Supporting Information for

Chiral Sulfoxides as Metabolites of 2-Thioimidazole-based p38α Mitogen-Activated Protein Kinase Inhibitors: Enantioselective Synthesis and Biological Evaluation

Stefanie Bühler[†], *Marcia Goettert*[†], *Dieter Schollmeyer*[‡], *Wolfgang Albrecht*[§], *Stefan A. Laufer**[,†]

[†]Department of Pharmaceutical/Medicinal Chemistry, Eberhard-Karls-University Tübingen, Auf der Morgenstelle 8, 72076 Tübingen, Germany, [‡]University Mainz, Institute of Organic Chemistry, Duesbergweg 10-14, 55099 Mainz, Germany, and [§]c-a-i-r biosciences GmbH, Paul-Ehrlich-Str. 15, 72076 Tübingen, Germany

stefan.laufer@uni-tuebingen.de

Contents of Supporting Information

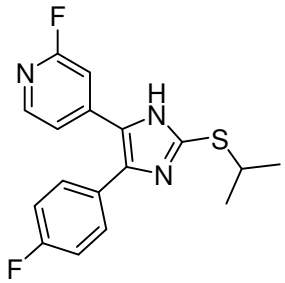
General Information: All reagents and solvents were of commercial quality and used without further purification. Melting points were determined on a Büchi Melting Point B-545 apparatus. ^{1}H- and ^{13}C-NMR spectra were generally collected on a Bruker Avance 200 at 200 MHz and 50 MHz or on a Bruker Avance 400 at 400 MHz and 100 MHz, respectively. Chemical shifts (δ) are reported in ppm. IR spectra were recorded by ATR technique on a Perkin–Elmer Spectrum One spectrophotometer. High-Resolution mass spectral analyses were performed on a Bruker APEX II spectrometer using electron spray ionisation (ESI) or on a Finnigan Sektorfield-mass spectrometer using electron impact (EI). Optical rotations were measured on a Perkin-Elmer Polarimeter 241 (λ = 589 nm, T = 20 °C, l = 1 dm, *c* in g/100 mL). TLC analyses were performed on fluorescent silica gel 60 plates from Merck. Spots were visualized under UV illumination at 254 and 365 nm. Flash column chromatography was performed over PharmPrep® 60CC silica gel (25-40 μm). The purity of the final compounds were determined by HPLC on a HPLC Hewlett-Packard HP 1090 Series II liquid chromatograph equipped with a UV diode array detector (DAD) (detection at 230 nm and 254 nm) using a Thermo Betasil C_8 column (150 mm × 4.6 mm, dp = 5 μm) or a ZORBAX Eclipse XDB-C_8 column (150 mm x 4.6 mm, dp = 5 μm), employing a gradient of 0.01 M KH_2PO_4 (pH = 2.3) and methanol as the solvent system with a flow rate of 1.5 mL/min. All final compounds have a purity of >95%. HPLC separation of the sulfoxide enantiomers was achieved on Daicel CHIRALPAK IA (250 mm x 4.6 mm, dp = 5 μm, CH_2Cl_2/MeOH/TEA 98: 2: 0.1) on an HP 1090 instrument using 0.8 mL/min flow rate and UV detection at 254 nm.

The following compounds were prepared according to common literature procedures: **5**[13; 23], **6a**[13; 24], **7a**[11; 25], **8a** and **9a**[26-28], (***S***)**-12a**, (***S***)**-12b**, (**S**)**-12c**, (***S***)**-12d**, (***S***)**-12e**, (***S***)**-12h**, (***S***)**-12l**, (***S***)**-12m** and (***S***)**-12n**[32-39]; commercially available L-DET, D-DET, *S*-BINOL and *R*-BINOL were used.

1. The Synthesis of Tri- and Tetrasubstituted 2-Thioimidazoles

General Procedure A: The reaction mixture, composed of the specific amine and the 2-thioimidazol derivative, was heated at T = 160 °C in a high pressure reactor from Berghof. The progress was monitored until HPLC analysis indicated complete conversion. After cooling to room temperature, an aqueous saturated solution of $NaHCO_3$ was added (pH = 8-9) and the mixture was extracted with EtOAc, dried over Na_2SO_4 and evaporated. The crude product was purified by recrystallization from an appropriate solvent.

2-Fluoro-4-(4-(4-fluorophenyl)-2-(isopropylthio)-1*H*-imidazol-5-yl)pyridine 6b

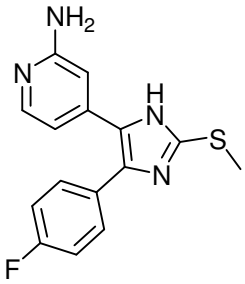


To a suspension of compound **5** (1.0 g, 3.5 mmol)) in 30.0 mL methanol was added initially K_2CO_3 (0.44 g, 3.15 mmol) and then isopropyl bromide (0.65 g, 5.25 mmol). The resulting mixture was heated at T = 65 °C for 18 h. After cooling the reaction to room temperature, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, EtOAc/PE 1:1) to yield 0.75 g (64.7%) of the beige product **6b**.

$C_{17}H_{15}F_2N_3S$ (M_r = 331.39 g/mol); **HPLC**: t_R = 7.77 min, purity: 99.7% (λ = 254 nm), t_R = 7.77 min, purity: 100.0% (λ = 230 nm); **mp** = 206.5 °C; **^{1}H-NMR** (200 MHz, Methanol-d^4): δ [ppm] = 1.27 (d, J = 6.8 Hz, 6H, $CH(CH_3)_2$), 3.43-3.63 (m, 1H, $CH(CH_3)_2$), 7.01 (s, 1H, C^3-$H_{Pyridine}$), 7.06-7.25 (m, 3H, C^3-$H_{4\text{-Fluorophenyl}}$, C^5-$H_{4\text{-Fluorophenyl}}$, C^5-$H_{Pyridine}$), 7.33-7.46 (m, 2H, C^2-$H_{4\text{-Fluorophenyl}}$, C^6-$H_{4\text{-Fluorophenyl}}$), 7.97 (d, J = 5.4 Hz, 1H, C^6-$H_{Pyridine}$); **^{13}C-NMR**

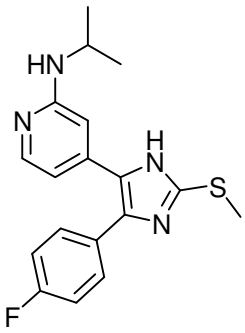
(50 MHz, Methanol-d^4): δ [ppm] = 22.3 (2C, CH(CH_3)$_2$), 39.6 (1C, CH(CH_3)$_2$), 105.9 (d, 1C, $^2J(C,F)$ = 38.2 Hz, $C^3_{Pyridine}$), 115.6 (d, 2C, $^2J(C,F)$ = 22.0 Hz, $C^3_{4\text{-Fluorophenyl}}$, $C^5_{4\text{-Fluorophenyl}}$), 118.9 (d, 1C, $^4J(C,F)$ = 3.8 Hz, $C^5_{Pyridine}$), 130.5 (d, 2C, $^3J(C,F)$ = 8.3 Hz, $C^2_{4\text{-Fluorophenyl}}$, $C^6_{4\text{-Fluorophenyl}}$), 146.9 (d, 1C, $^3J(C,F)$ = 14.9 Hz, $C^6_{Pyridine}$), 163.0 (d, 1C, $^1J(C,F)$ = 246.2 Hz, $C^4_{4\text{-Fluorophenyl}}$-F, quart.), 164.1 (d, 1C, $^1J(C,F)$ = 235.8 Hz, $C^2_{Pyridine}$-F, quart). The signals for $C^1_{4\text{-Fluorophenyl}}$, $C^4_{Pyridine}$, $C^2_{Imidazole}$, $C^4_{Imidazole}$ and $C^5_{Imidazole}$ are not seen in the spectrum; **FT-IR** (ATR, cm^{-1}): 2967, 2926, 1609, 1544, 1498, 1458, 1412, 1398, 1367, 1311, 1289, 1226, 1204, 1156, 1096, 1053, 1001, 976, 881, 838, 815, 743, 735, 713, 696, 684; **HR-MS** (ESI) calculated for $C_{17}H_{15}F_2N_3S$ [M+H^+] m/z = 332.1028, measured m/z = 332.1029.

4-(4-(4-Fluorophenyl)-2-(methylthio)-1*H*-imidazol-5-yl)pyridin-2-amine 7a



The reaction mixture, composed of compound **6a** (12.13 g, 40.0 mmol), NH_3 conc. (97.0 mL, 1600 mmol) and copper (I) iodide (1.14 g, 6.0 mmol), was heated at T = 180 °C for 18 h in a high pressure reactor from Berhof. After cooling the mixture to room temperature, water was added and the title compound **7a** precipitated as a beige solid, which was filtered off and washed with water and isopropylether (9.50 g, 79.1%). The spectral data were in agreement with those reported in the literature.[11, 25]

4-(4-(4-Fluorophenyl)-2-(methylthio)-1*H*-imidazol-5-yl)-*N*-isopropylpyridin-2-amine 8b

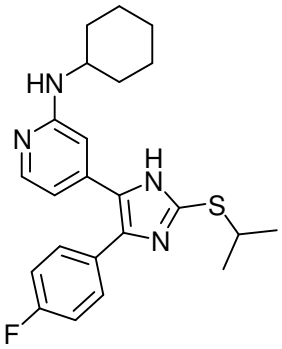


According to the General Procedure A, compound **6a** (20.0 g, 66.0 mmol) and isopropylamine (15.13 g, 251.0 mmol) were heated for 20 h at T = 160 °C in the high pressure reactor. After extraction with a solvent mixture of EtOAc/THF, the crude product was purified by recrystallization from EtOAc to yield 16.10 g (71.2%) of the pale yellow product **8b**.

$C_{18}H_{19}FN_4S$ (M_r = 342.44 g/mol); **HPLC**: t_R = 4.50 min, purity: 96.9% (λ = 254 nm), t_R = 4.50 min, purity: 97.5% (λ = 230 nm); **mp** = 218.2 °C. **^{1}H-NMR** (200 MHz, Methanol-d^4): δ [ppm] = 1.09 (d, J = 6.3 Hz, 6H, CH(CH_3)$_2$), 2.54 (s, 3H, SCH_3), 3.71-3.90 (m, 1H, CH(CH$_3$)$_2$), 6.39-6.50 (m, 2H, C^3-$H_{Pyridine}$, C^5-$H_{Pyridine}$), 6.99-7.13 (m, 2H, C^3-$H_{4\text{-Fluorophenyl}}$, C^5-$H_{4\text{-Fluorophenyl}}$), 7.31-7.45 (m, 2H, C^2-$H_{4\text{-Fluorophenyl}}$, C^6-$H_{4\text{-Fluorophenyl}}$), 7.74 (d, J = 5.9 Hz, 1H, C^6-$H_{Pyridine}$); **^{13}C-NMR** (50 MHz, Methanol-d^4): δ [ppm] = 15.4 (1C, SCH_3), 21.5 (2C, CH(CH_3)$_2$), 42.2 (1C, CH(CH$_3$)$_2$), 105.7 (1C, $C^3_{Pyridine}$), 110.0 (1C, $C^5_{Pyridine}$), 115.1 (d, 2C, $^2J(C,F)$ = 22.0 Hz, $C^3_{4\text{-Fluorophenyl}}$, $C^5_{4\text{-Fluorophenyl}}$), 130.2 (d, 2C, $^3J(C,F)$ = 8.2 Hz, $C^2_{4\text{-Fluorophenyl}}$, $C^6_{4\text{-Fluorophenyl}}$), 142.9 (1C, $C^4_{Pyridine}$, quart.), 146.7 (1C, $C^6_{Pyridin}$), 158.5 (1C, $C^2_{Pyridine}$, quart.), 162.5 (d, 1C, $^1J(C,F)$ = 244.9 Hz, $C^4_{4\text{-Fluorophenyl}}$-F). The signals for $C^1_{4\text{-Fluorophenyl}}$, $C^2_{Imidazole}$, $C^4_{Imidazole}$ and $C^5_{Imidazole}$ are not seen in the spectrum; **FT-IR** (ATR, cm^{-1}) = 2966, 1605, 1546, 1502, 1429, 1284, 1220, 1176, 1156, 1093, 973, 886, 837, 813, 738, 689; **HR-MS** (ESI) calculated for $C_{18}H_{19}FN_4S$ [M+H$^+$] m/z = 343.1387, measured m/z = 343.1386.

***N*-Cyclohexyl-4-(4-(4-fluorophenyl)-2-(isopropylthio)-1*H*-imidazol-5-yl)pyridin-2-amine**

8c

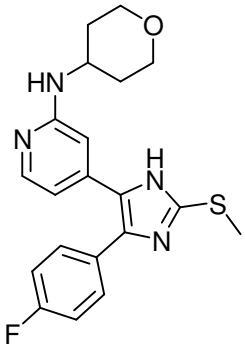


According to the General Procedure A, compound **6b** (5.0 g, 15.1 mmol) and cyclohexylamine (19.97 g, 197 mmol) were heated for 18 h at T = 160 °C in the high pressure reactor. After extraction with a solvent mixture of EtOAc/THF and evaporation, the title compound **8c** precipitated as a colorless solid of high analytical quality, which was filtered off and washed with isopropylether (4.10 g, 68.3%).

$C_{23}H_{27}FN_4S$ (M_r = 410.56 g/mol); **HPLC:** t_R = 7.06 min, purity: 99.7% (λ = 254 nm), t_R = 7.06 min, purity: 99.7% (λ = 230 nm); **mp** = 234.4 °C; **^{1}H-NMR** (200 MHz, DMSO-*d*^{6}): δ [ppm] = 0.96-1.24 (m, 5H, *CH*$_2$, Cyclohexyl); 1.31 (d, *J* = 6.7 Hz, 6H, CH(*CH*$_3$)$_2$), 1.46-1.74 (m, 3H, *CH*$_2$, Cyclohexyl), 1.75-1.92 (m, 2H, *CH*$_2$, Cyclohexyl), 3.38-3.54 (m, 1H, *CH*, Cyclohexyl), 3.60 (sept, *J* = 6.7 Hz, 1H, *CH*(CH$_3$)$_2$); 6.28 (d, *J* = 7.8 Hz, *NH*$_{Cyclohexyl}$), 6.40 (d, *J* =5.6 Hz, 1H, C^5-H$_{Pyridine}$), 6.51 (s, 1H, C^3-H$_{Pyridine}$), 7.21 (t, *J* = 8.8 Hz, 2H, C^3-H$_{4\text{-}Fluorophenyl}$, C^5-H$_{4\text{-}Fluorophenyl}$), 7.40-7.56 (m, 2H, C^2-H$_{4\text{-}Fluorophenyl}$, C^6-H$_{4\text{-}Fluorophenyl}$), 7.83 (d, *J* = 5.3 Hz, 1H, C^6-H$_{Pyridine}$), 11.85 (brs, 1H, *NH*$_{Imidazole}$); **^{13}C-NMR** (50 MHz, DMSO-*d*^{6}): δ [ppm] = 23.7 (2C, CH(*CH*$_3$)$_2$), 25.1 (2C, *CH*$_2$, C$^3_{Cyclohexyl}$, C$^5_{Cyclohexyl}$), 25.9 (1C, *CH*$_2$, C$^4_{Cyclohexyl}$), 33.1 (2C, *CH*$_2$, C$^2_{Cyclohexyl}$, C$^6_{Cyclohexyl}$), 38.9 (1C, *CH*(CH$_3$)$_2$), 49.3 (1C, *CH*, C$^1_{Cyclohexyl}$), 105.6 (1C, C$^3_{Pyridine}$), 109.9 (1C, C$^5_{Pyridine}$), 115.8 (d, 2C, ^{2}*J(C,F)* = 21.5 Hz, C$^3_{4\text{-}Fluorophenyl}$, C$^5_{4\text{-}Fluorophenyl}$), 130.5 (2C, C$^2_{4\text{-}Fluorophenyl}$, C$^6_{4\text{-}Fluorophenyl}$), 139.9 (1C, C$^4_{Pyridine}$, quart.), 148.1 (1C, C$^6_{Pyridine}$), 158.9 (1C, C$^2_{Pyridine}$, quart.), 161.9 (d, 1C, ^{1}*J(C,F)* = 242.9 Hz, C$^4_{4\text{-}Fluorophenyl}$-F, quart.); **FT-IR** (ATR, cm$^-$

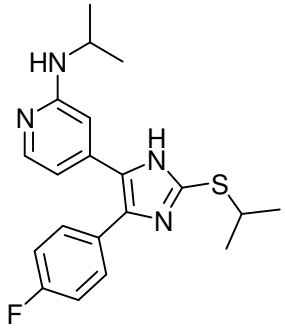
[1]) = 3351, 2932, 2851, 1608, 1547, 1494, 1450, 1384, 1352, 1306, 1262, 1220, 1152, 1091, 1053, 1017, 990, 970, 910, 888, 851, 837, 812, 743, 711, 699, 657; **HR-MS** (ESI) calculated for $C_{23}H_{27}FN_4S$ [M+H$^+$] m/z = 411.2013, measured m/z = 411.2013.

4-(4-(4-Fluorophenyl)-2-(methylthio)-1*H*-imidazol-5-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)pyridin-2-amine 8d



According to the General Procedure A, compound **6a** (19.0 g, 62.6 mmol)) and tetrahydro-2*H*-pyran-4-amine (19.39 g, 184.0 mmol) were heated for 24 h at T = 160 °C in the high pressure reactor. After extraction with a solvent mixture of EtOAc/MeOH and evaporation, the crude product was purified by recrystallization from EtOH/H_2O to achieve 16.15 g (68.5%) of the pale yellow product **8d**. The spectral data were in agreement with those reported in the literature.[23]

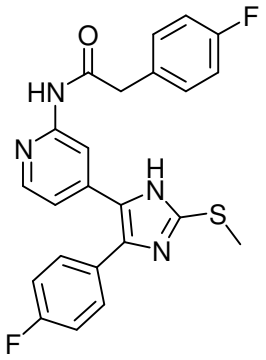
4-(4-(4-Fluorophenyl)-2-(isopropylthio)-1*H*-imidazol-5-yl)-*N*-isopropylpyridin-2-amine 8e



According to the General Procedure A, the title compound **8e** was obtained from compound **6b** (1.50 g, 4.6 mmol) and isopropylamine (6.38 g, 106.0 mmol) after heating for 27 h at T = 160 °C in the high pressure reactor and treatment with isopropylether as a colorless solid (1.30 g, 79.7%).

$C_{20}H_{23}FN_4S$ (M_r = 370.50 g/mol); **HPLC**: t_R = 5.82 min, purity: 96.2% (λ = 254 nm), t_R = 5.82 min, purity: 96.0% (λ = 230 nm); **mp** = 186.8 °C; **^{1}H-NMR** (200 MHz, DMSO-d^6): δ [ppm] = 1.07 (d, J = 5.3 Hz, 6H, SCH(CH_3)$_2$), 1.31 (d, J = 6.2 Hz, 6H, NHCH(CH_3)$_2$), 3.48-3.74 (m, 1H, SCH(CH_3)$_2$), 3.77- 4.10 (m, 1H, NHCH(CH_3)$_2$), 6.19- 6.64 (m, 2H, C^3-$H_{Pyridine}$, C^5-$H_{Pyridine}$), 7.02- 7.37 (m, 2H, C^3-$H_{4\text{-Fluorophenyl}}$, C^5-$H_{4\text{-Fluorophenyl}}$), 7.38- 7.63 (m, 2H, C^2-$H_{4\text{-Fluorophenyl}}$, C^6-$H_{4\text{-Fluorophenyl}}$); 7.74- 7.94 (m, 1H, C^6-$H_{Pyridine}$); 12.66 (brs, 1H, $NH_{Imidazole}$); **^{13}C-NMR** (50 MHz, DMSO-d^6): δ [ppm] = 23.0 (2C, SCH(CH_3)$_2$), 23.7 (2C, NHCH(CH_3)$_2$), 38.9 (1C, SCH(CH_3)$_2$), 42.0 (1C, NHCH(CH_3)$_2$), 105.9 (1C, $C^3_{Pyridine}$), 110.0 (1C, $C^5_{Pyridine}$), 115.7 (d, 2C, $^2J(C,F)$ = 22.2 Hz, $C^3_{4\text{-Fluorophenyl}}$, $C^5_{4\text{-Fluorophenyl}}$), 130.4 (2C, $C^2_{4\text{-Fluorophenyl}}$, $C^6_{4\text{-Fluorophenyl}}$), 139.9 (1C, $C^4_{Pyridine}$, quart.), 148.0 (1C, $C^6_{Pyridine}$), 159.0 (1C, $C^2_{Pyridine}$, quart.), 161.9 (d, 1C, $^1J(C,F)$ = 243.1 Hz, $C^4_{4\text{-Fluorophenyl}}$-F, quart.), The signals for $C^1_{4\text{-Fluorophenyl}}$, $C^2_{Imidazole}$, $C^4_{Imidazole}$ and $C^5_{Imidazole}$ are not seen in the spectrum; **FT-IR** (ATR, cm^{-1}) = 3408, 2970, 2934, 2868, 2801, 1602, 1546, 1505, 1430, 1385, 1364, 1325, 1314, 1283, 1243, 1220, 1184, 1155, 1124, 1111, 1089, 1058, 1023, 990, 973, 890, 862, 838, 821, 813, 734, 721, 703, 686; **HR-MS** (ESI) calculated for $C_{20}H_{23}FN_4S$ [M+H$^+$] m/z = 371.1700, measured m/z = 371.1700.

2-(4-Fluorophenyl)-*N*-(4-(4-(4-fluorophenyl)-2-(methylthio)-1*H*-imidazol-5-yl)pyridin-2-yl)acetamide 8f

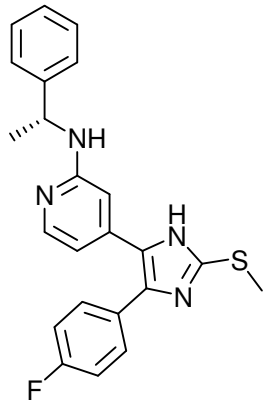


Under an argon atmosphere, *N*,*N*'-carbonyldiimidazole (2.59 g, 15.7 mmol) was added to a stirred solution of 4-fluorophenylacetic acid (2.31 g, 14.7 mmol) in 12.0 mL dry NMP at room temperature. When gas evolution ceased, compound **7a** (1.50 g, 5.0 mmol) was added and the resulting reaction mixture was stirred at T = 120 °C for 2 h. After cooling to room temperature, an aqueous saturated solution of $NaHCO_3$ was added (pH = 8-9) and the mixture was extracted with EtOAc, dried over Na_2SO_4 and concentrated *in vacuo*. The title compound **8f** was achieved as a yellow solid (1.56 g, 72.8%) of high analytical quality without further purification.

$C_{23}H_{18}F_2N_4OS$ (M_r = 436.49 g/mol); **HPLC:** t_R = 7.67 min, purity: 99.6% (λ = 254 nm), t_R = 7.67 min, purity: 99.6% (λ = 230 nm); **mp** = 197.1 °C; **^{1}H-NMR** (200 MHz, DMSO-d^6): δ [ppm] = 2.59 (s, 3H, SCH_3), 3.67 (s, 2H, CH_2), 6.99 (d, J = 5.1 Hz, 1H, C^5-$H_{Pyridine}$), 7.06-7.53 (m, 8H, C^2-$H_{4\text{-Fluorophenyl}}$, C^3-$H_{4\text{-Fluorophenyl}}$, C^5-$H_{4\text{-Fluorophenyl}}$, C^6-$H_{4\text{-Fluorophenyl}}$, C^2-$H_{4\text{-Fluorophenylacetamide}}$, C^3-$H_{4\text{-Fluorophenylacetamide}}$, C^5-$H_{4\text{-Fluorophenylacetamide}}$, C^6-$H_{4\text{-Fluorophenylacetamide}}$), 8.11 (d, J = 5.3 Hz, 1H, C^6-$H_{Pyridine}$), 8.29 (s, 1H, C^3-$H_{Pyridine}$), 10.58 (s, 1H, *NH*CO), 12.69 (s, 1H, $NH_{Imidazole}$); **^{13}C-NMR** (50 MHz, DMSO-d^6): δ [ppm] = 15.4 (1C, SCH_3), 42.4 (1C, CH_2), 110.9 (1C, $C^3_{Pyridine}$), 115.3 (d, 2C, $^2J(C,F)$ = 21.0 Hz, $C^3_{4\text{-Fluorophenylacetamide}}$, $C^5_{4\text{-Fluorophenylacetamide}}$), 116.2 (d, 2C, $^2J(C,F)$ = 21.3 Hz, $C^3_{4\text{-Fluorophenyl}}$, $C^5_{4\text{-Fluorophenyl}}$), 116.9 (1C, $C^5_{Pyridine}$), 126.9 (1C, $C^1_{4\text{-Fluorophenyl}}$, quart.), 130.5 (1C, $C^5_{Imidazole}$, quart.), 131.1 (d, 2C, $^2J(C,F)$

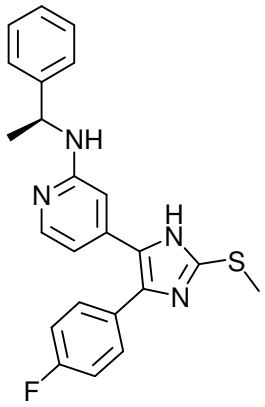
= 8.5 Hz, $C^2_{4\text{-Fluorophenyl}}$, $C^6_{4\text{-Fluorophenyl}}$), 131.3 (d, 2C, $^3J(C,F)$ = 8.0 Hz, $C^2_{4\text{-Fluorophenylacetamide}}$, $C^6_{4\text{-Fluorophenylacetamide}}$), 132.4 (d, 1C, $^4J(C,F)$ = 3.0 Hz, $C^1_{4\text{-Fluorophenylacetamide}}$, quart.), 134.7 (1C, $C^4_{\text{Imidazole}}$, quart), 142.6 (1C, $C^2_{\text{Imidazole}}$, quart), 144.2 (1C, C^4_{Pyridine}, quart.), 148.0 (1C, C^6_{Pyridine}), 152.8 (1C, C^2_{Pyridine}, quart.), 161.5 (d, 1C, $^1J(C,F)$ = 240.7 Hz, $C^4_{4\text{-Fluorophenylacetamide}}$-F, quart.), 162.3 (d, 1C, $^1J(C,F)$ = 246.0 Hz, $C^4_{4\text{-Fluorophenyl}}$-F, quart.), 170.0 (1C, *C*=*O*, quart.); **FT-IR** (ATR, cm^{-1}) = 3279, 3074, 3044, 2931, 2878, 1694, 1608, 1548, 1500, 1457, 1420, 1366, 1319, 1286, 1256, 1224, 1156, 1133, 1109, 1094, 998, 980, 972, 960, 895, 834, 817, 797, 783, 742, 704, 689, 655; **HR-MS** (ESI) calculated for $C_{23}H_{18}F_2N_4OS$ [M+H^+] m/z = 437.1242, measured m/z = 437.1246.

