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Michael addition of *N*-sulfinyl metalloenamines to β-trifluoromethyl-α,β-unsaturated ester: an efficient access to chiral 4-trifluoromethyl-2-piperidones

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ABSTRACT

Michael addition of *N*-sulfinyl metalloenamines to β-trifluoromethyl-α,β-unsaturated ester was investigated. High diastereoselectivities and excellent yields were obtained. The conversion of addition products into 4-trifluoromethyl-2-piperidones asymmetrically, which involved a DIBAL-H reduction and the following cyclization, was illustrated. The absolute configuration of Michael addition products and 4-trifluoromethyl-2-piperidones were determined by X-ray crystallographic analysis and NOESY experiment, respectively. This method affords an efficient and asymmetric approach to a variety of chiral 4-trifluoromethyl-2-piperidones.

1. Introduction

Piperidones are of particular value due to their unique biochemical properties.[1] They also serve as precursors to the corresponding piperidine ring, which is a ubiquitous moiety in many alkaloid natural products and drug candidates.[2,3a] In this frame, considerable efforts have been devoted to the synthesis of novel substituted piperidones.[3] Owing to the special properties of fluorine, the introduction of trifluoromethyl group into piperidone ring may modify the chemical and biological properties of the target molecule.[4] Despite approaches to non-fluoro substituted piperidones have been well developed, methodologies to introduce trifluoromethyl group into piperidone rings were less explored relatively.[5]

As one of the most powerful chiral auxiliaries, *N*-*tert*-butanesulfinyl amine has been widely used in organic synthesis. Different from *N*-*tert*-butanesulfinyl aldimine, except for being a good electrophilic reagent, *N*-*tert*-butanesulfinyl ketimine can be deprotonated to form *N*-*tert*-sulfinyl metalloenamine and further react with electrophilic reagents. For example, *N*-*tert*-butanesulfinyl metalloenamine has been employed in the addition to aldehydes,[6a,b] trifluoromethyl ketones,[6c] and imines.[6d–f]

In 2005, Ellman et al. reported the conjugate addition of *N*-*tert*-butanesulfinyl metalloenamines to unsaturated ketones.[6g] Moderate yields were obtained when LDA (lithium diisopropylamide) was used as base and $ZnBr_2$ was utilized as additive to improve the results. Nevertheless, the substrates were largely limited due to the competitive deprotonation of the Michael acceptor.

β-Trifluoromethyl-α,β-unsaturated esters are easily available fluorine-containing compounds and have been used in the synthesis of many fluorine-containing compounds. Due to the electron withdrawing effect of trifluoromethyl group, the C=C bond is greatly activated and easy to undergo conjugate addition. On the other hand, deprotonation under base conditions could be avoided due to the trifluoromethyl substituent. Therefore, we envisioned that the conjugate addition reaction of *N*-*tert*-butanesulfinyl metalloenamine could be improved when β-trifluoromethyl-α,β-unsaturated esters are employed as acceptors. Herein we report a practical asymmetric carbon–carbon bond formation reaction of chiral *N*-((*R*)-*tert*-butanesulfinyl) ketimines and β-trifluoromethyl-α,β-unsaturated ester, whose adducts could be easily converted into 4-trifluoromethyl-2-piperidones asymmetrically in excellent yields.

2. Results and discussion

We embarked on our investigation by examining the reaction of *N*-((*R*)-*tert*-butanesulfinyl) ketimine **1a** and β-trifluoromethyl-α,β-unsaturated ester **2** (as shown in Table 1). When potassium *tert*-butoxide and sodium ethoxide were used as bases, Michael adducts were obtained in moderate yields but low diastereoseletivities (entries 1 and 2). However, the use of LHMDS (Lithium bis(trimethylsilyl)amide) and LDA greatly improved both yields and

