



# One-pot asymmetric synthesis of $\alpha$ -trifluoromethylated amines from $\alpha$ -trifluoromethyl ketones

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## ABSTRACT

Diastereoselective reduction of (*Rs*)-*N*-*tert*-butanesulfinyl  $\alpha$ -trifluoromethyl ketimines formed in situ from the corresponding  $\alpha$ -trifluoromethyl ketones and *N*-*tert*-butanesulfinamide has been achieved, and either diastereomer of *N*-*tert*-butanesulfinyl  $\alpha$ -trifluoromethyl amines was obtained in good yields with excellent diastereoselectivities (up to 99:1 dr) using NaBH<sub>4</sub> and L-Selectride as the reductants, respectively.

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## 1. Introduction

Trifluoromethyl-containing compounds have gained growing interest in the field of agrochemistry, pharmaceutical industry, and materials science during the past decades<sup>1</sup> because the introduction of a trifluoromethyl group with strong electron-withdrawing ability can lead to significant changes in the physical, chemical, and biological properties of the molecules. Among such compounds enantiomerically pure  $\alpha$ -trifluoromethyl amines have attracted considerable attention since these chiral synthons are important and common subunits in the synthesis of chiral fluorinated pharmaceuticals and agrochemicals.<sup>1a,b,d</sup> Based on its prime importance in the drug industry, a variety of methodologies have been developed for their asymmetric synthesis,<sup>2–6</sup> such as nucleophilic trifluoromethylation of *N*-(*tert*-butylsulfinyl)-imines,<sup>3</sup> addition of organometallic reagents to chiral trifluoromethyl imines or analogues,<sup>4</sup> reduction of enantiopure trifluoromethyl imines<sup>5a,b</sup> or catalytic asymmetric reduction of prochiral trifluoromethyl ketimines<sup>5c</sup> and so on.<sup>6</sup> However, most of them have suffered from some drawbacks, like for instance, only one enantiomer obtained, or restricted by the availability of organometallic derivatives, or having a narrow substrate scope. Therefore, there is still desirable

to develop a more practical and general method suitable for the rapid synthesis of chiral  $\alpha$ -trifluoromethyl amines.

Recently, much attention has been paid to the synthesis of chiral CF<sub>3</sub>-substituted *N*-sulfinyl imines and their applications in the diastereoselective synthesis of trifluoromethyl amine derivatives.<sup>7</sup> During our studies on the reactions of CF<sub>3</sub>-containing ketones,<sup>8</sup> we have synthesized a new class of chiral CF<sub>3</sub>-substituted  $\alpha,\beta$ -unsaturated *N*-*tert*-butanesulfinyl ketimines and explored their preliminary applications in the asymmetric synthesis of either diastereomer of trifluoromethyl allylic amines.<sup>9</sup> As part of our ongoing research in the development of practical methods for the synthesis of chiral  $\alpha$ -CF<sub>3</sub> amines, we herein wish to report a facile one-pot approach for the asymmetric synthesis of either (*Rs*, *R*) or (*Rs*, *S*) isomer of *N*-*tert*-butanesulfinyl  $\alpha$ -trifluoromethyl amines by the diastereoselective reduction of (*Rs*)-*N*-*tert*-butanesulfinyl  $\alpha$ -trifluoromethyl ketimines, which are generated in situ from the condensation of  $\alpha$ -trifluoromethyl ketones and (*Rs*)-*N*-*tert*-butanesulfinamide.

## 2. Results and discussion

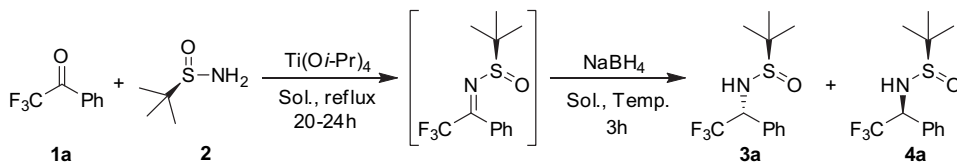
We began our investigation with the NaBH<sub>4</sub>-mediated one-pot reductive amination of 2,2,2-trifluoroacetophenone (**1a**) according to the conditions previously reported by Ellman and co-workers for the one-pot reductive amination of ketones with *N*-*tert*-butanesulfinamide.<sup>10</sup> Condensation of **1a** with **2** in dry THF in the presence of 2.5 equiv of Ti(Oi-Pr)<sub>4</sub> under reflux for 24 h,<sup>11</sup> followed by in situ reduction with 3.0 equiv of NaBH<sub>4</sub> at –78 °C for 3 h afforded the

