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PAPER

A facile process for the asymmetric synthesis of β-trifluoromethylated β-amino ketones *via* addition of ketone enolates to sulfinylimine†‡

Haibo Mei,[a] Yiwen Xiong,[a] Jianlin Han*[a] and Yi Pan*[a,b]

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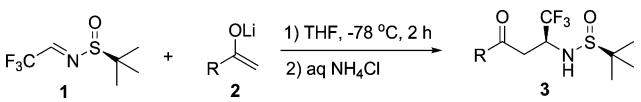
An efficient method for the asymmetric synthesis of β-trifluoromethylated β-amino ketones *via* addition of ketone-derivative enolates to trifluoromethylated sulfinylimine has been developed, with good chemical yields and excellent diastereoselectivities. This practical method was also proved to be suitable for large-scale preparation.

Introduction

β-Amino ketones represent an important class of compounds in modern organic and medicinal chemistry because of their diverse biological properties.[1] They are also useful building blocks for the synthesis of various pharmaceuticals and biologically active natural products.[2] They can be converted into the corresponding γ-amino alcohols that are also biologically important molecules and can serve as chiral ligands for asymmetric synthesis.[3] The fluorinated molecules often show some significant changes in their chemical, physical and biological properties.[4] Consequently, fluorinated β-amino carbonyl compounds, especially the β-trifluoromethylated β-amino ketones have been attracting many attentions in the field of biochemistry and pharmacology.[5,6] However, there were only a few methods reported for the synthesis of chiral β-trifluoromethylated β-amino ketones until now,[7–9] which were focused on the organocatalytic asymmetric synthesis.[8] So the development of efficient and facile methods for synthesis of chiral β-trifluoromethylated β-amino ketones becomes great challenges now.

Mannich-type reaction of imines or their precursors have been the most widespread synthetic routes to β-amino carbonyl compounds.[10] Besides, *N-tert*-butanesulfinamides have been proved to be highly efficient chiral auxiliaries in the synthesis of various active chiral amines by the virtue of their excellent diastereocontrol and easy cleavage.[11] Herein, we reported, for the first time, an auxiliary-based process for the asymmetric synthesis of chiral β-trifluoromethylated β-amino ketones, which proceeds through the addition of ketone enolates to trifluoromethylated *N-tert*-butylsulfinylimine with good yields and excellent diastereoselectivities (Scheme 1).



Scheme 1 Addition of ketone-derivative enolates to sulfinylimine.

Results and discussion

Base on the previous studies on the synthesis of β-amino ketones,[10] and the reported examples with *N-tert*-butylsulfinylimine as starting material,[6b,6c,12] the initial reaction condition was focused on the using of sulfinylimine **1** with 1.5 equiv of acetophenone in the presence of LDA with THF as solvent at −78 °C. The reaction proceeded smoothly, affording the desired β-trifluoromethyl-β-amino ketone **3a** in 72% yield with 96 : 4 dr after 1 h (entry 1, Table 1). Further optimizing the reaction conditions was then carried out to improve both the yields and the diastereoselectivities of the reaction. The screening of the reaction time demonstrated that this transformation could complete in 2 h (entry 2), and extending reaction time resulted in a decrease in both yield and diastereoselectivity (entry 3). Temperature was founded to be crucial for this reaction. Elevating reaction temperature brought an obvious increase in the yields (up to 90%), but caused dramatic decrease in diastereoselectivities (entries 4–6). The investigation of various solvents was shown in entries 7–10, and THF was found to be the best choice. Notably, the best diastereoselectivity (>99 : 1 dr) was obtained with CH_2Cl_2 as solvent, but along with really lower yield (43%, entry 8). Furthermore, the loading amount of acetophenone enolate **2a** was examined and it was found that the use of 1.7 equiv of **2a** gave the highest yield and excellent diastereoselectivity (84% yield and 99 : 1 dr, entry 12).

