), 7.28 (2H, dd, *J* 8.8, 7.3, 2×Ph*H*-meta), 7.32-7.38 (5H, m, 5×OCH$_2$Ph*H*); δ_C (100 MHz, $CDCl_3$) 33.7 (*C*H$_2$CH$_2$OCH$_2$Ph), 51.7 (PhN*C*H$_2$CH=CH), 66.7

($CH_2CH_2OCH_2Ph$), 73.1 (OCH_2Ph), 75.1 ($PhNCH_2CH=CHCH$), 115.4 (2×Ph*C*-ortho), 121.9 (Ph*C*-para), 123.0 ($PhNCH_2CH=CH$), 127.6, 127.7, 128.4 (5×OCH_2PhC), 128.8 (2×Ph*C*-meta), 129.9 ($PhNCH_2CH=CH$), 138.5 (OCH_2PhC-ipso), 150.6 (Ph*C*-N); *m/z* (ES) found 296.1645 ($[M+H]^+$ $C_{19}H_{22}NO_2$), requires 296.1651; HPLC (Chiralpak AD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(major) 19.9 min, t_R(minor) 23.0 min.

(6*R*)-6-(3-(*tert*-Butyldimethylsilyloxy)propyl)-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (3o). Prepared according to the general procedure from 5-(*tert*-butyldimethylsilyloxy)pentanal (0.14 g, 0.61 mmol) to provide the title compound as a yellow oil (64 mg, 38%, 96% ee) after flash column chromatography (2:1, petrol/CH_2Cl_2). R_f 0.40 (1:1, petrol/CH_2Cl_2); $[\alpha]_D^{25}$ +3.4 (*c* 0.53 in $CHCl_3$); ν_{max} (film) 2953, 2928, 2856, 1598, 1491, 1472, 1389, 1361, 1254, 1212, 1094, 1004, 939, 833, 813, 774, 753, 718, 690, 661 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.06 (6H, s, $Si(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.26-1.27 (2H, m, $CH_2CH_2CH_2OSi$), 1.68-1.84 (2H, m, $CH_2CH_2CH_2OSi$), 3.63-3.77 (3H, m, $PhNCHH'CH=CHCHCH_2CH_2CH_2O$), 3.88 (1H, dddd, *J* 15.8, 4.0, 1.9, 1.5, $PhNCHH'CH=CH$), 4.57-4.63 (1H, m, $PhNCH_2CH=CHCHCH_2$), 5.89 (1H, app dq, *J* 10.0, 1.9, $PhNCH_2CH=CH$), 5.94 (1H, dddd, *J* 10.0, 4.0, 2.3, 1.9, $PhNCH_2CH=CH$), 6.97 (1H, tt, *J* 7.3, 1.1, Ph*H*-para), 7.11 (2H, dd, *J* 8.8, 1.1, 2×Ph*H*-ortho), 7.30 (2H, dd, *J* 8.8, 7.3, 2×Ph*H*-meta); δ_C (100 MHz, $CDCl_3$) -5.3 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 29.3 ($CH_2CH_2CH_2OSi$), 29.9 ($CH_2CH_2CH_2OSi$), 51.7 ($PhNCH_2CH=CH$), 63.0 (CH_2CH_2OSi), 77.6 ($PhNCH_2CH=CHCH$), 115.4 (2×Ph*C*-ortho), 121.9 (Ph*C*-para), 123.0 ($PhNCH_2CH=CH$), 128.7 (2×Ph*C*-meta), 130.1 ($PhNCH_2CH=CH$), 150.7 (Ph*C*-N); *m/z* (ES) found 334.2207 ($[M+H]^+$ $C_{19}H_{32}NO_2Si$), requires 334.2202; SFC (Chiralcel OD, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 210 nm) t_R(minor) 12.2 min, t_R(major) 13.2 min.

(6*R*)-6-(3-(Benzyloxy)propyl)-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (3p). Prepared according to the general procedure from 5-(benzyloxy)pentanal (0.12 g, 0.60

mmol) to provide the title compound as a yellow oil (52 mg, 33%, 98% ee) after flash column chromatography (20:1, petrol/EtOAc). R_f 0.60 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ +4.1 (*c* 0.86 in $CHCl_3$); ν_{max} (film) 3035, 2854, 1598, 1490, 1454, 1360, 1212, 1099, 1029, 1002, 754, 691 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.72-1.97 (4H, m, C*H*$_2$C*H*$_2$CH$_2$OCH$_2$Ph), 3.50-3.60 (2H, m, CH$_2$CH$_2$C*H*$_2$OCH$_2$Ph), 3.74 (1H, app dq, *J* 15.8, 2.2, PhNC*H*H'CH=CH), 3.88 (1H, dddd, *J* 15.8, 4.1, 2.2, 1.7, PhNCH*H*'CH=CH), 4.52 (2H, s, OC*H*$_2$Ph), 4.57-4.64 (1H, m, PhNCH$_2$CH=CHC*H*CH$_2$), 5.88 (1H, app dq, *J* 10.0, 2.2, PhNCH$_2$CH=C*H*), 5.94 (1H, dddd, *J* 10.0, 4.1, 2.2, 2.1, PhNCH$_2$C*H*=CH), 6.98 (1H, tt, *J* 7.3, 1.1, Ph*H*-para), 7.11 (2H, dd, *J* 8.7, 1.1, 2×Ph*H*-ortho), 7.30 (2H, dd, *J* 8.7, 7.3, 2×Ph*H*-meta), 7.34 (3H, m, OCH$_2$Ph*H*-meta and para), 7.35 (2H, m, OCH$_2$Ph*H*-ortho); δ_C (100 MHz, $CDCl_3$) 25.9 (CH$_2$*C*H$_2$CH$_2$OCH$_2$Ph), 30.2 (*C*H$_2$CH$_2$CH$_2$OCH$_2$Ph), 51.7 (PhN*C*H$_2$CH=CH), 70.1 (CH$_2$*C*H$_2$OCH$_2$Ph), 72.9 (O*C*H$_2$Ph), 77.6 (PhNCH$_2$CH=CH*C*H), 115.4 (2×Ph*C*-ortho), 121.9 (Ph*C*-para), 123.1 (PhNCH$_2$*C*H=CH), 127.5 (2×Ph*C*-meta), 127.6, 128.3, 128.8 (5×OCH$_2$Ph*C*), 129.9 (PhNCH$_2$CH=*C*H), 138.6 (OCH$_2$Ph*C*-ipso), 150.7 (Ph*C*-N); *m/z* (ES) found 332.1624 ($[M+Na]^+$ $C_{20}H_{23}NO_2Na$), requires 332.1626; HPLC (Chiralpak AD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm, t_R(major) 18.7 min, t_R(minor) 19.5 min.

(3*R*,6*R*)-6-Isopropyl-3-methyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (9b, major). Prepared according to the general procedure from isovaleraldehyde (0.13 ml, 1.20 mmol) and (*E*)-triphenyl(prop-1-enyl)phosphonium bromide (0.64 g, 1.50 mmol). After filtration through a pad of silica gel, followed by flash column chromatography (80:1, petrol/EtOAc), a by-product was first isolated (**9d**), minor product (**9c**) and then the title compound (major product) as a pale yellow oil (0.11 g, 51%, 99% ee). R_f 0.34 (20:1, petrol/EtOAc); $[\alpha]_D^{25}$ +248.2 (*c* 0.38 in $CHCl_3$); ν_{max} (film) 3676, 2966, 2930, 1599, 1491, 1454, 1386, 1364, 1253, 1189, 1101, 1074, 1029, 1005, 892, 802, 752, 706, 691 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.03 (3H, d, *J* 6.9, (C*H*$_3$)(CH'$_3$)CH), 1.06 (3H, d, *J* 6.9, (CH$_3$)(C*H*'$_3$)CH), 1.12 (3H, d, *J* 6.5, PhNCHC*H*$_3$), 1.91 (1H, app sep d, *J* 6.9, 5.2, (CH$_3$)(CH'$_3$)C*H*), 4.13-4.16 (1H, m,

CH=CHC*H*CH(CH_3)$_2$), 4.35-4.37 (1H, m, PhNC*H*CH_3), 5.80 (1H, app dt, *J* 10.1, 1.4, CH=C*H*CHCH(CH_3)$_2$), 6.00 (1H, ddd, *J* 10.1, 5.0, 2.2, C*H*=CHCHCH(CH_3)$_2$), 6.91 (1H, tt, *J* 7.3, 1.1, Ph*H*-para), 7.03 (2H, dd, *J* 8.7, 1.1, 2×Ph*H*-ortho), 7.28 (2H, dd, *J* 8.7, 7.3, 2×Ph*H*-meta); δ_C (150 MHz, $CDCl_3$) 14.4 (PhNCH*C*H_3), 17.6, 18.4, ((*C*H_3)(*C*H'$_3$)CH), 31.3 ((CH$_3$)(CH'$_3$)*C*H), 54.4 (PhN*C*HCH$_3$), 81.5 (CH=CH*C*HCH(CH_3)$_2$), 115.4 (2×Ph*C*-ortho), 120.8 (Ph*C*-para), 127.2 (*C*H=CHCHCH(CH_3)$_2$), 128.7 (2×Ph*C*-meta), 130.0 (CH=*C*HCHCH(CH_3)$_2$), 148.9 (Ph*C*-N); *m/z* (ES) found 218.1539 ([M+H]$^+$ $C_{14}H_{20}NO$), requires 218.1545; HPLC (Chiralcel OD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(minor) 8.1 min, t_R(major) 12.8 min.

(3*S*,6*R*)-6-Isopropyl-3-methyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (**9c, minor**) was obtained as a pale yellow solid (18 mg, 8%, 99% ee). R_f 0.39 (20:1, petrol/EtOAc); m.p. 69-71 °C; $[\alpha]_D^{25}$ -278.0 (*c* 0.15 in $CHCl_3$); ν_{max} (film) 3675, 2972, 2932, 2878, 1599, 1489, 1467, 1393, 1361, 1257, 1191, 1072, 1052, 1034, 991, 887, 845, 812, 756, 728, 696 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.9, PhNCHC*H*$_3$), 1.03 (3H, d, *J* 6.7, (C*H*$_3$)(CH'$_3$)CH), 1.06 (3H, d, *J* 6.7, (CH$_3$)(C*H*'$_3$)CH), 2.05 (1H, app oct, *J* 6.7, (CH$_3$)(CH'$_3$)C*H*), 3.98-4.02 (1H, m, PhNC*H*CH$_3$), 4.02-4.05 (1H, m, CH=CHC*H*CH(CH_3)$_2$), 5.90 (1H, ddd, *J* 10.1, 3.8, 1.8, CH=C*H*CHCH(CH_3)$_2$), 5.96 (1H, ddd, *J* 10.1, 2.8, 1.7, C*H*=CHCHCH(CH_3)$_2$), 6.98 (1H, tt, *J* 7.3, 1.1, Ph*H*-para), 7.14 (2H, dd, *J* 8.6, 1.1, 2×Ph*H*-ortho), 7.30 (2H, dd, *J* 8.6, 7.3, 2×Ph*H*-meta); δ_C (150 MHz, $CDCl_3$) 18.6 (PhNCH*C*H_3), 19.8, 19.8, ((*C*H_3)(*C*H'$_3$)CH), 31.7 ((CH$_3$)(CH'$_3$)*C*H), 55.8 (PhN*C*HCH$_3$), 83.3 (CH=CH*C*HCH(CH_3)$_2$), 117.6 (2×Ph*C*-ortho), 121.9 (Ph*C*-para), 127.2 (*C*H=CHCHCH(CH_3)$_2$), 128.6 (2×Ph*C*-meta), 129.7 (CH=*C*HCHCH(CH_3)$_2$), 155.0 (Ph*C*-N); *m/z* (ES) found 218.1546 ([M+H]$^+$ $C_{14}H_{20}NO$), requires 218.1545; SFC (Chiralcel OD-H, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 210 nm) t_R(major) 5.9 min, t_R(minor) 6.0 min.

