ELECTRONIC SUPPORTING INFORMATION

Access towards enantiopure $\alpha,\alpha$-difluoromethyl alcohols
by means of sulfoxides as traceless chiral auxiliaries

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1. General experimental methods and equipment

Starting materials, if commercially available, were purchased from standard suppliers (Sigma-Aldrich, Fluorochem, ABCR, Acros, Alfa Aesar or Apollo scientific) and used as such, provided that adequate checks by NMR analysis had confirmed the claimed purity. When needed, solvents were purified and dried following standard procedures. THF was dried by distillation over sodium/benzophenone prior to use. Toluene, when used anhydrous, was either dried over 4 Å molecular sieves previously activated overnight at 300 °C under vacuum or dried by distillation over sodium. Anhydrous DMF purchased from Sigma Aldrich was used as received. Air- and moisture- sensitive materials were stored and handled under an atmosphere of argon. Reactions were carried out under an atmosphere of argon when needed. Reactions were monitored by using thin-layer chromatography with precoated silica on aluminum foils (0.25 mm, Merck silica-gel (60-F254)). Flash column chromatography was performed on VWR silica gel (40–63 μm) using the indicated solvents, the solvent systems being indicated in v/v. Butyllithium (1.6 M in hexanes, Aldrich) was used as a solution in hexanes and its concentration was determined following the Wittig-Harborth double titration method ((total base) - (residual base after reaction with 1,2-dibromoethane)).\(^{[1]}\) Spectroscopic NMR and MS data were obtained using chromatographically homogeneous samples. \(^1\)H NMR (400 or 500 MHz), \(^{19}\)F NMR (376 or 472 MHz) and \(^{13}\)C NMR (101 or 126 MHz) spectra were recorded in CDCl\(_3\) on Bruker Avance III HD 400 and 500 MHz instruments respectively. Chemical shifts are reported in parts per million (ppm) and are referred to partially deuterated chloroform (δ\(^{[1]}\)H = 7.26 ppm and δ\(^{[13]}\)C = 77.16 ppm). Multiplicities were abbreviated as br s (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), td (triplet of doublets), dd (doublet of doublets). Coupling constants J were given in Hz. Spectra were processed with the program NMR notebook (Version 2.80, NMRtec). IR spectra were recorded on a Perkin Elmer’s Spectrum one\(^{\text{TM}}\), the frequencies being reported in cm\(^{-1}\). Chiral HPLC analyses were performed on a Shimadzu Prominence chromatograph. High-resolution mass spectra (HRMS) were recorded with a TOF mass analyser under ESI in positive ionization mode detection by the analytical facility at the Université de Strasbourg. The X-ray crystallographic structure analysis was performed by the radiocrystallographic facility at the Université de Strasbourg. The analysis was carried out on a Nonius Kappa-CCD diffractometer equipped with an Oxford Cryosystem liquid N\(_2\) device, using Mo-K\(\alpha\) radiation (\(\lambda = 0.71073\) Å).
2. Synthesis of racemic aryl α,α-difluoromethyl sulfoxides 3a and 3b

a. Ethyl 2,2-difluoro-2-(p-tolylthio)acetate 1a

A solution of p-toluenethiol (1 equiv., 5 g, 39.5 mmol) dissolved in anhydrous DMF (15 mL) was cannulated dropwise onto a suspension of sodium hydride (60% dispersion in mineral oil; 1.1 equiv., 1.74 g, 43.4 mmol) in anhydrous DMF (15 mL) at 0 °C under an atmosphere of argon. Ethyl bromodifluoroacetate (1 equiv., 5.22 mL, 39.5 mmol) was then syringed dropwise into the previous solution. The reaction mixture was stirred at 40 °C for 20 hours, then cooled to 0 °C and quenched with water. The aqueous phase was extracted three times with CH₂Cl₂. The combined organic layers were washed with large amounts of water and with a saturated solution of NaCl. The resulting organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 95/5). Ethyl 2,2-difluoro-2-(p-tolylthio)acetate 1a (7.55 g, 78%) was obtained as a light yellow oil.

\[ \text{^1H NMR (400 MHz, CDCl}_3 \] \( \delta \) (ppm) 7.50 (d, \( J = 8.2 \) Hz, 2H), 7.20 (d, \( J = 8.2 \) Hz, 2H), 4.26 (q, \( J = 7.2 \) Hz, 2H), 2.38 (s, 3 H), 1.27 (t, \( J = 7.2 \) Hz, 3H). \text{^19F NMR (376 MHz, CDCl}_3 \] \( \delta \) (ppm) –82.6 (s, 2F). These data are consistent with those already reported in the literature.⁴

b. Ethyl 2,2-difluoro-2-(p-tolylsulfinyl)acetate 2a

a. Periodic acid and iron (III) chloride

Eff 2,2-difluoro-2-(p-tolylthio)acetate 1a (1 equiv., 12 g, 48.7 mmol) and FeCl₃ (3 mol%, 244 mg, 1.46 mmol) were dissolved in 75 mL of acetonitrile. After 10 minutes of stirring, periodic acid (1.1 equiv., 12.3 g, 53.6 mmol) was added to the mixture which was mechanically stirred at 25 °C. After 3 days (ca. 80% conversion, determined by \text{^1H} and \text{^19F} NMR analysis) were added more periodic acid (0.3 equiv.) and FeCl₃ (1 mol%). After 4 days of stirring, the reaction was slowly quenched with a saturated solution of Na₂S₂O₃ and extracted three times with CH₂Cl₂. The combined organic layers were washed with water and with a saturated solution of NaCl, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by chromatography on
demetalated silica gel with cyclohexane/AcOEt (100/0 to 80/20). Ethyl 2,2-difluoro-2-(p-tolylsulfinyl)acetate 2a (12.1 g, 95%) was obtained as a yellow oil.

**β. Hydrogen peroxide and trifluoroacetic acid**

To a solution of trifluoroperoxyacetic acid (TFPAA) at 0 °C (1 equiv., prepared by mixing 415 µL of H₂O₂, 30% w/w in water, with 1.36 mL of trifluoroacetic acid, TFA, at 0 °C) was added dropwise ethyl 2,2-difluoro-2-(p-tolythio)acetate 1a (1 equiv., 1 g, 4.06 mmol) dissolved in 6.5 mL of TFA. The solution was warmed to 25 °C and stirred at this temperature for 23 hours. The reaction mixture was carefully poured onto a saturated solution of NaHCO₃. The aqueous phase was extracted three times with AcOEt. The combined organic phases were washed with water and with a saturated solution of NaCl, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by chromatography on demetalated silica gel with cyclohexane/AcOEt (100/0 to 80/20). Ethyl 2,2-difluoro-2-(p-tolylsulfinyl)acetate 2a (800 mg, 75%) was obtained as a yellow oil.

**1H NMR (400 MHz, CDCl₃) δ (ppm) 7.61 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 4.26 (qd, J = 7.2 Hz, 1.7 Hz, 2H), 2.44 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H).**

**19F NMR (376 MHz, CDCl₃) δ (ppm) −110.6 (AB system, J_{AB} = 228.0 Hz, Δν_{AB} = 722.5 Hz, 2F).** These data are consistent with those already reported in the literature. [2]

**c. α,α-Difluoromethyl p-tolyl sulfoxide 3a**

**Thermal conditions**

Ethyl 2,2-difluoro-2-(p-tolylsulfinyl)acetate 2a (1 equiv., 3 g, 10.9 mmol) was dissolved in 85 mL of DMSO. LiCl (2 equiv., 931 mg, 21.8 mmol) and H₂O (2 equiv., 391 µL, 21.8 mmol) were then introduced. The reaction mixture was stirred at 110 °C for 24 hours. The mixture was cooled to room temperature and then poured onto cold water. The aqueous layer was saturated with NaCl and then extracted three times with AcOEt. The combined organic layers were washed with water and with a saturated solution of NaCl, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 80/20). α,α-Difluoromethyl p-tolyl sulfoxide 3a (1.83 g, 89%) was obtained as a white solid.
**d. Ethyl 2-(4-chlorophenylthio)-2,2-difluoroacetate 1b**

A solution of 4-chlorothiophenol (1 equiv., 12 g, 81.3 mmol) dissolved in anhydrous DMF (35 mL) was cannulated dropwise onto a suspension of sodium hydride (60% dispersion in mineral oil; 1.1 equiv., 3.58 g, 89.5 mmol) in anhydrous DMF (30 mL) at 0 °C under argon. Ethyl bromodifluoroacetate (1 equiv., 10.8 mL, 81.32 mmol) was then syringed dropwise into the previous solution. The reaction mixture was heated at 40 °C for 21 hours, then cooled to 0 °C, quenched with water and extracted three times with CH₂Cl₂. The combined organic layers were washed with large amounts of water and a saturated solution of NaCl. The resulting organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 90/10). Ethyl 2-(4-chlorophenylthio)-2,2-difluoroacetate (20.4 g, 94%) 1b was obtained as a light-yellow oil.

**e. Ethyl 2-(4-chlorophenylsulfinyl)-2,2-difluoroacetate 2b**

**α. Periodic acid and iron (III) chloride**

Ethyl 2-(4-chlorophenylthio)-2,2-difluoroacetate 1b (1 equiv., 5 g, 18.7 mmol) and FeCl₃ (3 mol%, 94.1 mg, 562 µmol) were dissolved in 50 mL of acetonitrile. After 10 minutes of stirring, periodic acid (1 equiv., 4.32 g, 18.7 mmol) was added to the mixture which was mechanically stirred at 25 °C. After 24 h (ca. 80% conversion), 39 h (ca. 87% conversion) and 48 h (ca. 92% conversion), were added each time 0.1 equiv. of oxidizing agent (total = 0.3 equiv. of H₅IO₆). After 50 hours of stirring, the reaction
was slowly quenched with a saturated solution of Na$_2$S$_2$O$_3$. The aqueous phase was extracted several times with CH$_2$Cl$_2$. The combined organic layers were washed with water and with a saturated solution of NaCl, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by chromatography on demetalated silica gel with cyclohexane/AcOEt (100/0 to 90/10). Ethyl 2-(4-chlorophenylsulfinyl)-2,2-difluoroacetate 2b (4.97 g, 94%) was obtained as a yellow oil.