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$\alpha$ -trifluoromethyl sulfonamide **3a** in 52% yield and with a diastereomeric ratio of 98:2 (Table 1, entry 1). To achieve better results, the effect of the solvent was then surveyed. As shown in Table 1, using Et<sub>2</sub>O instead of THF as the solvent, the yield of **3a** could be dramatically improved to 85% without any loss in the diastereomeric ratio (**3a/4a**=98:2, entry 2). When *n*-hexane was used as the solvent, the reaction gave similar yield and diastereoselectivity as using THF (entry 3). Other solvents, such as toluene, CH<sub>2</sub>Cl<sub>2</sub>, and CH<sub>3</sub>CN furnished the  $\alpha$ -trifluoromethyl sulfonamides **3a** and **4a** in moderate selectivity but gave lower yields (entries 4–6).

**Table 1**  
Solvent screen for the NaBH<sub>4</sub>-mediated one-pot reductive amination of **1a**



Entry <sup>a</sup>	Solvent	Temp (°C)	Yield <sup>b</sup> (%)	<b>3a/4a</b> <sup>c</sup>
1	THF	–78	52	98:2
2	Et <sub>2</sub> O	–78	85	98:2
3	<i>n</i> -hexane	–78	54	98:2
4	Toluene	–78	34 <sup>d</sup>	82:18
5	CH <sub>2</sub> Cl <sub>2</sub>	–78	31 <sup>d</sup>	71:29
6	CH <sub>3</sub> CN	–30 to –40	45 <sup>d</sup>	60:40

<sup>a</sup> All reductions were performed using 3.0 equiv of NaBH<sub>4</sub> in the appropriate solvent for 3 h.

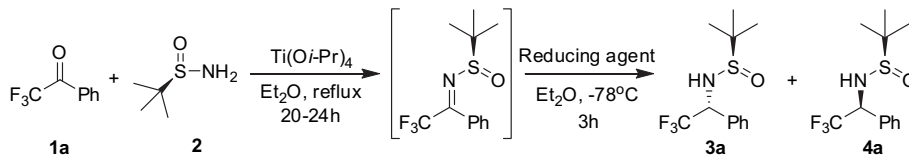
<sup>b</sup> Isolated yield of **3a** in two steps unless otherwise noted.

<sup>c</sup> Diastereomeric ratios were determined by <sup>19</sup>F NMR of the crude reaction mixture.

<sup>d</sup> The overall yield of **3a** and **4a** in two steps. Determined by <sup>19</sup>F NMR of the crude reaction mixture.

Encouraged by the above results, we then examined a series of metal hydrides to test the possibility of stereoselectivity reversal using ether as the solvent.<sup>9,10a,12</sup> The results were promising, as revealed in Table 2. When DIBAL-H was used instead of NaBH<sub>4</sub> as the reductant, a slight improvement in diastereoselectivity (**3a/4a**=99:1) was observed but in a lower yield (entry 2). Catecholborane was less reactive and only 14% overall yield of **3a** and **4a** was obtained after 3 h (entry 3). NaBH<sub>3</sub>CN and LiBH<sub>4</sub> exhibited poor levels of diastereoselection in favor of isomer **3a** (entries 4–5). We were gratified to find the reversal of the diastereofacial selectivity when LiBHET<sub>3</sub> was used as the reducing agent (entry 6). More excitingly, performing the reduction with L-Selectride resulted in the opposite stereoisomer **4a** in good yield with high diastereoselectivity (**4a/3a**=98:2, entry 7).<sup>13</sup>

**Table 2**  
The one-pot reductive amination of **1a** with various reducing agents



Entry <sup>a</sup>	Reducing agent	Yield <sup>b</sup> (%)	<b>3a/4a</b> <sup>c</sup>
1	NaBH <sub>4</sub>	85 ( <b>3a</b> )	98:2
2	DIBAL-H	46 <sup>d</sup>	99:1
3	Catecholborane	14 <sup>d</sup>	98:2
4	NaBH <sub>3</sub> CN	40 ( <b>3a</b> )	72:28
5	LiBH <sub>4</sub>	58 ( <b>3a</b> )	80:20
6	LiBHET <sub>3</sub>	43 <sup>d</sup>	18:82
7	L-Selectride	78 ( <b>4a</b> )	2:98

<sup>a</sup> All reductions were performed using 3.0 equiv of reducing agent in Et<sub>2</sub>O at –78 °C for 3 h.

<sup>b</sup> Isolated yield of **3a** or **4a** in two steps unless otherwise noted.