6-Isopropyl-3-methyl-2-phenyl-2*H*-1,2-oxazine (**9d, by-product**) was isolated as a yellow oil (17 mg, 8%). R_f 0.45 (20:1, petrol/EtOAc); ν_{max} (film) 3065, 2961, 2925, 2870, 1598, 1498, 1452, 1411, 1382, 1361, 1321, 1301, 1223, 1208, 1157, 1109, 1071, 1039, 993, 916, 774, 756, 714, 702, 674 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.07 (3H, s, (C*H*$_3$)(CH'$_3$)CH), 1.09 (3H, s, (CH$_3$)(C*H*'$_3$)CH), 2.00 (3H, d, *J* 0.6, C*H*$_3$C=CHCH=C), 2.68 (1H, app sep, *J* 6.8, (CH$_3$)(CH'$_3$)C*H*), 5.93-5.95 (2H, m, CH$_3$C=C*H*C*H*=C), 7.24 (2H, dd, *J* 8.2, 1.4, 2×Ph*H*-ortho), 7.39-7.49 (3H, m, 3×Ph*H*-meta and para); δ_C (100 MHz, $CDCl_3$) 12.8 (*C*H$_3$C=CHCH=C), 23.2 ((*C*H$_3$)(*C*H'$_3$)CH), 25.9 ((CH$_3$)(CH'$_3$)*C*H), 102.1 (CH$_3$C=CH*C*H=C), 105.5 (CH$_3$C=*C*HCH=C), 127.7, 128.7, 129.0 (5×Ph*C*H), 129.1 (CH$_3$*C*=CHCH=C), 139.1 (Ph*C*-N), 140.6 (CH$_3$C=CHCH=*C*); *m/z* (ES) found 216.1388 ($[M+H]^+$ $C_{14}H_{18}NO$), requires 216.1388.

General procedure for the synthesis of 1,2-oxazines using 4-nitrosoanisole

To a stirred solution of (2*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole (28 mg, 0.20 mmol, 20 mol%) in DMSO (2 ml) was added a solution of 4-nitrosoanisole (0.15 g, 1.00 mmol, 1.0 eq) and the appropriate aldehyde (1.20 mmol, 1.2 eq) in DMSO (3 ml) dropewise *via* syringe over 1 h. The mixture was allowed to stir for further 1 h and then cooled to 0 °C and THF (5 ml) was added. Vinyltriphenylphosphonium bromide (0.57 g, 1.50 mmol, 1.5 eq) was added, followed by sodium hydride (0.08 g, 2.00 mmol, 2.0 eq). After stirring for 20 min at 0 °C, the reaction mixture was quenched using saturated aqueous NH_4Cl (20 ml) and extracted with ether (3 × 20 ml). The combined organic layers were washed with saturated aqueous LiCl (20 ml) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (solvents noted) to provide the title compounds.

(6*R*)-6-Isopropyl-2-(4-methoxyphenyl)-3,6-dihydro-2*H*-1,2-oxazine (5a). Prepared according to the general procedure from isovaleraldehyde (0.13 ml, 1.20 mmol) to provide the title compound as a pale yellow solid (84 mg, 36%, >98% ee)

after flash column chromatography (10:1, petrol/EtOAc). R_f 0.55 (3:1, petrol/EtOAc); m.p. 54-55 °C; $[\alpha]_D^{25}$ +11.5 (*c* 0.48 in $CHCl_3$); ν_{max} (film) 3676, 2971, 2902, 1505, 1463, 1385, 1245, 1210, 1175, 1066, 1037, 991, 867, 832, 726, 714, 659 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.8, (C*H*$_3$)(CH'$_3$)CH), 1.03 (3H, d, *J* 6.8, (CH$_3$)(C*H*'$_3$)CH), 1.94 (1H, app oct, *J* 6.8, (CH$_3$)(CH'$_3$)C*H*), 3.67 (1H, app ddt, *J* 15.7, 5.0, 1.7, ArNC*H*H'CH=CH), 3.74-3.80 (1H, m, ArNCH*H*'CH=CH), 3.78 (3H, s, OC*H*$_3$), 4.31-4.34 (1H, m, (CH$_3$)$_2$CHC*H*CH=CH), 5.92-5.98 (2H, m, (CH$_3$)$_2$CHCHC*H*=C*H*), 6.86 (2H, d, *J* 9.0, 2×Ar*H*-ortho), 7.10 (2H, d, *J* 9.0, 2×Ar*H*-meta); δ_C (150 MHz, $CDCl_3$) 18.3 ((*C*H$_3$)(CH'$_3$)CH), 18.4 ((CH$_3$)(*C*H'$_3$)CH), 31.5 ((CH$_3$)(CH'$_3$)*C*H), 52.7 (ArN*C*H$_2$CH=CH), 55.5 (O*C*H$_3$), 82.4 ((CH$_3$)$_2$CH*C*HCH=CH), 114.1 (2×Ar*C*-ortho), 117.7 (2×Ar*C*-meta), 123.8 (ArNCH$_2$*C*H=CH), 128.5 (ArNCH$_2$CH=*C*H), 144.6 (Ar*C*N), 155.3 (Ar*C*O); *m/z* (ES) found 234.1490 ($[M+H]^+$ $C_{14}H_{20}NO_2$), requires 234.1494; HPLC (Chiralcel OD-H, 99:1, hexane/^{i}PrOH, 1.0 ml min^{-1}, 254 nm) t_R(minor) 6.9 min, t_R(major) 9.3 min.

(6*S*)-6-*tert*-Butyl-2-(4-methoxyphenyl)-3,6-dihydro-2*H*-1,2-oxazine (5h). Prepared according to the general procedure from 3,3-dimethylbutyraldehyde (0.16 ml, 1.20 mmol) to provide the title compound as a yellow solid (0.16 g, 63%, >98% ee) after flash column chromatography (10:1, petrol/EtOAc). R_f 0.55 (3:1, petrol/EtOAc); m.p. 82-84 °C; $[\alpha]_D^{25}$ +76.7 (*c* 0.57 in $CHCl_3$); ν_{max} (film) 3676, 2960, 2902, 2833, 2805, 1612, 1506, 1475, 1462, 1439, 1394, 1366, 1252, 1216, 1173, 1118, 1099, 1062, 1033, 1005, 986, 890, 856, 822, 786, 713, 660 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.02 (9H, s, (C*H*$_3$)$_3$CCH), 3.63 (1H, app ddt, *J* 15.7, 3.6, 1.8, ArNC*H*H'CH=CH), 3.79 (3H, s, OC*H*$_3$), 3.79-3.83 (1H, m, ArNCH*H*'CH=CH), 4.29-4.31 (1H, m, (CH$_3$)$_3$CC*H*CH=CH), 5.96-6.02 (2H, m, ArNCH$_2$C*H*=C*H*), 6.87 (2H, d, *J* 9.1, 2×Ar*H*-ortho), 7.08 (2H, d, *J* 9.1, 2×Ar*H*-meta); δ_C (150 MHz, $CDCl_3$) 25.9 ((*C*H$_3$)$_3$CCH), 34.2 ((CH$_3$)$_3$*C*CH), 52.5 (ArN*C*H$_2$CH=CH), 55.5 (O*C*H$_3$), 84.8 ((CH$_3$)$_3$C*C*HCH=CH), 114.1 (2×Ar*C*-meta), 117.4 (2×Ar*C*-ortho), 124.5 (ArNCH$_2$*C*H=CH), 127.4 (ArNCH$_2$CH=*C*H), 144.7 (Ar*C*N), 155.2 (Ar*C*O); *m/z* (ES)

found 248.1652 ($[M+H]^+$ $C_{15}H_{22}NO_2$), requires 248.1651; HPLC (Chiralcel OD-H, 99:1, hexane/^{i}PrOH, 1.0 ml min^{-1}, 254 nm) t_R(minor) 5.5 min, t_R(major) 9.2 min.

General procedure for the synthesis of 1,2-oxazines from ketones

To a stirred solution of (2*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole (7 mg, 0.05 mmol, 5 mol%) and the appropriate ketone (3.00 mmol, 3.0 eq) in DMSO (3 ml) was added a solution of nitrosobenzene (0.11 g, 1.00 mmol, 1.0 eq) in DMSO (2 ml) dropwise *via* syringe over 1 h. The reaction mixture was allowed to stir for a further 1 h, then vinyltriphenylphosphonium bromide (0.57 g, 1.50 mmol, 1.5 eq) was added. The resulting solution was added to a stirred suspension of KH (0.40 g, 30% in mineral oil, washed with hexane, 3.00 mmol, 3.0 eq) in THF (5 ml) at 0 °C. After 2 h of vigorous stirring at 0 °C, the reaction mixture was quenched using saturated aqueous NH_4Cl (20 ml), extracted with ether (3 × 30 ml) and washed with saturated aqueous LiCl (20 ml). The combined organic phase was dried using $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (solvent noted) to provide the oxazine products.

(8a*R*)-2-Phenyl-3,5,6,7,8,8a-hexahydro-2*H*-benzo[*e*][1,2]oxazine (8a). Prepared according to the general procedure from cyclohexanone (0.32 ml, 3.00 mmol) to provide the title compound as an orange solid (0.13 g, 60%, 99% ee) after flash column chromatography (20:1, petrol/EtOAc). R_f 0.64 (3:1, petrol/EtOAc); m.p. 51-53 °C; $[\alpha]_D^{25}$ +133.3 (*c* 0.73 in $CHCl_3$); ν_{max} (film) 3059, 2934, 2854, 2818, 1597, 1486, 1445, 1437, 1361, 1342, 1220, 1193, 1180, 1149, 1093, 1064, 1014, 993, 921, 880, 860, 835, 820, 785, 751, 722, 689 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.25-1.33 (1H, m, CH=CCH$_2$C*H*H'), 1.36-1.48 (2H, m, CH=C(CH$_2$)$_2$CH*H*'C*H*H'), 1.76-1.80 (1H, m, CH=CCH$_2$CH*H*'), 1.85-1.89 (1H, m, CH=C(CH$_2$)$_2$C*H*H'), 2.02-2.09 (1H, m, CH=CCH*H*'(CH$_2$)$_3$), 2.14-2.18 (1H, m, CH=C(CH$_2$)$_3$CH*H*'), 2.38 (1H, dddd, *J* 14.2, 4.2, 2.1, 2.1, CH=CC*H*H'(CH$_2$)$_3$), 3.72 (1H, app dq, *J* 15.4, 2.7, PhNC*H*H'CH=C), 3.88 (1H, dddd, *J* 15.4, 5.1, 2.5, 2.5, PhNCH*H*'CH=C), 4.49-4.54 (1H, m, PhNOC*H*(CH$_2$)$_4$), 5.58-5.60 (1H, m, PhNCH$_2$C*H*=C), 6.98 (1H, tt, *J* 7.3, 1.0, Ph*H*-

para), 7.14 (2H, dd, *J* 8.7, 1.0, 2×Ph*H*-ortho), 7.30 (2H, dd, *J* 8.7, 7.3, 2×Ph*H*-meta); δ_C (150 MHz, $CDCl_3$) 23.9 (CH=C$(CH_2)_2$*C*H_2CH_2), 26.8 (CH=CCH_2*C*$H_2(CH_2)_2$), 31.4 (CH=C$(CH_2)_3$*C*H_2), 32.2 (CH=C*C*$H_2(CH_2)_3$), 52.1 (PhN*C*H_2CH=C), 78.3 (NO*C*H$(CH_2)_4$), 114.8 (PhNCH_2*C*H=C), 115.9 (2×Ph*C*-ortho), 122.0 (Ph*C*-para), 128.7 (2×Ph*C*-meta), 140.3 (PhNCH_2CH=*C*), 150.6 (Ph*C*-N); *m/z* (ES) found 216.1380 ($[M+H]^+$ $C_{14}H_{18}NO$), requires 216.1388; HPLC (Chiralpak AD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(major) 10.1 min, t_R(minor) 10.8 min.

(8a*S*)-2-Phenyl-3,5,6,7,8,8a-hexahydro-2*H*-benzo[*e*][1,2]oxazine (**11a**) was obtained when the reaction was catalysed by (2*R*)-5-pyrrolidin-2-yl-1*H*-tetrazole (57%, 99% ee). $[\alpha]_D^{25}$ -154.7 (*c* 1.06 in $CHCl_3$); HPLC (Chiralpak AD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(minor) 10.1 min, t_R(major) 10.8 min.