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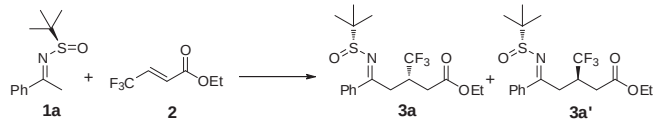
Table 1
Screening of reaction conditions



Entry	Solvent	Base (equiv)	Temperature (°C)	Time (h)	Yield[a] (%)	**3a**:**3a′**[b]
1	CH_3CN	^{t}BuOK (0.5)	−30	1	72	70:30
2	CH_3CN	EtONa (1.0)	−30	3	63	Nd[c]
3	THF	LHMDS (1.2)	−78	1	80	93:7
4	THF	LDA (1.2)	−78	1	93	95:5
5	THF	LDA (1.2)	0	1	91	92:8
6	Et_2O	LDA (1.2)	0	1	89	92:8
7	Toluene	LDA (1.2)	0	1	90	91:9

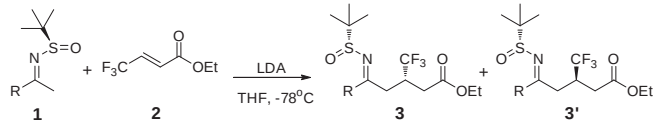
[a] Combined isolated yields of **3a** and **3a′**.
[b] dr values were determined by ^{19}F NMR.
[c] Not determined.

diastereoselectivities (entries 3 and 4). Scrutinizing reaction temperature and solvent (entries 5–7) found that excellent yield (93%) and diastereoselectivity (95:5) were obtained at −78 °C in THF while LDA was employed (entry 4). Even though it was reported that additives could improve the results through affecting the reaction intermediates in related reactions,[6] since excellent yields have been achieved, we did not try to add any additives to the reaction system but chose entry 4 as the model reaction condition.

Having established the optimized conditions of the reaction, we turned to investigate its generality by probing an array of structurally diverse *N*-(*tert*-butanesulfinyl) ketimines **1**. As outlined in Table 2, under similar conditions, a range of aryl and heterocyclic *N*-((*R*)-*tert*-butanesulfinyl) ketimines, including tolyl, methoxyphenyl, chlorophenyl, nitrophenyl, and morphlino substituted sulfinyl ketimines, were all uniformly transferred into the corresponding Michael adducts in high to quantitative yields with high dr values (entries 1–6). Additionally, this new protocol was also applied to alkyl substituted sulfinyl ketimines. The addition of the metalloenamine derived from **1h** exhibited excellent diastereoselectivity and afforded the desired products in good yield (entry 8). However, even in good yield, the addition of **1g** and **2** gave the corresponding adduct with low and converse diastereoselectivity (entry 7).

The steric repulsions between sulfinyl ketimine **1** and unsaturated ester **2** might play an important role in the diastereoselectivity.

Table 2
Michael addition of *N*-((*R*)-*tert*-butanesulfinyl) ketimines to 3-trifluoromethyl acrylic ester



Entry	R	Time (h)	Product	Yield[a] (%)	**3a**–**g**:**3a′**–**g′**[b]
1	Ph (**1a**)	1	**3a**+**3a′**	93	95:5
2	4-$CH_3C_6H_4$ (**1b**)	1	**3b**+**3b′**	96	96:4
3	4-$CH_3OC_6H_4$ (**1c**)	3	**3c**+**3c′**	90	>95:5
4	4-ClC_6H_4 (**1d**)	1	**3d**+**3d′**	96	96:4
5	4-$NO_2C_6H_4$ (**1e**)	1	**3e**+**3e′**	95	>95:5
6		1	**3f**+**3f′**	96	95:5
7	^{i}Pr (**1g**)	1	**3g**+**3g′**	91	43:57[c]
8	^{t}Bu (**1h**)	1	**3h**+**3h′**	90	>95:5

[a] Combined isolated yields of **3a**–**g** and **3a′**–**g′**.
[b] Determined by ^{19}F NMR.
[c] Determined by ^{1}H NMR.

