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Regiospecific and diastereoselective aldol reaction of chiral *N*-sulfinyl metalloenamines with α,β-unsaturated trifluoromethyl ketones: Asymmetric synthesis of tertiary trifluoromethyl allylic carbinols

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ABSTRACT

Regiospecific and diastereoselective aldol type reaction of chiral *N*-sulfinyl metalloenamines with α,β-unsaturated trifluoromethyl ketones was reported, which affords the corresponding tertiary trifluoromethyl allylic carbinols in high yields with good diastereoselectivities (dr up to 90:10). The reduction of the condensation product **3a** with $LiBHEt_3$ and Catecholborane provides CF_3-substituted *syn*- and *anti*-1,3-amino alcohols **5a** and **5b** in high yields with excellent diastereoselectivities (dr > 99:1).

1. Introduction

Trifluoromethyl-containing compounds have currently attracted widespread interest in the fields of agricultural, medicinal and material sciences [1] because the introduction of a trifluoromethyl group with strong electron-withdrawing ability can lead to significant changes in the physical, chemical, and biological properties of the molecules. Among such compounds, enantiomerically pure α-trifluoromethyl tertiary alcohols have received considerable attention [2] since they can serve as liquid crystals [3a] and drugs such as Efavirenz (anti-HIV) [3b,c] and so on. On the other hand, trifluoromethyl allylic alcohols are increasingly popular as chiral synthons in the design of new drugs or materials. However, few methods are available for their asymmetric synthesis [4], especially for the synthesis of trifluoromethyl allylic carbinols bearing a stereogenic quaternary carbon center [5]. Recently, our group and Yuan's group have independently developed an organocatalytic approach for the assemble of tertiary trifluoromethyl allylic carbinols [6]. Nevertheless, the substrate scope was largely limited. Therefore, it's highly desirable to develop new methods for the efficient synthesis of chiral tertiary trifluoromethyl allylic carbinols.

N-*tert*-Butanesulfinyl imines are versatile synthetic intermediates and are increasingly being used in organic synthesis [7]. In particular, *N*-*tert*-butanesulfinyl ketimines can be deprotonated to form *N*-sulfinyl metalloenamines and further react with a number of electrophiles, including aldehydes [8a,b], trifluoromethyl ketones [8c], imines [8d,e] and alkylating agents [8f]. Recently, Ellman and Peltier reported the conjugate addition of *N*-*tert*-butanesulfinyl metalloenamines to α,β-unsaturated ketones and only 1,4-adducts were obtained [9]. More recently, we described a highly diastereoselective Michael addition of *N*-sulfinyl metalloenamines to β-trifluoromethyl-α,β-unsaturated ester and further expanded the scope of *N*-sulfinyl metalloenamine chemistry [10]. As a continuation of our interests on the reactions of trifluoromethyl substituted ketones [6a,8c,11], we found that in contrast to the reaction of *N*-sulfinyl metalloenamines with nonfluorinated α,β-unsaturated ketones [9], the reaction of *N*-sulfinyl metalloenamines with α,β-unsaturated trifluoromethyl ketones proceeded only in 1,2-addition mode and no 1,4-adducts were observed. Herein, we wish to report the regiospecific and diastereoselective nucleophilic addition of chiral *N*-sulfinyl metalloenamines to various α,β-unsaturated trifluoromethyl ketones, which provides a practical method for the asymmetric synthesis of tertiary trifluoromethyl allylic carbinols in high yields with good diastereoselectivities.

2. Results and discussion

We began our investigation by examining the reaction of (*R*)-*N*-*tert*-butanesulfinyl ketimine **1a** and α,β-unsaturated trifluoromethyl ketone **2a** (as shown in Table 1). Deprotonation of **1a** with 2.0 equiv. of LDA at −78 °C in THF followed by addition of **2a**

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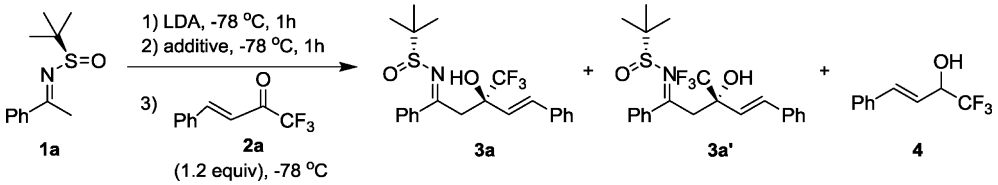
Table 1
The reaction of **1a** and **2a** under different conditions



