Journal of Fluorine Chemistry 165 (2014) 67–75

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Large-scale Mannich-type reactions of (S_S)-*N*-*tert*-butanesulfinyl-(3,3,3)-trifluoroacetaldimine with *C*-nucleophiles

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ARTICLE INFO

Article history:
Received 6 May 2014
Received in revised form 11 June 2014
Accepted 14 June 2014
Available online 20 June 2014

Keywords:
CF_3-imine
Large-scale
Mannich reaction
Trifluoromethyl-amino compounds
Biologically active compounds

ABSTRACT

Here we describe the first attempts to scale up five addition reactions between (S_S)-*N*-*tert*-butanesulfinyl-(3,3,3)-trifluoroacetaldimine **6** with *C*-nucleophiles derived from ketones (two examples), glycine Schiff base and heterocycles (two examples). In all cases studied, the observed stereochemical outcome of the scaled up (5.0–25.0 mmol) reactions was lower as compared with the original 0.5 mmol scale. However, the observed worsening of yields and diastereoselectivity was not identical and depended on the reaction conditions and reaction mechanisms. In general, scaling up of the reactions conducted at ambient temperatures presented no problems while the low-temperature (−78 °C) processes would require special equipment to provide strict maintenance of the reaction temperature to obtain the desirable outcome. Importantly, using procedures described here, series of biologically relevant compounds containing 2,2,2-trifluoro-1-(amino)ethyl [CF_3–$CH(NH_2)$-] pharmacophore unit can be prepared in enantiomerically pure form on up to 5 g scale, allowing their systematic biological studies.

1. Introduction

Considering the unprecedented growth in the number of marketed fluorine-containing drugs, the development of synthetic methodology for preparation of organofluorine compounds is currently an extremely active research subject [1]. In particular, the recent upsurge in the development of trifluoromethylation methods is driven by the apparent pharmaceutical potential of CF_3-containing drugs. However, most of the research in this area focuses on installation of CF_3-group onto aromatic, heteroaromatic and sp^2 carbon species [2]. Thus, preparation of more structurally complex compounds, possessing aliphatic CF_3-group along with other functional groups, still presents a significant synthetic challenge. For example, 2,2,2-trifluoro-1-(amino)ethyl [CF_3–$CH(NH_2)$-] structural feature **1** (Fig. 1), has attracted considerable interest as a pharmacophore unit in the design of bioactive compounds [3,4]. One of the recent achievements in this area is the development of new drug Odanacatib (**2**) (Fig. 1) awaiting approval for treatment for osteoporosis and bone metastasis [5].

Methodological choice for preparation of CF_3–$CH(NH_2)$-pharmacophore unit **1** is rather limited including trifluoromethylation of imines **3** (Scheme 1) [6], reductive amination of ketones **4** [7] and additions of *C*-nucleophiles to imines **5** [8]. Among these methods, the reductive amination is by far most general and practical being used for large-scale preparation of Odanacatib **2** [5]. Of particular synthetic potential is the biomimetic version of a reductive amination using base-catalyzed 1,3-azomethine–azomethine isomerization [9,10] (Scheme 2).

Motivated by this limited choice of synthetic methodology, it was envisioned that chiral (*S*)-*N*-*tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine (*R*)- or (*S*)-**6** can serve as a universal reagent for generalized preparation of various types of compounds **1** [11]. Considering this quite stimulating synthetic potential of imine **6**, large-scale synthesis of both enantiomers of (*R*)- and (*S*)-**6** was developed rendering these compounds relatively inexpensive and commercially available [12]. Since 2011, our and other groups have been actively studying chemistry of CF_3-imine-**6** discovering its

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http://dx.doi.org/10.1016/j.jfluchem.2014.06.015
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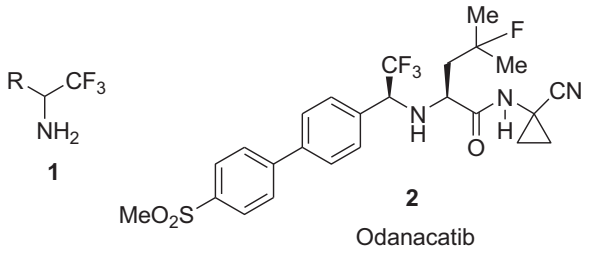
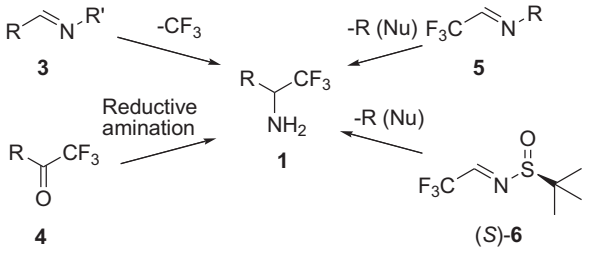
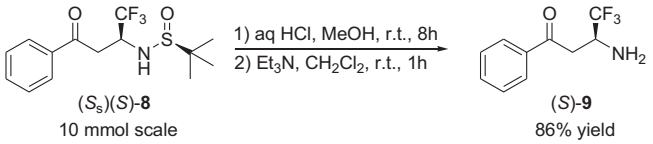


Fig. 1. 2,2,2-Trifluoro-1-(amino)ethyl pharmacophore **1** and new drug Odanacatib **2**.



Scheme 1. Synthetic approach for preparation of pharmacophore unit **1**.



Scheme 2. Large-scale (3.21 g) deprotection of product **8** to free amine **9**.

reactivity and mode of the asymmetric induction [13]. Justifiably, as it is always proper for the original research, all these reported data have been acquired using about 100 mg imine **6** scale. Taking into account that the ultimate goal in standing the chemistry of imine **6** is the synthesis of compounds with potentially new and useful biological properties, one may agree that the target compounds have to be prepared on gram scale to provide for their systematic biological studies. To this goal, we initiated a special project aiming at scaling up previously reported processes to estimate their practicality and limitations.

