Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Concise and scalable asymmetric synthesis of 5-(1-amino-2,2,2-trifluoroethyl)thiazolo[3,2-*b*][1,2,4]triazoles

Haibo Mei,[a,b] Yiwen Xiong,[a] Chen Xie,[a] Vadim A. Soloshonok,[d,e] Jianlin Han,*[a,b,c] and Yi Pan[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

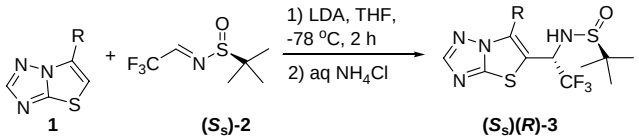
DOI: 10.1039/b000000x

This study describes asymmetric Mannich-type additions between C-5 lithiated thiazolo[3,2-*b*][1,2,4]triazoles and enantiomerically pure (S_S)-*N*-*tert*-butanesulfinyl-(3,3,3)-trifluoroacetaldimine. Under the optimized conditions, these reactions proceed with good (up to 78%) chemical yields and virtually complete (98:2 to >99:1 dr) diastereoselectivity. The same stereochemical outcome was obtained using 1.05 g scale of the starting (3,3,3)-trifluoroacetaldimine. The method developed in this work provides a concise and generalized access to thiazolo[3,2-*b*][1,2,4]triazoles containing chiral (trifluoro)ethylamine group.

Introduction

Heterocyclic compounds are quite commonly found in nature and have been attracting passionate attention of organic chemists for many decades.[1] In particular, the thiazolo[3,2-*b*][1,2,4]triazole fragment is found in many biologically active natural products.[2] Consequently, synthesis and biological study of new thiazolo[3,2-*b*][1,2,4]triazole derivatives is currently an active field of multidisciplinary research.[3-5] It was found, that the most promising biologically active types of thiazolo[3,2-*b*][1,2,4]triazoles are usually containing functional chiral moieties.[2-5] Accordingly, the development of concise and scalable methods for asymmetric modification of thiazolo[3,2-*b*][1,2,4]triazoles is important, yet challenging goal in synthetic organic and medicinal chemistry.[6-8]

Taking into account the remarkable impact of fluorine on the development of biologically active compounds and pharmaceuticals,[9-14] synthesis of fluorinated thiazolo[3,2-*b*][1,2,4]triazoles might be of great interest. Therefore, considering our[15] and others[16] recent interest in the chemistry of (S_S)-*N*-*tert*-butanesulfinyl-(3,3,3)-trifluoroacetaldimine[17] we envisioned a direct, one-step introduction of the pharmacophoric 1-amino-2,2,2-trifluoroethyl moiety onto the thiazolo[3,2-*b*][1,2,4]triazole rings. Herein, we report a study of asymmetric Mannich-type reactions between C-5 lithiated thiazolo[3,2-*b*][1,2,4]triazoles and (S_S)-*N*-*tert*-butanesulfinyl-(3,3,3)-trifluoroacetaldimine. These reactions were found to proceed with exceptional diastereoselectivity diving rise to virtually one product in good chemical yields (Scheme 1). Mechanism, structural generality of this method and its scalability are discussed.



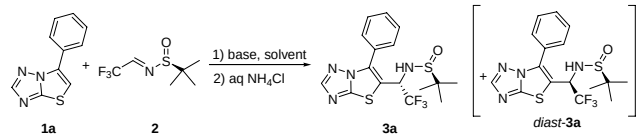
Scheme 1. Mannich-type addition reactions between of thiazolo[3,2-*b*][1,2,4]triazoles and chiral CF_3-sulfinylimine.