A possible stereochemical model was proposed to explain the stereochemistry of the products. As shown in Figure 1, the reaction may proceed via four possible pathways: A and D, which provide the major diastereoisomer **3**, and B and C, which provide the minor diastereoisomer **3′**. Model A apparently is most favored due to lest stereo hindrances, while model B, C and D are disfavored owing to the repulsion between R and CF_3, or the hindrance between the bulky *tert*-butanesulfinyl group and the ester group. When R is isopropyl (**1g**), the stereo repulsion between R and CF_3 in model B could be greatly diminished. Therefore, **1g** may approach **2** via model A and B at the same time. Accordingly, **3g** and **3g′** could be obtained in a similar ratio, just as Table 2, entry 7 shown.

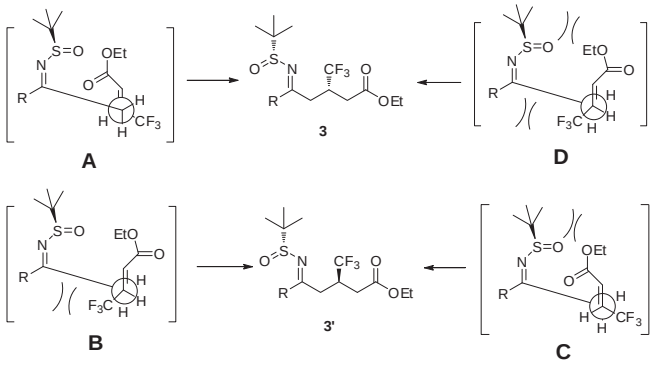


Figure 1.

The absolute configuration of **3f** was assigned to be (*Rs*,*S*) by X-ray crystallographic analysis (Fig. 2),[7] and the absolute configurations of **3a**–**e**, **3g**, **3h** were deduced to be (*Rs*,*S*) accordingly.

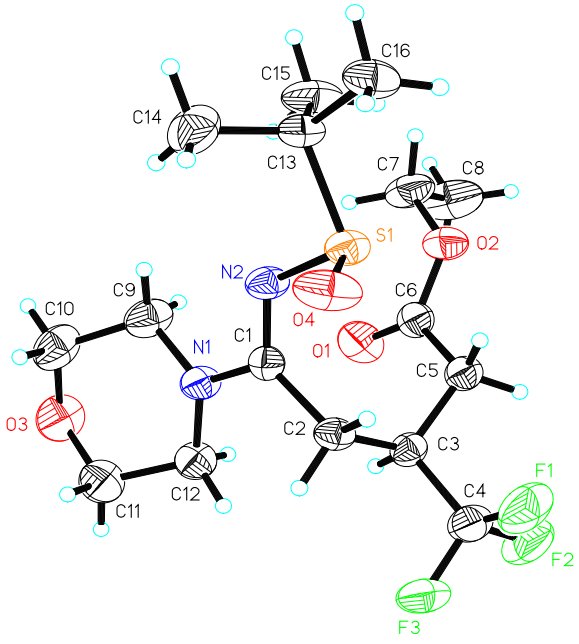
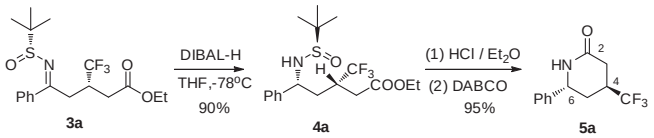


Figure 2. X-ray crystal structure of **3f**.

The above Michael adducts are versatile multifunctional fluorine containing building blocks. To demonstrate their synthetic applications, we next performed the transformation of **3a** to 4-trifluoromethyl-2-piperidone **5a** (Scheme 1). Reduction of **3a** with DIBAL-H at −78 °C gave **4a** in 90% yield with a dr value of >95:5.



Scheme 1. Synthesis of 4-trifluoromethyl-2-piperidone **5a**.