4-(4-(4-Fluorophenyl)-2-(methylthio)-1*H*-imidazol-5-yl)-*N*-((*R*)-1-phenylethyl)pyridin-2-amine 8g



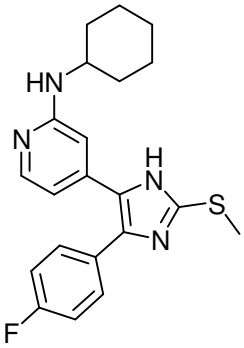
According to the General Procedure A, compound **6a** (0.61 g, 2.0 mmol) and (*R*)-(+)-1-phenylethylamine (0.68 g, 5.47 mmol) were heated for 30 h at T = 160 °C in the high pressure reactor. After extraction with EtOAc and evaporation, the crude product was purified by flash chromatography (silica gel, EtOAc 100%) to achieve 0.45 g (61.6%) of the yellow product **8g**. The spectral data were in agreement with those reported in the literature.[13]

4-(4-(4-Fluorophenyl)-2-(methylthio)-1*H*-imidazol-5-yl)-*N*-((*S*)-1-phenylethyl)pyridin-2-amine 8h



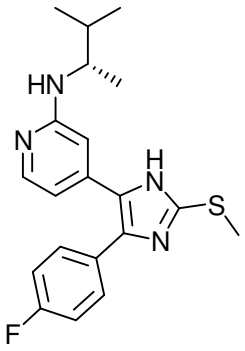
According to the General Procedure A, compound **6a** (13.35 g, 44.0 mmol) and (*S*)-(-)-1-phenylethylamine (36.45 g, 294.80 mmol) were heated for 48 h at T = 160 °C in the high pressure reactor. After extraction with EtOAc and evaporation, the crude product was purified by flash chromatography on silica gel (EtOAc/hexane 7:3) to achieve 13.54 g (76.1%) of the pale yellow product **8h**. The spectral data were in agreement with those reported in the literature.[13]

***N*-Cyclohexyl-4-(4-(4-fluorophenyl)-2-(methylthio)-1*H*-imidazol-5-yl)pyridin-2-amine 8i**



According to the General Procedure A, compound **6a** (1.21 g, 4.0 mmol) and cyclohexylamine (3.97 g, 40.0 mmol) were heated for 24 h at T = 160 °C in the high pressure reactor. After extraction with EtOAc and evaporation, the crude product was purified by flash chromatography on silica gel (EtOAc/DCM 1:1) to achieve 0.76 g (49.7%) of the colorless product **8i**. The spectral data were in agreement with those reported in the literature.[10]

4-(4-(4-Fluorophenyl)-2-(methylthio)-1*H*-imidazol-5-yl)-*N*-((*S*)-3-methylbutan-2-yl)pyridin-2-amine 8j

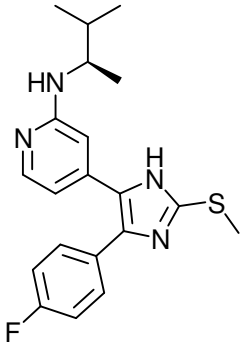


According to the General Procedure A, compound **6a** (2.0 g, 6.60 mmol) and (*S*)-(+)-3-methyl-2-butylamine (2.47 g, 27.7 mmol) were heated for 20 h at T = 160 °C in the high pressure reactor. After extraction with EtOAc, the crude product was purified by flash chromatography on silica gel (EtOAc/hexane 2:3) to yield 1.40 g (57.3%) of the pale yellow product **8j**.

$C_{20}H_{23}FN_4S$ (M_r = 370.49 g/mol); **HPLC:** t_R = 5.80 min, purity: 99.0% (λ = 254 nm), t_R = 5.80 min, purity: 98.9% (λ = 230 nm). **$[\alpha]^{20}_D$** = + 24.71 (*c* = 0.526 in Methanol); **mp** = 130.4 °C; **^{1}H-NMR** (Methanol-d^4, 400 MHz) δ = 0.82-0.97 (m, 6H, CH(CH_3)$_2$), 1.08 (d, *J* = 6.6 Hz, 3H, NHCHCH_3), 1.65-1.81 (m, 1H, CH(CH$_3$)$_2$), 2.63 (s, 3H, S-CH_3), 3.44-3.57 (m, 1H, NHCHCH$_3$) 6.46-6.60 (m, 2H, C^5-H$_{Pyridine}$ and C^3-H$_{Pyridine}$), 7.14 (t, *J* = 8.5 Hz, 2H, C^3-H$_{4\text{-Fluorophenyl}}$, C^5-H$_{4\text{-Fluorophenyl}}$) 7.40-7.51 (m, 2H, C^2-H$_{4\text{-Fluorophenyl}}$, C^6-H$_{4\text{-Fluorophenyl}}$), 7.80 (d, *J* = 5.1 Hz, 1H, C^6-H$_{Pyridine}$); **^{13}C-NMR** (Methanol-d^4, 100 MHz) δ = 16.9 (1C, S-CH$_3$), 17.3 (1C, CH(CH_3)$_2$), 18.4 (1C, NHCHCH_3), 19.5 (1C, CH(CH_3)$_2$), 34.0 (1C, CH(CH$_3$)$_2$), 53.1 (1C, NHCHCH$_3$), 107.0 (1C, C$^3_{Pyridine}$), 111.4 (1C, C$^5_{Pyridine}$), 116.6 (d, 2C, $^2J(C,F)$ = 21.8 Hz, C$^3_{4\text{-Fluorophenyl}}$, C$^5_{4\text{-Fluorophenyl}}$), 131.8 (2C, $^3J(C,F)$ = 8.0 Hz, C$^2_{4\text{-Fluorophenyl}}$, C$^6_{4\text{-Fluorophenyl}}$), 144.5 (1C, C$^4_{Pyridine}$, quart.), 148.0 (1C, C$^6_{Pyridine}$), 160.2 (1C, C$^2_{Pyridine}$, quart.), 164.1 (d, 1C, $^1J(C,F)$ = 245.0 Hz, C$^4_{4\text{-Fluorophenyl}}$-F, quart.); **FT-IR** (ATR, cm^{-1}); 3056, 2961, 2927, 2871, 1650, 1606, 1576, 1546, 1517, 1503, 1433, 1388, 1369, 1307, 1294, 1221, 1183, 1156, 1094,

1042, 1013, 979, 904, 837, 813, 738, 703, 688, 657; **HR-MS** calculated for $C_{20}H_{23}FN_4S$ m/z = 370.1622 , measured m/z = 370.1629.

4-(4-(4-Fluorophenyl)-2-(methylthio)-1*H*-imidazol-5-yl)-*N*-((*R*)-3-methylbutan-2-yl)pyridin-2-amine 8k

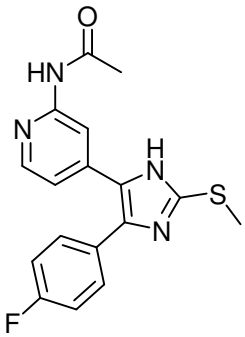


According to the General Procedure A, **6a** (0.76 g, 2.5 mmol) and (*R*)-(-)-3-methyl-2-butylamine (0.67 g, 7.5 mmol) were heated for 24 h at T = 160 °C in the high pressure reactor. After extraction with EtOAc, the crude product was purified by flash chromatography on silica gel (EtOAc/hexane 2:3) to yield 0.56 g (60.5%) of the pale yellow product **8k**.

$C_{20}H_{23}FN_4S$ (M_r = 370.49 g/mol); **HPLC:** t_R = 5.96 min, purity: 98.8% (λ = 254 nm), t_R = 5.96 min, purity: 99.5% (λ = 230 nm); **$[\alpha]^{20}_D$** = -20.74 (*c* = 0.266 in Methanol); **mp** = 111.2 °C; **^{1}H-NMR** (Methanol-d^4, 400 MHz) δ = 0.85-0.97 (m, 6H, CH(CH_3)$_2$), 1.09 (d, *J* = 6.6 Hz, 3H, NHCHCH_3), 1.67-1.80 (m, 1H, CH(CH$_3$)$_2$), 2.63 (s, 3H, S-CH_3), 3.46-3.56 (m, 1H, NHCHCH$_3$), 6.48-6.63 (m, 2H, C^5-$H_{Pyridine}$ and C^3-$H_{Pyridine}$), 7.16 (t, *J* = 8.3 Hz, 2H, C^3-$H_{4\text{-Fluorophenyl}}$, C^5-$H_{4\text{-Fluorophenyl}}$), 7.42-7.52 (m, 2H, C^2-$H_{4\text{-Fluorophenyl}}$, C^6-$H_{4\text{-Fluorophenyl}}$), 7.80 (d, *J* = 4.6 Hz, 1H, C^6-$H_{Pyridine}$); **^{13}C-NMR** (Methanol-d^4, 100 MHz) δ = 16.8 (1C, S-CH$_3$), 17.3 (1C, CH(CH_3)$_2$), 18.4 (1C, NHCHCH_3), 19.5 (1C, CH(CH_3)$_2$), 34.0 (1C, CH(CH$_3$)$_2$), 52.2 (1C, NHCHCH$_3$), 107.1 (1C, $C^3_{Pyridine}$), 111.4 (1C, $C^5_{Pyridine}$), 116.7 (d, 2C, $^2J(C,F)$ = 21.1 Hz, $C^3_{4\text{-Fluorophenyl}}$, $C^5_{4\text{-Fluorophenyl}}$), 131.8 (2C, $^3J(C,F)$ = 8.0 Hz, $C^2_{4\text{-Fluorophenyl}}$, $C^6_{4\text{-Fluorophenyl}}$), 144.6 (1C, $C^4_{Pyridine}$, quart.), 148.0 (1C, $C^6_{Pyridine}$), 159.9 (1C, $C^2_{Pyridine}$, quart.),

164.1 (d, 1C, $^{1}J(C,F)$ = 242.1 Hz, $C^{4}_{4\text{-Fluorophenyl}}$-F, quart.); **FT-IR** (ATR, cm^{-1}): 2961, 2928, 2871, 1649, 1606, 1577, 1546, 1518, 1503, 1433, 1389, 1369, 1307, 1221, 1183, 1157, 1094, 1041, 979, 906, 838, 813, 739, 702, 689; **HR-MS** calculated for $C_{20}H_{23}FN_4S$ m/z = 370.1622, measured m/z = 370.1620.

***N*-(4-(4-(4-Fluorophenyl)-2-(methylthio)-1*H*-imidazol-5-yl)pyridin-2-yl)acetamide 8l**



Compound **7a** (0.51 g, 1.70 mmol) was dissolved in 5.0 mL pyridine. The solution was cooled in an ice bath, and acetylchloride (0.47 g, 6.0 mmol) was added dropwise. The resulting mixture was stirred at T = 0- 5 °C. After 1 h, the solution was allowed to warm to room temperature and an aqueous solution of $NaHCO_3$ was added. The aqueous/organic mixture was extracted with EtOAc, dried over Na_2SO_4 and the solvents of the combined organic phases were removed under reduced pressure. The crude product was purified by flash chromatography (silica gel, EtOAc/EtOH 9/1) to obtain 0.3 g (52.4%) of the yellow solid **8l**.

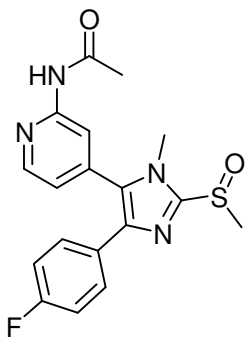
$C_{17}H_{15}FN_4OS$ (M_r = 342.39 g/mol); **HPLC:** t_R = 5.10 min, purity: 98.3% (λ = 254 nm), t_R = 5.10 min, purity: 98.6% (λ = 230 nm); **mp** = 206.5 °C; **^{1}H-NMR** (Methanol-d^4, 400 MHz) δ = 2.14 (s, 3H, CO-CH_3), 2.65 (s, 3H, S-CH_3), 7.11-7.19 (m, 3H, C^{5}-$H_{Pyridine}$ and C^{3}-$H_{4\text{-Fluorophenyl}}$, C^{5}-$H_{4\text{-Fluorphenyl}}$), 7.40-7.52 (m, 2H, C^{2}-$H_{4\text{-Fluorophenyl}}$, C^{6}-$H_{4\text{-Fluorophenyl}}$), 8.05-8.22 (m, 2H, C^{6}-$H_{Pyridine}$ and C^{3}-$H_{Pyridine}$); **^{13}C-NMR** (Methanol-d^4, 100 MHz) δ = 16.6 (1C, S-CH_3), 23.9 (1C, CO-CH_3), 113.2 (1C, $C^{3}_{Pyridine}$), 116.8 (d, 2C, $^{2}J(C,F)$ = 21.8 Hz, $C^{3}_{4\text{-Fluorophenyl}}$, $C^{5}_{4\text{-Fluorophenyl}}$), 118.9 (1C, $C^{5}_{Pyridine}$), 129.0 (1C, $C^{1}_{4\text{-Fluorophenyl}}$, quart.), 131.7 (2C,

$^{3}J(C,F)$ = 8.0 Hz, $C^{2}_{4\text{-Fluorophenyl}}$, $C^{6}_{4\text{-Fluorophenyl}}$), 145.1 (1C, C^{4}_{Pyridine}, quart.), 148.9 (1C, C^{6}_{Pyridine}), 153.3 (1C, C^{2}_{Pyridine}, quart.), 164.2 (d, 1C, $^{1}J(C,F)$ = 245.7 Hz, $C^{4}_{4\text{-Fluorophenyl}}$-F, quart.) 172.0 (1C, C=O, quart); **FT-IR** (ATR, cm^{-1}): 3017, 2927, 2849, 1675, 1643, 1608, 1547, 1503, 1412, 1369, 1315, 1283, 1267, 1221, 1177, 1157, 1094, 1015, 996, 968, 889, 836, 814, 732, 696, 683; **HR-MS** calculated for $C_{17}H_{15}FN_4OS$ m/z = 342.0945, measured m/z = 342.0978.

2. The Synthesis of the Racemic Sulfoxides

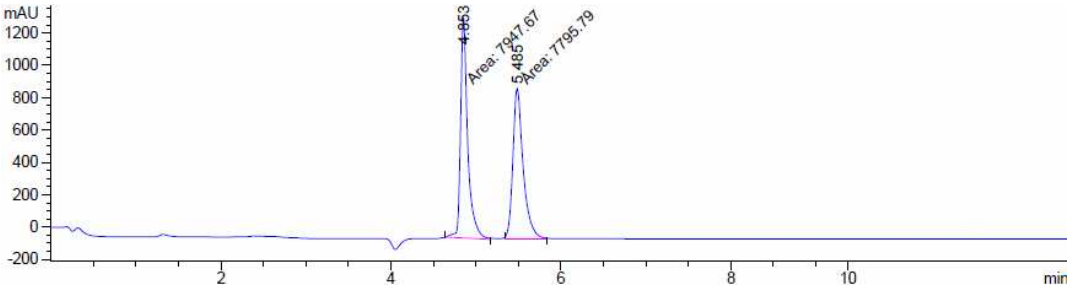
General Procedure B: The respective 2-thioimidazole derivative was dissolved in THF and water was added. The mixture was cooled in an ice bath, and an aqueous solution of potassium peroxomonosulfate (Oxone®) was added dropwise. The resulting mixture was stirred at T = 0 °C. The progress was monitored until HPLC analysis indicated complete conversion. After reaction completion, the solution was allowed to warm to room temperature and an aqueous solution of $NaHCO_3$ (pH = 8) was added. The aqueous/organic mixture was extracted with EtOAc, dried over Na_2SO_4 and the solvents of the combined organic phases were removed under reduced pressure. The crude product was purified by recrystallization from an appropriate solvent or by flash chromatography.

***N*-(4-(4-(4-Fluorophenyl)-1-methyl-2-(methylsulfinyl)-1*H*-imidazol-5-yl)pyridin-2-yl)acetamide 9a**



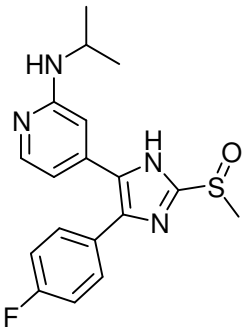
The synthesis and the spectral data for the tetrasubstituted 2-thioimidazole **9a** are known from the literature.[26-28]

enantioselective, analytical HPLC:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.853	MM	0.0958	7947.67187	1383.00684	50.4824
2	5.485	MM	0.1392	7795.78564	933.31146	49.5176

4-(4-(4-Fluorophenyl)-2-(methylsulfinyl)-1*H*-imidazol-5-yl)-*N*-isopropylpyridin-2-amine 9b

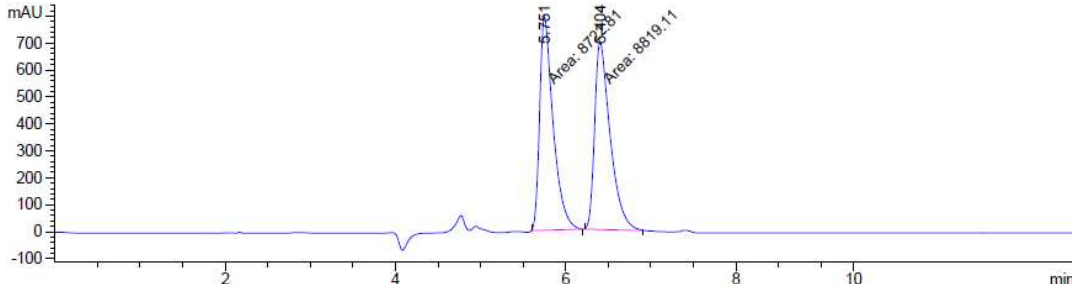


According to the General Procedure B, the title compound **9b** was obtained by the sulfoxidation of compound **8b** (9.31 g, 27.2 mmol), dissolved in 177.0 mL THF, with an aqueous solution of potassium peroxomonosulfate (Oxone®) (8.76 g, 14.3 mmol in 183 mL water) after stirring for 2 h at T = 0 °C and recrystallization from EtOAc as a beige solid (7.97 g, 81.9%).

$C_{18}H_{19}FN_4OS$ (M_r = 358.44 g/mol); **HPLC**: t_R = 3.12 min, purity: 98.2% (λ = 254 nm), t_R = 3.12 min, purity: 98.1% (λ = 230 nm); **mp** = 214.5 °C; **^{1}H-NMR** (200 MHz, DMSO-d^6):

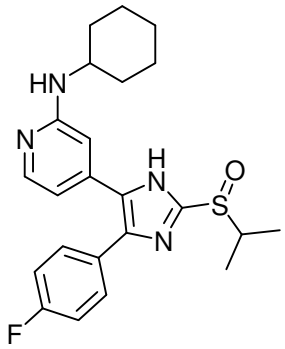
δ [ppm] = 1.10 (d, *J* = 6.3 Hz, 6H, NHCH(*CH*$_3$)$_2$), 3.07 (s, 3H, SO*CH*$_3$), 3.74-4.07 (m, 1H, *CH*(CH$_3$)$_2$), 6.34 (s, 1H, *NH*CH(CH$_3$)$_2$, exchangeable with D$_2$O), 6.42 (d, *J* = 5.2 Hz, 1H, C^5-H$_{Pyridine}$), 6.58 (s, 1H, C^3-H$_{Pyridine}$), 7.26 (t, *J* = 8.6 Hz, 2H, C^3-H$_{4\text{-Fluorophenyl}}$, C^5-H$_{4\text{-Fluorophenyl}}$), 7.42-7.63 (m, 2H, C^2-H$_{4\text{-Fluorophenyl}}$, C^6-H$_{4\text{-Fluorophenyl}}$), 7.89 (d, *J* = 5.1 Hz, 1H, C^6-H$_{Pyridine}$), 13.73 (s, 1H, *NH*$_{Imidazole}$, exchangeable with D$_2$O); **^{13}C-NMR** (50 MHz, DMSO-*d*^{6}): δ [ppm] = 23.0 (2C, CH(*CH*$_3$)$_2$), 39.3 (1C, SO*CH*$_3$), 42.0 (1C, *CH*(CH$_3$)$_2$), 106.3 (1C, C$^3_{Pyridine}$), 110.1 (1C, C$^5_{Pyridine}$), 115.9 (d, 2C, ^{2}*J(C,F)* = 21.6 Hz , C$^3_{4\text{-Fluorophenyl}}$, C$^5_{4\text{-Fluorophenyl}}$); 128.2 (1C, C$^1_{4\text{-Fluorophenyl}}$, quart.), 130.8 (d, 2C, ^{3}*J(C,F)* = 7.6 Hz , C$^2_{4\text{-Fluorophenyl}}$, C$^6_{4\text{-Fluorophenyl}}$), 140.4 (1C, C$^2_{Imidazole}$, quart.), 148.2 (1C, C$^4_{Pyridine}$, quart.), 148.5 (1C, C$^6_{Pyridine}$), 159.0 (1C, C$^2_{Pyridine}$, quart.), 162.3 (d, 1C, ^{1}*J(C,F)* = 244.0 Hz, C$^4_{4\text{-Fluorophenyl}}$-F, quart.). The signals for C$^5_{Imidazole}$ and C$^4_{Imidazole}$ are not seen in the spectrum; **FT-IR** (ATR, cm^{-1}) = 3299, 2971, 2942, 2871, 1609, 1550, 1499, 1461, 1436, 1420, 1405, 1381, 1332, 1306, 1283, 1221, 1193, 1175, 1159, 1128, 1097, 1049, 1015, 987, 965, 894, 852, 841, 812, 743, 723, 707, 681, 656. **HR-MS** (ESI) calculated for $C_{18}H_{19}FN_4OS$ [M+H$^+$] m/z = 359.1336, measured m/z = 359.1336.

enantioselective, analytical HPLC:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.751	MM	0.1828	8722.81152	795.39435	49.7255
2	6.404	MM	0.2107	8819.11035	697.54224	50.2745

***N*-Cyclohexyl-4-(4-(4-fluorophenyl)-2-(isopropylsulfinyl)-1*H*-imidazol-5-yl)pyridin-2-amine 9c**

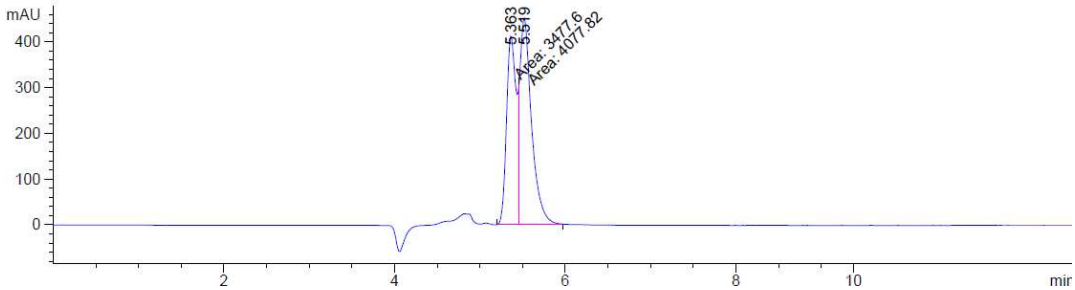


According to the General Procedure B, the title compound **9c** was obtained by the sulfoxidation of compound **8c** (0.31 g, 0.76 mmol), dissolved in 15.0 mL THF and 3.0 mL H_2O, with an aqueous solution of potassium peroxomonosulfate (Oxone®) (0.25 g, 0.4 mmol in 4.5 mL H_2O) after stirring for 3.5 h at T = 0 °C as a colorless solid without further purification (0.21 g, 65.8%).

$C_{23}H_{27}FN_4OS$ (M_r = 426.56 g/mol); **HPLC**: t_R = 5.55 min, purity: 98.7% (λ = 254 nm), t_R = 5.55 min, purity: 98.6% (λ = 230 nm); **mp** = 190.3°C; **^{1}H-NMR** (200 MHz, DMSO-d^6): δ [ppm] = 0.96-1.24 (m, 7H, CH_2, Cyclohexyl and SOCH(CH_3)$_2$), 1.19-1.34 (4H, CH_2, Cyclohexyl and SOCH(CH_3)$_2$), 1.44-1.90 (m, 5H, CH_2, Cyclohexyl), 3.33-3.62 (m, 2H, *CH*, Cyclohexyl and SO*CH*(CH_3)$_2$), 6.29 (brs, 1H, $NH_{Cyclohexyl}$, exchangeable with D_2O), 6.39 (d, J = 5.6 Hz, 1H, C^5-$H_{Pyridine}$), 6.53 (s, 1H, C^3-$H_{Pyridine}$), 7.12-7.34 (m, 2H, C^3-$H_{4\text{-Fluorophenyl}}$, C^5-$H_{4\text{-Fluorophenyl}}$), 7.40-7.56 (m, 2H, C^2-$H_{4\text{-Fluorophenyl}}$, C^6-$H_{4\text{-Fluorophenyl}}$), 7.83 (s, 1H, C^6-$H_{Pyridine}$), 13.66 (s, 1H, $NH_{Imidazole}$, exchangeable with D_2O); **^{13}C-NMR** (50 MHz, DMSO-d^6): δ [ppm] = 15.2 (1C, SOCH(CH_3)$_2$), 15.6 (1C, SOCH(CH_3)$_2$), 25.1 (2C, CH_2, $C^3_{Cyclohexyl}$, $C^5_{Cyclohexyl}$), 25.8 (1C, CH_2, $C^4_{Cyclohexyl}$), 33.0 (2C, CH_2, $C^2_{Cyclohexyl}$, $C^6_{Cyclohexyl}$), 49.3 (1C, SO*CH*(CH_3)$_2$), 53.2 (1C, *CH*, $C^1_{Cyclohexyl}$), 106.0 (1C, $C^3_{Pyridine}$), 110.1 (1C, $C^5_{Pyridine}$), 115.9 (d, 2C, $^2J(C,F)$ = 21.6 Hz, $C^3_{4\text{-Fluorophenyl}}$, $C^5_{4\text{-Fluorophenyl}}$), 130.9 (2C, $C^2_{4\text{-Fluorophenyl}}$, $C^6_{4\text{-Fluorophenyl}}$), 146.1 (1C, $C^4_{Pyridin}$, quart.), 148.1 (1C, $C^6_{Pyridine}$), 158.7 (1C, $C^2_{Pyridine}$, quart.). The signals for

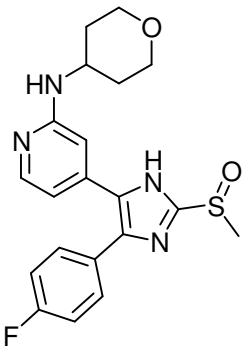
$C^4_{4\text{-Fluorophenyl}}$-F, $C^1_{4\text{-Fluorophenyl}}$, $C^2_{\text{Imidazole}}$, $C^4_{\text{Imidazole}}$ and $C^5_{\text{Imidazole}}$ are not seen in the spectrum; **FT-IR** (ATR, cm^{-1}) = 3298, 2932, 2855, 1608, 1551, 1498, 1455, 1407, 1370, 1344, 1322, 1304, 1292, 1263, 1221, 1187, 1152, 1126, 1087, 1056, 1041, 1029, 987, 978, 964, 931, 911, 887, 841, 807, 744, 722, 709, 689, 655. **HR-MS** (ESI) calculated for $C_{23}H_{27}FN_4OS$ $[M+H^+]$ m/z = 427.1962, measured m/z = 427.1964.

enantioselective, analytical HPLC:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.363	MF	0.1400	3477.59668	413.96536	46.0279
2	5.519	FM	0.1503	4077.81714	452.16553	53.9721

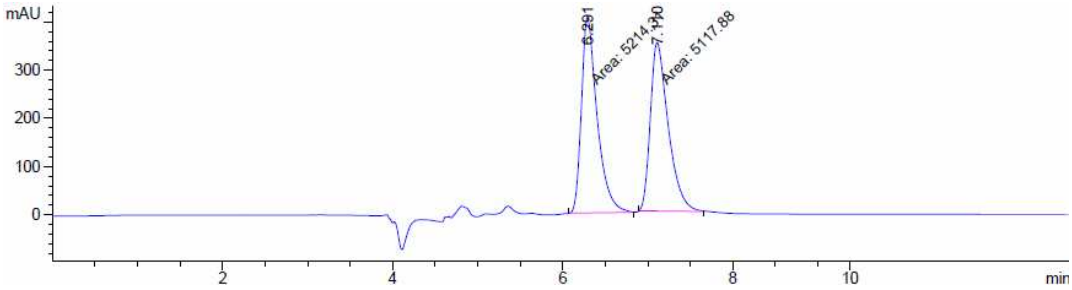
4-(4-(4-Fluorophenyl)-2-(methylsulfinyl)-1*H*-imidazol-5-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)pyridin-2-amine 9d



According to the General Procedure B, the title compound **9d** was obtained by the sulfoxidation of compound **8d** (8.0 g, 20.8 mmol), dissolved in 154.0 mL THF and 52.0 mL H_2O, with an aqueous solution of potassium peroxomonosulfate (Oxone®) (7.0 g, 11.4 mmol in 77.0 mL H_2O) after stirring for 2 h at T = 0 °C and recrystallization from methanol as a colorless solid (6.86 g, 85.7%).