β. Hydrogen peroxide and trifluoroacetic acid

\[
\begin{align*}
\text{Cl} & \quad \text{S} & \quad \text{O} & \quad \text{F} & \quad \text{F} \\
\text{Cl} & \quad \text{S} & \quad \text{O} & \quad \text{F} & \quad \text{F}
\end{align*}
\]

To a solution of trifluoroperoxyacetic acid (TFPAA) at 0 °C (1 equiv., prepared by mixing 383 µL of H$_2$O$_2$, 30% w/w in water, with 1.25 mL of trifluoroacetic acid, TFA, at 0 °C) was added dropwise ethyl 2-(4-chlorophenylthio)-2,2-difluoroacetate 1b (1 equiv., 1 g, 3.75 mmol) dissolved in 6 mL of TFA. The solution was warmed to 25 °C and stirred at this temperature for 23 hours. The reaction mixture was carefully poured onto a saturated solution of NaHCO$_3$. The aqueous phase was extracted three times with AcOEt. The combined organic phases were washed with water and with a saturated solution of NaCl, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by chromatography on demetalated silica gel with cyclohexane/AcOEt (100/0 to 80/20). Ethyl 2-(4-chlorophenylsulfinyl)-2,2-difluoroacetate 2b (800 mg, 75%) was obtained as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.67 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H). $^{19}$F NMR (376 MHz, CDCl$_3$) δ (ppm) −110.0 (AB system, $J_{AB} = 228.0$ Hz, $\Delta\nu_{AB} = 994.3$ Hz, 2F). These data are consistent with those already reported in the literature.[$^2$]

f. 1-Chloro-4-((difluoromethyl)sulfinyl)benzene 3b

α. Thermal conditions

\[
\begin{align*}
\text{Cl} & \quad \text{S} & \quad \text{O} & \quad \text{F} & \quad \text{F} \\
\text{Cl} & \quad \text{S} & \quad \text{O} & \quad \text{F} & \quad \text{F}
\end{align*}
\]

Ethyl 2-(4-chlorophenylsulfinyl)-2,2-difluoroacetate 2b (1 equiv., 100 mg, 354 µmol) was dissolved in 3 mL of DMSO. LiCl (2 equiv., 30.3 mg, 707 µmol) and H$_2$O (2 equiv., 12.7 µL, 707 µmol) were then introduced. The reaction mixture was stirred at 110 °C for 21 hours, cooled to room temperature and then poured onto ice-cold water. The aqueous layer was saturated with NaCl and then extracted three
times with AcOEt. The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel with cyclohexane/AcOEt (90/10 to 70/30). 1-Chloro-4-((difluoromethyl)sulfinyl)benzene 3b (75 mg, quantitative yield) was obtained as a white solid.

β. Microwave conditions

To a suspension of LiCl (2 equiv., 15.1 mg, 354 µmol) and ethyl 2-(4-chlorophenylsulfinyl)-2,2-difluoroacetate 2b (1 equiv., 50 mg, 177 µmol) in 3 mL of N-methylpyrrolidine (NMP) was added H₂O (2 equiv., 6.37 mL, 354 µmol). The reaction mixture was heated to 100 °C under microwave irradiation for 15 minutes. The dark brown reaction mixture was cooled to room temperature. An aqueous solution of 1M HCl was added to the mixture. The aqueous layer was extracted three times with AcOEt. The combined organic layers were washed three times with ice-cold water and with a cold saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 70/30). 1-Chloro-4-((difluoromethyl)sulfinyl)benzene 3b (38 mg, quantitative yield) was obtained as a white solid.

1H NMR (400 MHz, CDCl₃) δ (ppm) 7.67 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 6.19 (t, J = 55.2 Hz, 1H). 19F NMR (376 MHz, CDCl₃) δ (ppm) –119.3 (ABX system, Jₓₓ = Jₓ₋ₓ = 262.3 Hz, Jₓₓ = Jₓ₋ₓ = Jₓ₋ₓ = 55.2 Hz, Δ νₓₓ = 256.7 Hz, 2F). These data are consistent with those already reported in the literature.[4]

3. Synthesis of enantiopure α,α-difluoromethyl p-tolyl sulfoxide (S)-3a

a. (+)-Phenylalaninol 4

Following a reported procedure,[5] to a slurry of LiAlH₄ (2.1 equiv., 1.7 g, 44.7 mmol) in 60 mL of freshly distilled THF at 0 °C was added D-phenylalanine (1 equiv., 3.55 g, 21.3 mmol) under an atmosphere of argon. The slurry was stirred for 1 h at 0 °C and then heated under reflux for 21 h. The reaction mixture was cooled to 0 °C. 25 mL of an aqueous solution of NaOH 1M were added dropwise over 2 h. The slurry was filtered. The cake was washed several times with AcOEt. The organic layer was washed with a saturated solution of NaCl, dried over anhydrous sodium sulfate and concentrated under reduced
pressure. The D(+)-phenylalaninol 4 (3.13 g, 97%) was obtained after crystallisation in Et₂O as a white solid.

\[ ^1H \text{NMR (400 MHz, CDCl}_3\] \( \delta \) (ppm) 7.33-7.29 (m, 2H), 7.26-7.18 (m, 3H), 3.64 (dd, \( J = 3.8 \) Hz, 10.6 Hz, 1H), 3.38 (dd, \( J = 7.2 \) Hz, 10.6 Hz, 1H), 3.16-3.09 (m, 1H), 2.80 (dd, \( J = 5.1 \) Hz, 13.4 Hz, 1H), 2.53 (dd, \( J = 8.7 \) Hz, 13.4 Hz, 1H), 2.30-1.70 (br s, 3H). These data are consistent with those already reported in the literature.\[5\]

b. \((R)-4\)-Benzyl-2-oxazolidinone 5

Following a reported procedure,\[6\] D(+)-phenylalaninol 4 (1 equiv., 1 g, 6.61 mmol) and dried \( \text{K}_2\text{CO}_3 \) (0.9 equiv., 823 mg, 5.95 mmol) were put in presence of freshly distilled diethyl carbonate (2 equiv., 1.62 mL, 13.2 mmol). The slurry was heated to 145 °C and EtOH was removed by distillation until elution ceased. The reaction mixture was cooled to room temperature and the remaining volatiles were removed under reduced pressure. \( \text{CH}_2\text{Cl}_2 \) was added to the resulting oil. The organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 50/50). \((R)-4\)-Benzyl-2-oxazolidinone 5 (986 mg, 84%) was obtained as an orange solid.

\[ ^1H \text{NMR (400 MHz, CDCl}_3\] \( \delta \) (ppm) 7.33 (t, \( J = 7.1 \) Hz, 2H), 7.26 (t, \( J = 5.4 \) Hz, 1H), 7.17 (d, \( J = 7.2 \) Hz, 2H), 5.58 (br s, 1H), 4.44 (t, \( J = 8.3 \) Hz, 1H), 4.16-4.04 (m, 2H), 2.87 (d, \( J = 6.8 \) Hz, 2H). These data are consistent with those already reported in the literature.\[6\]

c. \((R)-4\)-benzyl-3-((R)-p-tolylsulfinyl) oxazolidin-2-one, \((R,R)-6\), and \((R)-4\)-benzyl-3-((S)-p-tolylsulfinyl) oxazolidin-2-one, \((R,S)-6\)

Preliminary synthesis of \( p \)-tolylsulfinyl chloride
SOCl₂ (5 equiv., 1.57 mL, 21.4 mmol) was diluted in 9 mL of freshly distilled toluene under argon. The solution was cooled to 0 °C. Sodium p-tolylsulfinate (1 equiv., 762 mg, 4.28 mmol) was slowly added to the previous solution. The reaction mixture was warmed to room temperature (25 °C) and it was stirred for 2 h. The remaining SOCl₂ was distilled (azeotrope with toluene) followed by removal of the residual solvent under reduced pressure, to afford p-tolylsulfinyl chloride.

Procedure

To a solution of (R)-4-benzyl-2-oxazolidinone 5 (1 equiv., 500 mg, 2.85 mmol) in 6 mL of freshly distilled THF under an atmosphere of argon at 0 °C was added dropwise n-BuLi (1.1 equiv., 1.58 M in hexanes, 1.99 mL, 3.14 mmol) over a 5 to 10 minute-period. The resultant suspension was stirred at this temperature for 10 minutes and then cooled to -78 °C. It was stirred 10 minutes at this temperature. The freshly prepared p-tolylsulfinyl chloride (1.5 equiv., 747 mg, 4.28 mmol) dissolved in 4 mL of freshly distilled THF was then added as a slurry to the previous mixture. The reaction mixture was stirred at -78 °C for 25 minutes. It was quenched with a saturated solution of NH₄Cl and diluted with AcOEt. The aqueous phase was extracted three times with AcOEt. The combined organic layers were washed with a saturated solution of NaHCO₃ and with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. An NMR analysis of the crude mixture revealed total conversion with a ratio (R,R):(R,S) of 61:39. The crude product was purified by chromatography on demetalated silica gel with cyclohexane/AcOEt (100/0 to 80/20). The (R)-4-benzyl-3-((R)-p-tolylsulfinyl)oxazolidin-2-one (R,R)-6 (426 mg, 48%) was obtained as a white solid and (R)-4-benzyl-3-((S)-p-tolylsulfinyl)oxazolidin-2-one (R,S)-6 (209 mg, 23%) was obtained as an orange oil. It is also possible to crystallise (R)-4-benzyl-3-((R)-p-tolylsulfinyl)oxazolidin-2-one (R,R)-6 from Et₂O from the crude mixture.