Then **4a** was hydrolyzed in the presence of hydrochloride ether solution at room temperature to remove *tert*-butanesulfinyl group. Without further purification, the crude hydrolysis product underwent cyclization easily under 1.0 equiv DABCO (1,4-diazabicyclo [2.2.2]octane) to give **5a** in satisfactory results (95% yield and >95:5 dr value).

The stereochemistry of **5a** was determined by NOESY experiment (Fig. 3). While compound (4*S*,5*S*,6*S*)-5-nitro-6-phenyl-4-trifluoromethyl-piperidin-2-one (**I**) showed strong correlation between H_a and H_b in NOESY experiment,[5a] no correlation between the corresponding hydrogens in **5a** (H_c and H_d) was detected, revealing that H_c and H_d were in the trans configuration. Since the absolute configuration of C4 in **5a** is *S* based on the previously established configuration in the Michael addition step, the absolute configuration of C6 in **5a** was assigned to be *R* accordingly. As far as **4a** was concerned, its absolute configuration was determined to be (3*S*,5*R*) according to **5a**.

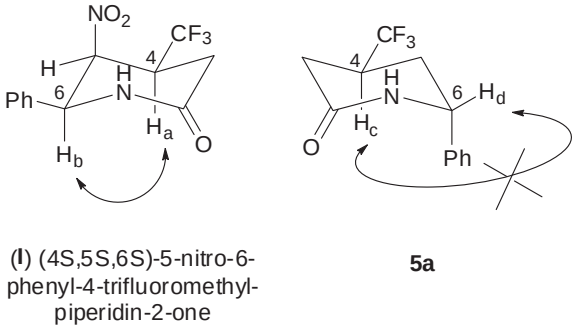


Figure 3. Absolute configuration assignment of **5a**.

3. Conclusion

In conclusion, we have developed a practical asymmetric carbon–carbon bond formation method, which provides an efficient stereoseletive approach to the synthesis of 4-trifluoromethyl-2-piperidones. In the presence of LDA, chiral *N*-((*R*)-*tert*-butanesulfinyl) ketimines reacted with β-trifluoromethyl-α,β-unsaturated ester readily to give the corresponding Michael addition adducts in excellent yields with high diastereoselectivites. Further transformation of the Michael adducts, which involves a DIBAL-H reduction and a base promoted cyclization, provides 4-trifluoromethyl-2-piperidone asymmetrically in excellent yield.

4. Experimental

4.1. General

All manipulations were performed under a nitrogen atmosphere using standard Schlenk techniques. Solvents were freshly distilled using general method to remove water. Column chromatography was performed on silica gel employing petroleum ether–ethyl acetate mixture as eluant. Compounds **1a**–**h**, and **2** were prepared following literature procedures.[8]

Melting points were taken on a Melt-Temp apparatus and uncorrected. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AM-300 spectrometer (300 MHz) with TMS as an internal standard. ^{19}F NMR spectra were taken on a Bruker AM-300 (282 MHz) spectrometer using $CFCl_3$ as an external standard. ^{13}C NMR spectra were recorded on Bruker DPX-400 (100.7 MHz) spectrometer. Mass spectra were obtained on a Shimadzu LCMS-2010EV spectrometer. High-resolution mass data were obtained on Bruker Daltonics, Inc. APEXIII 7.0 TESLA FTMS spectrometer. Elemental analyses were performed by this institute.