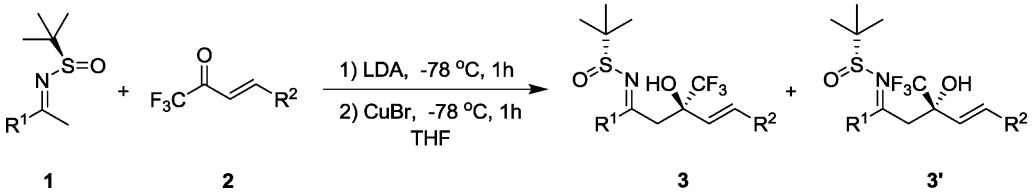
Entry	Solvent	LDA (equiv.)	Additive (equiv.)	Yield (%)[a]	**3a**:**3a′**:**4**[b]
1	THF	2.0	–	32 (49:51)	15:15:70
2	THF	1.5	–	63 (78:22)	52:15:32
3[c]	THF	1.5	–	71 (70:30)	49:21:31
4[c]	THF	1.5	$ZnBr_2$ (1.5)	98 (70:30)	67:30:3
5[c]	THF	1.5	$MgBr_2$ (2.0)	25 (70:30)	69:31:0
6[c]	THF	1.5	CuBr (2.0)	>99 (87:13)	87:13:0
7[c]	THF	1.5	CuCN (1.2)	>99 (71:29)	71:29:0
8[c]	Et_2O	1.5	CuBr (1.0)	61 (82:18)	82:18:0

[a] Isolated overall yield of **3a** and **3a′**. The diastereomeric ratio of **3a** and **3a′** in parentheses.
[b] Determined by ^{19}F NMR spectroscopy of the crude reaction mixture.
[c] The substrate **2a** in the third step was cooled to −78 °C and then added.

afforded three new products, as indicated by ^{19}F NMR spectroscopy monitoring of the crude reaction mixture (−80.01 ppm (d), −81.35 ppm (s), −82.56 ppm (s)), which were identified as the 1,2-addition products **3a** (−82.56 ppm) and **3a′** (−81.35 ppm) as well as the reduction product **4** (−80.01 ppm) [12] from ^1H, ^{13}C, and ^{19}F NMR. Although the reaction gave 1,2-adducts in low yield with poor selectivity (Table 1, entry 1), this is largely different from the reaction of *N*-sulfinyl metalloenamines with nonfluorinated α,β-unsaturated ketones reported by Ellman and co-workers, where only 1,4-addition occurred [9]. To achieve better results and test the possibility of 1,4-addition [13], then the reaction conditions were optimized by changing solvents or adding additives. Lowering the amounts of LDA to 1.5 equiv. greatly improved both the yields and the diastereoselectivities of 1,2-adducts, and led to a dramatic decrease of the reduction product **4** (Table 1, entries 2–3). Furthermore, addition of metal salts could thoroughly prevent the reduction reaction (Table 1, entries 4–8) [14]. Among the metal salts tested, CuBr gave the best result (quantitative yields and 87:13 dr) (Table 1, entry 6). Both changing the solvent to Et_2O and lowering the amount of CuBr led to a decrease in the yield (Table 1, entry 8). It is noteworthy that no 1,4-adduct was observed under all the tested reaction conditions.

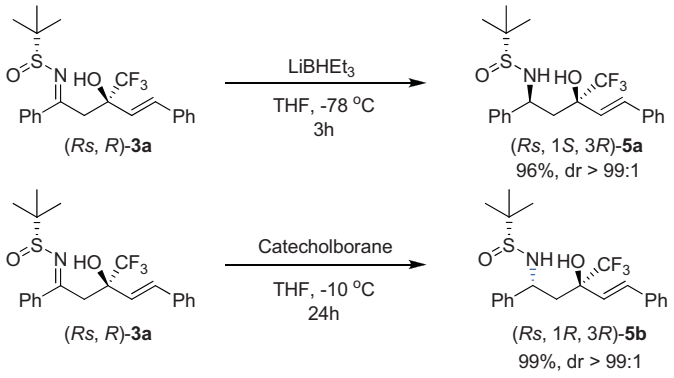
Using the condition of entry 6 in Table 1, we next explored the substrate scope of the condensation reaction with a variety of *N*-(*tert*-butanesulfinyl) ketimines and α,β-unsaturated trifluoromethyl ketones. As summarized in Table 2, all reactions took place readily in 1,2-addition mode and afforded the corresponding tertiary trifluoromethyl allylic carbinols in high yields with good diastereoselectivities. *N*-Sulfinyl ketimines containing both aryl and alkyl substituents proved to be excellent substrates for the reaction (entries 1–7). It is worthwhile to mention that in the case of *N*-sulfinyl ketimine **1g** the reaction occurred at the less substituted α-carbon selectively (entry 7). The reaction also tolerated heteroaromatic substituted *N*-sulfinyl ketimine, giving the condensation product in almost quantitative yield with a dr of 80:20 (entry 8). Additionally, α,β-unsaturated trifluoromethyl

