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A practical diastereoselective synthesis of β-hydroxy-β-trifluoromethyl imines

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Abstract—The asymmetric carbon–carbon bond formation reaction affording chiral β-hydroxy-β-trifluoromethyl imines is reported involving the nucleophilic addition of sulfinimine anions derived from chiral *N*-(*tert*-butanesulfinyl) ketimines to trifluoromethyl ketones. The reaction tolerates a wide range of nucleophiles, giving the condensation products in good to excellent total yields with good diastereoselectivities (up to 85:15 dr).

1. Introduction

Trifluoromethyl-containing compounds are of great interest in various fields[1] because the trifluoromethyl group has an electronegativity similar to that of oxygen[2] and a high hydrophobic parameter.[3] Furthermore, the high lipophilicity brought about by the CF_3 moiety confers a better bioavailability to the molecules bearing this group.[4] Among various trifluoromethyl-containing compounds, enantiomerically pure α-trifluoromethylated alcohols and amines are of primary significance since these chiral synthons are among the most important and common subunits in chiral drugs[1c,5] or materials.[6] Therefore, it is very important to develop new methodologies for the efficient synthesis of these chiral trifluoromethylated molecules.[7] In 2002 Röschenthaler and co-workers reported the racemic synthesis of β-hydroxy-β-trifluoromethyl imines from α-trifluoromethylated ketones.[8] β-Hydroxy-β-trifluoromethyl imines are important precursors of β-hydroxy-β-trifluoromethyl ketones and α-trifluoromethyl-γ-amino alcohols. To the best of our knowledge there is only one report about the enantiomeric synthesis of β-hydroxy-β-trifluoromethyl imines,[9] but the method is based on microbial transformations. Herein we report a practical asymmetric carbon–carbon bond formation reaction of chiral *N*-(*tert*-butanesulfinyl) ketimines and α-trifluoromethylated ketones, which affords chiral β-hydroxy-β-trifluoromethyl imines with good diastereoselectivities.

2. Results and discussion

We began our investigation with the reaction of (*R*)-*N*-(*tert*-butanesulfinyl) ketimine **1a** and trifluoroacetone **2a**. Deprotonation of **1a** with LDA at −78 °C in THF followed by addition of **2a** gave the desired products, β-hydroxy-β-trifluoromethyl imines **3a** and **3a′**, in almost quantitative yield and 85:15 dr. Then the reaction conditions were optimized to improve the diastereoselectivity by changing solvents, bases or adding additives. Unfortunately no better result was obtained. As shown in Table 1, addition of metal salts gave lower diastereoselectivity and yield (entries 2 and 3).[10] Using ether as solvent also made the diastereoselectivity decrease (entry 4). When LHMDS was used as the base, the reaction gave similar diastereoselectivity and yield as using LDA (entry 5). Further attempt by cooling **2a** to −78 °C before addition and adding it dropwise via cannula did not improve the diastereoselectivity either (entry 6). The absolute configuration of **3a** was assigned to be (*Rs*,*S*) by X-ray crystallographic analysis (Fig. 1).[11]

Using the condition as in entry 1 of Table 1, the reaction of a series of enantiomerically pure *N*-(*tert*-butanesulfinyl) ketimines with trifluoromethylated ketones **2** was examined.[12] The results are summarized in Table 2. *N*-Sulfinyl ketimines containing both aryl and alkyl substituents reacted readily with **2** to give the corresponding β-hydroxy-β-trifluoromethyl imines in moderate to excellent total yields with moderate to high diastereoselectivities (up to 85:15 dr). But lower diastereoselectivities were obtained with alkyl substituted *N*-sulfinyl ketimines when compared with their aryl counterparts (entries 6–9). In the case of *N*-sulfinyl ketimine **1g** the reaction took place at the less substituted α-carbon selectively. It is worthy mentioning that the

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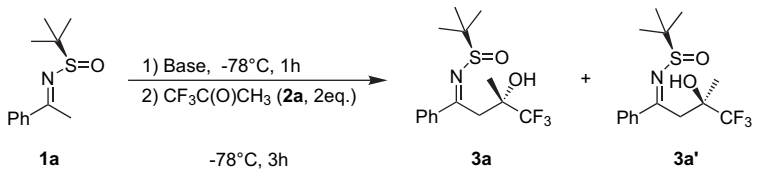
Table 1. The reaction of **1a** and **2a** under different conditions



Entry	Solvent	Base	Additive	Yield (%)[a]	**3a**:**3a′** (dr)[b]
1	THF	LDA	—	99	85:15
2	THF	LDA	$MgBr_2$	86	82:18
3	THF	LDA	$ZnBr_2$	91	75:25
4	Et_2O	LDA	$MgBr_2$	86	75:25
5	THF	LHMDS	—	>99	84:16
6[c]	THF	LDA	—	86	85:15

[a] Isolated total yield of **3a** and **3a′**.
[b] Determined by ^{19}F NMR spectroscopy of the crude reaction mixture.
[c] Compound **2a** was added at −78 °C.

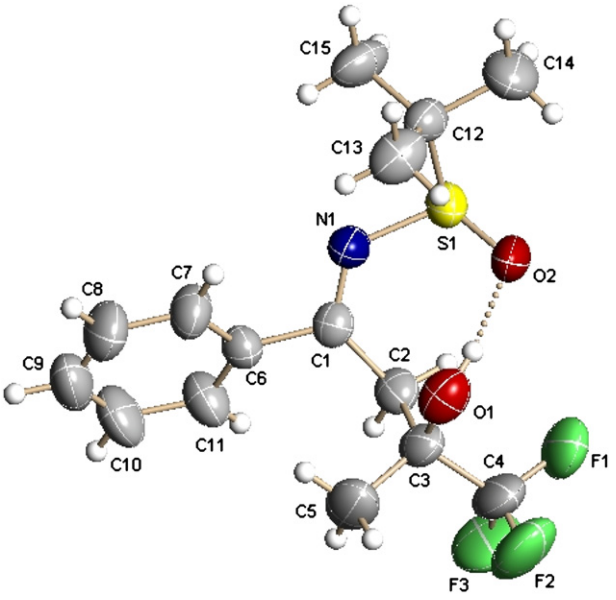


Figure 1. X-ray crystal structure of **3a**.

addition of $MgBr_2$ could dramatically improve the total yields of the reaction of alkyl substituted *N*-sulfinyl ketimines and **2a** (entries 7 and 9).