After obtaining the optimized reaction conditions, varieties of ketones were used as substrates to investigate the scope of the current system (Table 2). As shown in Table 2, almost all of the tested substrates worked well in this reaction. Generally, the

[a]*School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, 210093, China. E-mail: hanjl@nju.edu.cn; Fax: +86-25-83592846; Tel: +86-25-83593153*
[b]*State of Key Laboratory of Coordination, Nanjing University, Nanjing, 210093, China. E-mail: yipan@nju.edu.cn*

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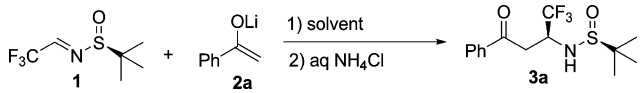
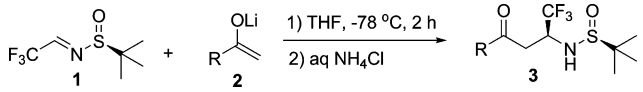
Table 1 Optimization of reaction conditions[a]



Entry	**2a** (equiv)	Solvent	*T*/°C	Time (h)	Yield (%)[b]	dr[c]
1	1.5	THF	−78	1	72	96 : 4
2	1.5	THF	−78	2	79	95 : 5
3	1.5	THF	−78	3	74	91 : 9
4	1.5	THF	−41	2	76	83 : 17
5	1.5	THF	−22	2	90	89 : 11
6	1.5	THF	0	2	83	83 : 17
7	1.5	Toluene	−78	2	74	83 : 17
8	1.5	CH_2Cl_2	−78	2	43	>99 : 1
9	1.5	Hexane	−78	2	57	84 : 16
10	1.5	Et_2O	−78	2	70	92 : 8
11	1.1	THF	−78	2	67	98 : 2
12	1.7	THF	−78	2	84	99 : 1

[a] Reaction conditions: sulfinylimine (0.5 mmol), LDA (1.1 equiv of ketone), solvent (5 mL). [b] Isolated yields. [c] Determined by ^{1}H NMR analysis.

Table 2 Scope of ketones for the asymmetric addition[a]

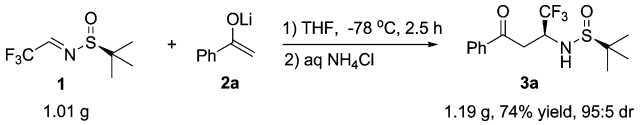


Entry	*R*	Product	Yield (%)[b]	dr[c]
1	Ph	**3a**	84	99 : 1
2	4-MeC_6H_4	**3b**	81	>99 : 1
3	4-$MeOC_6H_4$	**3c**	84	>99 : 1
4	4-FC_6H_4	**3d**	74	>99 : 1
5	4-ClC_6H_4	**3e**	70	86 : 14
6	4-BrC_6H_4	**3f**	66	74 : 26
7	4-PhC_6H_4	**3g**	73	97 : 3
8	4-EtC_6H_4	**3h**	68	97 : 3
9	4-$EtOC_6H_4$	**3i**	87	>99 : 1
10	2-Naphthyl	**3j**	76	88 : 12
11	2-Furyl	**3k**	42	>99 : 1
12	*t*-Bu	**3l**	61	93 : 7

[a] Reaction conditions: sulfinylimine (0.5 mmol), ketone (0.85 mmol), LDA (0.94 mmol), solvent (5 mL). [b] Isolated yields. [c] Determined by ^{1}H NMR analysis.

ketones with electron-donating substituent on the aromatic ring could participate better in the reaction, resulting in the desired products with higher yields (81%–87%) and diastereoselectivities (>99 : 1 dr) (entries 2, 3 and 9). However, the substrates with electron-withdrawing substituent on the aromatic ring usually gave slightly lower yields and diastereoselectivities (entries 5–7), except for the case of *p*-fluoro acetophenone enolate **2d** (entry 4). Notably, 2-naphthyl ketone enolate **2j** was also well tolerated in this reaction with good yield (76%) and good diastereoselectivity (88 : 12) (entry 10). More significantly, the reaction from the substrate with heteroaromatic ring also proceeded well, affording the desired product with high diastereoselectivity (>99 : 1) (entry 11). It was found that the aliphatic ketone also worked well as substrate in the current system (entry 12),[13] and the reaction from pinacolone gave 61% chemical yield and good diastereoselectivity.