Table 2
The reaction of *N*-(*tert*-butanesulfinyl) ketimines 1 with α,β-unsaturated trifluoromethyl ketones **2**



Entry	R^1	R^2	Product	Yield (%)[a]	3:3′ (dr)[b]
1	Ph (**1a**)	Ph (**2a**)	**3a** + **3a′**	>99	87:13
2	4-$MeOC_6H_4$ (**1b**)	Ph (**2a**)	**3b** + **3b′**	97	83:17
3	4-FC_6H_4 (**1c**)	Ph (**2a**)	**3c** + **3c′**	85	80:20
4	4-ClC_6H_4 (**1d**)	Ph (**2a**)	**3d** + **3d′**	75	85:15
5	4-$NO_2C_6H_4$ (**1e**)	Ph (**2a**)	**3e** + **3e′**	96	86:14
6	*t*-Bu (**1f**)	Ph (**2a**)	**3f** + **3f′**	98	73:27
7	*i*-Pr (**1g**)	Ph (**2a**)	**3g** + **3g′**	98	90:10
8	2-furyl (**1h**)	Ph (**2a**)	**3h** + **3h′**	>99	80:20
9	Ph (**1a**)	4-$MeOC_6H_4$ (**2b**)	**3i** + **3i′**	89	83:17
10	Ph (**1a**)	4-ClC_6H_4 (**2c**)	**3j** + **3j′**	95	88:12
11	Ph (**1a**)	n-C_8H_{17} (**2d**)	**3k** + **3k′**	48	88:12

[a] Isolated overall yield of **3** and **3′**.
[b] Determined by ^{19}F NMR spectroscopy of the crude reaction mixture.



Scheme 1. Stereoselective reduction of **3a** with $LiBHEt_3$ and Catecholborane.

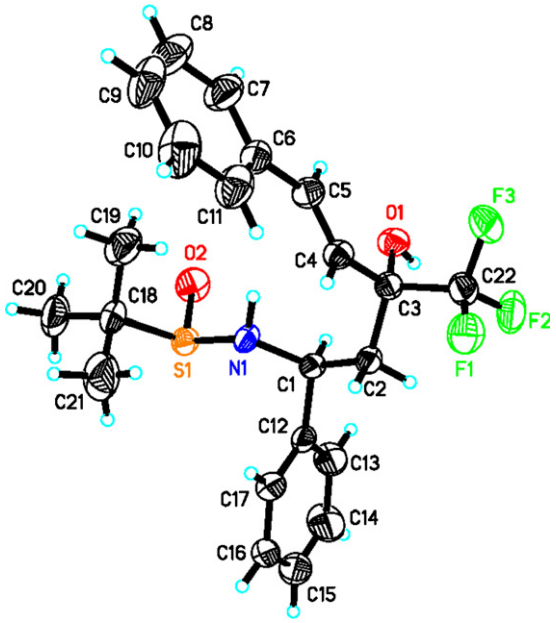


Fig. 1. X-ray crystal structure of **5a**.

ketones with different phenyl-substituents at the β-position could also be applied to the reaction and high yields as well as good diastereoselectivities were obtained (entries 9–10). However, when α,β-unsaturated trifluoromethyl ketone with an alkyl-substituent at the β-position was used as the electrophile, moderate yield was given albeit with good diastereoselectivity (entry 11).

Further elaboration by stereoselective reduction of the condensation product **3a** with $LiBHEt_3$ and Catecholborane, respectively, gave CF_3-substituted *syn*- and *anti*-1,3-amino alcohols **5a** and **5b** in high yields with excellent diastereoselectivities (dr > 99:1) (Scheme 1), which are of potential interest as building blocks for biologically active compounds. The absolute configuration of **5a** was assigned to be (*Rs*, *1S*, *3R*) by X-ray crystallographic analysis (Fig. 1) [15]. Therefore, we deduced the absolute configuration of **3a-k** was (*Rs*, *R*) and the absolute configuration of **5b** was (*Rs*, *1R*, *3R*) [8a,b].

3. Conclusions

In summary, we have developed a practical method for the asymmetric synthesis of tertiary trifluoromethyl allylic carbinols. In the presence of CuBr, the condensation reaction of chiral *N*-sulfinyl metalloenamines with α,β-unsaturated trifluoromethyl ketones occurred in 1,2-addition mode regiospecifically to give the corresponding allylic carbinols in high yields with good diastereoselectivities. Further reduction of the condensation product **3a** with $LiBHEt_3$ and Catecholborane provides CF_3-substituted *syn*- and *anti*-1,3-amino alcohols **5a** and **5b** in high yields with excellent diastereoselectivities.