Results and discussion

Based on our previous studies of the asymmetric reactions with *N*-*tert*-butylsulfinylimine,[15a,15b] the initial choice of the reaction conditions was focused on using sulfinylimine **2** with 1.5 equiv of 6-phenylthiazolo[3,2-*b*][1,2,4]triazole **1a** in the presence of *n*-BuLi with THF as solvent at -78 °C. The reaction proceeded smoothly within 2 hrs, affording (entry 1, Table 1) the desired product **3a** in 61% yield. Determination of the diastereomeric purity by ^{1}H-NMR has revealed two diastereomeric products (see SI) in a ratio of 83:17. Attempts to separate these two CF3-containing products by column chromatography have failed, indicating insufficient difference in the physicochemical properties of the diastereomers. The fact that the separation of diastereomeric products is problematic, has added an extra challenge to this work as only complete diastereoselectivity in these additions could render this method synthetically useful. Thus, systematic optimization was carried out to improve both the yield and, most importantly, the diastereoselectivity. First, the effect of a base used in these reactions was investigated. It was found that strong bases could give good results while the week ones could not even catalyze the reaction (entries 2-6). LDA was found to be the best choice, providing for an acceptable yield and the desired high diastereoselectivity (62% yield and 97:3 dr, entry 2). Next, the loading amount of 6-phenylthiazolo[3,2-*b*][1,2,4]triazole **1a** was examined. The experiments have revealed that use of 1.7 equiv of **1a** leads to the high yield and excellent diastereoselectivity (71% yield and 98:2 dr, entry 8).

Reducing the amount of **1a** resulted in an obvious decrease in both yield and diastereoselectivity (entry 7). Solvent was found to have significant effect on the stereochemical outcome (entries 9-12), and THF was finally confirmed to be the best choice. Furthermore, temperature was also found to be an important factor in these reactions. Elevated reaction temperature brought a slight decrease in both yield and diastereoselectivity (entries 13-15). Finally, the screening of the reaction time demonstrated that this transformation could be reasonably completed within 2 hrs. Thus, extending the reaction time resulted in a noticeable decrease in the yield, although it has almost no effect on the diastereoselectivity (entry 17).

Table 1. Optimization of the asymmetric Mannich-type addition reaction conditions[a]



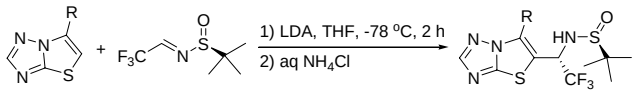
1a **2** **3a** *diast*-**3a**

Entry	Base	**1a** (equiv)	Solvent	Time (h)	T (°C)	Yield (%)[b]	Dr[c]
1	*n*-BuLi	1.5	THF	2	-78	61	83:17
2	LDA	1.5	THF	2	-78	68	97:3
3	LiHDMS	1.5	THF	2	-78	42	76:24
4	$(CH_3)_3COLi$	1.5	THF	2	-78	trace	ND[d]
5	$(CH_3)_3COK$	1.5	THF	2	-78	trace	ND[d]
6	Cs_2CO_3	1.5	THF	2	-78	NR[e]	-
7	LDA	1.2	THF	2	-78	40	87:13
8	LDA	1.7	THF	2	-78	71	98:2
9	LDA	1.7	Toluene	2	-78	26	79:21
10	LDA	1.7	Hexane	2	-78	27	82:18
11	LDA	1.7	CH_2Cl_2	2	-78	13	92:8
12	LDA	1.7	Et_2O	2	-78	37	90:10
13	LDA	1.7	THF	2	-41	72	93:7
14	LDA	1.7	THF	2	-22	64	91:9
15	LDA	1.7	THF	2	0	61	94:6
16	LDA	1.7	THF	1	-78	66	97:3
17	LDA	1.7	THF	3	-78	65	98:2

[a] Reaction conditions: sulfinylimine (0.5 mmol), base (1.1 equiv of **1a**), solvent (5 mL). [b] Isolated yields. [c] Determined by ^{19}F or ^{1}H NMR analysis. [d] Not determined. [e] No reaction.

Having optimized the reaction conditions, ournext goal was to examine the scope of these reactions using available thiazolo[3,2-*b*][1,2,4]triazoles (Table 2). Under the standard reaction conditions, all tested substrates reacted smoothly pointing to generality of this method. As shown in Table 2, the diastereoselectivity of the reactions was excellent, producing virtually single diastereomer **3**. Variation of substituents on the aromatic ring showed no significant effect on either chemical yield or diastereoselectivity. Both electron-deficient (entries 2-6) and electron-rich (entry 7) aryl-substituted thiazolo[3,2-*b*][1,2,4]triazoles gave equally good stereochemical outcome. In particular, thiazolo[3,2-*b*][1,2,4]triazoles with di-substituted aromatic ring **1h** or naphthyl substituted **1i** were also well tolerated in this reaction affording products **3h, i** in good yields and with excellent diastereoselectivity (entries 8 and 9). In the case of alkyl substituted derivative **1j** the reaction yield was noticeably lower, however the corresponding product **3j** was isolated as a single diastereomer. (entry 10).