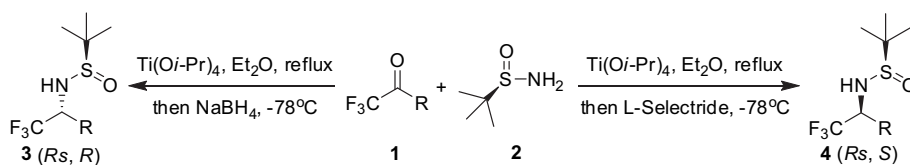
<sup>c</sup> Diastereomeric ratios were determined by <sup>19</sup>F NMR of crude reaction mixture.

<sup>d</sup> The overall yield of **3a** and **4a** in two steps. Determined by <sup>19</sup>F NMR of crude reaction mixture.

With the two optimized reaction conditions in hand (Table 2, entries 1 and 7), a variety of  $\alpha$ -trifluoromethyl ketones were employed as the substrate to explore the scope of the one-pot reductive amination procedures and test the generality of the reversal in diastereofacial selectivity upon using NaBH<sub>4</sub> versus L-Selectride. As summarized in Table 3, all the one-pot reductive aminations of both  $\alpha$ -trifluoromethyl aryl and  $\alpha$ -trifluoromethyl alkyl ketones went smoothly and afforded the corresponding  $\alpha$ -trifluoromethyl amines from **1** in good to excellent yields as well as high diastereoselectivities.  $\alpha$ -Trifluoromethyl aryl ketones containing both

electron-donating and electron-withdrawing substituents at the *para* position proved to be excellent substrates in both systems, giving 90–96% de (entries 1–8). It is worth to be mentioned that both systems gave even better diastereoselectivities (dr up to 99:1) for  $\alpha$ -trifluoromethyl alkyl ketones (entries 9–12). Thus, with two different reduction systems, the opposite stereocontrol could be easily achieved. The absolute configuration of product **3a** and **3d**, **4a** and **4d** was unequivocally assigned as (*R*,*R*) and (*R*,*S*) by cleaving the sulfonamide with HCl and examining the optical rotation of the known salts. By analogy, the absolute configuration of products **3b–c**, **e–f**, and **4b–c**, **e–f** is tentatively assigned as (*R*,*R*) and (*R*,*S*).

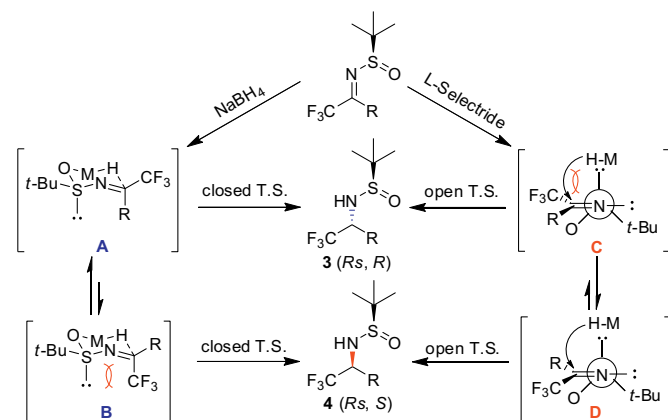
On the basis of the diastereoselectivity observed (Table 3), the rationale of the reversal in diastereofacial selectivity upon changing reductant from NaBH<sub>4</sub> to L-Selectride may be explained via a cyclic

**Table 3**The one-pot reductive amination of **1** with NaBH<sub>4</sub> and L-Selectride

Entry <sup>a</sup>	R	Reductant	Product	Yield <sup>b</sup> (%)	dr <sup>c</sup>
1	Ph ( <b>1a</b> )	NaBH <sub>4</sub>	<b>3a</b>	85	98:2
2	Ph ( <b>1a</b> )	L-Selectride	<b>4a</b>	78	98:2
3	4-MeOC <sub>6</sub> H <sub>4</sub> ( <b>1b</b> )	NaBH <sub>4</sub>	<b>3b</b>	78	95:5
4	4-MeOC <sub>6</sub> H <sub>4</sub> ( <b>1b</b> )	L-Selectride	<b>4b</b>	68	96:4
5	4-MeC <sub>6</sub> H <sub>4</sub> ( <b>1c</b> )	NaBH <sub>4</sub>	<b>3c</b>	72	97:3
6	4-MeC <sub>6</sub> H <sub>4</sub> ( <b>1c</b> )	L-Selectride	<b>4c</b>	70	96:4
7	4-BrC <sub>6</sub> H <sub>4</sub> ( <b>1d</b> )	NaBH <sub>4</sub>	<b>3d</b>	66	98:2
8	4-BrC <sub>6</sub> H <sub>4</sub> ( <b>1d</b> )	L-Selectride	<b>4d</b>	60	96:4
9	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>3</sub> ( <b>1e</b> )	NaBH <sub>4</sub>	<b>3e</b>	69	99:1
10	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>3</sub> ( <b>1e</b> )	L-Selectride	<b>4e</b>	68	99:1
11	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>1f</b> )	NaBH <sub>4</sub>	<b>3f</b>	79	99:1
12	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>1f</b> )	L-Selectride	<b>4f</b>	84	99:1