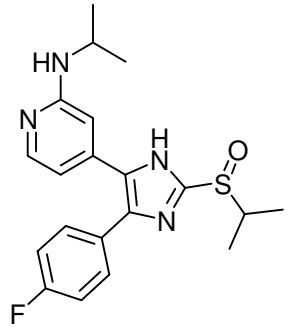
$C_{20}H_{21}FN_4O_2S$ (M_r = 400.48 g/mol); **HPLC**: t_R = 2.67 min, purity: 99.1% (λ = 254 nm), t_R = 2.67 min, purity: 98.8% (λ = 230 nm); **mp** = 230.0 °C; **^{1}H-NMR** (200 MHz, DMSO-d^6): δ [ppm] = 1.24-1.53 (m, 2H, C^3-$H_{Tetrahydropyranyl}$, C^5-$H_{Tetrahydropyranyl}$), 1.67-1.90 (m, 2H, C^3-$H_{Tetrahydropyranyl}$, C^5-$H_{Tetrahydropyranyl}$), 3.06 (s, 3H, SOCH_3), 3.22-3.44 (m, 2H, C^2-$H_{Tetrahydropyranyl}$, C^6-$H_{Tetrahydropyranyl}$); 3.64-3.94 (m, 3H, C^2-$H_{Tetrahydropyranyl}$, C^4-$H_{Tetrahydropyranyl}$, C^6-$H_{Tetrahydropyranyl}$), 6.47 (d, J = 5.1 Hz, 1H, C^5-$H_{Pyridine}$), 6.50-6.71 (m, 2H, C^3-$H_{Pyridine}$ and $NH_{Tetrahydropyranyl}$, exchangeable with D_2O), 7.27 (t, J = 8.7 Hz, 2H, C^3-$H_{4\text{-}Fluorophenyl}$, C^5-$H_{4\text{-}Fluorophenyl}$), 7.43-7.62 (m, 2H, C^2-$H_{4\text{-}Fluorophenyl}$, C^6-$H_{4\text{-}Fluorophenyl}$), 7.89 (brs, 1H, C^6-$H_{Pyridine}$), 13.75 (s, 1H, $NH_{Imidazole}$, exchangeable with D_2O); **^{13}C-NMR** (50 MHz, DMSO-d^6): δ [ppm] = 33.2 (2C, CH_2, $C^3_{Tetrahydropyranyl}$, $C^5_{Tetrahydropyranyl}$), 39.3 (1C, SOCH_3), 46.8 (1C, CH, $C^4_{Tetrahydropyranyl}$), 66.4 (2C, CH_2, $C^2_{Tetrahydropyranyl}$, $C^6_{Tetrahydropyranyl}$), 106.3 (1C, $C^3_{Pyridine}$), 110.4 (1C, $C^5_{Pyridine}$), 116.0 (d, 2C, $^2J(C,F)$ = 21.6 Hz, $C^3_{4\text{-}Fluorophenyl}$, $C^5_{4\text{-}Fluorophenyl}$), 130.9(2C, $C^2_{4\text{-}Fluorophenyl}$, $C^6_{4\text{-}Fluorophenyl}$), 148.2 (1C, $C^4_{Pyridine}$, quart.), 148.5 (1C, $C^6_{Pyridine}$), 158.7 (1C, $C^2_{Pyridine}$, quart.), 162.3 (d, 1C, $^1J(C,F)$ = 243.2 Hz, $C^4_{4\text{-}Fluorophenyl}$-F, quart.). The signals for $C^1_{4\text{-}Fluorophenyl}$, $C^2_{Imidazole}$, $C^4_{Imidazole}$ and $C^5_{Imidazole}$ are not seen in the spectrum; **FT-IR** (ATR, cm^{-1}) = 3292, 2969, 2946, 2850, 1609, 1552, 1499, 1460, 1418, 1375, 1344, 1311, 1296, 1264, 1220, 1193, 1160, 1139, 1087, 1052, 1013, 986, 958, 939, 900, 875, 842, 815, 744, 711, 680, 658. **HR-MS** (ESI) calculated for $C_{20}H_{21}FN_4O_2S$ [M+H^+] m/z = 401.1442, measured m/z = 401.1442.

enantioselective, analytical HPLC:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.291	MM	0.2139	5214.31299	406.24594	50.4667
2	7.110	MM	0.2438	5117.87939	349.89838	49.5333

4-(4-(4-Fluorophenyl)-2-(isopropylsulfinyl)-1*H*-imidazol-5-yl)-*N*-isopropylpyridin-2-amine 9e

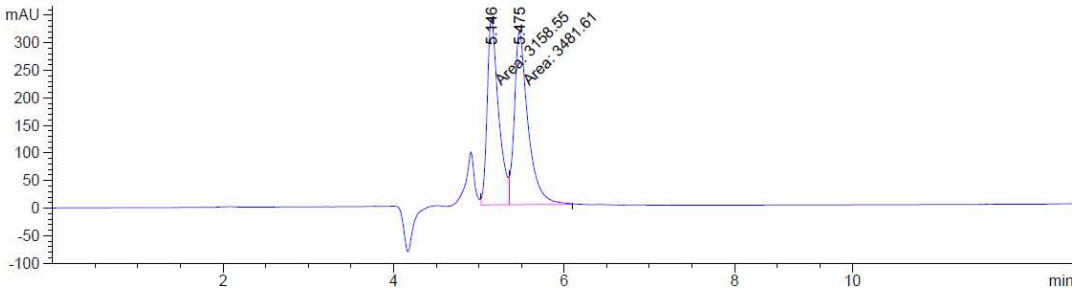


According to the General Procedure B, the title compound **9e** was obtained by the sulfoxidation of compound **8e** (0.25 g, 0.68 mmol), dissolved in 5.0 mL THF and 1.7 mL H_2O, with an aqueous solution of potassium peroxomonosulfate (Oxone®) (0.24 g, 0.4 mmol in 1.3 mL H_2O) after stirring for 3 h at T = 0 °C and treatment with isopropyl ether as a beige solid (0.21 g, 83.8%).

$C_{20}H_{23}FN_4OS$ (M_r = 386.49 g/mol); **HPLC**: t_R = 4.23 min, purity: 99.0% (λ = 254 nm), t_R = 4.23 min, purity: 99.1% (λ = 230 nm); **mp** = 170.6 °C; **^{1}H-NMR** (200 MHz, DMSO-d^6): δ = 1.08 (d, *J* = 6.2 Hz, 6H, NHCH(CH_3)$_2$), 1.15 (d, *J* = 6.95 Hz, 3H, SOCH(CH_3)$_2$), 1.25 (d, *J* = 6.8 Hz, 3H, SOCH(CH_3)$_2$), 3.37-3.55 (m, 1H, SO*CH*(CH_3)$_2$), 3.77-4.02 (m, 1H, NH*CH*(CH_3)$_2$), 6.27-6.47 (m, 2H, C^5-$H_{Pyridine}$ and *NH*CH(CH_3)$_2$, exchangeable with D_2O),

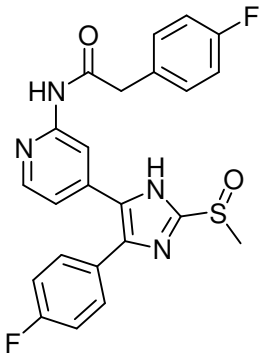
6.59 (s, 1H, C^3-$H_{Pyridine}$), 7.09-7.38 (m, 2H, C^3-$H_{4\text{-Fluorophenyl}}$, C^5-$H_{4\text{-Fluorophenyl}}$), 7.42-7.60 (m, 2H, C^2-$H_{4\text{-Fluorophenyl}}$, C^6-$H_{4\text{-Fluorophenyl}}$), 7.85 (s, 1H, C^6-$H_{Pyridine}$), 13.69 (s, 1H, $NH_{Imidazole}$, exchangeable with D_2O); **^{13}C-NMR** (50 MHz, DMSO-*d*^{6}): δ [ppm] = 15.2 (1C, SOCH(CH_3)$_2$), 15.7 (1C, SOCH(CH_3)$_2$), 23.0 (2C, NHCH(CH_3)$_2$), 42.0 (1C, NH*C*H(CH_3)$_2$), 53.2 (1C, SO*C*H(CH_3)$_2$), 106.2 (1C, $C^3_{Pyridine}$), 110.2 (1C, $C^5_{Pyridine}$), 115.9 (d, 2C, $^2J(C,F)$ = 21.6 Hz, $C^3_{4\text{-Fluorophenyl}}$, $C^5_{4\text{-Fluorophenyl}}$), 131.3 (2C, $C^2_{4\text{-Fluorophenyl}}$, $C^6_{4\text{-Fluorophenyl}}$), 146.3 (1C, $C^4_{Pyridine}$, quart.), 148.1 (1C, $C^6_{Pyridine}$), 158.9 (1C, $C^2_{Pyridine}$, quart.). The signals for $C^4_{4\text{-Fluorophenyl}}$, $C^1_{4\text{-Fluorophenyl}}$, $C^2_{Imidazole}$, $C^4_{Imidazole}$ and $C^5_{Imidazole}$ are not seen in the spectrum; **FT-IR** (ATR, cm^{-1}) = 3297, 2969, 2937, 2872, 1609, 1552, 1500, 1462, 1383, 1368, 1327, 1306, 1285, 1223, 1193, 1176, 1160, 1126, 1097, 1054, 1040, 1025, 987, 963, 893, 841, 810, 743, 722, 707, 688, 656; **HR-MS** (ESI) calculated for $C_{20}H_{23}FN_4OS$ [M+H$^+$] m/z = 387.1649, measured m/z = 387.1649.

enantioselective, analytical HPLC:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.146	MF	0.1544	3158.55273	340.89478	47.5674
2	5.475	FM	0.1839	3481.60937	315.49997	52.4326

2-(4-Fluorophenyl)-*N*-(4-(4-(4-fluorophenyl)-2-(methylsulfinyl)-1*H*-imidazol-5-yl)pyridin-2-yl)acetamide 9f

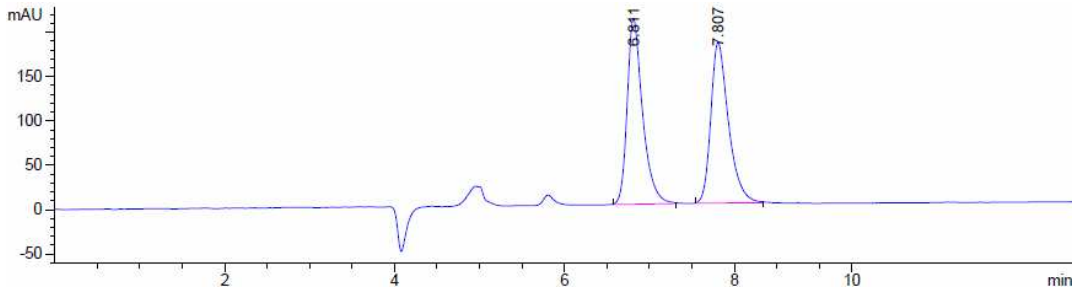


According to the General Procedure B, the title compound **9f** was obtained by the sulfoxidation of compound **8f** (0.30 g, 0.69 mmol), dissolved in 5.0 mL THF and 0.9 mL H_2O, with an aqueous solution of potassium peroxomonosulfate (Oxone®) (0.23 g, 0.4 mmol in 1.3 mL water) after stirring for 1.5 h at T = 0 °C and flash chromatography on silica gel (THF/hexane 1:1) as a yellow solid (0.16 g, 51.5%).

$C_{23}H_{18}F_2N_4O_2S$ (M_r = 452.49 g/mol); **HPLC**: t_R = 6.78 min, purity: 98.5% (λ = 254 nm), t_R = 6.78 min, purity: 99.1% (λ = 230 nm); **mp** = 222.7 °C; **^{1}H-NMR** (200 MHz, DMSO-d^6): δ [ppm] = 3.06 (s, 3H, SOCH_3), 3.68 (s, 2H, CH_2), 7.01 (d, 1H, J = 5.1 Hz, 1H, C^5-$H_{Pyridine}$), 7.13 (t, J = 8.7 Hz, 2H, C^3-$H_{4\text{-Fluorophenylacetamide}}$, C^5-$H_{4\text{-Fluorophenylacetamide}}$), 7.20-7.41 (m, 4H, C^3-$H_{4\text{-Fluorophenyl}}$, C^5-$H_{4\text{-Fluorophenyl}}$, C^2-$H_{4\text{-Fluorophenylacetamide}}$, C^6-$H_{4\text{-Fluorophenylacetamide}}$), 7.43-7.60 (m, 2H, C^2-$H_{4\text{-Fluorophenyl}}$, C^6-$H_{4\text{-Fluorophenyl}}$), 8.20 (d, 1H, J = 5.1 Hz, 1H, C^6-$H_{Pyridine}$), 8.30 (s, 1H, C^3-$H_{Pyridine}$), 10.70 (s, 1H, NHCO, exchangeable with D_2O), 13.89 (s, 1H, $NH_{Imidazole}$, exchangeable with D_2O); **^{13}C-NMR** (50 MHz, DMSO-d^6): δ [ppm] = 39.9 (1C, SOCH_3), 42.4 (1C, CH_2), 111.5 (1C, $C^3_{Pyridin}$), 115.4 (d, 2C, $^2J(C,F)$ = 21.1 Hz, $C^3_{4\text{-Fluorophenylacetamide}}$, $C^5_{4\text{-Fluorophenylacetamide}}$), 116.1 (d, 2C, $^2J(C,F)$ = 21.6 Hz, $C^3_{4\text{-Fluorophenyl}}$, $C^5_{4\text{-Fluorophenyl}}$), 117.5 (1C, $C^5_{Pyridine}$), 126.6 (1C, $C^1_{4\text{-Fluorophenyl}}$, quart.), 131.3 (d, 2C, $^3J(C,F)$ = 8.0 Hz, $C^2_{4\text{-Fluorophenylacetamide}}$, $C^6_{4\text{-Fluorophenylacetamide}}$), 132.3 (d, 1C, $^4J(C,F)$ = 3.1 Hz, $C^1_{4\text{-Fluorophenylacetamide}}$, quart.), 148.4 (1C, $C^4_{Pyridine}$, quart.), 149.1 (1C, $C^6_{Pyridine}$), 152.9 (1C,

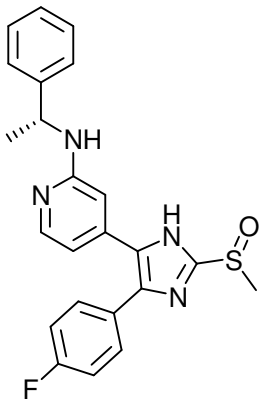
$C^2_{Pyridine}$, quart.), 161.5 (d, 1C, $^1J(C,F)$ = 240.8 Hz, $C^4_{4\text{-Fluorophenylacetamide}}$-F, quart.), 162.5 (d, 1C, $^1J(C,F)$ = 244.9 Hz, $C^4_{4\text{-Fluorophenyl}}$-F, quart.), 170.2 (1C, *C*=*O*, quart.). The signals for $C^4_{Imidazole}$, $C^2_{Imidazole}$, $C^5_{Imidazole}$, $C^2_{4\text{-Fluorophenyl}}$ and $C^6_{4\text{-Fluorophenyl}}$ are not seen in the spectrum; **FT-IR** (ATR, cm^{-1}) = 3040, 2035, 1689, 1608, 1550, 1501, 1455, 1414, 1371, 1339, 1302, 1258, 1225, 1181, 1157, 1116, 1093, 1019, 996, 980, 961, 885, 835, 813, 790, 751, 718, 704, 689. **HR-MS** (ESI) calculated for $C_{23}H_{18}F_2N_4O_2S$ [M+Na^+] m/z = 475.1011, measured m/z = 475.1013.

enantioselective, analytical HPLC:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.811	BB	0.1853	2643.84790	209.91438	50.1578
2	7.807	BB	0.2172	2627.21289	181.17534	49.8422

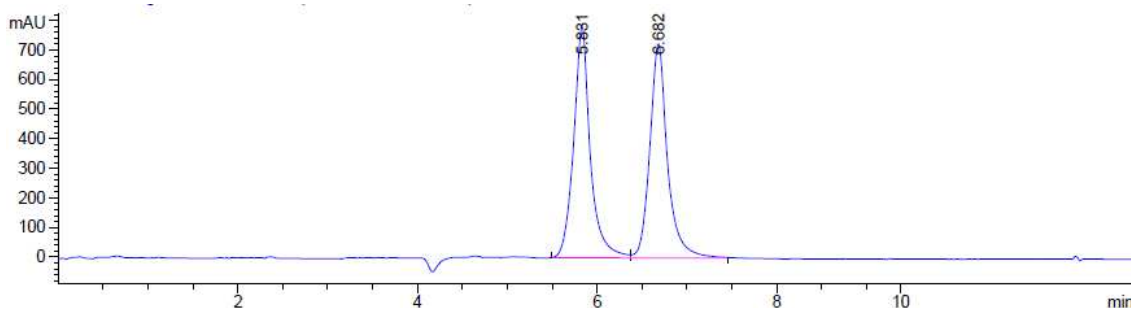
4-(4-(4-Fluorophenyl)-2-(methylsulfinyl)-1*H*-imidazol-5-yl)-*N*-((*R*)-1-phenylethyl)pyridin-2-amine 9g



According to the General Procedure B, the title compound **9g** was obtained by the sulfoxidation of compound **8g** (0.12 g, 0.30 mmol), dissolved in 3.0 mL THF and 0.5 mL H_2O, with an aqueous solution of potassium peroxomonosulfate (Oxone®) (0.10 g, 0.17 mmol in 1.0 mL water) after stirring for 2.5 h at T = 0 °C and flash chromatography (silica gel, EtOAc/MeOH 9:1) as a pale yellow solid (0.08 g, 63. 4%).

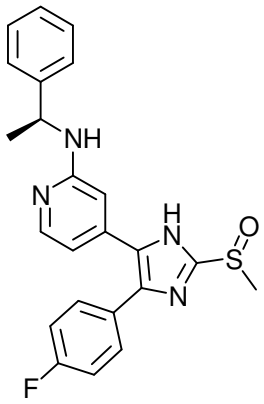
$C_{23}H_{21}FN_4OS$ (M_r = 420.5 g/mol); **HPLC**: t_R = 5.24 min, purity: 98.9% (λ = 254 nm), t_R = 5.24 min, purity: 98.9% (λ = 230 nm); $[\alpha]^{20}_D$ = +39.14 (*c* = 0.419 in Methanol); **mp** = 197.1 °C; **^{1}H-NMR** (Methanol-d^4, 400 MHz) δ = 1.42-1.50 (m, 3H, CHCH_3), 3.11 (s, 3H, SO-CH_3), 4.63-4.73 (m, 1H, CHCH$_3$), 6.56 (s, 1H, C^3-$H_{Pyridine}$), 6.65 (d, *J* = 5.31 Hz, 1H, C^5-$H_{Pyridine}$), 7.06-7.20 (m, 3H, C^3-$H_{4\text{-Fluorophenyl}}$, C^5-$H_{4\text{-Fluorophenyl}}$, C^4-$H_{Phenylethylamine}$), 7.21-7.31 (m, 4H, C^2-$H_{Phenylethylamine}$, C^3-$H_{Phenylethylamine}$, C^5-$H_{Phenylethylamine}$, C^6-$H_{Phenylethylamine}$), 7.39-7.49 (m, 2H, C^2-$H_{4\text{-Fluorophenyl}}$, C^6-$H_{4\text{-Fluorophenyl}}$), 7.85 (d, *J* = 5.3 Hz, 1H, C^6-$H_{Pyridine}$); **^{13}C-NMR** (Methanol-d^4, 100 MHz) δ = 24.4 (1C, CHCH_3), 39.9 (1C, SO-CH$_3$), 52.5 (1C, CHCH$_3$), 107.5 (1C, $C^3_{Pyridine}$), 112.4 (1C, $C^5_{Pyridine}$), 116.7 (d, 2C, $^2J(C,F)$ = 21.8 Hz, $C^3_{4\text{-Fluorophenyl}}$, $C^5_{4\text{-Fluorophenyl}}$), 126.9 (2C, $C^2_{Phenylethylamine}$, $C^6_{Phenylethylamine}$), 127.8 (1C, $C^4_{Phenylethylamine}$), 129.2 (d, 1C, $^4J(C,F)$ = 2.2 Hz, $C^1_{4\text{-Fluorophenyl}}$, quart), 129.5 (2C, $C^3_{Phenylethylamine}$, $C^5_{Phenylethylamine}$), 131.9 (2C, $^3J(C,F)$ = 8.0 Hz, $C^2_{4\text{-Fluorophenyl}}$, $C^6_{4\text{-Fluorophenyl}}$), 135.4 (1C, $C^5_{Imidazole}$, quart.), 136.8 (1C, $C^4_{Imidazole}$, quart.), 143.4 (1C, $C^4_{Pyridine}$, quart.), 146.3 (1C, $C^1_{Phenylethylamine}$, quart.), 148.2 (1C, $C^6_{Pyridine}$), 149.2 (1C, $C^2_{Imidazole}$, quart.), 159.7 (1C, $C^2_{Pyridine}$, quart.), 164.3 (d, 1C, $^1J(C,F)$ = 245.7 Hz, $C^4_{4\text{-Fluorophenyl}}$-F, quart.); **FT-IR** (ATR, cm^{-1}): 2972, 1607, 1549, 1502, 1424, 1297, 1222, 1158, 1095, 1025, 956, 839, 814, 762, 700; **HR-MS** calculated for $C_{23}H_{21}FN_4OS$ m/z = 420.1415, measured m/z = 420.1418.

enantioselective, analytical HPLC:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.831	BV	0.1824	1.01103e4	784.28589	50.5248
2	6.682	VB	0.2009	9900.27441	725.15692	49.4752

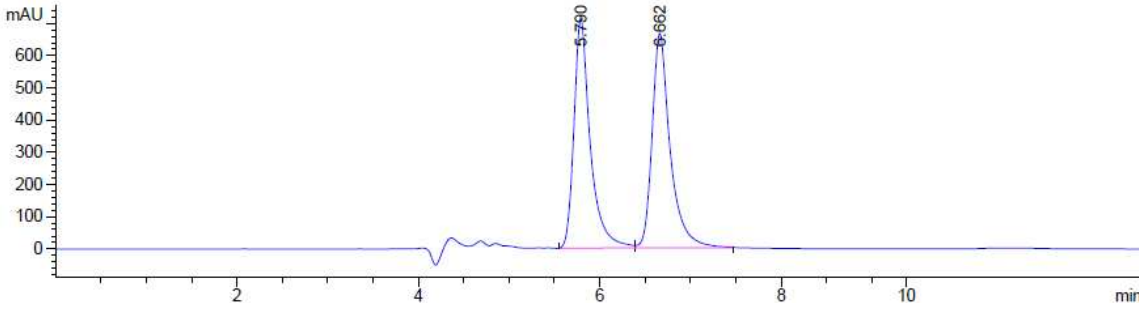
4-(4-(4-Fluorophenyl)-2-(methylsulfinyl)-1*H*-imidazol-5-yl)-*N*-((*S*)-1-phenylethyl)pyridin-2-amine 9h



According to the General Procedure B, the title compound **9h** was obtained by the sulfoxidation of compound **8h** (12.14 g, 30.0 mmol), dissolved in 273.0 mL THF and 90.0 mL H_2O, with an aqueous solution of potassium peroxomonosulfate (Oxone®) (9.77 g, 15.9 mmol in 176.0 mL water) after stirring for 2.5 h at T = 0 °C and treatment with a solvent mixture of cyclohexane and isopropyl ether as a colorless solid (11.26 g, 91.8%). $C_{23}H_{21}FN_4OS$ (M_r = 420.5 g/mol); **HPLC**: t_R = 5.24 min, purity: 96.9% (λ = 254 nm), t_R = 5.24 min, purity: 96.7% (λ = 230 nm); $[\alpha]^{20}_D$ = -41.17 (*c* = 1.014 in Methanol); **mp** = 140.2 °C; **^{1}H-NMR** (Methanol-d^4, 400 MHz) δ = 1.45-1.49 (m, 3H, CHCH_3), 3.11 (s, 3H, SO-CH_3), 4.68 (q, *J* = 6.6 Hz, 1H, CHCH$_3$), 6.57 (s, 1H, C^3-$H_{Pyridine}$), 6.60-6.69 (m, 1H, C^5-$H_{Pyridine}$),

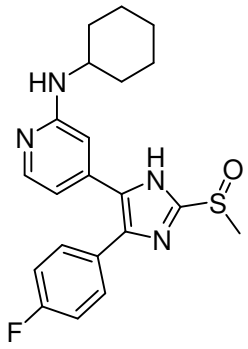
7.07-7.20 (m, 3H, C^3-$H_{4\text{-Fluorophenyl}}$, C^5-$H_{4\text{-Fluorophenyl}}$, C^4-$H_{\text{Phenylethylamine}}$), 7.20-7.30 (m, 4H, C^2-$H_{\text{Phenylethylamine}}$, C^3-$H_{\text{Phenylethylamine}}$, C^5-$H_{\text{Phenylethylamine}}$, C^6-$H_{\text{Phenylethylamine}}$), 7.38-7.51 (m, 2H, C^2-$H_{4\text{-Fluorophenyl}}$, C^6-$H_{4\text{-Fluorophenyl}}$), 7.85 (d, J = 5.6 Hz, 1H, C^6-H_{Pyridine}); **^{13}C-NMR** (Methanol-d^4, 100 MHz) δ = 24.4 (1C, CH*CH*$_3$), 40.0 (1C, SO-*C*H$_3$), 52.6 (1C, *CH*CH$_3$), 107.5 (1C, C^3_{Pyridine}), 112.3 (1C, C^5_{Pyridine}), 116.8 (d, 2C, $^2J(C,F)$ = 21.8 Hz, $C^3_{4\text{-Fluorophenyl}}$, $C^5_{4\text{-Fluorophenyl}}$), 126.9 (2C, $C^2_{\text{Phenylethylamine}}$, $C^6_{\text{Phenylethylamine}}$), 127.9 (1C, $C^4_{\text{Phenylethylamine}}$), 128.6 (d, 1C, $^4J(C,F)$ = 2.2 Hz, $C^1_{4\text{-Fluorophenyl}}$, quart), 129.5 (2C, $C^3_{\text{Phenylethylamine}}$, $C^5_{\text{Phenylethylamine}}$), 131.9 (2C, $^3J(C,F)$ = 8.0 Hz, $C^2_{4\text{-Fluorophenyl}}$, $C^6_{4\text{-Fluorophenyl}}$), 135.2 (1C, $C^5_{\text{Imidazole}}$, quart.), 136.3 (1C, $C^4_{\text{Imidazole}}$, quart.), 143.1 (1C, C^4_{Pyridine}, quart.), 146.3 (1C, $C^1_{\text{Phenylethylamine}}$, quart.), 148.2 (1C, C^6_{Pyridine}), 148.7 (1C, $C^2_{\text{Imidazole}}$, quart.), 159.7 (1C, C^2_{Pyridine}, quart.), 164.4 (d, 1C, $^1J(C,F)$ = 245.7 Hz, $C^4_{4\text{-Fluorophenyl}}$-F, quart.); **FT-IR** (ATR, cm^{-1}): 3250, 3061, 3027, 2971, 2926, 2850, 1647, 1608, 1550, 1518, 1504, 1450, 1375, 1354, 1290, 1224, 1183, 1158, 1094, 1041, 1026, 977, 957, 909, 839, 814, 762, 744, 700; **HR-MS** calculated for $C_{23}H_{21}FN_4OS$ m/z = 420.1415 , measured m/z = 420.1419.

enantioselective, analytical HPLC:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.790	PV	0.1837	8906.28418	715.07404	49.0472
2	6.662	VB	0.2035	9252.32031	666.81482	50.9528

***N*-Cyclohexyl-4-(4-(4-fluorophenyl)-2-(methylsulfinyl)-1*H*-imidazol-5-yl)pyridin-2-amine 9i**

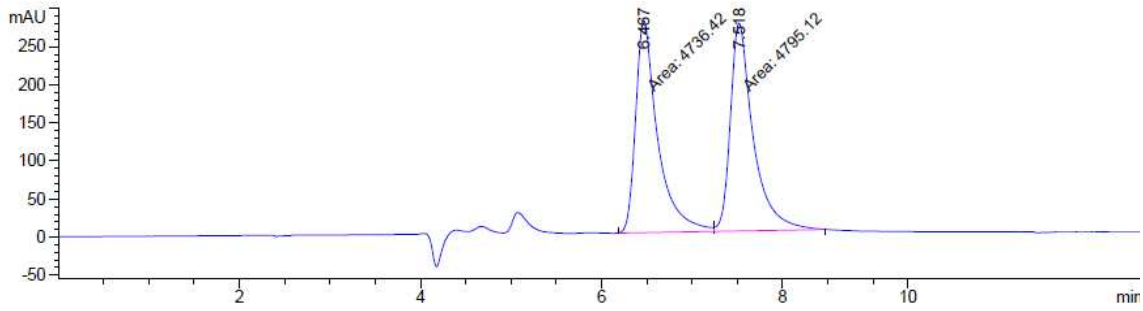


According to the General Procedure B, the title compound **9i** was obtained by the sulfoxidation of compound **8i** (0.15 g, 0.4 mmol), dissolved in 4.0 mL THF and 1.0 mL H_2O, with an aqueous solution of potassium peroxomonosulfate (Oxone®) (0.14 g, 0.22 mmol in 1.0 mL water) after stirring for 2 h at T = 0 °C and flash chromatography (silica gel, EtOAc/MeOH 9:1) as a colorless solid (0.09 g, 56.5%).

