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Asymmetric synthesis of trifluoromethylated propargylamines via 1,2-additions of trifluoromethylacetylide to *N*-*tert*-butanesulfinyl imines

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Abstract

An efficient method for the asymmetric synthesis of the trifluoromethylated propargylamines was described. Addition of lithium trifluoromethylacetylide, in situ prepared from lithium diisopropylamide and the 2-bromo-3,3,3-trifluoropropene, to various *N*-*tert*-butanesulfinyl imines provided a range of trifluoromethylated propargyl sulfinamides. Besides high yields and excellent diastereoselectivities, the additions featured that the diastereoselectivities could be reversed when polar or nonpolar solvent was used. Acidic cleavage of the *tert*-butanesulfinyl groups delivered highly optically pure trifluoromethylated propargylamines.

Keywords: Asymmetric synthesis; Trifluoromethyl group; Propargylamine; 1,2-Addition

1. Introduction

Propargylamines, especially chiral propargylamines, are important building blocks in the synthesis of many pharmaceutical intermediates and natural products.[1] Recently, developing the novel and efficient access to the chiral propargylamines has received increasing attention of organic chemists. Generally, two major strategies were used to prepare chiral propargylamines. One tactics utilized the chiral metal–ligand complexes to induce the addition of alkynes to enamines or imines. For example, Knochel group described the addition of functionalized alkynes to enamines catalyzed by Cu(I)–Quinap complexes.[2] This group also found that Cu(I)–Quinap complexes were also efficient in one-pot three-component addition of trimethylsilylacetylene, aldehydes, and Bn_2NH.[3] In addition, asymmetric addition of alkynes to imines with a recyclable Cu(I)–bis(oxazoline)/stearic acid system was also reported by Li et al.[4] The other strategy was asymmetric addition of alkynyl metal reagent to chiral sulfinylimine. As the chiral auxiliary, chiral sulfinylimine appeared to be very successful in the asymmetric synthesis of propargylamines. Almost at the same time, Hou group[5] and Ellman group[6] documented the highly asymmetric synthesis of α-monobranched and α,α-dibranched propargylamines through addition of lithium acetylide to *N*-*tert*-butanesulfinimines and *N*-*tert*-butanesulfinyl ketimines, respectively. Very recently, diastereoselective synthesis of propargylamines via addition of alkynyl dimethyl aluminum compounds onto *N*-*p*-tolylsulfinylimines was also investigated.[7] With chiral prolinol derivatives as chiral auxiliaries, Che group also fulfilled the diastereoselective synthesis of propargylamines by means of gold(III) salen complex-catalyzed three-component coupling reaction of aldehydes, amines, and alkynes.[8]

Currently, it is well known that trifluoromethyl-containing compounds play important roles in pharmaceutical, agrochemical, and materials sciences.[9] Trifluoromethyl group has an

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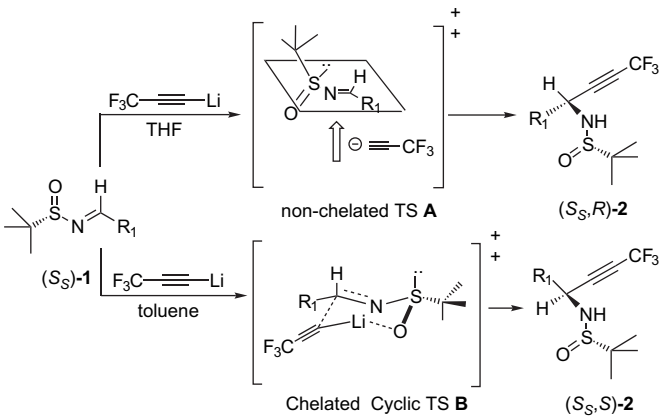
electronegativity similar to that of oxygen[10] and a high hydrophobic parameter.[11] Furthermore, the high lipophilicity brought about by the CF_3 moiety confers a better bioavailability to the molecules bearing this group.[12] However, to the best of our knowledge, there is no report about the preparation of chiral trifluoromethylated propargylamines although many methodologies were developed to access propargylamines. Recently, our group described the nucleophilic addition of 3,3,3-trifluoropropynyllithium to D-glyceraldimine and the resultant products were successfully used in the synthesis of the chiral 5,5,5-trifluoronorvaline.[13] As a part of our ongoing research about developing the versatile fluorine-containing building blocks, herein reported our results for the asymmetric synthesis of 4,4,4-trifluoromethylated propargylamines via addition of lithium trifluoromethylacetylide to the various *N-tert*-butanesulfinyl imines.