Comparing the above reaction with Ellman's enamide–aldehyde condensation,[10] it is obvious that the same mechanism is involved. The stereochemistry of the addition reaction is consistent with a Zimmerman–Traxler-type six-membered ring transition state (Fig. 2).[13] The fact that reactions of different aryl substituted *N*-sulfinyl ketimines with **2** give similar diastereoselectivities indicates that the diastereoselectivity of the reaction is primarily controlled by the stereochemistry of the *N*-sulfinyl group and the steric hindrance of R_2 rather than electronic effect. Therefore, less hindered trifluoroacetone (**2a**, R_2=Me) gives better diastereoselectivity (up to 85:15 dr) because transition state **A** is preferred over **B** due to 1,3-diaxial interaction. The difference between **A** and **B** becomes less when bigger R_2 substituent is present in ketone **2** (R_2=Ph, entries 10–14) or alkyl substituted *N*-sulfinyl ketimines is used (entries 6–9), resulting in the decrease in diastereoselectivity.[14]

Hydrolysis of **3a** and **3a′** in the presence of HCl in MeOH/H_2O at room temperature for 1 h afforded enantiomerically pure β-hydroxy-β-trifluoromethyl ketones **4a** and **4a′** (Scheme 1).

3. Conclusions

In summary, we have demonstrated an asymmetric carbon–carbon bond formation reaction of sulfinimine anions derived from chiral *N*-(*tert*-butanesulfinyl) ketimines with α-trifluoromethylated ketones. Under appropriate conditions, the reaction gave the corresponding chiral β-hydroxy-β-trifluoromethyl imines in high yields with good diastereoselectivities, providing a convenient and practical method for the synthesis of enantiomerically pure β-hydroxy-β-trifluoromethyl ketones.

4. Experimental section

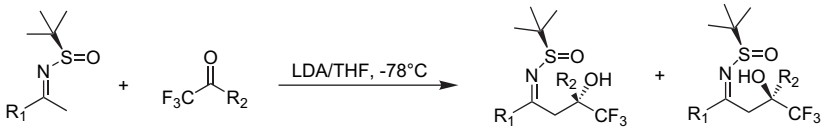
4.1. General experimental methods

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. THF was freshly distilled over sodium. *N*-(*tert*-Butanesulfinyl) ketimines were prepared using known procedures.[12] Melting points were taken on a Melt-Temp apparatus and are uncorrected. ^1H NMR spectra were recorded on Bruker AM-300 or Mercury 300 (300 MHz) spectrometer with TMS as an internal standard. ^{19}F NMR spectra were recorded on Bruker AM-300 or Mercury 300 (282 MHz) spectrometer with $CFCl_3$ as an external standard. ^{13}C NMR spectra were recorded on Bruker 300 (75.5 MHz) or DPX-400 (100.7 MHz) spectrometer. Mass spectra were taken on a HP5989A spectrometer. High-resolution mass data were obtained on a high-resolution mass spectrometer in the EI mode.

4.2. General experimental procedure for the reaction of *N*-(*tert*-butanesulfinyl) ketimines (*R*)-1 and trifluoromethyl ketones 2

Into a dried 20-mL Schlenk flask containing *N*-(*tert*-butanesulfinyl) ketimine (***R*)-1a** (56 mg, 0.25 mmol) in 2 mL THF

Table 2. The reaction of *N*-(*tert*-butanesulfinyl) ketimines **1** with trifluoromethylated ketones



1 **2** **3** **3'**

Entry	R_1	R_2	Product	Yield (%)[a]	**3**:**3′** (dr)[b]
1	Ph (**1a**)	Me (**2a**)	**3a+3a′**	99	85:15
2	4-$MeOC_6H_4$ (**1b**)	Me (**2a**)	**3b+3b′**	72	78:22
3	4-FC_6H_4 (**1c**)	Me (**2a**)	**3c+3c′**	88	82:18
4	4-ClC_6H_4 (**1d**)	Me (**2a**)	**3d+3d′**	81	84:16
5	4-$NO_2C_6H_4$ (**1e**)	Me (**2a**)	**3e+3e′**	62	85:15
6[c]	^{t}Bu (**1f**)	Me (**2a**)	**3f+3f′**	63	64:36
7[c,d]	^{t}Bu (**1f**)	Me (**2a**)	**3f+3f′**	98	64:36
8	^{i}Pr (**1g**)	Me (**2a**)	**3g+3g′**	50	51:49
9[d]	^{i}Pr (**1g**)	Me (**2a**)	**3g+3g′**	76	50:50
10	Ph (**1a**)	Ph (**2b**)	**3h+3h′**	81	59:41
11	4-FC_6H_4 (**1c**)	Ph (**2b**)	**3i+3i′**	84	63:37
12	4-ClC_6H_4 (**1d**)	Ph (**2b**)	**3j+3j′**	82	63:37
13[c]	^{t}Bu (**1f**)	Ph (**2b**)	**3k+3k′**	62	71:29
14	^{i}Pr (**1g**)	Ph (**2b**)	**3l+3l′**	53	50:50

[a] Isolated total yield of **3** and **3′**.
[b] Determined by ^{19}F NMR spectroscopy of crude reaction mixture.
[c] The diastereoisomers can't be isolated by silica gel column chromatography.
[d] $MgBr_2$ was added.