2. Results and discussion

2.1. Addition of ketone-derivative enolates to sulfinylimine (S)-6.

β-Keto-amino compounds and the related γ-amino alcohols are very important intermediates in preparation of various biologically relevant compounds pharmaceuticals [14]. Accordingly, fluorine-containing derivatives of these compounds have been attractive targets for synthetic chemists for quite some time [15]. Application of imines **6** for preparation of α-CF_3-β-keto-amines of type **8** (Table 1), through addition reactions with Li-enolates **7**, was shown to be quite generalized affording compounds **8** in 42–87% yields and good-to-excellent diastereoselectivity (74/26 to >99/1) [16]. In particular, under optimized reaction conditions, imine (*S*)-**6** readily reacted with acetophenone derived enolate **7** giving rise to the addition product (*Ss*)(*S*)-**8** in 84% yield and excellent (99/1) diastereoselectivity (Table 1, entry 1) [16].

Quite unexpectedly, scaling up this procedure from 0.5 to 5.0 and 25 mmol of starting imine (*S*)-**6** resulted in noticeable worsening of all major reaction factors, including chemical yield and diastereoselectivity. As shown in the original work, the stereochemical outcome of this Mannich addition is very sensible to the reaction temperature. Thus, the observed gradual decrease in the diastereoselectivity (entries 1, 2, 3) may indicate the problem with maintenance of −78 °C, required for the optimal stereoselectivity. For example, the diastereomeric ratio of 83/17 was obtained for 0.5 mmol reaction conducted at 0 °C [16]. Nevertheless, the target (S_s)(*S*)-**8** was isolated via column chromatography as a white solid in a reasonably good yield (61%) and markedly improved diastereoselectivity (97:3 dr).

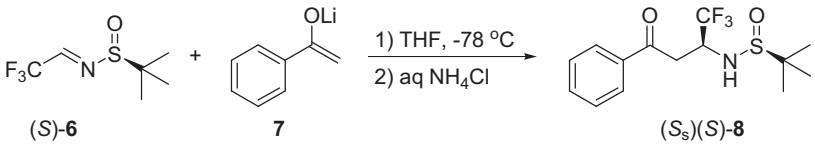
Thus prepared addition product (S_s)(*S*)-**8** was deprotected to furnish β-keto-amine (*S*)-**9**. Conducting this large-scale (3.21 g) process under the same conditions used previously for 0.5 mmol scale reaction, afforded amine (*S*)-**9** in 86% isolated yield, which is quite agreeable with the 90% yield obtained on the 0.5 mmol scale [16].

2.2. Addition of glycine Schiff base esters to sulfinylimine (S)-6

Our next goal was preparation of α,β-(diamino)acids, an important type of polyfunctional natural and tailor-made amino acids [17] with some specific biological properties [18]. Reports on asymmetric synthesis of fluorinated derivatives of α,β-(diamino)acids are rare [19] and their biological properties still await investigation. Therefore it was quite motivating to explore the application of imines **6** for large-scale preparation of enantiomerically pure 2,3-diamino-4,4,4-trifluorobutanoic acid. Previously we reported that reactions of imine (*S*)-**6** with glycine Schiff base/methyl ester **10** easily take place at ambient temperatures in the presence of organic or medium-strength inorganic bases (Table 2) [20]. Under the optimized conditions (THF, r.t., Cs_2CO_3) (entry 1) the target addition product (*Ss*)(*S*)-11 was isolated in both excellent yield (98%) and diastereomeric purity(dr 99/1).

Using the same conditions but scaling up the amount of the starting (sulfinyl)imine (*S*)-**6** from 1.0 mmol (entry 1) to 10.0 mmol (entry 2) and 25.0 mmol (entry 3) resulted in a gradual decrease in

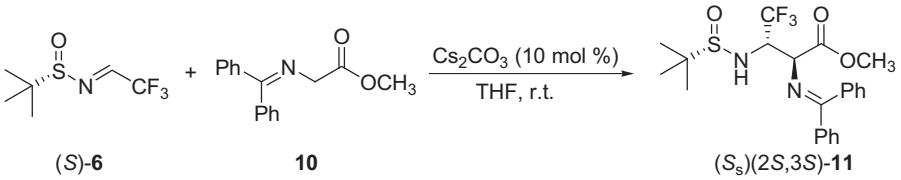
Table 1
Reactions of imine (*S*)-**6** (0.5–25.0 mmol) with Li-enolate **7**.



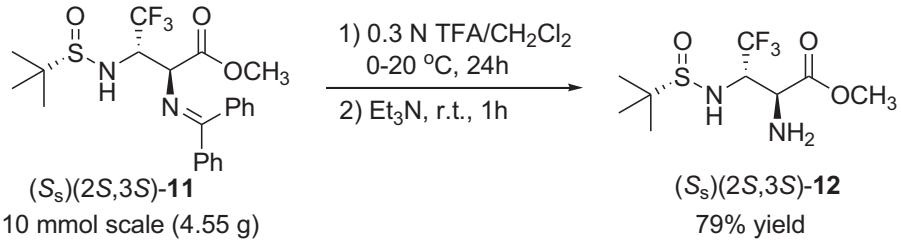
Entry	Scale of the reaction (mmol sulfinylimine)	Time (h)	Yield (%)	dr
1	0.5	2	84	99:1
2	5.0	2.5	74	95:5
3	25.0	4	61[a]	82:18

[a] Isolated yield of product **8** in diastereomeric ratio of 97/3.

Table 2
Reactions of imine (*S*)-**6** (1.0–25.0 mmol) with glycine Schiff base **10**.



Entry	Scale of the reaction (mmol sulfinylimine)	Time (h)	Yield (%)	Isomer ratio
1	1.0	1	98	99:1
2	10.0	1	95	99:1
3	25.0	1	86	>99:1



Scheme 3. Chemo-selective deprotection of the α-amino group in **11** giving rise to product **12**.

the isolated yield of product (S_s)(2*S*,3*S*)-**11** from 98% to 95% and 86%, respectively. However, the diastereoselectivity of the reactions remained constantly perfect 99/1. While the loss in the chemical yield was disappointing, the observed reproducibility in the diastereoselectivity rendered, in our opinion, this scaling up process rather encouraging. Obviously, one of the reasons for this successful outcome is that the process can be conducted under operationally convenient conditions [21], without recourse to controlled low temperatures, specially dried solvents or air/water-sensitive reagents.

