Organocatalytic Enantioselective Synthesis of 2,3-Dihydropyridazines

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**General Methods.** NMR spectra were acquired on a Bruker 300 spectrometer, running at 300 and 75 MHz for $^1$H and $^{13}$C, respectively. Chemical shifts ($\delta$) are reported in ppm relative to residual solvent signals (CHCl$_3$, 7.26 ppm for $^1$H NMR, CDCl$_3$, 77.0 ppm for $^{13}$C NMR). The following abbreviations are used to indicate the multiplicity in $^1$H NMR spectra: s, singlet; d, doublet; t, triplet; m, multiplet; bs, broad signal. $^{13}$C NMR spectra were acquired on a broad band decoupled mode. IR spectra were measured in a Jasco FT/IR 4100 and only characteristic bands are given. Mass spectra (MS) were recorded on an Agilent 7890A gas chromatograph coupled to an Agilent 5975 mass spectrometer (EI). High resolution mass spectra (HRMS) were recorded on a micromass GCT spectrometer using chemical ionization (CI). X-ray data collections were performed in a Oxford Diffraction Xcalibur 2 diffractometer equipped with a Sapphire 2 CCD area detector, and a MoK$\alpha$ sealed-tube source with graphite monochromator ($\lambda = 0.71073\text{Å}$, 0.5mm collimator). The sample was kept at 100(1)K with a Oxford Cryosystems Cryostream 700 cooler. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or p-anisaldehyde dip.$^2$ Melting points (M.p.) were measured in a Büchi B-540 apparatus and are uncorrected. Optical rotations were measured on a Jasco P-2000 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC in a Waters 2695 chromatograph with a Waters 2998 photodiode array detector (Daicel Chiralpak IC and AD-H columns).

**Materials.** Analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC) silica gel (Silica gel 60, 230-400 mesh, Merck) was employed.

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Experimental Procedures and Characterizations

General Procedure for the Preparation of the hydrazone 2.

\((E)-4\text{-methyl-}N'-(1\text{-oxopropan-2-ylidene})\text{benzenesulfonylhydrazide} \ (2)\). To a suspension of \(p\text{-toluenesulfonyl hydrazide (5.0 g, 26.8 mmol)}\) in \(\text{ether (15 mL)}\), a 40% methyl glyoxal solution in \(\text{water (5.5 mL, 32.2 mmol)}\) was added, followed by the addition of \(\text{NaN}_2\) anhydre. The reaction mixture was vigorously stirr ed at room temperature for 18 h. Solids were removed by filtration and washed with ether. The filtrates were concentrated \(\text{in vacuo}\). The crude was purified by FC (n-hexane/EtOAc gradient from 19:1 to 7:3) yielding the corresponding hydrazone \(2\) (955 mg, 3.97 mmol) in 15%. \(^1\text{H NMR (300 MHz, CDCl}_3\) \(\delta 9.33 (s, 1H), 9.08 (s, 1H), 7.87 (d, \(J = 8.2 \text{ Hz, 2H)}\), 7.35 (d, \(J = 8.2 \text{ Hz, 2H)}\), 2.44 (s, 3H), 1.87 (s, 3H). \(^{13}\text{C NMR (75 MHz, CDCl}_3\) \(\delta 190.4, 150.8, 145.1, 134.5, 129.9, 128.0, 21.6, 8.3. \) IR: 3220.5, 1696.1, 1338.4, 1166.7 cm\(^{-1}\)). MS (EI) \(m/z\) (%): 214 (2), 197 (3), 184 (4), 155 (25), 139 (100), 123 (40), 108 (4), 91 (56), 77 (14), 65 (15), 51 (3). M.p. (n-hexane/EtOAc): 123-125 °C.

General Procedure for the Preparation of 2,3-Dihydropyridazines 4. An ordinary vial equipped with a magnetic stirring bar was charged with catalyst \(3b\) (0.06 mmol, 20 mol%), PhCOOH (0.30 mmol) and toluene (6 mL). Then, the \(\alpha,\beta\)-unsatured aldehyde \(1\) (0.30 mmol) was added and the mixture was stirred for 10 minutes prior to the addition of hydrazone \(2\) (0.60 mmol). The stirring was maintained at room temperature until the reaction was complete (3-6 days). The reaction mixture was washed twice with a saturated solution of NaHCO\(_3\), dried over Na\(_2\)SO\(_4\) and concentrated \(\text{in vacuo}\). The crude was charged onto silica gel and subjected to FC. The racemic standards for HPLC separation conditions were prepared using a mixture of \((R)\) and \((S)\) catalyst \(3b\) (0.06 mmol, 20 mol%).