4.2. Typical procedure

4.2.1. Typical procedure for the Michael addition of N-sulfinyl metalloenamine. Into a dried 20 mL Schlenk flask containing a mixture of *N*-(*tert*-butanesulfinyl) ketimine (***R***)-**1a** (92 mg, 0.4 mmol) and **2** (33 mg, 0.2 mmol) in THF (5 mL) was added LDA (0.5 mmol, 0.5 mL, 1.0 M in THF) at −78 °C under N_2 atmosphere. After stirring for 1 h at this temperature, the reaction was quenched with saturated aqueous ammonium chloride (2.5 mL). After warming up to room temperature, the resulting mixture was extracted with dichloromethane (30 mL×3) and washed with saturated aqueous NaCl solution (20 mL×2). The combined organic layer was dried over anhydrous sodium sulfate. Filtration and evaporation of the volatile solvents under vacuum afforded the crude product, which was purified by flash column chromatography on silica gel (pet. ether/EtOAc=9/1) to give **3**.

*4.2.1.1. (S)-Ethyl 5-((R)-tert-butanesulfinylimino)-5-phenyl-3-(trifluoromethyl)pentanoate (**3a**).* Yellowish solid, yield 93%; mp 48–49 °C; $[\alpha]_D^{20}$ −23.4 (*c* 1.01, $CHCl_3$); FTIR (KBr, cm^{-1}): *ν* 2984, 1739, 1693, 1606, 1574, 1449, 1159, 1117, 1072, 1026; ^{1}H NMR ($CDCl_3$): *δ* 7.83–7.81 (m, 2H), 7.48–7.45 (m, 3H), 4.12 (q, *J*=6.9 Hz, 2H), 3.85–3.83 (m, 1H), 3.47–3.44 (m, 1H), 3.18–3.15 (m, 1H), 2.74–2.56 (m, 2H), 1.32 (s, 9H), 1.23 (t, *J*=6.9 Hz, 3H); ^{19}F NMR ($CDCl_3$): *δ* −71.85 (d, *J*=5.4 Hz, 3F); ESI MS (*m*/*z*): 392 (M^++1). Anal. Calcd for $C_{18}H_{24}F_3NO_3S$: C, 55.23; H, 6.18; N, 3.58. Found: C, 55.29; H, 6.18; N, 3.49.

*4.2.1.2. (S)-Ethyl 5-((R)-tert-butanesulfinylimino)-5-p-tolyl-3-(trifluoromethyl)pentanoate (**3b**).* Yellowish viscous oil, yield 96%; $[\alpha]_D^{20}$ −15.8 (*c* 1.18, $CHCl_3$); FTIR (KBr, cm^{-1}): *ν* 2983, 1740, 1596, 1566, 1449, 1269, 1158, 1116, 1074, 1017; ^{1}H NMR ($CDCl_3$): *δ* 7.73–7.71 (m, 2H), 7.27–7.24 (m, 2H), 4.11 (q, *J*=6.9 Hz, 2H), 3.80–3. 78 (m, 1H), 3.41–3.40 (m, 1H), 3.20–3.18 (m, 1H), 2.73–2.55 (m, 2H), 2.40 (s, 3H), 1.31 (s, 9H), 1.23 (t, *J*=6.9 Hz, 3H); ^{19}F NMR ($CDCl_3$): *δ* −71.20 (d, *J*=5.9 Hz, 3F); ESI MS (*m*/*z*): 406 (M^++1). Anal. Calcd for $C_{19}H_{26}F_3NO_3S$: C, 56.25; H, 6.46; N, 3.45. Found: C, 56.56; H, 6.60; N, 3.36.

*4.2.1.3. (S)-Ethyl 5-((R)-tert-butanesulfinylimino)-5-(4-methoxyphenyl)-3-(trifluoromethyl)pentanoate (**3c**).* Yellowish viscous oil, yield 90%; $[\alpha]_D^{20}$ −15.9 (*c* 0.88, $CHCl_3$); FTIR (KBr, cm^{-1}): *ν* 2987, 2237, 1740, 1613, 1438, 1372, 1248, 1141; ^{1}H NMR ($CDCl_3$): *δ* 7.83–7.81 (m, 2H), 6.97–6.94 (m, 2H), 4.11 (q, *J*=6.9 Hz, 2H), 3.86 (s, 3H), 3. 87–3.75 (m, 1H), 3.39–3.21 (m, 2H), 2.72–2.56 (m, 2H), 1.31 (s, 9H), 1.23 (t, *J*=6.9 Hz, 3H); ^{19}F NMR ($CDCl_3$): *δ* −71.88 (d, *J*=5.9 Hz, 3F); ESI MS (*m*/*z*): 422 (M^++1). Anal. Calcd for $C_{19}H_{26}F_3NO_4S$: C, 54.14; H, 6.22; N, 3.32. Found: C, 54.39; H, 6.16; N, 3.21.