The product (S_s)(2*S*,3*S*)-**11**, obtained as a white solid (4.55 g, 10 mmol, entry 3, 86% yield, >99:1 dr) was chemo-selectively deprotected (Scheme 3) to free the α-amino group giving rise to diastereomerically pure product **12**.

Product (S_s)(*S*)-**12** possesses α-free and β-protected amino groups and therefore can be used for selective incorporation of this type of fluorinated amino acid into peptides through one or another amino functionality.

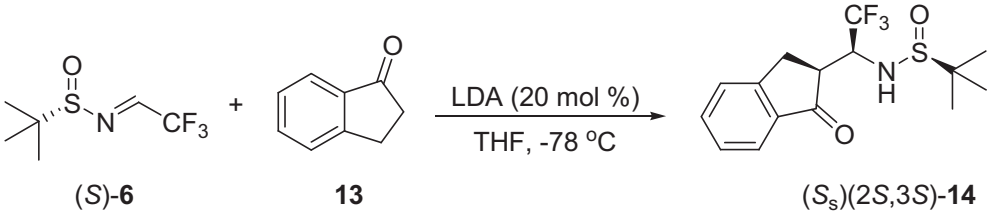
2.3. Addition of indanone-derivative enolates to sulfinylimine (*S*)-**6**

With these rather successful results we turned again to low-temperature reactions of imine (*S*)-**6** (1.0–25.0 mmol) with indanone-derivative enolates. Interest in these reactions was motivated by the fact that indanone derived fluorine-containing β-amino ketones are unknown type of compounds. However, one may envision that combination of indanone skeleton with CF3–CH(NH2)-pharmacophore unit might result in derivatives of pharmaceutical importance.

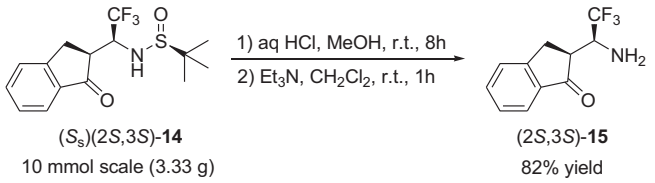
Previously we reported that the addition reaction between imine (*S*)-**6** and indanone-derived Li-enolate, conducted on 1.0 mmol scale [22], resulted in β-amino-ketone (S_s)(2*S*,3*S*)-**14** isolated in 94% yield and 99/1 dr (Table 3, entry 1).

Reproducing this reaction on 5.0 mmol scale (entry 2) resulted in 8% decrease in the chemical yield, while the diastereoselectivity was intact (99/1). Further fivefold increase of the reaction scale (entry 3) gave β-amino-ketone (S_s)(2*S*,3*S*)-**14** in 79% yield and 94/6

Table 3
Reactions of imine (*S*)-**6** (1.0–25.0 mmol) with indanone-derivative enolates.



Entry	Scale of the reaction (mmol sulfinylimine)	Time (h)	Yield (%)	Isomer ratio
1	1.0	4	94	99:1
2	5.0	5	86	99:1
3	25.0	6	79	94:6



Scheme 4. Deprotection of $(S_s)(S)$-**14** (3.33 g, 10.0 mmol) to free β-amino-ketone **15**.

diastereomeric ratio. Taking into account that this reaction was conducted at −78 °C, the obtained stereochemical outcome was rather encouraging. It should be pointed out that further purification of the product $(S_s)(2S,3S)$-**14**, from 94/6 dr to diastereomerically pure state (>99/1 dr) can be achieved simply by washing the crude product with hexane/ethyl acetate mixture (4:1). It should be noted that in this reaction, due to the formation of two new stereogenic centers, up to four diastereomerically products can be expected. Since the process is conducted at −78 °C and therefore may be sensitive to the reaction temperature, the observed stereochemical outcome for scaled up reactions is rather impressive. The reason for still high stereoselectivity might be in the reaction mechanism. In particular, considering importance of the geometric homogeneity of reaction species for the stereochemical outcome of the addition reactions [23], one may suggest that the results obtained in the reaction with indanone is due to its rigid cyclic structure and the formation of geometrically homogeneous enolates.

Diastereomerically pure 3.33 g of product $(S_s)(S)$-**14** was deprotected under the standard conditions (MeOH/HCl) furnishing free β-amino-ketone **15** in 82% yield (Scheme 4). Though the yield of (S)-**15** on the much smaller 0.5 mmol scale was 87%, it seems that this stage presents no problems for further scaling up of this procedure.

2.4. Addition of imidazo[2,1-b]-thiazole-derived nucleophiles to sulfinylimine (S)-6

With these results in hand, we decided to focus the rest of this study on the addition reactions between imine (S)-**6** with *C*-nucleophiles derived from heterocyclic compounds. For instance, the imidazo[2,1-*b*]thiazole moiety features prominently in numerous natural as well as synthetic biologically active compounds [24]. However, its fluorinated derivatives containing amino functionality have not been described.

Recently, we reported that imine (S)-**6** can be reacted with Li-nucleophile derived from imidazo[2,1-*b*]thiazole **16** to furnish new family of potentially biologically interesting compounds of type 17 (Table 4) [25]. The original addition procedure conducted on 0.5 mmol scale gave rise to the product $(S_s)(S)$-**17** in 70% yield and perfect diastereoselectivity (>99/1) (entry 1). Delightfully, scaling up the reaction by 10 fold gave virtually the same yield and stereochemical outcome (entry 2). On the other hand, further increase of the reaction scale, to 25.0 mmol of imine (S)-**6**, resulted in slightly reduced yield 65% (entry 3) but noticeably worsened diastereoselectivity. This outcome was quite similar to the results obtained in 0.5 mmol scale reaction conducted at 0 °C [25]. The data obtained, clearly suggested that the stereochemical outcome of this large-scale reaction is critically sensitive to strict-controlling the reaction temperature and may be improved by using appropriate low-temperature equipment.