(R)-4-Benzyl-3-((R)-p-tolylsulfinyl)oxazolidin-2-one (R,R)-6

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.71 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.29-7.18 (m, 3H), 6.98-6.91 (m, 2H), 4.07 (dd, J = 3.8 Hz, 9.0 Hz, 1H), 3.97 (t, J = 8.0 Hz, 1H), 3.76-3.68 (m, 1H), 3.37 (dd, J = 3.5 Hz, 13.8 Hz, 1H), 2.90 (dd, J = 10.4 Hz, 13.9 Hz, 1H), 2.51 (s, 3H). These data are consistent with those already reported in the literature.[7]

(R)-4-Benzyl-3-((S)-p-tolylsulfinyl)oxazolidin-2-one (R,S)-6

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.76 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.28-7.17 (m, 3H), 6.98-6.92 (m, 2H), 4.59-4.48 (m, 1H), 4.16 (t, J = 8.8 Hz, 1H), 4.08 (dd, J = 4.7 Hz, 8.9 Hz, 1H), 2.43 (s, 3H), 2.20-2.14 (m, 2H). These data are consistent with those already reported in the literature.[7]
d. Ethyl (S)-2,2-difluoro-2-(p-tolylsulfinyl)acetate (S)-2a

\[ \text{BrCF}_2CO_2Et (2.4 \text{ equiv.}) \]
\[ \text{Zn (2.4 equiv.)} \]
\[ \text{THF, 66 °C, 41 h} \]
\[ 72\%, 97\% \text{ e.e.} \]

To a suspension of freshly activated Zn (Zn was activated with an aqueous solution of 4M HCl then washed several times with water and acetone and finally put under vacuum at 120 °C overnight; 2.4 equiv., 34.8 mg, 533 µmol) in 3 mL of freshly distilled THF was added one drop of ethyl bromodifluoroacetate. The mixture was stirred at 66 °C. A solution of (R)-4-benzyl-3-((R)-p-tolylsulfinyl)oxazolidin-2-one (R,R)-6 (1 equiv., 70 mg, 222 µmol) and ethyl bromodifluoroacetate (2.4 equiv., 70.4 mL, 533 µmol) in 3 mL of freshly distilled THF was then added dropwise to the previous mixture. The reaction mixture was stirred at 66 °C for 41 hours, then cooled to room temperature and quenched with an aqueous solution of KHSO₄. The mixture was stirred for 30 minutes at 25 °C. It was then filtered through Celite® and washed carefully with diethyl ether. To the filtrate was added a saturated solution of NaCl. The filtrate was extracted three times with Et₂O. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on demetalated silica gel in cyclohexane/AcOEt (100/0 to 90/10). Ethyl (S)-2,2-difluoro-2-(p-tolylsulfinyl)acetate (S)-2a (42 mg, 0.16 mmol, 72%, 97% e.e.) was obtained as a light yellow oil. The enantiomeric excess of the product was determined by chiral HPLC using a Chiracel IC column (n-hexane/i-PrOH = 80/20, flow rate: 0.5 mL/min, λ = 206 nm, τ = 23.9 min and 31.3 min).

\[ \text{β. Honda-Reformatsky-type reaction} \]

\[ \text{BrCF}_2CO_2Et (3 \text{ equiv.}) \]
\[ \text{ZnEt}_2 (2 \text{ equiv.}) \]
\[ \text{RhCl(PPh}_3)_3 (3 \text{ mol%}) \]
\[ \text{THF, -20 °C, 1 h} \]
\[ 65\%, 86\% \text{ e.e.} \]

(R)-4-Benzyl-3-((R)-p-tolylsulfinyl)oxazolidin-2-one (R,R)-6 (1 equiv., 70 mg, 222 µmol) and RhCl(PPh₃)₃ (3 mol%, 6.16 mg, 6.7 µmol) were dissolved in 6 mL of freshly distilled THF. The mixture was cooled to -20 °C. Ethyl bromodifluoroacetate (3 equiv., 88 µL, 670 µmol) was added to the mixture followed by dropwise addition of diethylzinc (2 equiv., 1 M in hexanes, 444 µL, 444 µmol). The mixture was stirred at -20 °C for 1 h. Stirring was continued at 20 °C for 4 h. The reaction mixture was quenched with a saturated solution of NH₄Cl. The aqueous phase was extracted three times with AcOEt and the combined organic layers were washed with a saturated solution of NaCl, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by chromatography.
on demetalated silica gel using cyclohexane/AcOEt (100/0 to 90/10). Ethyl (S)-2,2-difluoro-2-(p-tolylsulfinyl)acetate (S)-2a (38 mg, 145 µmol, 65%, 86% e.e.) was obtained as a transparent oil. The enantiomeric excess of the product was determined by chiral HPLC using a Chiracel IC column (n-hexane/i-PrOH = 80/20, flow rate: 0.5 mL/min, λ = 206 nm, τ = 24.0 min and 31.6 min).

$^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.61 (d, $J = 8.0$ Hz, 2H), 7.38 (d, $J = 8.2$ Hz, 2H), 4.26 (qd, $J = 7.2$ Hz, 1.7 Hz, 2H), 2.44 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H).

$^{19}$F NMR (376 MHz, CDCl$_3$) δ (ppm) −110.6 (AB system, $J_{AB} = 227.0$ Hz, $\Delta V_{AB} = 727.0$ Hz, 2F). These data are consistent with those already reported in the literature.[2]

e. (S)-α,α-Difluoromethyl p-tolyl sulfoxide (S)-3a

The enantioenriched ethyl (S)-2,2-difluoro-2-(p-tolylsulfinyl)acetate (S)-2a (92% e.e.) was decarboxylated under Krapcho’s conditions previously optimized for the synthesis of the corresponding racemic compound 2a (see § 1.f.).

α. Thermal conditions

Under thermal conditions, after 19 h of stirring at 110 °C, (S)-α,α-difluoromethyl p-tolyl sulfoxide (S)-3a (107 mg, 98%, 84% e.e.) was obtained as a white solid. The enantiomeric excess of the product was determined by chiral HPLC using a Chiracel IC column (n-hexane/i-PrOH = 80:20, flow rate: 0.5 mL/min, λ = 205 nm, τ = 17.2 min and 23.2 min).

β. Microwave conditions

Under microwave conditions, after 15 minutes of stirring at 100 °C, (S)-α,α-difluoromethyl p-tolyl sulfoxide (S)-3a (69 mg, 83%, 92% e.e.) was obtained as a white solid. The enantiomeric excess of the product was determined by chiral HPLC using a Chiracel IC column (n-hexane/i-PrOH = 80/20, flow rate: 0.5 mL/min, λ = 205 nm, τ = 17.1 min and 23.2 min).

$^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.62 (d, $J = 8.1$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H), 6.00 (t, $J = 55.5$ Hz, 1H), 2.46 (s, 3H). $^{19}$F NMR (376 MHz, CDCl$_3$) δ (ppm) −119.4 (d, 2F, $J = 55.9$ Hz). These data are consistent with those already reported in the literature.[3]
y. Crystallographic structure of (S)-α,α-difluoromethyl p-tolyl sulfoxide (S)-3a

It should be noted that (S)-enantioenriched α,α-difluoromethyl p-tolyl sulfoxide 3a can be further enantioenriched by crystallisation from Et₂O to obtain (S)-3a with > 97% e.e.. It was possible to get suitable crystals for a crystallographic analysis that confirmed the (S) configuration of the sulfur atom.

The crystals were placed in oil, and a single crystal was selected, mounted on a glass fibre and placed in a low-temperature N₂ stream. X-ray diffraction data collection was carried out on a Nonius Kappa-CCD diffractometer equipped with an Oxford Cryosystem liquid N₂ device, using Mo-Kα radiation (λ = 0.71073 Å). The crystal-detector distance was 36 mm. The cell parameters were determined (Denzo software) from reflections taken from one set of 10 frames (1.0° steps in phi angle), each at 20 s exposure. The structure was solved by Direct methods using the program SHELXS-2014. The refinement and all further calculations were carried out using SHELXL-2014. The H-atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least-squares on F².

X-Ray analysis of (S)-α,α-difluoromethyl p-tolyl sulfoxide (S)-3a

<table>
<thead>
<tr>
<th>Formule</th>
<th>C₈H₈F₂OS</th>
<th>Cell volume</th>
<th>834.253 Å³</th>
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<tr>
<td>m</td>
<td>190.20</td>
<td>Z, Calculated density</td>
<td>4, 1.514 Mg/m³</td>
</tr>
<tr>
<td>Temperature</td>
<td>173 (2)</td>
<td>F(000)</td>
<td>392</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073</td>
<td>Crystal size</td>
<td>0.340 x 0.180 x 0.120 mm</td>
</tr>
<tr>
<td>Crystalline structure</td>
<td>Orthorhombic</td>
<td>Theta range for data collection</td>
<td>2.511 to 27.475</td>
</tr>
<tr>
<td>Space group</td>
<td>P 2₁2₁2₁</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4. Details concerning the synthesis of α,α-difluoro-β-hydroxy sulfoxides 7a-n

a. Determination of the best reaction conditions – Detailed general procedures

\[
\text{SCH}_2\text{CF}_2 + \text{C}=\text{O} \rightarrow \text{SCH}_2\text{CF}_2\text{OH}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Time</th>
<th>d.r(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-BuOK(^b)</td>
<td>THF</td>
<td>40 min</td>
<td>40:60</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>DMF</td>
<td>2 h</td>
<td>53:47</td>
</tr>
<tr>
<td>3</td>
<td>P(_4)t-Bu(^c)</td>
<td>THF</td>
<td>2 h</td>
<td>84:16</td>
</tr>
<tr>
<td>4</td>
<td>P(_4)t-Bu(^d)</td>
<td>DMF</td>
<td>2 h</td>
<td>55:45 to 99:1</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>THF</td>
<td>2 h</td>
<td>99:1</td>
</tr>
</tbody>
</table>

\(^a\) Diastereomeric ratios were determined by \(^{19}\)F NMR and confirmed by reversed-phase HPLC – \(^b\) **Procedure A**: potassium tert-butoxide was solubilized in the solvent of the reaction – \(^c\) **Procedure B**: P\(_4\)t-Bu was used as a commercially available solution in hexane – \(^d\) **Procedure C**: P\(_4\)t-Bu was added as a solution in freshly distilled THF.

\(\alpha\). Procedure A

In a vial under argon were dissolved α,α-difluoromethyl \(p\)-tolyl sulfoxide 3a (1 equiv., 15 mg, 78.9 \(\mu\)mol) and benzaldehyde (1 equiv., 8.13 \(\mu\)L, 78.9 \(\mu\)mol) in 1 mL of the appropriate anhydrous solvent. The mixture was stirred at -30 °C for 10 minutes. Potassium tert-butoxide (2 equiv., 17.7 mg, 158 \(\mu\)mol) previously put in suspension or solubilised in 1.5 mL of the same anhydrous solvent was added dropwise to the previous solution. The reaction mixture was stirred at -30 °C for 40 minutes up to
2 hours, then quenched with water at this temperature. The aqueous layer was extracted three times with Et₂O. The combined organic layers were washed with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The diastereomeric ratio was determined by $^{19}$F NMR and confirmed by reverse-phase HPLC. The crude product was purified by chromatography on silica gel using cyclohexane/AcOEt (100/0 to 80/20) to obtain 2,2-difluoro-1-phenyl-2-(p-tolylsulfinyl)ethan-1-ol 7a as an oil.