*4.2.1.4. (S)-Ethyl 5-((R)-tert-butanesulfinylimino)-5-(4-chlorophenyl)-3-(trifluoromethyl)pentanoate (**3d**).* Yellowish viscous oil, yield 96%; $[\alpha]_D^{20}$ −3.7 (*c* 1.00, $CHCl_3$); FTIR (KBr, cm^{-1}): *ν* 2984, 1737, 1607, 1589, 1491, 1423, 1399, 1369, 1268, 1159, 1118, 1095, 1012; ^{1}H NMR ($CDCl_3$): *δ* 7.80–7.77 (m, 2H), 7.45–7.41 (m, 2H), 4.13 (q, *J*=6.9 Hz, 2H), 3.90–3.82 (m, 1H), 3.40–3.34 (m, 1H), 3.12–3.10 (m,

1H), 2.75–2.55 (m, 2H), 1.31 (s, 9H), 1.25 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 174.4, 170.6, 137.9, 135.8, 129.0, 125.6, 61.2, 58.3, 38.8 (m), 32.9, 30.2, 22.7, 14.0; ^{19}F NMR ($CDCl_3$): δ −71.09 (d, J=5.3 Hz, 3F); ESI MS (m/z): 426 (M^++1); HRMS calcd for $C_{18}H_{23}ClF_3NNaO_3S$ [M+Na^+]: 448.0932; Found: 448.0937.

*4.2.1.5. (S)-Ethyl 5-((R)-tert-butanesulfinylimino)-5-(4-nitrophenyl)-3-(trifluoromethyl)pentanoate (**3e**).* Yellowish viscous oil, yield 95%; $[\alpha]_D^{20}$ +28.9 (c 0.88, $CHCl_3$); FTIR (KBr, cm^{-1}): ν 2983, 2930, 1737, 1599, 1526, 1349, 1268, 1160, 1118; ^{1}H NMR ($CDCl_3$): δ 8.33–8.30 (m, 2H), 8.03–8.00 (m, 2H), 4.16 (q, J=6.6 Hz, 2H), 4.02–4.00 (m, 1H), 3.47–3.40 (m, 1H), 3.04–3.01 (m, 1H), 2.78–2.57 (m, 2H), 1.33 (s, 9H), 1.25 (t, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.5, 170.7, 149.4, 142.8, 128.5, 123.9, 61.4, 58.9, 38.7 (m), 32.8, 30.3, 22.8, 14.3; ^{19}F NMR ($CDCl_3$): δ −70.90 (d, J=5.3 Hz, 3F); ESI MS (m/z): 437 (M^++1); HRMS calcd for $C_{18}H_{23}F_3N_2NaO_5S$ [M+Na^+]: 459.1170. Found: 459.1180.

*4.2.1.6. (S)-Ethyl 5-((R)-tert-butanesulfinylimino)-5-morpholino-3-(trifluoromethyl)pentanoate (**3f**).* Colorless crystal, yield 96%; mp 82–83 °C; $[\alpha]_D^{20}$ −117.3 (c 0.95, $CHCl_3$); FTIR (KBr, cm^{-1}): ν 2982, 1737, 1540, 1481, 1359, 1301, 1256, 1207, 1113, 1057; ^{1}H NMR ($CDCl_3$): δ 4.13 (q, J=7.5 Hz, 2H), 3.77–3.68 (m, 5H), 3.57–3.39 (m, 3H), 3.18–3.16 (m, 1H), 2.90–2.83 (m, 1H), 2.70–2.62 (m, 1H), 1.43–1.33 (m, 1H), 1.26 (t, J=7.5 Hz, 3H), 1.19 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −72.03 (d, J=9.3 Hz, 3F); ESI MS (m/z): 401 (M^++1). Anal. Calcd for $C_{16}H_{27}F_3N_2O_4S$: C, 47.99; H, 6.80; N, 7.00. Found: C, 47.96; H, 6.67; N, 6.95.

