Synthesis K. Fjelbye et al. Paper

A Magnesium-Based Diastereoselective Preparation of Pyridylic 1,3-Amino Alcohols Using the *tert*-Butyl Sulfinamide Auxiliary

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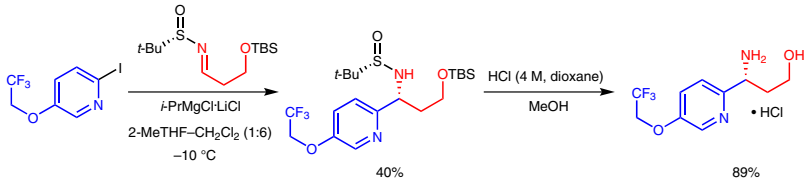

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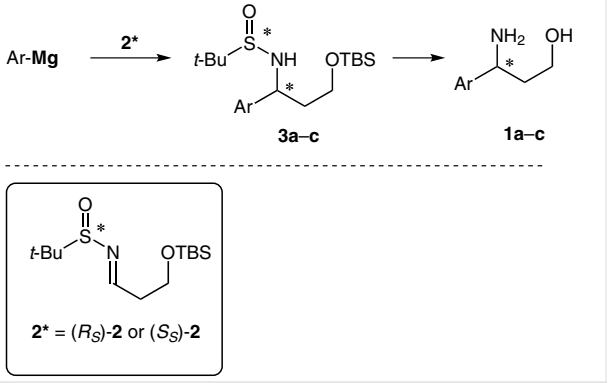
Abstract 1,3-Amino alcohols were prepared by using a two-step approach and an interesting reversal in diastereoselectivity is discussed.

Key words organometallic addition, diastereoselectivity, sulfinamides, halogen-metal exchange, amino alcohol

In a recent medicinal chemistry project we needed access to 1,3-amino alcohols (*S*)-**1a**–**c**, and (*R*)-**1a**–**c** (Scheme 1 and Table 4). Although trifluoroethoxy derivative (*R*)-**1c** has previously been prepared through a nine-step synthesis,[1] we decided to investigate a shorter route utilizing the diastereoselective addition of an organometallic reagent to the TBS-protected chiral sulfinylimine shown in Scheme 1. Both enantiomers of **2** and their reactions have been described in a patent,[2] and the diastereoselective addition of an ester enolate to some closely related reagents have been described.[3]

The optically active *tert*-butyl sulfinamide auxiliary described by Ellman,[4] provides a feasible way to prepare a wide range of primary amines, including amino alcohols, diastereoselectively.[5–11] Both enantiomers of the *tert*-butyl sulfinamide are commercially available and are readily condensed with aldehydes or ketones to provide the corresponding aldimines or ketimines, which can function as common precursors for the preparation of optically active amines after nucleophilic addition and deprotection.

Whereas the preparation of chiral 1,2-amino alcohols has been described in detail,[5,9,11–13] syntheses of 1,3-amino alcohols using a common precursor are much less abundant. Our first approach towards the synthesis of **1c** using lithium-based chemistry did not afford any of the desired product, likely as a result of the elimination of HF from the

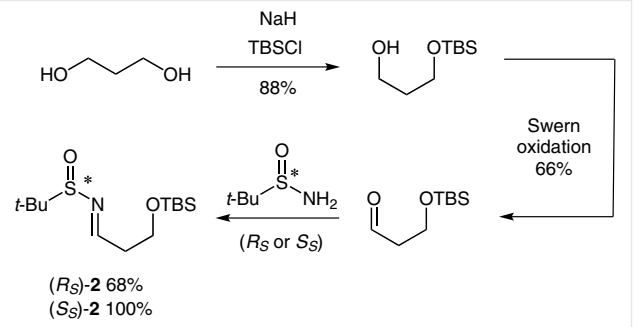


Scheme 1 Preparation of 1,3-amino alcohols employing reagent **2***. The structures of **3a**–**c** are shown in Table 3; the structures of **1a**–**c** are shown in Table 4.

trifluoroethoxy functionality, which has often been noted;[14] thus, the development of a milder magnesium-based protocol was desired. Halogen–Li exchange is usually performed at very low temperatures (e.g., –78 °C), whereas halogen–magnesium exchange can be carried out at higher temperatures (e.g., room temperature).

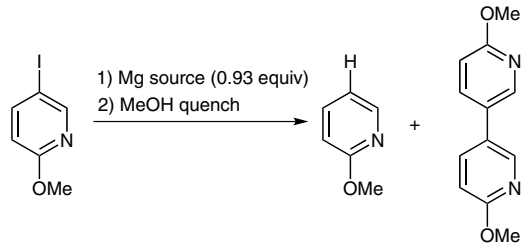
The enantiomeric imines (*R*$_S$)-**2** and (*S*$_S$)-**2** were prepared as described in Scheme 2, based on reported procedures,[5,15,16] and were stable for several months at room temperature.

In the search for an optimized protocol for the construction of pyridylic 1,3-amino alcohols, the preparation of Grignard reagents from deactivated (e.g., alkoxylated) iodopyridines was examined using different magnesium sources (Table 1). The lower reactivity of the corresponding alkoxylated bromopyridines, made those substrates less attractive as precursors of Grignard reagents.



Scheme 2 Preparation of (R_S)-**2** and (S_S)-**2** enantiomers from propane-1,3-diol

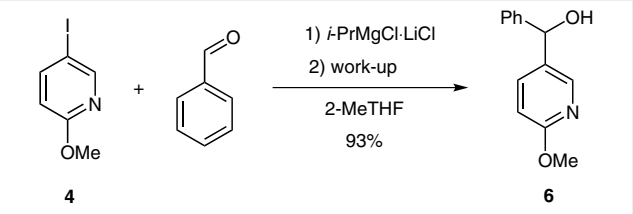
Table 1 Iodine–Magnesium Exchange of a Deactivated Iodopyridine at Room Temperature



Entry	Solvent	Mg source	Time	**A**/**B** (%)[a]
1	THF	Mg(0)	2 h	10:0
2	THF	*i*-PrMgCl	90 min	71:3
3	THF	*n*-PrMgCl	48 h	32:21
4	2-MeTHF	*i*-PrMgCl·LiCl	75 min	61:0
5	2-MeTHF	*i*-PrMgCl·LiCl	24 h	47:43
6	2-MeTHF	(*s*-Bu)$_2$Mg·LiCl	10 min	71:0

[a] Determined by LC (UV) MS analysis.

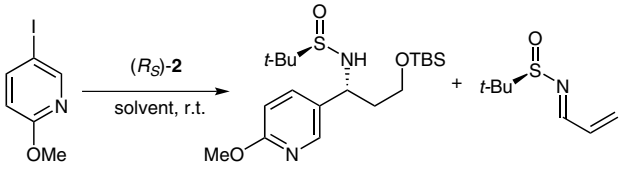
Compound **4** was included in a slight excess to fully consume the magnesium source (0.93 equiv) and the reaction was followed by LC MS until complete conversion. The presence of the dehalogenated starting material 2-methoxypyridine **A**, after MeOH quench, supports the assumption that the C–metal bond had formed. Initial attempts to prepare the Grignard species was performed by using magnesium insertion with magnesium(0), which only allowed formation of 10% **A**, under the activation of 1,2-diiodoethane. Applying *i*-PrMgCl significantly increased the amount of **A** formed, although a small amount of 6,6′-dimethoxy-3,3′-bipyridine **B**, was also detected. Conducting the exchange by using *n*-PrMgCl over the course of 48 h led to the formation of **A** and **B** in 32 and 21%, respectively. Employing the TurboGrignard reagent *i*-PrMgCl·LiCl[17,18], led to exclusive formation of **A** if prolonged reaction times were avoided (Table 1, entries 4 and 5). Furthermore, the use of commercially available (*s*-Bu)$_2$Mg·LiCl complex solution led to the rapid and exclusive formation of **A**. The optimized conditions summarized in entry 4 were then used to prepare **6** to validate the method by using the simple electrophile benzaldehyde (Scheme 3).