2. Result and discussion

The *N-tert*-butanesulfinyl aldimines **1** were prepared by a simple $CuSO_4$-mediated condensation of *tert*-butanesulfinamide with aldehydes according to the reported procedure.[14] The 1,2-addition of lithium trifluoromethylacetylide to **1** was performed by the dropwise addition of a solution of **1** to a solution of lithium trifuoromethylacetylide, in situ prepared through the reaction of 2 equiv of LDA with 2-bromo-3,3,3-trifluoropropene at −78 °C. Uniformly, good diastereoselectivities and medium yields were observed for a broad range of aldimines (S_S)-**1** (Table 1). When the additions were performed in THF, the desired trifluoromethylated propargyl sulfinamides **2** were obtained in 89:11 to 94:6 dr and (S_S,*R*)-**2a**–**d** observed to be the major diastereoisomers (entries 1–4, Table 1). Purification of the crude products **2a**–**d** by silica gel chromatography readily delivered two pure isomers (S_S,*R*)-**2a**–**d** and (S_S,*S*)-**2a**–**d**. The absolute configuration of the major isomer (S_S,*R*)-**2a** was determined by X-ray crystallographic analysis (Fig. 1).[15] Interestingly, reactions carried out in toluene were found to favor the formation of the (S_S,*S*)-**2a**–**d**, which were obtained in 86:14 to 99:1 dr (entries 5–8, Table 1). A rationale for the observed switchover in diastereoselectivities through changing the solvent could be provided through two different transition states, the non-chelated transition state **A** and chelated transition state **B**.[16] That is, chelated solvent THF could efficiently inhibit the formation of transition state **B** and the trifluoropropynyl anion mainly attacked the less shielded side of *N-tert*-butanesulfinyl aldimines, which resulted in the formation of (S_S,*R*)-**2** as the major isomers. However, nonchelating solvent toluene would be essential to prevent competitive coordination of the solvent to the metal cation and chelated cyclic transition state **B** predominantly occurred, which delivered the isomers (S_S,*S*)-**2** as the dominant adducts.

The addition of lithium trifluoromethylacetylide to *N-tert*-butanesulfinyl ketimines **3** was also investigated (Table 2). The sulfinyl ketimines **3** used in this study were prepared by $Ti(OEt)_4$-mediated condensations of *N-tert*-butylsulfinamide with ketones.[14] For the ketimines **3a**, **3c**, and **3d**, only the *E* isomers were observed. The ketimine **3b** was isolated as a mixture of *E* and *Z* isomers (6:1). We found that the 1,2-addition of lithium trifluoromethylacetylide to *N-tert*-butanesulfinyl

Table 1
The 1,2-addition of lithium trifluoromethylacetylide to *N-tert*-butanesulfinyl aldimines



Entry	R_1	Solvent	Product[a]	Yield[b] (%)	(S_S,*S*)-**2**/(S_S,*R*)-**2** (dr)
1	Et (**1a**)	THF	(S_S,*R*)-**2a**	69	7:93[c]
2	^{i}Pr (**1b**)	THF	(S_S,*R*)-**2b**	73	8:92[d]
3	Pr (**1c**)	THF	(S_S,*R*)-**2c**	67	6:94[c]
4	^{i}Bu (**1d**)	THF	(S_S,*R*)-**2d**	76	11:89[c]
5	Et (**1a**)	Toluene	(S_S,*S*)-**2a**	79	86:14[c]
6	^{i}Pr (**1b**)	Toluene	(S_S,*S*)-**2b**	85	87:13[d]
7	Pr (**1c**)	Toluene	(S_S,*S*)-**2c**	76	91:9[c]
8	^{i}Bu (**1d**)	Toluene	(S_S,*S*)-**2d**	85	99:1[c]

[a] Configurations were assigned by the transition state model.
[b] Isolated yields of diastereomerically and analytically pure products after chromatography.
[c] Diastereomeric ratios were determined by ^{1}H NMR from the crude products.
[d] Diastereomeric ratios were confirmed by ^{19}F NMR from the crude products.

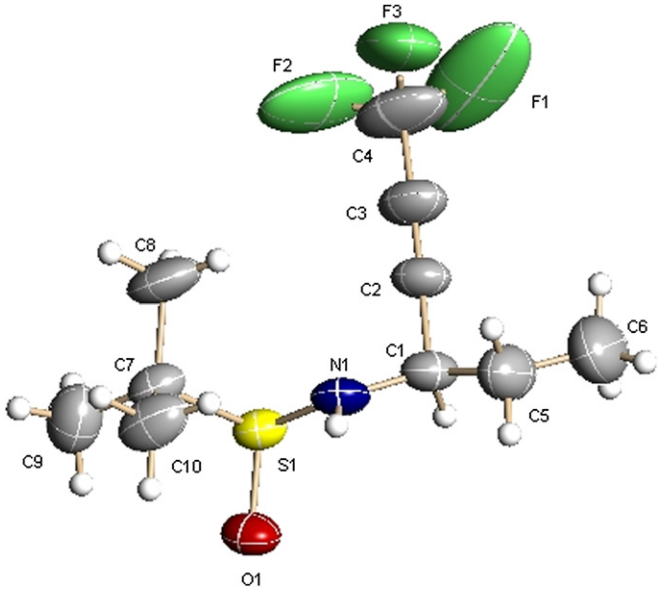
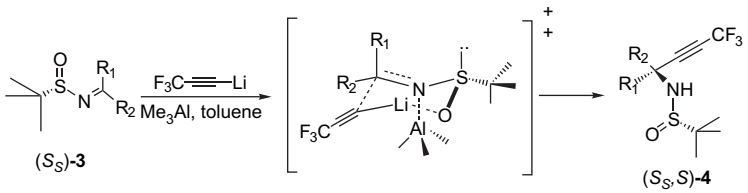


Figure 1. X-ray crystal structure of (S_S,*R*)-**2a**.