**β. Procedure B**

In a vial under argon were dissolved $\alpha,\alpha$-difluoromethyl $\rho$-tolyl sulfoxide 3a (1 equiv., 15 mg, 78.9 µmol) and benzaldehyde (1 equiv., 8.13 µL, 78.9 µmol) in 1 mL of the appropriate anhydrous solvent. P$_{4}$t-Bu (0.8 M solution in hexane, 2 equiv., 0.197 mL, 0.158 mmol) was added dropwise to this solution cooled to -30 °C. The reaction mixture was stirred at -30 °C for 2 hours, then quenched with water at this temperature. The aqueous layer was extracted three times with Et₂O. The combined organic layers were washed with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The diastereomeric ratio was determined by $^{19}$F NMR and confirmed by reverse-phase HPLC. The crude product was purified by chromatography on silica gel using cyclohexane/AcOEt (100/0 to 80/20) to obtain 2,2-difluoro-1-phenyl-2-(p-tolylsulfinyl)ethan-1-ol 7a as an oil.

**γ. Procedure C**

Hexane was removed under vacuum from 197 µL of the commercially available solution of P$_{4}$t-Bu (0.8 M in hexane, 2 equiv., 197 µL, 158 µmol). The solid obtained was dissolved in 0.7 mL of freshly distilled THF previously cooled to -30 °C. To a solution of $\alpha,\alpha$-difluoromethyl $\rho$-tolyl sulfoxide 3a (1 equiv., 15 mg, 78.9 µmol) and benzaldehyde (1 equiv., 8.13 µL, 78.9 µmol) dissolved in 1.8 mL of freshly distilled THF at -30 °C was added dropwise the previous solution of P$_{4}$t-Bu in THF. The reaction mixture was stirred at -30 °C for 2 hours, then quenched with water at this temperature. The aqueous layer was extracted three times with Et₂O. The combined organic layers were washed with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The diastereomeric ratio was determined by $^{19}$F NMR and confirmed by reverse-phase HPLC. The crude product was purified by chromatography on silica gel using cyclohexane/AcOEt (100/0 to 80/20) to obtain 2,2-difluoro-1-phenyl-2-(p-tolylsulfinyl)ethan-1-ol 7a as an oil.

**b. Determination of the diastereomeric ratios by $^{19}$F NMR and reverse-phase HPLC**

To confirm the accuracy of the diastereomeric ratio measured by $^{19}$F NMR, the ratio was compared with a determination by reverse-phase HPLC. See below one example (Table 1, Entry 2 of the corpus).
\( ^{19}\text{F} \) NMR analysis – d.r. = 52.4 (diastereomer 1) : 47.6 (diastereomer 2)

Reverse-phase HPLC analysis – d.r. = 52.35 (diastereomer 1) : 47.65 (diastereomer 2)
Using $^{19}$F NMR, we could measure a d.r. of 52.4:47.6 while using reverse-phase HPLC we measured a d.r. of 52.35:47.65. Both results being identical within experimental error, it was decided to use $^{19}$F NMR to determine the diastereomeric ratios on each crude mixture.

c. Mechanistic hypothesis

α. Evolution of the diastereomeric ratio over time

The diastereomeric excess of the reaction mixture (comprising 1 equiv. of benzaldehyde, 1 equiv. of sulfoxide and 2 equiv. of $P_4t$-Bu at -30 °C) increases over time. Hereafter are presented the procedure that has been employed, the $^{19}$F NMR analysis performed and the graphics showing this evolution over time for the conditions cited above.

![Chemical structure](image)

Procedure E

Hexane was removed under vacuum from 197 µL of the commercially available solution of $P_4t$-Bu (0.8 M in hexane, 2 equiv., 197 µL, 158 µmol). The solid obtained was dissolved in 0.7 mL of freshly distilled THF previously cooled to -30 °C. To a solution of $\alpha,\alpha$-difluoromethyl $p$-tolyl sulfoxide 3a (1 equiv., 15 mg, 78.9 µmol) and benzaldehyde (1 equiv., 8.13 µL, 78.9 µmol) dissolved in 1.8 mL of freshly distilled THF at -30 °C was added dropwise the previously prepared solution of $P_4t$-Bu in THF. 0.4 mL of the reaction mixture were collected after 5 min, 15 min, 45 min and 2 h. These samples were each time immediately quenched by syringing them into 2 mL of water. The aqueous phases were extracted with Et$_2$O three times. The combined organic layers were washed with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The diastereomeric ratio was determined by $^{19}$F NMR.
$^{19}$F NMR of the reaction mixture sampled after 5, 15, 45 and 120 minutes

Evolution of the diastereomeric excess over time for two equivalents of $\text{P}_{4}\text{-}t\text{-Bu}$ – Data

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Diastereomer 1(^a)</th>
<th>Diastereomer 2(^a)</th>
<th>Diastereomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>62</td>
<td>38</td>
<td>24</td>
</tr>
<tr>
<td>15</td>
<td>73</td>
<td>27</td>
<td>46</td>
</tr>
<tr>
<td>45</td>
<td>93</td>
<td>7</td>
<td>86</td>
</tr>
<tr>
<td>120</td>
<td>99,5</td>
<td>0,5</td>
<td>99</td>
</tr>
</tbody>
</table>

\(^a\) The percentage of each diastereomer was determined via quantitative $^{19}$F NMR integration

Evolution of the diastereomeric excess over time for two equivalents of $\text{P}_{4}\text{-}t\text{-Bu}$ – Graphic
\[ \text{\(\beta\). Presence of \(\alpha\)-fluoro-\(\beta\)-ketosulfoxide in the crude mixtures} \]

![Chemical reaction image](image)

Here is one example of the \(^{19}\text{F} \) NMR of a crude mixture showing the presence of the corresponding \(\alpha\)-fluoro-\(\beta\)-ketosulfoxide as side product of the reaction. The presence of this side product correlates the assumed mechanism (cf. Scheme 3 of the manuscript).

\[^{19}\text{F} \text{NMR spectra of the crude mixture}\]

\textbf{Two diastereomers}

\[^{1}\text{H} \text{NMR (400 MHz, CDCl}_{3}\)] \(\delta\) (ppm) 8.22 (d, \(J = 2.8\text{ Hz}, 1\text{H}\)), 7.93 (d, \(J = 2.9\text{ Hz}, 0.9\text{H}\)), 7.54 (d, \(J = 8.2\text{ Hz}, 2\text{H}\)), 7.48 (d, \(J = 8.1\text{ Hz}, 1.8\text{H}\)), 7.44 (t, \(J = 1.6\text{ Hz}, 1\text{H}\)), 7.37 (t, \(J = 1.5\text{ Hz}, 0.9\text{H}\)), 7.35 (d, \(J = 8.1\text{ Hz}, 2\text{H}\)), 7.28 (d, \(J = 8.1\text{ Hz}, 1.8\text{H}\)), 6.81 (d, \(J = 1.6\text{ Hz}, 1\text{H}\)), 6.72 (d, \(J = 1.7\text{ Hz}, 0.9\text{H}\)), 5.87 (d, \(J = 50.5\text{ Hz}, 0.9\text{H}\)), 5.63 (d, \(J = 48.5\text{ Hz}, 1\text{H}\)), 2.43 (s, 3H), 2.39 (s, 2.7H). \(^{19}\text{F} \text{NMR (376 MHz, CDCl}_{3}\)] \(\delta\) (ppm) –189.6 (dd, \(J = 3.4\text{ Hz}, 50.4\text{ Hz}, 1\text{F}\)) and –190.7 (dd, \(J = 2.7\text{ Hz}, 48.4\text{ Hz}, 1\text{F}\)). IR \(\nu\) (cm\(^{-1}\)) 2926, 2874, 1725, 1669, 1596, 1514, 1493, 1456, 1382, 1288, 1161, 1143, 1119, 1080, 1057, 1016, 943, 873, 811, 745, 703. \textbf{HRMS (ESI positive)} calcld for C\(_{13}\)H\(_{11}\)FNaO\(_3\)S: 289.0305, found: 289.0294.
5. Synthesis of α,α-difluoro-β-hydroxy sulfoxides 7a-n

a. 2,2-Difluoro-1-phenyl-2-(p-tolylsulfinyl)ethan-1-ol 7a

**Crude mixture** – Diastereomeric ratio = 99:1 (19F NMR)

**One diastereomer** (major one with procedure C)

1H NMR (400 MHz, CDCl3) δ (ppm) 7.63 (d, J = 7.9 Hz, 2H), 7.54-7.48 (m, 2H), 7.43-7.34 (m, 5H), 5.37 (dd, J = 8.3 Hz, 16.4 Hz, 1H), 3.54 (s, 1H), 2.45 (s, 3H).

19F NMR (376 MHz, CDCl3) δ (ppm) –114.5 (ABX system, JAB = JF-F = 219.3 Hz, JAB = JH-F = 16.3 Hz, ΔνAB = 4311 Hz, 2F). 13C NMR (126 MHz, CDCl3) δ (ppm) 143.8, 134.2, 132.8, 130.1, 129.6, 128.7, 128.2, 126.5, 123.4 (dd, J = 292.9 Hz, 311.5 Hz), 73.7 (t, J = 21.8 Hz), 21.8. IR ν (cm⁻¹) 3265, 1595, 1493, 1456, 1205, 1106, 1085, 1067, 1033, 975, 812, 726, 697. HRMS (ESI positive) calcd for C15H14F2NaO2S: 319.0575, found: 319.0588.

b. 2,2-Difluoro-1-phenyl-2-(p-tolylsulfinyl)ethan-1-ol 7b

**Crude mixture** – Diastereomeric ratio = 56:44 (19F NMR)

**Two diastereomers** – Diastereomeric ratio = 55:45 (19F NMR)

1H NMR (500 MHz, CDCl3) δ (ppm) 7.60 (d, J = 7.8 Hz, 1.6H), 7.58 (m 3.6H), 7.54 (d, J = 8.1 Hz, 2.0H), 7.51-7.39 (m, 2.8H), 7.38-7.31 (m, 6.2H), 4.77 (br s, 0.7H), 4.35 (br s, 1H), 2.44 (s, 2.5H), 2.42 (s, 3H), 2.08 (s, 3H), 1.74 (s, 2.5H).