$C_{21}H_{23}FN_4OS$ (M_r = 398.5 g/mol); **HPLC**: t_R = 4.95 min, purity: 96.0% (λ = 254 nm), t_R = 4.95 min, purity: 95.4% (λ = 230 nm); **mp** = 221.8 °C; **^{1}H-NMR** (DMSO-d^6, 400 MHz) δ = 1.04-1.34 (m, 5H, *CH*$_2$, Cyclohexyl), 1.49-1.91 (m, 5H, *CH*$_2$, Cyclohexyl), 3.07 (s, 3H, SO-*CH*$_3$), 3.47-3.58 (m, 1H, *CH*, Cyclohexyl), 6.38 (d, *J* = 7.1 Hz, 1H, *NH*$_{Cyclohexyl}$), 6.44 (d, *J* = 5.1 Hz, 1H, C^5-$H_{Pyridine}$), 6.54 (s, 1H, C^3-$H_{Pyridine}$), 7.27 (t, *J* = 8.5 Hz, 2H, C^3-$H_{4\text{-}Fluorphenyl}$, C^5-$H_{4\text{-}Fluorphenyl}$), 7.53 (dd, J_1 = 8.5 Hz, J_2 = 5.7 Hz, 2H, C^2-$H_{4\text{-}Fluorphenyl}$, C^6-$H_{4\text{-}Fluorphenyl}$), 7.89 (d, *J* = 4.8 Hz, 1H, C^6-$H_{Pyridine}$), 13.83 (brs, 1H, *NH*$_{Imidazole}$); **^{13}C-NMR** (DMSO-d^6, 100 MHz) δ = 24.7 (2C, CH_2, $C^3_{Cyclohexyl}$, $C^5_{Cyclohexyl}$), 25.5 (1C, CH_2, $C^4_{Cyclohexyl}$), 32.6 (2C, CH_2, $C^2_{Cyclohexyl}$, $C^6_{Cyclohexyl}$), 38.9 (1C, SO-*CH*$_3$), 49.0 (1C, CH, $C^1_{Cyclohexyl}$), 105.6 (1C, $C^3_{Pyridine}$), 109.7 (1C, $C^5_{Pyridine}$), 115.6 (d, 2C, $^2J(C,F)$ = 21.1 Hz, $C^3_{4\text{-}Fluorophenyl}$, $C^5_{4\text{-}Fluorophenyl}$), 130.5 (2C, $C^2_{4\text{-}Fluorophenyl}$, $C^6_{4\text{-}Fluorophenyl}$), 147.9 (1C, $C^6_{Pyridine}$), 148.1 (1C, $C^4_{Pyridine}$, quart.), 158.5 (1C, $C^2_{Pyridine}$, quart.), 161.9 (d, 1C, $^1J(C,F)$ = 243.6 Hz, $C^4_{4\text{-}Fluorophenyl}$-F, quart.); **FT-IR** (ATR, cm^{-1}): 3299, 2936, 2859, 1609, 1550, 1498, 1458, 1419, 1374, 1343, 1291, 1219, 1161, 1088,

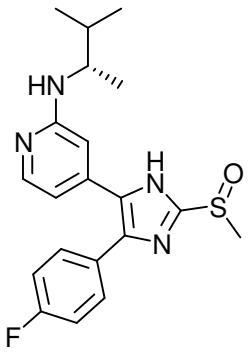
1041, 966, 935, 888, 841, 810, 744, 708, 680; **HR-MS** calculated for $C_{21}H_{23}FN_4OS$ m/z = 398.1571, measured m/z = 398.1580.

enantioselective, analytical HPLC:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.467	MF	0.2827	4736.42090	279.25186	49.6921
2	7.518	FM	0.2921	4795.11768	273.57434	50.3079

4-(4-(4-Fluorophenyl)-2-(methylsulfinyl)-1*H*-imidazol-5-yl)-*N*-((*S*)-3-methylbutan-2-yl)pyridin-2-amine 9j

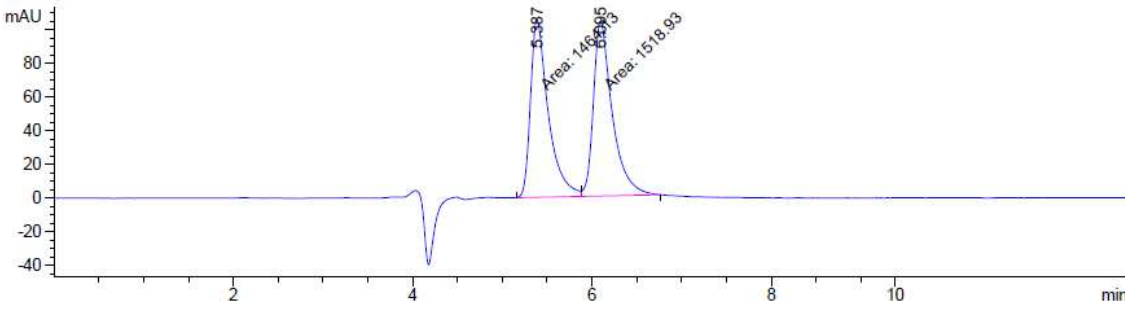


According to the General Procedure B, the title compound **9j** was obtained by the sulfoxidation of compound **8j** (0.93 g, 2.51 mmol), dissolved in 20.0 mL THF and 5.0 mL H_2O, with an aqueous solution of potassium peroxomonosulfate (Oxone®) (0.79 g, 1.30 mmol in 22.0 mL water) after stirring for 2.0 h at T = 0 °C and treatment with a solvent mixture of EtOAc and isopropyl ether as a colorless solid (0.74 g, 78.5%).

$C_{20}H_{23}FN_4OS$ (M_r = 386.49 g/mol); **HPLC:** t_R = 4.74 min, purity: 97.8% (λ = 254 nm), t_R = 4.74 min, purity: 98.3% (λ = 230 nm); $[\alpha]^{20}_D$ = +25.24 (*c* = 0.525 in Methanol); **mp** = 163.8

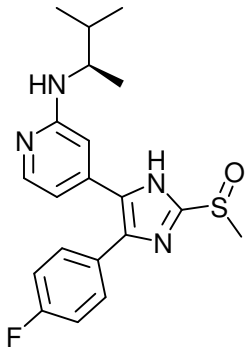
°C; **^{1}H-NMR** (Methanol-d^4, 400 MHz) δ = 0.92 (t, J = 6.7 Hz, 6H, CH(CH_3)$_2$), 1.09 (d, J = 6.6 Hz, 3H, NHCHCH_3), 1.67-1.81 (m, 1H, CH(CH$_3$)$_2$), 3.15 (s, 3H, SO-CH$_3$), 3.46-3.60 (m, 1H, CH(CH$_3$)$_2$), 6.60 (dd, J_1 = 5.6 Hz, J_2 = 1.3 Hz, 1H, C^5-H$_{Pyridine}$), 6.63 (s, 1H, C^3-H$_{Pyridine}$), 7.13-7.24 (m, 2H, C^3-H$_{4\text{-Fluorophenyl}}$, C^5-H$_{4\text{-Fluorophenyl}}$), 7.56-7.58 (m, 2H, C^2-H$_{4\text{-Fluorophenyl}}$, C^6-H$_{4\text{-Fluorphenyl}}$), 7.84 (d, J = 5.6 Hz, 1H, C^6-H$_{Pyridine}$); **^{13}C-NMR** (Methanol-d^4, 100 MHz) δ = 17.3 (1C, CH(CH_3)$_2$), 18.4 (1C, NHCHCH_3), 19.5 (1C, CH(CH_3)$_2$), 34.0 (1C, CH(CH$_3$)$_2$), 40.0 (1C, SO-CH_3), 53.2 (1C, NHCHCH$_3$), 107.6 (1C, C^3$_{Pyridine}$), 111.6 (1C, C^5$_{Pyridine}$), 116.8 (d, 2C, $^2J(C,F)$ = 21.8 Hz, C^3$_{4\text{-Fluorophenyl}}$, C^5$_{4\text{-Fluorophenyl}}$), 129.0 (d, 1C, $^4J(C,F)$ = 2.9 Hz, C^1$_{4\text{-Fluorophenyl}}$, quart.), 132.0 (2C, $^3J(C,F)$ = 8.0 Hz, C^2$_{4\text{-Fluorophenyl}}$, C^6$_{4\text{-Fluorophenyl}}$), 135.3 (1C, C^5$_{Imidazole}$, quart.), 136.7 (1C, C^4$_{Imidazole}$, quart.), 143.7 (1C, C^4$_{Pyridine}$, quart.), 147.7 (1C, C^6$_{Pyridine}$), 149.0 (1C, C^2$_{Imidazole}$, quart.), 160.0 (1C, C^2$_{Pyridine}$, quart.), 164.4 (d, 1C, $^1J(C,F)$ = 245.7 Hz, C^4$_{4\text{-Fluorophenyl}}$-F, quart.); **FT-IR** (ATR, cm^{-1}): 3305, 2965, 2877, 2739, 1608, 1549, 1499, 1459, 1419, 1406, 1390, 1371, 1312, 1296, 1284, 1223, 1185, 1160, 1120, 1098, 1052, 1015, 1001, 985, 967, 954, 934, 906, 880, 839, 812, 770, 744, 724, 707, 678; **HR-MS** calculated for $C_{20}H_{23}FN_4OS$ m/z = 386.1571, measured m/z = 386.1559 .

enantioselective, analytical HPLC:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.387	MF	0.2304	1464.12915	105.90085	49.0814
2	6.095	FM	0.2430	1518.93176	104.17654	50.9186

4-(4-(4-Fluorophenyl)-2-(methylsulfinyl)-1*H*-imidazol-5-yl)-*N*-((*R*)-3-methylbutan-2-yl)pyridin-2-amine 9k

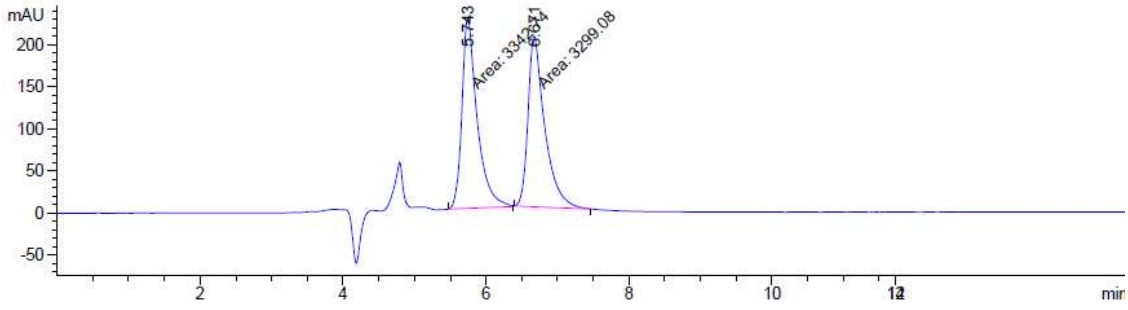


According to the General Procedure B, the title compound **9k** was obtained by the sulfoxidation of compound **8k** (0.38 g, 1.03 mmol), dissolved in 8.0 mL THF and 3.0 mL H_2O, with an aqueous solution of potassium peroxomonosulfate (Oxone®) (0.32 g, 0.5 mmol in 9.0 mL water) after stirring for 4.0 h at T = 0 °C and flash chromatography on silica gel (EtOAc/EtOH 95:5) as a beige solid (0.24 g, 61.1%).

$C_{20}H_{23}FN_4OS$ (M_r = 386.49 g/mol); **HPLC:** t_R = 3.99 min, purity: 95.4% (λ = 254 nm), t_R = 3.99 min, purity: 95.5% (λ = 230 nm); **$[\alpha]^{20}_D$** = -27.60 (*c* = 0.253 in Methanol); **mp** = 147.9 °C; **^{1}H-NMR** (Methanol-d^4, 400 MHz) δ = 0.93 (t, *J* = 6.2 Hz, 6H, CH(CH_3)$_2$), 1.11 (d, *J* = 6.6 Hz, 3H, NHCHCH_3), 1.69-1.82 (m, 1H, CH(CH_3)$_2$), 3.15 (s, 3H, SO-CH_3), 3.48-3.58 (m, 1H, CH(CH_3)$_2$), 6.66 (d, *J* = 5.8 Hz, 1H, C^5-$H_{Pyridine}$), 6.72 (s, 1H, C^3-$H_{Pyridine}$), 7.21 (t, *J* = 8.6 Hz, 2H, C^3-$H_{4\text{-Fluorophenyl}}$, C^5-$H_{4\text{-Fluorphenyl}}$), 7.54 (dd, J_1 = 8.1 Hz, J_2 = 5.3 Hz, 2H, C^2-$H_{4\text{-Fluorophenyl}}$, C^6-$H_{4\text{-Fluorophenyl}}$), 7.82 (d, *J* = 5.6 Hz, 1H, C^6-$H_{Pyridine}$); **^{13}C-NMR** (Methanol-d^4, 100 MHz) δ = 17.2 (1C, CH(CH_3)$_2$), 18.4 (1C, NHCHCH_3), 19.5 (1C, CH(CH_3)$_2$), 34.0 (1C, CH(CH_3)$_2$), 40.0 (1C, SO-CH_3), 53.5 (1C, NHCHCH$_3$), 107.9 (1C, $C^3_{Pyridine}$), 111.5 (1C, $C^5_{Pyridine}$), 116.9 (d, 2C, $^2J(C,F)$ = 21.8 Hz, $C^3_{4\text{-Fluorophenyl}}$, $C^5_{4\text{-Fluorophenyl}}$), 128.6 (1C, $C^1_{4\text{-Fluorophenyl}}$, quart.), 132.0 (2C, $^3J(C,F)$ = 8.7 Hz, $C^2_{4\text{-Fluorophenyl}}$, $C^6_{4\text{-Fluorophenyl}}$), 135.1 (1C, $C^5_{Imidazole}$, quart.), 136.8 (1C, $C^4_{Imidazole}$, quart.), 144.1 (1C, $C^4_{Pyridine}$, quart.), 145.8 (1C, $C^6_{Pyridine}$), 149.1 (1C, $C^2_{Imidazole}$, quart.), 159.0 (1C, $C^2_{Pyridine}$, quart.), 164.5 (d, 1C, $^1J(C,F)$ =

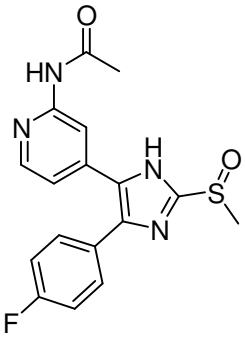
245.7 Hz, $C^{4}_{4\text{-Fluorophenyl}}$-F, quart.); **FT-IR** (ATR, cm^{-1}): 3302, 2965, 2876, 1646, 1608, 1549, 1499, 1459, 1419, 1406, 1390, 1370, 1317, 1296, 1284, 1223, 1186, 1159, 1142, 1121, 1098, 1051, 1015, 985, 967, 954, 935, 906, 880, 840, 812, 766, 744, 724, 707, 679; **HR-MS** calculated for $C_{20}H_{23}FN_4OS$ m/z = 386.1571, measured m/z = 386.1587.

enantioselective analytical HPLC:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.743	MM	0.2462	3342.73779	226.27547	50.3287
2	6.671	MM	0.2706	3299.07617	203.22368	49.6713

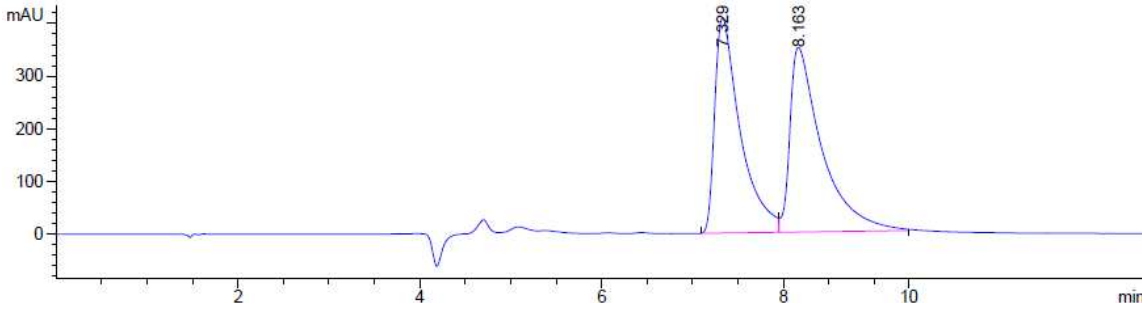
***N*-(4-(4-(4-Fluorophenyl)-2-(methylsulfinyl)-1*H*-imidazol-5-yl)pyridin-2-yl)acetamide 9l**



According to the General Procedure B, the title compound **9l** was obtained by the sulfoxidation of compound **8l** (0.28 g, 0.82 mmol), dissolved in 6.0 ml THF and 1.0 ml H_2O, with an aqueous solution of potassium peroxomonosulfate (Oxone®) (0.28 g, 0.45 mmol in 1.5 ml water) after stirring for 4.0 h at T = 0 °C and flash chromatography on silica gel (EtOAc/EtOH 95:5) as a colorless solid (0.19 g, 64.7 %).

$C_{17}H_{15}FN_4O_2S$ (M_r = 358.39 g/mol); **HPLC:** t_R = 4.11 min, purity: 99.8% (λ = 254 nm), t_R = 4.11 min, purity: 99.8% (λ = 230 nm); **mp** = 226.0 °C; **^{1}H-NMR** (DMSO-*d*^{6}, 400 MHz) δ = 2.02 (s, 3H, CO-*CH*$_3$), 3.05 (s, 3H, SO-*CH*$_3$), 7.09 (d, *J* = 4.0 Hz, 1H, C^5-$H_{Pyridine}$), 7.21 (t, *J* = 8.1 Hz, 2H, C^3-$H_{4\text{-Fluorophenyl}}$, C^5-$H_{4\text{-Fluorophenyl}}$), 7.36-7.49 (m, 2H, C^2-$H_{4\text{-Fluorophenyl}}$, C^6-$H_{4\text{-Fluorophenyl}}$), 8.06-8.21 (m, 2H, C^6-$H_{Pyridine}$, C^3-$H_{Pyridine}$); **^{13}C-NMR** (Methanol-*d*^{4}, 100 MHz) δ = 23.6 (1C, CO-*C*H$_3$), 38.6 (1C, SO-*CH*$_3$), 111.2 (1C, $C^3_{Pyridine}$), 115.9 (d, 2C, $^2J(C,F)$ = 21.1 Hz, $C^3_{4\text{-Fluorophenyl}}$, $C^5_{4\text{-Fluorophenyl}}$), 117.4 (1C, $C^5_{Pyridine}$), 130.8 (2C, $C^2_{4\text{-Fluorophenyl}}$, $C^6_{4\text{-Fluorophenyl}}$), 147.6 (1C, $C^4_{Pyridine}$, quart.), 148.1 (1C, $C^6_{Pyridine}$), 151.8 (1C, $C^2_{Pyridine}$, quart.), 162.2 (d, 1C, $^1J(C,F)$ = 241.4 Hz, $C^4_{4\text{-Fluorophenyl}}$-F, quart.), 170.1 (1C, C=O, quart.); **FT-IR** (ATR, cm^{-1}): 3201, 3145, 3069, 3037, 3004, 2963, 2924, 2897, 2842, 1690, 1610, 1550, 1531, 1502, 1455, 1434, 1417, 1370, 1286, 1272, 1227, 1183, 1158, 1137, 1124, 1097, 1038, 1009, 997, 979, 961, 946, 885, 835, 816, 744, 720, 704, 685, 669; **HR-MS** calculated for $C_{17}H_{15}FN_4O_2S$ m/z = 358.0894, measured m/z = 358.0901.

enantioselective, analytical HPLC:

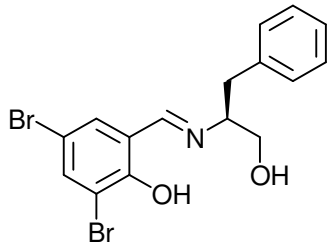


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.329	BV	0.2856	7980.02100	408.28711	48.3020
2	8.163	VB	0.3513	8541.07520	350.73383	51.6980

3. The Synthesis of Chiral Schiff Base Ligands

General Procedure C: The amino alcohol was added to a stirred solution or suspension of the respective salicylaldehyde derivative in ethanol or methanol. The resulting deep-yellow mixture was stirred at room temperature until HPLC analysis indicated complete conversion. The solvent was removed under reduced pressure and the residue was purified by recrystallization from an appropriate solvent or by flash chromatography.

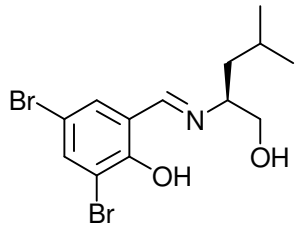
(*S*)-2,4-dibromo-6-((1-hydroxy-3-phenylpropan-2-ylimino)methyl)phenol (*S*)-12f



According to the General Procedure C, the title compound **(*S*)-12f** was obtained from **(*S*)-11b** (0.15 g, 1.0 mmol) and **10b** (0.28 g, 1.0 mmol) in 6.0 mL ethanol after stirring for 5 h at room temperature and recrystallization from cyclohexane as a yellow solid (0.21 g, 51.9%). $[\alpha]^{20}_{D}$ = -248.76 (*c* = 1.007 in CH_2Cl_2). **HPLC**: t_R = 9.07 min (94.3% purity, ZORBAX Eclipse XDB-C_8). **mp** = 111.9 °C. **^{1}H-NMR** (200 MHz, $CDCl_3$): δ [ppm] = 2.74-2.94 (m, 1H, *CH*$_2$-Phenyl), 3.01 (dd, J_1 = 13.9, J_2 = 4.0 Hz, 1H, *CH*$_2$-Phenyl), 3.53-3.78 (m, 2H, *CH*CH_2OH and *CH*$_2$OH), 3.81-3.99 (m, 1H, *CH*$_2$OH), 7.02-7.19 (m, 3H, C^3-H_{Benzyl}, C^4-H_{Benzyl} and C^5-H_{Benzyl}), 7.22-7.36 (m, 3H, C^2-H_{Benzyl}, C^6-H_{Benzyl} and C^5-$H_{Dibromophenol}$), 7.60 (d, *J* = 2.4 Hz, 1H, C^3-$H_{Dibromophenol}$), 7.86 (s, 1H, *CH*=N). **^{13}C-NMR** (50 MHz, $CDCl_3$): δ [ppm] = 38.3 (1C, *CH*$_2$-Phenyl), 65.2 (1C, *CH*$_2$OH), 70.9 (1C, *CH*CH_2OH), 107.9 (1C, $C^4_{Dibromophenol}$-Br, quart.), 113.8 (1C, $C^6_{Dibromophenol}$-Br, quart.), 118.1 (1C, $C^2_{Dibromophenol}$, quart.), 126.8 (1C, C^4_{Benzyl}), 128.6 (2C, C^3_{Benzyl}, C^5_{Benzyl}), 129.2 (2C, C^2_{Benzyl}, C^6_{Benzyl}), 133.1 (1C, C^1_{Benzyl}, quart.), 136.7 (1C, $C^3_{Dibromophenol}$), 138.3 (1C, $C^5_{Dibromophenol}$), 161.1 (1C, $C^1_{Dibromophenol}$-OH, quart.), 164.2 (1C, *CH*=N). **FT-IR** (ATR, cm^{-1}): 3254, 3065, 2909, 2162, 1629, 1492, 1454, 1410, 1380,

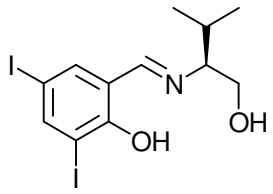
1341, 1211, 1183, 1139, 1114, 1069, 1043, 1029, 894, 876, 856, 833, 754, 704, 686. **HR-MS** (EI) calculated for $C_{16}H_{15}Br_2NO_2$ [M+H$^+$] m/z = 412.9449, measured m/z = 412.9446.

(*S*)-2,4-dibromo-6-((1-hydroxy-4-methylpentan-2-ylimino)methyl)phenol (*S*)-12g



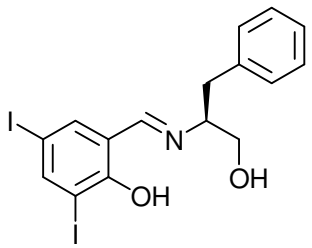
According to the General Procedure C, the title compound **(*S*)-12g** was obtained from **(*S*)-11c** (0.12 g, 1.0 mmol) and **10b** (0.28 g, 1.0 mmol) in 6.0 mL ethanol after stirring for 5 h at room temperature and recrystallisation from cyclohexane as a yellow solid (0.29 g, 78.1%). **$[\alpha]^{20}_D$** = -91.25 (*c* = 1.042 in CH_2Cl_2). **HPLC**: t_R = 9.34 min (94.1% purity, ZORBAX Eclipse XDB-C_8). **mp** = 136.7 °C. **^{1}H-NMR** (200 MHz, $CDCl_3$): δ [ppm] = 0.87 (d, *J* = 6.4 Hz, 3H, CH(*CH*$_3$)$_2$), 0.92 (d, *J* = 6.4 Hz, 3H, CH(*CH*$_3$)$_2$), 1.26-1.45 (m, 1H, *CH*(CH$_3$)$_2$), 1.46-1.72 (m, 2H, *CH*$_2$CH(CH$_3$)$_2$), 3.44-3.67 (m, 2H, *CH*CH$_2$OH and *CH*$_2$OH), 3.70-3.89 (m, 1H, *CH*$_2$OH), 7.21 (d, *J* = 2.4 Hz, 1H, C^3-H$_{Dibromophenol}$), 7.56 (d, *J* = 2.4 Hz, 1H, C^5-H$_{Dibromophenol}$), 8.13 (s, 1H, *CH*=N). **^{13}C-NMR** (50 MHz, $CDCl_3$): δ [ppm] = 21.4, 23.2 (2C, CH(*CH*$_3$)$_2$), 24.6 (1C, *CH*(CH$_3$)$_2$), 39.9 (1C, *CH*$_2$CH(CH$_3$)$_2$), 65.7 (1C, *CH*CH$_2$OH), 66.5 (1C, *CH*$_2$OH), 106.6 (1C, C$^4_{Dibromophenol}$-Br, quart.), 115.1 (1C, C$^6_{Dibromophenol}$-Br, quart.), 117.1 (1C, C$^2_{Dibromophenol}$, quart.), 133.4 (1C, C$^3_{Dibromophenol}$), 138.8 (1C, C$^5_{Dibromophenol}$), 164.2 (1C, *CH*=N). The signal for C$^1_{Dibromophenol}$ is not seen in the spectrum. **FT-IR** (ATR, cm^{-1}): 3321, 2960, 2932, 2869, 2848, 1632, 1492, 1417, 1382, 1369, 1328, 1213, 1139, 1068, 1018, 955, 899, 856, 832, 756, 690. **HR-MS** (EI) calculated for $C_{13}H_{17}Br_2NO_2$ [M+H$^+$] m/z = 378.9605, measured m/z = 378.9611.

(*S*)-2-((1-hydroxy-3-methylbutan-2-ylimino)methyl)-4,6-diiodophenol (*S*)-12i



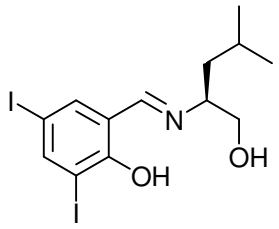
According to the General Procedure C, the title compound **(*S*)-12i** was obtained from **(*S*)-11a** (0.10 g, 1.0 mmol) and **10c** (0.37 g, 1.0 mmol) in 6.0 mL ethanol after stirring for 5 h at room temperature and recrystallization from cyclohexane as a deep-yellow solid (0.30 g, 66.0%). $[\alpha]^{20}_{D}$ = -65.01 (*c* = 1.039 in CH_2Cl_2). **HPLC**: t_R = 8.51 min (99.3% purity, Betasil C_8). **mp** = 133.4 °C. **^{1}H-NMR** (200 MHz, $CDCl_3$): δ [ppm] = 0.99 (d, *J* = 6.8 Hz, 6H, CH(*CH*$_3$)$_2$), 1.86-2.07 (m, 1H, *CH*$(CH_3)_2$), 3.16-3.31 (m, 1H, *CH*CH_2OH), 3.72 (dd, J_1 = 11.4 Hz, J_2 = 8.84 Hz, 1H, *CH*$_2$OH), 3.90 (dd, J_1 = 11.1 Hz, J_2 = 3.2 Hz, 1H, *CH*$_2$OH), 7.47 (d, *J* = 2.2 Hz, 1H, C^3-$H_{Diiodophenol}$), 7.97 (d, *J* = 2.2 Hz, 1H, C^5-$H_{Diiodophenol}$), 8.08 (s, 1H, *CH*=N). **^{13}C-NMR** (50 MHz, $CDCl_3$): δ [ppm] = 18.4, 19.6 (2C, CH(*CH*$_3$)$_2$), 29.5 (1C, *CH*$(CH_3)_2$), 63.8 (1C, *CH*$_2$OH), 74.0 (1C, *CH*CH_2OH), 75.8 (1C, $C^4_{Diiodophenol}$-I, quart.), 92.8 (1C, $C^6_{Diiodophenol}$-I, quart.), 116.9 (1C, $C^2_{Diiodophenol}$, quart.), 141.0 (1C, $C^3_{Diiodophenol}$), 149.8 (1C, $C^5_{Diiodophenol}$), 164.5 (1C, *CH*=N), 166.7 (1C, $C^1_{Diiodophenol}$-OH, quart.). **FT-IR** (ATR, cm^{-1}): 3283, 2960, 2863, 2161, 1630, 1582, 1506, 1481, 1410, 1372, 1322, 1254, 1213, 1125, 1100, 1065, 1041, 1013, 948, 897, 858, 819, 756, 662. **HR-MS** (EI) calculated for $C_{12}H_{15}I_2NO_2$ [M+H$^+$] m/z = 458.9193, measured m/z = 458.9207.