(8a*S*)-2-Phenyl-2,3,5,6,8,8a-hexahydropyrano[4,3-*e*][1,2]oxazine (8b). Prepared according to the general procedure from tetrahydropyran-4-one (0.28 ml, 3.00 mmol) to provide the title compound as a yellow solid (72 mg, 33%, 99% ee) after flash column chromatography (10:1, petrol/EtOAc). R_f 0.49 (3:1, petrol/EtOAc); m.p. 53-55 °C; $[\alpha]_D^{25}$ +143.1 (*c* 0.36 in $CHCl_3$); ν_{max} (film) 3057, 2967, 2893, 2860, 1601, 1498, 1455, 1429, 1354, 1327, 1294, 1279, 1216, 1114, 1098, 1073, 1027, 1011, 990, 968, 932, 896, 857, 833, 790, 763, 749, 696, 686 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.30 (1H, m, CH=CC*H*H'CH_2O), 2.42-2.52 (1H, m, CH=CCH*H*'CH_2O), 3.22 (1H, app t, *J* 10.3, NOCHCH*H*'O), 3.35 (1H, ddd, *J* 12.4, 10.9, 2.7, CH=CCH_2C*H*H'O), 3.76 (1H, ddd, *J* 15.7, 5.0, 2.8, PhNC*H*H'CH=C), 3.93 (1H, dddd, *J* 15.7, 5.1, 2.5, 2.5, PhNCH*H*'CH=C), 4.03 (1H, app ddt, *J* 10.9, 5.9, 1.0, CH=CCH_2CH*H*'O), 4.23 (1H, dd, *J* 10.3, 6.1, NOCHC*H*H'O), 4.66-4.71 (1H, m, NOC*H*CH_2O), 5.69-5.72 (1H, m, C*H*=CCH_2), 7.01 (1H, tt, *J* 7.3, 1.1, Ph*H*-para), 7.13 (2H, dd, *J* 8.7, 1.1, 2×Ph*H*-ortho), 7.30 (2H, dd, *J* 8.7, 7.3, 2×Ph*H*-meta); δ_C (100 MHz, $CDCl_3$) 32.8 (CH=C*C*H_2CH_2O), 52.8 (PhN*C*H_2CH=C), 69.2 (CH=CCH_2*C*H_2O), 70.1 (NOCH*C*H_2O), 75.1 (NO*C*HCH_2O), 116.6 (*C*H=CCH_2 and 2×Ph*C*-ortho), 123.1 (Ph*C*-para), 129.2 (2×Ph*C*-meta), 136.8 (CH=*C*CH_2), 150.6 (Ph*C*-N); *m/z* (ES) found

218.1171 ([M+H]$^+$ $C_{13}H_{16}NO_2$), requires 218.1181; HPLC (Chiralcel OD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(major) 17.6 min, t_R(minor) 23.2 min.

(8a*S*)-2-Phenyl-2,3,5,6,8,8a-hexahydrothiopyrano[4,3-*e*][1,2]oxazine (8c). Prepared according to the general procedure from tetrahydrothiopyran-4-one (0.35 g, 3.00 mmol) to provide the title compound as a pale yellow solid (0.12 g, 51%, 99% ee) after flash column chromatography (10:1, petrol/EtOAc). R_f 0.33 (10:1, petrol/EtOAc); m.p. 78-79 °C; $[\alpha]_D^{25}$ +40.0 (*c* 0.37 in $CHCl_3$); ν_{max} (film) 3673, 2988, 2912, 2885, 1598, 1491, 1455, 1424, 1352, 1274, 1212, 1176, 1076, 1048, 1019, 981, 927, 914, 892, 865, 823, 805, 759, 737, 696, 688 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 2.52-2.64 (3H, m, CH=CC*H*$_2$C*H*H'S), 2.74 (1H, dt, *J* 13.4, 2.5, CH=CCH$_2$CH*H*'S), 2.81-2.89 (2H, m, NOCHC*H*$_2$S), 3.75-3.84 (2H, m, PhNC*H*$_2$CH=C), 4.66-4.69 (1H, m, NOC*H*CH$_2$S), 5.69-5.71 (1H, m, C*H*=CCH$_2$), 7.00 (1H, tt, *J* 7.4, 1.1, Ph*H*-para), 7.10 (2H, dd, *J* 8.4, 1.1, 2×Ph*H*-ortho), 7.31 (2H, dd, *J* 8.4, 7.4, 2×Ph*H*-meta); δ_C (150 MHz, $CDCl_3$) 29.7 (CH=C*C*H$_2$CH$_2$S), 32.4 (NOCH*C*H$_2$S), 36.3 (CH=CCH$_2$*C*H$_2$S), 52.0 (PhN*C*H$_2$CH=C), 78.0 (NO*C*HCH$_2$S), 116.0 (2×Ph*C*-ortho), 117.9 (*C*H=CCH$_2$), 122.4 (Ph*C*-para), 128.8 (2×Ph*C*-meta), 138.0 (CH=*C*CH$_2$), 150.2 (Ph*C*-N); *m/z* (ES) found 234.0943 ([M+H]$^+$ $C_{13}H_{16}NOS$), requires 234.0953; HPLC (Chiralcel OD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(major) 17.9 min, t_R(minor) 20.4 min.

(8a*R*)-2-Phenyl-2,3,5,6,8,8a-hexahydrospiro[benzo[*e*][1,2]oxazine-7,2'-[1,3]dioxolane] (8d). Prepared according to the general procedure from 1,4-cyclohexanedione monoethylene ketal (0.48 g, 3.00 mmol) to provide the title compound as a very pale yellow solid (0.14 g, 50%, 99% ee) after flash column chromatography (10:1, petrol/EtOAc). R_f 0.48 (3:1, petrol/EtOAc); m.p. 95-97 °C; $[\alpha]_D^{25}$ +132.2 (*c* 0.66 in $CHCl_3$); ν_{max} (film) 2951, 2939, 2856, 2813, 1598, 1492, 1485, 1444, 1434, 1376, 1347, 1328, 1253, 1213, 1190, 1122, 1102, 1048, 1029, 1019, 1006, 951, 933, 906, 804, 806, 766, 754, 702, 693, 672 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.60-1.65 (1H, m, CH=CCH$_2$C*H*H'C), 1.72 (1H, app t, *J* 12.0, NOCHC*H*H'C), 1.81 (1H, ddd, *J* 12.9, 6.9, 3.0, CH=CCH$_2$CH*H*'C), 2.24 (1H, ddd, *J*

12.0, 5.8, 3.0, NOCHCH*H*'C), 2.34-2.37 (2H, m, CH=CC*H*$_2$CH$_2$C), 3.72-3.75 (1H, m, PhNC*H*H'CH=C), 3.86-3.90 (1H, m, PhNCH*H*'CH=C), 3.96-4.05 (4H, m, OC*H*$_2$C*H*$_2$O), 4.68-4.74 (1H, m, NOC*H*CH$_2$C), 5.64-5.68 (1H, m, PhNCH$_2$C*H*=C), 6.98 (1H, t, *J* 7.3, Ph*H*-para), 7.11 (2H, d, *J* 8.3, 2×Ph*H*-ortho), 7.30 (2H, dd, *J* 8.3, 7.3, 2×Ph*H*-meta); δ_C (150 MHz, $CDCl_3$) 28.1 (CH=C*C*H$_2$CH$_2$C), 35.0 (CH=CCH$_2$*C*H$_2$C), 39.3 (NOCH*C*H$_2$C), 51.8 (PhN*C*H$_2$CH=C), 64.4, 64.6 (O*C*H$_2$*C*H$_2$O), 76.0 (NO*C*HCH$_2$C), 108.9 (NOCHCH$_2$*C*), 115.9 (PhNCH$_2$*C*H=C and 2×Ph*C*-ortho), 122.2 (Ph*C*-para), 128.7 (2×Ph*C*-meta), 138.2 (PhNCH$_2$CH=*C*), 150.4 (Ph*C*-N); *m/z* (ES) found 274.1438 ($[M+H]^+$ $C_{16}H_{20}NO_3$), requires 274.1443; HPLC (Chiralpak AD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(major) 32.5 min, t_R(minor) 35.0 min.

(8a*S*)-2-Phenyl-2,3,5,6,8,8a-hexahydrospiro[benzo[*e*][1,2]oxazine-7,2'-[1,3]dioxolane] (**11d**) was obtained when the reaction was catalysed by (2*R*)-5-pyrrolidin-2-yl-1*H*-tetrazole (54%, 99% ee). $[\alpha]_D^{25}$ -124.1 (*c* 1.03 in $CHCl_3$); HPLC (Chiralpak AD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(minor) 32.5 min, t_R(major) 35.0 min.

(6*R*)-5,6-Dimethyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (8e). Prepared according to the general procedure from butan-2-one (1.8 ml, 20 mmol) and catalyst (28 mg, 0.20 mmol, 20 mol%) to provide the title compound as a yellow oil (87 mg, 46%, 99% ee) after flash column chromatography (4:1, petrol/toluene). R_f 0.65 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ -4.8 (*c* 0.29 in $CHCl_3$); ν_{max} (film) 2972, 2934, 2815, 1599, 1489, 1436, 1350, 1304, 1213, 1130, 1091, 1032, 1000, 885, 838, 794, 755, 723, 692 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.7, C*H*$_3$CHC(CH$_3$)=CH), 1.72-1.73 (3H, m, CH$_3$CHC(C*H*$_3$)=CH), 3.76-3.78 (2H, m, PhNC*H*$_2$CH=C(CH$_3$)), 4.49-4.54 (1H, m, CH$_3$C*H*C(CH$_3$)=CH), 5.59-5.61 (1H, m, PhNCH$_2$C*H*=C(CH$_3$)), 6.97 (1H, tt, *J* 7.3, 1.0, Ph*H*-para), 7.11 (2H, dd, *J* 8.7, 1.0, 2×Ph*H*-ortho), 7.29 (2H, dd, *J* 8.7, 7.3, 2×Ph*H*-meta); δ_C (150 MHz, $CDCl_3$) 17.4 (*C*H$_3$CHC(CH$_3$)=CH), 18.4 (CH$_3$CHC(*C*H$_3$)=CH), 51.6 (PhN*C*H$_2$CH=C(CH$_3$)), 76.8 (CH$_3$*C*HC(CH$_3$)=CH), 115.5

(2×Ph*C*-ortho), 117.4 (PhNCH$_2$*C*H=C(CH$_3$)), 121.8 (Ph*C*-para), 128.7 (2×Ph*C*-meta), 137.4 (CH$_3$CH*C*(CH$_3$)=CH), 150.6 (Ph*C*-N); *m/z* (ES) found 190.1228 ([M+H]$^+$ C$_{12}$H$_{16}$NO), requires 190.1232; HPLC (Chiralcel OD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(major) 10.7 min, t_R(minor) 18.0 min.

(6*S*)-5,6-Dimethyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (**11e**) was obtained when the reaction was catalysed by (2*R*)-5-pyrrolidin-2-yl-1*H*-tetrazole (38%, 99% ee). $[\alpha]_D^{25}$ +6.8 (*c* 1.14 in CHCl$_3$); HPLC (Chiralcel OD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(minor) 10.7 min, t_R(major) 18.0 min.