Scheme 3 Studying the applicability of the organometallic addition protocol with benzaldehyde as a simple electrophile

The optimized conditions were used in the following addition to **2**. Exploring a small series of solvents, and their influence on the diastereoselective addition, led to the somewhat surprising results that the most commonly employed ethereal solvents, Et_2O and THF provided the adduct (R_S,*R*)-**3a** in only 2–8% yield (Table 2). The study was performed by preparing the Grignard species and allowing it to react with (R_S)-**2** in the solvent indicated (Table 2). An increase in both yield and selectivity was observed when the reaction was performed in 2-methyltetrahydrofuran (2-MeTHF). The improved outcome of organometallic reactions in 2-MeTHF has also been noted by Zhang et al.[19] and by Aycock.[20]

Table 2 Screening of Ethereal Solvents[a]



Entry	Solvent	Molarity [M]	dr (crude)[b]	Yield of (R_S,*R*)-**3a** (%)[c]
1	THF	0.15	–	8
2	Et_2O	0.15	–	2
3	dioxane	0.15	–	7
4	2-MeTHF	0.15	81:19	23
5	2-MeTHF	0.05	87:13	35

[a] Reaction conditions: *i*-PrMgCl·LiCl.
[b] The dr was determined by LC (UV) MS analysis of the crude reaction mixture.
[c] The yields are based on the isolated major isomer.

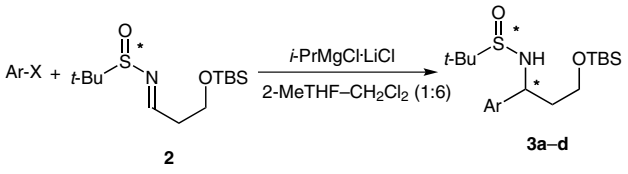
The lower yields observed when the reaction was conducted in THF and Et_2O may be explained by the increased formation of an elimination product **5**, in these solvents.

When the second generation TurboGrignard conditions (Table 1, entry 6) were employed on **2**, compound **5** was formed as the major product, which can be attributed to the increased basicity of the magnesium species [Ar_2Mg or Ar(*s*-Bu)Mg] formed in situ.

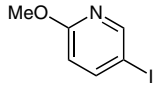
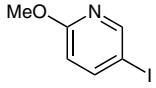
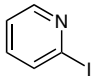
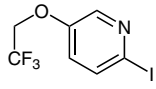
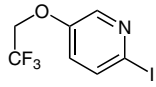
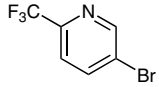
When the reaction between **4** and a TBDPS O-protected aldimine **7**,[21] which is closely related to **2**, was performed, it was possible to isolate **5** in 23% yield, thereby confirming the identity of the byproduct. To suppress the formation of **5** and increase the yield of the adduct, the temperature was decreased to 0 °C and the Grignard reagent in 2-MeTHF was diluted with ice-cold CH_2Cl_2 prior to the addition of **2**. Dilution by the chlorinated solvent was found to improve the outcome significantly, and the method was applied to heteroaromatic analogues of interest (Table 3), affording a small series of protected 1,3-amino alcohols **3a**–**c**. Under these conditions, it was also possible to prepare **3d** from 5-bromo-2-(trifluoromethyl)pyridine, being slightly activated to organometallic exchange reactions. In the case of **3d**, it was not possible to separate the two diastereomers (R_S,*R*)-**3d** and (R_S,*S*)-**3d** by using silica gel chromatography.

To gain access to both enantiomers of **3a** and **3c**, both enantiomers of **2** were employed. The diastereoselective outcome of the addition for the 2-halopyridines was in accordance with the transition-state model proposed by Barrow et al.[5] for related additions forming 1,2-amino alcohols. This selectivity is opposite to that predicted by Ellman for aldimines without additional heteroatoms on the aliphatic chain, and isomerization of the C–N double bond is believed to occur prior to the addition.[7] The formation of so-called 'anti-Ellman' products has also been recognized by Davis et al.,[22] where chelating effects overrule the traditional chair-like transition-state model. On the basis of the experimentally observed selectivity, and confirmed by X-ray crystallography of the products (see below), we have proposed a bicyclic transition state (Figure 1) that resembles that proposed by Barrow et al.[5] for 1,2-amino alcohols.

Table 3 Optimized Magnesium-Based Protocol Using Aromatic Starting Materials



2 **3a–d**

Product[a]	Ar-X	Absolute config. of **2**	Yield (*R*)-**3a–d** (%)[b]	Yield (*S*)-**3a–d** (%)[b]
3a		*S*	–	40
3a[c]		*R*	52	–
3b		*S*	52	3
3c		*R*	–	44
3c[d]		*S*	40	–
3d		*R*	39[e]	–

[a] The major isomer formed for the 3-halopyridines was opposite to that of the 2-halopyridines.
[b] Isolated yield of the major diastereomer.
[c] A dr of 80:20 was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.
[d] A dr of 82:18 was determined by LC MS UV analysis of the crude reaction mixture.
[e] Contaminated by the minor isomer; a dr of 77:23 was determined by ^{1}H NMR spectroscopic analysis.

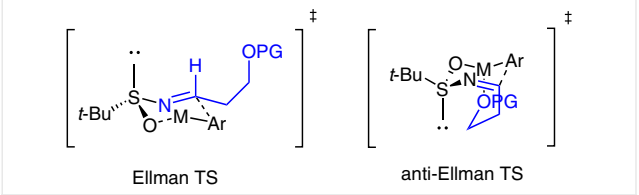


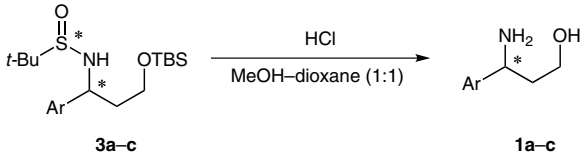
Figure 1 Proposed transition-state models accounting for the observed selectivity. The 'Ellman TS' (left) reflects the selectivity observed for the 3-halopyridines, whereas the 'anti-Ellman TS' (right) is in agreement with the experimental observations for the formation of **3b**.

The acidic deprotection of **3a**–**c** (Table 4) was facilitated by HCl in MeOH/dioxane, and, in contrast to the carbamate-based *tert*-butoxycarbonyl protecting group that forms volatile products upon acidic treatment, the OTBS and Ellman auxiliary produces nonvolatile compounds (i.e., *tert*-butylmethylsulfinate and *tert*-butyldimethylmethoxysilane), which are easily recognized in the ^{1}H NMR spectra.[24–28] The purity of the hydrochloride salts are thus highly dependent on the precipitation of the products upon deprotection.

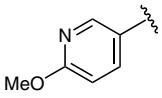
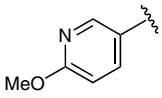
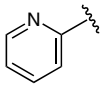
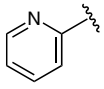
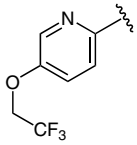
The enantiopure products **1a** and **1b** were found to be dihydrochloride salts, whereas (*R*)-**1c** was a monohydrochloride salt, as determined by elemental analysis. In the case of (*S*)-**1a** (Figure 2) and (*R*)-**1b** (Figure 3), it was possible to confirm the absolute configurations of the stereogenic centers through X-ray crystallographic analysis of the dihydrochloride salts.