\((R)-3\text{-butyl-6-methyl-2-} (p\text{-toluenesulfonyl})\text{-2,3-dihydropyridazine-4-carbaldehyde} \ (4a)\). Following the general procedure \(4a\) (84 mg, 0.25 mmol) was isolated by FC (n-hexane/EtOAc gradient from 19:1 to 7:3) in 84% yield starting from aldehyde \(1a\) (41 \(\mu\text{L, 0.30 mmol})\) and hydrazone \(2\) (144 mg, 0.60 mmol) in the presence of \(3b\) (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. \(^1\text{H NMR (300 MHz, CDCl}_3\) \(\delta 9.55 (s, 1H), 7.77 (d, \(J = 8.3 \text{ Hz, 2H)}\), 7.26 (d, \(J = 8.3 \text{ Hz, 2H)}\), 6.37 (s, \(1H), 5.45 (t, \(J = 6.4 \text{ Hz, 1H)}\), 2.40 (s, 3H), 2.16 (s, 3H), 1.44–1.32 (m, 2H), 1.29-1.09 (m, 3H), 1.08–0.97 (m, 3H), 0.78 (t, \(J = 7.0 \text{ Hz, 3H)}\). \(^{13}\text{C NMR (75 MHz, CDCl}_3\) \(\delta 190.1, 148.2, 144.0, 138.0, 136.0, 129.5, 127.7, 49.3, 32.8, 26.0, 22.3, 21.6, 21.2, 13.8. IR: 1680.7, 1597.7, 1356.7, 1165.8 cm\(^{-1}\)). MS (EI) \(m/z\) (%): 334 (M\(^+\), 20), 320 (2), 291 (7), 179 (100), 137.1 (76), 122 (8), 108 (14), 91 (25), 77 (12), 53 (6).
HRMS: Calculated for \([\text{C}_{17}\text{H}_{23}\text{N}_{2}\text{O}_{3}\text{S}]^{+}\): 335.1429 \([\text{M+H}]^{+}\); found: 335.1443. The ee was determined by HPLC using a Chiralpak AD-H column \([n\text{-hexane/i-PrOH (90:10)}]\); flow rate 1.0 mL/min; \(\tau_{\text{major}} = 12.64\) min, \(\tau_{\text{minor}} = 16.44\) min (97% ee). \([\alpha]_{D}^{n}\): -428.3 \((c = 1.0, \text{CH}_{2}\text{Cl}_{2})\).

\((R)-3\text{-methyl-6-methyl-2-(p-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4b)}\). Following the general procedure 4b (80 mg, 0.27 mmol) was isolated by FC \((n\text{-hexane/EtOAc gradient from 19:1 to 7:3})\) in 91% yield starting from aldehyde 1b (29 \(\mu\text{L}, 0.30\) mmol) and hydrazone 2 (144 mg, 0.60 mmol) in the presence of 3b (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. 

\(1^H \text{NMR (300 MHz, CDCl}_3\delta 9.55 (s, 1H), 7.84 (d, } J = 8.4 \text{ Hz, 2H), 7.29 (d, } J = 8.4 \text{ Hz, 2H), 6.40 (s, 1H), 5.45 (q, } J = 6.5 \text{ Hz, 1H), 2.41 (s, 3H), 2.18 (s, 3H), 0.97 (d, } J = 6.5 \text{ Hz, 3H).}^{13}\text{C NMR (75 MHz, CDCl}_3\delta 189.7, 147.4, 144.2, 140.0, 136.4, 130.4, 129.6, 128.0, 45.4, 21.6, 21.2, 17.2. IR: 1679.7, 1596.8, 1354.8, 1165.8 cm}^{-1}. \text{MS (EI) m/z (%): 292 (M+, 20), 207 (3), 155 (2), 137 (100), 122 (2), 109 (16), 91 (14), 77 (7), 65 (9), 53 (5). HRMS: Calculated for [C}_{14}\text{H}_{17}\text{N}_{2}\text{O}_{3}\text{S}]^{+}: 293.0960 \([\text{M+H}]^{+}\); found: 293.0972. \)

The ee was determined by HPLC using a Chiralpak AD-H column \([n\text{-hexane/i-PrOH (90:10)})\>; flow rate 1.0 mL/min; \(\tau_{\text{major}} = 18.16\) min, \(\tau_{\text{minor}} = 23.38\) min (89% ee). \([\alpha]_{D}^{rt}\): -274.7 \((c = 1.0, \text{CH}_{2}\text{Cl}_{2})\).