The current system was found to tolerate broad scope of the ketone substrates. Furthermore, it has also been proved to be efficient on large scale preparation (gram-scale or greater). Good yield (74%) and excellent diastereoselectivity (95 : 5 dr) were obtained, even the loading amount of sulfinylimine **1** was increased from 0.10 g to 1.01 g in the reaction (Scheme 2). To our delight, only slight decrease in the yield and diastereoselectivity were detected, comparing to the 0.10 g scale reaction. This result allows the large scale preparation of chiral β-trifluoromethylated β-amino ketones.[14]



Scheme 2 Large scale application of the reaction.

The structure of these β-trifluoromethylated β-amino ketones has been confirmed by the X-ray diffraction analysis of **3a** (Fig. 1). As shown in Fig. 1, the absolute configuration of the newly generated chiral center in this process is *S*. The absolute configurations of other corresponding products were assigned by analogy.

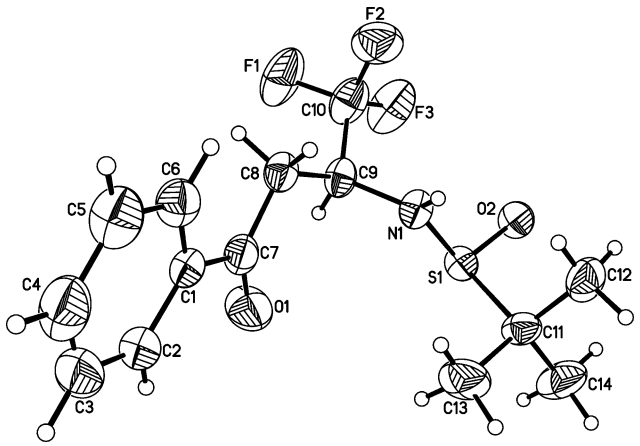


Fig. 1 ORTEP diagram showing of compound **3a**.

Based on the absolute configuration detected by X-ray diffraction analysis, the asymmetric addition of ketone enolates was suggested to proceed *via* a non-chelated transition state model.[15] In this model, enolates preferably added to the imine from the less hindered face to afford (S_s,*S*)-**3a** as major diastereomer (Fig. 2).

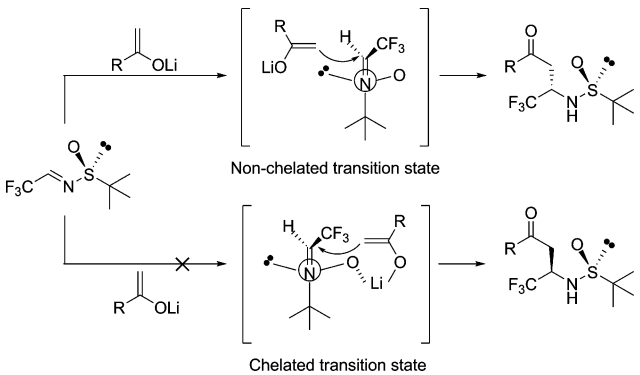
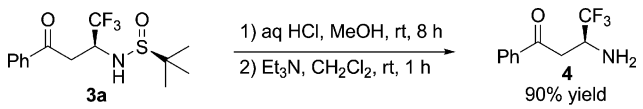


Fig. 2 Proposed mechanism for the asymmetric addition.

The *N*-*tert*-butylsulfinyl group can serve as not only an efficient chiral auxiliary for the asymmetric synthesis of β-amino ketones, but also an amine protecting group.[11] It can be readily cleaved by treatment with aqueous HCl in methanol under mild condition (Scheme 3).[12a,16] Free β-trifluoromethylated β-amino ketone **4** was obtained in high isolated yield of 90%. The resulting chirality of the β-carbon center was proved again to be *S* by comparison of the optical rotation with the literature value.[7]



Scheme 3 Conversion of **3a** to free β-trifluoromethylated β-amino ketone.