The optimized procedure for preparation of pyridylic 1,3-amino alcohols was used in the formation of the desired trifluoroethoxylated compound **1c** (Scheme 4). 2-Bromo-5-hydroxypyridine was alkylated in 91% yield with tri-

Table 4 Deprotection of Diastereomers **3a–c**



3a–c **1a–c**

Starting material	Ar	Product	Yield (%)
(*S*)-**3a**		(*S*)-**1a**	75
(*R*)-**3a**		(*R*)-**1a**	90
(*S*)-**3b**		(*S*)-**1b**	82
(*R*)-**3b**		(*R*)-**1b**	84
(*R*)-**3c**		(*R*)-**1c**	89

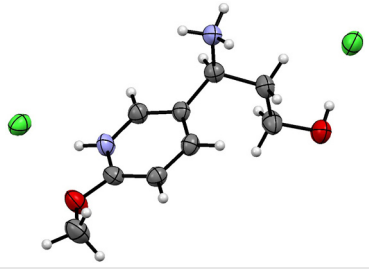


Figure 2 X-ray crystal structure of (*S*)-**1a** obtained from EtOH/Et_2O. The green circles represent the chlorine, blue nitrogen and red oxygen. Mercury software was used for the ORTEP representation.

fluoroethyl triflate by using $CsCO_3$ in *N*,*N*-dimethylformamide (DMF) to afford **8**. Attempts to install the trifluoroethyl group by using the iodide or the mesylate leaving groups were unsuccessful. The subsequent *trans*-halogenation employing aromatic Finkelstein conditions, described by Buchwald et al.[29] for the conversion of aryl bromides into iodides, furnished **9** in 90% yield. Halogen–metal exchange of **9** in 2-MeTHF followed by dilution with an excess volume of CH_2Cl_2 and reaction with the aldimine (S_S)-**2** afforded (*R*)-**1c** in 40% yield, followed by acidic

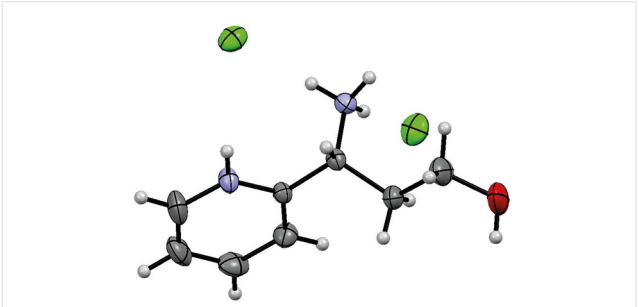
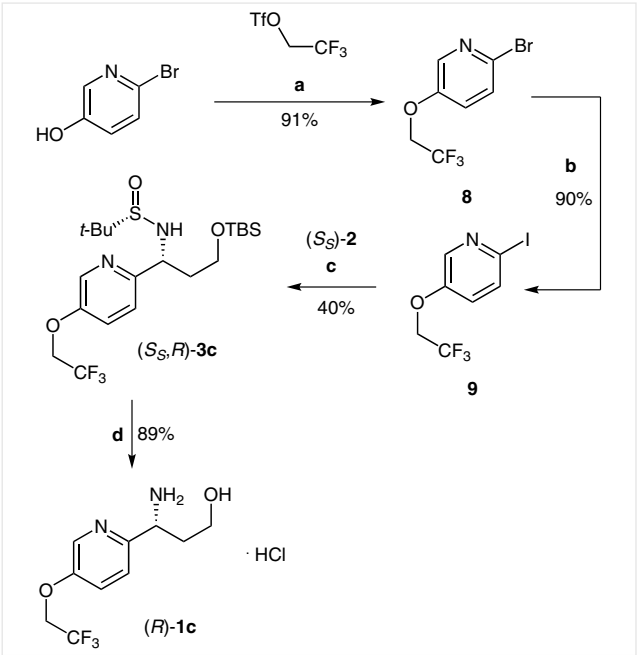


Figure 3 X-ray crystal structure of (*R*)-**1b** obtained from EtOH. The green circles represent the chlorine, blue nitrogen and red oxygen. Mercury software was used for the ORTEP representation.

deprotection to yield the desired enantiopure amino alcohol (*R*)-**1c** in 89% yield (Scheme 4). The absolute configuration of (*R*)-**1c** is tentatively assigned based on the biological activity of some derivatives (see Eskildsen et al.[23]) and by analogy with the stereochemistry of **1b**.



Scheme 4 Optimized preparation of compound (*R*)-**1c** in four steps from 2-bromo-5-hydroxypyridine. *Reagents and conditions*: (a) $CsCO_3$, DMF; (b) NaI (3 equiv), cat. CuI, cat. diamine ligand, MeCN, 100 °C; (c) 2-MeTHF–CH_2Cl_2 (1:6), –10 °C; (d) HCl, MeOH–dioxane (1:1).

We have thus developed a short stereodivergent synthesis of 1,3-amino alcohols that tolerates base-labile groups, for example (*R*)-**1c**.

GC MS data was obtained with a Varian gas chromatograph equipped with an EI mass spectrometer. Melting points were measured with a Büchi apparatus and are uncorrected. TLC was performed on Silica

Gel 60 F_{254} from Merck visualized under UV at 254 nm. Starting materials that were not synthesized by the author were purchased from Sigma–Aldrich, Chemetall GmbH or Across Chemicals. All reaction solvents were HPLC grade and dried over 4 Å molecular sieves. All reactions were carried out under a nitrogen or argon atmosphere. LC-MS data were acquired with a Waters Acquity UPLC-MS consisting of a Waters Acquity system including column manager, binary solvent manager, sample organizer, PDA detector (operating at 254 nm), ELS detector, and TQ-MS equipped with APPI-source operating in positive ion mode. LC-conditions: The column was Acquity UPLC BEH C18 1.7 µm; 2.1 × 50 mm operating at 60 °C with 1.2 mL/min binary gradient consisting of H_2O+0.05% trifluoroacetic acid (TFA) (A) and MeCN+5% H_2O+0.05% TFA (B). Gradient: 0.00 min: 10% B; 1.00 min: 100% B; 1.01 min: 10% B; 1.15 min: 10% B. The retention times provided in the experimental section shall be compared to the total run time of 1.15 min. HRMS data were acquired with a Bruker Daltonic MicroTOF with internal calibration using ESI in the positive mode. NMR data were collected with a Bruker 600-Avance-III spectrometer equipped with a 5 mm TCI cryoprobe operating at 600 and 151 MHz for ^{1}H and ^{13}C, respectively. ^{19}F NMR spectra were recorded with a Bruker 500-Avance spectrometer equipped with a 5 mm QNP probe operating at 470.6 Hz, using $CFCl_3$ as point-zero. The solvents used for NMR were $CDCl_3$, with reference signals for $CHCl_3$ (δ = 7.26 ppm, ^{1}H) and (δ = 77.16 ppm, ^{13}C), and DMSO-d_6 with the reference signals for residual DMSO (δ = 2.50 ppm, ^{1}H) and (δ = 39.51 ppm, ^{13}C) using TMS as internal reference.[30] The chemical shifts are provided in ppm and broad proton signals are labeled (br). Organometallic reagents were purchased from Chemetall as THF solutions; *i*-PrMgCl·LiCl and (*s*-Bu)$_2$Mg·LiCl (0.6 M) were titrated with molecular iodine in anhydrous THF prior to use.