Table 2. Scope of thiazolo[3,2-*b*][1,2,4]triazoles for the asymmetric addition[a]

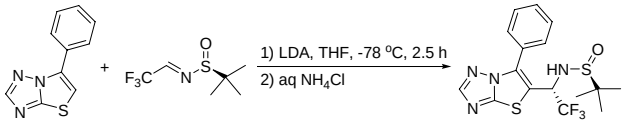


1a-j **2** **3a-j**

Entry	Substrate	R	Product	Yield (%)[b]	Dr[c]
1	**1a**	Ph	**3a**	71	98:2
2	**1b**	3-ClC_6H_4	**3b**	73	>99:1
3	**1c**	3-BrC_6H_4	**3c**	74	>99:1
4	**1d**	4-FC_6H_4	**3d**	72	98:2
5	**1e**	4-ClC_6H_4	**3e**	66	>99:1
6	**1f**	4-BrC_6H_4	**3f**	70	99:1
7	**1g**	4-MeC_6H_4	**3g**	73	>99:1
8	**1h**	3,4-$Cl_2C_6H_3$	**3h**	78	>99:1
9	**1i**	2-Naphthyl	**3i**	68	>99:1
10	**1j**	Me	**3j**	40	>99:1

[a] Reaction conditions: sulfinylimine (0.5 mmol), **1** (0.85 mmol), LDA (0.94 mmol), THF (5 mL). [b] Isolated yields. [c] Determined by ^{19}F NMR analysis.

Finally, this newly developed method we tested for its reproducibility and efficiency on a gram-scale. As one can see from the Scheme 2, the reaction conducted under the standard conditions using 1.05 g of sulfinylimine **2** afforded the target product **3a** with good yield (68%) and diastereoselectivity (94:6 dr). Diastereomerically pure **3a** can be prepared by crystallization of the crude product. Thus, only a slight decrease in the yield and diastereoselectivity were detected as compared to the best result obtained on a 0.10 g scale. Consequently, this approach can be reliably used for relatively large scale synthesis of various fluorinated chiral thiazolo[3,2-*b*][1,2,4]triazoles derivatives allowing for a systematic biological studies of these new compounds.



1a **2** **3a**
1.05 g 1.43 g, 68% yield, 94:6 dr

Scheme 2. Example of a large-scale asymmetric synthesis of compound **3a**.

To determine the absolute configuration of the products **3**, we took advantage of good crystallinity of compound **3a** and conducted its crystallographic analysis (Figure 1). As shown in Figure 1, the absolute configuration of the newly generated chiral center in this process is *R*. The absolute configurations of other corresponding products were assigned by analogy, based on similarity of their chiroptic properties and spectral data.

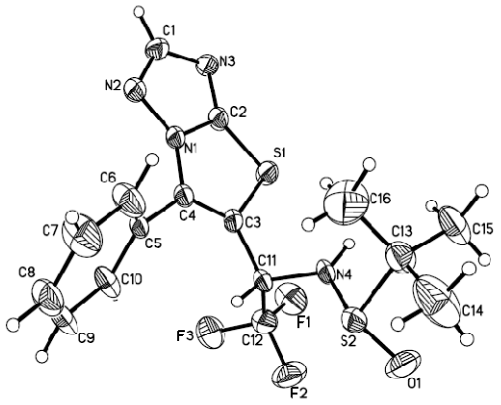


Figure 1. ORTEP diagram showing of compound (S_s)(R)-**3a**.