(8a*R*)-4-Methyl-2-phenyl-3,5,6,7,8,8a-hexahydro-2*H*-benzo[e][1,2]oxazine (8f). Prepared according to the general procedure from cyclohexanone (0.32 ml, 3.00 mmol) and triphenyl(prop-1-en-2-yl)phosphonium bromide (0.57 g, 1.50 mmol) to provide the title compound as a yellow solid (89 mg, 39%, 99% ee) after flash column chromatography (20:1, petrol/EtOAc). R_f 0.71 (3:1, petrol/EtOAc); m.p. 33-35 °C; $[\alpha]_D^{25}$ +145.8 (*c* 1.65 in CHCl$_3$); ν_{max} (film) 3676, 2926, 2857, 1598, 1493, 1453, 1438, 1379, 1344, 1301, 1224, 1069, 1046, 1015, 952, 872, 848, 797, 751, 721, 690, 668 cm^{-1}; δ_H (500 MHz, CDCl$_3$) 1.16-1.25 (1H, m, (CH$_3$)C=CCH$_2$C*H*H'(CH$_2$)$_2$), 1.30-1.48 (2H, m, (CH$_3$)C=C(CH$_2$)$_2$C*H*H'C*H*H'), 1.67-1.78 (5H, m, (C*H*$_3$)C=CC*H*H'CH*H*'(CH$_2$)$_2$), 1.81-1.86 (1H, m, (CH$_3$)C=C(CH$_2$)$_2$CH*H*'CH$_2$), 2.07-2.12 (1H, m, (CH$_3$)C=C(CH$_2$)$_3$CH*H*'), 2.69-2.73 (1H, m, (CH$_3$)C=CCH*H*'(CH$_2$)$_3$), 3.61-3.70 (2H, m, PhNC*H*$_2$C=C), 4.37-4.42 (1H, m, PhNOC*H*(CH$_2$)$_4$), 6.95 (1H, tt, *J* 7.3, 1.1, Ph*H*-para), 7.11 (2H, dd, *J* 8.7, 1.1, 2×Ph*H*-ortho), 7.27 (2H, dd, *J* 8.7, 7.3, 2×Ph*H*-meta); δ_C (125 MHz, CDCl$_3$) 15.7 ((*C*H$_3$)C=C(CH$_2$)$_4$), 24.2 ((CH$_3$)C=C(CH$_2$)$_2$*C*H$_2$CH$_2$), 26.4 ((CH$_3$)C=CCH$_2$*C*H$_2$(CH$_2$)$_2$), 26.7 ((CH$_3$)C=C*C*H$_2$(CH$_2$)$_3$), 31.6 ((CH$_3$)C=C(CH$_2$)$_3$*C*H$_2$), 56.5 (PhN*C*H$_2$C=C), 78.2 (NO*C*H(CH$_2$)$_4$), 115.8 (2×Ph*C*-ortho), 120.2 (PhNCH$_2$*C*=C), 122.0 (Ph*C*-para), 128.7 (2×Ph*C*-meta), 132.1 (C=*C*(CH$_2$)$_4$), 150.4 (Ph*C*-N); *m/z* (ES) found 230.1537 ([M+H]$^+$ C$_{15}$H$_{20}$NO), requires 230.1545; HPLC (Chiralpak AD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(major) 9.6 min, t_R(minor) 10.5 min.

(3*R*,8a*R*)-3-Methyl-2-phenyl-3,5,6,7,8,8a-hexahydro-2*H*-benzo[e][1,2]oxazine (8g). Prepared according to the general procedure from cyclohexanone (0.32 ml, 3.00 mmol) and (*E*)-triphenyl(prop-1-enyl)phosphonium bromide (0.57 g, 1.50 mmol) to provide the title compound as a pale yellow solid (0.15 g, 65%, 99% ee) after flash column chromatography (20:1, petrol/EtOAc). R_f 0.72 (3:1, petrol/EtOAc); m.p. 65-67 °C; $[\alpha]_D^{25}$ +342.2 (*c* 0.45 in $CHCl_3$); ν_{max} (film) 2935, 2855, 1596, 1490, 1451, 1431, 1364, 1341, 1256, 1138, 1099, 1067, 1033, 959, 928, 898, 884, 858, 824, 764, 738, 694, 688 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.4, PhNCHC*H*$_3$CH=C), 1.22-1.48 (3H, m, CH=CCH$_2$C*H*H'C*H*H'C*H*H'), 1.74-1.80 (1H, m, CH=CCH$_2$CH*H*'(CH$_2$)$_2$), 1.83-1.90 (1H, m, CH=C(CH$_2$)$_2$CH*H*'), 1.97-2.06 (1H, m, CH=CCH*H*'(CH$_2$)$_3$), 2.14-2.21 (1H, m, CH=C(CH$_2$)$_3$CH*H*'), 2.32 (1H, dddd, *J* 14.2, 4.3, 2.3, 2.3, CH=CCH*H*'(CH$_2$)$_3$), 4.09-4.16 (1H, m, PhNC*H*CH$_3$CH=C), 4.39-4.45 (1H, m, PhNOC*H*(CH$_2$)$_4$), 5.60-5.62 (1H, m, PhNCHCH$_3$C*H*=C), 6.91 (1H, tt, *J* 7.3, 1.1, Ph*H*-para), 7.05 (2H, dd, *J* 8.7, 1.1, 2×Ph*H*-ortho), 7.28 (2H, dd, *J* 8.7, 7.3, 2×Ph*H*-meta); δ_C (100 MHz, $CDCl_3$) 14.6 (PhNCH*C*H$_3$CH=C), 23.8 (CH=C(CH$_2$)$_2$*C*H$_2$), 26.7 (CH=CCH$_2$*C*H$_2$), 31.5 (CH=C(CH$_2$)$_3$*C*H$_2$), 31.9 (CH=C*C*H$_2$(CH$_2$)$_3$), 54.7 (PhN*C*HCH$_3$CH=C), 77.6 (NO*C*H(CH$_2$)$_4$), 115.5 (2×Ph*C*-ortho), 120.8 (Ph*C*-para), 121.3 (PhNCHCH$_3$*C*H=C), 128.7 (2×Ph*C*-meta), 139.0 (PhNCHCH$_3$CH=*C*), 148.8 (Ph*C*-N); *m/z* (ES) found 230.1539 ($[M+H]^+$ $C_{15}H_{20}NO$), requires 230.1545; HPLC (Chiralcel OD-H, 99:1, hexane/^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(minor) 9.7 min, t_R(major) 12.8 min.

General procedure for the synthesis of 1,2-oxazines catalysed by the Maruoka Catalyst

To a stirred solution of the Maruoka catalyst (4 mg, 0.006 mmol, 10 mol%) in THF (0.5 ml) was added nitrosobenzene (7 mg, 0.060 mmol, 1.0 eq) in one portion at 0 °C. The resulting solution was stirred vigorously for 10 min before dropwise addition of the appropriate aldehyde (0.180 mmol, 3.0 eq). The reaction mixture was stirred at

0 °C for 1 h until the reaction was determined to be complete by TLC. Vinyltriphenylphosphonium bromide (34 mg, 0.090 mmol, 1.5 eq) was added, followed by additional THF (0.2 ml), DMSO (0.3 ml) and sodium hydride (5 mg, 0.132 mmol, 2.2 eq). After 1 h 30 min of stirring at 0 °C, the reaction mixture was quenched using saturated aqueous NH_4Cl (5 ml) and extracted with ether (3 × 5 ml). The combined organic layers were washed with saturated aqueous LiCl (10 ml), then H_2O (10 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (solvents noted) to provide the title compounds.

(3*R*)-3-Methyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (16a). Prepared according to the general procedure from propionaldehyde (0.13 µl, 0.180 mmol) to provide the title compound as a yellow oil (4 mg, 33%) after flash column chromatography (3:1, petrol/CH_2Cl_2). R_f 0.72 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ +183.3 (*c* 0.06 in $CHCl_3$); ν_{max} (film) 2959, 2928, 2859, 1726, 1599, 1492, 1460, 1379, 1268, 1121, 1072, 1057, 958, 878, 754, 693 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.6, C*H*$_3$CHCH=CH), 4.09-4.14 (1H, m, CH$_3$C*H*CH=CH), 4.37 (1H, dddd, *J* 15.6, 3.2, 1.8, 1.8, CH=CHC*H*H'O), 4.57 (1H, app dq, *J* 15.6, 1.8, CH=CHCH*H'*O), 5.89 (1H, dddd, *J* 10.0, 3.2, 1.8, 1.8, CH=C*H*CH$_2$O), 5.94 (1H, dddd, *J* 10.0, 4.1, 1.8, 1.8, C*H*=CHCH$_2$O), 6.98 (1H, tt, *J* 7.3, 1.1, Ph*H*-para), 7.09 (2H, dd, *J* 8.7, 1.1, 2×Ph*H*-ortho), 7.30 (2H, dd, *J* 8.7, 7.3, 2×Ph*H*-meta); δ_C (150 MHz, $CDCl_3$) 14.6 (*C*H$_3$CHCH=CH), 55.5 (CH$_3$*C*HCH=CH), 68.7 (CH=CH*C*H$_2$O), 116.8 (2×Ph*C*-ortho), 122.0 (Ph*C*-para), 124.9 (CH=*C*HCH$_2$O), 128.8 (2×Ph*C*-meta), 129.4 (*C*H=CHCH$_2$O), 148.8 (Ph*C*-N); *m/z* (ES) found 176.1078 ($[M+H]^+$ $C_{11}H_{14}NO$), requires 176.1075.

(3*R*)-3-(Cyclohexylmethyl)-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (16b). Prepared according to the general procedure from 3-cyclohexylpropanal (25 µl, 0.180 mmol) to provide the title compound as a yellow oil (7 mg, 45%) after flash column chromatography (3:1, petrol/CH_2Cl_2). R_f 0.73 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ +240.3 (*c* 0.35 in $CHCl_3$); ν_{max} (film) 2921, 2851, 1599, 1491, 1449, 1022, 754, 692 cm^{-1}; δ_H

(600 MHz, $CDCl_3$) 0.83-0.91 (2H, m, $CH_2CH(CH'CH_2)_2CH_2$), 1.08-1.26 (3H, m, $CH_2CH(CH_2CH')_2CH'$), 1.34-1.41 (1H, m, $CH_2CH(CH_2CH_2)_2CH_2$), 1.49-1.55 (2H, m, $CH_2CH(CH_2CH_2)_2CH_2$), 1.60-1.71 (4H, m, $CH_2CH(CH_2CH')_2CH'$ and one of $CH_2CH(CH'CH_2)_2CH_2$), 1.76-1.81 (1H, m, one of $CH_2CH(CH'CH_2)_2CH_2$), 4.08-4.12 (1H, m, $CH_2CHCH=CH$), 4.27 (1H, dddd, *J* 15.8, 3.5, 2.6, 0.7, $OCH'CH=CH$), 4.54 (1H, app dtd, *J* 15.8, 2.6, 2.0, $OCH'CH=CH$), 5.86 (1H, dddd, *J* 10.2, 3.5, 2.0, 2.0, $OCH_2CH=CH$), 6.07 (1H, dddd, *J* 10.2, 4.5, 2.6, 2.6, $OCH_2CH=CH$), 6.93 (1H, tt, *J* 7.3, 1.1, Ph*H*-para), 7.03 (2H, dd, *J* 8.7, 1.1, 2×Ph*H*-ortho), 7.29 (2H, dd, *J* 8.7, 7.3, 2×Ph*H*-meta); δ_C (150 MHz, $CDCl_3$) 26.2 (one of $CH_2CH(CH_2CH_2)_2CH_2$ and $CH_2CH(CH_2CH_2)_2CH_2$), 26.5 (one of $CH_2CH(CH_2CH_2)_2CH_2$), 32.7 (one of $CH_2CH(CH_2CH_2)_2CH_2$), 34.1 (one of $CH_2CH(CH_2CH_2)_2CH_2$), 34.3 ($CH_2CH(CH_2CH_2)_2CH_2$), 37.9 ($CH_2CH(CH_2CH_2)_2CH_2$), 55.7 ($CH_2CHCH=CH$), 67.1 ($CH=CHCH_2O$), 116.0 (2×Ph*C*-ortho), 121.2 (Ph*C*-para), 124.9 ($CH=CHCH_2O$), 127.8 ($CH=CHCH_2O$), 128.8 (2×Ph*C*-meta), 148.4 (Ph*C*-N); *m/z* (ES) found 258.1856 ($[M+H]^+$ $C_{17}H_{24}NO$), requires 258.1858.

General procedure for the synthesis of *cis*-allylic alcohols through N-O cleavage

To a stirred solution of the 1,2-oxazine (1 eq) in MeOH was added zinc powder (5 eq) and 3N aqueous HCl (20 eq). The resulting suspension was stirred vigorously at room temperature until the reaction was determined to be complete by TLC. The reaction mixture was quenched using saturated aqueous $NaHCO_3$, diluted with H_2O and extracted with EtOAc three times. The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (solvents noted) to provide the desired compound.