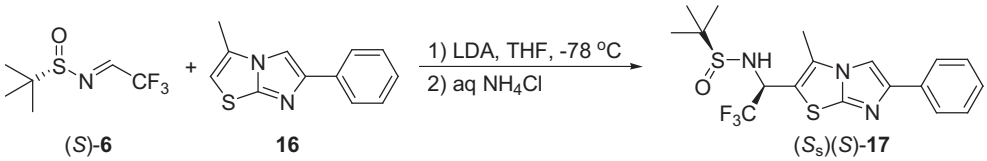
Nevertheless, the product $(S_s)(S)$-**17** was obtained in diastereomerically pure state via column chromatography and deprotected to free amine (S)-**18** (Scheme 5). Again, the isolated yield (87%) of amine (S)-**18** was just a bit lower than that (91%) obtained on the 0.5 mmol scale reaction (Scheme 6).

2.5. Addition of thiazolo[3,2-b] [1,2,4]triazole-derived nucleophiles to sulfinylimine (S)-6

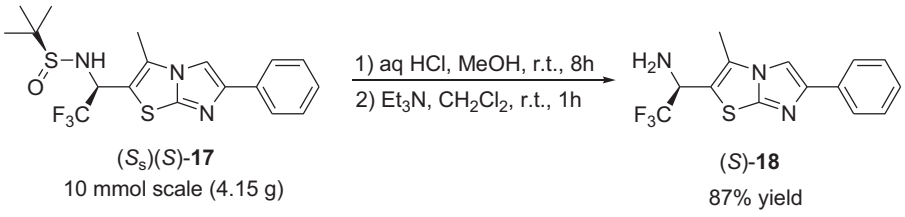
The thiazolo[3,2-*b*][1,2,4]triazole structural fragment is found in biologically active natural products [26]. Like in the discussed above case of imidazo[2,1-*b*]thiazoles, fluorinated amino-derivatives of thiazolo[3,2-*b*][1,2,4]triazoles are virtually unknown compounds.

We demonstrated that the nucleophile derived from heterocycle **19** can be cleanly added to imine (S)-**6** resulting the corresponding addition products $(S_s)(S)$-**20** (Table 5) [27]. In the small-scale reactions (0.5 mmol, entry 1) amine $(S_s)(S)$-**20** was obtained in 71% yield and good 98/2 dr. Gradual increase of the

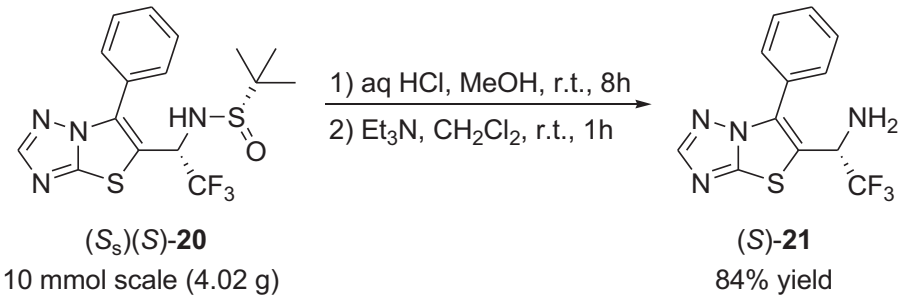
Table 4
Addition reactions between imine (S)-**6** (0.5–25.0 mmol) with imidazo[2,1-*b*]-thiazole-derived nucleophiles **16**.



Entry	Scale of the reaction (mmol sulfinylimine)	Time (h)	Yield (%)	dr
1	0.5	2	70	>99:1
2	5.0	2.5	69	>99:1
3	25.0	3	65	90:10

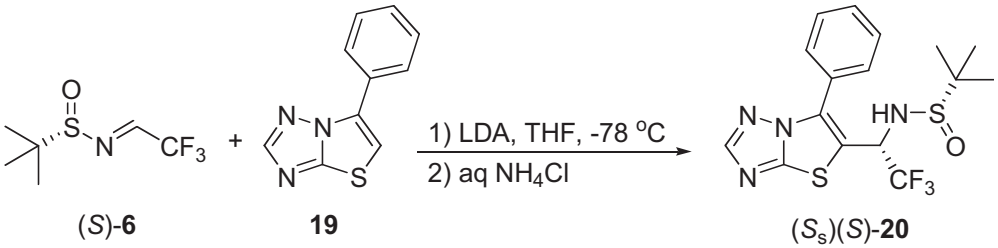


Scheme 5. Deprotection of $(S_s)(S)$-**17** (4.15 g, 10.0 mmol) to free amine **18**.



Scheme 6. Deprotection of (S_s)(S)-**20** (4.02 g, 10.0 mmol) to free amine (S)-**21**.

Table 5
Addition reactions between imine (S)-**6** (0.5–25.0 mmol) with thiazolo[3,2-*b*] [1,2,4]triazole-derived nucleophiles **19**.



Entry	Scale of the reaction (mmol sulfinylimine)	Time (h)	Yield (%)	dr
1	0.5	2	71	98:2
2	5.0	2.5	68	94:6
3	25.0	3	63	90:10

reaction scale to 5.0 (entry 2) and 25.0 mmol (entry 3) of starting imine (S)-**6** led to worsening of the stereochemical outcome. However, the decrease in chemical yield and diastereoselectivity was rather moderate and in a line with the other examples discussed in this study. Importantly, the target product (S_s)(S)-**20** was obtained in diastereomerically pure form (63%) via purification by column chromatography.

Deprotection of product (S_s)(S)-**20** was conducted on 4.02 scale using standard conditions (MeOH/HCl). The isolated yield of enantiomerically pure free amine (S)-**21** was 84% which is just 2% lower as compared with 0.5 scale reaction (86%) [27].