\((R)-3\text{-ethyl-6-methyl-2-(p-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4c)}\). Following the general procedure 4c (68 mg, 0.22 mmol) was isolated by FC \((n\text{-hexane/EtOAc gradient from 19:1 to 7:3})\) in 74% yield starting from aldehyde 1c (32 \(\mu\text{L}, 0.30\) mmol) and hydrazone 2 (144 mg, 0.60 mmol) in the presence of 3b (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent.

\(1^H \text{NMR (300 MHz, CDCl}_3\delta 9.56 (s, 1H), 7.77 (d, } J = 8.3 \text{ Hz, 2H), 7.26 (d, } J = 8.3 \text{ Hz, 2H), 6.40 (s, 1H), 5.42 (t, } J = 6.4 \text{ Hz, 1H), 2.40 (s, 3H), 2.15 (s, 3H), 1.58–1.37 (m, 2H), 0.74 (t, } J = 7.5 \text{ Hz, 3H).}^{13}\text{C NMR (75 MHz, CDCl}_3\delta 190.2, 147.9, 144.0, 137.6, 136.2, 130.8, 129.5, 127.7, 50.3, 26.3, 21.6, 21.1, 8.6. IR: 1680.7, 1597.6, 1357.6, 1166.7 cm}^{-1}. \text{MS (EI) m/z (%): 306 (M+, 16), 207 (2), 155 (2), 137 (100), 122 (2), 109 (16), 91 (14), 77 (7), 65 (9), 53 (5). HRMS: Calculated for [C}_{15}\text{H}_{19}\text{N}_{2}\text{O}_{3}\text{S}]^{+}: 307.1116 \([\text{M+H}]^{+}\); found: 307.1103. The ee was determined by HPLC using a Chiralpak AD-H column \([n\text{-hexane/i-PrOH (90:10)})\>; flow rate 1.0 mL/min; \(\tau_{\text{major}} = 14.76\) min, \(\tau_{\text{minor}} = 21.22\) min (96% ee). \([\alpha]_{D}^{n}\): -391.7 \((c = 1.0, \text{CH}_{2}\text{Cl}_{2})\).

\((R)-6\text{-methyl-3-propyl-2-(p-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4d)}\). Following the general procedure 4d (69 mg, 0.22 mmol) was isolated by FC \((n\text{-hexane/EtOAc gradient from 19:1 to 7:3})\) in 72% yield starting from
aldehyde 1d (36 µL, 0.30 mmol) and hydrazone 2 (144 mg, 0.60 mmol) in the presence of 3b (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ¹H NMR (300 MHz, CDCl₃) δ 9.55 (s, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 6.37 (s, 1H), 5.46 (t, J = 6.4 Hz, 1H), 2.40 (s, 3H), 2.16 (s, 3H), 1.44–1.36 (m, 2H), 1.34-1.19 (m, 1H), 1.19-1.01 (m, 1H), 0.80 (t, J = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 190.1, 148.2, 144.0, 138.0, 136.2, 130.6, 129.5, 127.7, 49.1, 35.3, 21.6, 21.2, 17.3, 13.7. IR: 1681.6, 1597.5, 1355.7, 1167.7 cm⁻¹. MS (EI) m/z (%): 320 (M+, 21), 291 (6), 207 (8), 165 (10), 151 (3), 137 (25), 122 (11), 108 (14), 91 (26), 65 (14), 51 (6). HRMS: Calculated for [C₁₆H₂₁N₂O₃S⁺]: 321.1273 [(M+H)⁺]; found: 321.1286. The ee was determined by HPLC using a Chiralpak AD-H column [n-hexane/i-PrOH (90:10)]; flow rate 1.0 mL/min; τ_major = 12.87 min, τ_minor = 17.57 min (96% ee). [α]D: -359.5 (c = 1.0, CH₂Cl₂).