(*R*,*Z*)-2-(2-(Phenylamino)ethylidene)cyclohexanol (13a). Prepared according to the general procedure from (6*R*)-2-phenyl-3,5,6,7,8,8a-hexahydro-2*H*-benzo[*e*][1,2]oxazine (19 mg, 0.084 mmol) for 48 h to provide the title compound as a brown solid (15 mg, 83%, 99% ee) after flash column chromatography (3:1, petrol/EtOAc with 1% triethylamine). R_f 0.28 (3:1, petrol/EtOAc with 1%

triethylamine); m.p. 56-57 °C; $[\alpha]_D^{25}$ -48.4 (*c* 0.55 in $CHCl_3$); ν_{max} (film) 3675, 3257, 2930, 2901, 2808, 1601, 1522, 1497, 1439, 1408, 1301, 1251, 1234, 1146, 1089, 1060, 1037, 986, 914, 857, 749, 691 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.37 (1H, m, CH=CCH$_2$C*H*H'(CH$_2$)$_2$), 1.49-1.61 (2H, m, CH=C(CH$_2$)$_2$C*H*H'C*H*H'), 1.69-1.90 (3H, m, CH=CCH$_2$CH*H*'CH*H*'CH*H*'), 2.00 (1H, app dt, *J* 13.5, 4.2 CH=CC*H*H'(CH$_2$)$_3$), 2.39-2.46 (1H, m, CH=CCH*H*'(CH$_2$)$_3$), 3.73-3.82 (2H, m, PhNHC*H*$_2$CH=C), 4.70 (1H, t, *J* 3.7, CH=CC*H*OH), 5.38-5.42 (1H, m, PhNHCH$_2$C*H*=C), 6.64 (2H, dd, *J* 8.6, 1.1, 2×Ph*H*-ortho), 6.73 (1H, tt, *J* 7.3, 1.1, Ph*H*-para), 7.18 (2H, dd, *J* 8.6, 7.3, 2×Ph*H*-meta); δ_C (125 MHz, $CDCl_3$) 20.8 (CH=C(CH$_2$)$_2$ *C*H$_2$CH$_2$), 27.8 (CH=CCH$_2$*C*H$_2$(CH$_2$)$_2$), 32.7 (CH=C*C*H$_2$(CH$_2$)$_3$), 34.6 (CH=C(CH$_2$)$_3$*C*H$_2$), 40.9 (PhNH*C*H$_2$), 65.5 (CH=C*C*HOH), 113.4 (2×Ph*C*-ortho), 118.0 (Ph*C*-para), 120.9 (PhNHCH$_2$*C*H=C), 129.2 (2×Ph*C*-meta), 144.3 (PhNHCH$_2$CH=*C*), 147.9 (Ph*C*-N); *m/z* (ES) found 240.1365 ($[M+Na]^+$ $C_{14}H_{19}NONa$), requires 240.1364; HPLC (Chiralcel OD-H, 90:10, hexane/^{i}PrOH, 1.0 ml min^{-1}, 254 nm) t_R(minor) 28.6 min, t_R(major) 35.1 min.

(*S*,*Z*)-4-(2-(Phenylamino)ethylidene)-tetrahydro-2H-pyran-3-ol (13b). Prepared according to the general procedure from (6*S*)-2-phenyl-2,3,5,6,8,8a-hexahydropyrano[4,3-*e*][1,2]oxazine (7 mg, 0.032 mmol) to provide the title compound as a yellow liquid (7 mg, quant., 99% ee) after flash column chromatography (1:2, petrol/EtOAc with 1% triethylamine). R_f 0.53 (1% triethylamine in EtOAc); $[\alpha]_D^{25}$ -51.0 (*c* 0.20 in $CHCl_3$); ν_{max} (film) 3675, 3357, 2969, 2902, 1601, 1501, 1463, 1429, 1315, 1252, 1233, 1180, 1103, 1057, 1021, 932, 880, 838, 749, 723, 693 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.02-2.06 (1H, m, CH=CC*H*H'CH$_2$O), 2.69-2.77 (1H, m, CH=CCH*H*'CH$_2$O), 3.45 (1H, app dt, *J* 11.2, 2.9, CH=CCH$_2$C*H*H'O), 3.53 (1H, dd, *J* 11.9, 1.9, OCH*H*'CHOH), 3.81 (1H, ddd, *J* 13.6, 6.8, 1.3, PhNHC*H*H'CH=C), 3.82 (1H, ddd, *J* 13.6, 6.8, 1.6, PhNHCH*H*'CH=C), 3.93-3.99 (2H, m, CH=CCH$_2$CH*H*'OCH*H*'), 4.48-4.50 (1H, m, OCH$_2$C*H*OH), 5.48-5.52 (1H, m, C*H*=CCH$_2$), 6.64 (2H, dd, *J* 8.6, 1.1, 2×Ph*H*-ortho), 6.74 (1H, tt, *J* 7.3, 1.1, Ph*H*-para), 7.19 (2H, dd, *J* 8.6, 7.3, 2×Ph*H*-meta); δ_C (125

MHz, $CDCl_3$) 32.6 (CH=C*C*H_2CH$_2$O), 40.7 (PhNH*C*H$_2$CH=C), 65.6 (CH=C*C*HOH), 69.2 (CH=CCH$_2$*C*H$_2$O), 73.4 (O*C*H$_2$CHOH), 113.4 (2×Ph*C*-ortho), 118.2 (Ph*C*-para), 123.0 (*C*H=C(CH$_2$)$_2$O), 129.3 (2×Ph*C*-meta), 138.8 (CH=*C*(CH$_2$)$_2$O), 147.6 (Ph*C*-N); *m/z* (ES) found 220.1338 ([M+H]$^+$ $C_{13}H_{18}NO_2$), requires 220.1338; HPLC (Chiralcel OD-H, 90:10, hexane/^{i}PrOH, 1.0 ml min^{-1}, 254 nm) t_R(minor) 52.1 min, t_R(major) 55.4 min.

(*R*,*Z*)-3-Methyl-5-(phenylamino)pent-3-en-2-ol (13e). Prepared according to the general procedure from (6*R*)-5,6-dimethyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (13 mg, 0.071 mmol) to provide the title compound as a colourless oil (12 mg, 88%, 99% ee) after flash column chromatography (3:1, petrol/EtOAc with 1% triethylamine). R_f 0.20 (3:1, petrol/EtOAc with 1% triethylamine); $[\alpha]_D^{25}$ +10.4 (*c* 0.63 in $CHCl_3$); ν_{max} (film) 3367, 2972, 2919, 1601, 1502, 1432, 1375, 1315, 1251, 1179, 1094, 1067, 1032, 992, 896, 818, 747, 691 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.5, C*H*$_3$CHOH), 1.76 (3H, dd, *J* 2.6, 1.2, C*H*$_3$C=CH), 3.67-3.73 (1H, m, PhNHC*H*H'CH=C), 3.76-3.82 (1H, m, PhNHCH*H*'CH=C), 4.80 (1H, qd, *J* 6.5, 0.7, CH$_3$C*H*OH), 5.38-5.42 (1H, m, CH$_3$C=C*H*), 6.62 (2H, dd, *J* 8.6, 1.1, 2×Ph*H*-ortho), 6.72 (1H, tt, *J* 7.3, 1.1, Ph*H*-para), 7.18 (2H, dd, *J* 8.6, 7.3, 2×Ph*H*-meta); δ_C (125 MHz, $CDCl_3$) 17.5 (*C*H$_3$C=CHCH$_2$), 21.5 (*C*H$_3$CHOH), 41.0 (PhNH*C*H$_2$), 65.9 (CH$_3$*C*HOH), 113.2 (2×Ph*C*-ortho), 117.8 (Ph*C*-para), 123.2 (CH$_3$C=*C*HCH$_2$), 129.2 (2×Ph*C*-meta), 142.10 (CH$_3$*C*=CHCH$_2$), 148.0, (Ph*C*-N); *m/z* (ES) found 192.1392 ([M+H]$^+$ $C_{12}H_{18}NO$), requires 192.1388; HPLC (Chiralcel OD-H, 90:10, hexane/^{i}PrOH, 1.0 ml min^{-1}, 254 nm) t_R(minor) 24.0 min, t_R(major) 32.5 min.

General procedure for the synthesis of 3,6-dihydropyridazines from aldehydes

To a stirred solution of the appropriate aldehyde (1.2 eq) and aminating agent (1.0 eq) in CH_2Cl_2 (3 ml/mmol of the aminating agent) was added (2*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole catalyst (10 mol%). The resulting suspension was stirred at room temperature until the yellow colour of the azodicarboxylate or the red colour of the *N*-

phenyl-triazolinedione, respectively, disappeared. The mixture was then cooled to 0 °C, THF (1 ml/ml of CH_2Cl_2) added. Vinyltriphenylphosphonium bromide (1.5 eq) was added, followed by NaH (2.5 eq). After 45 min of stirring at 0 °C, the reaction mixture was quenched using saturated aqueous NH_4Cl (2 ml/ml reaction volume) and extracted with CH_2Cl_2 (3 × 1 ml/ml reaction volume). The combined organic layers were washed with brine (2 ml/ml reaction volume) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (solvents noted) to provide the title compounds.

(3*R*)-3-Isopropyl-3,6-dihydro-pyridazine-1,2-dicarboxylic acid diethyl ester (18a). Prepared according to the general procedure from isovaleraldehyde (130 µl, 103 mg, 1.2 mmol) and diethyl azodicarboxylate (97% purity, 162 µl, 179 mg, 1.0 mmol). Purification by gradient flash column chromatography (10:1 → 2:1, petrol/EtOAc) gave the title compound as a colourless oil (241 mg, 89%, 94% ee). R_f 0.45 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ -98.3 (*c* 1.00 in $CHCl_3$); ν_{max} (film) 2961, 2872, 1705, 1467, 1407, 1378, 1337, 1287, 1211, 1173, 1111, 1059, 1024, 926, 872, 826, 755, 707 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.95-1.02 (3H, m, CH(C*H*$_3$)(CH'$_3$)), 1.06 (2.25H, d, *J* 6.6, CH(CH$_3$)(C*H*'$_3$) of major rotamer), 1.11 (0.75H, d, *J* 6.6, CH(CH$_3$)(C*H*'$_3$) of minor rotamer), 1.19-1.33 (6H, m, 2×CH$_2$C*H*$_3$), 1.71-1.85 (1H, m, C*H*(CH$_3$)$_2$), 3.62-3.95 (1H, m, NC*H*H'), 4.02-4.30 (5H, m, NC*H* and 2×CO$_2$C*H*$_2$CH$_3$), 4.30-4.40 (1H, m, NCH*H*'), 5.66-5.82 and 5.83-5.95 (2H, m, C*H*=C*H*); δ_C (100 MHz, $CDCl_3$) 14.5 and 14.6 (CH$_2$*C*H$_3$), 19.1 and 20.1 (CH(*C*H$_3$)$_2$), 32.2 (*C*H(CH$_3$)$_2$), 42.5 (N*C*H$_2$), 60.7 (N*C*H), 62.0 and 62.3 (2×CO$_2$*C*H$_2$CH$_3$), 122.8 and 127.1 (*C*H=*C*H), 155.4 (2×*C*O$_2$CH$_2$CH$_3$); *m/z* (ESI) found 293.1476 ($[M+Na]^+$ $C_{13}H_{22}N_2O_4Na$), requires 293.1477; SFC (Chiralcel OD-H, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 200 nm) t_R(major) 6.0 min, t_R(minor) 4.9 min.

(3*R*)-3-*tert*-Butyl-3,6-dihydro-pyridazine-1,2-dicarboxylic acid diethyl ester (18h). Prepared according to the general procedure from 3,3-dimethylbutanal (95% purity, 79 µl, 63 mg, 0.6 mmol) and diethyl azodicarboxylate (97% purity, 81 µl, 90

mg, 0.5 mmol) using the general procedure. Purification by gradient flash column chromatography (10:1 → 2:1, petrol/EtOAc) gave the title compound as a colourless oil (119 mg, 84%, 99% ee). R_f 0.60 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ -138.6 (*c* 1.00 in $CHCl_3$); ν_{max} (film) 2959, 1706, 1466, 1404, 1379, 1338, 1314, 1287, 1209, 1173, 1150, 1117, 1094, 1070, 1027, 989, 942, 916, 864, 831, 793, 769, 755, 710, 684 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.96-1.03 (9H, m, $C(CH_3)_3$), 1.22-1.31 (6H, m, $2\times CH_2CH_3$), 3.60-3.93 (1H, m, NC*H*H'), 4.10-4.30 (4.4H, m, NC*H* and $2\times CO_2CH_2CH_3$), 4.30-4.45 (1.6H, m, NC*H* and NCH*H*'), 5.80-5.95 (2H, m, C*H*=C*H*); δ_C (100 MHz, $CDCl_3$) 14.5 ($2\times CH_2CH_3$), 26.6 ($C(CH_3)_3$), 35.7 ($C(CH_3)_3$), 42.1 (NCH_2), 61.9 and 61.9 ($2\times CO_2CH_2CH_3$), 62.4 (NCH), 123.6 and 124.8 (CH=CH), 155.1 ($2\times CO_2CH_2CH_3$); *m/z* (ESI) found 307.1636 ($[M+Na]^+$ $C_{14}H_{24}N_2O_4Na$), requires 307.1634; SFC (Chiralcel AD-H + AD, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 210 nm) t_R(major) 9.4 min, t_R(minor) 10.1 min.