19F NMR (472 MHz, CDCl3) δ (ppm) –110.5 (AB system, JAB = JF-F = 221.1 Hz, ΔνAB = 5729 Hz, 1F); diastereomer 2, δ (ppm) –112.5 (AB system, JAB = JF-F = 219.3 Hz, ΔνAB = 6289 Hz, 0.7F). 13C NMR (126 MHz, CDCl3) δ (ppm) 143.9, 143.8, 140.4, 139.0, 132.4, 132.3, 130.0, 130.0, 128.7, 128.7, 128.5, 128.2, 126.9, 126.8, 126.7, 126.4, 78.9 (t, J = 21.3 Hz), 77.9 (dd, J = 40.9 Hz, 20.4 Hz), 25.3, 24.3, 21.8, 21.7. IR ν (cm⁻¹) 3350, 2922, 2852, 1597, 1494, 1449, 1379, 1123, 1082, 1066, 1042, 1016, 969, 810, 761, 699. HRMS (ESI positive) calcd for C16H17F202S: 311.0912, found: 311.0895.

c. 2,2-Difluoro-1-(naphthalen-1-yl)-2-(p-tolylsulfinyl)ethan-1-ol 7c

**Crude mixture** – Diastereomeric ratio = 56:44 (19F NMR)

**Two diastereomers** – Diastereomeric ratio = 34:66 (19F NMR)

1H NMR (400 MHz, CDCl3) δ (ppm) 8.06 (d, J = 8.1 Hz, 0.5H), 7.93-7.83 (m, 4.5H), 7.79 (d, J = 7.7 Hz, 1H), 7.70-7.62 (m, 3H), 7.57-5.41 (m, 4.5H), 7.40-7.34 (m, 3H), 6.34 (dd, J = 1.8 Hz, 22.6 Hz, 1H) 6.26 (dd, J = 5.1 Hz, 17.9 Hz,
d. 2,2-Difluoro-1-(naphthalen-2-yl)-2-{p-tolylsulfinyl}ethan-1-ol 7d

**Crude mixture** – Diastereomeric ratio = 73:27 \(^{19}\)F NMR

**Two diastereomers** – Diastereomeric ratio = 70:30 \(^{19}\)F NMR

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 8.00 (s, 0.7H), 7.94 (s, 0.3H), 7.90-7.81 (m, 3H), 7.67-7.59 (m, 2.7H), 7.57-7.47 (m, 2.3H), 7.4-7.34 (m, 2H), 5.63-5.50 (m, 1H), 4.33-4.15 (br s, 0.4H), 3.79-3.58 (br s, 0.8H), 2.44 (s, 3H). \(^{19}\)F NMR (472 MHz, CDCl\(_3\)) \(\delta\) (ppm) –114.5 (ABX system, \(J_{AB} = J_{e-F} = 218.5\) Hz, \(J_{AX} = J_{\text{HX}} = 8.7\) Hz, \(J_{BX} = J_{\text{HX}} = 14.7\) Hz, \(\Delta\nu_{AB} = 4735\) Hz, 0.7F), diastereomer \(1\), \(\delta\) (ppm) –114.6 (ABX system, \(J_{AB} = J_{e-F} = 218.5\) Hz, \(J_{AX} = J_{\text{HX}} = 8.7\) Hz, \(J_{BX} = J_{\text{HX}} = 14.7\) Hz, \(\Delta\nu_{AB} = 4735\) Hz, 0.7F). diastereomer \(2\), \(\delta\) (ppm) –113.5 (ABX system, \(J_{AB} = J_{e-F} = 225.4\) Hz, \(J_{BX} = J_{\text{HX}} = 21.7\) Hz, \(\Delta\nu_{AB} = 2483\) Hz, 0.3F). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) (ppm) 143.9, 143.8, 133.9, 133.8, 133.1, 131.3, 132.7, 132.7, 132.0, 131.6, 131.1, 130.2, 130.1, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 126.9, 126.8, 126.6, 126.5, 126.4, 125.9, 125.8, 125.4, 123.3, 123.1, 69.7 (dd, \(J = 20.4\) Hz, 23.6 Hz), 66.9 (dd, \(J = 19.5\) Hz, 28.6 Hz), 21.8, 21.7.

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) (ppm) –122.4 (ABX system, \(J_{AB} = J_{e-F} = 212.2\) Hz, \(J_{AX} = J_{\text{HX}} = 4.8\) Hz, \(J_{BX} = J_{\text{HX}} = 18.4\) Hz, \(\Delta\nu_{AB} = 5566\) Hz, 2F). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) (ppm) 143.9, 133.8, 133.0, 132.6, 131.5, 130.3, 130.2, 129.0, 127.1, 126.8, 126.4, 125.9, 125.4, 123.3 (d, \(J = 1.8\) Hz), 69.7 (dd, \(J = 21.3\) Hz, 23.8 Hz), 21.8.

IR \(\nu\) (\(\text{cm}^{-1}\)) 3307, 2925, 1597, 1514, 1493, 1398, 1192, 1087, 1041, 1015, 967, 789, 772, 739. HRMS (ESI positive) calcd for C\(_{19}\)H\(_{17}\)F\(_2\)O\(_2\)S: 347.0912, found: 347.0889.
126.8, 126.6, 126.5, 125.1, 125.0, 73.9 (t, \( J = 21.8 \) Hz), 71.7 (dd, \( J = 20.4 \) Hz, 28.6 Hz), 21.8, 21.8. IR ν (cm\(^{-1}\)) 3320, 2958, 2924, 2869, 1724, 1597, 1380, 1272, 1193, 1107, 1085, 1041, 963, 795, 749.

IR ν (cm\(^{-1}\)) 2957, 2925, 2856, 2872, 1726, 1596, 1491, 1463, 1380, 1274, 1142, 1122, 1075, 1040, 967, 810, 743, 703.

HRMS (ESI positive) calcd for C\(_{19}\)H\(_{16}\)F\(_2\)NaO\(_2\)S: 369.0731, found: 369.0718.

e. 2,2-Difluoro-1-(pyridin-2-yl)-2-(p-tolylsulfinyl)ethan-1-ol 7e

**Crude mixture** – Diastereomeric ratio = 88:12 (\(^{19}\)F NMR)

**Two diastereomers** – Diastereomeric ratio = 90:10 (\(^{19}\)F NMR)

\(^{1}\)H NMR (400 MHz, CDCl\(_3\)) δ (ppm) 8.60 (br s, 1H), 7.81-7.72 (m, 2.7H), 7.65 (d, \( J = 7.8 \) Hz, 0.3H), 7.44-7.34 (m, 4H), 5.48 (d, \( J = 24.0 \) Hz, 0.1H), 4.92 (d, \( J = 15.0 \) Hz, 0.9H), 2.45 (s, 2.7H), 2.43 (s, 0.3H).

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)) diastereomer 1, δ (ppm) –114.8 (ABX system, \( J_{AB} = J_{F-F} = 220.0 \) Hz, \( J_{AX} = J_{H-F} = 15.7 \) Hz, \( \Delta \nu_{AB} = 2776 \) Hz, 0.9F); diastereomer 2, δ (ppm) –117.4 (ABX system, \( J_{AB} = J_{F-F} = 220.7 \) Hz, \( J_{AX} = J_{H-F} = 2.0 \) Hz, \( J_{BX} = J_{H-F} = 23.8 \) Hz, \( \Delta \nu_{AB} = 1145 \) Hz, 0.1F).

One diastereomer (major one with procedure C)

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) δ (ppm) 151.5, 148.2, 143.5, 137.7, 134.0, 130.1, 127.7 (dd, \( J = 299.7 \) Hz, 309.3 Hz), 126.7, 124.5, 123.0, 70.9 (t, \( J = 25.0 \) Hz), 21.8.

HRMS (ESI positive) calcd for C\(_{14}\)H\(_{14}\)F\(_2\)NO\(_2\)S: 298.0708, found: 298.0699.

f. 2,2-Difluoro-1-(pyridin-3-yl)-2-(p-tolylsulfinyl)ethan-1-ol 7f

**Crude mixture** – Diastereomeric ratio = 69:31 (\(^{19}\)F NMR)

**Two diastereomers** – Diastereomeric ratio = 70:30 (\(^{19}\)F NMR)

\(^{1}\)H NMR (400 MHz, CDCl\(_3\)) δ (ppm) 8.67-8.47 (m, 2H), 7.94-7.84 (m, 1H), 7.67-7.60 (m, 2H), 7.42-7.28 (m, 3H), 5.45 (d, \( J = 22.6 \) Hz, 0.3H), 5.34 (dd, \( J = 7.5 \) Hz, 16.8 Hz, 0.7H), 2.44 (s, 3H).

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)) diastereomer 1, δ (ppm) –113.9 (ABX system, \( J_{AB} = J_{F-F} = 221.4 \) Hz, \( J_{AX} = J_{H-F} = 7.5 \) Hz, \( J_{BX} = J_{H-F} = 16.3 \) Hz, \( \Delta \nu_{AB} = 4311 \) Hz, 0.7F); diastereomer 2, δ (ppm) –114.3 (ABX system, \( J_{AB} = J_{F-F} = 226.8 \) Hz, \( J_{AX} = J_{H-F} = 22.5 \) Hz, \( J_{BX} = J_{H-F} = 2403 \) Hz, 0.3F). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) δ (ppm) 150.1, 149.9, 149.0, 148.8, 144.1, 143.9, 136.5, 136.3, 132.5 (d, \( J = 3.2 \) Hz), 132.1 (d, \( J = 3.6 \) Hz), 131.1, 131.0, 130.2, 129.0,
126.5, 126.4, 123.8, 123.7, 122.9 (dd, J = 292.0 Hz, 311.5 Hz), 71.9 (t, J = 22.7 Hz), 69.0 (dd, J = 19.5 Hz, 29.5 Hz), 21.8, 21.8.

One diastereomer (minor one with procedure C)

$^1$H NMR (500 MHz, CDCl$_3$) δ (ppm) 8.60 (s, 1H), 8.57 (d, J = 4.0 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.64 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.32 (dd, J = 7.9 Hz, 4.9 Hz, 1H), 5.45 (dd, J = 1.1 Hz, 2.2 Hz, 1H), 2.45 (s, 3H).

$^{19}$F NMR (472 MHz, CDCl$_3$) δ (ppm) −113.8 (ABX system, $J_{AB} = J_{F-F} = 227.1$ Hz, $J_{AX} = J_{F-F} = 23.4$ Hz, $\Delta \nu_{AB} = 3303$ Hz, 2F).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ (ppm) 150.2, 149.1, 143.9, 136.0, 132.0 (d, J = 2.3 Hz), 131.1, 130.2, 126.5, 124.2 (dd, J = 297.5 Hz, 305.2 Hz), 123.6, 69.0 (dd, J = 20.0 Hz, 29.1 Hz), 21.8.