(R)-6-methyl-3-octyl-2-(p-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4e). Following the general procedure 4e (74 mg, 0.19 mmol) was isolated by FC (n-hexane/EtOAc gradient from 19:1 to 7:3) in 63% yield starting from aldehyde 1e (60 µL, 0.30 mmol) and hydrazone 2 (144 mg, 0.60 mmol) in the presence of 3b (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ¹H NMR (300 MHz, CDCl₃) δ 9.56 (s, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 6.37 (s, 1H), 5.44 (t, J = 6.4 Hz, 1H), 2.40 (s, 3H), 2.16 (s, 3H), 1.48–1.07 (m, 14H), 0.86 (t, J = 7.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 190.1, 148.2, 144.0, 138.0, 136.3, 130.6, 129.5, 127.7, 49.3, 33.1, 31.8, 29.3, 29.3, 29.2, 23.9, 22.6, 21.6, 21.2, 14.1. IR: 1681.6, 1596.5, 1358.6, 1167.7 cm⁻¹. MS (EI) m/z (%): 390 (M+, 14), 291 (7), 235 (100), 207 (12), 137 (45), 109 (10), 91 (15), 65 (6). HRMS: Calculated for [C₂₁H₃₁N₂O₃S⁺]: 391.2055 [(M+H)⁺]; found: 391.2056. The ee was determined by HPLC using a Chiralpak AD-H column [n-hexane/i-PrOH (90:10)]; flow rate 1.0 mL/min; τ_major = 9.22 min, τ_minor = 10.83 min (97% ee). [α]D: -274.0 (c = 1.0, CH₂Cl₂).

(S)-3-dimethoxymethyl-6-methyl-2-(p-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4f). Following the general procedure 4f (64 mg, 0.18 mmol) was isolated by FC (n-hexane/EtOAc gradient from 19:1 to 7:3) in 61% yield starting from aldehyde 1f (38 µL, 0.30 mmol) and hydrazone 2 (144 mg, 0.60 mmol) in the presence of 3b (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ¹H NMR (300 MHz, CDCl₃) δ 9.57 (s, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 6.48 (s, 1H), 5.59 (d, J = 5.0 Hz, 1H), 4.15 (d, J = 5.0 Hz, 1H), 3.31 (s, 3H), 3.25 (s, 3H), 2.40 (s, 3H), 2.15 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 189.7, 147.9, 144.1, 136.0, 133.4, 130.5, 129.4, 127.9, 104.0, 56.0, 55.1, 49.1, 21.6, 21.2. IR: 1685.5, 1353.8, 1168.7, 1119.5 cm⁻¹. MS (EI) m/z (%): 278 (14), 214 (6), 185 (9), 171 (4), 155 (8), 139 (2), 123 (100), 106 (6), 91 (31), 79 (5), 65 (16), 51 (4). HRMS: Calculated for
[C_{16}H_{21}N_{2}O_{5}S]^+: 353.1171 [(M+H)^+]; found: 353.1176. The ee was determined by HPLC using a Chiralpak AD-H column [n-hexane/i-PrOH (90:10)]; flow rate 1.0 mL/min; \( \tau_{\text{major}} = 17.42 \) min, \( \tau_{\text{minor}} = 21.97 \) min (97% ee). \([\alpha]_D^n = -545.1 \) (c = 1.0, CH_{2}Cl_{2}).