Crystal Structure of (*S*)-1a

Crystals were prepared by dissolving (*S*)-**1a** (6 mg) in EtOH (1.5 mL) in an open Pyrex glass vial placed in a closed blue cap flask surrounded by excess Et_2O. After two weeks, colorless crystals of (*S*)-**1a** appeared. The colorless crystals of (*S*)-**1a** $[(C_9H_{16}N_2O_2)^{2+}, (Cl^-)_2]$ are orthorhombic. At 298 K *a* = 8.3763(3), *b* = 8.5964(3), *c* = 17.6648(6) Å; V = 1271.97(8) Å$^{3;}$ *M* = 255.14; *Z* = 4; space group *P* $2_12_12_1$, F(000) = 536. Intensities of 2225 reflections. CuKα radiation. The structure was solved using SHELXL-2014/4 and the absolute stereochemistry was determined with the stereocenter at C6 assigned as *S* with a Flack parameter of –0.003(16).

Crystal Structure of (*R*)-1b

The crystals were prepared by recrystallization from boiling EtOH. The colorless crystals of (*R*)-**1b** $[(C_8H_{14}N_2O)^{2+}, (Cl^-)_2]$ are orthorhombic. At 293 K, *a* = 6.7297(6), *b* = 9.3506(9), *c* = 17.5779(13) Å; V = 1106.12(16) Å^3; *M* = 225.11; *Z* = 4; space group *P* $2_12_12_1$; F(000) = 472. Intensities of 2323 reflections, Final R1, (I > 2σ(I)) = 2.51%. CuKα radiation. The structure was solved by direct methods using the SHELXL-2013 package. The absolute stereochemistry was determined with the stereocenter assigned as *R* with a Flack parameter of –0.007(5). The Flack equivalent and its uncertainty are calculated to be –0.003(6).

(*S*)-3-Amino-3-(6-methoxypyridin-3-yl)propan-1-ol Dihydrochloride [(*S*)-1a]

To a flask containing (S_S,*S*)-**3a** (143 mg, 0.357 mmol) in MeOH (0.9 mL) was added HCl (4 M in dioxane, 0.9 mL) at r.t. and the reaction mixture was stirred overnight, after which it was placed at 2–8 °C for 1 h. The suspension was then transferred to a frit funnel by using a syringe and triturated with Et_2O (3 × 10 mL) to give (*S*)-**1a**.

Yield: 82 mg (0.321 mmol, 90%); white powder; mp 134.4–141.0 °C; $[\alpha]_D^{20}$ = 22.42 (MeOH).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.52 (br, 3 H), 8.25 (d, *J* = 2.5 Hz, 1 H), 7.90 (dd, *J* = 8.6, 2.5 Hz, 1 H), 6.91 (d, *J* = 8.6 Hz, 1 H), 6.11 (br, 3 H), 4.37–4.31 (m, 1 H), 3.86 (s, 3 H), 3.39 (dt, *J* = 11.0, 5.5 Hz, 1 H), 3.20 (ddd, *J* = 11.0, 8.1, 5.5 Hz, 1 H), 2.15 (ddt, *J* = 12.0, 8.1, 5.9 Hz, 1 H), 1.98–1.91 (m, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 163.61, 146.68, 138.35, 126.29, 110.65, 56.70, 53.40, 49.29, 36.51.

Anal. Calcd for $C_9H_{16}Cl_2N_2O_2$: C, 42.37; H, 6.32; N, 10.98. Found: C, 41.99; H, 6.37; N, 10.67.

(*R*)-3-Amino-3-(6-methoxypyridin-3-yl)propan-1-ol Dihydrochloride [(*R*)-1a]

To a flask containing (S_S,*R*)-**3a** (41 mg, 0.102 mmol) in MeOH (0.3 mL) was added HCl (4 M in dioxane, 0.3 mL) at r.t. and the reaction mixture was stirred for 3 h while precipitation occurred. The suspension was then transferred to a frit funnel and triturated with Et_2O (3 × 30 mL) to give (*R*)-**1a**.

Yield: 19.6 mg (0.077 mmol, 75%); white solid; mp 137.8–144.4 °C; $[\alpha]_D^{20}$ –19.5 (MeOH).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.50 (br, 3 H), 8.25 (d, *J* = 2.5 Hz, 1 H), 7.89 (dd, *J* = 8.6, 2.5 Hz, 1 H), 6.91 (d, *J* = 8.6 Hz, 1 H), 5.93 (br, 3 H), 4.37–4.31 (m, 1 H), 3.85 (s, 3 H), 3.39 (dt, *J* = 11.0, 5.5 Hz, 1 H), 3.23–3.18 (m, 1 H), 2.18–2.11 (m, 1 H), 1.98–1.91 (m, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 163.63, 146.69, 138.32, 126.27, 110.65, 56.70, 53.39, 49.30, 36.50.

Anal. Calcd for $C_9H_{16}Cl_2N_2O_2$·1/4 H_2O: C, 41.63; H, 6.41; N, 10.79. Found: C, 41.68; H, 6.31; N, 10.76.

(*S*)-3-Amino-3-(pyridin-2-yl)propan-1-ol Dihydrochloride [(*S*)-1b]

To a flask containing (S_S,*S*)-**3b** (0.065 g, 0.175 mmol) in MeOH (0.4 mL) was added HCl (4 M in dioxane, 0.4 mL, 47.7 mmol) and the reaction mixture was stirred at r.t. overnight. The precipitated salt was placed on a filter and triturated with Et_2O (4 × 5 mL) followed by evaporation of excess volatiles in vacuo at 60 °C overnight. The anhydrous material afforded (*S*)-**1b**.

Yield: 32.3 mg (0.143 mmol, 82%); white powder; $[\alpha]_D^{20}$ +2.7 (*c* 1.00, MeOH).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.67 (ddd, *J* = 4.9, 1.6, 0.8 Hz, 1 H), 8.64 (br, 2 H), 8.01–7.97 (m, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.51 (dd, *J* = 7.4, 5.1 Hz, 1 H), 6.54 (br, 3 H), 4.56–4.50 (m, 1 H), 3.43 (dt, *J* = 11.9, 6.2 Hz, 1 H), 3.34–3.29 (m, 1 H), 2.09 (td, *J* = 13.4, 6.2 Hz, 1 H), 2.00–1.94 (m, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 155.88, 148.20, 138.57, 124.09, 123.19, 56.55, 51.81, 36.69.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{13}N_2O$: 153.1022; found: 153.1016.

(*R*)-3-Amino-3-(pyridin-2-yl)propan-1-ol Dihydrochloride [(*R*)-1b]

To a flask containing (S_S,*R*)-**3b** (1.79 g, 4.83 mmol) in MeOH (12 mL) was added HCl (4 M in dioxane, 11.93 mL, 47.7 mmol) and the reaction mixture was stirred at r.t. overnight. The precipitated salt was placed on a filter and triturated with Et_2O (4 × 75 mL) followed by evaporation of excess volatiles in vacuo at 60 °C for 3 h. The anhydrous material afforded (*R*)-**1b** (0.912 g, 4.05 mmol, 84% yield) as a white powder. Recrystallization from boiling EtOH (5.5 mL) provided very large transparent crystals that were analyzed by X-ray crystallography.

Mp 148–158 °C (decomp); $[\alpha]_D^{20}$ –3.4 (*c* 1.00, MeOH).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.72–8.66 (m, 4 H), 8.04–8.00 (m, 1 H), 7.70 (d, *J* = 7.8 Hz, 1 H), 7.53 (ddd, *J* = 7.5, 5.0, 0.7 Hz, 1 H), 6.93 (br, 2 H), 4.58–4.52 (m, 1 H), 3.43 (dt, *J* = 11.8, 6.0 Hz, 1 H), 3.34–3.29 (m, 1 H), 2.11 (td, *J* = 13.5, 6.0 Hz, 1 H), 1.98 (td, *J* = 13.5, 6.0 Hz, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 155.72, 147.86, 138.97, 124.24, 123.33, 56.55, 51.70, 36.66.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{13}N_2O$: 153.1022; found: 153.1022.