4. Experimental

4.1. General experimental methods

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. *N*-(*tert*-Butanesulfinyl) ketimines **1** were prepared using known procedures [16]. THF and Et_2O were freshly distilled over Na/benzophenone. Melting points were measured on a Melt-Temp apparatus and uncorrected. ^1H NMR spectra were recorded on Bruker AM-300 or Mercury 300 (300 MHz) spectrometers with TMS as internal standard. ^{19}F NMR spectra were recorded on Bruker AM-300 or Mercury 300 (282 MHz) spectrometers with $CFCl_3$ as external standard. ^{13}C NMR spectra were recorded on Bruker 300 (75.5 MHz) or DPX-400 (100.7 MHz) spectrometers. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Mass spectra were taken on HP5989A or Shimadzu LCMS-2010EV spectrometer. High-resolution mass data were obtained on a high-resolution mass spectrometer in the EI or MALDI mode.

4.2. General procedure for the 1,2-addition reaction of N-sulfinyl metalloenamines 1 to α,β-unsaturated trifluoromethyl ketones 2

Into a dried 20 mL Schlenk flask containing *N*-(*tert*-butanesulfinyl) ketimine **(R)-1** (0.3 mmol) in 2 mL THF was slowly added a solution of LDA (0.23 mL, 0.46 mmol, 2 M solution in THF/heptane/ethylenebenzene) at −78 °C under N_2 atmosphere. After stirring at −78 °C for 1 h, CuBr (0.6 mmol) was added and the solution was stirred for 1 h. A solution of **2** (0.33 mmol) in 2 mL THF cooled to −78 °C was added dropwise via cannula to the mixture and stirring was continued at −78 °C for 5 h (monitored by TLC). After the reaction was complete, the mixture was quenched with saturated aqueous NH_4Cl solution (5 mL) at −78 °C and then gradually warmed to room temperature. The resulting mixture was extracted with EtOAc (10 mL × 3). The combined organic solution was dried over Na_2SO_4. After the removal of volatile solvents under vacuum, the residue was further purified by silica gel column chromatography to give product **3** and **3′**. The identity and purity of the major diastereomer **3** was fully characterized.

4.2.1. (Rs,R)-N-((E)-3-hydroxy-1,5-diphenyl-3-(trifluoromethyl)pent-4-enylidene)-tert-butane sulfinamide (3a)

White solid, yield 82%; $[\alpha]_D^{20}$ +569.67 (*c* = 0.88, $CHCl_3$); FT-IR (KBr, cm^{-1}): *ν* 3133, 2989, 2966, 1603, 1592, 1573, 1447, 1278, 1261, 1181, 1133, 1043, 1029; ^1H NMR ($CDCl_3$): *δ* 7.60 (d, *J* = 6.9 Hz, 2H), 7.32–7.34 (m, 3H), 7.11–7.14 (m, 4H), 6.76–6.78 (m, 2H), 6.67 (d, *J* = 15.6 Hz, 1H), 5.71 (d, *J* = 15.6 Hz, 1H), 3.79 (AB, J_{AB} = 12.8 Hz, 2H), 1.42 (s, 9H); ^{19}F NMR ($CDCl_3$): *δ* −82.07 (s, 3F); ^{13}C NMR ($CDCl_3$): *δ* 173.19, 140.54, 135.93, 132.98, 131.24, 128.74, 128.04, 127.72, 127.41, 126.47, 125.24 (q, *J* = 287.9 Hz), 124.99, 73.08 (q, *J* = 29.0 Hz), 60.03, 37.50, 23.19; EI MS (*m/z*, %): 367 (M^+-^{t}Bu + 1, 9.88), 319 (6.45), 57 (100.00); Anal. Calcd. for $C_{22}H_{24}F_3NO_2S$: C, 62.39; H, 5.71; N, 3.31. Found: C, 62.46; H, 5.53; N, 3.14.