*4.2.1.7. Ethyl 5-((R)-tert-butylsulfinylimino)-6-methyl-3-(trifluoromethyl)heptanoate (**3g** and **3g′**).* Yellow liquid, yield 91%; FTIR (KBr, cm^{-1}): ν 2976, 1741, 1625, 1365, 1265, 1165, 1115, 1077; ^{1}H NMR ($CDCl_3$): δ 4.15 (q, J=7.2 Hz, 1.14H), 3.86–3.65 (m, 0.57H), 3.47 (q, J=7.2 Hz, .86H), 3.35–3.09 (m, 0.57H), 3.03–2.87 (m, 0.43H), 2. 83–2.45 (m, 3.43H), 1.29–1.13 (m, 19H); ^{19}F NMR ($CDCl_3$): δ −71.4 (s, 1.29F), −71.6 (s, 1.71F); ESI MS (m/z): 358 (M^++1). Anal. Calcd for $C_{15}H_{26}F_3NO_3S$: C, 50.40; H, 7.33; N, 3.92. Found: C, 50.48; H, 7.35; N, 3.98.

*4.2.1.8. (S)-Ethyl 5-((R)-tert-butanesulfinylimino)-6,6-dimethyl-3-trifluoromethyl)heptanoate (**3h**).* Yellow liquid, yield 90%; $[\alpha]_D^{20}$ −100.1 (c 0.85, $CHCl_3$); FTIR (KBr, cm^{-1}): ν 2966, 2872, 1738, 1611, 1478, 1393, 1367, 1299, 1267, 1220, 1164, 1111, 1073, 1029; ^{1}H NMR ($CDCl_3$): δ 4.15 (q, J=6.9 Hz, 2H), 3.67–3.46 (m, 1H), 3.27–3.21 (m, 1H), 2.97–2.85 (m, 1H), 2.70–2.49 (m, 2H), 1.35–1.14 (m, 21H); ^{13}C NMR ($CDCl_3$): δ 187.1, 170.7, 127.1 (q, J=280.1 Hz), 61.1, 57.7, 44.0, 38.1 (q, 26.9 Hz), 33.0, 29.6, 28.5, 22.5, 14.0; ^{19}F NMR ($CDCl_3$): δ −71.72 (d, J=8.2 Hz, 3F); ESI MS (m/z): 372 (M^++1); HRMS calcd for $C_{16}H_{28}F_3NO_3S$ [M+H^+]: 372.1815. Found: 372.1810.

*4.2.2. Reduction of **3a**.* DIBAL-H (0.7 mL, 1.0 M in THF) was added to a solution of **3a** (90 mg, 0.23 mmol) in THF at −78 °C under N_2 atmosphere. After stirring for 1 h at this temperature, the reaction was quenched with saturated aqueous ammonium chloride (2.5 mL). The resulting mixture was then allowed to return to room temperature and aqueous hydrochloric acid (2.5 mL, 1.0 M) was added dropwise. The mixture was extracted with dichloromethane (30 mL×3) and washed with saturated aqueous NaCl solution (20 mL×2). The combined organic layer was dried over anhydrous sodium sulfate. Filtration and evaporation of the solvents afforded the crude product, which was purified by flash column chromatography on silica gel (pet. ether/EtOAc=3/1) to give **4a**.