3. Conclusions

This work describes the first attempt to scale up the addition reactions between (S_S)-*N*-*tert*-butanesulfinyl-(3,3,3)-trifluoroacetaldimine **6** with *C*-nucleophiles derived from ketones, glycine Schiff base and heterocycles. In all five reactions studied, the stereochemical outcome of the scaled up (5.0–25.0 mmol) reactions was lower as compared with 0.5 mmol processes. However, the observed decrease in yields and diastereoselectivity is not identical and depends on the original reaction conditions and reaction mechanisms. For example, scaling up the room temperature reactions (additions of glycine Schiff base **10**, Table 2) gave the corresponding addition products (S_s)(2*S*,3*S*)-**11** comparable to small scale (0.5 mmol) reactions chemical yields and even better diastereoselectivity. On the other hand low-temperature (−78 °C) reactions gave the target product with noticeably (~10%) lower yields and stereoselectivity. These data clearly suggested that special equipment to control and maintain the reaction temperature must be used to obtain desirable outcome. Taking advantage of diastereomeric nature of the resultant products, all target compounds were obtained in optically pure state by washing out the minor diastereomer or by column chromatography. In this regard, we would like to emphasize that the development of alternative, nonconventional methods for optical purifications using SDE [28] (self-disproportionation of enantiomers) via sublimation [29] or achiral chromatography [30] should receive due attention. All target products were deprotected on large scale to free amino compounds. These room temperature reactions generally presented no scaling problems and proceeded with close to original (0.5 scale) chemical yields.

4. Experimental

4.1. General

All commercial reagents and solvents were used without additional purification unless otherwise specified. CF_3-Sulfinylimine **6** was obtained from Accela ChemBio Co., Ltd. All experiments were monitored by thin layer chromatography (TLC). TLC was performed on pre-coated silica gel plated. Column chromatography was performed using silica gel 60 (300–400 mesh).

^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz) and ^{19}F NMR (376 MHz) were measured on a Bruker AVANCE III-400 spectrometer. Chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.0 ppm) or with the solvent reference relative to TMS employed as the internal standard ($CDCl_3$, δ 7.26 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants [Hz], integration). Melting points are uncorrected. Values of optical rotation were measured on a Rudolph Automatic Polarimeter A21101. HRMS were recorded on a LTQ-Orbitrap XL (Thermofisher, U.S.A.).

*4.2. Procedure for the addition of ketone-derivative enolates **7** to sulfinylimine (S)-**6** (25 mmol scale)*

Into an oven-dried round-bottom flask flushed with N_2 were taken acetophenone (5.11 g, 42.5 mmol) and anhydrous THF (100 mL). The reaction flask was cooled to −78 °C and LDA (2 M in THF, 23.4 mL) was added dropwise with stirring. After 45 min at −78 °C, sulfinylimine (*S*)-**6** (5.03 g, 25.0 mmol) dissolved in anhydrous THF (50 mL) was added dropwise. Stirring was continued at −78 °C for 4 h, then the reaction was quenched with saturated NH_4Cl (50 mL) followed by H_2O (75 mL) and the mixture was brought to room temperature. The organic layer was taken and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with H_2O (2 × 200 mL) and brine solution (1 × 200 mL) and dried with anhydrous Na_2SO_4, filtered and the solvent was removed to give the crude product (82:18 dr, determined by ^{19}F NMR analysis of the crude product), which was purified by column chromatography (hexanes/EtOAc = 4:1) to afford the corresponding product **8** as a white solid in 61% isolated yield with 97:3 dr.

(S)-2-methyl-N-((S)-1,1,1-trifluoro-4-oxo-4-phenylbutan-2-yl)propane-2-sulfinamide (8). White solid (4.89 g, 61% yield), mp 140–142 °C. $[\alpha]_D^{25}$ + 45.8 (*c* = 0.94, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.89 − 7.93 (m, 2H), 7.63 − 7.57 (m, 1H), 7.52 − 7.45 (m, 2H), 4.61 − 4.48 (m, 1H), 3.89 (d, *J* = 8.5 Hz, 1H), 3.70 (dd, *J* = 17.7, 9.7 Hz, 1H), 3.30 (dd, *J* = 17.7, 3.1 Hz, 1H), 1.16 (s, 9H), ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 195.0, 136.2, 133.9, 128.9, 128.2, 125.4 (q, *J* = 281.8 Hz), 57.0, 54.0 (q, *J* = 30.8 Hz), 38.1, 22.4, ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −74.3. HRMS [M + Na^+]: calcd for $C_{14}H_{18}F_3NO_2SNa^+$: 344.0903, found: 344.0893.

*4.3. Procedure for the large-scale (10 mmol scale) deprotection of product **8** to free amine **9***

The product **8** (3.21 g, 10.0 mmol) and MeOH (100 mL) were placed in a 250 mL round-bottom flask and aq. HCl (36%, 20 mL) was added dropwise. The reaction was stirred at r.t. 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 (200 mL) and Et_3N (30.36 g, 300 mmol) was added. The mixture was stirred at r.t. for 1 h, then H_2O (200 mL) was added. The organic layer was taken, washed with H_2O (2 × 200 mL), dried with anhydrous Na_2SO_4, filtered and the solvent was removed to give the crude product, which was purified by column chromatography (hexanes/EtOAc = 2:1) to afford the corresponding deprotection product **9** as a white solid in 86% isolated yield.

(S)-3-amino-4,4,4-trifluoro-1-phenylbutan-1-one (9). White solid (1.86 g, 86% yield), mp 30–31 °C. $[\alpha]_D^{25}$ − 55.0 (*c* = 0.44, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.00 − 7.91 (m, 2H), 7.63 − 7.56 (m, 1H), 7.52 − 7.44 (m, 2H), 4.06 − 3.95 (m, 1H), 3.31 (dd, *J* = 17.5, 2.7 Hz, 1H), 3.18 (dd, *J* = 17.5, 9.7 Hz, 1H), 1.61 (s, 2H), ^{13}C NMR ($CDCl_3$, 101 MHz): δ =196.3, 136.4, 133.8, 128.9, 128.2, 126.6 (q, *J* = 280.3 Hz), 50.3 (q, *J* = 29.8 Hz), 39.4 (d, *J* = 1.0 Hz), ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −78.2. HRMS [M + H^+]: calcd for $C_{10}H_{11}F_3NO^+$: 218.0787, found: 218.0796.