IR $\nu$ (cm$^{-1}$) 3059, 1597, 1493, 1429, 1186, 1110, 1086, 1057, 1043, 1033, 1016, 983, 810, 764, 710. HRMS (ESI positive) calcd for C$_{14}$H$_{14}$F$_2$NO$_2$S: 298.0708, found: 298.0720.

g. 2,2-Difluoro-1-(thiophen-2-yl)-2-(p-tolylsulfinyl)ethan-1-ol 7g

Crude mixture – Diastereomeric ratio = 70:30 ($^{19}$F NMR)

Two diastereomers – Diastereomeric ratio = 60:40 ($^{19}$F NMR)

$^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.63 (d, J = 7.7 Hz, 2H), 7.43-7.34 (m, 3H), 7.25 (d, J = 3.3 Hz, 0.6H), 7.14 (d, J = 3.1 Hz, 0.4H), 7.05 (dd, J = 3.5 Hz, 4.9 Hz, 0.6H), 7.02 (dd, J = 5.0 Hz, 3.5 Hz, 0.4H), 5.73-5.59 (m, 1H), 4.86-4.62 (br s, 0.4H), 3.98-3.70 (br s, 0.6H), 2.45 (s, 3H). $^{19}$F NMR (376 MHz, CDCl$_3$) diastereomer 1, δ (ppm) −114.8 (ABX system, $J_{AB} = J_{F-F} = 218.0$ Hz, $J_{AX} = J_{F-F} = 8.9$ Hz, $J_{BX} = J_{F-F} = 14.3$ Hz, $\Delta \nu_{AB} = 3787$ Hz, 0.6F); diastereomer 2, δ (ppm) −114.0 (ABX system, $J_{AB} = J_{F-F} = 222.1$ Hz, $J_{AX} = J_{F-F} = 15.7$ Hz, $\Delta \nu_{AB} = 2026$ Hz, 0.4F). $^{13}$C NMR (126 MHz, CDCl$_3$) δ (ppm) 143.9, 143.8, 137.2, 136.4 (d, J = 2.1 Hz), 132.6 (d, J = 3.6 Hz), 132.2 (d, J = 3.2 Hz), 130.2, 130.2, 128.3, 127.6, 127.4, 127.2, 127.0, 126.7, 126.5, 126.5, 123.4 (dd, J = 297.0 Hz, 305.2 Hz), 122.9 (dd, J = 293.8 Hz, 311.5 Hz), 70.2 (t, J = 22.7 Hz), 68.4 (dd, J = 20.4 Hz, 29.5 Hz), 21.8, 21.7. IR $\nu$ (cm$^{-1}$) 3295, 2923, 1596, 1493,1435, 1198, 1179, 1113, 1085, 1041, 1015, 965, 856, 810, 785, 705. HRMS (ESI positive) calcd for C$_{13}$H$_{12}$F$_2$O$_2$S$_2$: 325.0139, found: 325.0148.
h. 2,2-Difluoro-1-(thiophen-3-yl)-2-(p-tolylsulfinyl)ethan-1-ol 7h

**Crude mixture** – Diastereomeric ratio = 55:45 (19F NMR)

**Two diastereomers** – Diastereomeric ratio = 54:46 (19F NMR)

\[ \text{1H NMR (400 MHz, CDCl}_3\text{)} \delta (\text{ppm}) 7.66-7.58 (m, 2H), 7.51 (d, J = 2.4 Hz, 0.56H), 7.44 (d, J = 2.8 Hz, 0.44H), 7.40-7.30 (m, 3H), 7.22 (d, J = 4.9 Hz, 0.56H), 7.15 (d, J = 5.0 Hz, 0.44H), 5.56-5.42 (m, 1H), 4.34 (d, J = 5.7 Hz, 0.44H), 3.58 (d, J = 3.9 Hz, 0.56H), 2.44 (s, 3H).

\[ \text{19F NMR (376 MHz, CDCl}_3\text{)} \delta (\text{ppm}) 22.7 (\text{ppm}) \]

\[ \text{13C NMR (126 MHz, CDCl}_3\text{)} \delta (\text{ppm}) 148.0, 147.5, 147.5, 143.9, 143.8, 143.7, 132.8 (d, J = 2.7 Hz), 132.1 (d, J = 3.2 Hz), 130.1, 130.1, 126.6, 126.5, 123.6 (dd, J = 297.0 Hz, 307.5 Hz), 123.5 (dd, J = 294.7 Hz, 308.4 Hz), 111.2, 110.9, 110.9, 110.7, 67.6 (t, J = 23.2 Hz), 66.2 (dd, J = 20.9 Hz, 30.0 Hz), 21.8, 21.8.

i. 2,2-Difluoro-1-(furan-2-yl)-2-(p-tolylsulfinyl)ethan-1-ol 7i

**Crude mixture** – Diastereomeric ratio = 57:43 (19F NMR)

**Two diastereomers** – Diastereomeric ratio = 56:44 (19F NMR)

\[ \text{1H NMR (400 MHz, CDCl}_3\text{)} \delta (\text{ppm}) 7.68-7.60 (m, 2H), 7.47 (d, J = 1.1 Hz, 0.56H), 7.44 (d, J = 1.0 Hz, 0.44H), 7.38 (d, J = 7.8 Hz, 2H), 6.58 (d, J = 3.3 Hz, 0.56H), 6.53 (d, J = 3.2 Hz, 0.44H), 6.42 (dd, J = 1.7 Hz, 3.2 Hz, 0.56H), 6.40 (dd, J = 1.7 Hz, 3.3 Hz, 0.44H), 5.43 (d, J = 21.2 Hz, 0.44H), 5.30 (dd, J = 10.3 Hz, 14.2 Hz, 0.56H), 4.32 (s, 0.44H), 3.56 (s, 0.56H), 2.44 (s, 3H).

\[ \text{19F NMR (376 MHz, CDCl}_3\text{)} \delta (\text{ppm}) -114.5 (\text{ABX system, } J_{\text{AB}} = J_{\text{F-F}} = 219.3 \text{ Hz, } J_{\text{AX}} = J_{\text{H-F}} = 10.2 \text{ Hz, } J_{\text{BX}} = J_{\text{H-F}} = 14.3 \text{ Hz, } \Delta_{\text{VAB}} = 3009 \text{ Hz, 0.56F}); \text{ diastereomer 2, } \delta (\text{ppm}) -113.9 (\text{ABX system, } J_{\text{AB}} = J_{\text{F-F}} = 224.1 \text{ Hz, } J_{\text{AX}} = J_{\text{H-F}} = 21.1 \text{ Hz, } \Delta_{\text{VAB}} = 1381 \text{ Hz, 0.44F}). \text{ 13C NMR (126 MHz, CDCl}_3\text{)} \delta (\text{ppm}) 148.0, 147.5, 147.5, 143.9, 143.8, 143.7, 132.8 (d, J = 2.7 Hz), 132.1 (d, J = 3.2 Hz), 130.1, 130.1, 126.6, 126.5, 123.6 (dd, J = 297.0 Hz, 307.5 Hz), 123.5 (dd, J = 294.7 Hz, 308.4 Hz), 111.2, 110.9, 110.9, 110.7, 67.6 (t, J = 23.2 Hz), 66.2 (dd, J = 20.9 Hz, 30.0 Hz), 21.8, 21.8.
One diastereomer (minor one with procedure C)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.62 (d, \(J = 6.7\) Hz, 2H), 7.42 (d, \(J = 1.2\) Hz, 1H), 7.36 (d, \(J = 6.4\) Hz, 2H), 6.53 (d, \(J = 3.1\) Hz, 1H), 6.37 (m, 1H), 5.51 (d, \(J = 19.5\) Hz, 1H), 5.22 (m, 1H), 2.43 (s, 3H). \(^{19}\)F NMR (472 MHz, CDCl\(_3\)) \(\delta\) (ppm) –114.0 (AB system, \(J_{AB} = J_{FF} = 221.1\) Hz, \(\Delta v_{AB} = 1461\) Hz, 2F). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) (ppm) 148.3, 143.7, 143.6, 132.3, 130.0, 126.7, 110.7, 110.5, 65.4 (dd, \(J = 20.4\) Hz, 29.1 Hz), 21.7.

IR \(\nu\) (cm\(^{-1}\)) 3296, 2925, 1597, 1495, 1196, 1147, 1115, 1085, 1047, 1014, 987, 936, 926, 795, 809, 745. HRMS (ESI positive) calcd for C\(_{13}\)H\(_{13}\)F\(_2\)O\(_3\)S: 287.0548, found: 287.0560.

j. 2,2-Difluoro-1-(furan-3-yl)-2-(p-tolylsulfinyl)ethan-1-ol \(^7\)j

Crude mixture – Diastereomeric ratio = 98:2 (\(^{19}\)F NMR)

One diastereomer (major one with procedure C)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.66-7.60 (m, 3H), 7.45 (t, \(J = 1.7\) Hz, 1H), 7.38 (d, \(J = 8.1\) Hz, 2H), 6.54 (s, 1H), 5.35 (dd, \(J = 9.5\) Hz, 15.5 Hz, 1H), 3.30-3.10 (br s, 1H), 2.45 (s, 3H). \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) (ppm) –114.9 (ABX system, \(J_{AB} = J_{FF} = 219.3\) Hz, \(J_{AX} = J_{HF} = 9.5\) Hz, \(J_{BX} = J_{HH} = 15.0\) Hz, \(\Delta v_{AB} = 3627\) Hz, 0.98F); [diastereomer 2 (minor one with procedure C) \(\delta\) (ppm) –114.0 (ABX system, \(J_{AB} = J_{FF} = 224.8\) Hz, \(J_{AX} = J_{HF} = 20.4\) Hz, \(\Delta v_{AB} = 1921\) Hz, 0.02F)]. \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) (ppm) 143.8, 142.1, 132.6, 132.6, 130.0, 126.4, 123.4 (dd, \(J = 293.4\) Hz, 310.2 Hz), 119.4 (d, \(J = 2.7\) Hz), 109.3, 67.1 (t, \(J = 23.2\) Hz), 21.7. IR \(\nu\) (cm\(^{-1}\)) 3324, 2926, 1761, 1730, 1596, 1494, 1454, 1286, 1196, 1161, 1112, 1085, 1042, 1016, 980, 953, 875, 811, 790. HRMS (ESI positive) calcd for C\(_{13}\)H\(_{13}\)F\(_2\)O\(_3\)S: 287.0548, found: 287.0558.