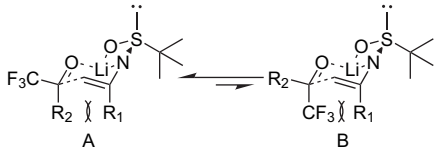
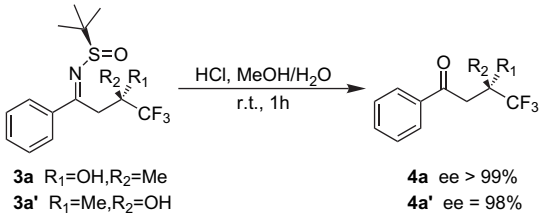


Figure 2.



Scheme 1.

was slowly added a solution of LDA (0.25 mL, 0.5 mmol, 2 M solution in THF/heptane/ethylenebenzene) at −78 °C under N_2 atmosphere. After stirring at −78 °C for 1 h, **2a** (0.05 mL, 0.5 mmol) was added and the mixture was stirred for 3 h at −78 °C. Then saturated aqueous NH_4Cl solution (10 mL) was added at −78 °C. The resulting mixture was extracted with EtOAc (15 mL×3). The combined organic solution was dried over $MgSO_4$. After the removal of volatile solvents under vacuum, the crude product was purified by silica gel column chromatography to give **3a** (69 mg) and **3a′** (14 mg) in 99% overall yield.

4.2.1. (*Rs*,*S*)-*N*-(4,4,4-Trifluoro-3-hydroxy-3-methyl-1-phenylbutylidene)-*tert*-butanesulfinamide (3a). White solid, yield 83%; mp 113–115 °C; $[\alpha]_D^{20}$ +130.5 (*c* 1.01, $CHCl_3$); FTIR (KBr, cm^{-1}): *ν* 3163, 2985, 2966, 1604, 1595, 1575, 1280, 1149, 1100, 1031; ^{1}H NMR ($CDCl_3$): *δ* 7.79 (d, *J*=6.9 Hz, 2H), 7.46–7.56 (m, 3H), 6.59 (s, 1H), 3.76 (d, *J*=12.6 Hz, 1H), 3.48 (d, *J*=12.6 Hz, 1H), 1.43 (s, 9H), 1.07 (s, 3H); ^{19}F NMR ($CDCl_3$): *δ* −83.81 (s, 3F); MS (*m*/*z*, %): 335 (M^+, 2.34), 279 (38.35), 57 (100). Anal. Calcd for $C_{15}H_{20}F_3NO_2S$: C, 53.72; H, 6.01; N, 4.18. Found: C, 53.98; H, 6.02; N, 3.74; HPLC (Chiralpak AD-H column, 95:5 hexane/2-propanol; 0.5 mL/min; 214 nm; (*Ss*,*R*), t_R=9.47 min, (*Rs*,*S*), t_R=9.99 min).

4.2.2. (*Rs*,*R*)-*N*-(4,4,4-Trifluoro-3-hydroxy-3-methyl-1-phenylbutylidene)-*tert*-butanesulfinamide (3a′). White solid, yield 16%; mp 64–66 °C; FTIR (KBr, cm^{-1}): *ν* 3260, 2928, 1604, 1593, 1573, 1282, 1151, 1098; ^{1}H NMR ($CDCl_3$): *δ* 7.60–7.85 (m, 2H), 7.25–7.52 (m, 3H), 5.95 (s, 1H), 3.93 (d, *J*=12.9 Hz, 1H), 3.21 (d, *J*=12.9 Hz, 1H), 1.29 (s, 9H), 1.19 (s, 3H); ^{19}F NMR ($CDCl_3$): *δ* −82.16 (s, 3F); ^{13}C NMR ($CDCl_3$): *δ* 171.76, 139.48, 131.61, 128.64, 127.32, 125.71 (q, *J*=214.3 Hz), 73.05 (q, *J*=21.5 Hz), 59.84, 35.03, 23.29, 22.16; MS (*m*/*z*, %): 336 (M^++1, 3.36), 279 (41.01), 57 (100); HRMS calcd for $C_{11}H_{12}F_3NO_2S$ [$M^+-{}^t$Bu+1]: 279.0541; Found: 279.0540.

4.2.3. (*Rs*,*S*)-*N*-(4,4,4-Trifluoro-3-hydroxy-1-(4-methoxyphenyl)-3-methyl-butylidene)-*tert*-butanesulfinamide (3b). White solid, yield 55%; mp 130–131 °C; FTIR (KBr, cm^{-1}): *ν* 3154, 3007, 2965, 1608, 1595, 1568, 1241, 1148, 1033; ^{1}H NMR ($CDCl_3$): *δ* 7.76 (d, *J*=8.4 Hz, 2H), 6.95 (d, *J*=8.4 Hz, 2H), 6.69 (s, 1H), 3.88 (s, 3H), 3.67 (d, *J*=12.9 Hz, 1H), 3.42 (d, *J*=12.9 Hz, 1H), 1.39 (s, 9H), 1.09 (s, 3H); ^{19}F NMR ($CDCl_3$): *δ* −83.74 (s, 3F); MS (*m*/*z*, %): 366 (M^++1, 0.57), 309 ($M^+-{}^t$Bu+1, 45.19), 57 (100), 149 (87.08). Anal. Calcd for $C_{16}H_{22}F_3NO_3S$: C, 52.59; H, 6.07; N, 3.83. Found: C, 52.99; H, 6.04; N, 3.66.