Anal. Calcd for $C_8H_{14}Cl_2N_2O_2{\cdot}1/4\,H_2O$: C, 41.85; H, 6.37; N, 12.20. Found: C, 42.13; H, 6.26; N, 12.20.

(*R*)-3-Amino-3-[5-(2,2,2-trifluoroethoxy)pyridin-2-yl]propan-1-ol Hydrochloride [(*R*)-1c]

A round-bottom flask was charged with (*R*)-**3c** (0.85 g, 1.81 mmol) in MeOH (4.5 mL) followed by the dropwise addition of HCl (4 M in dioxane, 4.5 mL, 17.92 mmol). The yellow mixture was stirred overnight, followed by concentration in vacuo to provide a crude oily amorphous mass. The crude material was transferred by using a spatula onto a filter where it was triturated with Et_2O (10 × 80 mL) and stored in vacuo at 60 °C overnight. The resulting solid was identified as being (*R*)-**1c** (0.464 g, 1.62 mmol, 89% yield) as a pale solid that was recrystallized from first MeOH/MTBE then MeCN to afford a white powder; mp 168.9–169.3 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.45 (d, *J* = 2.9 Hz, 1 H), 7.63 (dd, *J* = 8.6, 2.9 Hz, 1 H), 7.54 (d, *J* = 8.6 Hz, 1 H), 4.93 (q, *J* = 8.8 Hz, 2 H), 4.44 (dd, *J* = 12.5, 5.9 Hz, 1 H), 3.53 (br, 1 H), 3.40 (dt, *J* = 11.3, 5.8 Hz, 1 H), 3.27 (dt, *J* = 11.3, 6.7 Hz, 1 H), 2.10–2.02 (m, 1 H), 1.92 (td, *J* = 13.6, 5.9 Hz, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 153.10, 149.89, 137.31, 123.87 (q, *J* = 277.9 Hz), 123.45, 122.68, 64.81 (q, *J* = 34.2 Hz), 56.55, 51.56, 36.70.

^{19}F NMR (471 MHz, DMSO-d_6): δ = –72.97.

LCMS: *m*/*z* = 251.1 [M + H]$^+$ (t_R = 0.31 min; UV).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{14}F_3N_2O_2$: 251.1002; found: 251.1007.

Anal. Calcd for $C_{10}H_{14}ClF_3N_2O_2$: C, 41.90; H, 4.92; N, 9.77. Found: C, 42.44; H, 5.09; N, 9.40.

(R_S)-*N*-{3-[(*tert*-Butyldimethylsilyl)oxy]propylidene}-2-methylpropane-2-sulfinamide [(R_S)-2]

A round-bottom flask was charged with (R_S)-2-methylpropane-2-sulfinamide (0.20 g, 1.65 mmol), pyridinium *p*-toluenesulfonate (0.02 g, 0.08 mmol), and magnesium sulfate (0.99 g, 8.23 mmol) in CH_2Cl_2 (4 mL) at r.t. A solution of 3-[(*tert*-butyldimethylsilyl)oxy]propanal (0.62 g, 3.29 mmol) in CH_2Cl_2 (2 mL) was then added dropwise and the reaction mixture was stirred at r.t. overnight and then filtered. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography (EtOAc–heptanes, 5–100%) to provide (R_S)-**2**.

Yield: 0.48 g (1.65 mmol, 100%); yellow oil; TLC: R_f = 0.6 (EtOAc–heptanes, 50%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.09 (t, *J* = 4.7 Hz, 1 H), 3.96–3.90 (m, 2 H), 2.76–2.68 (m, 2 H), 1.19 (s, 9 H), 0.87 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.93, 59.61, 56.61, 39.46, 25.88, 22.37, 18.29, –5.35.

LCMS: *m*/*z* = 292.3 [M + H]$^+$ (t_R 0.95 min; UV).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{30}NO_2SSi$: 292.1761; found: 292.1763.

(S_S)-*N*-{3-[(*tert*-Butyldimethylsilyl)oxy]propylidene}-2-methylpropane-2-sulfinamide [(S_S)-2]

A round-bottom flask was charged with (*S*)-2-methylpropane-2-sulfinamide (5.02 g, 41.5 mmol), pyridinium *p*-toluenesulfonate (0.521 g, 2.07 mmol), and magnesium sulfate (24.95 g, 207 mmol) in CH_2Cl_2 (83 mL, 0.5 M). A solution of 3-[(*tert*-butyldimethylsilyl)oxy]propanal (9.37 g, 49.8 mmol) in CH_2Cl_2 (35 mL) was added dropwise at r.t. and the reaction mixture was stirred overnight followed by filtration. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography (EtOAc–heptanes, 5–100%) to provide (S_S)-**2**.

Yield: 8.25 g (28.3 mmol, 68%); yellow oil; R_f = 0.60 (EtOAc–heptanes, 50%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.09 (t, *J* = 4.7 Hz, 1 H), 3.93 (td, *J* = 6.2, 1.7 Hz, 2 H), 2.75–2.71 (m, 2 H), 1.19 (s, 9 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.05 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.05, 59.73, 39.58, 26.00, 22.49, –5.24, –5.24.

LCMS: *m*/*z* = 292.3 [M + H]$^+$ (t_R 1.00 min; UV).

(S_S)-*N*-{(*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-(6-methoxypyridin-3-yl)propyl}-2-methylpropane-2-sulfinamide [(S_S,*S*)-3a]

To a solution of **4** (0.594 g, 2.53 mmol) in 2-MeTHF (6 mL) was added *i*-PrMgCl·LiCl (0.73 M in THF, 3.23 mL, 2.36 mmol) at –10 °C. Generation of the active nucleophile was followed by LCMS analysis and, after 1 h, the solution was diluted with CH_2Cl_2 (30 mL) at –10 °C, then (S_S)-**2** (0.491 g, 1.69 mmol) in CH_2Cl_2 (5 mL) was added. The reaction mixture was stirred for 2.5 h followed by the addition of half-saturated aq NH_4Cl (10 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (35 mL) and the organic phases were combined and concentrated in vacuo to provide a colorless oil that was subjected to purification by silica gel chromatography (40 g SiO_2; EtOAc–heptanes, 10–80%; eluting at 63%) followed by examination of the UV-active fractions by LCMS analysis. The desired fractions were combined and concentrated in vacuo to provide the major isomer (S_S,*S*)-**3a**.

Yield: 272 mg (0.679 mmol, 40%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 2.5 Hz, 1 H), 7.59 (dd, *J* = 8.6, 2.5 Hz, 1 H), 6.74 (d, *J* = 8.6 Hz, 1 H), 4.58–4.54 (m, 1 H), 3.93 (s, 3 H), 3.71 (d, *J* = 5.1 Hz, 1 H), 3.62 (ddd, *J* = 10.5, 6.6, 5.4 Hz, 1 H), 3.52 (ddd, *J* = 10.4, 6.7, 5.3 Hz, 1 H), 2.18 (dtd, *J* = 11.9, 6.6, 5.5 Hz, 1 H), 1.97–1.90 (m, 1 H), 1.20 (s, 9 H), 0.87 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.93, 145.81, 138.03, 130.48, 111.12, 59.70, 56.04, 54.13, 53.64, 39.37, 26.04, 22.72, 18.30 –5.24, –5.28.