(*S*)-2-((1-hydroxy-3-phenylpropan-2-ylimino)methyl)-4,6-diiodophenol (*S*)-12j



According to the General Procedure C, the title compound **(*S*)-12j** was obtained from **(*S*)-11b** (0.15 g, 1.0 mmol) and **10c** (0.37 g, 1.0 mmol) in 6.0 mL ethanol after stirring for 5 h at room temperature and recrystallization from cyclohexane as an orange solid (0.21 g, 42.3%). **$[\alpha]^{20}_{D}$** = -226.30 (*c* = 0.27 in CH_2Cl_2). **HPLC**: t_R = 9.02 min (93.5% purity, Betasil C_8). **mp** = 62-66 °C. **^{1}H-NMR** (200 MHz, $CDCl_3$): δ [ppm] = 2.85 (dd, J_1 = 13.6 Hz, J_2= 8.3 Hz, 1H, *CH*$_2$-Phenyl), 2.94-3.09 (m, 1H, *CH*$_2$-Phenyl), 3.52-3.67 (m, 1H, *CH*CH_2OH), 3.67-3.80 (m, 1H, *CH*$_2$OH), 3.82-3.96 (m, 1H, *CH*$_2$OH); 7.07-7.16 (m, 2H, C^3-H_{Benzyl} and C^5-H_{Benzyl}), 7.17-7.30 (m, 3H, C^2-H_{Benzyl}, C^4-H_{Benzyl} and C^6-H_{Benzyl}), 7.33 (d, *J* = 2.2 Hz, 1H, C^3-$H_{Diiodophenol}$), 7.79 (s, 1H, *CH*=N), 7.99 (d, *J* = 2.2 Hz, 1H, C^5-$H_{Diiodophenol}$). **^{13}C-NMR** (50 MHz, $CDCl_3$): δ [ppm] = 38.2 (1C, *CH*$_2$-Ph), 65.1 (1C, *CH*$_2$OH), 70.2 (1C, *CH*CH_2OH), 76.9 (1C, $C^4_{Diiodophenol}$-I, quart.), 91.3 (1C, $C^6_{Diiodophenol}$-I, quart.), 117.6 (1C, $C^2_{Diiodophenol}$, quart.), 126.9 (1C, C^4_{Benzyl}), 128.7 (2C, C^3_{Benzyl}, C^5_{Benzyl}), 129.2 (2C, C^2_{Benzyl}, C^6_{Benzyl}); 136.6 (1C, C^1_{Benzyl}, quart.), 140.5 (1C, $C^3_{Diiodophenol}$), 149.4 (1C, $C^5_{Diiodophenol}$), 164.1 (1C, *CH*=N), 164.8 (1C, $C^1_{Diiodophenol}$-OH, quart.). **FT-IR** (ATR, cm^{-1}): 3304, 3027, 2921, 2848, 1627, 1583, 1496, 1480, 1436, 1369, 1282, 1218, 1155, 1133, 1031, 901, 861, 748, 699, 658. **HR-MS** (EI) calculated for $C_{16}H_{15}I_2NO_2$ [M+H$^+$] m/z = 506.9193, measured m/z = 506.9209.

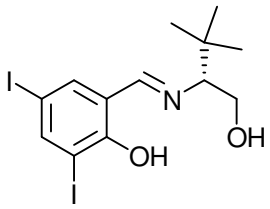
(*S*)-2-((1-hydroxy-4-methylpentan-2-ylimino)methyl)-4,6-diiodophenol (*S*)-12k



According to the General Procedure C, the title compound **(*S*)-12k** was obtained from **(*S*)-11c** (0.12 g, 1.0 mmol) and **10c** (0.37 g, 1.0 mmol) in 6.0 mL ethanol after stirring for 3 h at room temperature and recrystallization from cyclohexane as a yellow solid (0.331 g, 71.4%). **$[\alpha]^{20}_{D}$** = -76.82 (*c* = 1.037 in CH_2Cl_2). **HPLC**: t_R= 9.29 min (95.7% purity, Betasil C_8). **mp** =

159.4 °C. **^{1}H-NMR** (200 MHz, $CDCl_3$): δ [ppm] = 0.87 (d, *J* = 6.3 Hz, 3H, CH(*CH*$_3$)$_2$), 0.91 (d, *J* = 6.3 Hz, 3H, CH(*CH*$_3$)$_2$), 1.29-1.45 (m, 1H, *CH*(CH$_3$)$_2$), 1.47-1.67 (m, 2H, *CH*$_2$CH(CH$_3$)$_2$), 3.42-3.68 (m, 2H, *CH*CH$_2$OH, *CH*$_2$OH), 3.73-3.85 (m, 1H, *CH*$_2$OH), 7.47 (d, *J* = 2.2 Hz, 1H, C^3-H$_{Diiodophenol}$), 7.97 (d, *J* = 2.2 Hz, 1H, C^5-H$_{Diiodophenol}$), 8.09 (s, 1H, *CH*=N). **^{13}C-NMR** (50 MHz, $CDCl_3$): δ [ppm] = 21.4, 23.2 (2C, CH(*CH*$_3$)$_2$), 24.6 (1C, *CH*(CH$_3$)$_2$), 39.9 (1C, *CH*$_2$CH(CH$_3$)$_2$), 65.8 (1C, *CH*CH$_2$OH), 66.4 (1C, *CH*$_2$OH), 76.1 (1C, C^4$_{Diiodophenol}$-I, quart.), 92.3 (1C, C^6$_{Diiodophenol}$-I, quart.), 117.2 (1C, C^2$_{Diiodophenol}$, quart.), 140.8 (1C, C^3$_{Diiodophenol}$), 149.7 (1C, C^5$_{Diiodophenol}$), 164.0 (1C, *CH*=N), 166.0 (1C, C^1$_{Diiodophenol}$-OH, quart.). **FT-IR** (ATR, cm^{-1}): 3255, 2916, 2849, 2161, 1634, 1509, 1481, 1411, 1368, 1218, 1134, 1065, 954, 896, 855, 756, 718, 661. **HR-MS** (EI) calculated for $C_{13}H_{17}I_2NO_2$ [M+H$^+$] m/z = 472.9349, measured m/z = 472.9352.

(*R*)-2-((1-hydroxy-3,3-dimethylbutan-2-ylimino)methyl)-4,6-diiodophenol (*R*)-12l



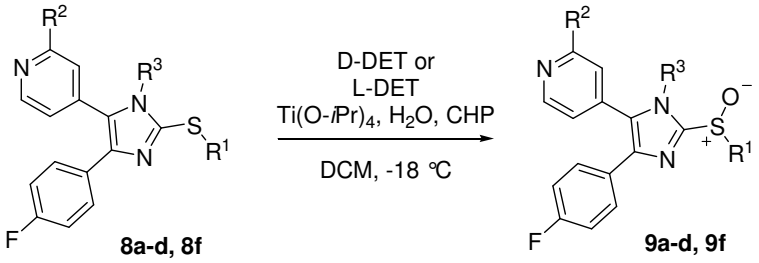
According to the General Procedure C, the title compound **(*R*)-12l** was obtained from **(*R*)-11d** (0.10 g, 0.86 mmol) and **10c** (0.32 g, 0.86 mmol) in 6.0 mL methanol after stirring for 3 h at room temperature and without further purification as a yellow solid (0.28 g, 70.6%). **$[\alpha]^{20}_D$** = +13.68 (*c* = 1.045 in acetone). **HPLC**: t_R = 9.59 min (97.7% purity, ZORBAX Eclipse XDB-C$_8$). **mp** = 159.5 °C. **^{1}H-NMR** (200 MHz, $CDCl_3$): δ [ppm] = 0.99 (s, 9H, C(*CH*$_3$)$_3$), 3.05-3.19 (m, 1H, *CH*C(CH$_3$)$_3$), 3.55-3.73 (m, 1H, *CH*$_2$OH), 3.92-4.07 (m, 1H, *CH*$_2$OH), 7.42 (d, *J* = 2.0 Hz, 1H, C^3-H$_{Diiodphenol}$), 7.90 (d, *J* = 2.2 Hz, 1H, C^5-H$_{Diiodphenol}$), 8.02 (s, 1H, *CH*=N), 14.75 (brs, 1H, *OH*). **^{13}C-NMR** (50 MHz, $CDCl_3$): δ [ppm] = 26.8 (3C, C(*CH*$_3$)$_3$), 32.8 (1C, *C*(CH$_3$)$_3$), 61.8 (1C, *CH*$_2$OH), 75.8 (1C, *CH*C(CH$_3$)$_3$), 78.1 (1C, C^4$_{Diiodophenol}$-I, quart.), 92.5

(1C, $C^6_{Diiodophenol}$-I, quart.), 116.9 (1C, $C^2_{Diiodophenol}$, quart.), 141.0 (1C, $C^3_{Diiodophenol}$), 149.8 (1C, $C^5_{Diiodophenol}$), 164.5 (1C, *CH*=N), 166.5 (1C, $C^1_{Diiodophenol}$-OH, quart.). **FT-IR** (ATR, cm^{-1}): 3305, 2966, 2871, 1635, 1583, 1508, 1478, 1422, 1383, 1364, 1335, 1249, 1215, 1130, 1058, 1013, 946, 900, 857, 820, 787, 755, 663. **HR-MS** (ESI) calculated for $C_{13}H_{17}I_2NO_2$ $[M+Na^+]$ m/z = 495.9241, measured m/z = 495.9245.

4. Asymmetric Oxidation of Tri- and Tetrasubstituted 2-Thioimidazoles with Ti(O-*i*Pr)$_4$, D-DET or L-DET and CHP

General Procedure D: Ti(O-*i*Pr)$_4$ (1.0- 2.0 eq.) was added rapidly to a solution of D-DET or L-DET (2.0- 4.0 eq.) in 10.0 mL dichloromethane at room temperature. After 2.5 min, water (1.0 eq.) was added slowly. The resulting mixture was stirred initially for 20 min at room temperature, followed by cooling to T= -18 °C for further 20 min. After addition of the respective 2-thioimidazole **8a-d**, **8f** (1.0 eq.) and CHP (2.0- 4.0 eq.), the resulting mixture was stirred at T = -18°C, until HPLC analysis (Thermo C_8 Betasil, MeOH/0.01 M KH_2PO_4, pH = 2.3) indicated complete conversion. The mixture was combined with water and extracted with dichloromethane. The organic layer was washed with brine and H_2O, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel to yield the pure sulfoxide. The enantiomer ratio of the sulfoxides **9a-d**, **9f** was determined by enantioselective, analytical HPLC (Daicel CHIRALPAK IA, 4.6 x 250 mm, 5 μm, CH_2Cl_2/MeOH/TEA 98: 2: 0.1, λ = 254 nm, 0.8 mL/min flow rate).

Table S1. The Enantioselective Sulfoxidation of the 2-Thioimidazoles Using the System Ti(O-*i*Pr)$_4$/D-DET or L-DET/H_2O/CHP

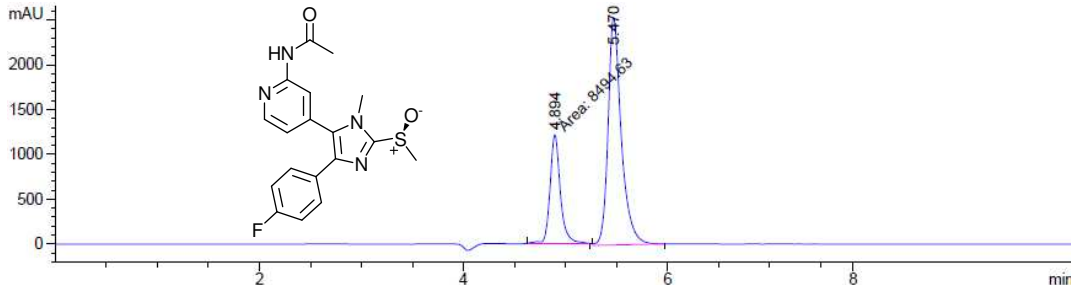


8a-d, 8f **9a-d, 9f**

Entry	Sulfide	Ligand	Conditions[a]	Conversion [%]	Enantio ratio E_1: E_2 [%][c]	*ee* [%]
1	**8a**	D-DET	A (24)[b]	74	27.1 : 72.9	46
2	**8a**	D-DET	B (19)[b]	84	12.2 : 87.8	76
3	**8b**	D-DET	A (2)[b]	64	40.0 : 60.0	20
4	**8c**	D-DET	B (19)[b]	46	60.2 : 39.8	20
5	**8d**	D-DET	A (3)[b]	40	53.3 : 46.7	7
6	**8f**	D-DET	C (4)[b]	70	34.6 : 65.4	31
7	**8a**	L-DET	A (24)[b]	78	87.8 : 12.2	76
8	**8a**	L-DET	B (19)[b]	76	92.6 : 7.4	**85**
9	**8b**	L-DET	A (2)[b]	80	65.6 : 34.4	31
10	**8c**	L-DET	B (19)[b]	53	17.5 : 82.5	65
11	**8d**	L-DET	A (3)[b]	32	45.5 : 54.5	9
12	**8f**	L-DET	A (3)[b]	77	70.3 : 29.7	41

[a]Conditions: A: Ti(O-*i*Pr)$_4$/D-DET or L-DET/H_2O/CHP 1: 2: 1: 2, CH_2Cl_2, -18 ºC. B: Ti(O-*i*Pr)$_4$/D-DET or L-DET/H_2O/CHP 2: 4: 1: 4, CH_2Cl_2, -18 °C. C: Ti(O-*i*Pr)$_4$/D-DET/H_2O/CHP 1.5: 3: 1: 3, CH_2Cl_2, -18 °C. [b]Reaction time in (h). [c]Determined by enantioselective analytical HPLC using a Daicel CHIRALPAK IA column.

Table S1, entry 1:



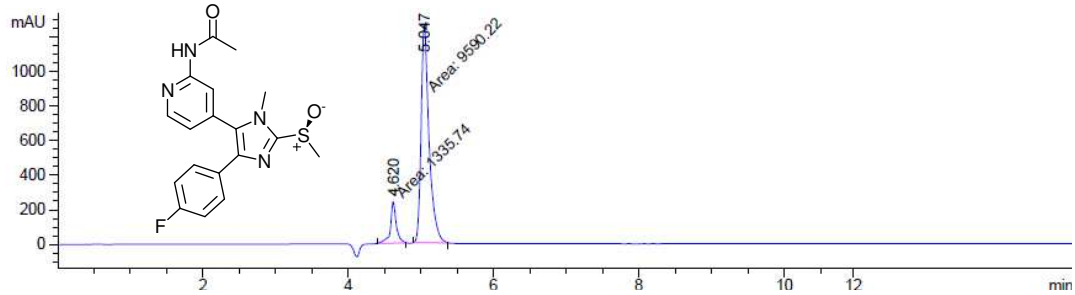
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.894	MM	0.1162	8494.63477	1218.60901	27.0558
2	5.470	VB	0.1306	2.29021e4	2544.04956	72.9442

Table S1, entry 2: (*S*)-9a

$[\alpha]^{20}_{D}$ = +17.66 (*c* = 0.440 in Methanol)

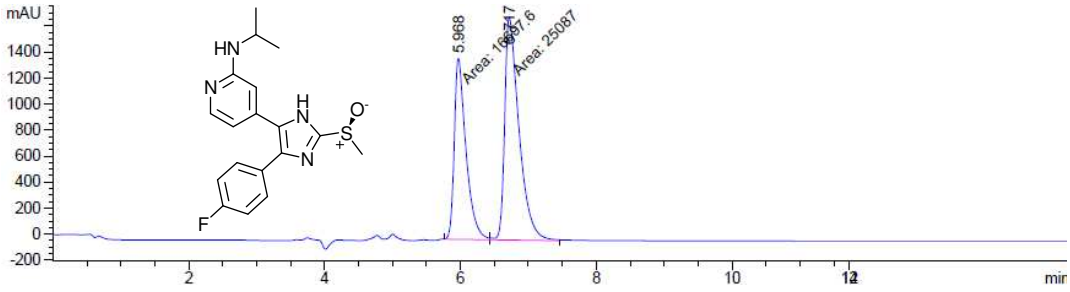
HPLC: t_R = 4.73 min, purity: 98.8% (λ = 254 nm), t_R = 4.73 min, purity: 98.4% (λ = 230 nm).

enantioselective analytical HPLC:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.620	MM	0.0911	1335.74402	244.34604	12.2254
2	5.047	MM	0.1259	9590.22266	1269.35742	87.7746

Table S1, entry 3:



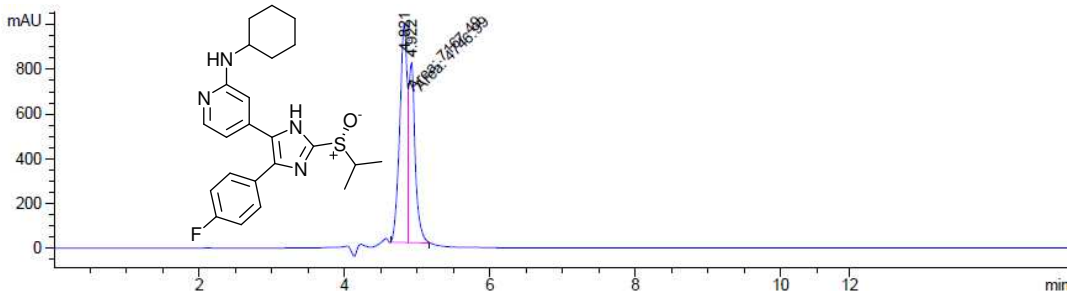
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.968	MF	0.1994	1.66976e4	1395.44336	39.9611
2	6.717	FM	0.2435	2.50870e4	1717.25171	60.0389

Table S1, entry 4: (*R*)-9c

$[\alpha]^{20}_{D}$ = +21.82 (*c* = 0.152 in Methanol)

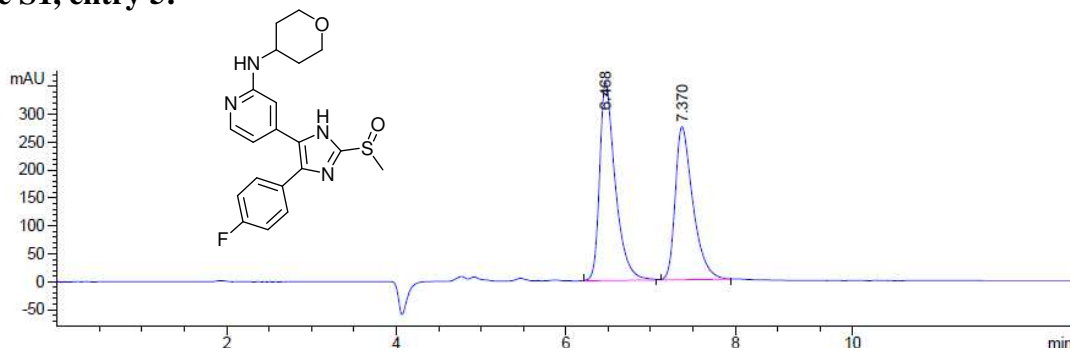
HPLC: t_R = 6.10 min, purity: 98.8% (λ = 254 nm), t_R = 6.10 min, purity: 99.7% (λ = 230 nm)

enantioselective analytical HPLC:



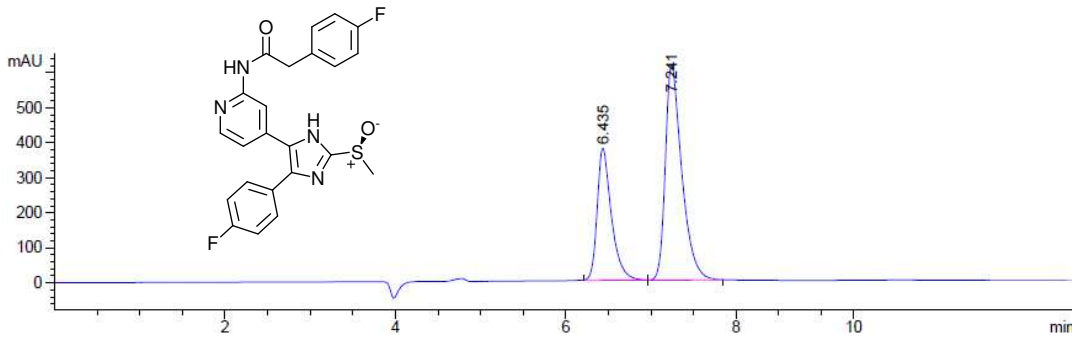
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.821	MF	0.1211	7167.49365	986.21497	60.1578
2	4.922	FM	0.0976	4746.98926	810.56329	39.8422

Table S1, entry 5:



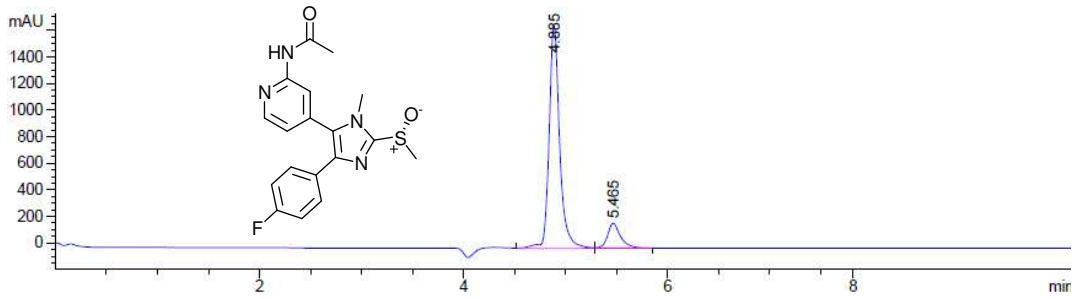
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.468	BB	0.1878	4551.16797	355.44589	53.3325
2	7.370	BB	0.2173	3982.40063	274.50888	46.6675

Table S1, entry 6:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.435	BV	0.1707	4386.38721	377.71722	34.6471
2	7.241	VB	0.2017	8273.78711	615.26544	65.3529

Table S1, entry 7:



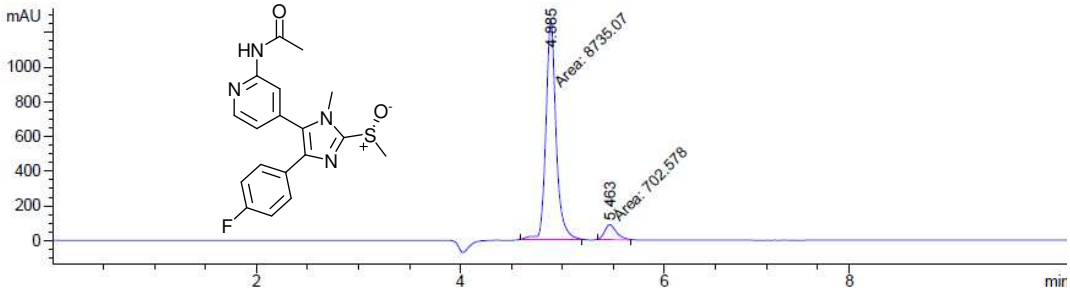
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.885	VV	0.1091	1.21111e4	1691.28357	87.8231
2	5.465	VB	0.1287	1679.22632	189.97368	12.1769

Table S1, entry 8: (*R*)-9a

$[\alpha]^{20}_{D}$ = -24.62 (*c* = 0.415 in Methanol)

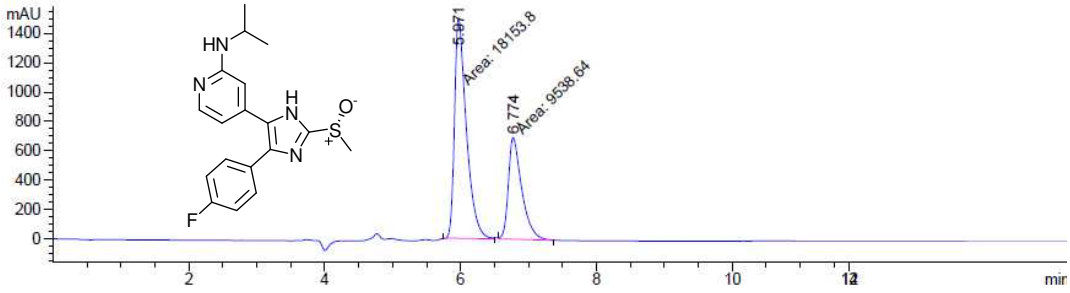
HPLC: t_R = 4.73 min, purity: 99.3% (λ = 254 nm), t_R = 4.73 min, purity: 99.4% (λ = 230 nm).

enantioselective analytical HPLC



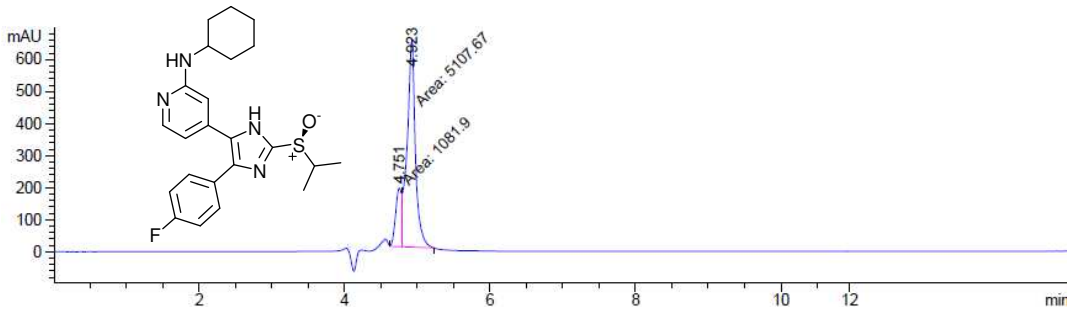
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.885	MM	0.1147	8735.07031	1269.05896	92.5556
2	5.463	MM	0.1348	702.57806	86.83472	7.4444

Table S1, entry 9:



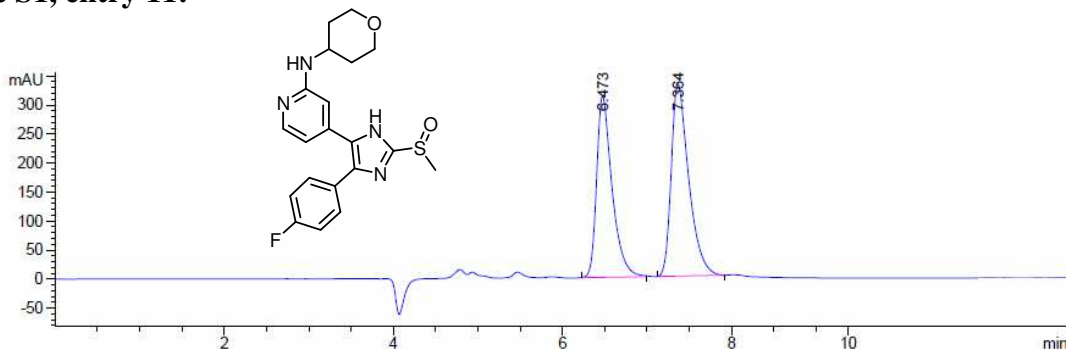
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.971	MM	0.2011	1.81538e4	1504.39783	65.5551
2	6.774	MM	0.2292	9538.64355	693.50909	34.4449

Table S1, entry 10:



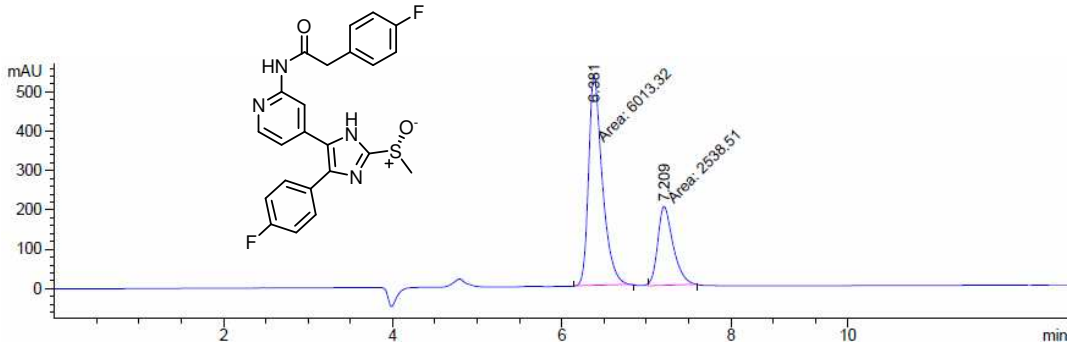
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.751	MF	0.0982	1081.89526	183.56537	17.4793
2	4.923	FM	0.1307	5107.66797	651.22919	82.5207

Table S1, entry 11:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.473	BB	0.1892	3962.22583	313.17130	45.4588
2	7.364	PP	0.2152	4753.84863	331.65970	54.5412

Table S1, entry 12:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.381	MM	0.1873	6013.31787	534.97937	70.3161
2	7.209	MM	0.2106	2538.51270	200.88330	29.6839

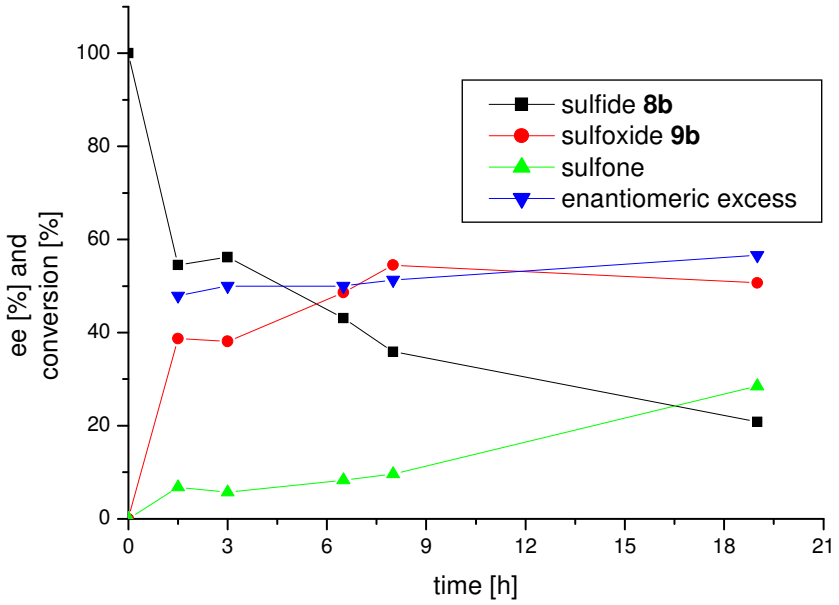


Figure S1. Time profile of the enantioselectivity (*%ee* of sulfoxide **9b**) and conversions (%) in the oxidation of the sulfide **8b** using the catalyst system Ti(O-*i*Pr)$_4$ (0.3 eq)/D-DET (0.6 eq)/H_2O (0.2 eq)/^{i}Pr$_2$NEt (0.3 eq)/CHP (1.0 eq).