4.2.4. (*Rs*,*R*)-*N*-(4,4,4-Trifluoro-3-hydroxy-1-(4-methoxyphenyl)-3-methyl-butylidene)-*tert*-butanesulfinamide (3b′). White solid, yield 17%; mp 80–82 °C; FTIR (KBr,

cm^{-1}): ν 3250, 3072, 2969, 2936, 1609, 1589, 1564, 1185, 1168, 1090; ^{1}H NMR ($CDCl_3$): δ 7.77 (d, J=7.4 Hz, 2H), 6.94 (d, J=7.4 Hz, 2H), 6.11 (s, 1H), 3.97 (d, J=13.2 Hz, 1H), 3.87 (s, 3H), 3.23 (d, J=13.2 Hz, 1H), 1.36 (s, 9H), 1.28 (s, 3H); ^{19}F NMR ($CDCl_3$): δ −82.22 (s, 3F); MS (*m*/*z*, %): 366 (M^++1, 0.57), 309 ($M^+-{}^t$Bu+1, 31.30), 149 (100), 57 (73.15). Anal. Calcd for $C_{16}H_{22}F_3NO_3S$: C, 52.59; H, 6.07; N, 3.83. Found: C, 53.01; H, 6.17; N, 3.46.

4.2.5. (*Rs*,*S*)-*N*-(4,4,4-Trifluoro-1-(4-fluorophenyl)-3-hydroxy-3-methyl-butylidene)-*tert*-butanesulfinamide (3c). White solid, yield 69%; mp 141–143 °C; $[\alpha]_D^{20}$ +133.7 (*c* 1.015, $CHCl_3$); FTIR (KBr, cm^{-1}): ν 3176, 3009, 2985, 1601, 1583, 1511, 1235, 1168, 1098, 1039; ^{1}H NMR ($CDCl_3$): δ 7.79 (dd, J_1=8.5 Hz, J_2=5.3 Hz, 2H), 7.13–7.18 (m, 2H), 6.55 (s, 1H), 3.73 (d, J=12.9 Hz, 1H), 3.40 (d, J=12.9 Hz, 1H), 1.40 (s, 9H), 1.07 (s, 3H); ^{19}F NMR ($CDCl_3$): δ −83.78 (s, 3F), −106.94 to −107.03 (m, 1F); MS (*m*/*z*, %): 354 (M^++1, 4.99), 297 ($M^+-{}^t$Bu+1, 26.48), 57 (100). Anal. Calcd for $C_{15}H_{19}F_4NO_2S$: C, 50.98; H, 5.42; N, 3.96. Found: C, 51.01; H, 5.13; N, 3.60.

4.2.6. (*Rs*,*R*)-*N*-(4,4,4-Trifluoro-1-(4-fluorophenyl)-3-hydroxy-3-methyl-butylidene)-*tert*-butanesulfinamide (3c′). White solid, yield 19%; mp 83–85 °C; FTIR (KBr, cm^{-1}): ν 3358, 2990, 2930, 1602, 1577, 1508, 1235, 1170, 1054; ^{1}H NMR ($CDCl_3$): δ 7.81 (dd, J_1=8.5 Hz, J_2=5.6 Hz, 2H), 7.11–7.17 (m, 2H), 6.04 (s, 1H), 3.98 (d, J=13.5 Hz, 1H), 3.28 (d, J=13.5 Hz, 1H), 1.39 (s, 9H), 1.31 (s, 3H); ^{19}F NMR ($CDCl_3$): δ −81.91 (s, 3F), −107.63 to −107.73 (m, 1F); ^{13}C NMR ($CDCl_3$): δ 170.55, 164.89 (d, J=202.3 Hz), 135.74, 129.69 (d, J=7.1 Hz), 125.70 (q, J=228.3 Hz), 115.79 (d, J=17.5 Hz), 73.03 (q, J=22.7 Hz), 59.98, 35.48, 23.39, 22.48; MS (*m*/*z*, %): 354 (M^++1, 6.73), 297 ($M^+-{}^t$Bu+1, 53.18), 57 (100); HRMS calcd for $C_{11}H_{11}F_4NO_2S$ [$M^+-{}^t$Bu+1]: 297.0447; Found: 297.0456.

4.2.7. (*Rs*,*S*)-*N*-(1-(4-Chlorophenyl)-4,4,4-trifluoro-3-hydroxy-3-methyl-butylidene)-*tert*-butanesulfinamide (3d). White solid, yield 66%; mp 153–154 °C; $[\alpha]_D^{20}$ +152.7 (*c* 1.035, $CHCl_3$); FTIR (KBr, cm^{-1}): ν 3177, 3010, 2985, 1602, 1589, 1564, 1280, 1148, 1098, 1039; ^{1}H NMR ($CDCl_3$): δ 7.71 (d, J=9.0 Hz, 2H), 7.44 (d, J=9.0 Hz, 2H), 6.51 (s, 1H), 3.73 (d, J=13.5 Hz, 1H), 3.39 (d, J=13.5 Hz, 1H), 1.40 (s, 9H), 1.06 (s, 3H); ^{19}F NMR ($CDCl_3$): δ −83.78 (s, 3F); MS (*m*/*z*, %): 313 ($M^+-{}^t$Bu+1, 21.10), 315 (6.96), 57 (100). Anal. Calcd for $C_{15}H_{19}ClF_3NO_2S$: C, 48.71; H, 5.18; N, 3.79. Found: C, 48.91; H, 4.94; N, 3.46.