Experimental section

General information

All imine addition reactions were performed in oven-dried vials under N_2 atmosphere. Solvent THF was dried and distilled prior to use. Sulfinylimine **1** was obtained from TOSOH F-TECH, INC. LDA (2 M in THF) was from Aldrich. These and other chemicals were used as obtained from commercial sources without further purification. Flash chromatography was performed using silica gel 60 (200–300 mesh). Thin layer chromatography was carried out on silica gel 60 F-254 TLC plates of 20 cm × 20 cm. Melting points are uncorrected. IR spectra were collected on Bruker Vector 22 in KBr pellets. Values of optical rotation were measured on Rudolph Automatic Polarimeter A21101. ^{1}H and ^{13}C NMR (TMS used as internal standard) spectra were recorded with a Bruker ARX 300 spectrometer and a Bruker ARX 500 spectrometer.^{19}F NMR spectra (referenced to external CF_3COOH) were recorded wirh a Bruker ARX 400 spectrometer. High resolution mass spectra for all the new compounds were done by Micromass Q-Tof instrument (ESI‡).

Typical procedure for asymmetric addition of sulfinylimine

Into an oven-dried reaction vial flushed with N_2 were taken ketone (0.85 mmol) and anhydrous THF (3.0 mL). The reaction vial was cooled to −78 °C and LDA (2 M in THF, 0.47 mL) was added dropwise with stirring. After 40 min at −78 °C, sulfinylimine **1** (0.5 mmol) dissolved in anhydrous THF (2.0 mL) was added dropwise. Stirring was continued at −78 °C for 2 h, then the reaction was quenched with saturated NH_4Cl (3.0 mL), followed by H_2O (5.0 mL) and the mixture was brought to room temperature. The organic layer was taken and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was removed to give the crude product, which was purified by TLC plate (hexane–EtOAc, 2 : 1).

(*S*)-2-Methyl-*N*-((*S*)-1,1,1-trifluoro-4-oxo-4-phenylbutan-2-yl)propane-2-sulfinamide (3a)

Colorless solid, yield 84%, mp 146–148 °C, $[\alpha]_D^{25}$ +47.2 (*c* 0.46, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.93–7.97 (m, 2 H), 7.56–7.62 (m, 1 H), 7.45–7.50 (m, 2 H), 4.49–4.63 (m, 1 H), 4.25 (d, *J* = 8.7 Hz, 1 H), 3.75 (dd, *J* = 9.6, 17.7 Hz, 1 H), 3.31 (dd, *J* = 3.3, 17.7 Hz, 1 H), 1.15 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 194.9, 136.2, 133.8, 128.8, 128.2, 123.5 (q, *J* = 280.0 Hz), 56.9, 53.8 (q, *J* = 30.2 Hz), 38.0, 22.3. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −74.5. IR (KBr): ν = 3277, 2966, 2925, 1685, 1292, 1269, 1168, 1121, 1060, 690, 753 cm^{-1}. HRMS [M+Na$^+$]: calcd for $C_{14}H_{18}O_2SNF_3Na$: 344.0903, found: 344.0893.

(*S*)-2-Methyl-*N*-((*S*)-1,1,1-trifluoro-4-oxo-4-p-tolylbutan-2-yl)propane-2-sulfinamide (3b)