Consistent with the literature data,[18] the asymmetric Mannich-type addition reactions of thiazolo[3,2-*b*][1,2,4]triazoles to sulfinylimine **2** is suggested to proceed *via* a non-chelated transition state model. Thus, the lithiated thiazolo[3,2-*b*][1,2,4]triazoles preferably approaches the imine double bond from the less hindered face, occupied by the lone pair of electrons on sulphur, to afford the major diastereomer (Figure 2). Furthermore, via this general approach, two possible orientations of the thiazolo[3,2-*b*][1,2,4]triazoles anion **A** and **B** are possible. Considering obvious steric interactions of the CF_3 group and the substituent R in B, it is most likely that the transition state **A** might be preferred.

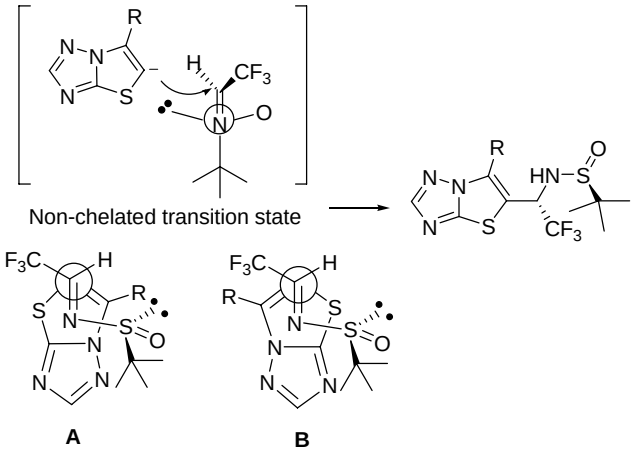
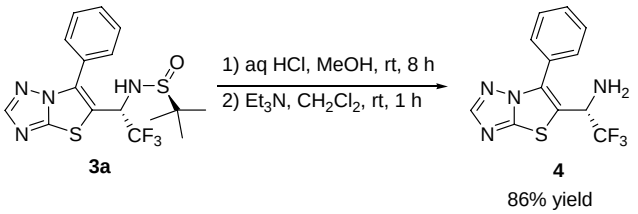


Figure 2. Proposed mechanism for the asymmetric Mannich-type addition.

As the final task of this work, we studied an example of the chiral auxiliary removal and preparation of the compound **4** with free amino function. Using relatively common conditions,[15a, 15b] such as treatment of **3a** with aqueous HCl in methanol (Scheme 3), the target amine **4** was obtained in high isolated yield of 86%.



Scheme 3. Conversion of **3a** to free chiral primary amine **4**.

Conclusions

In summary, we have demonstrated that the asymmetric Mannich-type addition reactions between lithium-derived of imidazo[2,1-*b*]thiazoles and CF_3-sulfinylimine **2** occur with reasonably good yields and excellent diastereoselectivity. This reactions are reproducible on relatively large scale and can be reliably used for preparation of various thiazolo[3,2-*b*][1,2,4]triazoles containing chiral 1-amino-2,2,2-trifluoroethyl group for systematic biological studies.

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. Thiazolo[3,2-*b*][1,2,4]triazoles **1** were synthesized according to literature [1]. Sulfinylimine **2** was obtained from Accela ChemBio Co., Ltd.. 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. Values of optical rotation were measured on Rudolph Automatic Polarimeter A21101. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AVANCE400M spectrometer. HRMS spectra were carried out at Micromass GCT (TOF MS EI$^+$).

Typical procedure for asymmetric addition of sulfinylimine

Into an oven-dried reaction vial flushed with N_2 were taken compound **1** (0.85 mmol) and anhydrous THF (3.0 mL). The reaction vial was cooled to -78 ^{o}C and LDA (2 M in THF, 0.47 mL) was added dropwise with stirring. After 1 h at -78 ^{o}C, sulfinylimine **2** (0.5 mmol) dissolved in anhydrous THF (2.0 mL) was added dropwise. Stirring was continued at -78 ^{o}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, 1:1).

3a: white solid, mp 192-193 ^{o}C, $[\alpha]_D^{25}$ +107.3 (*c* 1.05, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.18 (s, 1 H), 7.71-7.74 (m, 2 H), 7.57-7.62 (m, 3 H), 5.31-5.36 (m, 1 H), 3.91 (s, 1 H), 1.29 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.2, 155.8, 135.5, 130.9, 129.5, 129.4, 126.0, 125.1 (q, *J* = 281.0 Hz), 118.1, 56.9, 54.9 (q, *J* = 32.0 Hz), 22.4. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -73.8. HRMS (TOF MS EI$^+$) *m/z*: calcd for $[C_{16}H_{17}N_4OF_3S_2]$ 402.0796, found 402.0785.