*4.4. Procedure for the addition of glycine Schiff base esters to sulfinylimine (S)-**6** (25 mmol scale)*

Sulfinylimine (*S*)-**6** (5.03 g, 25.0 mmol), glycine Schiff base ester **10** (6.97 g, 27.5 mmol) and Cs_2CO_3 (0.81 g, 2.5 mmol) were dissolved in THF (125 mL), and the resulting reaction mixture was stirred at r.t. for 1 h. After the reaction was complete, the reaction was quenched with saturated NH_4Cl (20 mL), followed by H_2O (50 mL). The organic layer was taken and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (2 × 200 mL) and brine solution (1 × 200 mL) and dried over anhydrous Na_2SO_4, filtered and the solvent was removed to give the crude product (99:1 dr, determined by ^{19}F NMR analysis of the crude product), which was purified by column chromatography (hexanes/EtOAc = 4:1) to afford the corresponding product **11** as a white solid in 86% isolated yield with virtually complete diastereoselectivity (>99:1 dr).

(2S,3S)-methyl 3-((S)-1,1-dimethylethylsulfinamido)-2-((diphenylmethylene)amino)-4,4,4-trifluorobutanoate (11). White solid (9.79 g, 86% yield), mp 160–161 °C. $[\alpha]_D^{25}$ − 80.2 (*c* = 1.02, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.62 − 7.58 (m, 2H), 7.48 − 7.43 (m, 4H), 7.39 − 7.33 (m, 2H), 7.16 − 7.11 (m, 2H), 5.08 (d, *J* = 10.7 Hz, 1H), 4.52 − 4.40 (m, 2H), 3.72 (s, 3H), 1.26 (s, 9H), ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 174.0, 169.0, 138.7, 135.7, 131.2, 129.3, 129.0, 128.8, 128.3, 127.2, 124.5 (q, *J* = 284.8 Hz), 63.9, 59.8 (q, *J* = 29.8 Hz), 57.3, 52.9, 22.5, ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −72.5. HRMS [M + Na^+]: calcd for $C_{22}H_{25}F_3N_2O_3SNa^+$: 477.1436, found: 477.1430.

*4.5. Procedure for the chemo-selective deprotection of the α-amino group in **11** giving rise to product **12** (10 mmol scale)*

The product **11** (4.55 g, 10 mmol) was dissolved in CH_2Cl_2 (100 mL) in a round-bottom flask, and the resulting mixture was cooled to 0 °C. TFA (3.42 g, 30 mmol) was added dropwise with stirring, and the reaction was allowed to continue at 20 °C for 24 h (monitored by TLC). Upon completion, Et_3N (6.07 g, 60 mmol) was added, and the mixture was stirred at r.t. for 1 h. H_2O (200 mL) was then added. The organic layer was separated, washed with H_2O (2 × 200 mL), dried with anhydrous Na_2SO_4, and filtered. The solvent was removed to give the crude product, which was purified by column chromatography (hexanes/EtOAc = 2:1) to afford the corresponding deprotection product **12** as a colorless oil in 79% isolated yield.

(2S,3S)-methyl 2-amino-3-((S)-1,1-dimethylethylsulfinamido)-4,4,4-trifluorobutanoate (12). Colorless oil (2.28 g, 79% yield). $[\alpha]_D^{25}$ + 5.20 (*c* = 0.88, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.67 (d, *J* = 10.5 Hz, 1H), 4.26 − 4.14 (m, 1H), 4.07 (s, 1H), 3.75 (s, 3H), 1.75 (s, 2H), 1.14 (s, 9H), ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 171.5, 124.8 (q, *J* = 284.2 Hz), 58.4 (q, *J* = 29.3 Hz), 57.2, 53.1, 52.9 (d, *J* = 1.4 Hz), 22.4, ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −72.6. HRMS [M + Na^+]: calcd for $C_9H_{17}F_3N_2O_3SNa^+$: 313.0804, found: 313.0806.

*4.6. Procedure for the addition of indanone-derivative enolates to sulfinylimine (S)-**6** (5 mmol scale)*

Into an oven-dried round-bottom flask flushed with N_2 were taken 1-indanone **13** (0.73 g, 5.5 mmol) and anhydrous THF (25 mL). The reaction flask was cooled to −78 °C and LDA (2 M in THF, 0.55 mL) was added dropwise with stirring. After 40 min at −78 °C, sulfinylimine **6** (1.01 g, 5.0 mmol) dissolved in anhydrous THF (10 mL) was pre-cooled to −78 °C, then added dropwise to the reaction mixture. Stirring was continued at −78 °C for 5 h, then the reaction was quenched with saturated NH_4Cl (20 mL), followed by H_2O (50 mL) and the mixture was brought to room temperature. The organic layers were taken and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (2 × 100 mL) and brine solution (1 × 100 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the crude mixture was co-concentrated with hexane (99:1 dr, determined by ^{19}F NMR analysis of the crude product). The solid product was washed with a minimum amount of hexane/ethyl acetate mixture (8:1) to afford pure product **14** in 86% isolated yield with virtually complete diastereoselectivity.

(S)-2-methyl-N-((S)-2,2,2-trifluoro-1-((S)-1-oxo-2,3-dihydro-1H-inden-2-yl)ethyl)propane-2-sulfinamide (14). White solid (5 mmol scale: 1.44 g, 86% yield, 25 mmol scale: 6.58 g, 79% yield), mp 193–195 °C. $[\alpha]_D^{25}$ − 104.3 (*c* = 1.21, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.76 (d, *J* = 7.7 Hz, 1H), 7.65 (td, *J* = 7.6, 1.1 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.3 Hz, 1H), 4.72 − 4.61 (m, 1H), 3.44 − 3.29 (m, 2H), 3.15 − 3.05 (m, 2H), 0.93 (s, 9H), ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 203.6, 153.4, 136.1, 135.7, 128.0, 126.7, 125.3 (q, *J* = 282.9 Hz), 124.1, 58.1 (q, *J* = 30.5 Hz), 57.2, 47.0, 27.2, 22.3, ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −73.1. HRMS [M + Na^+]: calcd for $C_{15}H_{18}F_3NO_2SNa^+$: 356.0908, found: 356.0906.