\((R,Z)\)-3-\((\text{hex-3-en-1-yl})\)-6-methyl-2-(p-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4g). Following the general procedure 4g (74 mg, 0.21 mmol) was isolated by FC (n-hexane/EtOAc gradient from 19:1 to 7:3) in 68% yield starting from aldehyde 1g (45 \( \mu \)L, 0.30 mmol) and hydrazone 2 (144 mg, 0.60 mmol) in the presence of 3b (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. \(^1\)H NMR (300 MHz, CDCl_{3}) \( \delta \) 9.55 (s, 1H), 7.77 (d, \( J = 8.3 \) Hz, 2H), 7.26 (d, \( J = 8.3 \) Hz, 2H), 6.39 (s, 1H), 5.48 (t, \( J = 6.4 \) Hz, 1H), 5.37–5.26 (m, 1H), 5.19–5.07 (m, 1H), 2.40 (s, 3H), 2.17 (s, 3H), 2.03–1.79 (m, 4H), 1.49–1.39 (m, 2H), 0.91 (t, \( J = 7.5 \) Hz, 3H). \(^{13}\)C NMR (75 MHz, CDCl_{3}) \( \delta \) 190.0, 148.4, 144.1, 137.8, 136.2, 132.8, 130.6, 129.5, 127.7, 127.1, 49.1, 33.2, 22.0, 21.6, 21.2, 20.5, 14.2. IR: 1681.6, 1595.8, 1353.6, 1166.7 cm\(^{-1}\). MS (EI) m/z (%): 360 (M^+, 2), 291 (100), 226 (1), 205 (92), 155 (3), 135 (52), 106 (46), 91 (25), 65 (13). HRMS: Calculated for [C_{19}H_{25}N_{2}O_{3}S]^+: 361.1586 [(M+H)^+]; found: 361.1601. The ee was determined by HPLC using a Chiralpak AD-H column [n-hexane/i-PrOH (93:7)]; flow rate 1.0 mL/min; \( \tau_{\text{major}} = 16.54 \) min, \( \tau_{\text{minor}} = 21.86 \) min (97% ee). \([\alpha]_D^n = -236.3 \) (c = 1.0, CH_{2}Cl_{2}).

\((S)-3-\{(\text{benzyloxy)methyl}\}-6\text{-methyl}-2-(p\text{-toluenesulfonyl})\)-2,3-dihydropyridazine-4-carbaldehyde (4h). Following the general procedure 4h (82 mg, 0.21 mmol) was isolated by FC (n-hexane/EtOAc gradient from 19:1 to 7:3) in 69% yield starting from aldehyde 1h (53 mg, 0.30 mmol) and hydrazone 2 (144 mg, 0.60 mmol) in the presence of 3b (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. \(^1\)H NMR (300 MHz, CDCl_{3}) \( \delta \) 9.55 (s, 1H), 7.83 (d, \( J = 8.3 \) Hz, 2H), 7.40–7.17 (m, 5H), 7.14–7.07 (m, 2H), 6.47 (s, 1H), 5.63 (t, \( J = 4.4 \) Hz, 1H), 4.33–4.18 (m, 2H), 3.48–3.31 (m, 2H), 2.37 (s, 3H), 2.11 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl_{3}) \( \delta \) 189.8, 147.0, 144.1, 137.6, 136.2, 135.3, 132.1, 129.4, 128.2, 128.0, 127.5, 127.3, 73.0, 69.9, 48.8, 21.6, 21.1. IR: 1679.7, 1595.8, 1353.8, 1165.8, 1090.6 cm\(^{-1}\). MS (EI) m/z (%): 398 (M^+, 2), 355 (4), 281 (4), 241 (5), 207 (18), 171 (4), 121 (4), 107 (63), 91 (100), 77 (90), 65 (14), 51 (25). HRMS: Calculated for [C_{21}H_{23}N_{2}O_{4}S]^+: 399.1379 [(M+H)^+]; found: 399.1375. The ee was determined by HPLC using a Chiralpak IC column [n-hexane/i-PrOH (85:15)]; flow rate 1.0 mL/min; \( \tau_{\text{major}} = 73.07 \) min, \( \tau_{\text{minor}} = 62.73 \) min (96% ee). \([\alpha]_D^n = -103.8 \) (c = 1.0, CH_{2}Cl_{2}).
(R)-6-methyl-3-phenyl-2-(p-toluenesulfonfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4i). Following the general procedure 4i (52 mg, 0.15 mmol) was isolated by FC (n-hexane/EtOAc gradient from 19:1 to 7:3) in 49% yield starting from aldehyde 1i (76 µL, 0.60 mmol) and hydrazone 2i (72 mg, 0.30 mmol) in the presence of 3b (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ³H NMR (300 MHz, CDCl₃) δ 9.55 (s, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.23–7.14 (m, 1H), 7.14–7.08 (m, 4H), 7.03 (d, J = 8.2 Hz, 2H), 6.51 (s, 1H), 6.43 (s, 1H), 2.33 (s, 3H), 2.22 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 189.7, 145.7, 143.7, 138.3, 137.9, 135.6, 129.9, 128.9, 128.7, 128.5, 127.3, 127.9, 127.3, 52.8, 21.5, 21.2. IR: 1688.4, 1599.7, 1359.6, 1168.7 cm⁻¹. MS (EI) m/z (%): 354 (M+, 100), 327 (2), 281 (3), 226 (1), 199 (53), 171 (60), 155 (30), 144 (11), 115 (24), 91 (32), 65 (16). HRMS: Calculated for [C₁₉H₁₉N₂O₃S]⁺: 355.1116 [(M+H)⁺]; found: 355.1117. The ee was determined by HPLC using a Chiralpak IC column [n-hexane/i-PrOH (80:20)]; flow rate 1.0 mL/min; τ_major = 84.87 min, τ_minor = 45.38 min (89% ee). [α]D: -33.3 (c = 1.0, CH₂Cl₂).