Table 2
The 1,2-addition of lithium trifluoromethylacetylide to *N*-*tert*-butanesulfinyl ketimines



Entry	R_1	R_2	Conditions	Product	Yield[c] (%)	(S_S,*S*)-**4**/(S_S,*R*)-**4** (dr)
1	Me	^{i}Pr (**3a**)	THF	(S_S,*S*)-**4a**[a]	55	74:26[d]
2	Me	^{i}Bu (**3b**)	THF	(S_S,*S*)-**4b**[b]	45	62:38[d]
3	Me	^{i}Pr (**3a**)	Toluene	(S_S,*S*)-**4a**[a]	79	93:7[d]
4	Me	^{i}Bu (**3b**)	Toluene	(S_S,*S*)-**4b**[b]	74	83:17[d]
5	Me	^{i}Pr (**3a**)	Toluene/Me_3Al	(S_S,*S*)-**4a**[a]	88	94:6[d]
6	Me	^{i}Bu (**3b**)	Toluene/Me_3Al	(S_S,*S*)-**4b**[b]	83	93:7[e]
7	Me	Et (**3c**)	Toluene/Me_3Al	(S_S,*S*)-**4c**[b]	69	>99:1[e]
8	Me	Ph (**3d**)	Toluene/Me_3Al	(S_S,*S*)-**4d**[b]	31	>99:1[e]

[a] Configuration was confirmed by X-ray crystal structure.
[b] Configurations were deduced from **4a** based on the comparison of TLC, ^{1}H NMR, and ^{13}C NMR.
[c] Isoalted yields of diastereomerically and analytically pure products after chromatography.
[d] Diastereomeric ratios were determined by ^{1}H NMR of the crude products.
[e] Diastereomeric ratios were confirmed by ^{19}F NMR of the crude products.

ketimines **3a** and **3b** in THF gave the desired α,α-dibranched trifluoromethylated propargylamine **4** only in low diastereoselectivity and (S_S,*S*)-**4** were isolated as the main isomers (entries 1 and 2, Table 2). Slightly surprisingly, also with (S_S,*S*)-**4** as the main isomers, the corresponding propargylamines were obtained in good diastereoselectivity when the same reactions were carried out in toluene (entries 3–4). Additionally, we were pleased to find that addition of $AlMe_3$ to the reaction systems could further increase the diastereoselectivities and yields (entries 5 and 6). Especially noteworthy was that, for the substrate (S_S)-**3b**, the addition of $AlMe_3$ could significantly improve the diastereoselectivity from 83:17 to 93:7 despite that a mixture of *E* and *Z* isomers (6:1) (S_S)-**3b** was used (entry 4 vs 6). Most excitingly, performing the addition of lithium trifluoromethylacetylide to *N*-*tert*-butanesulfinyl ketimine **3c** in toluene/$AlMe_3$ gave the corresponding trifluoromethylated propargylamine (S_S,*S*)-**4c** without any detectable diastereoisomer (entry 7). Additions of trifluoromethylacetylide to the aryl-substituted *N*-*tert*-butanesulfinyl ketimine **3d** also delivered the diastereoisomer (S_S,*S*)-**4d** in very high diastereoselectivity (>99:1) although the yield was low (entry 8). In our opinion, the stereochemistry of the addition reaction was consistent with a cyclic six-membered transition state with the bulky *tert*-butyl group preferring the equatorial position and $AlMe_3$ chelating with the nitrogen atom of ketimine. The absolute configuration of the major isomer (S_S,*S*)-**4a** was confirmed by X-ray crystallographic analysis (Fig. 2).[17]

As the several representative examples, the enantiomerically pure trifluoromethylated propargylamines **5b** and **6a** could be readily accessed via acidic cleavage of the *tert*-butanesulfinyl groups of the prepared sulfonamide derivatives **2b** and **4a** (Scheme 1).[18]

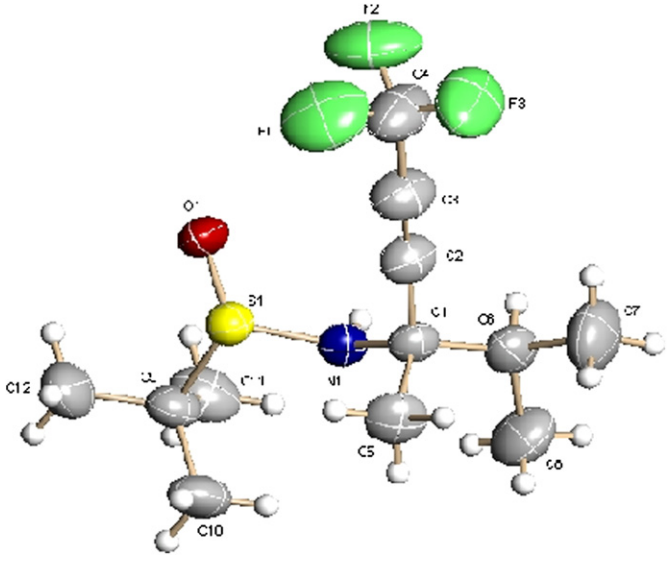
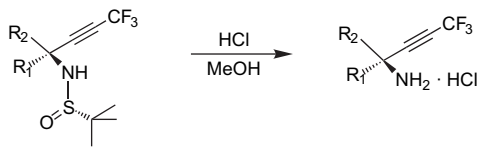


Figure 2. X-ray crystal structure of (S_S,*S*)-**4a**.