Colorless solid, yield 81%, mp 148–150 °C, $[\alpha]_D^{25}$ +36.1 (*c* 0.17, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.87 (d, *J* = 6.9 Hz, 2 H), 7.30 (d, *J* = 5.7 Hz, 2 H), 4.51–4.60 (m, 1 H), 4.07 (d, *J* = 26.7 Hz, 1 H), 3.71 (dd, *J* = 9.3, 17.4 Hz, 1 H), 3.29 (dd, *J* = 2.7, 17.7 Hz, 1 H), 2.43 (d, *J* = 1.2 Hz, 3 H), 1.16 (d, *J* = 2.4 Hz, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 194.4, 144.8, 133.8, 129.5, 128.3, 123.5 (q, *J* = 280.0 Hz), 56.9, 53.9 (q, *J* = 30.8 Hz), 37.9, 22.3, 21.7. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −74.5. IR (KBr): ν = 3265, 2962, 2924, 1683, 1610, 1345, 1292, 1270, 1167, 1118, 1060, 804 cm^{-1}. HRMS [M+Na$^+$]: calcd for $C_{15}H_{20}O_2SNF_3Na$: 358.1059, found: 358.1048.

(*S*)-2-Methyl-*N*-((*S*)-1,1,1-trifluoro-4-(4-methoxyphenyl)-4-oxobutan-2-yl)propane-2-sulfinamide (3c)

White solid, yield 84%, mp 99–100 °C, $[\alpha]_D^{25}$ +87.5 (*c* 0.17, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.92–7.97 (m, 2 H), 6.94–6.98 (m, 2 H), 4.50–4.60 (m, 1 H), 4.12 (d, *J* = 6.3 Hz, 1 H), 3.88 (s, 3 H), 3.69 (dd, *J* = 9.6, 17.4 Hz, 1 H), 3.26 (dd, *J* = 3.3, 17.4 Hz, 1 H), 1.16 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 193.3, 164.1, 130.5, 129.3, 123.5 (q, *J* = 279.6 Hz), 114.0, 56.9, 55.5, 54.0 (q, *J* = 30.9 Hz), 37.6, 22.3. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −74.5. IR (KBr): ν = 3265, 2963, 2927, 1678, 1603, 1369, 1291, 1267, 1168, 1121, 1058, 820 cm^{-1}. HRMS [M+Na$^+$]: calcd for $C_{15}H_{20}O_3SNF_3Na$: 374.1008, found: 374.1004.

(*S*)-2-Methyl-*N*-((*S*)-1,1,1-trifluoro-4-(4-fluorophenyl)-4-oxobutan-2-yl)propane-2-sulfinamide (3d)

Colorless solid, yield 74%, mp 149–151 °C, $[\alpha]_D^{25}$ +99.0 (*c* 0.19, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.96–8.03 (m, 2 H), 7.11–7.19 (m, 2 H), 4.49–4.59 (m, 1 H), 4.15 (d, *J* = 7.5 Hz, 1 H), 3.76 (dd, *J* = 9.3, 17.7 Hz, 1 H), 3.29 (dd, *J* = 3.3, 17.7 Hz, 1 H), 1.16 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 193.3, 167.8, 164.5, 131.0 (d, *J* = 9.5 Hz), 123.4 (q, *J* = 280.1 Hz), 116.1 (d, *J* = 21.9 Hz), 56.9, 53.6 (q, *J* = 30.5 Hz), 37.9, 22.3. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −74.4, −103.8. IR (KBr): ν = 3271, 2966, 2926, 2871, 1687, 1599, 1293, 1271, 1233, 1169, 1121, 1061, 821 cm^{-1}. HRMS [M+Na$^+$]: calcd for $C_{14}H_{17}O_2SNF_4Na$: 362.0808, found: 362.0810.

(*S*)-*N*-((*S*)-4-(4-Chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (3e)

Colorless solid, yield 70%, mp 147–148 °C, $[\alpha]_D^{25}$ +95.8 (*c* 0.14, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.89–7.93 (m, 2 H), 7.44–7.49 (m, 2 H), 4.49–4.59 (m, 1 H), 4.06 (d, *J* = 8.4 Hz, 1 H), 3.77 (dd, *J* = 9.9, 17.7 Hz, 1 H), 3.30 (dd, *J* = 3.0, 18 Hz, 1 H), 1.17 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 193.7, 140.4, 134.5, 129.6, 129.2, 123.4 (q, *J* = 279.0 Hz), 56.9, 53.5 (q, *J* = 30.8 Hz),

38.0, 22.3. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −74.3. IR (KBr): ν = 3267, 2964, 2923, 1686, 1592, 1290, 1270, 1176, 1120, 1095, 1060, 813 cm^{-1}. HRMS [M+Na$^+$]: calcd for $C_{14}H_{17}O_2SNF_3ClNa$: 378.0513, found: 378.0498.