4.7. Procedure for the addition of indanone-derivative enolates to sulfinylimine (S)-**6** (25 mmol scale)

Into an oven-dried round-bottom flask flushed with N_2 were taken 1-indanone **13** (3.63 g, 27.5 mmol) and anhydrous THF (125 mL). The reaction flask was cooled to −78 °C and LDA (2 M in THF, 2.75 mL) was added dropwise with stirring. After 40 min at −78 °C, sulfinylimine **6** (5.03 g, 25.0 mmol) dissolved in anhydrous THF (50 mL) was pre-cooled to −78 °C, then added dropwise to the reaction mixture. Stirring was continued at −78 °C for 6 h, then the reaction was quenched with saturated NH_4Cl (50 mL), followed by H_2O (100 mL) and the mixture was brought to room temperature. The organic layers were taken and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with H_2O (2 × 200 mL) and brine solution (1 × 200 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the crude mixture was co-concentrated with hexane (94:6 dr, determined by ^{19}F NMR analysis of the crude product). The solid product was washed with a minimum amount of hexane/ethyl acetate mixture (4:1) to afford pure product **14** in 79% isolated yield with virtually complete diastereoselectivity.

4.8. Procedure for the deprotection of product **14** (10 mmol scale) to free β-amino-ketone **15**

The product **14** (3.33 g, 10.0 mmol) and MeOH (100 mL) were placed in a 250 mL round-bottom flask and aq. HCl (36%, 20 mL) was added dropwise. The reaction was stirred at r.t. 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 (200 mL) and Et_3N (30.36 g, 300 mmol) was added. The mixture was stirred at r.t. for 1 h, then H_2O (200 mL) was added. The organic layer was taken, washed with H_2O (2 × 200 mL), dried with anhydrous Na_2SO_4, filtered and the solvent was removed to give the crude product, which was purified by column chromatography (hexanes/EtOAc = 2:1) to afford the corresponding deprotection product **15** as a white solid in 82% isolated yield.

(S)-2-((S)-1-amino-2,2,2-trifluoroethyl)-2,3-dihydro-1H-inden-1-one (15). White solid (1.89 g, 82% yield), mp 76–77 °C. $[\alpha]_D^{25}$ − 58.1 (*c* = 1.58, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.75 (d, *J* = 7.7 Hz, 1H), 7.60 (td, *J* = 7.6, 1.1 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 4.16 − 4.05 (m, 1H), 3.23 − 3.18 (m, 2H), 3.04 − 2.97 (m, 1H), 1.33 (s, 2H), ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 204.9, 154.1, 136.3, 135.3, 127.7, 126.7, 126.7 (q, *J* = 281.5 Hz), 124.1, 52.6 (q, *J* = 29.4 Hz), 47.3, 26.4 (d, *J* = 0.7 Hz), ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −76.2. HRMS [M + H^+]: calcd for $C_{11}H_{11}F_3NO^+$: 230.0793, found: 230.0778.

4.9. Procedure for the addition of imidazo[2,1-b]-thiazole-derived nucleophiles to sulfinylimine (S)-**6** (25 mmol scale)

Into an oven-dried round-bottom flask flushed with N_2 were taken imidazo[2,1-*b*]-thiazole **16** (9.11 g, 42.5 mmol) and anhydrous THF (100 mL). The reaction flask was cooled to −78 °C and LDA (2 M in THF, 19.1 mL) was added dropwise with stirring. After 1 h at −78 °C, sulfinylimine **6** (5.03 g, 25.0 mmol) dissolved in anhydrous THF (50 mL) was added dropwise. Stirring was continued at −78 °C for 3 h, then the reaction was quenched with saturated NH_4Cl (50 mL) followed by H_2O (75 mL) and the mixture was brought to room temperature. The organic layer was taken and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with H_2O (2 × 200 mL) and brine solution (1 × 200 mL) and dried with anhydrous Na_2SO_4, filtered and the solvent was removed to give the crude product (90:10 dr, determined by ^{19}F NMR analysis of the crude product), which was purified by column chromatography (hexanes/EtOAc = 2:1) to afford the corresponding product **17** as a white solid in 65% isolated yield with virtually complete diastereoselectivity.

(S)-2-methyl-N-((R)-2,2,2-trifluoro-1-(3-methyl-6-phenylimidazo[2,1-b]thiazol-2-yl)ethyl)propane-2-sulfinamide (17). White solid (6.74 g, 65% yield), mp 182–183 °C. $[\alpha]_D^{25}$ + 153.1 (*c* = 1.04, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.86 − 7.82 (m, 2H), 7.64 (s, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 5.19 (qd, *J* = 6.5, 2.1 Hz, 1H), 3.84 (s, 1H), 2.53 (s, 3H), 1.28 (s, 9H), ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 148.6, 147.7, 133.8, 129.7, 128.7, 127.6, 125.3, 123.9 (q, *J* = 282.0 Hz), 114.4, 106.2, 56.7, 54.0 (q, *J* = 32.6 Hz), 22.4, 12.1, ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −74.0. HRMS [M + Na^+]: calcd for $C_{18}H_{20}F_3N_3OS_2Na^+$: 438.0892, found: 438.0894.

4.10. Procedure for the deprotection of product **17** (10 mmol scale) to free amine 18

The product **17** (4.15 g, 10.0 mmol) and MeOH (100 mL) were placed in a 250 mL round-bottom flask and aq. HCl (36%, 20 mL) was added dropwise. The reaction was stirred at r.t. 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 (200 mL) and Et_3N (30.36 g, 300 mmol) was added. The mixture was stirred at r.t. for 1 h, then H_2O (200 mL) was added. The organic layer was taken, washed with H_2O (2 × 200 mL), dried with anhydrous Na_2SO_4, filtered and the solvent was removed to give the crude product, which was purified by column chromatography (hexanes/EtOAc = 1:1) to afford the corresponding deprotection product **18** as a white solid in 87% isolated yield.