<sup>a</sup> All reductions were performed using 3.0 equiv of NaBH<sub>4</sub> or L-Selectride in Et<sub>2</sub>O at –78 °C for 3 h.<sup>b</sup> Isolated yield of **3a–f** or **4a–f** in two steps.<sup>c</sup> Diastereomeric ratios were determined by <sup>19</sup>F NMR of the crude reaction mixture.

transition state in the former reduction (NaBH<sub>4</sub>) and an open transition state in the latter case (L-Selectride) as previously proposed by Andersen and co-workers<sup>12c</sup> (Scheme 1). Although the steric hindrance of CF<sub>3</sub> group is similar to phenyl and between those of <sup>i</sup>Pr and <sup>t</sup>Bu,<sup>14</sup> high diastereoselectivities were observed in all the cases examined (Table 3). These results indicated that the electronic effect of the C–F bond in the CF<sub>3</sub> group might play an important role in achieving high diastereoselectivities in both reduction systems. The electrostatic repulsion<sup>15</sup> of the lone pairs between the sulfur atom and the fluorine atom makes CF<sub>3</sub> group be far away from the sulfur atoms in both systems. Therefore TS-A is more stable than TS-B in the six-membered chairlike models under the NaBH<sub>4</sub> reduction and TS-D is more favored than TS-C in the open transition state under the L-Selectride reduction. Hence, the six-membered transition state in which the sulfinyl oxygen participates in the delivery of hydride in the NaBH<sub>4</sub> system gives (*R*,*S*)-**3** as the major product, while an open transition state in the L-Selectride system affords the major product (*R*,*S*)-**4**.

**Scheme 1.** Proposed transition state for the one-pot reductive amination of **1**.

### 3. Conclusions

In summary, we have developed a facile protocol for the asymmetric synthesis of either stereoisomer of  $\alpha$ -trifluoromethylated amines. The diastereoselective reduction of  $\alpha$ -trifluoromethyl *N*-*tert*-butanesulfinyl ketoimines formed in situ from the corresponding

$\alpha$ -trifluoromethyl ketones and *N*-*tert*-butanesulfinamide took place readily to give either diastereomer of the *tert*-butanesulfinyl-protected trifluoromethylated amines in good yields and with excellent diastereoselectivities by simply choosing the appropriate reducing agents. Further studies on the application of this method in the preparation of CF<sub>3</sub>-containing natural product analogues are in progress in our laboratory.

## 4. Experimental section

### 4.1. General experimental methods

Unless otherwise mentioned, solvents, and reagents were purchased from commercial sources and used as received. Et<sub>2</sub>O and THF were freshly distilled over Na/benzophenone. Melting points were measured on a Melt-Temp apparatus and uncorrected. <sup>1</sup>H NMR spectra were recorded on Bruker AM-300 or Mercury 300 (300 MHz) spectrometers with TMS as internal standard. <sup>19</sup>F NMR spectra were recorded on Bruker AM-300 or Mercury 300 (282 MHz) spectrometers with CFCl<sub>3</sub> as an external standard. <sup>13</sup>C NMR spectra were recorded on Bruker 300 (75.5 MHz) or DPX-400 (100.7 MHz) spectrometers. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Mass spectra were taken on a HP5989A spectrometer. High-resolution mass data were obtained on a high-resolution mass spectrometer in the EI or MALDI mode.

### 4.2. General procedure for the one-pot reductive amination of **1** with NaBH<sub>4</sub>

Trifluoromethyl ketones **1** (0.4 mmol) were added to a solution of (*R*)-**2** (0.5 mmol) and Ti(O*i*-Pr)<sub>4</sub> (1.0 mmol) in Et<sub>2</sub>O (4 mL) at room temperature. The reaction mixture was stirred under reflux and the reaction was monitored by <sup>19</sup>F NMR. After the reaction was complete, the mixture was cooled to room temperature and then to –78 °C NaBH<sub>4</sub> (1.2 mmol) was added dropwise, and the resulted mixture was stirred at –78 °C for 3 h (monitored by TLC). After reaction, the mixture was quenched with saturated NaCl solution (5 mL) at –78 °C and then warmed to room temperature while being rapidly stirred. The resulting suspension was filtered through a plug of Celite, and the filter cake was washed with EtOAc. The filtrate was washed with saturated NaCl solution. The aqueous layer

was extracted with EtOAc (10 mL×3). The combined organic solution was dried over Na<sub>2</sub>SO<sub>4</sub>. After the removal of volatile solvents under vacuum, the crude product was further purified by column chromatography on silica gel to give product **3**.