(*S*)-*N*-((*S*)-4-(4-Bromophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (3f)

White solid, yield 66%, mp 142–144 °C, $[\alpha]_D^{25}$ +61.1 (*c* 0.55, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.84 (d, *J* = 8.7 Hz, 2 H), 7.65 (d, *J* = 8.7 Hz, 2 H), 4.49–4.59 (m, 1 H), 4.06 (d, *J* = 8.1 Hz, 1 H), 3.77 (dd, *J* = 9.6, 17.4 Hz, 1 H), 3.29 (dd, *J* = 3.3, 17.7 Hz, 1 H), 1.17 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 193.9, 134.9, 132.2, 129.7, 129.2, 123.3 (q, *J* = 280.2 Hz), 56.9, 53.5 (q, *J* = 30.5 Hz), 38.0, 22.3. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −74.3. IR (KBr): ν = 3202, 2964, 2923, 1688, 1586, 1397, 1348, 1287, 1175, 1112, 1056, 835 cm^{-1}. HRMS [M+Na$^+$]: calcd for $C_{14}H_{17}O_2SNF_3BrNa$: 423.9988, found: 424.0010.

(*S*)-*N*-((*S*)-4-(Biphenyl-4-yl)-1,1,1-trifluoro-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (3g)

White solid, yield 73%, mp 147–148 °C, $[\alpha]_D^{25}$ +91.2 (*c* 0.19, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.06 (d, *J* = 7.8 Hz, 2 H), 7.70–7.73 (m, 2 H), 7.62–7.65 (m, 2 H), 7.40–7.52 (m, 3 H), 4.54–4.68 (m, 1 H), 4.29 (d, *J* = 2.1 Hz, 1 H), 3.83 (dd, *J* = 9.6, 17.4 Hz, 1 H), 3.37 (dd, *J* = 2.7, 17.4 Hz, 1 H), 1.19 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 194.5, 146.5, 139.6, 135.0, 129.0, 128.8, 128.4, 127.5, 127.3, 123.5 (d, *J* = 278.4 Hz), 56.9, 53.8 (q, *J* = 31.3 Hz), 38.1, 22.4. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −74.4. IR (KBr): ν = 3163, 2960, 2922, 1685, 1604, 1273, 1158, 1122, 1061, 765 cm^{-1}. HRMS [M+Na$^+$]: calcd for $C_{20}H_{22}O_2SNF_3Na$: 420.1216, found: 420.1199.

(*S*)-*N*-((*S*)-4-(4-Ethylphenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (3h)

Colorless solid, yield 68%, mp 97–98 °C, $[\alpha]_D^{25}$ +100.0 (*c* 0.07, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.88–7.91 (m, 2 H), 7.28–7.33 (m, 2 H), 4.51–4.61 (m, 1 H), 3.95 (d, *J* = 8.4 Hz, 1 H), 3.73 (dd, *J* = 9.6, 17.4 Hz, 1 H), 3.31 (dd, *J* = 3.0, 17.4 Hz, 1 H), 2.76 (q, *J* = 7.2 Hz, 2 H), 1.30 (t, *J* = 7.8 Hz, 3 H), 1.17 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 194.4, 151.0, 134.0, 128.4, 128.3, 123.5 (q, *J* = 279.8 Hz), 56.9, 53.9 (q, *J* = 30.5 Hz), 37.9, 29.0, 22.3, 15.1. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −74.4. IR (KBr): ν = 3262, 2975, 2875, 1685, 1609, 1293, 1269, 1169, 1117, 1060, 819 cm^{-1}. HRMS [M+Na$^+$]: calcd for $C_{16}H_{22}O_2SNF_3Na$: 372.1216, found: 372.1206.