4.2.8. (*Rs*,*R*)-*N*-(1-(4-Chlorophenyl)-4,4,4-trifluoro-3-hydroxy-3-methyl-butylidene)-*tert*-butanesulfinamide (3d′). White solid, yield 15%; mp 98–102 °C; FTIR (KBr, cm^{-1}): ν 3359, 1603, 1589, 1563, 1281, 1170, 1093, 1057; ^{1}H NMR ($CDCl_3$): δ 7.71 (d, J=8.3 Hz, 2H), 7.42 (d, J=8.3 Hz, 2H), 5.98 (s, 1H), 3.96 (d, J=13.4 Hz, 1H), 3.25 (d, J=13.4 Hz, 1H), 1.37 (s, 9H), 1.29 (s, 3H); ^{19}F NMR ($CDCl_3$): δ −81.91 (s, 3F); ^{13}C NMR ($CDCl_3$): δ 170.67, 138.08, 137.90, 128.98, 128.69, 128.15 (q, J=214.7 Hz), 73.02 (q, J=28.7 Hz), 60.10, 35.38, 23.26, 22.45; MS (*m*/*z*, %): 313 ($M^+-{}^t$Bu+1, 23.16), 315 (8.78), 57 (100); HRMS calcd for $C_{11}H_{11}ClF_3NO_2S$ [$M^+-{}^t$Bu+1]: 313.0151; Found: 313.0155.

4.2.9. (*Rs*,*S*)-*N*-(4,4,4-Trifluoro-3-hydroxy-3-methyl-1-(4-nitrophenyl)butylidene)-*tert*-butanesulfinamide (3e). Pale yellow solid, yield 51%; mp 142–143 °C; FTIR (KBr, cm^{-1}): ν 3208, 3009, 2980, 1612, 1601, 1528, 1349, 1274, 1098, 1040; ^{1}H NMR ($CDCl_3$): δ 8.33 (d, J=7.1 Hz, 2H), 7.94 (d, J=7.1 Hz, 2H), 6.38 (s, 1H), 3.82 (d, J=13.2 Hz, 1H), 3.46 (d, J=13.2 Hz, 1H), 1.43 (s, 9H), 1.05 (s, 3H); ^{19}F NMR ($CDCl_3$): δ −83.76 (s, 3F); MS (*m*/*z*, %): 324 ($M^+-{}^t$Bu+1, 6.28), 57 (100), 41 (23.97). Anal. Calcd for $C_{15}H_{19}F_3N_2O_4S$: C, 47.36; H, 5.03; N, 7.36. Found: C, 47.65; H, 5.07; N, 7.02.

4.2.10. Mixture of (*Rs*,*S*)-*N*-(6,6,6-trifluoro-5-hydroxy-2,2,5-trimethylhexan-3-ylidene)-*tert*-butanesulfonamide (3f) and (*Rs*,*R*)-*N*-(6,6,6-trifluoro-5-hydroxy-2,2,5-trimethylhexan-3-ylidene)-*tert*-butanesulfonamide (3f′). Viscous pale yellow oil, total yield 98%; FTIR (film, cm^{-1}): ν 3176, 2967, 2931, 1606, 1461, 1367, 1279, 1155, 1098, 1039; ^{1}H NMR ($CDCl_3$): δ 7.04 (s, 0.64H), 6.52 (s, 0.36H), 3.50 (d, J=14.1 Hz, 0.36H), 3.03 (d, J=14.3 Hz, 0.64H), 2.98 (d, J=14.3 Hz, 0.64H), 2.76 (d, J=14.1 Hz, 0.36H), 1.32 (s, 1.92H), 1.27 (s, 1.08H), 1.23 (s, 9H), 1.17 (s, 5.76H), 1.13 (s, 3.24H); ^{19}F NMR ($CDCl_3$): δ −83.69 (s, 1.92F), −83.89 (s, 1.08F); ^{13}C NMR ($CDCl_3$): δ 185.16, 184.90, 126.16 (q, J=215.8 Hz), 125.92 (q, J=214.6 Hz), 73.45 (q, J=21.2 Hz), 70.66 (q, J=20.9 Hz), 59.25, 58.76, 44.80, 43.97, 36.76, 32.86, 29.16, 28.34, 23.19, 22.96, 22.85, 21.62; MS (*m*/*z*, %): 316 (M^++1, 2.15), 259 ($M^+-{}^t$Bu+1, 10.74), 83 (56.54), 57 (100); HRMS calcd for $C_9H_{16}F_3NO_2S$ [$M^+-{}^t$Bu+1]: 259.0854; Found: 259.0863.

4.2.11. (*Rs*,*S*)-*N*-(6,6,6-Trifluoro-5-hydroxy-2,5-dimethylhexan-3-ylidene)-*tert*-butanesulfonamide (3g). Viscous pale yellow oil, yield 40%; FTIR (film, cm^{-1}): ν 3196, 2970, 2933, 1626, 1463, 1366, 1279, 1156, 1102, 1041; ^{1}H NMR ($CDCl_3$): δ 6.66 (s, 1H), 3.38 (d, J=12.0 Hz, 1H), 2.71 (d, J=12.0 Hz, 1H), 2.59–2.66 (m, 1H), 1.40 (s, 3H), 1.29 (s, 9H), 1.18 (d, J=2.1 Hz, 3H), 1.16 (d, J=1.5 Hz, 3H); ^{19}F NMR ($CDCl_3$): δ −83.99 (s, 3F); ^{13}C NMR ($CDCl_3$): δ 184.23, 126.02 (q, J=215.3 Hz), 70.56 (q, J=21.1 Hz), 59.21, 42.75, 40.30, 22.95, 21.45, 19.21; MS (*m*/*z*, %): 302 (M^++1, 1.69), 245 ($M^+-{}^t$Bu+1, 24.62), 197 (54.44), 57 (100); HRMS calcd for $C_8H_{14}F_3NO_2S$ [$M^+-{}^t$Bu+1]: 245.0697; Found: 245.0702.