**4.2.1. (R<sub>s</sub>,R)-N-(2,2,2-Trifluoro-1-phenylethyl)-tert-butanesulfonamide (3a).** Colorless viscous oil, yield 85%; FT-IR (film, cm<sup>-1</sup>):  $\nu$  3196, 2962, 2930, 2872, 1495, 1366, 1265, 1173, 1125, 1073, 693; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.46–7.40 (m, 5H), 4.94–4.81 (m, 1H), 3.90 (s, 1H), 1.24 (s, 9H); <sup>19</sup>F NMR (CDCl<sub>3</sub>):  $\delta$  -74.33 (d,  $J$ =7.1 Hz, 3F); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  131.67, 129.70, 129.26, 128.73, 124.47 (q,  $J$ =281.8 Hz), 60.52 (q,  $J$ =30.4 Hz), 56.35, 22.31; EIMS ( $m/z$ , %): 280 ( $M^+$ +1, 4.29), 223 ( $M^+$ -<sup>t</sup>Bu+1, 9.94), 159 (17.29), 57 (100.00); HRMS (EI) calcd for C<sub>12</sub>H<sub>16</sub>F<sub>3</sub>NOS [ $M^+$ ]: 279.0905; found: 279.0901.

**4.2.2. (R<sub>s</sub>,R)-N-(2,2,2-Trifluoro-1-(4-methoxyphenyl)ethyl)-tert-butanesulfonamide (3b).** Colorless viscous oil, yield 78%; FT-IR (film, cm<sup>-1</sup>):  $\nu$  3209, 2962, 2910, 2871, 1615, 1518, 1466, 1366, 1253, 1172, 1126, 1073, 829, 732, 585; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.29 (d,  $J$ =8.7 Hz, 2H), 6.86 (d,  $J$ =8.7 Hz, 2H), 4.83–4.68 (m, 1H), 3.84 (s, 1H), 3.75 (s, 3H), 1.24 (s, 9H); <sup>19</sup>F NMR (CDCl<sub>3</sub>):  $\delta$  -74.70 (d,  $J$ =5.6 Hz, 3F); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  160.57, 130.58, 123.32, 114.13, 124.55 (q,  $J$ =281.5 Hz), 59.85 (q,  $J$ =30.4 Hz), 56.16, 55.17, 22.31; EIMS ( $m/z$ , %): 310 ( $M^+$ +1, 5.26), 253 ( $M^+$ -<sup>t</sup>Bu+1, 6.01), 189 (100.00), 57 (84.83); HRMS (EI) calcd for C<sub>13</sub>H<sub>18</sub>F<sub>3</sub>NO<sub>2</sub>S [ $M^+$ ]: 309.1010; found: 309.1012.

**4.2.3. (R<sub>s</sub>,R)-N-(2,2,2-Trifluoro-1-*p*-tolylethyl)-tert-butanesulfonamide (3c).** Colorless viscous oil, yield 72%; FT-IR (film, cm<sup>-1</sup>):  $\nu$  3198, 2960, 2929, 2870, 1458, 1365, 1266, 1172, 1126, 1075, 811, 728, 670; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.32 (d,  $J$ =7.2 Hz, 2H), 7.22 (d,  $J$ =7.2 Hz, 2H), 4.80–4.85 (m, 1H), 3.84 (s, 1H), 2.38 (s, 3H), 1.24 (s, 9H); <sup>19</sup>F NMR (CDCl<sub>3</sub>):  $\delta$  -74.50 (d,  $J$ =7.1 Hz, 3F); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  139.55, 129.34, 129.05, 128.60, 124.48 (q,  $J$ =281.7 Hz), 60.19 (q,  $J$ =30.2 Hz), 56.16, 22.20, 21.05; EIMS ( $m/z$ , %): 294 ( $M^+$ +1, 1.52), 237 ( $M^+$ -<sup>t</sup>Bu+1, 12.76), 173 (36.95), 57 (100.00); HRMS (EI) calcd for C<sub>13</sub>H<sub>18</sub>F<sub>3</sub>NOS [ $M^+$ ]: 293.1061; found: 293.1073.