(3*R*)-3-Allyl-3,6-dihydro-pyridazine-1,2-dicarboxylic acid diethyl ester (18e). Prepared according to the general procedure from 4-pentenal (97% purity, 122 µl, 104 mg, 1.2 mmol) and diethyl azodicarboxylate (97% purity, 162 µl, 179 mg, 1.0 mmol). Purification by flash column chromatography (10:1 → 2:1, petrol/EtOAc) gave the title compound as a colourless oil (100 mg, 75%, 90% ee). R_f 0.50 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ -170.0 (*c* 0.11 in $CHCl_3$); ν_{max} (film) 2981, 2935, 2853, 1703, 1643, 1466, 1410, 1378, 1339, 1306, 1273, 1211, 1173, 1120, 1063, 1023, 916, 869, 755, 735, 709 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.17-1.32 (6H, m, $2\times CH_2CH_3$), 2.16-2.30 (1H, m, CHH'$CH=CH_2$), 2.32-2.55 (1H, m, CH*H*'$CH=CH_2$), 3.60-3.93 (1H, m, NC*H*H'), 4.08-4.32 (4H, m, $2\times CO_2CH_2CH_3$), 4.39 (1H, br d, *J* 17.2, NCH*H*'), 4.45-4.70 (1H, m, NC*H*), 5.01-5.16 (2H, m, $CH=CH_2$), 5.67-5.98 (3H, m, C*H*=C*H* and C*H*=CH_2); δ_C (100 MHz, $CDCl_3$) 14.9 ($2\times CH_2CH_3$), 37.8 ($CH_2CH=CH_2$), 42.9 (NCH_2), 54.9 (NCH), 62.4 and 62.7 ($2\times CO_2CH_2CH_3$), 117.5 ($CH=CH_2$), 123.4 and 128.0 (CH=CH), 134.9 ($CH=CH_2$), 155.9 ($2\times CO_2CH_2CH_3$); *m/z* (ESI) found 269.1495 ($[M+H]^+$ $C_{13}H_{21}N_2O_4$), requires 269.1501; SFC (Chiralcel OD-H, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 210 nm) t_R(major) 6.0 min, t_R(minor) 5.2 min.

(3*R*)-3-Benzyl-3,6-dihydro-pyridazine-1,2-dicarboxylic acid diethyl ester (18g). Prepared according to the general procedure from 3-phenylpropionaldehyde (95% purity, 166 μl, 169 mg, 1.2 mmol) and diethyl azodicarboxylate (97% purity, 162 μl, 179 mg, 1.0 mmol) using the general procedure. Purification by gradient flash column chromatography (10:1 → 2:1, petrol/EtOAc) gave the title compound as a colourless oil (186 mg, 58%, 79% ee). R_f 0.45 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ -94.3 (*c* 1.13 in $CHCl_3$); ν_{max} (film) 3422, 2982, 2851, 2304, 1705, 1604, 1496, 1415, 1377, 1338, 1266, 1212, 1173, 1120, 1066, 1022, 981, 943, 889, 868, 846, 750, 699 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.00-1.36 (6H, m, 2×CH_2CH_3), 2.74 (1H, dd, *J* 7.8, 13.6, C*H*H'Ph), 3.00-3.20 (1H, m, CH*H*'Ph), 3.65-4.00 (1H, m, NC*H*H'), 4.10-4.30 (4H, m, 2×$CO_2CH_2CH_3$), 4.30-4.50 (1H, m, NCH*H*'), 4.55-5.00 (1H, m, NC*H*), 5.65-5.85 (2H, m, C*H*=C*H*), 7.15-7.38 (5H, m, C_6H_5); δ_C (100 MHz, $CDCl_3$) 14.7 (2×CH_2CH_3), 39.7 (CH_2Ph), 43.8 (NCH_2), 57.3 (N*C*H), 62.5 (2×$CO_2CH_2CH_3$), 125.1, 126.6, 127.4, 128.5 and 129.4, (*C*H=*C*H and C_{Ar}), 156.2 (2×$CO_2CH_2CH_3$); *m/z* (ESI) found 319.1667 ($[M+H]^+$ $C_{17}H_{23}N_2O_4$), requires 319.1685; SFC (Chiralcel OD-H, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 210 nm) t_R(major) 5.3 min, t_R(minor) 4.4 min.

(3*R*)-3-(3-Methoxycarbonyl-propyl)-3,6-dihydro-pyridazine-1,2-dicarboxylic acid diethyl ester (18f). Prepared according to the general procedure from adipic semialdehyde methyl ester (174 μl, 174 mg, 1.2 mmol) and diethyl azodicarboxylate (97% purity, 162 μl, 179 mg, 1.0 mmol) with 20 mol% catalyst. Purification by gradient flash column chromatography (10:1 → 2:1, petrol/EtOAc) gave the title compound as a colourless oil (220 mg, 67%, 69% ee). R_f 0.27 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ -80.8 (*c* 1.00 in $CHCl_3$); ν_{max} (film) 2983, 1703, 1412, 1377, 1338, 1285, 1212, 1169, 1122, 1092, 1065, 1023, 930, 870, 848, 755, 705 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.18-1.32 (6H, m, 2×CH_2CH_3), 1.47-1.63 (2H, m, $CH_2CH_2CH_2CO_2CH_3$), 1.70-1.84 (1H, m, C*H*H'$CH_2CO_2CH_3$), 1.84-2.00 (1H, m, CH*H*'$CH_2CO_2CH_3$), 2.25-2.45 (2H, m, $CH_2CO_2CH_3$), 3.66 (3H, s, OCH_3), 3.70-4.00 (1H, m, NC*H*H'), 4.08-4.30 (4H, m, 2×$CO_2CH_2CH_3$), 4.38 (1 H, d, *J* 17.2, NCH*H*'), 4.43-4.70 (1H, m, NC*H*), 5.65-5.83

(2H, m, C*H*=C*H*); δ_C (100 MHz, $CDCl_3$) 14.5 and 14.5 (2×CH_2CH_3), 21.9 ($CH_2CH_2CO_2CH_3$), 32.2 ($CH_2CH_2CH_2CO_2CH_3$), 33.6 ($CH_2CO_2CH_3$), 43.6 (NCH_2), 51.4 (OCH_3), 54.8 (N*C*H), 62.1 and 62.4 (2×$CO_2CH_2CH_3$), 123.7 and 127.2 (*C*H=*C*H), 155.3 (2×$CO_2CH_2CH_3$), 173.8 (CO_2CH_3); *m/z* (ESI) found 351.1532 ($[M+Na]^+$ $C_{15}H_{24}N_2O_6Na$), requires 351.1532; SFC (Chiralcel OD-H, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 210 nm) t_R(major) 3.9 min, t_R(minor) 3.6 min.

(3*R*,1'*R*)-3-(1',5'-Dimethyl-hex-4'-enyl)-3,6-dihydro-pyridazine-1,2-dicarboxylic acid diethyl ester (18i). Prepared according to the general procedure from (*R*)-citronellal (90% purity, 241 μl, 205 mg, 1.2 mmol) and diethyl azodicarboxylate (97% purity, 162 μl, 179 mg, 1.0 mmol). Purification by gradient flash column chromatography (10:1 → 2:1, petrol/EtOAc) gave the title compound as a colourless oil (255 mg, 75%). Material of dr 4:1 was characterised: R_f 0.55 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ -86.2 (*c* 1.00 in $CHCl_3$); ν_{max} (film) 2967, 2915, 2856, 1706, 1465, 1422, 1377, 1338, 1285, 1210, 1173, 1115, 1082, 1057, 1025, 980, 935, 923, 866, 830, 756, 709 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 6.8, NCHCH(CH_3)), 1.13-1.22 (1H, m, one of CH_2CH_2), 1.22-1.33 (6H, m, 2×$CO_2CH_2CH_3$), 1.56-1.70 (7H, m, $(CH_3)_2C$ and one of CH_2CH_2), 1.71-1.80 (1H, m, one of CH_2CH_2), 1.80-1.90 (1H, m, one of CH_2CH_2), 2.01-2.12 (1H, m, NCHC*H*(CH_3)), 3.67-3.96 (1H, m, NC*H*H'), 4.08-4.30 (4.5H, m, NC*H* and 2×$CO_2CH_2CH_3$), 4.30-4.42 (1.5H, m, NCH*H*' and NC*H*), 5.06-5.15 (1H, m, $(CH_3)_2C$=C*H*), 5.70-5.81 and 5.95-5.82 (2H, m, C*H*=C*H*); δ_C (100 MHz, $CDCl_3$) 14.9 (2×$CO_2CH_2CH_3$), 16.0 ($CHCH_3$), 18.0 ($C(CH_3)(CH'_3)$), 25.7 ($NCHCH(CH_3)$), 26.0 ($C(CH_3)(CH'_3)$), 33.6 and 37.1 (CH_2CH_2), 43.2 (NCH_2), 60.8 (N*C*H), 62.4 and 62.7 (2×$CO_2CH_2CH_3$), 123.2 (one of *C*H=*C*H), 125.0 ($(CH_3)_2C$=*C*H), 126.8 (one of *C*H=*C*H), 131.5 ($(CH_3)_2C$), 155.4 (2×$CO_2CH_2CH_3$); *m/z* (ESI) found 361.2105 ($[M+Na]^+$ $C_{18}H_{30}N_2O_4Na$), requires 361.2103.

(3*R*,1'*S*)-3-(1',5'-Dimethyl-hex-4'-enyl)-3,6-dihydro-pyridazine-1,2-dicarboxylic acid diethyl ester (18j). Prepared according to the general procedure

from (*S*)-citronellal (96% purity, 226 μl, 192 mg, 1.2 mmol) and diethyl azodicarboxylate (97% purity, 162 μl, 179 mg, 1.0 mmol). Purification by gradient flash column chromatography (10:1 → 2:1, petrol/EtOAc) gave the title compound as a colourless oil (283 mg, 84%). Material of dr >12:1 was characterised: R_f 0.60 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ -132.4 (*c* 1.00 in $CHCl_3$); ν_{max} (film) 2978, 2929, 2855, 1707, 1465, 1423, 1377, 1338, 1287, 1210, 1172, 1116, 1093, 1058, 1027, 978, 920, 865, 830, 756, 707 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.02 (3H, d, *J* 6.7, NCHCH(C*H*$_3$)), 1.20-1.32 (7H, m, 2×$CO_2CH_2CH_3$ and one of C*H*$_2$C*H*$_2$), 1.46-1.56 (1H, m, one of C*H*$_2$C*H*$_2$), 1.57-1.73 (7H, m, (C*H*$_3$)$_2$C and one of C*H*$_2$C*H*$_2$), 1.91-2.02 (1H, m, one of C*H*$_2$C*H*$_2$), 2.03-2.15 (1H, m, NCHC*H*(CH$_3$)), 3.69-3.98 (1H, m, NC*H*H'), 4.09-4.20 (4.5H, m, NC*H* and 2×CO_2C*H*$_2$CH$_3$), 4.30-4.44 (1.5H, m, NCH*H*' and NC*H*), 5.03-5.12 (1H, m, (CH$_3$)$_2$C=C*H*), 5.68-5.80 and 5.82-5.93 (2H, m, C*H*=C*H*); δ_C (100 MHz, $CDCl_3$) 14.9 (2×CO_2CH_2*C*H$_3$), 16.7 (CH*C*H$_3$), 18.0 (C(*C*H$_3$)(CH'$_3$)), 25.7 (NCH*C*H(CH$_3$)), 26.0 (C(CH$_3$)(*C*H'$_3$)), 33.4 and 37.4 (*C*H$_2$*C*H$_2$), 43.0 (N*C*H$_2$), 61.6 (N*C*H), 62.3 and 62.7 (2×CO_2*C*H$_2$CH$_3$), 122.9 (one of *C*H=*C*H), 124.8 ((CH$_3$)$_2$C=*C*H), 125.8 (one of *C*H=*C*H), 131.9 ((CH$_3$)$_2$*C*), 155.0 (2×*C*O$_2$CH$_2$CH$_3$); *m/z* (ESI) found 361.2092 ([M+Na]$^+$ $C_{18}H_{30}N_2O_4Na$), requires 361.2103.