4.2.2. (Rs,S)-N-((E)-3-hydroxy-1,5-diphenyl-3-(trifluoromethyl)pent-4-enylidene)-tert-butane sulfinamide (3a′)

White solid; FT-IR (KBr, cm^{-1}): *ν* 3077, 2992, 2926, 2869, 1604, 1592, 1574, 1448, 1367, 1296, 1269, 1218, 1176, 1147, 1051, 1025;

^{1}H NMR ($CDCl_3$): δ 7.64–7.70 (m, 2H), 7.39–7.41 (m, 3H), 7.14–7.24 (m, 3H), 6.99–7.10 (m, 2H), 6.94 (d, J = 15.6 Hz, 1H), 6.62 (s, 1H), 5.92 (d, J = 15.6 Hz, 1H), 3.83 (AB, J_{AB} = 13.2 Hz, 2H), 1.38 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −80.58 (s, 3F); ^{13}C NMR ($CDCl_3$): δ 171.46, 139.82, 135.86, 133.02, 131.28, 128.60, 128.29, 127.95, 127.41, 126.74, 124.87 (q, J = 286.6 Hz), 124.75, 75.22 (q, J = 29.1 Hz), 59.96, 35.32, 23.36; EI MS (*m/z*, %): 367 (M^+-^{t}Bu + 1, 11.00), 319 (7.95), 57 (100.00); HRMS (EI) calcd. for $C_{18}H_{16}F_3NO_2S$ [M^+-^{t}Bu + 1]: 367.0854; Found: 367.0847.

*4.2.3. (E)-1,1,1-trifluoro-4-phenylbut-3-en-2-ol (**4**)*

White solid; FT-IR (KBr, cm^{-1}): ν 3307, 2926, 1656, 1498, 1452, 1370, 1268, 1192, 1172, 1129, 1050; ^{1}H NMR ($CDCl_3$): δ 7.33–7.43 (m, 5H), 6.85 (d, J = 15.6 Hz, 1H), 6.20 (dd, J_1 = 15.6 Hz, J_2 = 6.6 Hz, 1H), 4.61–4.65 (m, 1H), 2.58 (s, 1H); ^{19}F NMR ($CDCl_3$): δ −79.46 (d, J = 4.8 Hz, 3F); ^{13}C NMR ($CDCl_3$): δ 136.29, 135.39, 128.73, 126.89, 124.30 (q, J = 282.0 Hz), 120.71, 71.61 (q, J = 32.4 Hz); EI MS (*m/z*, %): 202 (M^+, 27.21), 133 (100.00); HRMS (EI) calcd. for $C_{10}H_9F_3O$ [M^+]: 202.0605; Found: 202.0614.

*4.2.4. (Rs,R)-N-((E)-3-hydroxy-1-(4-methoxyphenyl)-5-phenyl-3-(trifluoromethyl)pent-4-enylidene)-tert-butanesulfinamide (**3b**)*

White solid, yield 81%; $[\alpha]_D^{20}$ +573.35 (c = 0.505, $CHCl_3$); FT-IR (KBr, cm^{-1}): ν 3149, 2997, 2951, 1604, 1588, 1563, 1437, 1363, 1264, 1165, 1134, 1043, 1029; ^{1}H NMR ($CDCl_3$): δ 7.59 (d, J = 8.7 Hz, 2H), 7.20 (s, 1H), 7.11–7.16 (m, 3H), 6.83–6.86 (m, 2H), 6.80 (d, J = 8.7 Hz, 2H), 6.64 (d, J = 15.6 Hz, 1H), 5.76 (d, J = 15.6 Hz, 1H), 3.74 (AB, J_{AB} = 12.6 Hz, 2H), 3.73 (s, 3H), 1.40 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −81.55 (s, 3F); ^{13}C NMR ($CDCl_3$): δ 171.96, 162.30, 136.07, 132.90, 132.73, 129.43, 128.02, 127.66, 126.50, 125.32 (q, J = 288.0 Hz), 125.11, 114.01, 73.20 (q, J = 28.5 Hz), 59.74, 55.36, 37.27, 23.13; ESI MS (*m/z*): 454.2 (M^++1); Anal. Calcd. for $C_{23}H_{26}F_3NO_3S$: C, 60.91; H, 5.78; N, 3.09. Found: C, 60.96; H, 5.73; N, 2.96.

*4.2.5. (Rs,R)-N-((E)-1-(4-fluorophenyl)-3-hydroxy-5-phenyl-3-(trifluoromethyl)pent-4-enylidene)-tert-butanesulfinamide (**3c**)*