(R)-6-methyl-3-(4-nitrophenyl)-2-(p-toluenesulfonfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4j). Following the general procedure 4j (62 mg, 0.16 mmol) was isolated by FC (n-hexane/EtOAc gradient from 19:1 to 7:3) in 52% yield starting from aldehyde 1j (108 mg, 0.60 mmol) and hydrazone 2j (72 mg, 0.30 mmol) in the presence of 3b (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ¹H NMR (300 MHz, CDCl₃) δ 9.55 (s, 1H), 7.95 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 6.79 (s, 1H), 6.54 (s, 1H), 6.54 (s, 1H), 2.36 (s, 3H), 2.25 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 189.5, 147.8, 146.0, 144.7, 144.6, 137.2, 137.3, 130.6, 129.3, 128.0, 127.8, 123.7, 123.5, 51.2, 21.5, 21.2. IR: 1681.6, 1597.7, 1521.6, 1346.1, 1303.6, 1166.7 cm⁻¹. MS (EI) m/z (%): 399 (M+, 100), 327 (2), 281 (14), 253 (9), 241 (70), 227 (77), 198 (66), 171 (60), 169 (37), 139 (16), 115 (21), 91 (69), 65 (21). HRMS: Calculated for [C₁₉H₁₈N₃O₅S]⁺: 400.0967 [(M+H)⁺]; found: 400.0984. The ee was determined by HPLC using a Chiralpak IC column [n-hexane/i-PrOH (80:20)]; flow rate 1.0 mL/min; τ_major = 103.45 min, τ_minor = 60.82 min (95% ee). [α]D: -96.7 (c = 1.0, CH₂Cl₂).

(R)-3-(4-methoxyphenyl)-6-methyl-2-(p-toluenesulfonfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4k). Following the general procedure 4k (69 mg, 0.18 mmol) was isolated by FC (n-hexane/EtOAc gradient from 19:1 to 7:3) in 60% yield starting from aldehyde 1k (98 mg, 0.60 mmol) and hydrazone 2k (72 mg, 0.30 mmol) in the presence of 3b (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ¹H NMR (300 MHz, CDCl₃) δ 9.53 (s, 1H), 7.41 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 6.79 (s, 1H), 6.53 (s, 1H), 6.53 (s, 1H), 2.35 (s, 3H), 2.24 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 189.4, 147.8, 146.0, 144.7, 144.6, 137.2, 135.3, 129.3, 128.0, 127.8, 123.7, 51.2, 21.5, 21.2. IR: 1681.6, 1597.7, 1521.6, 1346.1, 1303.6, 1166.7 cm⁻¹. MS (EI) m/z (%): 399 (M+, 100), 327 (2), 281 (14), 253 (9), 241 (70), 227 (77), 198 (66), 171 (60), 169 (37), 139 (16), 115 (21), 91 (69), 65 (21). HRMS: Calculated for [C₁₉H₂₈N₂O₅S]⁺: 432.0829 [(M+H)⁺]; found: 432.0827. The ee was determined by HPLC using a Chiralpak IC column [n-hexane/i-PrOH (80:20)]; flow rate 1.0 mL/min; τ_major = 60.82 min (95% ee). [α]D: -160.5 (c = 1.0, CH₂Cl₂).
Hz, 2H), 7.04 (d, J = 8.4 Hz, 4H), 6.61 (d, J = 8.7 Hz, 2H), 6.51 (s, 1H), 6.34 (s, 1H), 3.74 (s, 3H), 2.33 (s, 3H), 2.19 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 189.8, 160.0, 145.5, 143.5, 138.5, 135.7, 130.2, 129.6, 128.8, 127.9, 113.7, 55.3, 52.4, 21.5, 21.2. IR: 1682.6, 1608.3, 1354.8, 1168.7, 1085.7 cm$^{-1}$. MS (EI) m/z (%): 384 (M+, 100), 327 (2), 281 (6), 253 (5), 229 (50), 201 (44), 171 (15), 169 (37), 128 (11), 91 (35), 65 (14). HRMS: Calculated for [C$_{20}$H$_{21}$N$_{2}$O$_{4}$S]$^+$: 385.1222 [M+H]$^+$; found: 385.1237. The ee was determined by HPLC using a Chiralpak IC column [n-hexane/i-PrOH (80:20)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 133.94$ min, $\tau_{\text{minor}} = 77.78$ min (85% ee). $[\alpha]_D^{\text{rt}}$: +21.4 ($c = 1.0$, CH$_2$Cl$_2$).