(S_S,*S*)-**2b**: R_1 = H, R_2 = ^{i}Pr;
(S_S,*R*)-**2b**: R_1 = ^{i}Pr, R_2 = H;
(S_S,*S*)-**4a**: R_1 = Me, R_2 = ^{i}Pr;
(S_S,*R*)-**4a**: R_1 = ^{i}Pr, R_2 = Me.

(*S*)-**5b**: R_1 = H, R_2 = ^{i}Pr;
(*R*)-**5b**: R_1 = ^{i}Pr, R_2 = H;
(*S*)-**6a**: R_1 = Me, R_2 = ^{i}Pr;
(*R*)-**6a**: R_1 = ^{i}Pr, R_2 = Me.

Scheme 1.

3. Conclusion

In summary, we have developed a very practical method for the asymmetric syntheses of a range of trifluoromethylated propargylamines by 1,2-additions of lithium trifluoromethylacetylide to *N-tert*-butanesulfinyl aldimines and ketimines in good yields and in good diastereoselectivities. In many cases, the major isomers can be isolated by chromatography. For *N-tert*-butanesulfinyl aldimines' substrates, the diastereoselectivities could be tuned by changing the used solvent. With $AlMe_3$ as adductive in the addition to *N-tert*-butanesulfinyl ketimines, the diastereoselectivities were significantly improved. Acidic cleavage of the *tert*-butanesulfinyl groups delivered optically pure trifluoromethylated propargylamines.

4. Experimental section

4.1. General experimental methods

Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification. THF was distilled from sodium/benzophenone ketyl and toluene was distilled from sodium immediately before use. *N-tert*-Butanesulfinyl aldimines and ketimines were prepared using known procedures. All reactions were carried out in flame or dried glassware under a nitrogen atmosphere. IR spectra of liquids were recorded as thin film on KBr plates and IR spectra of solids were recorded as KBr pellets. Melting points were determined on a Melt-Temp apparatus and were uncorrected. ^{1}H NMR spectra were recorded on Bruker AM-400 spectrometer with TMS as an internal standard. ^{19}F NMR spectra were recorded on Bruker AM-400 spectrometer with $CFCl_3$ as an external standard. ^{13}C NMR spectra were recorded on Bruker 400 (100.6 MHz) spectrometer. Mass spectra were taken on a HP5989A spectrometer.

4.1.1. General procedure for the 1,2-addition of lithium trifluoromethylacetylide to N-tert-butanesulfinyl aldimines **1**

A 1.0 M solution of 2-bromo-3,3,3-trifluoropropene (1.5 equiv) in toluene was added slowly to a solution of LDA (3.0 equiv, 2.0 M in THF/*n*-heptane/ethylbenzene) at −78 °C. The resultant red/black solution was stirred at this temperature for a further 15 min before a solution of *N-tert*-butanesulfinyl aldimine **1** (1.0 equiv) in toluene was added dropwise. Stirring was continued at −78 °C for 2 h and then the mixture was allowed to warm up to −40 °C. Stirring was continued for 5 h. After that, the reaction mixture was quenched by the addition of satd aq NH_4Cl and diluted with EtOAc. The organic layer was removed and the aqueous layer was extracted with EtOAc. After the combined organic layers were dried with Na_2SO_4, filtered, and concentrated, the residue was purified by chromatography to give the diastereoisomerically pure trifluoromethylated propargylamines **2**.

*4.1.1.1. (S_S,S)-(+)-N-(1-Ethyl-4,4,4-trifluoro-but-2-ynyl)-2-methylpropanesulfinamide ((S_S,S)-**2a**).* White solid; mp 61–63 °C; $[\alpha]_D^{23}$ +41.4 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 1056, 1134, 1283, 1367, 1461, 2269, 3167; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, *J*=7.4 Hz, 3H), 1.23 (s, 9H), 1.77–1.86 (m, 2H), 3.42 (d, *J*=7.0 Hz, 1H), 4.07–4.13 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.11, 24.78, 31.59, 50.43, 58.85, 74.41 (q, *J*=52.7 Hz), 89.35 (q, *J*=6.4 Hz), 116.27 (q, *J*=255.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.27 (s, 3F). Anal. Calcd for $C_{10}H_{16}F_3NOS$: C, 47.05; H, 6.32; N, 5.49. Found: C, 47.18; H, 5.93; N, 5.46.