(*S*)-*N*-((*S*)-4-(4-Ethoxyphenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (3i)

White solid, yield 87%, mp 114–115 °C, $[\alpha]_D^{25}$ +78.8 (*c* 0.21, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.90–7.95 (m, 2 H), 6.90–6.96 (m, 2 H), 4.50–4.56 (m, 1 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 4.03 (d, *J* = 8.7 Hz, 1 H), 3.68 (dd, *J* = 9.3, 17.4 Hz, 1 H), 3.26 (dd, *J* = 3.0, 17.4 Hz, 1 H), 1.47 (t, *J* = 6.9 Hz, 3 H), 1.16 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 193.2, 163.5, 130.5, 129.1, 123.5 (q, *J* = 279.8 Hz), 114.4, 63.9, 56.9, 54.0 (q, *J* = 29.7 Hz), 37.6, 22.3, 14.6. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −74.5. IR (KBr): ν = 3167, 2980, 1682, 1602, 1366, 1287, 1261, 1231, 1171, 1117, 1061, 833 cm^{-1}. HRMS [M+Na$^+$]: calcd for $C_{16}H_{22}O_3SNF_3Na$: 388.1165, found: 388.1169.

(*S*)-2-Methyl-*N*-((*S*)-1,1,1-trifluoro-4-(naphthalen-2-yl)-4-oxobutan-2-yl)propane-2-sulfinamide (3j)

Colorless solid, yield 76%, mp 140–143 °C, $[\alpha]_D^{25}$ +34.2 (*c* 0.08, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.49 (s, 1 H), 7.98–8.05 (m, 2 H), 7.94 (t, *J* = 8.7 Hz, 2 H), 7.56–7.67 (m, 2 H), 4.56–4.72 (m, 1 H), 4.01 (s, 1 H), 3.92 (dd, *J* = 9.6, 17.7 Hz, 1 H), 3.48 (dd, *J* = 3.3, 17.7 Hz, 1 H), 1.18 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 194.7, 135.9, 133.6, 132.5, 130.1, 129.7, 128.9, 128.8, 127.8, 127.0, 123.6, 123.5 (d, *J* = 280.7 Hz), 56.9, 53.9 (q, *J* = 31.5 Hz), 38.2, 22.3. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −74.3. IR (KBr): ν = 3260, 2970, 2936, 1674, 1286, 1171, 1119, 1058, 1046, 822 cm^{-1}. HRMS [M+Na$^+$]: calcd for $C_{18}H_{20}O_2SNF_3Na$: 394.1059, found: 394.1050.

(*S*)-2-Methyl-*N*-((*S*)-1,1,1-trifluoro-4-(furan-2-yl)-4-oxobutan-2-yl)propane-2-sulfinamide (3k)

Colorless solid, yield 42%, mp 110–111 °C, $[\alpha]_D^{25}$ +48.8 (*c* 0.08, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.64 (dd, *J* = 0.6, 1.5 Hz, 1 H), 7.31 (dd, *J* = 0.6, 3.3 Hz, 1 H), 6.61 (q, *J* = 1.8 Hz, 1 H), 4.45–4.55 (m, 1 H), 3.88 (d, *J* = 9.0 Hz, 1 H), 3.59 (dd, *J* = 9.9, 17.4 Hz, 1 H), 3.21 (dd, *J* = 3.3, 17.1 Hz, 1 H), 1.17 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 183.8, 152.2, 147.1, 123.2 (q, *J* = 280.3 Hz), 118.1, 112.8, 57.0, 53.8 (q, *J* = 31.1 Hz), 37.9 (d, *J* = 1.3 Hz), 22.3. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −74.7. IR (KBr): ν = 3283, 3129, 3091, 2967, 1666, 1468, 1304, 1267, 1172, 1125, 1075, 767 cm^{-1}. HRMS [M+Na$^+$]: calcd for $C_{12}H_{16}O_3SNF_3Na$: 334.0695, found: 334.0699.