(R)-3-(4-cyanophenyl)-6-methyl-2-(p-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4l). Following the general procedure 4l (82 mg, 0.22 mmol) was isolated by FC (n-hexane/EtOAc gradient from 19:1 to 1:1) in 72% yield starting from aldehyde 1l (94 mg, 0.60 mmol) and hydrazone 2 (72 mg, 0.30 mmol) in the presence of 3b (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. $^1$H NMR (300 MHz, CDCl$_3$) δ 9.55 (s, 1H), 7.48 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 6.55 (s, 1H), 2.38 (s, 3H), 2.22 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 189.5, 145.9, 144.4, 142.8, 137.2, 135.3, 132.3, 130.5, 129.2, 127.8, 127.8, 118.2, 112.4, 52.2, 21.6, 21.2. IR: 2228.3, 1677.8, 1595.8, 1357.6, 1165.8 cm$^{-1}$. MS (EI) m/z (%): 379 (M+, 100), 281 (2), 224 (59), 196 (59), 155 (20), 127 (16), 91 (55), 65 (19). HRMS: Calculated for [C$_{20}$H$_{18}$N$_{3}$O$_{3}$S]$^+$: 380.1069 [M+H]$^+$; found: 380.1063. The ee was determined by HPLC using a Chiralpak IC column [n-hexane/i-PrOH (80:20)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 148.17$ min, $\tau_{\text{minor}} = 81.53$ min (94% ee). $[\alpha]_D^{\text{rt}}$: -48.3 ($c = 1.0$, CH$_2$Cl$_2$).

(S)-6-methyl-3-(5-nitrofuran-2-yl)-2-(p-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4m). Following the general procedure 4m (64 mg, 0.16 mmol) was isolated by FC (n-hexane/EtOAc gradient from 19:1 to 1:1) in 55% yield starting from aldehyde 1m (94 mg, 0.60 mmol) and hydrazone 2 (72 mg, 0.30 mmol) in the presence of 3b (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. $^1$H NMR (300 MHz, CDCl$_3$) δ 9.61 (s, 1H), 7.65 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 6.70 (s, 1H), 2.34 (s, 3H), 2.29 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 188.6, 151.7, 151.6, 146.6, 144.7, 134.4, 134.0, 131.8, 129.1, 127.9, 111.3, 111.3, 45.2, 21.5, 21.2. IR: 1681.6, 1532.2, 1501.3, 1348.0, 1310.4, 1161.9 cm$^{-1}$. MS (EI) m/z (%): 379 (M+, 100), 281 (2), 224 (59), 196 (59), 155 (20), 127 (16), 91 (55), 65 (19). HRMS: Calculated for [C$_{17}$H$_{16}$N$_{3}$O$_{6}$S]$^+$: 390.0760 [(M+H)$^+$]; found: 390.0757. The ee was determined by HPLC using a Chiralpak AD-H column [n-hexane/i-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 76.54$ min, $\tau_{\text{minor}} = 59.32$ min (90% ee). $[\alpha]_D^{\text{rt}}$: +19.9 ($c = 1.0$, CH$_2$Cl$_2$).
Determination of the absolute configuration.