(R)-2,2,2-trifluoro-1-(3-methyl-6-phenylimidazo[2,1-b]thiazol-2-yl)ethanamine (18). White solid (2.70 g, 87% yield), mp 121–122 °C. $[\alpha]_D^{25}$ + 35.0 (*c* = 1.14, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.85 − 7.80 (m, 2H), 7.58 (s, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 4.75 (q, *J* = 6.7 Hz, 1H), 2.43 (s, 3H), 1.98 (br, 2H), ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 148.2, 146.9, 133.9, 128.6, 127.4, 126.6, 125.0, 124.9 (q, *J* = 281.9 Hz), 118.8, 105.8, 51.9 (q, *J* = 32.0 Hz), 11.8, ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −76.7. HRMS [M + H^+]: calcd for $C_{14}H_{13}F_3N_3S^+$: 312.0777, found: 312.0769.

4.11. Procedure for the addition of thiazolo[3,2-b] [1,2,4]triazole-derived nucleophiles to sulfinylimine (S)-**6** (25 mmol scale)

Into an oven-dried round-bottom flask flushed with N_2 were taken thiazolo[3,2-*b*][1,2,4]triazole **19** (8.55 g, 42.5 mmol) and anhydrous THF (100 mL). The reaction flask was cooled to −78 °C and LDA (2 M in THF, 23.4 mL) was added dropwise with stirring. After 1 h at −78 °C, sulfinylimine (5.03 g, 25.0 mmol) dissolved in anhydrous THF (50 mL) was added dropwise. Stirring was continued at −78 °C for 3 h, then the reaction was quenched with saturated NH_4Cl (50 mL) followed by H_2O (75 mL) and the mixture was brought to room temperature. The organic layer was taken and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with H_2O (2 × 200 mL) and

brine solution (1 × 200 mL) and dried with anhydrous Na_2SO_4, filtered and the solvent was removed to give the crude product (90:10 dr, determined by ^{19}F NMR analysis of the crude product), which was purified by column chromatography (hexanes/EtOAc = 2:1) to afford the corresponding product **20** as a white solid in 63% isolated yield with virtually complete diastereoselectivity.

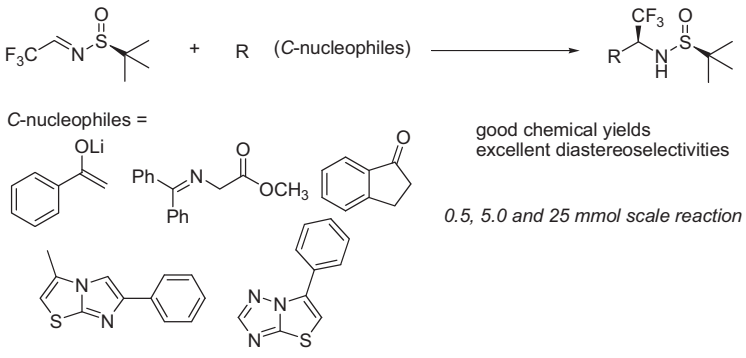
(S)-2-methyl-N-((R)-2,2,2-trifluoro-1-(6-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl)ethyl)propane-2-sulfinamide (20). White solid (6.35 g, 63% yield), mp 188–189 °C. $[\alpha]_D^{25}$ + 111.0 (c = 0.98, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.14 (s, 1H), 7.69 (dd, J = 7.7, 1.8 Hz, 2H), 7.59 – 7.52 (m, 3H), 5.30 (qd, J = 6.3, 2.4 Hz, 1H), 4.01 (s, 1H), 1.25 (s, 9H), ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 156.3, 156.0, 135.7, 131.0, 129.6, 129.5, 126.0, 123.7 (q, J = 282.4 Hz), 118.0, 57.0, 54.7 (q, J = 32.4 Hz), 22.5, ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −73.8. HRMS [M + Na^+]: calcd for $C_{16}H_{17}F_3N_4OS_2Na^+$: 425.0688, found: 425.0681.

*4.12. Procedure for the deprotection of product **20** (10 mmol scale) to free amine **21***

The product **20** (4.02 g, 10.0 mmol) and MeOH (100 mL) were placed in a 250 mL round-bottom flask and aq. HCl (36%, 20 mL) was added dropwise. The reaction was stirred at r.t. 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 (200 mL) and Et_3N (30.36 g, 300 mmol) was added. The mixture was stirred at r.t. for 1 h, then H_2O (200 mL) was added. The organic layer was taken, washed with H_2O (2 × 200 mL), dried with anhydrous Na_2SO_4, filtered and the solvent was removed to give the crude product, which was purified by column chromatography (hexanes/EtOAc = 1:1) to afford the corresponding deprotection product **21** as a white solid in 84% isolated yield.

(R)-2,2,2-trifluoro-1-(6-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl)ethanamine (21). White solid (2.52 g, 84% yield), mp 106–108 °C. $[\alpha]_D^{25}$ – 3.8 (c = 1.23, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.15 (s, 1H), 7.69 – 7.62 (m, 2H), 7.60 – 7.56 (m, 3H), 4.86 (q, J = 6.6 Hz, 1H), 1.95 (br, 2H), ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 155.9, 155.2, 132.5, 130.6, 129.4, 129.2, 126.6, 124.7 (q, J = 282.2 Hz), 122.8, 52.3 (q, J = 31.9 Hz), ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −75.8. HRMS [M + H^+]: calcd for $C_{12}H_{10}F_3N_4S^+$: 299.0573, found: 299.0580.

Table of contents



Acknowledgment

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 (Nos. 1107020522 and 1082020502). The Jiangsu 333 program (for Pan) and Changzhou Jin-Feng-Huang program (for Han) are also acknowledged.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2014.06.015.

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