(3*S*)-Diethyl 3-((*tert*-butyldimethylsilyloxy)methyl)pyridazine-1,2(3*H*,6*H*)-dicarboxylate (18k). Prepared according to the general procedure from 3-(tert-butyldimethylsilyloxy)propanal (226 mg, 1.2 mmol) and diethyl azodicarboxylate (97% purity, 162 μl, 179 mg, 1.0 mmol). Reaction time for the α-amination was 40 min. Purification by gradient flash column chromatography (10:1 → 2:1, hexane/EtOAc) gave the title compound as a colourless oil (339 mg, 67%, 87% ee). R_f 0.33 (3:1, hexane/EtOAc); $[\alpha]_D^{25}$ -117.5 (*c* 0.55 in $CHCl_3$); ν_{max} (film) 3492, 2955, 2930, 2857, 1709, 1466, 1415, 1378, 1339, 1290, 1254, 1215, 1173, 1116, 1093, 1058, 1024, 1007, 981, 940, 896, 835, 774, 756, 707 cm^{-1}; δ_H (400 MHz, $CDCl_3$) -0.10-0.05 (6H, m, OSi(C*H*$_3$)$_2$), 0.72-0.89 (9H, m, OSiC(C*H*$_3$)$_3$), 1.13-1.28 (6H, m, 2×CH$_2$C*H*$_3$), 3.53 (1H, t, *J* 7.7, C*H*H'OSi), 3.55-3.92 (2H, m, CH*H*'OSi and NC*H*H'), 4.03-4.35 (4H, m, 2×CO_2C*H*$_2$CH$_3$), 4.35-4.45 (1H, br d, NCH*H*'), 4.45-4.76 (1H, br s,

NC*H*), 5.72-6.00 (2H, m, C*H*=C*H*); δ_C (100 MHz, $CDCl_3$) -5.5 (Si(CH_3)$_2$), 14.6 (2×$CO_2CH_2CH_3$), 18.2 (SiC(CH_3)$_3$), 25.7 (SiC(CH_3)$_3$), 42.6 (NCH_2), 55.4 (NCH), 62.2 (2×$CO_2CH_2CH_3$), 63.8 (CH_2OSi), 123.9 and 126.3 (CH=CH), 155.5 (2×$CO_2CH_2CH_3$); *m/z* (ESI) found 373.2153 ($[M+H]^+$ $C_{17}H_{33}N_2O_5Si$), requires 373.2159; SFC (Chiralcel OD-H, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 200 nm) t_R(major) 6.0 min, t_R(minor) 5.1 min.

Diethyl 3-methylenepyridazine-1,2(3*H*,6*H*)-dicarboxylate (19). Prepared according to the general procedure from 3-(tert-butyldimethylsilyloxy)propanal (226 mg, 1.2 mmol) and diethyl azodicarboxylate (97% purity, 162 µl, 179 mg, 1.0 mmol) and proline as a catalyst. Reaction time for the α-amination was 48 h. Purification by gradient flash column chromatography (10:1 → 2:1, hexane/EtOAc) gave the title compound as a colourless oil (105 mg, 44%). R_f 0.50 (3:1, hexane/EtOAc); ν_{max} (film) 2983, 2937, 2910, 1713, 1646, 1600, 1466, 1398, 1372, 1327, 1282, 1257, 1207, 1172, 1127, 1090, 1037, 1022, 952, 910, 872, 754 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.13-1.31 (6H, m, 2×$CO_2CH_2CH_3$), 3.67-3.95 (1H, m, NC*H*H'), 4.04-4.31 (4H, m, 2×$CO_2CH_2CH_3$), 4.37-4.67 (1H, m, NCH*H*'), 4.93 (1H, s, C=C*H*H'), 5.21-5.56 (1H, m, C=CH*H*'), 5.85 (1H, br s, C*H*=CHC=CH_2), 6.06 (1H, d, CH=C*H*C=CH_2); δ_C (150 MHz, $CDCl_3$) 14.4 (2×$CO_2CH_2CH_3$), 43.8 (NCH_2), 62.5 and 62.6 (2×$CO_2CH_2CH_3$), 108.0 (CH=CHC=CH_2), 124.5 and 125.0 (CH=CHC=CH_2), 137.2 (CH=CHC=CH_2), 155.7 (2×$CO_2CH_2CH_3$); *m/z* (ESI) found 263.1000 ($[M+Na]^+$ $C_{11}H_{16}N_2O_4Na$), requires 263.1008.

(3*R*)-3-Isopropyl-3,6-dihydro-pyridazine-1,2-dicarboxylic acid di-*tert*-butyl ester (20b). Prepared according to the general procedure from isovaleraldehyde (130 µl, 103 mg, 1.2 mmol) and di-*tert*-butyl azodicarboxylate (98% purity, 235 mg, 1.0 mmol). Purification by gradient flash column chromatography (10:1 → 2:1, petrol/EtOAc) gave the title compound as a colourless oil (264 mg, 81%, 99% ee). R_f 0.80 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ -90.6 (*c* 0.75 in $CHCl_3$); ν_{max} (film) 2978, 1704, 1477, 1452, 1410, 1391, 1367, 1344, 1298, 1255, 1218, 1170, 1121, 1059, 959, 929,

869, 770, 752, 720 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.95-1.00 (3H, m, CH(C*H*$_3$)(CH'$_3$)), 1.02-1.10 (3H, m, CH(CH$_3$)(C*H*'$_3$)), 1.42-1.51 (18H, m, 2×OC(C*H*$_3$)$_3$), 1.70-1.85 (1H, m, C*H*(CH$_3$)$_2$), 3.56-3.78 (1H, m, NC*H*H'), 4.00-4.34 (2H, m, NC*H* and NCH*H*'), 5.67-5.90 (2H, m, C*H*=C*H*); δ_C (100 MHz, $CDCl_3$) 19.1 and 20.2 (CH(*C*H$_3$)$_2$), 28.3 (2×CO$_2$C(*C*H$_3$)$_3$), 32.1 (2×*C*H(CH$_3$)$_2$), 41.8 (N*C*H$_2$), 60.2 (N*C*H), 80.5 and 80.9 (2×CO$_2$*C*(CH$_3$)$_3$), 123.0 and 127.3 (*C*H=*C*H), 154.5 and 156.5 (2×*C*O$_2$C(CH$_3$)$_3$); *m/z* (ESI) found 349.2112 ([M+Na]$^+$ $C_{17}H_{30}N_2O_4Na$), requires 349.2103; SFC (Chiralcel AD-H + AD, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 200 nm) t_R(major) 8.0 min, t_R(minor) 8.3 min.

(3*R*)-3-Isopropyl-3,6-dihydro-pyridazine-1,2-dicarboxylic acid dibenzyl ester (20c). Prepared according to the general procedure from isovaleraldehyde (130 µl, 103 mg, 1.2 mmol) and dibenzyl azodicarboxylate (298 mg, 1.0 mmol). Purification by gradient flash column chromatography (10:1 → 2:1, petrol/EtOAc) gave the title compound as a colourless oil (293 mg, 74%, 89% ee). R_f 0.62 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ -61.8 (*c* 1.14 in $CHCl_3$); ν_{max} (film) 3035, 2960, 1705, 1498, 1446, 1403, 1357, 1338, 1315, 1285, 1210, 1137, 1110, 1054, 1029, 971, 859, 792, 750, 734, 695 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.84-1.18 (6H, m, CH(C*H*$_3$)$_2$), 1.65-1.90 (1H, m, C*H*(CH$_3$)$_2$), 3.63-4.00 (1H, m, NC*H*H'), 4.05-4.45 (2H, m, NC*H* and NCH*H*'), 4.97-5.30 (4H, m, 2×C*H*$_2$Ph), 5.62-5.82 and 5.82-5.97 (2H, m, C*H*=C*H*), 7.15-7.50 (10H, s, 2×C$_6$*H*$_5$); δ_C (100 MHz, $CDCl_3$) 19.0 and 20.2 (CH(*C*H$_3$)$_2$), 32.2 (*C*H(CH$_3$)$_2$), 42.8 (N*C*H$_2$), 61.0 (N*C*H), 67.8 and 67.9 (2×CO$_2$*C*H$_2$Ph), 122.7 and 127.7 (*C*H=*C*H), 128.1, 128.4, 128.5, 136.0 and 136.2, (*C*$_{Ar}$), 155.3 (2×*C*O$_2$Bn); *m/z* (ESI) found 417.1776 ([M+Na]$^+$ $C_{23}H_{26}N_2O_4Na$), requires 417.1790; SFC (Chiralcel AD-H + AD, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 210 nm) t_R(major) 12.4 min, t_R(minor) 18.6 min.

(5*R*)-5-Isopropyl-2-phenyl-5,8-dihydro-[1,2,4]triazolo[1,2-*a*]pyridazine-1,3-dione (20d). Prepared according to the general procedure from isovaleraldehyde (260 µl, 206 mg, 2.4 mmol) and *N*-phenyl-triazolinedione (350 mg, 2.0 mmol). Stirring for 240 min during the Wittig step was necessary to increase conversion. Purification by

flash column chromatography (10:5:2, petrol/CH_2Cl_2/EtOAc) gave the title compound as colourless crystals (245 mg, 45%, 57% ee). R_f 0.25 (3:1, petrol/EtOAc); $[\alpha]_D^{25}$ +89.6 (*c* 1.00 in $CHCl_3$); ν_{max} (film) 3450, 3053, 2966, 2932, 2869, 1766, 1697, 1597, 1494, 1455, 1415, 1337, 1316, 1300, 1282, 1242, 1159, 1129, 1083, 1020, 995, 939, 916, 875, 856, 820, 804, 768, 758, 740, 718, 703, 689 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.8, CH(C*H*$_3$)(CH'$_3$)), 1.04 (3H, d, *J* 7.0, CH(CH$_3$)(C*H*'$_3$)), 2.57-2.69 (1H, m, C*H*(CH$_3$)$_2$), 4.03-4.12 (1H, m, NC*H*H'), 4.23-4.35 (1H, m, NCH*H*'), 4.46-4.53 (1H, m, NC*H*), 5.93-5.98 (1H, m, one of C*H*=C*H*), 6.03-6.07 (1H, m, one of C*H*=C*H*), 7.34-7.38 (1H, m, Ph*H*), 7.45-7.49 (2H, m, 2×Ph*H*), 7.54-7.56 (2H, m, 2×Ph*H*); δ_C (100 MHz, $CDCl_3$) 17.1 and 19.6 (CH(*C*H$_3$)$_2$), 31.1 (*C*H(CH$_3$)$_2$), 43.8 (N*C*H$_2$), 58.7 (N*C*H), 121.8 and 122.5 (*C*H=*C*H), 125.9, 128.4, 129.5 and 131.8 (C_{Ar}), 150.8 and 152.9 (2×*C*O); *m/z* (ESI) found 294.1210 ($[M+Na]^+$ $C_{15}H_{17}N_3O_2Na$), requires 294.1218; SFC (Chiralcel OD-H, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 200 nm) t_R(major) 10.0 min, t_R(minor) 13.8 min.

General procedure for the synthesis of pyridazines from ketones

To a stirred solution of the appropriate ketone (1.2 eq) and diethyl azodicarboxylate (1.0 eq) in CH_2Cl_2 (5 ml/mmol of diethyl azodicarboxylate) was added (2*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole catalyst (20 mol%). The reaction mixture was stirred at room temperature for 24 h. DMSO (1 ml/ml of CH_2Cl_2) and vinyltriphenylphosphonium bromide (1.5 eq) were added. The solution was cooled to 0 °C and then added in one portion *via* syringe to a suspension of KH (2.5 eq, 30%, in mineral oil, washed with hexane (2 × 3 ml)) in THF (1 ml/ml of CH_2Cl_2) at 0 °C. The reaction mixture was slowly allowed to warm to room temperature and quenched after 270 min with saturated aqueous NH_4Cl (2 ml/ml reaction volume) and extracted with CH_2Cl_2 (2 × 1 ml/ml reaction volume). The combined organic layers were washed with saturated aqueous LiCl (2 ml/ml reaction volume), brine (2 ml/ml reaction volume) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting

residue was purified by flash column chromatography (solvents noted) to provide the title compounds.