4.2.12. (*Rs*,*R*)-*N*-(6,6,6-Trifluoro-5-hydroxy-2,5-dimethylhexan-3-ylidene)-*tert*-butanesulfonamide (3g′). Viscous pale yellow oil, yield 36%; FTIR (film, cm^{-1}): ν 3350, 2971, 2874, 1626, 1463, 1365, 1280, 1155, 1037; ^{1}H NMR ($CDCl_3$): δ 6.40 (s, 1H), 3.25 (d, J=13.2 Hz, 1H), 2.86 (d, J=13.2 Hz, 1H), 2.58–2.65 (m, 1H), 1.40 (s, 3H), 1.29 (s, 9H), 1.14 (d, J=2.4 Hz, 3H), 1.11 (d, J=2.7 Hz, 3H); ^{19}F NMR ($CDCl_3$): δ −81.34 (s, 3F); ^{13}C NMR ($CDCl_3$): δ 184.03, 125.87 (q, J=213.8 Hz), 72.34 (q, J=21.3 Hz), 59.00, 42.09, 40.47, 23.00, 20.54, 20.15; MS (*m*/*z*, %): 302 (M^++1, 1.40), 245 ($M^+-{}^t$Bu+1, 14.69), 197 (28.64), 57 (100); HRMS calcd for $C_8H_{14}F_3NO_2S$ [$M^+-{}^t$Bu+1]: 245.0697; Found: 245.0702.

4.2.13. (*Rs*,*R*)-*N*-(4,4,4-Trifluoro-3-hydroxy-1,3-diphenylbutylidene)-*tert*-butanesulfonamide (3h). White solid, yield 46%; mp 137–140 °C; $[\alpha]_D^{20}$ +319.7 (*c* 1.015, $CHCl_3$); FTIR (KBr, cm^{-1}): ν 3135, 2981, 2965, 1592, 1571, 1450,

1265, 1151, 1028; ^{1}H NMR ($CDCl_3$): δ 7.39 (d, J=7.5 Hz, 2H), 6.98–7.18 (m, 8H), 4.02 (d, J=12.5 Hz, 1H), 3.83 (d, J=12.5 Hz, 1H), 1.44 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −78.64 (s, 3F); MS (*m*/*z*, %): 341 ($M^+-{}^t$Bu+1, 3.80), 201 (100), 77 (53.23). Anal. Calcd for $C_{20}H_{22}F_3NO_2S$: C, 60.44; H, 5.58; N, 3.52. Found: C, 60.58; H, 5.60; N, 3.24.

4.2.14. (*Rs*,*S*)-*N*-(4,4,4-Trifluoro-3-hydroxy-1,3-diphenylbutylidene)-*tert*-butanesulfonamide (3h′). White solid, yield 35%; mp 144–146 °C; FTIR (KBr, cm^{-1}): ν 3124, 2984, 2970, 1594, 1576, 1446, 1258, 1171, 1030; ^{1}H NMR ($CDCl_3$): δ 7.60 (d, J=7.5 Hz, 4H), 7.33–7.45 (m, 6H), 7.06 (s, 1H), 4.34 (d, J=13.7 Hz, 1H), 3.56 (d, J=13.7 Hz, 1H), 1.40 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −76.76 (s, 3F); MS (*m*/*z*, %): 341 ($M^+-{}^t$Bu+1, 27.58), 201 (2.87), 77 (94.99), 57 (100). Anal. Calcd for $C_{20}H_{22}F_3NO_2S$: C, 60.44; H, 5.58; N, 3.52. Found: C, 60.49; H, 5.64; N, 3.40.

4.2.15. (*Rs*,*R*)-*N*-(4,4,4-Trifluoro-1-(4-fluorophenyl)-3-hydroxy-3-phenylbutylidene)-*tert*-butanesulfonamide (3i). White solid, yield 42%; mp 165–167 °C; $[\alpha]_D^{20}$ +328.7 (*c* 1.02, $CHCl_3$); FTIR (KBr, cm^{-1}): ν 3150, 2962, 1602, 1575, 1509, 1263, 1230, 1158, 1022; ^{1}H NMR ($CDCl_3$): δ 7.36–7.43 (m, 2H), 7.15–7.20 (m, 3H), 7.00–7.07 (m, 3H), 6.68–6.74 (m, 2H), 4.02 (d, J=12.6 Hz, 1H), 3.75 (d, J=12.6 Hz, 1H), 1.44 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −78.44 (s, 3F), −108.71 to −108.87 (m, 1F); MS (*m*/*z*, %): 359 ($M^+-{}^t$Bu+1, 16.18), 105 (49.63), 57 (100). Anal. Calcd for $C_{20}H_{21}F_4NO_2S$: C, 57.82; H, 5.09; N, 3.37. Found: C, 57.85; H, 5.09; N, 3.11.

4.2.16. (*Rs*,*S*)-*N*-(4,4,4-Trifluoro-1-(4-fluorophenyl)-3-hydroxy-3-phenylbutylidene)-*tert*-butanesulfonamide (3i′). White solid, yield 42%; mp 142–143 °C; FTIR (KBr, cm^{-1}): ν 3094, 2962, 1599, 1572, 1511, 1208, 1177, 1027; ^{1}H NMR ($CDCl_3$): δ 7.55–7.68 (m, 4H), 7.27–7.33 (m, 2H), 7.00–7.05 (m, 3H), 4.30 (d, J=12.9 Hz, 1H), 3.53 (d, J=12.9 Hz, 1H), 1.39 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −76.75 (s, 3F), −108.30 to −108.44 (m, 1F); MS (*m*/*z*, %): 359 ($M^+-{}^t$Bu+1, 14.08), 105 (54.09), 57 (100). Anal. Calcd for $C_{20}H_{21}F_4NO_2S$: C, 57.82; H, 5.09; N, 3.37. Found: C, 57.99; H, 5.09; N, 3.00.