k. 1,1-Difluoro-2-methyl-4-phenyl-1-(p-tolylsulfinyl)butan-2-ol \(^7\)l

Crude mixture – Diastereomeric ratio = 60:40 (\(^{19}\)F NMR)

First diastereomer (major one with procedure C)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.64 (d, \(J = 7.9\) Hz, 2H), 7.69 (d, \(J = 8.1\) Hz, 2H), 7.31-7.25 (m, 2H), 7.23-7.16 (m, 3H), 2.87-2.73 (m, 2H), 2.46 (s, 3H), 2.18 (td, \(J = 5.0\) Hz, 14 Hz, 1H), 1.98 (td, \(J = 5.5\) Hz, 13.4 Hz, 1H), 1.71 (s, 3H). \(^{19}\)F NMR (472 MHz, CDCl\(_3\)) \(\delta\) (ppm) –113.3 (AB system, \(J_{AB} = J_{FF} = 220.0\) Hz, \(\Delta v_{AB} = 6205\) Hz, 2F). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) (ppm) 143.8, 141.8, 132.5
(d, \( J = 3.6 \) Hz), 130.1, 128.6, 128.6, 126.8, 126.1, 123.8 (dd, \( J = 295.6 \) Hz, 318.8 Hz), 76.7 (unknown), 37.8, 29.1, 22.4, 21.8.

**Second diastereomer** (minor one with procedure C)

\(^1\)H NMR (500 MHz, CDCl\(_3\) \( \delta \) (ppm) 7.63 (d, \( J = 7.9 \) Hz, 2H), 7.39 (d, \( J = 8.1 \) Hz, 2H), 7.35-7.29 (m, 2H), 7.26-7.19 (m, 3H), 2.93 (td, \( J = 4.8 \) Hz, 13.0 Hz, 1H), 2.80 (td, \( J = 5.5 \) Hz, 12.2 Hz, 1H), 2.46 (s, 3H), 2.31 (td, \( J = 4.8 \) Hz, 13.3 Hz, 1H), 2.20 (tdd, \( J = 2.1 \) Hz, 5.4 Hz, 12.2 Hz, 1H), 1.50 (s, 3H).

\(^{19}\)F NMR (472 MHz, CDCl\(_3\) \( \delta \) (ppm) –112.9 (AB system, \( J_{AB} = J_{F-F} = 222.8 \) Hz, \( \Delta \nu_{AB} = 5686 \) Hz, 2F).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\) \( \delta \) (ppm) 143.9, 141.5, 132.4 (d, \( J = 4.1 \) Hz), 130.0, 128.7, 128.6, 126.3, 39.4, 29.2, 22.9, 21.8.

IR \( \nu \) (cm\(^{-1}\)) 3369, 2924, 1724, 1598, 1495, 1455, 1379, 1288, 1211, 1180, 1110, 1083, 1065, 1045, 1016, 985, 944, 809, 749, 701. HRMS (ESI positive) calcd for C\(_{18}\)H\(_{20}\)F\(_2\)NaO\(_2\): 361.1044, found: 361.1047.

\( \text{l. 2,2-Difluoro-1-(4-methoxyphenyl)-2-(p-tolylsulfinyl)ethan-1-ol 7m} \)

**Crude mixture** – Diastereomeric ratio = 79:21 (\(^{19}\)F NMR)

**Two diastereomers** – Diastereomeric ratio = 79:21 (\(^{19}\)F NMR)

\(^1\)H NMR (400 MHz, CDCl\(_3\) \( \delta \) (ppm) 7.66-7.58 (m, 2H), 7.48-7.34 (m, 4H), 6.96-6.86 (m, 2H), 5.38-5.25 (m, 1H), 3.82 (s, 2.3H), 3.80 (s, 0.7H), 2.44 (s, 3H).

\(^{19}\)F NMR (376 MHz, CDCl\(_3\) \( \delta \) (ppm) –114.9 (ABX system, \( J_{AB} = J_{F-F} = 218.0 \) Hz, \( J_{AX} = J_{H-F} = 8.9 \) Hz, \( J_{BX} = J_{H-F} = 15.7 \) Hz, \( \Delta \nu_{AB} = 3905 \) Hz, 0.79f); diastereomer 2, \( \delta \) (ppm) –113.8 (ABX system, \( J_{AB} = J_{F-F} = 226.2 \) Hz, \( J_{AX} = J_{H-F} = 21.8 \) Hz, \( \Delta \nu_{AB} = 2625 \) Hz, 0.21f).\(^{13}\)C NMR (126 MHz, CDCl\(_3\) \( \delta \) (ppm) 160.6, 160.4, 143.7, 143.6, 132.9 (dd, \( J = 2.3 \) Hz), 130.1, 129.6, 129.3, 126.6, 126.5, 126.4, 126.3 (d, \( J = 1.8 \) Hz), 123.6 (dd, \( J = 292.0 \) Hz, 309.7 Hz), 114.1, 114.0, 73.3 (t, \( J = 21.8 \) Hz), 71.0 (dd, \( J = 20.0 \) Hz, 29.1 Hz), 55.4, 55.4, 21.8, 21.7. IR \( \nu \) (cm\(^{-1}\)) 3325, 2925, 1611, 1498, 1589, 1513, 1463, 1443, 1305, 1249, 1175, 1105, 1085, 1032, 1016, 974, 841, 810, 789, 750, 703. HRMS (ESI positive) calcd for C\(_{18}\)H\(_{16}\)F\(_2\)NaO\(_2\): 349.0680, found: 349.0676.
6. Access to highly enantioenriched 2,2-difluoro-1-phenyl-2-(p-tolylsulfinyl)ethan-1-ol (S)-7a

Hexane was removed under vacuum from 197 µL of the commercially available solution of P₄t-Bu (0.8 M in hexane, 2 equiv., 197 µL, 158 µmol). The solid obtained was dissolved in 0.7 mL of freshly distilled THF previously cooled to -30 °C. To a solution of sulfoxide (S)-3a (1 equiv., 15 mg, 78.9 µmol) and benzaldehyde (1 equiv., 8.13 µL, 78.9 µmol) dissolved in 1.8 mL of freshly distilled THF at -30 °C was added dropwise the previous solution of P₄t-Bu in THF. The reaction mixture was stirred at -30 °C for 2 hours, then quenched with water at this temperature. The aqueous layer was extracted three times with Et₂O. The combined organic layers were washed with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The diastereomeric ratio was determined by ¹⁹F NMR. The crude product was purified by chromatography on silica gel using cyclohexane/AcOEt (100/0 to 80/20) to obtain 2,2-difluoro-1-phenyl-2-(p-tolylsulfinyl)ethan-1-ol (S)-7a (10 mg, 33.7 µmol, 43%, 97% e.e., 97:3 d.r.) as an oil. The enantiomeric excess of the product was determined by chiral HPLC using a Chiracel IC column (n-hexane/i-PrOH = 80/20, flow rate: 0.5 mL/min, λ = 210 nm, τ = 10.1 min, 11.1 min, 21.2 min and 25.1 min).

**Crude mixture** – Diastereomeric ratio = 97:3 (¹⁹F NMR)

**One diastereomer** (major one with procedure C)

**¹H NMR (400 MHz, CDCl₃)** δ (ppm) 7.63 (d, J = 7.9 Hz, 2H), 7.54-7.48 (m, 2H), 7.43-7.35 (m, 5H), 5.39 (dd, J = 8.4 Hz, 16.6 Hz, 1H), 3.47 (s, 1H), 2.45 (s, 3H).

**¹⁹F NMR (376 MHz, CDCl₃)** δ (ppm) -114.4 (ABX system, Jₙ₋ₙ - Jₙ₋ₙ = 219.3 Hz, Jₙ₋ₙ = Jₙ₋ₙ = 7.5 Hz, Jₙ₋ₙ = Jₙ₋ₙ = 17.0 Hz, Δν₃₄₃ = 4447 Hz, 0.97F); [diastereomer 2 (minor one with procedure C) δ (ppm) -113.4 (ABX system, Jₙ₋ₙ = Jₙ₋ₙ = 227.5 Hz, Jₙ₋ₙ = Jₙ₋ₙ = 23.2 Hz, Δν₃₄₃ = 2664 Hz, 0.03F)].
7. Access to highly enantioenriched 2,2-difluoro-1-phenyl-2-tosylethan-1-ol 9a

To a solution of 2,2-difluoro-1-phenyl-2-(p-tolylsulfinyl)ethan-1-ol (S)-7a (1 equiv., 3.3 mg, 11.1 µmol) in 0.2 mL of anhydrous CH$_2$Cl$_2$ was added m-CPBA (78% of active oxygen, 1.5 equiv., 3.74 mg, 16.7 µmol) at 25 °C. The solution was stirred at this temperature for 24 hours. The reaction was quenched with a saturated solution of Na$_2$S$_2$O$_3$. The aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic phases were washed with a saturated solution of NaHCO$_3$ and with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel using cyclohexane/AcOEt (100/0 to 80/20) to obtain 2,2-difluoro-1-phenyl-2-tosylethan-1-ol 9a (3.5 mg, 11.1 µmol, quantitative yield) as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.88 (d, $J = 8.3$ Hz, 2H), 7.51-7.45 (m, 2H), 7.41 (d, $J = 8.1$ Hz, 2H), 7.40-7.36 (m, 3H), 5.56 (dd, $J = 21.3$ Hz, 2.1 Hz, 1H), 3.44-3.17 (br s, 1H), 2.48 (s, 3H).

$^{19}$F NMR (376 MHz, CDCl$_3$) δ (ppm) -111.9 (ABX system, $J_{AB} = J_{F-F} = 237.1$ Hz, $J_{BX} = J_{H-F} = 21.1$ Hz, $\Delta J_{AB} = 5850$ Hz, 2F).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ (ppm) 147.4, 133.8, 130.9, 130.3, 129.7, 129.7, 128.7, 128.3, 120.2 (dd, $J = 288.8$ Hz, 298.4 Hz), 71.5 (dd, $J = 20.0$ Hz, 26.3 Hz), 22.1. IR ν (cm$^{-1}$) 3501, 3067, 2925, 1595, 1494, 1456, 1336, 1307, 1196, 1152, 1111, 1090, 1065, 996, 814, 736, 699. HRMS (ESI positive) calcd for C$_{15}$H$_{14}$F$_2$KO$_3$S: 351.0263, found: 351.0271.