3b: white solid, mp 185-187 °C, $[\alpha]_D^{25}$ +97.2 (*c* 0.79, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.19 (s, 1 H), 7.75 (d, *J* = 1.6 Hz, 1 H), 7.63-7.66 (m, 1 H), 7.52-7.58 (m, 2 H), 5.27-5.32 (m, 1 H), 3.93 (s, 1 H), 1.30 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.4, 156.0, 135.5, 134.0, 131.3, 130.8, 129.6, 127.7, 127.6, 125.0 (q, *J* = 281.0 Hz), 118.9, 57.0, 54.8 (q, *J* = 32.0 Hz), 22.4. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -73.7. HRMS [M+H$^+$]: calcd for [$C_{16}H_{17}ClN_4OF_3S_2$] 437.0484, found 437.0482.

3c: white solid, mp 190-191 °C, $[\alpha]_D^{25}$ +94.5 (*c* 0.95, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.19 (s, 1 H), 7.90 (t, *J* = 2.0 Hz, 1 H), 7.68-7.73 (m, 2 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 5.27-5.32 (m, 1 H), 3.92 (s, 1 H), 1.30 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.4, 155.9, 134.2, 133.9, 132.4, 131.0, 128.2, 127.8, 125.0 (q, *J* = 281.0 Hz), 123.5, 119.0, 57.0, 54.8 (q, *J* = 32.0 Hz), 22.5. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -73.7. HRMS [M+H$^+$]: calcd for [$C_{16}H_{17}BrN_4OF_3S_2$] 480.9979, found 480.9974.

3d: white solid, mp 61-63 °C, $[\alpha]_D^{25}$ +107.9 (*c* 0.25, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.18 (s, 1 H), 7.73-7.76 (m, 2 H), 7.26-7.31 (m, 2 H), 5.25-5.30 (m, 1 H), 3.91 (s, 1 H), 1.29 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.4 (d, *J* = 251.0 Hz), 156.4, 156.0, 134.7, 131.9 (d, *J* = 9.0 Hz), 125.0 (q, *J* = 280.0 Hz), 122.0 (d, *J* = 3.0 Hz), 118.1, 117.0 (d, *J* = 22.0 Hz), 57.0, 54.8 (q, *J* = 32.0 Hz), 22.4. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -73.8, -107.9. HRMS [M+Na$^+$]: calcd for [$C_{16}H_{16}N_4OF_4S_2Na$] 443.0599, found 443.0598.

3e: white solid, mp 67-69 °C, $[\alpha]_D^{25}$ +68.1 (*c* 0.23, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.18 (s, 1 H), 7.70 (d, *J* = 8.0 Hz, 2 H), 7.59 (d, *J* = 8.0 Hz, 2 H), 5.25-5.30 (m, 1 H), 3.92 (s, 1 H), 1.29 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.4, 156.0, 137.4, 134.5, 131.0, 129.9, 125.0 (q, *J* = 281.0 Hz), 124.3, 118.3, 57.0, 54.7 (q, *J* = 32.0 Hz), 22.4. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -73.8. HRMS [M+H$^+$]: calcd for [$C_{16}H_{17}ClN_4OF_3S_2$] 437.0484, found 437.0477.

3f: white solid, mp 72-74 °C, $[\alpha]_D^{25}$ +57.3 (*c* 0.22, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.18 (s, 1 H), 7.75 (d, *J* = 8.0 Hz, 2 H), 7.63 (d, *J* = 8.0 Hz, 2 H), 5.25-5.30 (m, 1 H), 3.92 (s, 1 H), 1.29 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.4, 156.0, 134.6, 132.9, 131.1, 125.8, 125.0 (q, *J* = 280.0 Hz), 124.8, 118.3, 57.0, 54.7 (q, *J* = 32.0 Hz), 22.4. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -73.8. HRMS [M+H$^+$]: calcd for [$C_{16}H_{17}BrN_4OF_3S_2$] 480.9979, found 480.9980.