(R)-[6-methyl-3-(4-nitrophenyl)-2-(p-toluenesulfonyl)-2,3-
dihydropyridazin-4-yl]methanol (5j). To a solution of the
dihydropyridazine 4j (42 mg, 0.10 mmol) in methanol (3 mL), NaBH₄ (~50
mg) was added at 0 ºC. The reaction mixture was stirred at this temperature
for 20 minutes prior to the addition of a saturated solution of aqueous NH₄Cl (3 mL) and CH₂Cl₂ (5 mL)
and then stirred at room temperature 30 minutes more. The mixture was extracted with CH₂Cl₂ (3 x 10
mL) and the collected organic fractions were dried over Na₂SO₄, filtered and the solvents were removed
under reduced pressure. The crude was purified by FC (n-hexane/EtOAc 1:1) yielding the corresponding
alcohol 5j (32 mg, 0.08 mmol) in 76%. ¹H NMR (300 MHz, CDCl₃) δ 7.96 (d, J = 8.7 Hz, 2H), 7.42 (d, J
= 8.3 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.3 Hz, 2H), 6.04 (s, 1H), 5.93 (s, 1H), 4.19–4.01 (m,
2H), 2.32 (s, 3H), 2.13 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 148.4, 147.9, 144.2, 143.9, 143.6, 135.6,
128.9, 128.5, 127.6, 123.6, 114.0, 62.1, 55.0, 21.7, 21.4. IR: 3418.2, 1596.8, 1520.6, 1343.2, 1304.5,
1161.9 cm⁻¹. MS (EI) m/z (%): 401 (M⁺, 2), 385 (49), 355 (12), 281 (11), 253 (20), 230 (72), 207 (90),
184 (100), 171 (19), 139 (22), 115 (19), 91 (91), 65 (22). HRMS: Calculated for [C₁₉H₂₀N₃O₅S]⁺:
402.1124[(M+H)⁺]; found: 402.1139. M.p. (n-hexane/EtOAc): 188-190 ºC. The ee was determined by
HPLC using a Chiralpak AD-H column [n-hexane/i-PrOH (90:10)]; flow rate 1.0 mL/min; τ_major = 70.74
min, τ_minor = 112.60 min (93 % ee). [α]D²⁰: -47.5 (c = 1.0, CH₂Cl₂).

The absolute configuration of the dihydropyrazidine 5j was determined by single-crystal X-ray analysis.
The same stereochemistry was assumed for assigning the configuration of the rest of the compounds.

Figure S1: X-ray determined crystal structure.
NMR spectra of compound 2

Figure S2: NMR spectra of compound 2.
NMR spectra of compounds 4a-q

Figure S3: NMR spectra of compound 4a.
Figure S4: NMR spectra of compound 4b.
Figure S5: NMR spectra of compound 4c.
Figure S6: NMR spectra of compound 4d.
Figure S7: NMR spectra of compound 4e.
Figure S8: NMR spectra of compound 4f.
Figure S9: NMR spectra of compound 4g.
Figure S10: NMR spectra of compound 4h.
Figure S11: NMR spectra of compound 4i.
Figure S12: NMR spectra of compound 4j.
Figure S13: NMR spectra of compound 4k.
Figure S14: NMR spectra of compound 4l.
Figure S15: NMR spectra of compound 4m.
NMR spectra of compounds 5j

Figure S16: NMR spectra of compound 5j.
HPLC chromatograms of racemic and enantioenriched compounds 4a-m

Figure S17: HPLC chromatogram of compound 4a.
Figure S18: HPLC chromatogram of compound 4b.
Figure S19: HPLC chromatogram of compound 4c.
Figure S20: HPLC chromatogram of compound 4d.
Figure S21: HPLC chromatogram of compound 4e.
Figure S22: HPLC chromatogram of compound 4f.
Figure S23: HPLC chromatogram of compound 4g.
Figure S24: HPLC chromatogram of compound 4h.
Figure S25: HPLC chromatogram of compound 4i.
Figure S26: HPLC chromatogram of compound 4j.
Figure S27: HPLC chromatogram of compound 4k.
Figure S28: HPLC chromatogram of compound 4l.
Figure S29: HPLC chromatogram of compound **4m**.
HPLC chromatograms of racemic and enantioenriched compound 5j

Figure S30: HPLC chromatogram of compound 5j.