LCMS: *m*/*z* = 401.1 $[M + H]^+$ (t_R 0.92 min; UV).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{37}N_2O_3SSi$: 401.2289; found: 401.2285.

(*R*$_S$)-*N*-{(*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-(6-methoxypyridin-3-yl)propyl}-2-methylpropane-2-sulfinamide [(*R*$_S$,*R*)-3a]

To a solution of **4** (470 mg, 2.00 mmol) in 2-MeTHF (5 mL) was slowly added *i*-PrMgCl·LiCl (0.73 M in THF, 2.56 mL, 1.87 mmol) at r.t. Generation of the active nucleophile was followed by LCMS analysis and, after 1 h, the solution was cooled to –10 °C and diluted with CH_2Cl_2 (25 mL), then (*R*$_S$)-**2** (389 mg, 1.33 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was stirred for 5 h when LCMS indicated full conversion of the electrophile (*R*$_S$)-**2**. The mixture became clear yellow, sat. aq. NH_4Cl (5 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) and the organic layers were combined, concentrated in vacuo, and purified by silica gel chromatography (120 g SiO_2; EtOAc–heptanes, 10–100%; eluting at ca. 60% EtOAc). The fractions containing the major isomer (as indicated by LCMS) were collected and evaporation of volatiles in vacuo at 60 °C afforded the major isomer (*R*$_S$,*R*)-**3a**.

Yield: 275 mg (0.69 mmol, 52%); yellow oil; dr 80:20% (determined by LCMS; UV).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 2.5 Hz, 1 H), 7.58 (dd, *J* = 8.5, 2.5 Hz, 1 H), 6.73 (d, *J* = 8.5 Hz, 1 H), 4.56–4.53 (m, 1 H), 3.91 (s, 3 H), 3.72 (d, *J* = 5.3 Hz, 1 H), 3.61 (ddd, *J* = 10.5, 6.6, 5.3 Hz, 1 H), 3.51 (ddd, *J* = 10.5, 6.8, 5.3 Hz, 1 H), 2.17 (dtd, *J* = 12.2, 6.6, 5.3 Hz, 1 H), 1.92 (dtd, *J* = 12.2, 6.8, 5.3 Hz, 1 H), 1.18 (s, 9 H), 0.86 (s, 9 H), 0.00 (s, 3 H), –0.01 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.89, 145.78, 137.99, 130.46, 111.09, 59.67, 56.04, 54.12, 53.61, 39.33, 26.02, 22.69, 18.34, –5.27, –5.31.

LCMS: *m*/*z* = 401.4 $[M + H]^+$ (t_R 0.92 min; UV).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{37}N_2O_3SSi$: 401.2289; found: 401.2280.

(*S*$_S$)-*N*-{(*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-(pyridin-2-yl)propyl}-2-methylpropane-2-sulfinamide (3b)

To a solution of 2-iodopyridine (2.67 g, 13.01 mmol) in 2-MeTHF (23 mL) was slowly added *i*-PrMgCl·LiCl (0.73 M in THF, 16.56 mL, 12.09 mmol) at –10 °C. Generation of the active nucleophile was followed by LCMS analysis and, after 1 h, the solution was diluted with ice-cold CH_2Cl_2 (200 mL), which was transferred by using a cannula followed by the addition of (*S*$_S$)-**2** (2.71 g, 9.30 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 5 h then sat. aq. NH_4Cl (30 mL) was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were concentrated in vacuo and purified by silica gel chromatography (330 g SiO_2; EtOAc–heptanes, 10–100%; eluting at ca. 60% EtOAc–heptanes). Examination of the UV-active fractions by LCMS followed by evaporation of volatiles in vacuo afforded (*S*$_S$,*S*)-**3b** and (*S*$_S$,*R*)-**3b**.

Major Isomer (*S*$_S$,*R*)-3b

Yield: 1.79 g (4.83 mmol, 52%); yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.57–8.55 (m, 1 H), 7.65 (td, *J* = 7.7, 1.8 Hz, 1 H), 7.33 (d, *J* = 7.7 Hz, 1 H), 7.17 (ddd, *J* = 7.7, 4.8, 0.9 Hz, 1 H), 4.72 (q, *J* = 5.5 Hz, 1 H), 4.68 (d, *J* = 5.5 Hz, 1 H), 3.70 (ddd, *J* = 10.6, 6.1, 4.5 Hz, 1 H), 3.67–3.62 (m, 1 H), 2.18 (dtd, *J* = 13.0, 7.4, 5.5 Hz, 1 H), 2.11 (dtd, *J* = 13.0, 5.5, 4.5 Hz, 1 H), 1.18 (s, 9 H), 0.88 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.67, 149.51, 136.53, 122.35, 122.11, 61.15, 59.63, 55.88, 39.72, 26.13, 22.83, 18.57, –5.22, –5.24.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{35}N_2O_2SSi$: 371.2183; found: 371.2181.

Minor Isomer (*S*$_S$,*S*)-3b

Yield: 0.098 g (0.26 mmol, 3%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 4.6 Hz, 1 H), 7.61 (td, *J* = 7.7, 1.7 Hz, 1 H), 7.28 (d, *J* = 7.7 Hz, 1 H), 7.13 (ddd, *J* = 7.7, 4.6, 0.8 Hz, 1 H), 4.88 (d, *J* = 7.5 Hz, 1 H), 4.59 (q, *J* = 7.5 Hz, 1 H), 3.68 (dt, *J* = 10.3, 6.4 Hz, 1 H), 3.56–3.52 (m, 1 H), 1.98–1.93 (m, 2 H), 1.23 (s, 9 H), 0.87 (s, 9 H), 0.01 (s, 3 H), –0.01 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.41, 149.22, 136.75, 122.41, 122.05, 59.46, 57.88, 56.03, 40.89, 26.00, 22.86, 18.32, –5.26, –5.27.

LCMS: *m*/*z* = 371.3 $[M + H]^+$ (t_R 0.75 min; UV).

(*R*$_S$)-*N*-{(*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-[5-(2,2,2-trifluoroethoxy)pyridin-2-yl]propyl}-2-methylpropane-2-sulfinamide [(*R*$_S$,*S*)-3c]

To a solution of **9** (0.303 g, 1.00 mmol) in 2-MeTHF (2.5 mL) was added dropwise *i*-PrMgCl·LiCl (0.73 M in THF, 1.28 mL, 0.93 mmol) at –10 °C. The exchange reaction was followed by LCMS analysis and, after 45 min, the mixture was diluted with CH_2Cl_2 (10 mL). A solution of (*R*$_S$)-**2** (0.194 g, 0.67 mmol) in CH_2Cl_2 (5 mL) was then added slowly and the mixture was stirred for 4 h at –10 °C after which sat. aq NH_4Cl (5 mL) was added. The mixture was diluted with CH_2Cl_2 (35 mL), the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 35 mL). The combined organic phases were washed with brine and the organic volatiles were removed in vacuo to provide a yellow oil that was subjected to silica gel chromatography (120 g SiO_2; EtOAc–heptanes, 10–100%) followed by examination of the UV-active fractions by LCMS. Combination of the desired fractions and removal of solvents in vacuo provided (*R*$_S$,*S*)-**3c**.