3g: white solid, mp 142-143 °C, $[\alpha]_D^{25}$ +74.1 (*c* 0.52, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.17 (s, 1 H), 7.61 (d, *J* = 8.0 Hz, 2 H), 7.40 (d, *J* = 8.0 Hz, 2 H), 5.30-5.36 (m, 1 H), 3.88 (s, 1 H), 2.44 (s, 3 H), 1.28 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.2, 155.9, 141.4, 135.8, 130.2, 129.4, 125.1 (q, *J* = 281.0 Hz), 123.0, 117.5, 56.9, 54.9 (q, *J* = 32.0 Hz), 22.4, 21.5. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -73.8. HRMS [M+Na$^+$]: calcd for [$C_{17}H_{19}N_4OF_3S_2Na$] 439.0850, found 439.0853.

3h: white solid, mp 66-68 °C, $[\alpha]_D^{25}$ +68.3 (*c* 0.33, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.19 (s, 1 H), 7.89 (d, *J* = 2.0 Hz, 1 H), 7.69 (d, *J* = 8.0 Hz, 1 H), 7.63 (dd, *J* = 2.0, 8.0 Hz, 1 H), 5.25-5.30 (m, 1 H), 3.95 (s, 1 H), 1.30 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.5, 156.0, 135.8, 134.1, 133.1, 131.6, 131.4, 128.7, 125.7, 124.9 (q, *J* = 280.0 Hz), 119.1, 57.0, 54.7 (q, *J* = 32.0 Hz), 22.5. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -73.7. HRMS [M+Na$^+$]: calcd for [$C_{16}H_{15}Cl_2N_4OF_3S_2Na$] 492.9914, found 492.9910.

3i: white solid, mp 166-167 °C, $[\alpha]_D^{25}$ +59.8 (*c* 1.13, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.28 (s, 1 H), 8.21 (s, 1 H), 8.08 (d, *J* = 8.0 Hz, 1 H), 8.00 (d, *J* = 8.0 Hz, 1 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.79 (dd, *J* = 4.0, 8.0 Hz, 1 H), 7.56-7.64 (m, 2 H), 5.41-5.46 (m, 1 H), 3.94 (s, 1 H), 1.31 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.3, 156.0, 135.7, 134.1, 133.1, 130.1, 129.5, 128.8, 127.9, 127.8, 127.1, 125.5, 125.1 (q, *J* = 281.0 Hz), 123.3, 118.2, 57.0, 55.0 (q, *J* = 32.0 Hz), 22.5. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -73.7. HRMS [M+Na$^+$]: calcd for [$C_{20}H_{19}N_4OF_3S_2Na$] 475.0850, found 475.0850.

3j: white solid, mp 193-194 °C, $[\alpha]_D^{25}$ +132.3 (*c* 0.56, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.18 (s, 1 H), 5.23-5.28 (m, 1 H), 3.91 (s, 1 H), 2.65 (s, 3 H), 1.29 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.0, 155.8, 131.6, 125.2 (q, *J* = 280.0 Hz), 116.4, 56.9, 54.1 (q, *J* = 32.0 Hz), 22.4, 11.5. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -74.0. HRMS (TOF MS EI$^+$) *m/z*: calcd for [$C_{11}H_{15}N_4OF_3S_2$] 340.0639, found 340.0633.

Reaction of large scale application study

Into an oven-dried round-bottom flask flushed with N_2 were taken compound **1a** (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 1 h at -78 °C, sulfinylimine **2** (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 (2 × 30 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, 1:1).

Conversion of 3a affording free chiral primary amine 4

3a (0.5 mmol) and MeOH (5.0 mL) were placed in a 25 mL round-bottom flask and aq HCl (36%, 1 mL) was added. The reaction was stirred at r.t. for 8 h, during which time the cleavage was monitored by TLC. Volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (10.0 mL) and Et_3N (15 mmol) was added. The reaction was stirred at rt for 1 h then H_2O (10.0 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, 1:1).