(8a*R*)-3,5,6,7,8,8a-Hexahydro-cinnoline-1,2-dicarboxylic acid diethyl ester (21a). Prepared according to the general procedure from cyclohexanone (124 μl, 118 mg, 1.2 mmol) to provide the title compound as a colourless oil (147 mg, 52%, 76% ee) after flash column chromatography (5:1, petrol/EtOAc). R_f 0.62 (2:1, petrol/EtOAc); $[\alpha]_D^{25}$ -101.2 (*c* 2.00 in $CHCl_3$); ν_{max} (film) 2933, 2856, 2295, 1704, 1415, 1382, 1342, 1298, 1240, 1216, 1172, 1141, 1115, 1094, 1070, 1047, 1026, 960, 884, 799, 755 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.08-1.35 (7H, m, one of $(CH_2)_4$ and 2×CH_2CH_3), 1.38-1.52 (2H, m, two of $(CH_2)_4$), 1.71-1.90 (2H, m, two of $(CH_2)_4$), 1.91-2.10 (2H, m, two of $(CH_2)_4$), 2.20-2.32 (1H, m, one of $(CH_2)_4$), 3.55-3.90 (1H, m, NCHH'), 4.15-4.22 (4H, m, 2×$CO_2CH_2CH_3$), 4.22-4.46 (2H, m, NCH and NCHH'), 5.42 (1H, br s, C=CH); δ_C (100 MHz, $CDCl_3$) 14.9 and 15.0 (2×$CO_2CH_2CH_3$); 25.5, 28.1, 32.6 and 35.1 ($(CH_2)_4$), 43.2 (NCH_2), 57.1 (NCH), 62.3 and 62.5 (2×$CO_2CH_2CH_3$), 114.4 (C=CH), 139.5 (C=CH), 155.7 and 156.0 (2×$CO_2CH_2CH_3$); *m/z* (ESI) found 305.1486 ($[M+Na]^+$ $C_{14}H_{22}N_2O_4Na$), requires 305.1477; SFC (Chiralcel OD-H, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 200 nm) t_R(major) 9.2 min, t_R(minor) 7.9 min.

(*S*)-Diethyl 5,6,8,8a-tetrahydro-1*H*-pyrano[3,4-*c*]pyridazine-1,2(3*H*)-dicarboxylate (21b). Prepared according to the general procedure from tetrahzdropyran-4-one (111 μl, 120 mg, 1.2 mmol). Reaction time for the α-amination was 13 h. Purification by gradient flash column chromatography (10:1 → 2:1, hexane/EtOAc) gave the title compound as a colourless oil (72 mg, 25%, 84% ee). R_f 0.23 (3:1, hexane/EtOAc); $[\alpha]_D^{25}$ -102.0 (*c* 0.53 in $CHCl_3$); ν_{max} (film) 2979, 2909, 2854, 1702, 1466, 1411, 1377, 1337, 1293, 1216, 1149, 1124, 1094, 1065, 1053, 1025, 999, 960, 913, 868, 843, 805, 755, 693 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.06-1.39 (6H, m, 2×$CO_2CH_2CH_3$), 2.22 (1H, d, *J* 13.12, OCH_2CHH'), 2.36-2.51 (1H, m, OCH_2CHH'), 3.12-3.37 (2H, m, OCH_2CH_2), 3.56-3.92 (1H, m, NCHH'), 3.92-4.07

(1H, m, OC*H*H'CHN), 4.07-4.31 (5H, m, 2×$CO_2CH_2CH_3$ and OCH*H*'CHN), 4.31-4.70 (2H, m, NC*H* and NCH*H*'), 5.62 (1H, br s, C=C*H*); δ_C (100 MHz, $CDCl_3$) 14.5 and 14.6 (2×$CO_2CH_2CH_3$), 34.9 (OCH_2CH_2), 42.8 (NCH_2), 55.4 (NCH), 62.3 and 62.5 (2×$CO_2CH_2CH_3$), 69.2 (OCH_2CH_2), 70.0 (OCH_2CHN), 116.1 (C=CH), 134.6 (C=CH), 155.3 (2×$CO_2CH_2CH_3$); *m/z* (ESI) found 285.1457 ($[M+H]^+$ $C_{13}H_{21}N_2O_5$), requires 285.1450; SFC (Chiralcel OD-H, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 200 nm) t_R(major) 9.7 min, t_R(minor) 7.9 min.

(*S*)-Diethyl 5,6,8,8a-tetrahydro-1*H*-thiopyrano[3,4-*c*]pyridazine-1,2(3*H*)-dicarboxylate (21c). Prepared according to the general procedure from tetrahydrothiopyran-4-one (139 mg, 1.2 mmol). Reaction time for the α-amination was 48 h. Purification by gradient flash column chromatography (10:1 → 2:1, hexane/EtOAc) gave the title compound as a colourless oil (131 mg, 40%, 83% ee). R_f 0.30 (3:1, hexane/EtOAc); $[\alpha]_D^{25}$ -79.9 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 2980, 2909, 2852, 1701, 1466, 1410, 1380, 1338, 1292, 1217, 1172, 1142, 1116, 1059, 1021, 980, 932, 875, 816, 754, 721 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.06-1.39 (6H, m, 2×CH_2CH_3), 2.42-2.67 (4H, m, SCH_2CH_2), 2.67-2.90 (2H, m, SCH_2CHN), 3.55-3.82 (1H, m, NC*H*H'), 4.00-4.32 (4H, m, 2×$CO_2CH_2CH_3$), 4.41 (1H, dd, *J* 4.8, 17.2, NCH*H*'), 4.50-4.76 (1H, m, NC*H*), 5.51 (1H, br s, C=C*H*), δ_C (150 MHz, $CDCl_3$) 14.5 (2×$CO_2CH_2CH_3$), 30.1 (SCH_2CH_2), 32.7 (SCH_2CHN), 38.2 (SCH_2CH_2), 43.2 (NCH_2), 56.9 (NCH), 62.2 and 62.4 (2×$CO_2CH_2CH_3$), 117.4 (C=CH), 136.3 (C=CH), 155.1 (2×$CO_2CH_2CH_3$); *m/z* (ESI) found 301.1215 ($[M+H]^+$ $C_{13}H_{21}N_2O_4S$), requires 301.1222; SFC (Chiralcel OD-H, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 200 nm) t_R(major) 11.4 min, t_R(minor) 9.5 min.

(*R*)-Diethyl 5,6,8,8a-tetrahydro-1*H*-spiro[cinnoline-7,2'-[1,3]dioxolane]-1,2(3*H*)-dicarboxylate (21d). Prepared according to the general procedure from 1,4-dioxaspiro[4.5]decan-8-one (193 mg, 1.2 mmol) and diethyl azodicarboxylate (97% purity, 162 μl, 179 mg, 1.0 mmol). Reaction time for the α-amination was 96 h. Purification by gradient flash column chromatography (10:1 → 2:1, hexane/EtOAc)

gave the title compound as a white solid (207 mg, 60%, 76% ee). R_f 0.20 (3:1, hexane/EtOAc); $[\alpha]_D^{25}$ -70.5 (*c* 0.42 in $CHCl_3$); ν_{max} (film) 2967, 2856, 1700, 1465, 1419, 1382, 1335, 1288, 1247, 1213, 1150, 1121, 1103, 1081, 1046, 1026, 968, 944, 930, 884, 862, 821, 755, 731, 692 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.05-1.30 (6H, m, 2×CH_2CH_3), 1.43-1.58 (1H, m, CH=CCH_2CHH'), 1.62-1.73 (1H, m, CH=$CCHH'CH_2$), 1.73-1.80 (1H, dd, *J* 2.6, 12.3, CH=CCH_2CHH'), 2.05-2.16 (1H, m, CH=$CCHH'CH_2$), 2.16-2.32 (2H, m, CH_2CHN), 3.56-3.81 (1H, m, $NCHH'$), 3.83-4.03 (4H, m, OCH_2CH_2O), 4.08-4.25 (4H, m, 2×$CO_2CH_2CH_3$), 4.42 (1 H, dd, *J* 4.9, 16.9, $NCHH'$), 4.56-4.70 (1H, m, NCH), 5.49 (1 H, br s, C=CH); δ_C (150 MHz, $CDCl_3$) 14.5 (2×$CO_2CH_2CH_3$), 29.9 (CH_2CHN), 36.0 (CH=CCH_2CH_2), 40.0 (CH=CCH_2CH_2), 42.6 (NCH_2), 53.4 (NCH), 62.2 and 62.3 (2×$CO_2CH_2CH_3$), 64.5 and 64.6 (OCH_2CH_2O), 108.5 (C_{spiro}), 115.6 (C=CH), 136.6 (C=CH), 154.9 and 155.4 (2×$CO_2CH_2CH_3$); *m/z* (ESI) found 341.1722 ($[M+H]^+$ $C_{16}H_{25}N_2O_6$), requires 341.1713; SFC (Chiralcel OD-H, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 200 nm) t_R(major) 13.3 min, t_R(minor) 15.1 min.

(3*R*)-diethyl 3,4-dimethylpyridazine-1,2(3*H*,6*H*)-dicarboxylate (21e) and **diethyl 4-ethylpyridazine-1,2(3*H*,6*H*)-dicarboxylate (21f)**. Prepared according to the general procedure from 2-butanone (450 µl, 361 mg, 5.0 mmol) and diethyl azodicarboxylate (97% purity, 162 µl, 179 mg, 1.0 mmol). Reaction time for the α-amination was 18 h. Purification by gradient flash column chromatography (10:1 → 2:1, hexane/EtOAc) gave the title compounds as a colourless oil (228 mg, 93%, 65% ee). R_f 0.30 (3:1, hexane/EtOAc); $[\alpha]_D^{25}$ -60.6 (*c* 0.54 in $CHCl_3$); ν_{max} (film, mixture of isomers) 2980, 2935, 2857, 1703, 1412, 1380, 1341, 1289, 1170, 1144, 1126, 1094, 1059, 1046, 1026, 984, 875, 847, 798, 756, 732 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.97 (3H, t, *J* 7.5, CH_3CH_2C=CH of minor isomer), 1.08-1.30 (15H, m, $NCHCH_3$ of major isomer and 2×$CO_2CH_2CH_3$ of both isomers), 1.64 (3H, s, CH_3C=CH of major isomer), 1.88-2.03 (2H, m, CH_3CH_2C=CH of minor isomer), 3.52-3.89 (2H, m, $NCHH'$ of both isomers), 4.00-4.23 (8H, m, 2×$CO_2CH_2CH_3$ of both isomers), 4.29 (2H, br d, *J* 17.2, $NCHH'$ of both isomers), 4.46 (3H, br s, NCH of major and NCH_2C

of minor isomer), 5.22-5.36 (1H, m, C=C*H* of major isomer), 5.39 (1H, br s, C=C*H* of minor isomer); δ_C (100 MHz, $CDCl_3$) 11.6 (*C*H_3CH_2C=CH of minor isomer), 14.4 and 14.5 (2×CO_2CH_2*C*H_3 of both isomers), 16.7 (NCH*C*H_3 of major isomer), 20.1 (*C*H_3C=CH of major isomer), 26.7 (CH_3*C*H_2C=CH of minor isomer), 42.7 (N*C*H_2 of both isomers), 53.5 (N*C*H of major isomer and N*C*H_2C of minor isomer), 61.8 and 62.1 (2×CO_2*C*H_2CH_3 of both isomers), 116.7 and 136.7 (*C*=*C*H of both isomers), 155.4 and 155.6 (2×*C*$O_2CH_2CH_3$ of both isomers); *m/z* (ESI) found 257.1508 ($[M+H]^+$ $C_{12}H_{21}N_2O_4$), requires 257.1501; SFC (Chiralcel OD-H, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 200 nm) t_R(major) 6.5 min, t_R(minor) 4.9 min.