Yield: 0.137 g (0.29 mmol, 44%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 2.8 Hz, 1 H), 7.30 (d, *J* = 8.5 Hz, 1 H), 7.22 (dd, *J* = 8.5, 2.8 Hz, 1 H), 4.70 (dt, *J* = 7.5, 5.4 Hz, 1 H), 4.61 (d, *J* = 5.4 Hz, 1 H), 4.39 (q, *J* = 8.0 Hz, 2 H), 3.69 (ddd, *J* = 10.4, 5.9, 4.4 Hz, 1 H), 3.62 (ddd, *J* = 10.6, 8.0, 4.4 Hz, 1 H), 2.14 (dtd, *J* = 14.2, 7.5, 4.4 Hz, 1 H), 2.09–2.03 (m, 1 H), 1.17 (s, 9 H), 0.87 (s, 9 H), 0.03 (s, 3 H), 0.01 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 155.79, 152.68, 137.54, 123.12 (q, *J* = 278.0 Hz), 122.62, 122.42, 66.23 (q, *J* = 36.0 Hz), 61.17, 58.91, 39.59, 26.10, 22.78, –5.24, –5.26.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –74.39.

LCMS: *m*/*z* = 469.1 $[M + H]^+$ (t_R 0.94 min; UV).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{36}F_3N_2O_3SSi$: 469.2163; found: 469.2157.

(*S*$_S$)-*N*-{(*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-[5-(2,2,2-trifluoroethoxy)pyridin-2-yl]propyl}-2-methylpropane-2-sulfinamide [(*S*$_S$,*R*)-3c]

To a solution of **9** (2.21 g, 7.29 mmol) in 2-MeTHF (20 mL) was added dropwise *i*-PrMgCl·LiCl (0.73 M in THF, 9.35 mL, 6.81 mmol) at –10 °C. The exchange reaction was followed by LCMS analysis and, after 1 h, the mixture was diluted with CH_2Cl_2 (110 mL). Subsequently, (*S*$_S$)-**2**

(1.42 g, 4.86 mmol) in CH_2Cl_2 (5 mL) was added slowly and the mixture was stirred for 5.5 h at –10 °C. The reaction was quenched by the addition of H_2O (30 mL), then the mixture was diluted with CH_2Cl_2 (75 mL), the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were washed with brine, filtered, and the volatiles were removed in vacuo to provide a yellow oil. The oil was purified by silica gel chromatography (330 g SiO_2; EtOAc–heptanes, 10–100%) followed by examination of the UV-active fractions by LCMS. Collection of the desired fractions and removal of solvent provided the major isomer (S_S,*R*)-**3c**.

Yield: 0.900 g (1.92 mmol, 40%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 3.0 Hz, 1 H), 7.31 (d, *J* = 8.6 Hz, 1 H), 7.23 (dd, *J* = 8.6, 3.0 Hz, 1 H), 4.73–4.69 (m, 1 H), 4.60 (d, *J* = 5.1 Hz, 1 H), 4.39 (q, *J* = 8.0 Hz, 2 H), 3.72–3.67 (m, 1 H), 3.65–3.61 (m, 1 H), 2.15 (dtd, *J* = 12.0, 7.7, 4.4 Hz, 1 H), 2.10–2.04 (m, 1 H), 1.18 (s, 9 H), 0.88 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 155.85, 152.69, 137.58, 122.63, 122.41 (coupling to fluorine not detected), 122.21, 66.26 (q, *J* = 36.0 Hz, 1C), 61.19, 58.92, 55.83, 39.62, 26.13, 22.82, –5.21, –5.23.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –74.39.

LCMS: *m*/*z* = 469.1 $[M + H]^+$ (t_R 0.94 min; UV).

(*R*$_S$)-*N*-{(*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-[6-(trifluoromethyl)pyridin-3-yl]propyl}-2-methylpropane-2-sulfinamide [(*R*$_S$,*R*)-3d]

To a solution of 5-bromo-2-(trifluoromethyl)pyridine (452 mg, 2.00 mmol) in 2-MeTHF (5 mL) was slowly added *i*-PrMgCl·LiCl (0.73 M in THF, 2.56 mL, 1.87 mmol) at r.t. Generation of the active nucleophile was followed by LCMS analysis and, after 1.25 h, the solution was cooled to –10 °C and diluted with CH_2Cl_2 (25 mL), after which (*R*$_S$)-**2** (389 mg, 1.33 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was stirred for 5 h until complete conversion was observed, then aq NH_4Cl (5 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) and the organic layers were combined, concentrated in vacuo and purified by silica gel chromatography (120 g SiO_2; EtOAc–heptanes, 10–100%) followed by examination of the UV-active fractions by LCMS. The desired fractions were combined and concentrated in vacuo to afford (*R*)-**3d** contaminated with the minor isomer (77:23).

Yield: 230 mg (0.523 mmol, 39%); yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.64 (d, *J* = 2.1 Hz, 1 H), 7.90 (dd, *J* = 8.1, 2.1 Hz, 1 H), 7.62 (d, *J* = 8.1 Hz, 1 H), 4.70 (dt, *J* = 13.2, 6.8 Hz, 1 H), 4.24 (d, *J* = 6.8 Hz, 1 H), 3.63–3.58 (m, 1 H), 3.56–3.51 (m, 1 H), 2.12–2.06 (m, 1 H), 2.01–1.95 (m, 1 H), 1.15 (s, 9 H), 0.83 (s, 9 H), –0.03 (s, 3 H), –0.04 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 149.14, 147.25 (q, *J* = 34.8 Hz), 141.42, 136.51, 124.70–118.66 (m), 61.59, 59.33, 56.37, 55.03, 39.35, 25.89, 22.55, 18.22, –5.42, –5.46.

LCMS: *m*/*z* = 439.4 $[M + H]^+$ (t_R 0.97 min; UV).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{34}F_3N_2O_2SSi$: 439.2057; found: 439.2055.

5-Iodo-2-methoxypyridine (4)

To an ice-cooled solution of isopropylmagnesium chloride (1.61 M in THF, 4.64 mL, 7.47 mmol) in THF (20 mL) was slowly added *n*-BuLi (1.5 M in hexane, 4.98 mL, 7.47 mmol). The mixture was then stirred for 5 min to give a yellow solution, then 5-bromo-2-methoxypyridine (1.405 g, 0.98 mL, 7.10 mmol, 95%) was added and the resulting solution was stirred for 45 min at 0 °C. Molecular iodine (3.79 g, 14.94 mmol) was added and the mixture was stirred for 30 min at 0 °C then for 1 h at r.t. Sat. aq NH_4Cl (5 mL) was then added, and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 75 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified by silica gel chromatography (EtOAc–heptanes, 5–80%) to afford **4**.

Yield: 1.34 g (5.72 mmol, 81%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.33 (dd, *J* = 2.4, 0.7 Hz, 1 H), 7.77 (dd, *J* = 8.7, 2.4 Hz, 1 H), 6.59 (dd, *J* = 8.7, 0.7 Hz, 1 H), 3.90 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.61, 152.84, 146.41, 113.52, 82.23, 53.76.

LCMS: *m*/*z* = 236.0 $[M + H]^+$.

The spectroscopic data are in good accordance with literature.[31]

(*R*)-*N*-Allylidene-2-methylpropane-2-sulfinamide (5)

To a stirred solution of **3** (0.470 g, 2.00 mmol) in 2-MeTHF (30 mL) was added *i*-PrMgCl·LiCl (0.73 M in THF, 2.56 mL, 1.88 mmol) dropwise at r.t. Generation of the active nucleophile was followed by LCMS analysis by monitoring the dehalogenation after quenching in a vial of MeOH. After 75 min, **7** (554 mg, 1.33 mmol) in 2-MeTHF (1.6 mL) was added and the reaction mixture was stirred until the electrophile disappeared on LCMS (ca. 1.5 h; the solution became clear yellow), after which half-saturated aq NH_4Cl (10 mL) was added and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 50 mL) and the organic layers were combined, washed with brine, dried over $MgSO_4$, concentrated in vacuo and purified by silica gel chromatography (40 g SiO_2; EtOAc–heptanes, 5–100%) followed by examination of the UV-active fractions by LCMS. Combination of UV-active fractions provided the byproduct **5**.