White solid, yield 60%; $[\alpha]_D^{20}$ +562.67 (c = 0.615, $CHCl_3$); FT-IR (KBr, cm^{-1}): ν 3155, 2968, 2930, 1612, 1581, 1509, 1462, 1367, 1280, 1261, 1184, 1167, 1135, 1019; ^{1}H NMR ($CDCl_3$): δ 7.59–7.63 (m, 2H), 7.15–7.17 (m, 3H), 7.11 (s, 1H), 6.96–7.02 (m, 2H), 6.84 (dd, J_1 = 6.8 Hz, J_2 = 2.9 Hz, 2H), 6.65 (d, J = 15.6 Hz, 1H), 5.73 (d, J = 15.6 Hz, 1H), 3.76 (AB, J_{AB} = 12.9 Hz, 2H), 1.42 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −81.61 (s, 3F), −107.97–108.07 (m, 1F); ^{13}C NMR ($CDCl_3$): δ 171.83, 164.56 (d, J = 253.8 Hz), 136.70 (d, J = 3.2 Hz), 135.72, 133.09, 129.69 (d, J = 9.0 Hz), 128.21, 127.96, 126.35, 125.19 (q, J = 287.4 Hz), 124.74, 115.76 (d, J = 21.9 Hz), 73.10 (q, J = 28.8 Hz), 60.04, 37.56, 23.19; ESI MS (*m/z*): 442.2 (M^++1); Anal. Calcd. for $C_{22}H_{23}F_4NO_2S$: C, 59.85; H, 5.25; N, 3.17. Found: C, 60.08; H, 5.29; N, 2.97.

*4.2.6. (Rs,R)-N-((E)-1-(4-chlorophenyl)-3-hydroxy-5-phenyl-3-(trifluoromethyl)pent-4-enylidene)-tert-butanesulfinamide (**3d**)*

White solid, yield 55%; $[\alpha]_D^{20}$ +525.24 (c = 0.765, $CHCl_3$); FT-IR (KBr, cm^{-1}): ν 3139, 2956, 2865, 1595, 1585, 1561, 1435, 1366, 1263, 1167, 1133, 1041, 1012; ^{1}H NMR ($CDCl_3$): δ 7.51 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 7.16–7.18 (m, 3H), 7.06 (s, 1H), 6.79–6.82 (m, 2H), 6.64 (d, J = 15.3 Hz, 1H), 5.69 (d, J = 15.3 Hz, 1H), 3.75 (AB, J_{AB} = 12.6 Hz, 2H), 1.42 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −81.61 (s, 3F); ^{13}C NMR ($CDCl_3$): δ 172.11, 139.00, 137.72, 135.70, 133.13, 128.96, 128.74, 128.24, 128.01, 126.37, 125.16 (q, J = 287.8 Hz), 124.80, 73.10 (q, J = 28.9 Hz), 60.16, 37.61, 23.21; ESI MS (*m/z*): 458.2 (M^++1); HRMS (MALDI) calcd. for $C_{22}H_{23}ClF_3NO_2SNa^{+1}$ [M^++Na]: 480.0982; Found: 480.0997; Anal. Calcd. for $C_{22}H_{23}ClF_3NO_2S$: C, 57.70; H, 5.06; N, 3.06. Found: C, 58.09; H, 5.22; N, 2.80.

*4.2.7. (Rs,R)-N-((E)-3-hydroxy-1-(4-nitrophenyl)-5-phenyl-3-(trifluoromethyl)pent-4-enylidene)-tert-butanesulfinamide (**3e**)*

White solid, yield 45%; $[\alpha]_D^{20}$ +545.30 (c = 0.57, $CHCl_3$); FT-IR (KBr, cm^{-1}): ν 3213, 2956, 2863, 1601, 1587, 1520, 1450, 1345, 1260, 1188, 1166, 1137, 1043; ^{1}H NMR ($CDCl_3$): δ 8.08 (d, J = 9.0 Hz, 2H), 7.68 (d, J = 9.0 Hz, 2H), 7.10–7.13 (m, 3H), 6.86 (s, 1H), 6.80-6.83 (m, 2H), 6.59 (d, J = 15.6 Hz, 1H), 5.66 (d, J = 15.6 Hz, 1H), 3.81 (AB, J_{AB} = 12.9 Hz, 2H), 1.45 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −81.60 (s, 3F); ^{13}C NMR ($CDCl_3$): δ 171.90, 148.72, 145.97, 135.05, 133.45, 129.42, 128.68, 128.31, 126.16, 125.43 (q, J = 294.5 Hz), 124.32, 123.79, 73.09 (q, J = 23.8 Hz), 60.60, 38.16, 23.21; ESI MS (*m/z*): 469.2 (M^++1); HRMS (MALDI) calcd. for $C_{22}H_{24}F_3N_2O_4S^{+1}$ [M^++1]: 469.1403; Found: 469.1412.