*4.1.1.2. (S_S,R)-(+)-N-(1-Ethyl-4,4,4-trifluoro-but-2-ynyl)-2-methylpropanesulfinamide ((S_S,R)-**2a**).* White solid; mp 69–71 °C; $[\alpha]_D^{23}$ +21.8 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 1059, 1142, 1279, 1365, 1460, 2273, 3194; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, *J*=7.4 Hz, 3H), 1.16 (s, 9H), 1.75–1.84 (m, 2H), 3.40 (d, *J*=7.0 Hz, 1H), 4.08–4.14 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 9.81, 22.29, 29.48, 49.06, 56.32, 71.85 (q, *J*=52.5 Hz), 86.72 (q, *J*=6.4 Hz), 113.93 (q, *J*=255.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.32 (s, 3F). Anal. Calcd for $C_{10}H_{16}F_3NOS$: C, 47.05; H, 6.32; N, 5.49. Found: C, 47.19; H, 6.23; N, 5.43.

*4.1.1.3. (S_S,S)-(+)-N-(1-Isopropyl-4,4,4-trifluoro-but-2-ynyl)-2-methylpropanesulfinamide ((S_S,S)-**2b**).* White solid; mp 72–74 °C; $[\alpha]_D^{23}$ +69.2 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 1062, 1141, 1279, 1367, 1468, 2255, 3190; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, *J*=6.8 Hz, 3H), 0.97 (d, *J*=6.8 Hz, 3H), 1.18 (s, 9H), 1.92–1.98 (m, 1H), 3.31 (d, *J*=7.4 Hz, 1H), 3.89–3.94 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.89, 21.01, 24.83, 35.79, 55.29, 59.04, 75.14 (q, *J*=52.7 Hz), 88.55 (q, *J*=6.4 Hz), 116.25 (q, *J*=255.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.10 (s, 3F). Anal. Calcd for $C_{11}H_{18}F_3NOS$: C, 49.05; H, 6.74; N, 5.20. Found: C, 49.53; H, 6.87; N, 4.94.

*4.1.1.4. (S_S,R)-(+)-N-(1-Isopropyl-4,4,4-trifluoro-but-2-ynyl)-2-methylpropanesulfinamide ((S_S,R)-**2b**).* White solid; mp 84–86 °C; $[\alpha]_D^{23}$ +59.2 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 1050, 1133, 1282, 1364, 1474, 2284, 3121; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96–0.98 (m, 6H), 1.15 (s, 9H), 1.92–2.01 (m, 1H), 3.36 (d, *J*=5.6 Hz, 1H), 3.89–3.94 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.07, 19.04, 22.27, 33.53, 53.61, 56.35, 72.73 (q, *J*=52.4 Hz), 85.54 (q, *J*=6.3 Hz), 113.89 (q, *J*=255.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.08 (s, 3F). Anal. Calcd for $C_{11}H_{18}F_3NOS$: C, 49.05; H, 6.74; N, 5.20. Found: C, 49.19; H, 6.76; N, 5.07.

*4.1.1.5. (S_S,S)-(+)-N-(1-Propyl-4,4,4-trifluoro-but-2-ynyl)-2-methylpropanesulfinamide ((S_S,S)-**2c**).* White solid; mp 49–51 °C; $[\alpha]_D^{23}$ +45.2 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 1059, 1140, 1279, 1365, 1459, 2264, 3186; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.4 Hz, 3H), 1.16 (s, 9H), 1.37–1.47 (m, 2H), 1.67–1.74 (m, 2H), 3.41 (d, *J*=7.3 Hz, 1H), 4.03–4.10 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.60, 20.97, 24.69, 40.34, 48.93, 58.82, 73.90 (q, *J*=52.1 Hz), 89.84 (q, *J*=6.4 Hz), 116.27 (q, *J*=255.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.30 (s, 3F). Anal. Calcd for $C_{11}H_{18}F_3NOS$: C, 49.05; H, 6.74; N, 5.20. Found: C, 49.05; H, 6.81; N, 5.15.

*4.1.1.6. (S_S,R)-(+)-N-(1-Propyl-4,4,4-trifluoro-but-2-ynyl)-2-methylpropanesulfinamide ((S_S,R)-**2c**).* White solid; mp 55–57 °C; $[\alpha]_D^{23}$ +42.8 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 1059, 1143, 1280, 1365, 1459, 2267, 3192; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J*=7.4 Hz, 3H), 1.16 (s, 9H), 1.42–1.48 (m, 2H), 1.71–1.77 (m, 2H), 3.30 (d, *J*=7.3 Hz, 1H), 4.13–4.19 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.39, 18.80, 22.28, 38.17, 47.54, 56.29, 71.71 (q, *J*=52.2 Hz), 86.96 (q, *J*=6.3 Hz), 113.95 (q, *J*=255.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.28 (s, 3F). Anal. Calcd for $C_{11}H_{18}F_3NOS$: C, 49.05; H, 6.74; N, 5.20. Found: C, 49.17; H, 6.44; N, 5.10.

*4.1.1.7. (S_S,S)-(+)-N-(1-Isobutyl-4,4,4-trifluoro-but-2-ynyl)-2-methylpropanesulfinamide ((S_S,S)-**2d**).* White solid; mp 91–93 °C; $[\alpha]_D^{23}$ +56.2 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 1040, 1140, 1287, 1365, 1468, 2275, 3157; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87–0.88 (m, 6H), 1.18 (s, 9H), 1.58–1.64 (m, 2H), 1.73–1.80 (m, 1H), 3.36 (d, *J*=5.2 Hz, 1H), 4.05–4.11 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.02, 21.12, 21.44, 23.71, 44.12, 44.54, 55.61, 70.85 (q, *J*=52.3 Hz), 86.58 (q, *J*=6.3 Hz), 112.99 (q, *J*=255.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.29 (s, 3F). Anal. Calcd for $C_{11}H_{20}F_3NOS$: C, 50.87; H, 7.11; N, 4.94. Found: C, 50.86; H, 7.33; N, 4.64.