Yield: 0.048 g (0.30 mmol, 23%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 9.3 Hz, 1 H), 6.70–6.61 (m, 1 H), 6.00–5.99 (m, 1 H), 5.98–5.96 (m, 1 H), 1.18 (s, 9 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.39, 134.68, 131.76, 57.49, 22.54.

LCMS: *m*/*z* = 160.1 $[M + H]^+$ (t_R 0.52 min; UV).

The spectroscopic data are in accordance with literature.[32]

(6-Methoxypyridin-3-yl)(phenyl)methanol (6)

To a stirred solution of **3** (0.470 g, 2.00 mmol) in 2-MeTHF (30 mL) was added *i*-PrMgCl·LiCl (0.73 M in THF, 2.56 mL, 1.88 mmol) dropwise at r.t. Generation of the active nucleophile was followed by LCMS analysis by monitoring the dehalogenation after quenching in a vial of MeOH. After 75 min, benzaldehyde (0.251 g, 0.24 mL, 2.36 mmol) in 2-MeTHF (2 mL) was added and the mixture was immediately analyzed by LCMS, which showed full conversion of **3**. Sat. aq. NH_4Cl (5 mL) was then added followed by H_2O (20 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 50 mL) and the organic layers were combined, washed with brine, dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography (40 g SiO_2; EtOAc–heptanes, 10–100%) followed by examination of the UV-active fractions by LCMS. The desired fractions were combined and concentrated to afford **6**.

Yield: 0.372 g (1.73 mmol, 93%); yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 2.5 Hz, 1 H), 7.54 (ddd, *J* = 8.6, 2.5, 0.4 Hz, 1 H), 7.39–7.32 (m, 4 H), 7.31–7.25 (m, 1 H), 6.73–6.68 (m, 1 H), 5.82 (s, 1 H), 3.91 (s, 3 H), 2.37 (br, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.87, 145.27, 143.35, 137.54, 132.26, 128.77, 127.92, 126.41, 111.11, 73.94, 53.64.

LCMS: *m*/*z* = 216.0 $[M + H]^+$ (t_R 0.50 min; UV).

The spectroscopic data are in good accordance with literature.[33]

(R_S)-*N*-{3-[(*tert*-Butyldiphenylsilyl)oxy]propylidene}-2-methylpropane-2-sulfinamide (7)

A round-bottom flask was charged with (*R*)-2-methylpropane-2-sulfinamide (1.68 g, 13.87 mmol), pyridinium *p*-toluenesulfonate (0.174 g, 0.69 mmol) and $MgSO_4$ (8.35 g, 69.3 mmol) as a suspension in CH_2Cl_2 (50 mL). To this mixture, a solution of 3-[(*tert*-butyldiphenylsilyl)oxy]propanal (6.5 g, 20.80 mmol) in CH_2Cl_2 (15 mL) was added dropwise at r.t. and the reaction mixture was stirred overnight then filtered. The solute was concentrated in vacuo and subjected to purification by silica gel chromatography (120 g SiO_2; EtOAc–heptanes, 10–80%). Investigation of the UV-active fractions by LCMS followed by combination of those desired and concentration in vacuo afforded **7**.

Yield: 4.16 g (10.01 mmol, 72%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.14 (t, *J* = 4.7 Hz, 1 H), 7.68–7.63 (m, 4 H), 7.47–7.41 (m, 2 H), 7.41–7.37 (m, 4 H), 3.96 (td, *J* = 6.1, 1.4 Hz, 2 H), 2.77–2.73 (m, 2 H), 1.19 (s, 9 H), 1.03 (s, 9 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.97, 135.68, 133.45, 129.89, 127.88, 60.56, 56.72, 39.38, 26.89, 22.49, 19.25.

LCMS: *m*/*z* = 416.3 $[M + H]^+$ (t_R 1.11 min; UV).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{34}NO_2SSi$: 416.2074; found: 416.2067.

The spectroscopic data are in accordance with literature.[21]

2-Bromo-5-(2,2,2-trifluoroethoxy)pyridine (8)

To a solution of 6-bromopyridin-3-ol (2.30 g, 13.23 mmol) in DMF (18 mL) was added Cs_2CO_3 (4.74 g, 14.55 mmol) in small portions. The reaction mixture was stirred for 10 min after which 2,2,2-trifluoroethyl trifluoromethanesulfonate (3.38 g, 14.55 mmol) in DMF (5 mL) was added slowly. After stirring for 1 h at r.t., the suspension was poured into H_2O and the aqueous mixture was extracted with EtOAc (75 mL). The organic phase was then washed with brine and dried over $MgSO_4$ followed by removal of the volatiles in vacuo. The resulting crude material was subjected to silica gel chromatography (120 g SiO_2; EtOAc–heptanes, 5–100%) followed by analysis of the UV active fractions by LCMS. Combination of the desired fractions followed by concentration in vacuo provided **8**.

Yield: 3.08 g (12.01 mmol, 91%); white solid; mp 37.6–38.5 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.12–8.11 (m, 1 H), 7.44 (dd, *J* = 8.7, 0.5 Hz, 1 H), 7.18 (dd, *J* = 8.7, 3.2 Hz, 1 H), 4.39 (q, *J* = 7.9 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 153.52, 137.77, 134.48, 128.69, 125.74. 122.91 (q, *J* = 278.2 Hz), 66.40 (q, *J* = 36.3 Hz).

^{19}F NMR (471 MHz, $CDCl_3$): δ = –74.30.

LCMS: *m*/*z* = 256.2 $[M + H]^+$ (t_R 0.60 min; UV).

Anal. Calcd for $C_7H_5BrF_3NO$: C, 32.84; H, 1.97; N, 5.47. Found: C, 32.45; H, 1.94; N, 5.35.

2-Iodo-5-(2,2,2-trifluoroethoxy)pyridine (9)

In an oven-dried vial, copper(I) iodide (0.136 g, 0.72 mmol), sodium iodide (4.09 g, 27.3 mmol), and **8** (3.58 g, 13.98 mmol) were placed and the vial was sealed. MeCN (5.3 mL) and *trans*-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (0.133 g, 0.932 mmol) were introduced and the mixture was stirred overnight at 100 °C. Aq NH_4Cl (1/4 sat., 5 mL) was added and the resulting mixture was poured into H_2O and extracted with CH_2Cl_2 (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography (220 g SiO_2; EtOAc–heptanes, 5–80%) to provide **9**.

Yield: 3.8 g (12.54 mmol, 90%); white crystals; mp 51.7–53.4 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 3.1 Hz, 1 H), 7.65 (dd, *J* = 8.6, 0.4 Hz, 1 H), 6.98 (dd, *J* = 8.6, 3.1 Hz, 1 H), 4.38 (q, *J* = 7.9 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 154.14, 138.89, 135.26, 124.94, 122.91 (q, *J* = 278.1 Hz), 108.48, 66.21 (q, *J* = 36.3 Hz).

^{19}F NMR (471 MHz, $CDCl_3$): δ = –74.27.

LCMS: *m*/*z* = 304.0 $[M + H]^+$ (t_R 0.68 min; UV).

Anal. Calcd for $C_7H_5F_3INO$: C, 27.75; H, 1.66; N, 4.62. Found: C, 27.60; H, 1.66; N, 4.49.

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Supporting Information

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