4: white solid, mp 105-106 °C, $[\alpha]_D^{25}$ -2.6 (*c* 0.61, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.15 (s, 1 H), 7.64-7.68 (m, 2 H), 7.57-7.60 (m, 3 H), 4.84-4.89 (m, 1 H), 1.94 (s, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.0, 155.3, 132.6, 130.7, 129.5, 129.3, 126.7, 126.2 (q, *J* = 280.0 Hz), 122.7, 52.6 (q, *J* = 32.0 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -75.8. HRMS (TOF MS EI$^+$) *m/z*: calcd for [$C_{12}H_9N_4F_3S$] 298.0500, found 298.0510.

Acknowledgments

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (No. 21102071) and the Fundamental Research Funds for the Central Universities (No. 1107020522 and No. 1082020502). The Jiangsu 333 program (for Pan) and Changzhou Jin-Feng-Huang program (for

Han) are also acknowledged.

Notes and references

[a] *School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, 210093, China. Fax: 86-25-83593153; Tel: 86-25-83593153; E-mail: hanjl@nju.edu.cn.*
[b] *Institute for Chemistry & BioMedical Sciences, Nanjing University, Nanjing, 210093, China.*
[c] *High-Tech Research Institute of Nanjing University, Changzhou, 213164, China.*
[d] *Department of Organic Chemistry I, Faculty of Chemistry, University of the Basque Country UPV/EHU, 20018 San Sebastian, Spain.*
[e] *IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain*

† Electronic Supplementary Information (ESI) available: [Experimental procedures, full spectroscopic data for compounds **3** and **4** and copies of ^{1}H NMR and ^{13}C NMR spectra]. See DOI: 10.1039/b000000x/

1 (*a*) R. Hili and A. K. Yudin, *Nat. Chem. Biol.*, 2006, **2**, 284–287; (b) J. C. Lewis, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2008, **41**, 1013–1025; (*c*) R. W. DeSimone, K. S. Currie, S. A. Mitchell, J. W. Darrow and D. A. Pippin, *Comb. Chem. High Throughput Screen*, 2004, **7**, 473–494.

2 (*a*) M. S. Karthikeyan, *Eur. J. Med. Chem.*, 2009, **44**, 827–833; (*b*) P. Roy, Y. Leblanc, R. G. Ball, C. Brideau, C. C. Chan, N. Chauret, W. Cromlish, D. Ethier, J. Y. Gauthier, R. Gordon, G. Greig, J. Guay, S. Kargman, C. K. Lau, G. O'Neil, J. Silva, M. Thérien, C. vanstaden, E. Wong, L. Xu and P. Prasit, Bioorg. *Med. Chem. Lett.*, 1997, **7**, 57–62; (*c*) S. Demirayak, G. Zitouni, P. Chevallet, K. Erol and F. S. Kilic, *Farmaco*, 1993, **48**, 707–712.

3 (*a*) B. Berk, G. Aktay, E. Yesilada, and M. Ertan, *Pharmazie*, 2001, **56**, 613–616; (*b*) B. S. Holla, K. N. Poojary, B. Kalluraya and P. V. Gowda, *Farmaco*, 1996, **51**, 793–799

4 (*a*) D. D. J. Cartwright, B. A. J. Clark and H. McNab, *J. Chem. Soc., Perkin Trans. 1*, 2001, 424–428; (*b*) H. A. H. El-Sherif, A. M. Mahmoud, A. A. O. Sarhan, Z. A. Hozien and O. M. A. Habib, *J. Sulfur Chem.*, 2006, **27**, 65–85

5 (*c*) K. Atsumi, K. Iwamatsu, A. Tamura and M. Shibahara, *Jpn. Kokai Tokkyo Koh.* JP1992339952, 1994.

6 (*a*) R. Lesyk, O. Vladzimirska, S. Holota, L. Zaprutko and A. Gzella, *Eur. J. Med. Chem.*, 2007, **42**, 641–648; (*b*) A. Davoodnia, S. Ameli and H. N. Tavakoli, *Asian J. Chem.*, 2011, **23**, 3707–3709.