8. Bibliographic references


$^1$H NMR (400 MHz, CDCl$_3$) – Purified 1a

$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified 1a
$^1$H NMR (400 MHz, CDCl$_3$) – Purified 1b

$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified 1b
$^1$H NMR (400 MHz, CDCl$_3$) – Purified 2a

$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified 2a
$^1$H NMR (400 MHz, CDCl$_3$) – Purified (S)-2a

$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified (S)-2a
Chiral HPLC – Reference racemic 2a

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Method Filename: Hex_IPA_0620_0-5ml.lcm
Batch Filename: 2016-04-21.lcb
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Injection Volume: 1 µL
Date Acquired: 21/04/2016 11:37:55
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Acquired by: User-Adv

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![Chromatogram Image]

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S35
Chiral HPLC – Reformatsky-type reaction

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- Method Filename: Hex_IPA_8020_0-5m.png
- Batch Filename: 2016-05-09.idc
- Vial #: 1-2
- Injection Volume: 1 µL
- Date Acquired: 09/05/2016 13:33:43
- Acquired by: User-Adv
- IC hexiproh 80/20 0.5mL

PDA Chromatogram:
- Peak Table:

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PDA Multi 1 206nm, 4nm
Chiral HPLC – Honda-Reformatsky-type reaction

Sample Name: CB119B-en01
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Method Filename: Hex_IPA_8020_0-05ml.txt
Batch Filename: 2016-05-09.txt
Vial #: 1-1
Injection Volume: 1 µL
Date Acquired: 09/05/2016 12:04:23
IC hex/ipro 80/20 0.5ml

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![Chromatogram Image]

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(S)-2a
$^1$H NMR (400 MHz, CDCl$_3$) – Purified 2b

$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified 2b
$^1$H NMR (400 MHz, CDCl$_3$) – Purified 3a

$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified 3a
$^1$C NMR (126 MHz, CDCl$_3$) – Purified 3a

$^1$H NMR (400 MHz, CDCl$_3$) – Purified (S)-3a
$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified (S)-3a
Chiral HPLC – Reference racemic 3a

Sample Name: CB129-rac06
Data Filename: CB129-rac06_06.lcd
Method Filename: Hex_IPA_8020_0.6mL/cm
Batch Filename: 2015-06-08.kcb
Vial #: 1-2
Injection Volume: 1 uL
Date Acquired: 09/06/2016 01:29:29
Acquired by: UserAdv
IC hex/IPR 80/20 0.5ml

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![PDA Chromatogram]

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Chiral HPLC – Krapcho decarboxylation under thermal conditions – (S)-3a
Chiral HPLC – Krapcho decarboxylation under microwave conditions – (S)-3a

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Chiral HPLC – (S)-3a crystallised in Et₂O

Sample Name: CB227-cryst-blanc-en01
Data Filename: CB227-cryst-blanc-en01_lcd
Method Filename: Hex_IPA_8020_0-5ml.lcm
Batch Filename: 2017-11-15.lcb
Vial #: 1-2
Injection Volume: 1 µL
Date Acquired: 16/11/2017 15:48:49
IC Hex/IPA 80/20 0.5 ml/min
Acquired by: User-Adv

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![PDA Chromatogram Image]

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$^1$H NMR (400 MHz, CDCl$_3$) – Purified 3b

$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified 3b
$^1$H NMR (400 MHz, CDCl$_3$) – Purified 4

$^1$H NMR (400 MHz, CDCl$_3$) – Purified 5
$^1$H NMR (400 MHz, CDCl$_3$) – Purified (R,R)-6

$^1$H NMR (400 MHz, CDCl$_3$) – Purified (S,R)-6
$^{19}$F NMR (376 MHz, CDCl$_3$) – Crude mixture of 7a

$^1$H NMR (400 MHz, CDCl$_3$) – One diastereomer – Purified 7a
$^1$H NMR (376 MHz, CDCl$_3$) – One diastereomer – Purified 7a

$^{13}$C NMR (126 MHz, CDCl$_3$) – One diastereomer – Purified 7a
$^{19}$F NMR (376 MHz, CDCl$_3$) – Crude mixture of 7b

$^1$H NMR (500 MHz, CDCl$_3$) – Purified 7b
$^{19}$F NMR (472 MHz, CDCl$_3$) – Purified 7b

$^{13}$C NMR (126 MHz, CDCl$_3$) – Purified 7b
$^{19}$F NMR (376 MHz, CDCl$_3$) – Crude mixture of 7c

$^1$H NMR (400 MHz, CDCl$_3$) – Purified 7c
\textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}) – One diastereomer – Purified 7c

\textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) – Purified 7c
$^{13}$C NMR (126 MHz, CDCl$_3$) – One diastereomer – Purified 7c

$^{19}$F NMR (376 MHz, CDCl$_3$) – Crude mixture of 7d
$^1$H NMR (400 MHz, CDCl$_3$) – Purified 7d

$^{19}$F NMR (472 MHz, CDCl$_3$) – Purified 7d
$^{13}$C NMR (126 MHz, CDCl$_3$) – Purified 7d

$^{19}$F NMR (376 MHz, CDCl$_3$) – Crude mixture of 7e
$^1$H NMR (400 MHz, CDCl$_3$) – Purified 7e

$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified 7e
$^{13}$C NMR (126 MHz, CDCl$_3$) – Purified 7e

$^{19}$F NMR (376 MHz, CDCl$_3$) – Crude mixture of 7f
\(^1\)H NMR (400 MHz, CDCl\(_3\)) – Purified 7f

\(^1\)H NMR (500 MHz, CDCl\(_3\)) – One diastereomer – Purified 7f
$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified 7f

$^{19}$F NMR (472 MHz, CDCl$_3$) – One diastereomer – Purified 7f
$^{13}$C NMR (126 MHz, CDCl$_3$) – Purified 7f

$^{13}$C NMR (126 MHz, CDCl$_3$) – One diastereomer – Purified 7f
$^1$H NMR (400 MHz, CDCl$_3$) – Purified 7g
$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified 7g

$^{13}$C NMR (126 MHz, CDCl$_3$) – Purified 7g
$^{19}$F NMR (376 MHz, CDCl$_3$) – Crude mixture of 7h

$^1$H NMR (400 MHz, CDCl$_3$) – Purified 7h
$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified 7h

$^{13}$C NMR (126 MHz, CDCl$_3$) – Purified 7h
$^{19}$F NMR (376 MHz, CDCl$_3$) – Crude mixture of 7i

$^1$H NMR (400 MHz, CDCl$_3$) – Purified 7i
$^1$H NMR (500 MHz, CDCl$_3$) – One diastereomer – Purified 7i

$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified 7i
\(^{19}\text{F NMR (472 MHz, CDCl}_3\text{)}\) – One diastereomer – Purified 7\text{i}

\(^{13}\text{C NMR (126 MHz, CDCl}_3\text{)}\) – Purified 7\text{i}
$^{13}$C NMR (126 MHz, CDCl$_3$) – One diastereomer – Purified 7i

$^{19}$F NMR (376 MHz, CDCl$_3$) – Crude mixture of 7j
$^1$H NMR (400 MHz, CDCl$_3$) – Purified 7j

$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified 7j
$^{13}$C NMR (126 MHz, CDCl$_3$) – Purified 7j

$^{19}$F NMR (376 MHz, CDCl$_3$) – Crude mixture of 7l
$^1$H NMR (500 MHz, CDCl$_3$) – First diastereomer – Purified 71

$^{19}$F NMR (472 MHz, CDCl$_3$) – First diastereomer – Purified 71
$^{13}$C NMR (126 MHz, CDCl$_3$) – First diastereomer – Purified 7l

$^1$H NMR (500 MHz, CDCl$_3$) – Second diastereomer – Purified 7l
$^{19}$F NMR (472 MHz, CDCl$_3$) – Second diastereomer – Purified 7I

$^{13}$C NMR (126 MHz, CDCl$_3$) – Second diastereomer – Purified 7I
$^{19}$F NMR (376 MHz, CDCl$_3$) – Crude mixture of 7m

$^1$H NMR (400 MHz, CDCl$_3$) – Purified 7m
$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified 7m

$^{13}$C NMR (126 MHz, CDCl$_3$) – Purified 7m
$^{19}$F NMR (376 MHz, CDCl$_3$) – Crude mixture of (S)$_2$-7a

$^1$H NMR (400 MHz, CDCl$_3$) – Purified (S)$_2$-7a
$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified (S$_3$)-7a
Chiral HPLC – Racemic 7a – Two diastereomers

Sample Name: CB255A-drac01
Data Filename: CB255A-drac01_02.1cd
Method Filename: Hex_IPA_8020_0.5ml1cm
Batch Filename: 2017-07-11.1cd
Vial # : 1-1
Injection Volume : 1 uL
Date Acquired : 11/07/2017 17:01:49
IC Hex/IPA 60/20 0.5ml/min

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Chiral HPLC – Diastereopure racemic 7a – One diastereomer

Sample Name: CB382A_en01
Data Filename: CB382A_en01_01.icd
Method Filename: Hex_IPA_0020_0-5ml.icm
Batch Filename: 2018-07-03.icb
Vial #: 1-1
Injection Volume: 1 uL
Date Acquired: 03/07/2018 18:29:42
IC Hex/IPA 80/20 0.5 mL/min
Acquired by: User-Adv

<PDA Chromatogram>
Chiral HPLC – Enantio- and diastereoenriched (S$_2$)-7a

Sample Name: CB003A_en01
Data Filename: CB003A_en01_01.kcd
Method Filename: Hex_IPA_0020_0-5mL.cm
Batch Filename: 2018-07-03.lcb
Vial #: 1-2
Injection Volume: 1 uL
Data Acquired: 03/07/2018 18:45:56
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Acquired by: User-Adv

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S83
$^{1}H$ NMR (400 MHz, CDCl$_3$) – Purified 8j

$^{19}F$ NMR (376 MHz, CDCl$_3$) – Purified 8j
$^1$H NMR (400 MHz, CDCl$_3$) – Purified 9a

$^{19}$F NMR (376 MHz, CDCl$_3$) – Purified 9a
$^{13}$C NMR (126 MHz, CDCl$_3$) – Purified 9a