*4.1.1.8. (S_S,R)-(+)-N-(1-Isobutyl-4,4,4-trifluoro-but-2-ynyl)-2-methylpropanesulfinamide ((S_S,R)-**2d**).* White solid; mp 98–101 °C; $[\alpha]_D^{23}$ 46.2 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 1041, 1136, 1288, 1365, 1468, 2273, 3117; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J*=6.6 Hz, 3H), 0.92 (d, *J*=6.6 Hz, 3H), 1.18 (s, 9H), 1.62–1.67 (m, 2H), 1.76–1.81 (m, 1H), 3.19 (d, *J*=5.2 Hz, 1H), 4.18–4.23 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.09, 24.59, 24.81, 27.29, 47.30, 48.48, 58.60, 74.01 (q, *J*=52.3 Hz), 89.49 (q, *J*=6.4 Hz), 116.30 (q, *J*=255.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.28 (s, 3F). Anal. Calcd for $C_{11}H_{20}F_3NOS$: C, 50.87; H, 7.11; N, 4.94. Found: C, 51.04; H, 7.18; N, 4.72.

4.1.2. General procedure for the 1,2-addition of lithium trifluoromethylacetylide to N-tert-butanesulfinyl ketimines with Me_3Al

A 1.0 M solution of 2-bromo-3,3,3-trifluopropene (1.5 equiv) in toluene was added slowly to a solution of LDA (3.0 equiv, 2.0 M solution in THF/*n*-heptane/ethylbenzene) at −78 °C. The resulting red/black solution was stirred at this temperature for a further 15 min before a toluene solution of *N-tert*-butanesulfinyl ketimine **3** (1.0 equiv, 0.5 M) and Me_3Al (1.2 equiv) was slowly added via cannula. Stirring was continued at −78 °C for 2 h and then the solution was allowed to warm up to room temperature over 4 h. Stirring was continued at room temperature for 12 h. After that, the reaction mixture was cooled in an ice water bath and satd aq Na_2SO_4 was added dropwise until no gas was released out. The slurry was filtered and the filtered cake was rinsed with EtOAc. The combined filtrates were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography to afford the diastereomerically pure trifluoromethylated propargylamines **4**.

*4.1.2.1. (S_S,S)-(+)-N-(1-Isopropyl-1-methyl-4,4,4-trifluoro-but-2-ynyl)-2-methylpropanesulfinamide ((S_S,S)-**4a**).* White solid; mp 69–71 °C; $[\alpha]_D^{23}$ +66.4 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 1049, 1140, 1278, 1370, 1469, 2269, 3156; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, *J*=6.8 Hz, 3H), 1.00 (d, *J*=6.8 Hz, 3H), 1.18 (s, 9H), 1.43 (s, 3H), 1.96 (septet, *J*=6.8 Hz, 1H), 3.23 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.08, 19.78, 24.70, 26.06, 33.15, 40.39, 58.74, 74.40 (q, *J*=52.7 Hz), 92.17 (q, *J*=6.5 Hz), 116.41 (q, *J*=255.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.10 (s, 3F). Anal. Calcd for $C_{12}H_{20}F_3NOS$: C, 50.87; H, 7.11; N, 4.94. Found: C, 50.79; H, 7.13; N, 4.65.

*4.1.2.2. (S_S,R)-(+)-N-(1-Isopropyl-1-methyl-4,4,4-trifluoro-but-2-ynyl)-2-methylpropanesulfinamide ((S_S,R)-**4a**).* White solid; mp 86–89 °C; $[\alpha]_D^{23}$ +43.4 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 1058, 1142, 1275, 1385, 1464, 2272, 3203; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, *J*=6.8 Hz, 3H), 1.01 (d, *J*=6.8 Hz, 3H), 1.15 (s, 9H), 1.57 (s, 3H), 1.87 (septet, *J*=6.8 Hz, 1H), 3.14 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.50, 22.37, 26.22, 38.70, 56.51, 58.29, 72.64 (q, *J*=52.2 Hz), 88.68 (q, *J*=6.4 Hz), 114.03 (q, *J*=255.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.08 (s, 3F). Anal. Calcd for $C_{12}H_{20}F_3NOS$: C, 50.87; H, 7.11; N, 4.94. Found: C, 50.69; H, 7.19; N, 4.60.

*4.1.2.3. (S_S,S)-(+)-N-(1-Isobutyl-1-methyl-4,4,4-trifluoro-but-2-ynyl)-2-methylpropanesulfinamide ((S_S,S)-**4b**).* White solid; mp 54–56 °C; $[\alpha]_D^{23}$ +73.6 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 1040, 1140, 1284, 1387, 1469, 2273, 3148; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95–0.99 (m, 6H), 1.15 (s, 9H), 1.51 (s, 3H), 1.60–1.64 (m, 2H), 1.75–1.83 (m, 1H), 3.27 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.65, 26.35, 26.51, 27.02, 30.60, 53.33, 55.16, 74.03 (q, *J*=53.0 Hz), 92.75 (q, *J*=6.0 Hz), 116.41 (q, *J*=255.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.42 (s, 3F). Anal. Calcd for $C_{13}H_{22}F_3NOS$: C, 52.50; H, 7.46; N, 4.71. Found: C, 51.93; H, 7.57; N, 4.48.