**4.2.4. (R<sub>s</sub>,R)-N-(1-(4-Bromophenyl)-2,2,2-trifluoroethyl)-tert-butanesulfonamide (3d).** Colorless viscous oil, yield 66%; FT-IR (film, cm<sup>-1</sup>):  $\nu$  3198, 2962, 2929, 2872, 1493, 1366, 1266, 1175, 1126, 1075, 728, 670; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.56 (d,  $J$ =7.5 Hz, 2H), 7.32 (d,  $J$ =7.5 Hz, 2H), 4.75–4.94 (m, 1H), 3.85 (s, 1H), 1.24 (s, 9H); <sup>19</sup>F NMR (CDCl<sub>3</sub>):  $\delta$  -74.41 (d,  $J$ =6.5 Hz, 3F); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  135.78, 132.06, 130.53, 127.59, 124.16 (q,  $J$ =281.6 Hz), 59.98 (q,  $J$ =31.0 Hz), 56.55, 22.24; EIMS ( $m/z$ , %): 357 ( $M^+$ , 2.40), 301 ( $M^+$ -<sup>t</sup>Bu+1, 1.82), 237 (10.46), 57 (100.00); HRMS (EI) calcd for C<sub>12</sub>H<sub>15</sub>BrF<sub>3</sub>NOS [ $M^+$ ]: 357.0010; found: 357.0017.

**4.2.5. (R<sub>s</sub>,R)-N-(1,1,1-Trifluoro-5-phenylpentan-2-yl)-tert-butanesulfonamide (3e).** White solid, yield 69%; mp 68–70 °C; FT-IR (KBr, cm<sup>-1</sup>):  $\nu$  3207, 3029, 2959, 2933, 2870, 1604, 1541, 1498, 1465, 1365, 1275, 1180, 1163, 1126, 1067, 749, 700; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.37–7.14 (m, 5H), 3.77–3.56 (m, 1H), 3.44 (d,  $J$ =9.0 Hz, 1H), 2.66 (t,  $J$ =4.5 Hz, 2H), 2.05–1.80 (m, 2H), 1.78–1.65 (m, 2H), 1.18 (s, 9H); <sup>19</sup>F NMR (CDCl<sub>3</sub>):  $\delta$  -75.13 (d,  $J$ =7.6 Hz, 3F); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  141.14, 128.36, 128.23, 125.97, 125.24 (q,  $J$ =282.8 Hz), 57.83 (q,  $J$ =29.0 Hz), 56.94, 35.15, 28.71, 26.85, 22.42; EIMS ( $m/z$ , %): 265 ( $M^+$ -<sup>t</sup>Bu+1, 11.18), 217 (2.68), 57 (100.00); HRMS (EI) calcd for C<sub>11</sub>H<sub>14</sub>F<sub>3</sub>NOS [ $M^+$ -<sup>t</sup>Bu+1]: 265.0748; found: 265.0755.

**4.2.6. (R<sub>s</sub>,R)-N-(1,1,1-Trifluorodecan-2-yl)-tert-butanesulfonamide (3f).** Colorless viscous oil, yield 79%; FT-IR (film, cm<sup>-1</sup>):  $\nu$  3297, 2958, 2928, 2859, 1468, 1366, 1276, 1168, 1133, 1112, 1066, 940, 885, 847, 795, 693, 580; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.72–3.55 (m, 1H), 3.43 (s, 1H), 1.90–1.47 (m, 4H), 1.37–1.26 (m, 10H), 1.25 (s, 9H), 0.88 (t,  $J$ =5.7 Hz, 3H); <sup>19</sup>F NMR (CDCl<sub>3</sub>):  $\delta$  -75.26 (d,  $J$ =6.5 Hz, 3F); <sup>13</sup>C NMR

(CDCl<sub>3</sub>):  $\delta$  125.30 (q,  $J$ =283.1 Hz), 57.99 (q,  $J$ =29.6 Hz), 56.90, 31.65, 29.12, 29.03, 28.94, 25.18, 22.49, 22.40, 13.90; EIMS ( $m/z$ , %): 316 ( $M^+$ +1, 6.09) 259 ( $M^+$ -<sup>t</sup>Bu+1, 2.70), 57 (100.00); HRMS (EI) calcd for C<sub>14</sub>H<sub>28</sub>F<sub>3</sub>NOS [ $M^+$ ]: 315.1844; found: 315.1833.