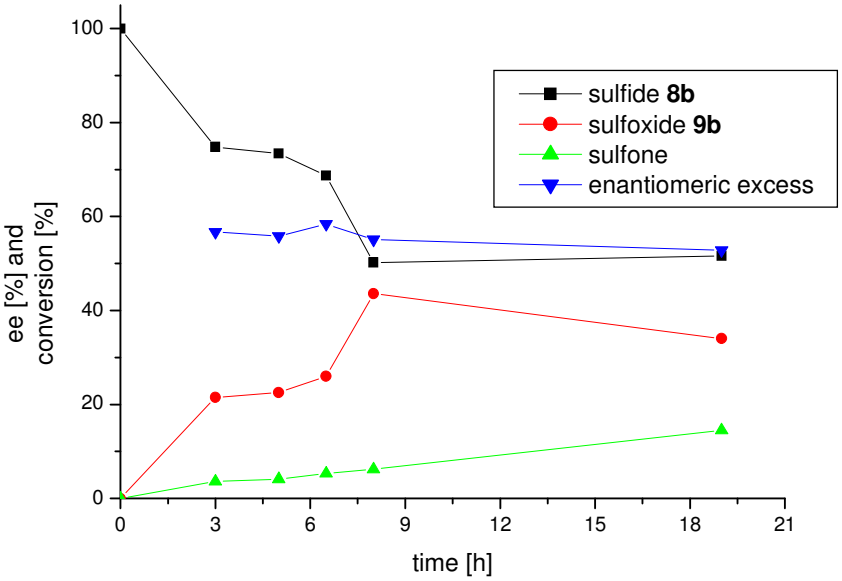
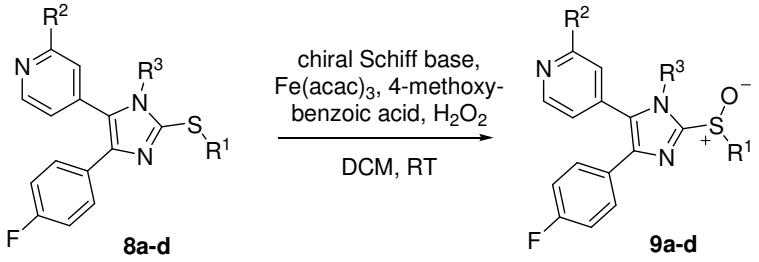


Figure S2. Time profile of the enantioselectivity (*%ee* of sulfoxide **9b**) and conversions (%) in the oxidation of the sulfide **8b** using the catalyst system Ti(O-*i*Pr)$_4$ (0.3 eq)/L-DET (0.6 eq)/H_2O (0.2 eq)/^{i}Pr$_2$NEt (0.3 eq)/CHP (1.0 eq).

5. Asymmetric Oxidation of Tri- and Tetrasubstituted 2-Thioimidazoles with $Fe(acac)_3$, H_2O_2 and chiral Schiff bases (*S*)-12d, (*S*)-12h, (*S*)-12l and (*R*)-12l.

General procedure E: $Fe(acac)_3$ (0.02- 0.2 eq) and the specific chiral Schiff base **(*S*)-12d, (*S*)-12h, (*S*)-12l** or **(*R*)-12l** (0.04- 0.4 eq.) were dissolved in 4.0 mL dichloromethane. After stirring at room temperature for 1 h, the resulting solution was added to a suspension of 4-methoxybenzoic acid (0.01- 0.2 eq.) in 1.0 mL dichloromethane. The mixture was stirred for 10 min, followed by the addition of the respective 2-thioimidazole **8a-d** (1.0 eq.). The solution was then treated with 32 % aqueous H_2O_2 (1.2- 2.0 eq.) and was stirred at room temperature; until HPLC analysis indicate complete conversion. The mixture was combined with water and extracted with dichloromethane. The organic extract was washed with brine and water, and dried over Na_2SO_4. After rotary evaporation, the crude product was purified by flash chromatography on silica gel to obtain the pure sulfoxide. The enantiomer ratio of the sulfoxides **9a-d** was determined by enantioselective, analytical HPLC (Daicel CHIRALPAK IA, 4.6 x 250 mm, 5 μm, 0.8 ml/min, CH_2Cl_2/MeOH/TEA 98: 2: 0.1, λ = 254 nm, 0.8 mL/min flow rate).

Table S2. The Catalytic Enantioselective Oxidation of the Selected 2-Thioimidazoles with $Fe(acac)_3$, H_2O_2 and Different Chiral Schiff Bases **(*S*)-12d**, **(*S*)-12h**, **(*S*)-12l** and **(*R*)-12l**.

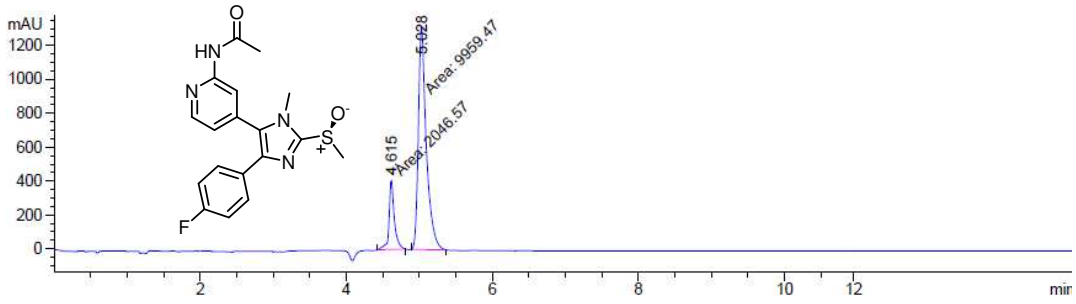


8a-d **9a-d**

Entry	Sulfide	Ligand	Conditions[a]	Conversion [%]	Enantio ratio E_1: E_2 [%][c]	*ee* [%]
1	**8a**	**(*S*)-12l**	A (18)[b]	43	17.0 : 83.0	66
2	**8a**	**(*S*)-12l**	B (23)[b]	52	17.8 : 82.2	64
3	**8a**	**(*S*)-12l**	C (23)[b]	48	29.4 : 70.6	41
4	**8a**	**(*S*)-12h**	D (19)[b]	17	39.0 : 61.0	22
5	**8a**	**(*S*)-12d**	D (22)[b]	34	29.4 : 70.6	41
6	**8b**	**(*S*)-12l**	E (22)[b]	65	6.8 : 93.2	86
7	**8b**	**(*S*)-12h**	E (19)[b]	73	5.8 : 94.2	88
8	**8b**	**(*S*)-12d**	E (19)[b]	54	24.3 : 75.7	51
9	**8c**	**(*S*)-12l**	E (18)[b]	33	3.4 : 96.6	**93**
10	**8c**	**(*S*)-12h**	E (22)[b]	45	2.7 : 97.3	**95**
11	**8c**	**(*S*)-12d**	E (18)[b]	35	18.3 : 81.7	63
12	**8d**	**(*S*)-12l**	E (20)[b]	38	13.6 : 86.4	73
13	**8d**	**(*S*)-12h**	E (20)[b]	39	2.2 : 97.8	**96**
14	**8d**	**(*S*)-12d**	E (19)[b]	31	11.9 : 88.1	76
15	**8a**	**(*R*)-12l**	D (24)[b]	46	80.0 : 20.0	60

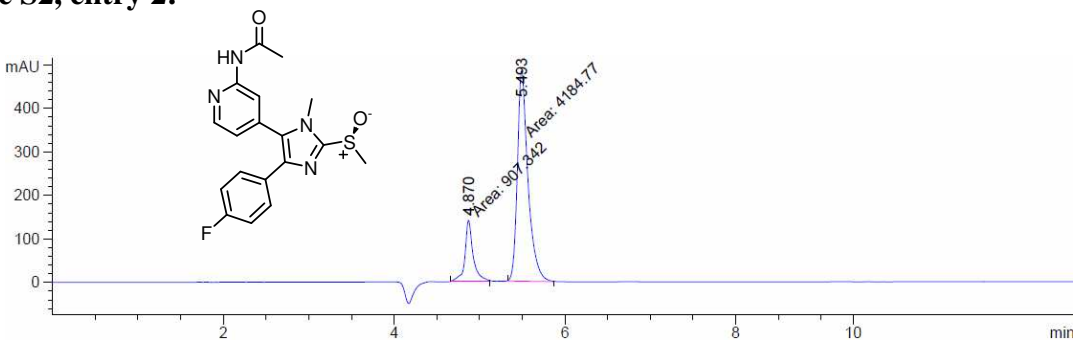
[a]Conditions: A: $Fe(acac)_3$ (0.02 eq)/ligand (0.04 eq)/4-methoxybenzoic acid (0.01 eq)/H_2O_2 (1.2 eq), CH_2Cl_2, RT. B: $Fe(acac)_3$ (0.04 eq)/ligand (0.08 eq)/4-methoxybenzoic acid (0.02 eq)/H_2O_2 (1.6 eq), CH_2Cl_2, RT. C: $Fe(acac)_3$ (0.08 eq)/ligand (0.16 eq)/4-methoxybenzoic acid (0.02 eq)/H_2O_2 (2.0 eq), CH_2Cl_2, RT. D: $Fe(acac)_3$ (0.02 eq)/ligand (0.04 eq)/4-methoxybenzoic acid (0.02 eq)/H_2O_2 (1.2 eq), CH_2Cl_2, RT. E: $Fe(acac)_3$ (0.2 eq)/ligand (0.4 eq)/4-methoxybenzoic acid (0.2 eq)/H_2O_2 (1.2 eq), CH_2Cl_2, RT. [b]Reaction time in (h). [c]Determined by enantioselective analytical HPLC using a Daicel CHIRALPAK IA column.

Table S2, entry 1:



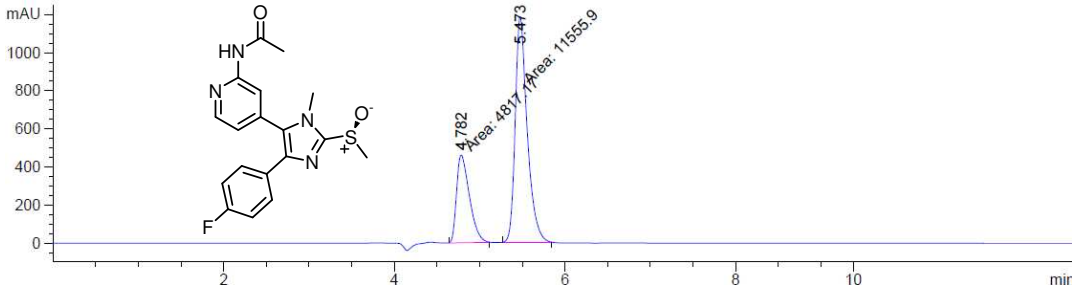
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.615	MM	0.0823	2046.56592	414.34912	17.0461
2	5.028	MM	0.1254	9959.46777	1323.58118	82.9539

Table S2, entry 2:



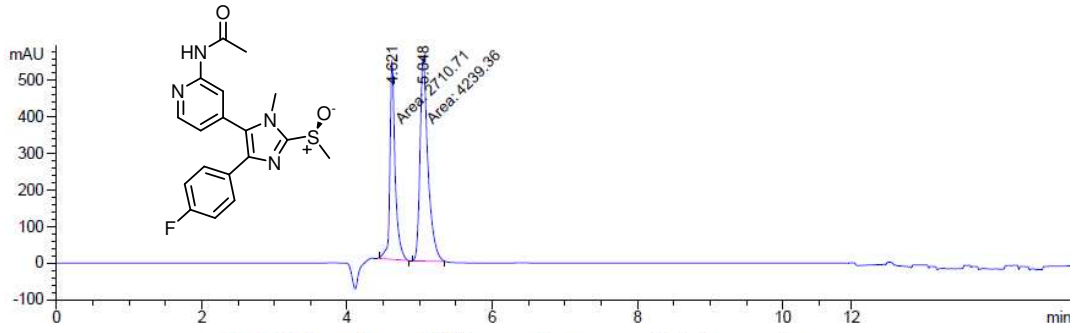
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.870	MM	0.1071	907.34222	141.24455	17.8186
2	5.493	MM	0.1430	4184.76855	487.59988	82.1814

Table S2, entry 3:



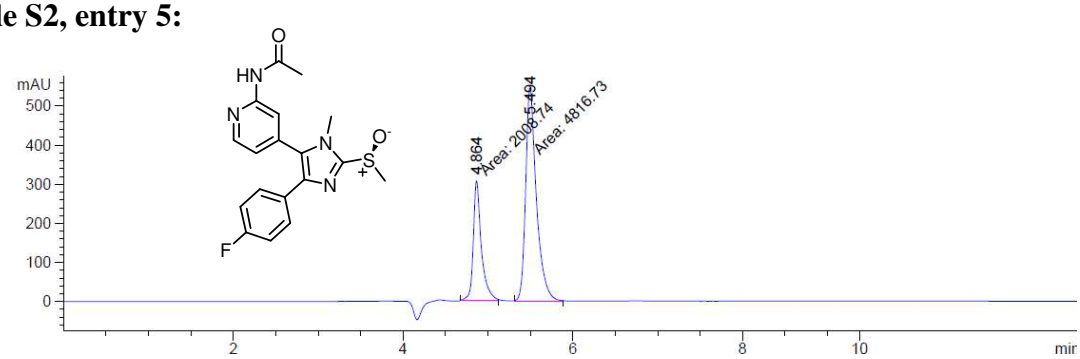
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.782	MM	0.1740	4817.17334	461.40613	29.4214
2	5.473	MM	0.1618	1.15559e4	1190.01233	70.5786

Table S2, entry 4:



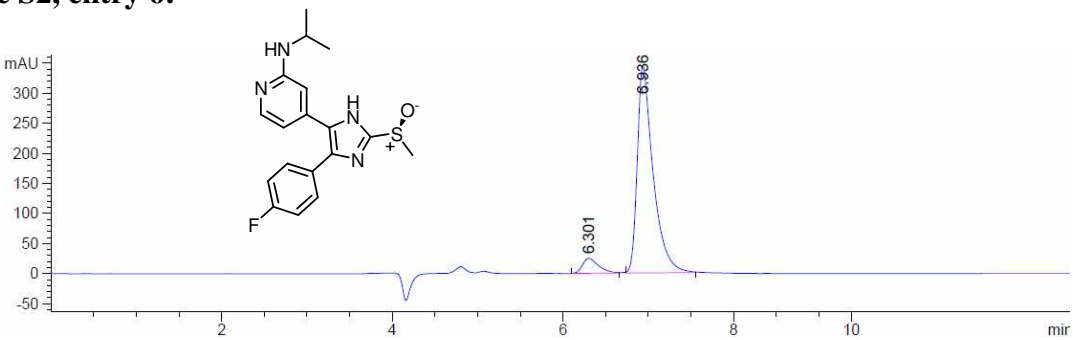
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.621	MM	0.0822	2710.70752	549.39825	39.0026
2	5.048	MM	0.1258	4239.36133	561.53796	60.9974

Table S2, entry 5:



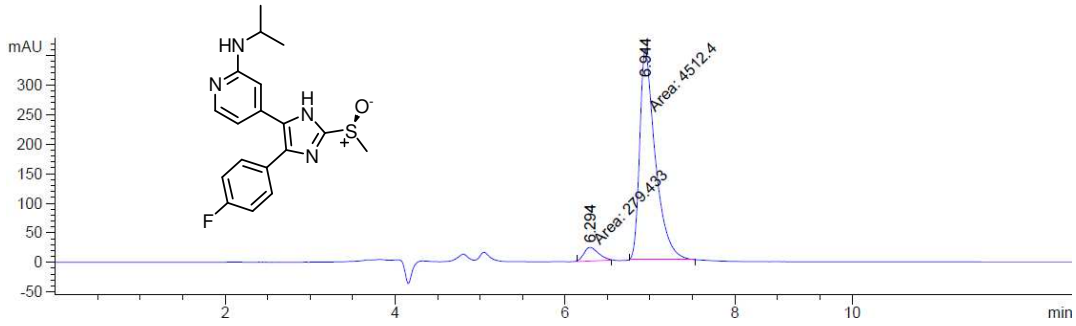
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.864	MM	0.1080	2008.74011	310.06665	29.4301
2	5.494	MM	0.1460	4816.73047	549.73486	70.5699

Table S2, entry 6:



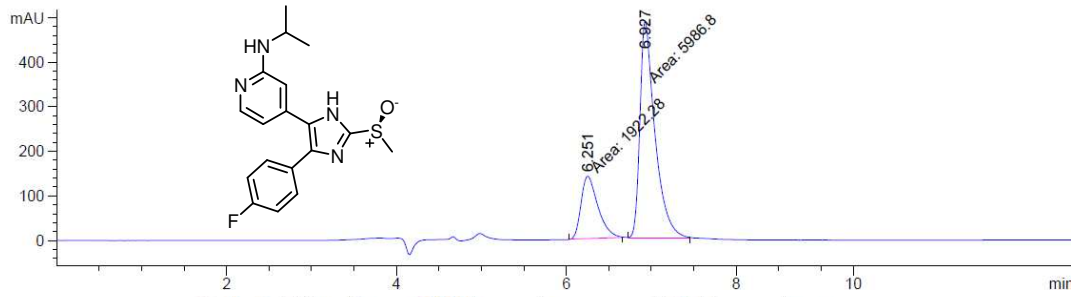
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.301	BB	0.1964	324.70361	24.98247	6.8215
2	6.936	BB	0.1858	4435.27588	343.65280	93.1785

Table S2, entry 7:



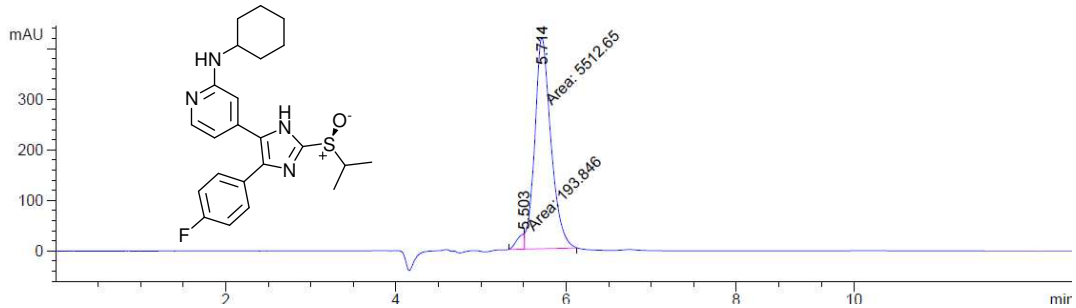
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.294	MM	0.1993	279.43314	23.36835	5.8314
2	6.944	MM	0.2120	4512.39844	354.70914	94.1686

Table S2, entry 8:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.251	MM	0.2289	1922.28076	139.96106	24.3047
2	6.927	MM	0.2049	5986.80273	487.04388	75.6953

Table S2, entry 9:



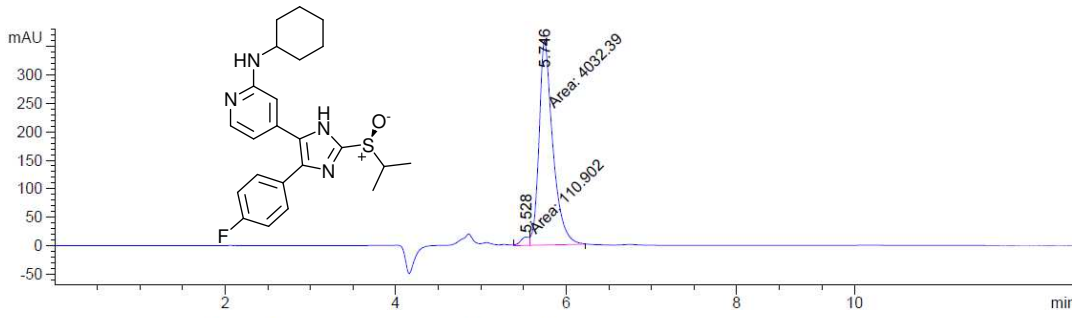
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.503	MF	0.1052	193.84630	30.71131	3.3969
2	5.714	FM	0.2199	5512.64551	417.81491	96.6031

Table S2, entry 10: (*S*)-9c

$[\alpha]^{20}_{D}$ = -43.33 (*c* = 0.150 in Methanol)

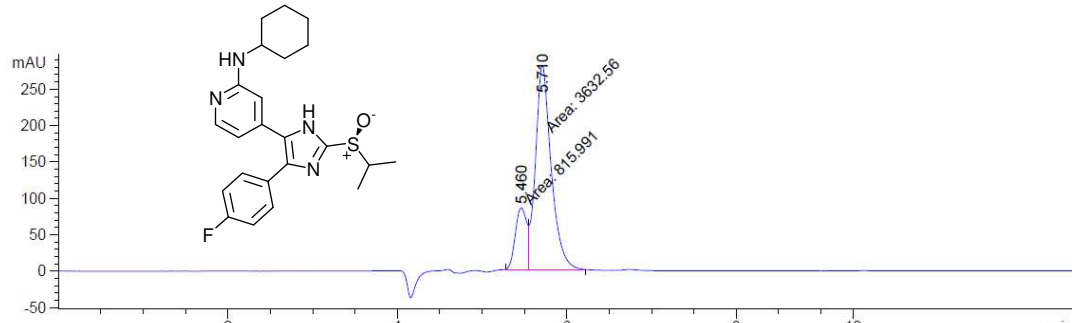
HPLC: t_R = 6.09 min, purity: 98.7% (λ = 254 nm), t_R = 6.09 min, purity: 99.0% (λ = 230 nm)

enantioselective analytical HPLC:



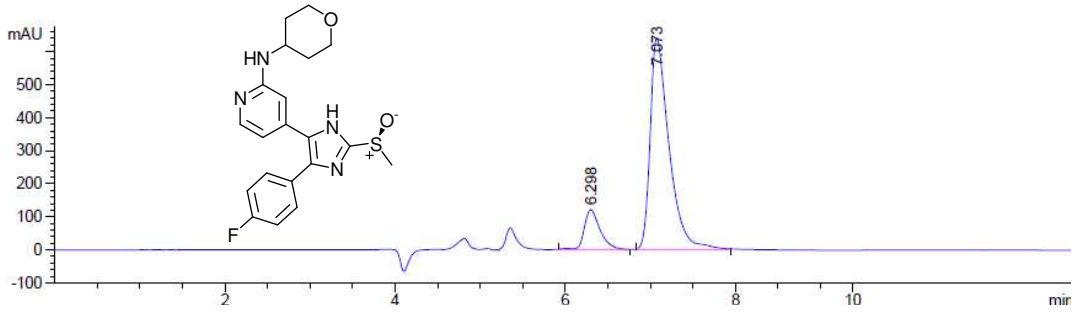
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.528	MF	0.1252	110.90154	14.75742	2.6766
2	5.746	FM	0.1865	4032.39478	360.31870	97.3234

Table S2, entry 11:



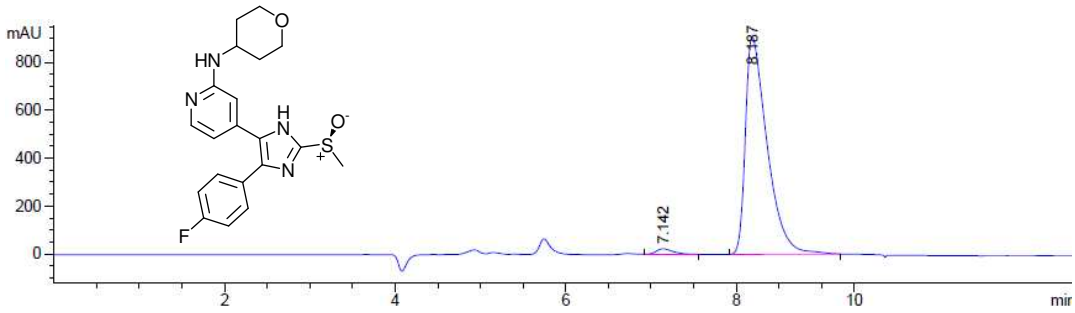
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.460	MF	0.1590	815.99078	85.51292	18.3428
2	5.710	FM	0.2154	3632.55908	281.06638	81.6572

Table S2, entry 12:



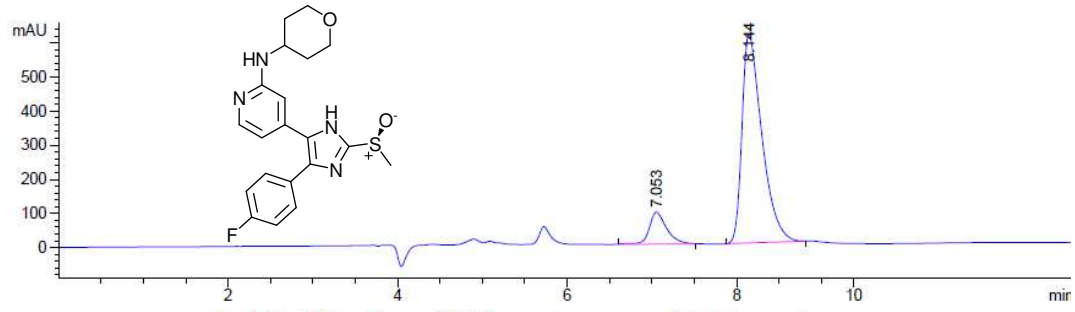
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.298	BB	0.1944	1548.33606	120.73755	13.6030
2	7.073	BB	0.2272	9833.97461	640.38538	86.3970