4.2.17. (*Rs*,*R*)-*N*-(1-(4-Chlorophenyl)-4,4,4-trifluoro-3-hydroxy-3-phenylbutylidene)-*tert*-butanesulfonamide (3j). Pale yellow solid, yield 40%; mp 138–140 °C; FTIR (KBr, cm^{-1}): ν 3150, 2958, 1586, 1560, 1450, 1261, 1158, 1024; ^{1}H NMR ($CDCl_3$): δ 7.38–7.40 (m, 2H), 7.17 (s, 1H), 6.99–7.11 (m, 7H), 4.02 (d, J=12.5 Hz, 1H), 3.74 (d, J=12.5 Hz, 1H), 1.43 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −78.48 (s, 3F); MS (*m*/*z*, %): 375 ($M^+-{}^t$Bu+1, 8.67), 377 (3.15), 105 (51.45), 57 (100). Anal. Calcd for $C_{20}H_{21}ClF_3NO_2S$: C, 55.62; H, 4.90; N, 3.24. Found: C, 55.83; H, 4.90; N, 3.14.

4.2.18. (*Rs*,*S*)-*N*-(1-(4-Chlorophenyl)-4,4,4-trifluoro-3-hydroxy-3-phenylbutylidene)-*tert*-butanesulfonamide (3j′). White solid, yield 40%; mp 132–134 °C; FTIR (KBr, cm^{-1}): ν 3094, 2984, 2929, 1585, 1560, 1261, 1165, 1027; ^{1}H NMR ($CDCl_3$): δ 7.47–7.67 (m, 4H), 7.22–7.38 (m, 5H), 6.98 (s, 1H), 4.30 (d, J=9.2 Hz, 1H), 3.53 (d, J=9.2 Hz, 1H), 1.39 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −76.74 (s, 3F); ^{13}C NMR ($CDCl_3$): δ 171.43, 138.28, 137.45, 128.52, 128.23, 127.87, 127.68 (q, J=206.8 Hz), 126.14, 75.75 (q, J=20.6 Hz), 60.12, 38.49, 23.32; MS (*m*/*z*, %): 375 ($M^+-{}^t$Bu+1, 7.35), 377 (2.74), 105 (42.59), 57 (100); HRMS calcd for $C_{16}H_{13}ClF_3NO_2S$ [$M^+-{}^t$Bu+1]: 375.0308; Found: 375.0320.

4.2.19. Mixture of (*Rs*,*R*)-*N*-(6,6,6-trifluoro-5-hydroxy-2,2-dimethyl-5-phenylhexan-3-ylidene)-*tert*-butanesulfonamide (3k) and (*Rs*,*S*)-*N*-(6,6,6-trifluoro-5-hydroxy-2,2-dimethyl-5-phenylhexan-3-ylidene)-*tert*-butanesulfonamide (3k′). Viscous pale yellow oil, total yield 62%; FTIR (film, cm^{-1}): ν 3163, 2984, 1600, 1451, 1260, 1161, 1024; ^{1}H NMR ($CDCl_3$): δ 7.66 (s, 0.7H), 7.55–7.62 (m, 2H), 7.27–7.32 (m, 3H), 7.19 (s, 0.3H), 3.85 (d, J=13.8 Hz, 0.3H), 3.39 (d, J=13.8 Hz, 0.7H), 3.44 (d, J=13.8 Hz, 0.7H), 2.99 (d, J=13.8 Hz, 0.3H), 1.28 (s, 6.3H), 1.26 (s, 2.7H), 0.75 (s, 2.7H), 0.63 (s, 6.3H); ^{19}F NMR ($CDCl_3$): δ −77.73 (s, 0.9F), −78.55 (s, 2.1F); MS (*m*/*z*, %): 378 (M^++1, 0.16), 321 ($M^+-{}^t$Bu+1, 9.69), 377 (3.15), 105 (30.23), 57 (100). Anal. Calcd for $C_{18}H_{26}F_3NO_2S$: C, 57.27; H, 6.94. Found: C, 57.16; H, 7.30.

4.2.20. (*Rs*,*R*)-*N*-(6,6,6-Trifluoro-5-hydroxy-2-methyl-5-phenylhexan-3-ylidene)-*tert*-butanesulfonamide (3l). Viscous oil, yield 26%; FTIR (film, cm^{-1}): ν 3135, 2972, 2933, 1623, 1450, 1365, 1262, 1156, 1039; ^{1}H NMR ($CDCl_3$): δ 7.60 (d, J=6.9 Hz, 2H), 7.30–7.33 (m, 3H), 7.17 (s, 1H), 3.63 (d, J=11.7 Hz, 1H), 3.11 (d, J=11.7 Hz, 1H), 1.31–1.40 (m, 1H), 1.25 (s, 9H), 0.84 (d, J=6.6 Hz, 3H), 0.52 (d, J=6.6 Hz, 3H); ^{19}F NMR ($CDCl_3$): δ −79.32 (s, 3F); ^{13}C NMR ($CDCl_3$): δ 184.42, 137.48, 128.65, 128.34, 126.12, 125.60 (q, J=216 Hz), 73.60 (q, J=21.4 Hz), 59.21, 42.22, 40.79, 22.85, 21.02, 18.88; MS (*m*/*z*, %): 364 (M^++1, 1.21), 307 ($M^+-{}^t$Bu+1, 24.47), 105 (54.11), 57 (100); HRMS calcd for $C_{13}H_{16}F_3NO_2S$ [$M^+-{}^t$Bu+1]: 307.0854; Found: 307.0856.