### 4.3. General procedure for the one-pot reductive amination of **1** with L-Selectride

Trifluoromethyl ketones **1** (0.4 mmol) were added to a solution of (*R*)-**2** (0.5 mmol) and Ti(Oi-Pr)<sub>4</sub> (1.0 mmol) in Et<sub>2</sub>O (4 mL) at room temperature. The reaction mixture was stirred under reflux and the reaction was monitored by <sup>19</sup>F NMR. After the reaction was completed, the mixture was cooled to room temperature and then to -78 °C. A solution of L-Selectride (1.2 mL, 1.2 mmol, 1.0 M solution in THF) was added slowly, and the resulted mixture was stirred at -78 °C for 3 h (monitored by TLC). After reaction, the mixture was quenched with saturated NaCl solution (5 mL) at -78 °C and then warmed to room temperature while being rapidly stirred. The resulting suspension was filtered through a plug of Celite, and the filter cake was washed with EtOAc. The filtrate was washed with saturated NaCl solution. The aqueous layer was extracted with EtOAc (10 mL×3). The combined organic solution was dried over Na<sub>2</sub>SO<sub>4</sub>. After the removal of volatile solvents under vacuum, the crude product was further purified by column chromatography on silica gel to give product **4**.

**4.3.1. (R<sub>s</sub>,S)-N-(2,2,2-Trifluoro-1-phenylethyl)-tert-butanesulfonamide (4a)**<sup>3a</sup>. White solid, yield 78%; mp 139–141 °C; FT-IR (KBr, cm<sup>-1</sup>):  $\nu$  2995, 2964, 1498, 1460, 1365, 1265, 1155, 1123, 1058, 1014, 930, 761, 702; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.47–7.36 (m, 5H), 4.90–4.76 (m, 1H), 3.70 (s, 1H), 1.24 (s, 9H); <sup>19</sup>F NMR (CDCl<sub>3</sub>):  $\delta$  -73.29 (d,  $J$ =7.1 Hz, 3F); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  133.68, 129.70, 129.12, 127.90, 124.58 (q,  $J$ =281.1 Hz), 61.35 (q,  $J$ =30.9 Hz), 58.89, 22.28; EIMS ( $m/z$ , %): 223 ( $M^+$ -<sup>t</sup>Bu+1, 7.80), 159 (13.71), 57 (100.00); HRMS (EI) calcd for C<sub>8</sub>H<sub>7</sub>F<sub>3</sub>NOS [ $M^+$ -<sup>t</sup>Bu]: 222.02000; found: 222.0193.

**4.3.2. (R<sub>s</sub>,S)-N-(2,2,2-Trifluoro-1-(4-methoxyphenyl)ethyl)-tert-butanesulfonamide (4b).** White solid, yield 68%; mp 164–167 °C; FT-IR (KBr, cm<sup>-1</sup>):  $\nu$  3247, 3116, 2989, 2966, 2906, 1616, 1519, 1467, 1365, 1263, 1183, 1121, 1058, 812, 711, 528; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.28 (d,  $J$ =8.1 Hz, 2H), 6.85 (d,  $J$ =8.1 Hz, 2H), 4.88–4.64 (m, 1H), 3.54 (s, 1H), 3.76 (s, 3H), 1.18 (s, 9H); <sup>19</sup>F NMR (CDCl<sub>3</sub>):  $\delta$  -73.52 (d,  $J$ =7.3 Hz, 3F); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  160.40, 129.20, 125.78, 114.54, 124.69 (q,  $J$ =281.4 Hz), 60.84 (q,  $J$ =30.9 Hz), 56.84, 55.29, 22.31; EIMS ( $m/z$ , %): 310 ( $M^+$ +1, 0.78), 253 ( $M^+$ -<sup>t</sup>Bu+1, 3.13), 189 (51.20), 57 (100.00); HRMS (EI) calcd for C<sub>13</sub>H<sub>18</sub>F<sub>3</sub>NO<sub>2</sub>S [ $M^+$ ]: 309.1010; found: 309.1013.

**4.3.3. (R<sub>s</sub>,S)-N-(2,2,2-Trifluoro-1-*p*-tolylethyl)-tert-butanesulfonamide (4c).** White solid, yield 70%; mp 174–176 °C; FT-IR (KBr, cm<sup>-1</sup>):  $\nu$  3198, 2971, 2927, 1517, 1458, 1365, 1268, 1156, 1124, 1064, 806, 724, 547; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.31 (d,  $J$ =8.1 Hz, 2H), 7.10 (d,  $J$ =8.1 Hz, 2H), 4.95–4.76 (m, 1H), 3.69 (s, 1H), 2.35 (s, 3H), 1.26 (s, 9H); <sup>19</sup>F NMR (CDCl<sub>3</sub>):  $\delta$  -73.38 (d,  $J$ =6.8 Hz, 3F); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  139.56, 130.78, 129.83, 127.78, 124.67 (q,  $J$ =281.6 Hz), 61.16 (q,  $J$ =30.2 Hz), 56.88, 22.32, 21.13; EIMS ( $m/z$ , %): 237 ( $M^+$ -<sup>t</sup>Bu+1, 7.44), 173 (26.30), 57 (100.00); HRMS (EI) calcd for C<sub>9</sub>H<sub>9</sub>F<sub>3</sub>NOS [ $M^+$ -<sup>t</sup>Bu]: 236.0357; found: 236.0365.