Table S2, entry 13:



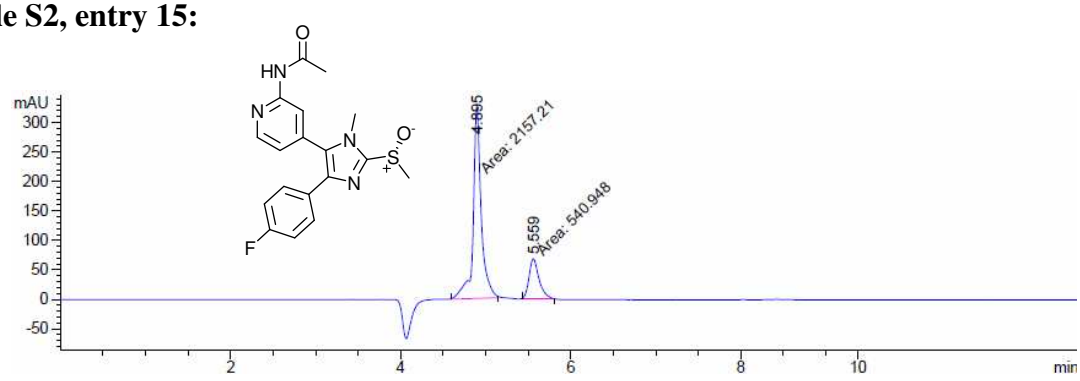
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.142	VB	0.2219	360.66196	24.65666	2.1896
2	8.187	BB	0.2613	1.61110e4	908.60681	97.8104

Table S2, entry 14:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.053	BB	0.2128	1354.03125	94.01967	11.9455
2	8.144	PB	0.2447	9981.02344	611.85815	88.0545

Table S2, entry 15:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.895	MM	0.1091	2157.21045	329.52838	79.9512
2	5.559	MM	0.1333	540.94830	67.62219	20.0488

6. Asymmetric Oxidation of Tri- and Tetrasubstituted 2-Thioimidazoles with Ti(O-*i*Pr)$_4$, (*S*)-BINOL and TBHP.

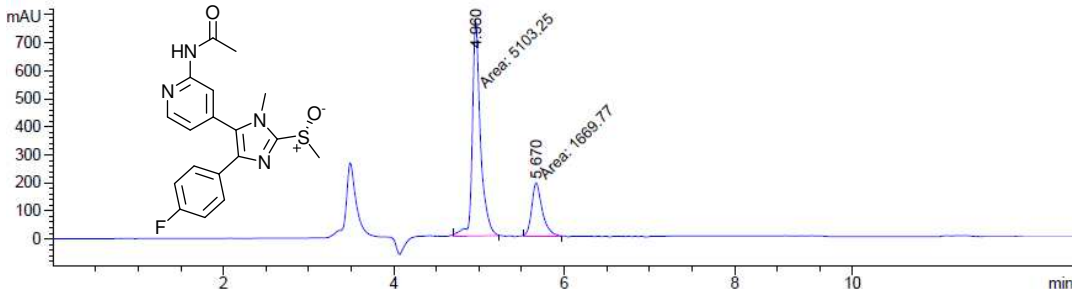
General Procedure F: Ti(O-*i*Pr)$_4$ (0.1 eq.) was added dropwise to a solution of (*S*)-BINOL (0.2 eq.) in 6.0 mL dichloromethane. After stirring for 20 min at room temperature, water (0.2 eq.) and the specific 2-thioimidazole **8a-b**, **8d-l** (1.0 eq.) were added. The resulting mixture was stirred initially at room temperature for 30 min and was then cooled to T = 5 °C (or room temperature for compound **8e**) for 20 min, followed by the dropwise addition of TBHP (70 % in water, 2.0 eq.). The progress of the reaction was monitored until HPLC analysis indicated complete conversion. After reaction completion, the reaction mixture was allowed to warm to room temperature and was stirred for another 45 min before being diluted with CH_2Cl_2 and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude product was purified by flash chromatography on silica gel to yield the pure sulfoxide. The enantiomer ratio of the sulfoxides **9a-b**, **9d-l** was determined by enantioselective, analytical HPLC (Daicel CHIRALPAK IA, 4.6 x 250 mm, 5 μm, 0.8 ml/min, CH_2Cl_2/MeOH/TEA 98: 2: 0.1, λ = 254 nm, 0.8 mL/min flow rate).

Table S3. Asymmetric Oxidation of the 2-Thioimidazoles with the System Ti(O-*i*Pr)$_4$/*S*-BINOL/H_2O/TBHP.

Entry	Sulfide	Cond.[a]	Conversion [%]	Enantio ratio $E_1 : E_2$ [%][c]	*ee* [%]	Config.
1	**8a**	A (22)[b]	74	75.3 : 24.7	51	***(R)***
2	**8b**	A (3)[b]	97	99.3 : 0.7	**99**	***(R)***
3	**8d**	A (20)[b]	77	98.8 : 1.2	**98**	***(R)***
4	**8e**	B (23)[b]	87	81.2 : 18.8	62	***(R)***
5	**8f**	A (7)[b]	63	97.6 : 2.4	**95**	***(R)***
6	**8g**	A (4)[b]	92	96.5 : 3.5	**93**	***(R)***
7	**8h**	A (4)[b]	90	98.6 : 1.4	**97**	***(R)***
8	**8i**	A (3)[b]	91	98.5 : 1.5	**97**	***(R)***
9	**8j**	A (3)[b]	90	98.2 : 1.8	**96**	***(R)***
10	**8k**	A (3)[b])	89	96.5 : 3.5	**93**	***(R)***
11	**8l**	A (7)[b]	85	94.4 : 5.6	89	***(R)***

[a]Conditions: A: Ti(O-*i*Pr)$_4$ (0.1 eq)/*S*-BINOL (0.2 eq)/H_2O (0.2 eq)/TBHP (2.0 eq), CH_2Cl_2, 5 °C. B: Ti(O-*i*Pr)$_4$ (0.1 eq)/*S*-BINOL (0.2 eq)/H_2O (0.2 eq)/TBHP (2.0 eq), CH_2Cl_2, RT. [b]Reaction time in (h). [c]Determined by enantioselective analytical HPLC using a Daicel CHIRALPAK IA column.

Table S3, entry 1:



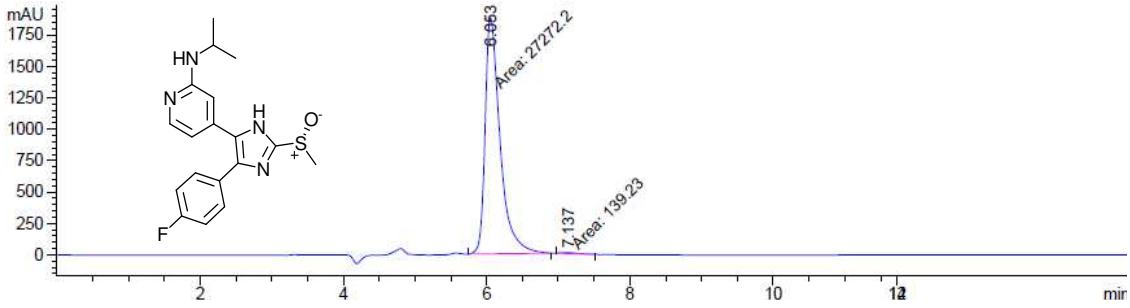
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.960	MM	0.1097	5103.25049	775.19940	75.3468
2	5.670	MM	0.1452	1669.76721	191.66132	24.6532

Table S3, entry 2: (*R*)-9b

$[\alpha]^{20}_{D}$ = -5.06 (*c* = 0.474 in Methanol)

HPLC: t_R = 2.87 min, purity: 98.3% (λ = 254 nm), t_R = 2.87 min, purity: 98.3% (λ = 230 nm).

enantioselective analytical HPLC:



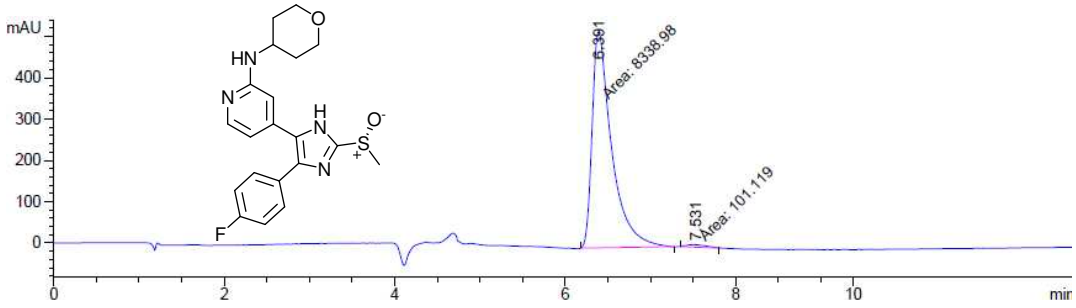
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.053	MM	0.2413	2.72722e4	1883.87976	99.4921
2	7.137	MM	0.2814	139.22957	8.24738	0.5079

Table S3, entry 3: (*R*)-9d

$[\alpha]^{20}_{D}$ = -8.36 (*c* = 0.528 in Methanol)

HPLC: t_R = 2.77 min, purity: 100.0% (λ = 254 nm), t_R = 2.77 min, purity: 100.0% (λ = 230 nm).

enantioselective analytical HPLC:



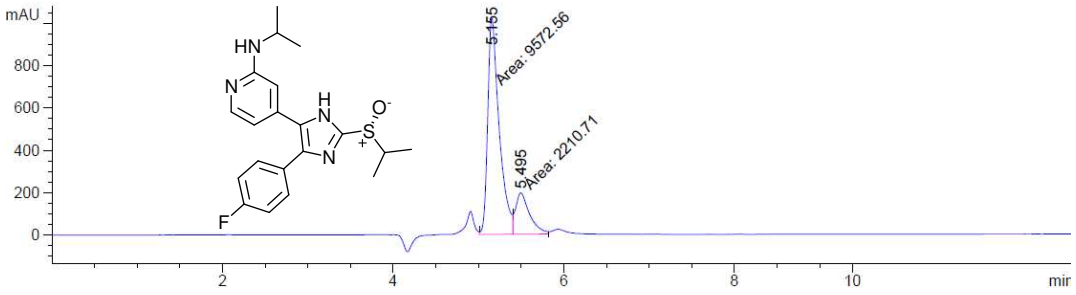
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.391	MM	0.2650	8338.97949	524.42279	98.8019
2	7.531	MM	0.2720	101.11868	6.19652	1.1981

Table S3, entry 4: (*R*)-9e

$[\alpha]^{20}_{D}$ = +32.65 (*c* = 0.269 in Methanol)

HPLC: t_R = 4.36 min, purity: 99.4% (λ = 254 nm), t_R = 4.36 min, purity: 99.6% (λ = 230 nm)

enantioselective analytical HPLC:



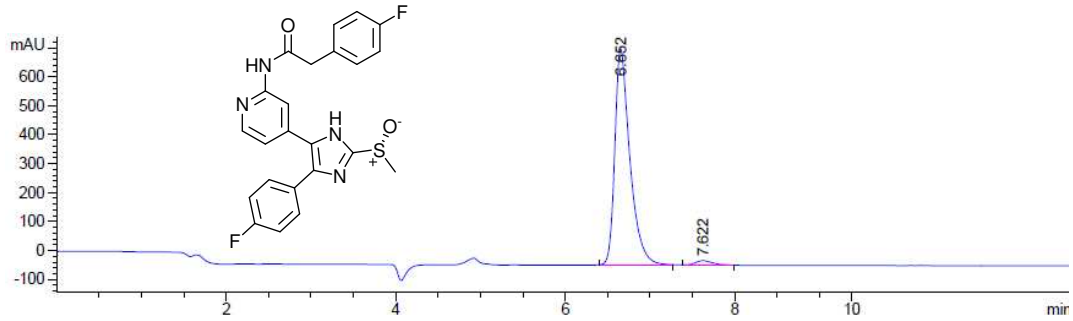
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.155	MF	0.1554	9572.55664	1026.70117	81.2386
2	5.495	MF	0.1881	2210.70972	195.90906	18.7614

Table S3, entry 5: (*R*)-9f

$[\alpha]^{20}_{D}$ = -3.25 (*c* = 0.529 in Methanol)

HPLC: t_R = 6.94 min, purity: 98.3% (λ = 254 nm), t_R = 6.94 min, purity: 96.8% (λ = 230 nm)

enantioselective analytical HPLC:



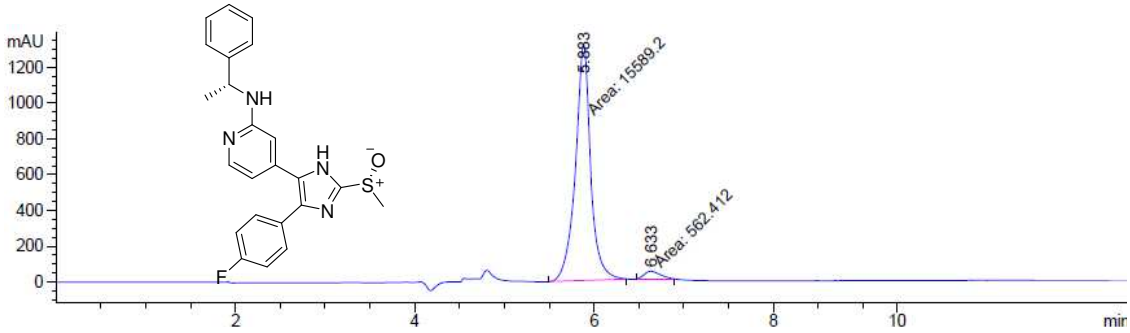
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.652	BB	0.1794	9244.79199	748.18036	97.5753
2	7.622	BB	0.2106	229.72818	15.85428	2.4247

Table S3, entry 6: (*R*)-9g

$[\alpha]^{20}_{D}$ = +46.46 (*c* = 0.419 in Methanol)

HPLC: t_R = 5.30 min, purity: 96.3% (λ = 254 nm), t_R = 5.30 min, purity: 96.4% (λ = 230 nm)

enantioselective analytical HPLC:



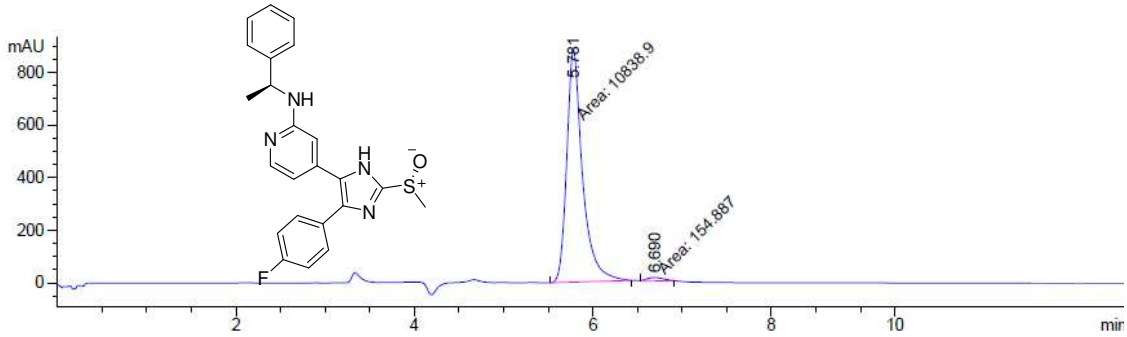
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.883	MM	0.1969	1.55892e4	1319.61340	96.5179
2	6.633	MM	0.2114	562.41199	44.34537	3.4821

Table S3, entry 7: (*R*)-9h

$[\alpha]^{20}_{D}$ = -59.09 (*c* = 1.012 in Methanol)

HPLC: t_R = 4.72 min, purity: 96.2% (λ = 254 nm), t_R = 4.72 min, purity: 98.8% (λ = 230 nm)

enantioselective analytical HPLC:



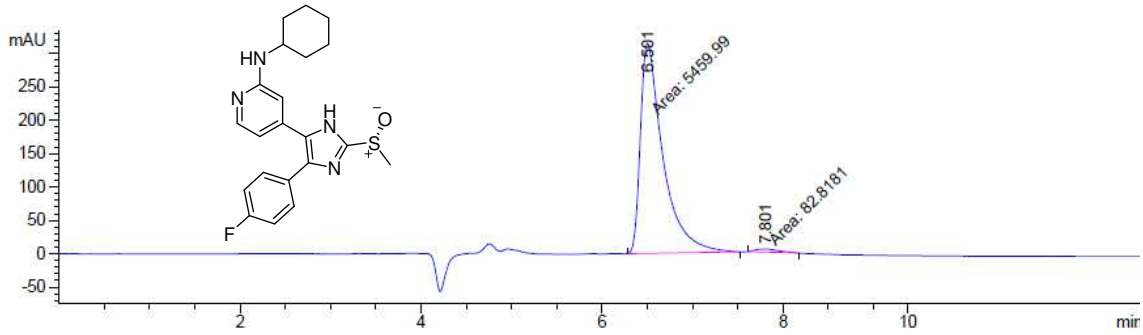
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.781	MM	0.2041	1.08389e4	885.02307	98.5911
2	6.690	MM	0.2127	154.88672	12.13928	1.4089

Table S3, entry 8: (*R*)-9i

$[\alpha]^{20}_{D}$ = -8.30 (*c* = 1.024 in Methanol).

HPLC: t_R = 4.81 min, purity: 98.3% (λ = 254 nm), t_R = 4.81 min, purity: 98.1% (λ = 230 nm)

enantioselective analytical HPLC:



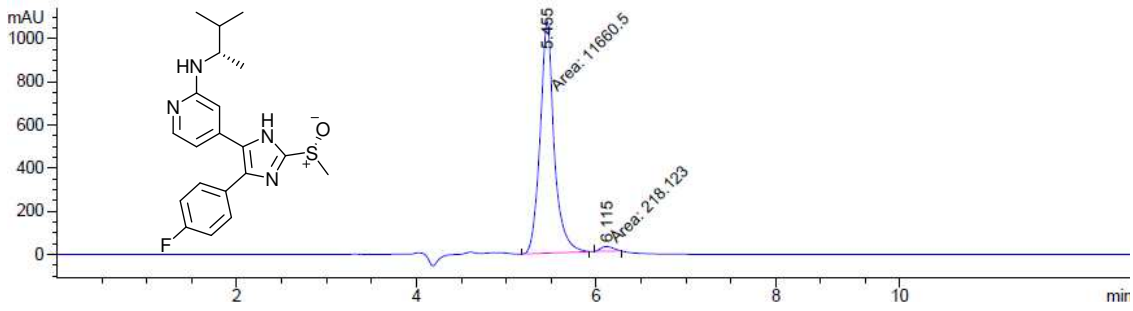
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.501	MM	0.2889	5459.98975	314.97009	98.5058
2	7.801	MM	0.2911	82.81809	4.74157	1.4942

Table S3, entry 9: (*R*)-9j

$[\alpha]^{20}_{D}$ = +31.17 (*c* = 0.515 in Methanol)

HPLC: t_R = 4.75 min, purity: 98.2% (λ = 254 nm), t_R = 4.75 min, purity: 98.2% (λ = 230 nm)

enantioselective analytical HPLC:



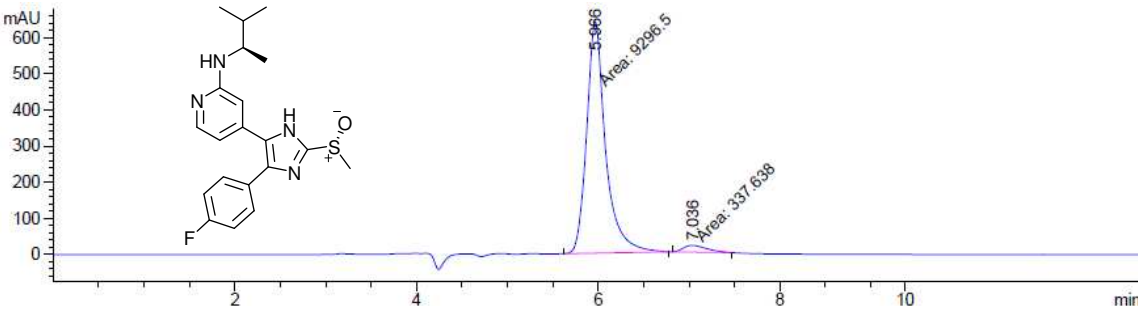
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.455	MM	0.1802	1.16605e4	1078.68335	98.1637
2	6.115	MM	0.1645	218.12263	22.10065	1.8363

Table S3, entry 10: (*R*)-9k

$[\alpha]^{20}_{D}$ = -24.35 (*c* = 0.232 in Methanol)

HPLC: t_R = 4.74 min, purity: 96.8% (λ = 254 nm), t_R = 4.74 min, purity: 96.4% (λ = 230 nm).

enantioselective analytical HPLC:



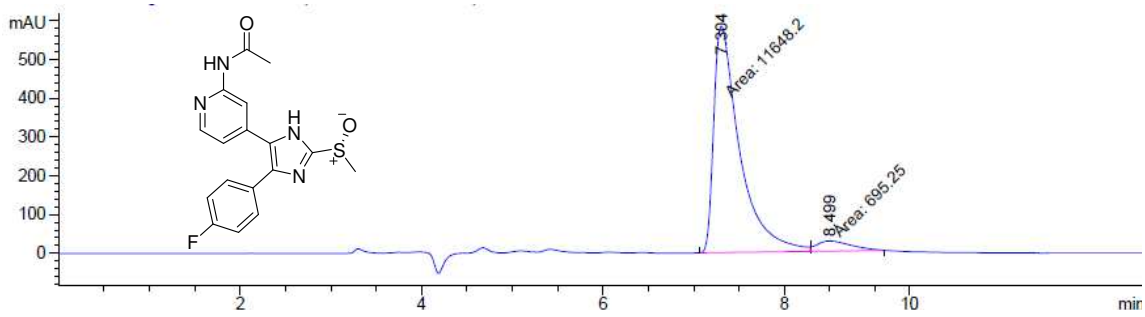
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.966	MM	0.2413	9296.50391	642.05768	96.4954
2	7.036	MM	0.3017	337.63812	18.65020	3.5046

Table S3, entry 11: (*R*)-9l

$[\alpha]^{20}_{D}$ = -7.00 (*c* = 0.533 in Methanol)

HPLC: t_R = 4.30 min, purity: 97.9% (λ = 254 nm), t_R = 4.30 min, purity: 98.1% (λ = 230 nm)

enantioselective analytical HPLC:

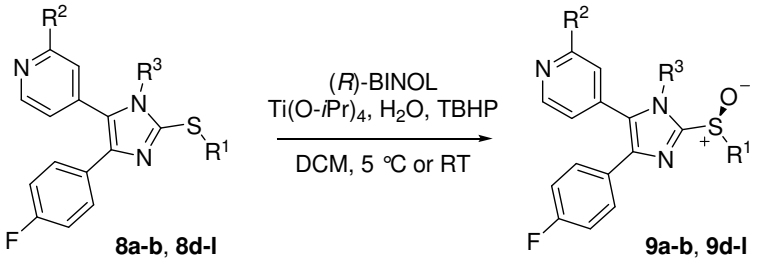


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.304	MF	0.3320	1.16482e4	584.71082	94.3674
2	8.499	FM	0.4389	695.25049	26.40201	5.6326

7. Asymmetric Oxidation of Tri- and Tetrasubstituted 2-Thioimidazoles with Ti(O-*i*Pr)$_4$, (*R*)-BINOL and TBHP.

General Procedure F: Ti(O-*i*Pr)$_4$ (0.1 eq.) was added dropwise to a solution of (*R*)-BINOL (0.2 eq.) in 6.0 mL dichloromethane. After stirring for 20 min at room temperature, water (0.2 eq.) and the specific 2-thioimidazole **8a-b**, **8d-l** (1.0 eq.) were added. The resulting mixture was stirred initially at room temperature for 30 min and was then cooled to T = 5 °C (or room temperature for compound **8e**) for 20 min, followed by the dropwise addition of TBHP (70 % in water, 2.0 eq.). The progress of the reaction was monitored until HPLC analysis indicated complete conversion. After reaction completion, the reaction mixture was allowed to warm to room temperature and was stirred for another 45 min before being diluted with CH_2Cl_2 and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude product was purified by flash chromatography on silica gel to yield the pure sulfoxide. The enantiomer ratio of the sulfoxides **9a-b**, **9d-l** was determined by enantioselective, analytical HPLC (Daicel CHIRALPAK IA, 4.6 x 250 mm, 5 μm, 0.8 ml/min, CH_2Cl_2/MeOH/TEA 98: 2: 0.1, λ = 254 nm, 0.8 mL/min flow rate).

Table S4. Asymmetric Oxidation of the 2-Thioimidazoles with the System Ti(O-*i*Pr)$_4$/*R*-BINOL/H_2O/TBHP.

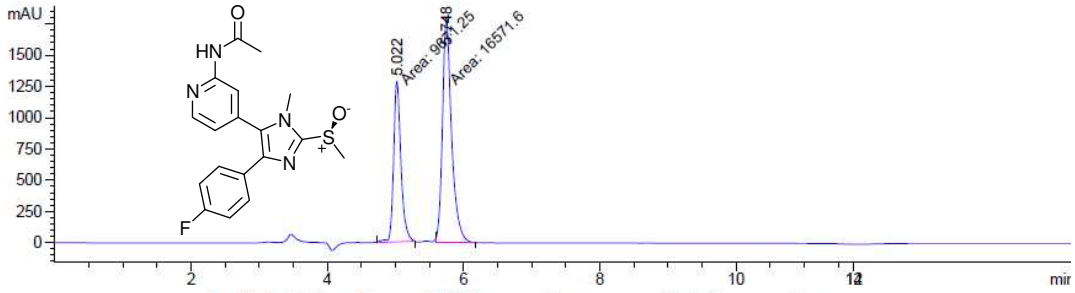


8a-b, **8d-l** **9a-b**, **9d-l**

Entry	Sulfide	Cond.[a]	Conversion [%]	Enantio ratio E_1 : E_2 [%][c]	*ee* [%]	Config.
1	**8a**	A (20)[b]	48	36.9 : 63.1	26	***(S)***
2	**8b**	A (4)[b]	95	0.9 : 99.1	**98**	***(S)***
3	**8d**	A (18)[b]	80	2.4 : 97.6	**95**	***(S)***
4	**8e**	B (24)[b]	63	21.2 : 78.8	58	***(S)***
5	**8f**	A (6)[b]	72	1.5 : 98.5	**97**	***(S)***
6	**8g**	A (6)[b]	88	3.4 : 96.6	**93**	***(S)***
7	**8h**	A (4)[b]	87	0.4 : 99.6	**99**	***(S)***
8	**8i**	A (3)[b]	90	1.1 : 98.9	**98**	***(S)***
9	**8j**	A (3)[b]	91	3.6 : 96.4	**93**	***(S)***
10	**8k**	A (4)[b]	87	3.2 : 96.8	**94**	***(S)***
11	**8l**	A (7)[b	74	6.5 : 93.5	87	***(S)***

[a]Conditions: A: Ti(O-*i*Pr)$_4$ (0.1 eq)/*R*-BINOL (0.2 eq)/H_2O (0.2 eq)/TBHP (2.0 eq), CH_2Cl_2, 5 °C. B: Ti(O-*i*Pr)$_4$ (0.1 eq)/*R*-BINOL (0.2 eq)/H_2O (0.2 eq)/TBHP (2.0 eq), CH_2Cl_2, RT. [b]Reaction time in (h). [c]Determined by enantioselective analytical HPLC using a Daicel CHIRALPAK IA column.