4.2.21. (*Rs*,*S*)-*N*-(6,6,6-Trifluoro-5-hydroxy-2-methyl-5-phenylhexan-3-ylidene)-*tert*-butanesulfonamide (3l′). White solid, yield 27%; mp 72–73 °C; FTIR (KBr, cm^{-1}): ν 3149, 2985, 2966, 1616, 1447, 1276, 1239, 1173, 1032; ^{1}H NMR ($CDCl_3$): δ 7.65 (d, J=7.2 Hz, 2H), 7.33–7.41 (m, 3H), 7.13 (s, 1H), 3.74 (d, J=12.9 Hz, 1H), 3.08 (d, J=12.9 Hz, 1H), 2.29–2.37 (m, 1H), 1.31 (s, 9H), 1.08 (d, J=6.8 Hz, 3H), 0.90 (d, J=6.8 Hz, 3H); ^{19}F NMR ($CDCl_3$): δ −77.23 (s, 3F); ^{13}C NMR ($CDCl_3$): δ 183.63, 138.77, 128.48, 128.34, 126.01, 125.22 (q, J=205.9 Hz), 75.43 (q, J=21.1 Hz), 59.11, 41.89, 41.63, 23.02, 20.46, 20.28; MS (*m*/*z*, %): 307 ($M^+-{}^t$Bu+1, 14.65), 105 (46.84), 70 (100), 57 (85.49); HRMS calcd for $C_{13}H_{16}F_3NO_2S$ [$M^+-{}^t$Bu+1]: 307.0854; Found: 307.0851.

4.3. General experimental procedure for the hydrolysis of 3a and 3a′

To a solution of **3a** (45 mg, 0.134 mmol) in 7 mL MeOH was added 3.0 M aqueous HCl solution (4 mL, 12 mmol) and the mixture was stirred for 1 h at room temperature (monitored by TLC). After reaction, about half amount of solvent was removed under reduced pressure. Then saturated NaCl solution was added to the residue and the resulted mixture was extracted with CH_2Cl_2 (15 mL×3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated.

The residue was purified by silica gel chromatography to give **4a** (26 mg).

4.3.1. (*S*)-4,4,4-Trifluoro-3-hydroxy-3-methyl-1-phenylbutan-1-one (4a). White solid, yield 84%; mp 49–50 °C; $[\alpha]_D^{20}$ −19.98 (*c* 0.64, $CHCl_3$); FTIR (KBr, cm^{-1}): *ν* 3525, 3080, 2912, 1682, 1599, 1582, 1450, 1346, 1215, 1165, 1102, 1068; ^1H NMR ($CDCl_3$): *δ* 7.96 (d, *J*=7.8 Hz, 2H), 7.65 (dd, J_1=7.8 Hz, J_2=7.8 Hz, 1H), 7.51 (dd, J_1=7.8 Hz, J_2=7.8 Hz, 2H), 5.29 (s, 1H), 3.51 (d, *J*=17.1 Hz, 1H), 3.11 (d, *J*=17.1 Hz, 1H), 1.51 (s, 3H); ^{19}F NMR ($CDCl_3$): *δ* −82.67 (s, 3F); ^{13}C NMR ($CDCl_3$): *δ* 200.16, 136.53, 134.31, 128.91, 128.30, 125.71 (q, *J*=213.7 Hz), 73.43 (q, *J*=21.6 Hz), 40.25, 22.07; MS (*m*/*z*, %): 232 (M^+, 1.36), 105 (100), 77 (52.78), 43 (15.88); HRMS calcd for $C_{11}H_{11}F_3O_2$ [M^+]: 232.0711; Found: 232.0718. Anal. Calcd for $C_{11}H_{11}F_3O_2$: C, 56.90; H, 4.77. Found: C, 57.25; H, 5.03; HPLC (Chiral-AS column, 98:2 hexane/2-propanol; 0.6 mL/min; 214 nm; **(*S*)-4a**, t_R=18.48 min, **(*R*)-4a′**, t_R=19.83 min).

4.3.2. (*R*)-4,4,4-Trifluoro-3-hydroxy-3-methyl-1-phenylbutan-1-one (4a′). White solid, yield 84%; mp 49–50 °C; $[\alpha]_D^{20}$ +19.50 (*c* 0.635, $CHCl_3$); FTIR (KBr, cm^{-1}): *ν* 3525, 3080, 2912, 1682, 1599, 1582, 1450, 1346, 1215, 1165, 1102, 1068; ^1H NMR ($CDCl_3$): *δ* 7.96 (d, *J*=7.5 Hz, 2H), 7.65 (dd, J_1=7.5 Hz, J_2=7.5 Hz, 1H), 7.51 (dd, J_1=7.5 Hz, J_2=7.5 Hz, 2H), 5.29 (s, 1H), 3.51 (d, *J*=17.1 Hz, 1H), 3.11 (d, *J*=17.1 Hz, 1H), 1.56 (s, 3H); ^{19}F NMR ($CDCl_3$): *δ* −83.10 (s, 3F); ^{13}C NMR ($CDCl_3$): *δ* 200.16, 136.54, 134.32, 128.93, 128.31, 125.71 (q, *J*=213.8 Hz), 73.44 (q, *J*=21.0 Hz), 40.27, 22.11; MS (*m*/*z*, %): 232 (M^+, 2.42), 105 (100), 77 (39.53), 43 (15.35); HRMS calcd for $C_{11}H_{11}F_3O_2$ [M^+]: 232.0711; Found: 232.0703; HPLC (Chiral-AS column, 98:2 hexane/2-propanol; 0.6 mL/min; 214 nm; **(*S*)-4a**, t_R=18.48 min, **(*R*)-4a′**, t_R=19.83 min).

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