*4.1.2.4. (S_S,R)-(+)-N-(1-Isobutyl-1-methyl-4,4,4-trifluoro-but-2-ynyl)-2-methylpropanesulfinamide ((S_S,R)-**4b**).* White solid; mp 61–63 °C; $[\alpha]_D^{23}$ +46.8 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 1039, 1141, 1285, 1366, 1469, 2277, 3152; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93–0.95 (m, 6H), 1.14 (s, 9H), 1.56–1.69 (m, 5H), 1.82–1.85 (m, 1H), 3.18 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.36, 23.01, 23.10, 23.94, 28.71, 50.41, 52.95, 55.35, 70.89 (q, *J*=52.3 Hz), 89.00 (q, *J*=6.4 Hz), 113.11 (q, *J*=255.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.43 (s, 3F). Anal. Calcd for $C_{13}H_{22}F_3NOS$: C, 52.50; H, 7.46; N, 4.71. Found: C, 52.37; H, 7.80; N, 4.49.

*4.1.2.5. (S_S,S)-(+)-N-(1-Ethyl-1-methyl-4,4,4-trifluoro-but-2-ynyl)-2-methylpropanesulfinamide ((S_S,S)-**4c**).* Viscous oil; $[\alpha]_D^{23}$ +81.4 (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}) ν_{max} 1059, 1140, 1273, 1365, 1460, 2270, 3186; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, *J*=7.4 Hz, 3H), 1.15 (s, 9H), 1.48 (s, 3H), 1.74–1.87 (m, 2H), 3.24 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.83, 24.63, 29.40, 37.86, 56.09, 58.59, 73.85 (q, *J*=52.1 Hz), 92.12

(q, J=6.4 Hz), 116.40 (q, J=255.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.18 (s, 3F). Anal. Calcd for $C_{11}H_{18}F_3NOS$: C, 49.05; H, 6.74; N, 5.20. Found: C, 49.64; H, 7.02; N, 4.95.

*4.1.2.6. (S_S,S)-(+)-N-(1-Methyl-1-phenyl-4,4,4-trifluoro-but-2-ynyl)-2-methylpropanesulfinamide ((S_S,S)-**4d**).* White solid; mp 107–109 °C; $[\alpha]_D^{23}$ +41.6 (c 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 697, 763, 1046, 1140, 2279, 3151; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H), 1.91 (s, 3H), 3.69 (s, 1H), 7.35–7.60 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.74, 33.30, 58.39, 58.99, 75.86 (q, J=52.8 Hz), 91.65 (q, J=6.6 Hz), 116.50 (q, J=256.4 Hz), 127.98, 131.12, 131.23, 143.77; ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.34 (s, 3F). Anal. Calcd for $C_{13}H_{22}F_3NOS$: C, 52.50; H, 7.46; N, 4.71. Found: C, 51.93; H, 7.57; N, 4.48.

4.1.3. General procedure for cleavage of the tert-butanesulfinyl groups

To a solution of propargyl sulfinamide (2.0 mmol) in MeOH (10 mL) was added 4 M HCl in 1,4-dioxane solution (2.0 mL, 8.0 mmol). The mixture was stirred at room temperature for 1 h. Then, hexane was added to precipitate the amine hydrochlorides (in some cases, the mixture was concentrated to near dryness before the addition of hexane to ensure a high yield of amine hydrochlorides). The precipitate was then filtered off and washed with hexane to provide the pure amine hydrochloride.

*4.1.3.1. (S)-(−)-1-Isopropyl-4,4,4-trifluoro-but-2-ynylamine hydrochloride ((S)-**5b**).* White solid; $[\alpha]_D^{23}$ −8.2 (c 1.0, CH_3OH); IR (KBr, cm^{-1}) ν_{max} 1152, 1279, 1512, 2000, 2283, 3446; ^{1}H NMR (400 MHz, CD_3OD) δ 1.05 (d, J=6.8 Hz, 3H), 1.06 (d, J=6.8 Hz, 3H), 2.16 (septet, J=6.8 Hz, 1H), 4.27–4.30 (m, 1H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 15.78, 17.76, 30.70, 73.93 (q, J=53.3 Hz), 81.75 (q, J=6.2 Hz), 113.61 (q, J=255.9 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ −52.42 (s, 3F). Anal. Calcd for $C_7H_{11}ClF_3N$: C, 41.70; H, 5.50; N, 6.95. Found: C, 41.45; H, 5.58; N, 6.80.