*4.2.2.1. (3S,5R)-Ethyl 5-((R)-tert-sulfinylamido)-5-phenyl-3-(trifluoromethyl)pentanoate (**4a**).* Yellowish viscous oil, yield 90%; FTIR (KBr, cm^{-1}): ν 3191, 2982, 1740, 1655, 1456, 1366, 1269, 1158, 1118, 1029; ^{1}H NMR ($CDCl_3$): δ 7.35–7.26 (m, 5H), 4.50–4.45 (m, 1H), 4.17 (q, J=6.9 Hz, 2H), 3.78–3.75 (m, 1H), 2.83–2.81 (m, 1H), 2.67–2.60 (m, 1H), 2.43–2.35 (m, 1H), 2.16–2.07 (m, 1H), 2.01–1.94 (m, 1H), 1.29–1.23 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 170.8, 141.5, 129.0, 128.3, 126.9, 61.2, 56.9, 56.2, 36.4 (m), 33.4, 22.6, 14.1; ^{19}F NMR ($CDCl_3$): δ −71.70 (d, J=8.7 Hz, 3F); ESI MS (m/z): 394 (M^++1); HRMS calcd for $C_{18}H_{27}F_3NO_3S$ [M^++1]: 394.1658; Found: 394.1671.

*4.2.3. Synthesis of **5a**.* Into a solution of **4a** (30 mg, 0.08 mmol) in CH_3OH (2 mL) was added saturated HCl/Et_2O solution (2 mL) slowly at room temperature. After stirring for 0.5 h at room temperature, CH_2Cl_2 (30 mL) was added. The mixture was washed with aqueous sodium hydroxide (10 mL×3, 1 N). Concentrating the combined organic layer under vacuum afforded crude hydrolysis product. Without further purification, this crude product was dissolved into Et_2O (2 mL). DABCO (1,4-diazabicyclo[2.2.2]octane, 8.5 mg, 0.08 mmol) was added at room temperature. After stirring at this temperature for 1 h, the reaction mixture was concentrating under vacuum. Pure **5a** was obtained via flash column chromatography on silica gel (pet. ether/EtOAc=2/1) in the yield of 95%.

*4.2.3.1. (4S,6R)-6-Phenyl-4-(trifluoromethyl)piperidin-2-one (**5a**).* Colorless solid, yield 95%; mp 153–154 °C; $[\alpha]_D^{20}$ 64.1 (c 0.23, $CHCl_3$); FTIR (KBr, cm^{-1}): ν 3214, 2926, 1625, 1474, 1402, 1270, 1175, 1113, 1060; ^{1}H NMR ($CDCl_3$): δ 7.41–7.26 (m, 5H), 5.96 (br, 1H), 4.56–4.51 (m, 1H), 2.76–2.71 (m, 2H), 2.54–2.43 (m, 1H), 2.34–2.29 (m, 1H), 1.78–1.64 (m, 1H); ^{19}F NMR ($CDCl_3$): δ −74.04 (d, J=8.7 Hz, 3F); ESI MS (m/z): 244 (M^++1). Anal. Calcd for $C_{12}H_{12}F_3NO$: C, 59.26; H, 4.97; N, 5.76. Found: C, 59.21; H, 5.17; N, 5.65.

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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.2010.06.047.

References and notes

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7. Crystal data: $C_{16}H_{27}F_3N_2O_4S$; M=400.46; Tetragonal, $P4(1)$; a=13.5525(11) Å, b=13.5525(11) Å, c=11.1134(13) Å; α=90.00, β=90.00, γ=90.00, V=2041.2(3) Å^3; Z=4; 4545 reflections; R_{int}=0.0887; R_1=0.0511 and wR_2=0.1047. Crystallographic data for the structures of **3f** reported in this paper, have been deposited with the Cambridge Crystallographic Data Centre (CCDC 756866). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, United Kingdom (Fax: 44 1223 336033 or email: deposit@ccdc.cam.uk).
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