*4.2.8. (Rs,R)-N-((E)-5-hydroxy-2,2-dimethyl-7-phenyl-5-(trifluoromethyl)hept-6-en-3-ylidene)-tert-butanesulfinamide (**3f**)*

White solid, yield 51%; $[\alpha]_D^{20}$ +446.20 (c = 0.615, $CHCl_3$); FT-IR (KBr, cm^{-1}): ν 3039, 2990, 2865, 1600, 1480, 1446, 1366, 1280, 1257, 1178, 1143, 1030; ^{1}H NMR ($CDCl_3$): δ 7.66 (s, 1H), 7.27–7.40 (m, 5H), 6.90 (d, J = 15.3 Hz, 1H), 6.26 (d, J = 15.3 Hz, 1H), 3.27 (AB, J_{AB} = 12.5 Hz, 2H), 1.34 (s, 9H), 1.12 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −81.49 (s, 3F); ^{13}C NMR ($CDCl_3$): δ 184.85, 135.77, 132.99, 128.70, 128.18, 126.83, 125.96, 125.37 (q, J = 288.7 Hz), 72.88 (q, J = 28.1 Hz), 59.48, 43.91, 37.65, 29.22, 23.26; ESI MS (*m/z*): 404.2 (M^++1); Anal. Calcd. for $C_{20}H_{28}F_3NO_2S$: C, 59.53; H, 6.99; N, 3.47. Found: C, 59.51; H, 7.07; N, 3.35.

*4.2.9. (Rs,R)-N-((E)-5-hydroxy-2-methyl-7-phenyl-5-(trifluoromethyl)hept-6-en-3-ylidene)-tert-butanesulfinamide (**3g**)*

White solid, yield 88%; $[\alpha]_D^{20}$ +509.34 (c = 0.815, $CHCl_3$); FT-IR (KBr, cm^{-1}): ν 3100, 2968, 2870, 1627, 1465, 1447, 1365, 1286, 1257, 1184, 1149, 1028; ^{1}H NMR ($CDCl_3$): δ 7.28–7.41 (m, 5H), 7.16 (s, 1H), 6.96 (d, J = 15.9 Hz, 1H), 6.25 (d, J = 15.9 Hz, 1H), 3.23 (AB, J_{AB} = 12.0 Hz, 2H), 2.52 (7, J = 6.9 Hz, 1H), 1.32 (s, 9H), 1.11 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H); ^{19}F NMR ($CDCl_3$): δ −81.73 (s, 3F); ^{13}C NMR ($CDCl_3$): δ 184.24, 135.88, 133.34, 128.67, 128.21, 126.74, 125.18 (q, J = 288.0 Hz), 124.55, 72.85 (q, J = 28.9 Hz), 59.19, 42.53, 40.92, 22.85, 21.16, 18.63; ESI MS (*m/z*): 390.2 (M^++1); HRMS (MALDI) calcd. for $C_{19}H_{27}F_3NO_2S^{+1}$ [M^++1]: 390.1709; Found: 390.1716.

*4.2.10. (Rs,R)-N-((E)-1-(furan-2-yl)-3-hydroxy-5-phenyl-3-(trifluoromethyl)pent-4-enylidene)-tert-butanesulfinamide (**3h**)*

White solid, yield 79%; $[\alpha]_D^{20}$ +546.87 (c = 0.475, $CHCl_3$); FT-IR (KBr, cm^{-1}): ν 3135, 2966, 2928, 1579, 1559, 1475, 1391, 1365, 1262, 1184, 1162, 1139, 1028; ^{1}H NMR ($CDCl_3$): δ 7.50 (d, J = 1.8 Hz, 1H), 7.18–7.26 (m, 4H), 7.09–7.12 (m, 2H), 6.91 (d, J = 3.3 Hz, 1H), 6.75 (d, J = 15.3 Hz, 1H), 6.37 (dd, J_1 = 3.3 Hz, J_2 = 1.8 Hz, 1H), 6.16 (d, J = 15.3 Hz, 1H), 3.66 (AB, J_{AB} = 12.8 Hz, 2H), 1.37 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −81.63 (s, 3F); ^{13}C NMR ($CDCl_3$): δ 160.88, 153.43, 145.43, 136.10, 132.66, 128.27, 127.78, 126.63, 125.27 (q, J = 287.5 Hz), 124.47, 114.69, 112.89, 73.17 (q, J = 29.4 Hz), 60.32, 36.81, 23.15; ESI MS (*m/z*): 414.2 (M^++1); HRMS (MALDI) calcd. for $C_{20}H_{22}F_3NO_3SNa^{+1}$ [M^++Na]: 436.1165; Found: 436.1177.