Table S4, entry 1:



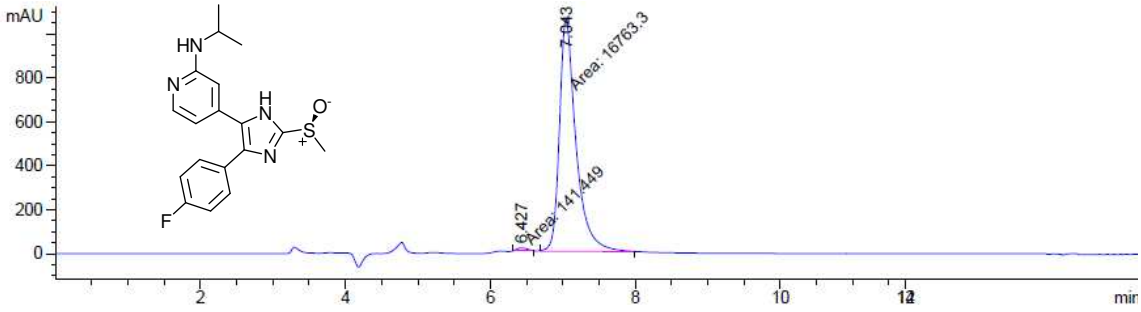
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.022	MM	0.1248	9671.25098	1291.36255	36.8529
2	5.748	MM	0.1535	1.65716e4	1799.25562	63.1471

Table S4, entry 2: (*S*)-9b

$[\alpha]^{20}_{D}$ = +14.89 (*c* = 0.470 in Methanol)

HPLC: t_R = 2.90 min, purity: 97.8% (λ = 254 nm), t_R = 2.90 min, purity: 97.0% (λ = 230 nm).

enantioselective analytical HPLC:



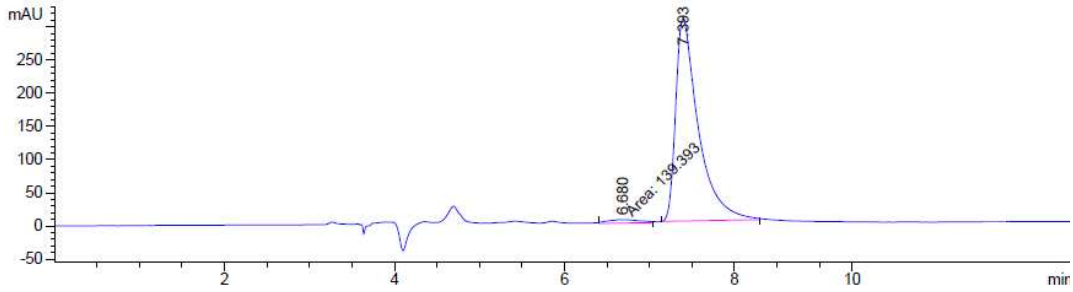
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.427	MM	0.1697	141.44910	13.89540	0.8367
2	7.043	MM	0.2642	1.67633e4	1057.38770	99.1633

Table S4, entry 3: (*S*)-9d

$[\alpha]^{20}_{D}$ = +5.32 (*c* = 0.533 in Methanol)

HPLC: t_R = 2.77 min, purity: 98.3% (λ = 254 nm), t_R = 2.77 min, purity: 97.5% (λ = 230 nm).

enantioselective analytical HPLC:



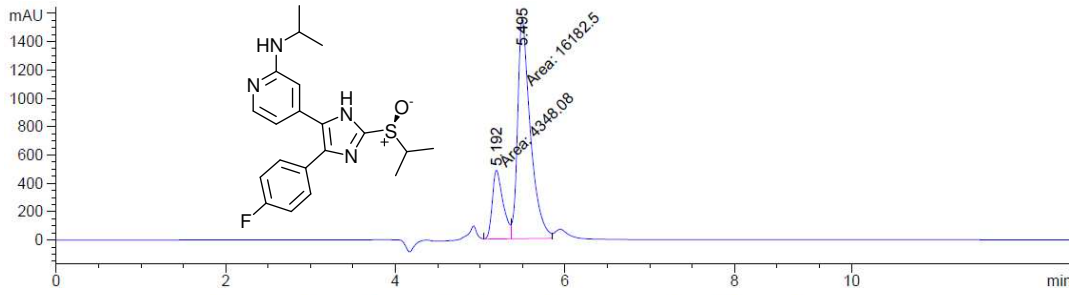
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.680	MM	0.4415	139.39279	5.26259	2.4085
2	7.393	PB	0.2667	5648.13379	305.82901	97.5915

Table S4, entry 4: (*S*)-9e

$[\alpha]^{20}_{D}$ = -29.60 (*c* = 0.272 in Methanol)

HPLC: t_R = 4.34 min, purity: 98.6% (λ = 254 nm), t_R = 4.34 min, purity: 98.2% (λ = 230 nm)

enantioselective analytical HPLC:



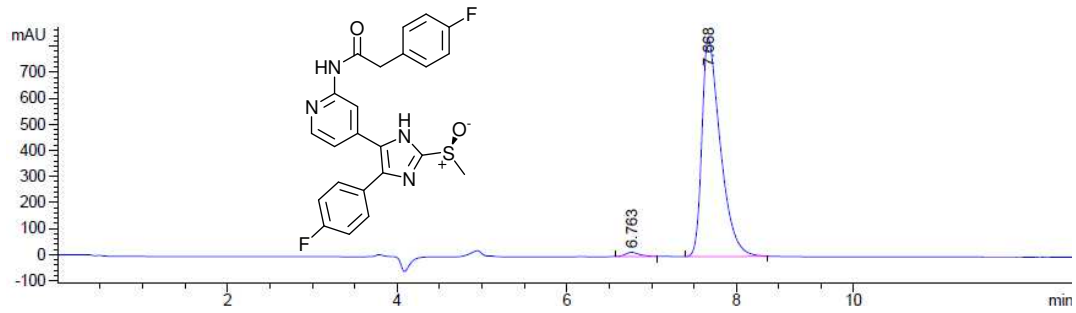
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.192	MF	0.1489	4348.07813	486.59494	21.1785
2	5.495	MF	0.1736	1.61825e4	1553.46033	78.8215

Table S4, entry 5: (*S*)-9f

$[\alpha]^{20}_{D}$ = +3.42 (*c* = 0.546 in Methanol)

HPLC: t_R = 6.94 min, purity: 97.8% (λ = 254 nm), t_R = 6.94 min, purity: 96.7% (λ = 230 nm)

enantioselective analytical HPLC:



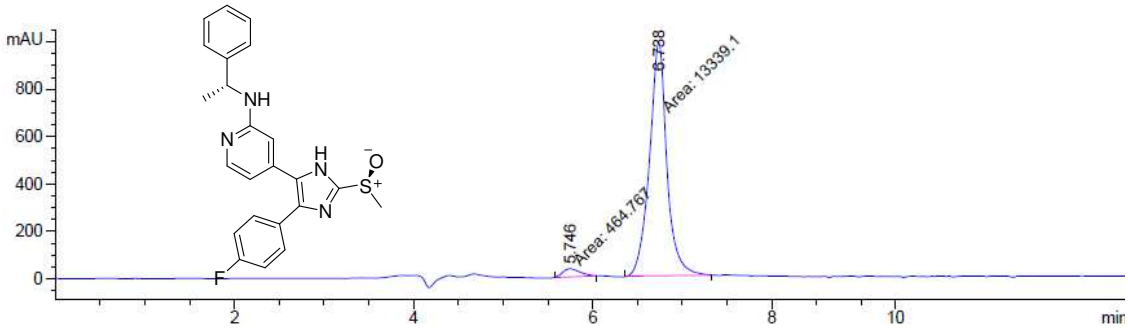
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.763	BB	0.1756	192.72313	16.38906	1.4987
2	7.668	PB	0.2279	1.26670e4	836.56354	98.5013

Table S4, entry 6: (*S*)-9g

$[\alpha]^{20}_{D}$ = +41.85 (*c* = 0.415 in Methanol)

HPLC: t_R = 4.73 min, purity: 98.5% (λ = 254 nm), t_R = 4.73 min, purity: 97.3% (λ = 230 nm)

enantioselective analytical HPLC:



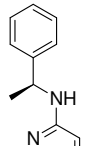
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.746	MM	0.2250	464.76706	34.42511	3.3669
2	6.738	MM	0.2253	1.33391e4	986.92981	96.6331

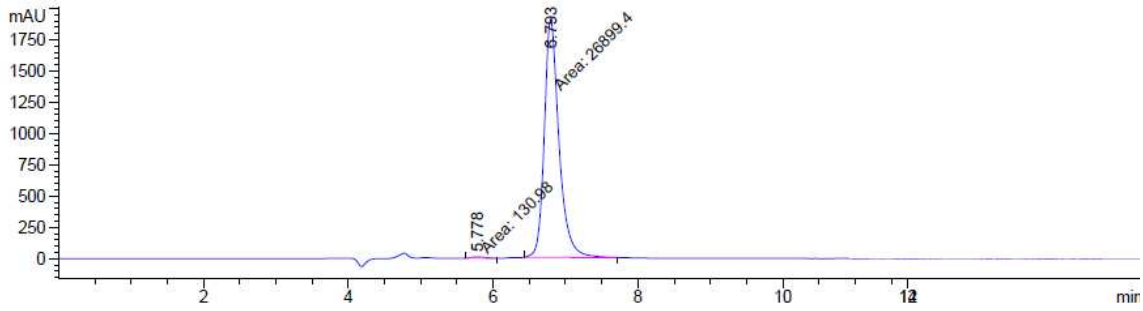
Table S4, entry 7: (*S*)-9h

$[\alpha]^{20}_{D}$ = -31.68 (*c* = 0.505 in Methanol)

HPLC: t_R = 4.69 min, purity: 100.0% (λ = 254 nm), t_R = 4.69 min, purity: 100.0% (λ = 230 nm)

enantioselective analytical HPLC:





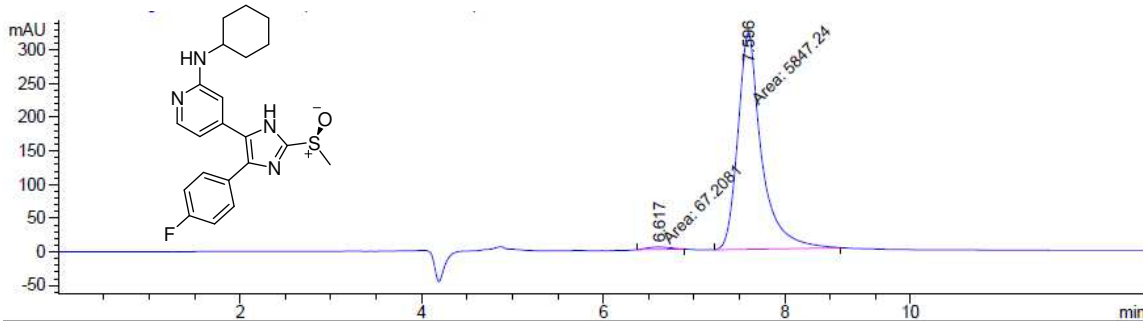
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.778	MM	0.2343	130.97951	9.31545	0.4846
2	6.793	MM	0.2354	2.68994e4	1904.34302	99.5154

Table S4, entry 8: (*S*)-9i:

$[\alpha]^{20}_{D}$ = +9.46 (*c* = 1.036 in Methanol)

HPLC: t_R = 4.75 min, purity: 97.8% (λ = 254 nm), t_R = 4.75 min, purity: 98.4% (λ = 230 nm)

enantioselective analytical HPLC:



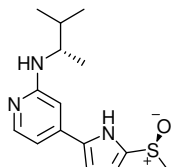
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.617	MM	0.3027	67.20812	3.70100	1.1363
2	7.596	MM	0.3026	5847.24170	322.09680	98.8637

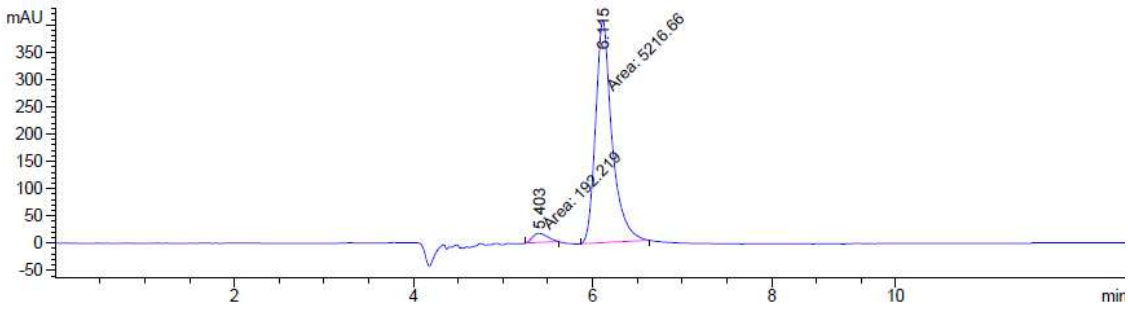
Table S4, entry 9: (*S*)-9j

$[\alpha]^{20}_{D}$ = +26.99 (*c* = 0.531 in Methanol)

HPLC: t_R = 4.71 min, purity: 99.3% (λ = 254 nm), t_R = 4.70 min, purity: 99.2% (λ = 230 nm)

enantioselective analytical HPLC:





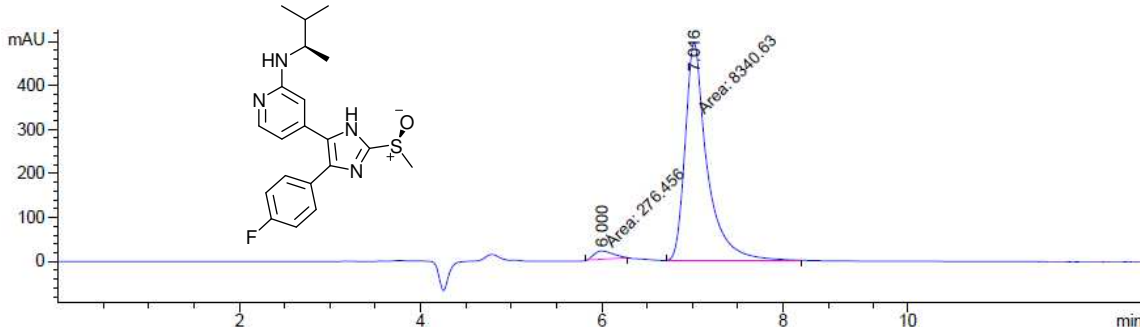
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.403	MM	0.1923	192.21909	16.65927	3.5538
2	6.115	MM	0.2126	5216.66357	408.99802	96.4462

Table S4, entry 10: (*S*)-9k

$[\alpha]^{20}_{D}$ = -16.18 (*c* = 0.238 in Methanol)

HPLC: t_R = 3.97 min, purity: 96.9% (λ = 254 nm), t_R = 3.97 min, purity: 96.7% (λ = 230 nm)

enantioselective analytical HPLC:



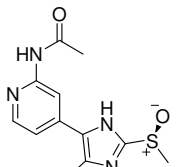
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.000	MM	0.2426	276.45648	18.99276	3.2082
2	7.016	MM	0.2803	8340.62695	495.86450	96.7918

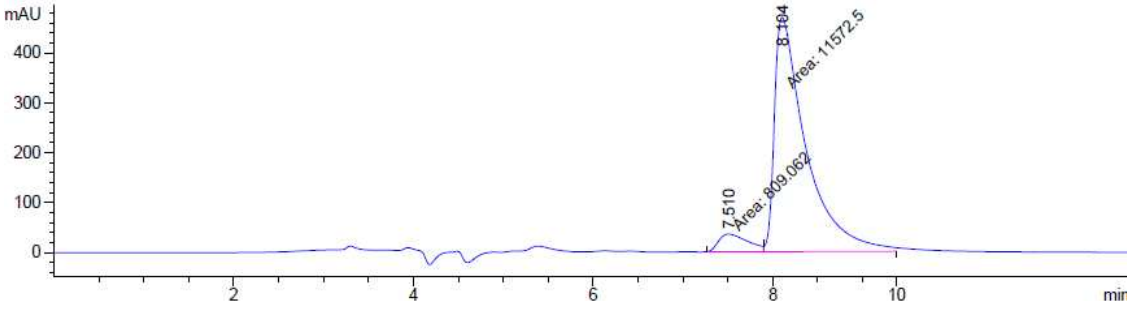
Table S4, entry 11: (*S*)-9l

$[\alpha]^{20}_{D}$ = +2.83 (*c* = 0.519 in Methanol)

HPLC: t_R = 4.30 min, purity: 98.6% (λ = 254 nm), t_R = 4.30 min, purity: 97.0% (λ = 230 nm)

enantioselective analytical HPLC:





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.510	MF	0.3792	809.06177	35.56417	6.5344
2	8.104	FM	0.4105	1.15725e4	469.81064	93.4656

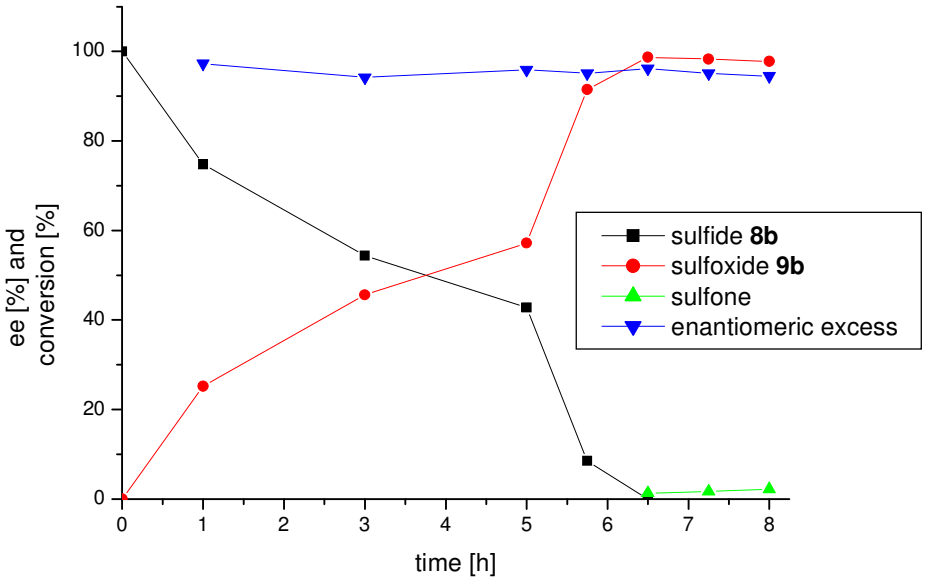


Figure S3. Time profile of the enantioselectivity (*%ee* of sulfoxide **9b**) and conversions (%) in the oxidation of the sulfide **8b** using the catalyst system Ti(O-*i*Pr)$_4$ (0.1 eq)/*S*-BINOL (0.2 eq)/H_2O (0.2 eq)/TBHP (2.0 eq.).

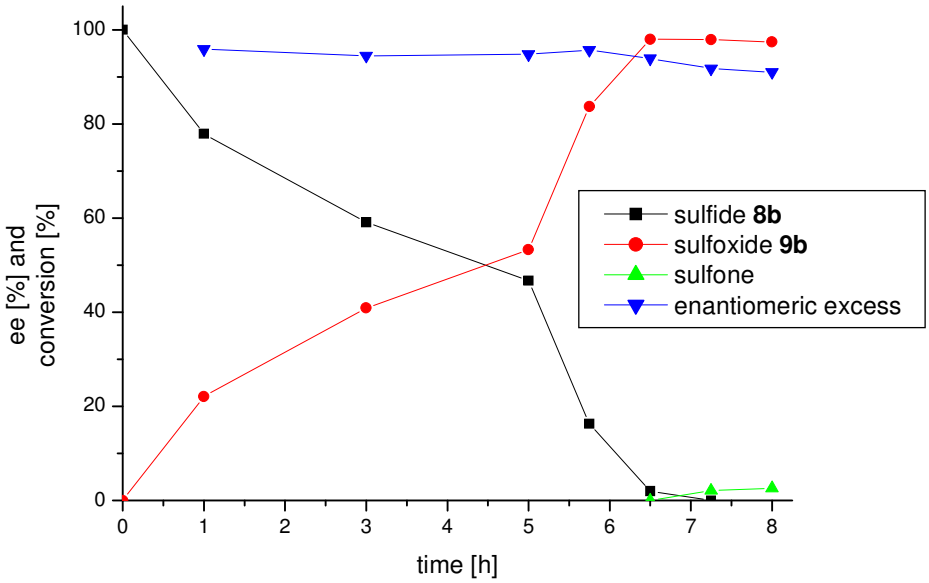
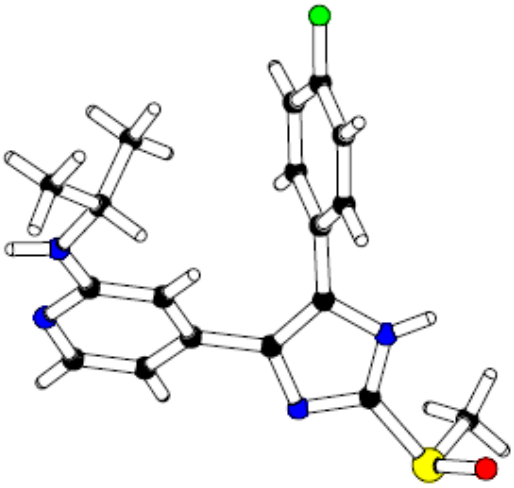


Figure S4. Time profile of the enantioselectivity (*%ee* of sulfoxide **9b**) and conversions (%) in the oxidation of the sulfide **8b** using the catalyst system Ti(O-*i*Pr)$_4$ (0.1 eq)/R-BINOL (0.2 eq)/H_2O (0.2 eq)/TBHP (2.0 eq.).

8. X-ray Data of Compound E_1 of 9b (CCDC 779553)

A)



B)

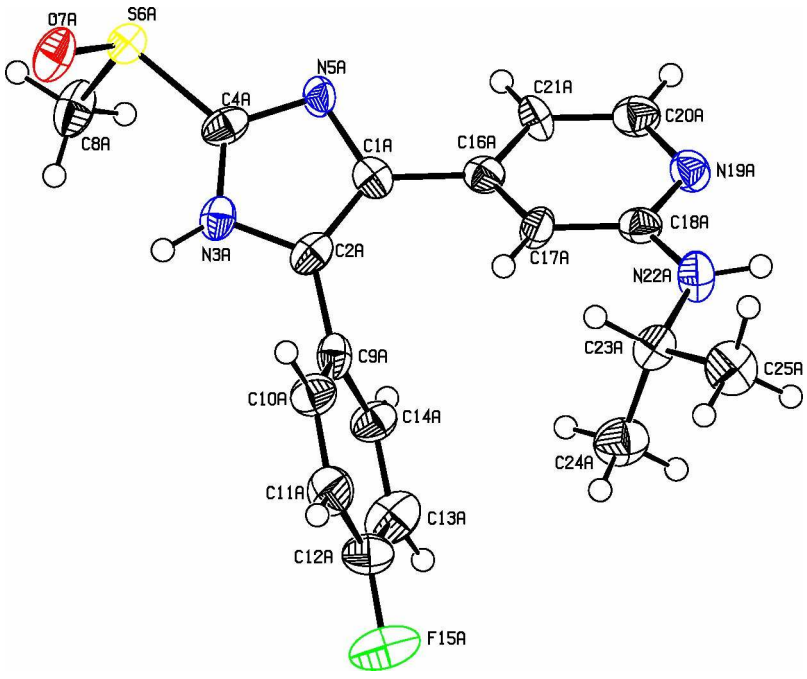
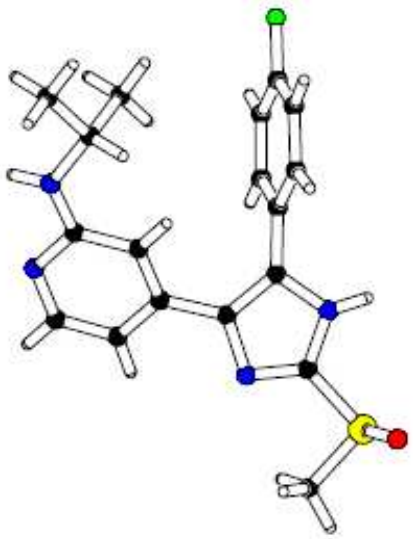


Figure S5. A) X-ray crystal structure of the first eluted enantiomer E_1 of the sulfoxide **9b** with (*R*)-configuration. B) Thermal ellipsoid plot of the enantiomer E_1 of the sulfoxide **9b** (CCDC779553).

E_1 of **9b** (CCDC 779553)	
Sum formula	$4(C_{18}H_{19}FN_4OS)*H_2O$
M_r [g/mol]	1451.74
Crystal size [mm]	a = 0.40 b = 0.30 c = 0.10 Plate, colourless
Space group	C2
Hall group	C2y
Cell setting	monoclinic
Cell length [Å]	a = 23.844(7) b = 17.635(2) c = 17.230(5)
Cell angle [°]	α = 90.0 β= 101.498(14) γ = 90.0
Cell volume [$Å^3$]	V = 7100(3)
Cell formula units Z	4
Temperature [K]	193(2)
Crystal density D_x [g/cm^3]	1.358
Absorpt coefficient μ [mm^{-1}]	1.84
F_{000}	3048
Measured reflections	13112
independent reflections	12933
Reflections with I>2σ(I)	9241
θ_{max} [°]	70.2
θ_{min} [°]	2.6
R	0.107
wR_2	0.310
S	1.11
Npar	910

9. X-ray Data of Compound E_2 of 9b (CCDC 779554)

A)



B)

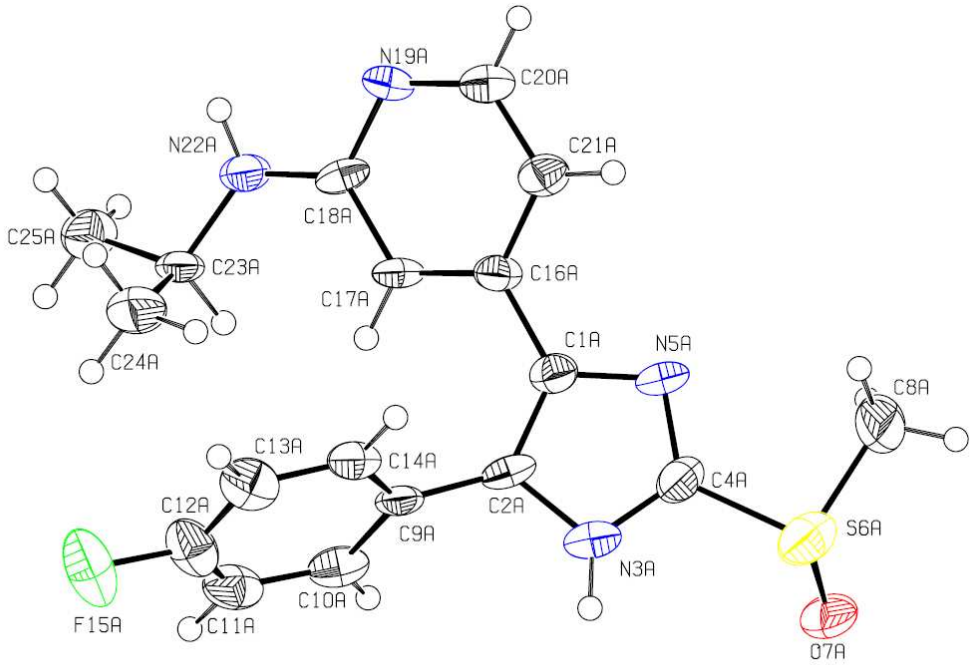


Figure S6. A) X-ray crystal structure of the second eluted enantiomer E_2 of the sulfoxide **9b** with (*S*)-configuration. B) Thermal ellipsoid plot of the enantiomer E_2 of the sulfoxide **9b** (CCDC779554).

E_2 of **9b** (CCDC 779554)	
Sum formula	$4(C_{18}H_{19}FN_4OS)*H_2O$
M_r [g/mol]	1451.74
Crystal size [mm]	a = 0.36 b = 0.24 c = 0.03 Plate, colourless
Space group	C2
Hall group	C2y
Cell setting	monoclinic
Cell length [Å]	a = 23.8564(11) b = 17.6833(8) c = 17.2479(8)
Cell angle [°]	α = 90.0 β= 101.489(3) γ = 90.0
Cell volume [$Å^3$]	V = 7130.4(6)
Cell formula units Z	4
Temperature [K]	173(2)
Crystal density D_x [g/cm^3]	1.352
Absorpt coefficient μ [mm^{-1}]	0.21
F_{000}	3048
Measured reflections	39716
independent reflections	16006
Reflections with I>2σ(I)	6570
θ_{max} [°]	28.0
θ_{min} [°]	1.2
R	0.069
wR_2	0.171
S	0.95
Npar	922