**4.3.4. (R<sub>s</sub>,S)-N-(1-(4-Bromophenyl)-2,2,2-trifluoroethyl)-tert-butanesulfonamide (4d)**<sup>3a</sup>. White solid, yield 60%; mp 164–167 °C; FT-IR (KBr, cm<sup>-1</sup>):  $\nu$  2968, 2928, 1493, 1365, 1265, 1161, 1123, 1058, 1014, 917, 811, 728; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.56 (d,  $J$ =7.5 Hz, 2H), 7.32 (d,  $J$ =7.5 Hz, 2H), 4.88–4.72 (m, 1H), 3.56 (s, 1H), 1.24 (s, 9H); <sup>19</sup>F NMR (CDCl<sub>3</sub>):  $\delta$  -73.95 (d,  $J$ =7.1 Hz, 3F); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  135.63, 132.35, 131.54, 127.54, 123.96 (q,  $J$ =281.1 Hz), 61.35 (q,  $J$ =30.9 Hz), 57.25, 22.17; EIMS ( $m/z$ , %): 301 ( $M^+$ -<sup>t</sup>Bu+1, 0.66), 237 (4.07), 57



(100.00); HRMS (EI) calcd for  $C_8H_6BrF_3NOS$  [ $M^+ - ^tBu$ ]: 299.9306; found: 299.9304.

**4.3.5. (*Rs,S*)-*N*-(1,1,1-Trifluoro-5-phenylpentan-2-yl)-*tert*-butanesulfonamide (4e).** White solid, yield 68%; mp 74–76 °C; FT-IR (KBr,  $cm^{-1}$ ):  $\nu$  3219, 3031, 2962, 2871, 1605, 1498, 1456, 1365, 1275, 1180, 1163, 1126, 1058, 750, 696;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  7.37–7.14 (m, 5H), 3.77–3.56 (m, 1H), 3.07 (s, 1H), 2.80–2.55 (m, 2H), 2.10–1.72 (m, 2H), 1.69–1.44 (m, 2H), 1.23 (s, 9H);  $^{19}F$  NMR ( $CDCl_3$ ):  $\delta$  –75.83 (d,  $J=7.2$  Hz, 3F);  $^{13}C$  NMR ( $CDCl_3$ ):  $\delta$  141.03, 128.36, 128.33, 125.89, 125.26 (q,  $J=288.8$  Hz), 58.56 (q,  $J=29.6$  Hz), 56.65, 34.93, 28.77, 26.30, 22.28; EIMS ( $m/z$ , %): 322 ( $M^+ + 1$ , 0.75), 265 ( $M^+ - ^tBu + 1$ , 14.95), 217 (3.25), 57 (100); HRMS (EI) calcd for  $C_{11}H_{14}F_3NOS$  [ $M^+ - ^tBu + 1$ ]: 265.0748; found: 265.0760.

**4.3.6. (*Rs,S*)-*N*-(1,1,1-Trifluorodecan-2-yl)-*tert*-butanesulfonamide (4f).** Colorless viscous oil, yield 84%; FT-IR (film,  $cm^{-1}$ ):  $\nu$  3209, 2958, 2929, 2860, 1495, 1366, 1276, 1168, 1133, 1111, 1046, 887, 723, 697;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  3.72–3.59 (m, 1H), 3.08 (d,  $J=7.2$  Hz, 1H), 1.67–1.40 (m, 4H), 1.36–1.26 (m, 10H), 1.24 (s, 9H), 0.88 (t,  $J=5.7$  Hz, 3H);  $^{19}F$  NMR ( $CDCl_3$ ):  $\delta$  –75.94 (d,  $J=7.1$  Hz, 3F);  $^{13}C$  NMR ( $CDCl_3$ ):  $\delta$  124.36 (q,  $J=281.1$  Hz), 58.75 (q,  $J=30.2$  Hz), 56.70, 31.74, 29.56, 29.14, 28.05, 24.87, 22.55, 22.33, 13.98; EIMS ( $m/z$ , %): 316 ( $M^+ + 1$ , 1.22), 259 ( $M^+ - ^tBu + 1$ , 4.02), 57 (100.00); HRMS (EI) calcd for  $C_{14}H_{28}F_3NOS$  [ $M^+$ ]: 315.1844; found: 315.1857.

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## Supplementary data

Supplementary data associated with this article can be found in the online version, at [doi:10.1016/j.tet.2010.09.047](https://doi.org/10.1016/j.tet.2010.09.047). These data include MOL files and InChIKeys of the most important compounds described in this article.

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