*4.1.3.2. (R)-(+)-1-Isopropyl-4,4,4-trifluoro-but-2-ynylamine hydrochloride ((R)-**5b**).* White solid; $[\alpha]_D^{23}$ +8.3 (c 1.0, CH_3OH); IR (KBr, cm^{-1}) ν_{max} 1152, 1277, 1511, 1995, 2285, 3442; ^{1}H NMR (400 MHz, CD_3OD) δ 1.04 (d, J=6.8 Hz, 3H), 1.06 (d, J=6.8 Hz, 3H), 2.16 (septet, J=6.8 Hz, 1H), 4.24–4.28 (m, 1H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 15.79, 17.78, 30.77, 73.80 (q, J=53.0 Hz), 82.03 (q, J=6.2 Hz), 113.64 (q, J=255.8 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ −52.37 (s, 3F). Anal. Calcd for $C_7H_{11}ClF_3N$: C, 41.70; H, 5.50; N, 6.95. Found: C, 41.36; H, 5.49; N, 6.67.

*4.1.3.3. (S)-(−)-1-Isopropyl-1-methyl-4,4,4-trifluoro-but-2-ynylamine hydrochloride ((S)-**6a**).* White solid; $[\alpha]_D^{23}$ −14.4 (c 1.0, CH_3OH); IR (KBr, cm^{-1}) ν_{max} 1145, 248, 1286, 1509, 2058, 2284, 2906, 3431; ^{1}H NMR (400 MHz, CD_3OD) δ 1.11 (d, J=6.8 Hz, 3H), 1.14 (d, J=6.8 Hz, 3H), 1.66 (s, 3H), 2.16 (septet, J=6.8 Hz, 1H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 18.39, 18.65, 24.08, 38.25, 57.25, 75.76 (q, J=53.1 Hz), 86.99 (q, J=6.3 Hz), 116.03 (q, J=256.0 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ −52.46 (s, 3F). Anal. Calcd for $C_8H_{13}ClF_3N$: C, 44.56; H, 6.08; N, 6.50. Found: C, 44.20; H, 6.00; N, 6.28.

*4.1.3.4. (R)-(+)-1-Isopropyl-1-methyl-4,4,4-trifluoro-but-2-ynylamine hydrochloride ((R)-**6a**).* White solid; $[\alpha]_D^{23}$ +14.2 (c 1.0, CH_3OH); IR (KBr, cm^{-1}) ν_{max} 1145, 1248, 1285, 1508, 2019, 2283, 2906, 3448; ^{1}H NMR (400 MHz, CD_3OD) δ 1.05 (d, J=6.8 Hz, 3H), 1.08 (d, J=6.8 Hz, 3H), 1.61 (s, 3H), 2.12 (septet, J=6.8 Hz, 1H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 16.03, 16.28, 21.73, 35.91, 54.87, 73.38 (q, J=53.3 Hz), 84.64 (q, J=6.2 Hz), 113.68 (q, J=256.1 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ −52.40 (s, 3F). Anal. Calcd for $C_8H_{13}ClF_3N$: C, 44.56; H, 6.08; N, 6.50. Found: C, 44.50; H, 6.16; N, 6.12.

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References and notes

1. For selected examples, see: (a) Brik, A.; Alexandratos, J.; Lin, Y.-C.; Elder, J. H.; Olson, A. J.; Wlodawer, A.; Goodsell, D. S.; Wong, C.-H. *ChemBioChem* **2005**, *6*, 1167; (b) Trost, B. M.; Chung, C. K.; Pinkerton, A. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 4327; (c) Porco, J. A., Jr.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410.
2. (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535; (b) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.
3. Gommermann, N.; Knochel, P. *Chem. Commun.* **2004**, 2324.
4. Liu, J.; Liu, B.; Jia, X.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007**, *18*, 396.
5. Ding, C.-H.; Chen, D.-D.; Luo, Z.-B.; Dai, L.-X.; Hou, X.-L. *Synlett* **2006**, 1272.
6. Patterson, A. W.; Ellman, J. A. *J. Org. Chem.* **2006**, *71*, 7110.
7. Turcaud, S.; Berhal, F.; Royer, J. *J. Org. Chem.* **2007**, *72*, 7893.
8. Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2006**, *8*, 1529.
9. (a) Ramachandran, P. V. *Asymmetric Fluoroorganic Chemistry:Synthesis, Application, and Future Directions*. ACS Symposium Series; American Chemical Society: Washington, DC, 2000; Vol. 746; (b) Ren, J.; Milton, J.; Weaver, K. L.; Short, S. A.; Stuart, D. I.; Stammers, D. K. *Structure* **2000**, *8*, 1089; (c) Pedersen, O. S.; Pedersen, E. B. *Synthesis* **2000**, 479; (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
10. Huheey, J. E. *J. Phys. Chem.* **1965**, *69*, 3284.
11. McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555.
12. (a) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3; (b) O'Hagan, D.; Rzepa, H. S. *Chem. Commun.* **1997**, 645.
13. Chen, Q.; Qiu, X.-L.; Qing, F.-L. *J. Fluorine Chem.* **2007**, *128*, 1182.
14. Liu, G.; Cogan, D. A.; Owens, T.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.
15. Crystal data have been deposited at the Cambridge Crystallographic Data Center with reference number: CCDC 669005.
16. Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869.
17. Crystal data have been deposited at the Cambridge Crystallographic Data Center with reference number: CCDC 667051.
18. Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913.