7 A. R. Katritzky, A. Pastor, and M. Voronkov, *Org. Lett.*, 2000, **2**, 429–431.

8 Z. Xie, X. Zhu, Y. Guan, D. Zhu, H. Hu, C. Lin, Y. Pan, J. Jiang and L. Wang, *Org. Biomol. Chem.*, 2013, **11**, 1390–1398.

9 J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, DOI 10.1021/cr4002879.

10 (*a*) C. Isanbor and D. O'Hagan, *J. Fluorine Chem.*, 2006, **127**, 303–319; (*b*) J. P. Begue and D. Bonnet-Delpon, *J. Fluorine Chem.*, 2006, **127**, 992–1012; (*c*) K. L. Kirk, *J. Fluorine Chem.*, 2006, **127**, 1013–1029.

11 W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359–4369.

12 V. P. Kukhar, A. E. Sorochinsky and V. A. Soloshonok, *Future Med. Chem.*, 2009, **1**, 793-819.

13 (*a*) D. O'Hagan, *J. Fluorine Chem.*, 2010, **131**, 1071–1081; (*b*) A. E. Sorochinsky and V. A. Soloshonok, *J. Fluorine Chem*., 2010, **131**, 127–139.

14 (*a*) J. L. Aceña, A. E. Sorochinsky and V. A. Soloshonok, *Synthesis*, 2012, 1591–1602; (*b*) K. Mikami, S. Fustero, M. Sánchez-Roselló, J. L. Aceña, V. A. Soloshonok and A. E. Sorochinsky, *Synthesis*, 2011, 3045–3079.

15 (*a*) H. Mei, Y. Xiong, J. Han and Y. Pan, *Org. Biomol. Chem.*, 2011, **9**, 1402–1406; (*b*) H. Mei, C. Xie, L. Wu, V. A. Soloshonok, J. Han, and Y. Pan, *Org. Biomol. Chem.*, 2013, **11**, 8018–8021; (*c*) N. Shibata, T. Nishimine, N. Shibata, E. Tokunaga, K. Kawada, T. Kagawa, A. E. Sorochinsky and V. A. Soloshonok, *Chem. Commun.*, 2012, **48**, 4124–4126; (*d*) K. V. Turcheniuk, K. O. Poliashko, V. P. Kukhar, A. B. Rozhenko, V. A. Soloshonok and A. E. Sorochinsky, *Chem. Commun.*, 2012, **48**, 11519–11521; (*e*) G. V. Röschenthaler, V. P. Kukhar, I. B. Kulik, M. Y. Belik, A. E. Sorochinsky, E. B. Rusanov and V. A. Soloshonok, *Tetrahedron Lett.*, 2012, **53**, 539–512; (*f*) C. Xie, H. B. Mei, L. M. Wu, V. A. Soloshonok, J. L. Han and Y. Pan, *RSC Adv.*, 2014, **4**, 4763–4768.

16 (*a*) M. V. Shevchuk, V. P. Kukhar, G. V. Roeschenthaler, B. S. Bassil, K. Kawada, V. A. Soloshonok and A. E. Sorochinsky, *RSC Adv.*, 2013, **3**, 6479–6484; (*b*) V. L. Truong and J. Y. Pfeiffer, *Tetrahedron Lett.*, 2009, **50**, 1633–1635; (*c*) Y. Liu, J. Liu, Y. Huang and F. L. Qing, *Chem. Commun.*, 2013, **49**, 7492–7494; (*d*) N. Plobeck, D. Powell, *Tetrahedron: Asymmetry*, 2002, **13**, 303–310; (*e*) W. Jiang, C. Chen, D. Marinkovic, J. A. Tran, C. W. Chen, L. M. Arellano, N. S. White and Tucci, F. C. *J. Org. Chem.*, 2005, **70**, 8924–8931; (*f*) H. Zhang, Y. Li, W. Xu, W. Zheng, P. Zhou and Z. Sun, *Org. Biomol. Chem.*, 2011, **9**, 6502–6505.

17 For the large scale synthesis, see: H. Mimura, K. Kawada, T. Yamashita, T. Sakamoto and Y. Kikugawa, *J. Fluorine Chem.*, 2010, **131**, 477–486.

18 M. T. Robak, M. A. Herbage and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 3600–3740.