(*S*)-2-Methyl-*N*-((*S*)-1,1,1-trifluoro-5,5-dimethyl-4-oxohexan-2-yl)propane-2-sulfinamide (3l)

Colorless solid, yield 61%, mp 85–86 °C, $[\alpha]_D^{25}$ +32.3 (*c* 0.76, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.33–4.39 (m, 1 H), 3.83 (d, *J* = 8.5 Hz, 1 H), 3.25 (dd, *J* = 9.5, 18.5 Hz, 1 H), 2.88 (dd, *J* = 3.5, 18.5 Hz, 1 H), 1.20 (s, 18 H).^{13}C NMR ($CDCl_3$, 125 MHz): δ = 210.5, 124.2 (d, *J* = 279.9 Hz), 56.8, 53.5 (q, *J* = 30.8 Hz), 44.2, 36.3, 26.3, 22.3. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −74.2. IR (KBr): ν = 3244, 2967, 2928, 1712, 1473, 1365, 1281, 1222, 1168, 1125, 1061 cm^{-1}. HRMS [M+Na$^+$]: calcd for $C_{12}H_{22}O_2SNF_3Na$: 324.1216, found: 324.1209.

Reaction of large scale application study

Into an oven-dried round-bottom flask flushed with N_2 were taken acetophenone (8.5 mmol) and anhydrous THF (20.0 mL). The reaction flask was cooled to −78 °C and LDA (2 M in THF, 4.7 mL) was added dropwise with stirring. After 45 min at −78 °C, sulfinylimine **1** (5 mmol) dissolved in anhydrous THF (10.0 mL) was added dropwise. Stirring was continued at −78 °C for 2.5 h, then the reaction was quenched with saturated NH_4Cl (10.0 mL), followed by H_2O (15.0 mL) and the mixture was brought to room temperature. The organic layer was taken and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent

was removed to give the crude product, which was purified by column chromatography (hexane–EtOAc, 4 : 1).

Conversion of 3a affording free β-amino ketone 4

3a (0.5 mmol) and MeOH (5 mL) were placed in a 25 mL round-bottom flask and aq HCl (36%, 1 mL) was added. The reaction was stirred at rt for 8 h, during which the cleavage was monitored by TLC. Volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and Et_3N (15 mmol) was added. The mixture was stirred at rt for 1 h, then H_2O (10 mL) was added. The organic layer was taken, washed with H_2O (2 × 10 mL), dried with anhydrous Na_2SO_4, filtered and the solvent was removed to give the crude product, which was purified by TLC plate (hexane–EtOAc, 2 : 1).

(*S*)-3-Amino-4,4,4-trifluoro-1-phenylbutan-1-one (4)

White solid, yield 90%, mp 31–32 °C, $[\alpha]_D^{25}$ −57.2 (*c* 0.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.97–8.00 (m, 2 H), 7.60–7.66 (m, 1 H), 7.49–7.54 (m, 2 H), 3.98–4.10 (m, 1 H), 3.38 (dd, *J* = 2.7, 17.7 Hz, 1 H), 3.25 (dd, *J* = 9.6, 17.1 Hz, 1 H), 1.66 (s, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 196.2, 136.3, 133.8, 128.8, 128.1, 124.6 (q, *J* = 278.8 Hz), 50.0 (q, *J* = 29.6 Hz), 39.3 (q, *J* = 1.4 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −78.3. IR (KBr): ν = 3391, 3332, 2937, 1684, 1596, 1333, 1257, 1221, 1177, 1106, 754, 687 cm^{-1}. HRMS [M+H$^+$]: calcd for $C_{10}H_{11}ONF_3$: 218.0787, found: 218.0796.

Conclusions

In summary, we have developed the first auxiliary-based process for the asymmetric synthesis of β-trifluoromethylated β-amino ketones *via* addition of ketone-derivative enolates to sulfinylimine. This facile and efficient system gives good yields and excellent diastereoselectivities, even on the large scale preparation. Further study on synthesis of α-branched β-trifluoromethylated β-amino ketones is presently under progress.

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