*4.2.11. (Rs,R)-N-((E)-3-hydroxy-5-(4-methoxyphenyl)-1-phenyl-3-(trifluoromethyl)pent-4-enylidene)-tert-butanesulfinamide (**3i**)*

White solid, yield 70%; $[\alpha]_D^{20}$ +624.69 (c = 0.82, $CHCl_3$); FT-IR (KBr, cm^{-1}): ν 3150, 2983, 2865, 1593, 1573, 1459, 1446, 1359, 1262, 1187, 1166, 1131, 1028; ^{1}H NMR ($CDCl_3$): δ 7.57–7.60 (m, 2H), 7.31–7.36 (m, 3H), 7.11 (s, 1H), 6.71 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 6.59 (d, J = 15.6 Hz, 1H), 5.56 (d, J = 15.6 Hz, 1H), 3.78 (AB, J_{AB} = 12.9 Hz, 2H), 3.75 (s, 3H), 1.42 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −82.17 (s, 3F); ^{13}C NMR ($CDCl_3$): δ 173.34, 159.37, 140.60, 132.29, 131.18, 128.76, 128.69, 127.70, 127.41, 125.30 (q, J = 288.0 Hz), 122.79, 113.49, 73.08 (q, J = 28.3 Hz), 60.00, 55.17,

37.63, 23.20; ESI MS (*m/z*): 454.2 (M^++1); HRMS (MALDI) calcd. for $C_{23}H_{26}F_3NO_3SNa^{+1}$ [M^++Na]: 476.1478; Found: 476.1473.

*4.2.12. (Rs,R)-N-((E)-5-(4-chlorophenyl)-3-hydroxy-1-phenyl-3-(trifluoromethyl)pent-4-enylidene)-tert-butanesulfinamide (**3j**)*

White solid, yield 80%; $[\alpha]_D^{20}$ +590.54 (*c* = 1.065, $CHCl_3$); FT-IR (KBr, cm^{-1}): ν 3093, 2986, 2865, 1603, 1591, 1571, 1492, 1366, 1257, 1189, 1162, 1135, 1070, 1041; ^1H NMR ($CDCl_3$): δ 7.57–7.59 (m, 2H), 7.30–7.37 (m, 3H), 7.17 (s, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 6.60 (d, *J* = 15.6 Hz, 1H), 5.68 (d, *J* = 15.6 Hz, 1H), 3.78 (AB, J_{AB} = 12.9 Hz, 2H), 1.42 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −82.01 (s, 3F); ^{13}C NMR ($CDCl_3$): δ 173.12, 140.54, 134.41, 133.46, 131.73, 131.33, 128.78, 128.23, 127.68, 127.38, 125.73, 125.15 (q, *J* = 287.1 Hz), 73.04 (q, *J* = 28.4 Hz), 60.02, 37.45, 23.16; ESI MS (*m/z*): 458.2 (M^++1); HRMS (MALDI) calcd. for $C_{22}H_{23}ClF_3NO_2SNa^{+1}$ [M^++Na]: 480.0982; Found: 480.1005.

*4.2.13. (Rs,R)-N-((E)-3-hydroxy-1-phenyl-3-(trifluoromethyl)tridec-4-enylidene)-tert-butanesulfinamide (**3k**)*

Yellowish oil; $[\alpha]_D^{20}$ +205.9 (*c* = 0.905, $CHCl_3$); FT-IR (KBr, cm^{-1}): ν 3207, 2926, 2855, 1603, 1592, 1573, 1456, 1267, 1184, 1047; ^1H NMR ($CDCl_3$): δ 7.51–7.60 (m, 2H), 7.28–7.41 (m, 3H), 6.81 (s, 1H), 5.67 (dt, J_1 = 15.3 Hz, J_2 = 6.9 Hz, 1H), 5.02 (d, *J* = 15.3 Hz, 1H), 3.58 (AB, J_{AB} = 12.9 Hz, 2H), 1.40–1.59 (m, 2H), 1.34 (s, 9H), 0.88–1.25 (m, 10H), 0.69–0.85 (m, 5H); ^{19}F NMR ($CDCl_3$): δ −81.96 (s, 3F); ^{13}C NMR ($CDCl_3$): δ 173.08, 140.45, 135.00, 131.44, 128.58, 127.65, 125.39 (q, *J* = 287.1 Hz), 124.57, 72.70 (q, *J* = 27.9 Hz), 60.01, 37.12, 31.88, 31.66, 29.36, 29.21, 29.10, 28.10, 23.29, 22.69, 14.11; ESI MS (*m/z*): 460 (M^++1); HRMS (MALDI) calcd. for $C_{24}H_{37}F_3NO_2S$ [M^++1]: 460.2492; Found: 460.2495.

*4.3. Reduction of **3a** with $LiBHEt_3$*

To a solution of **3a** (84 mg, 0.2 mmol) in 3 mL THF was slowly added $LiBHEt_3$ (0.5 mL, 0.5 mmol, 1.0 M solution in THF) at −78 °C and the resulting solution was stirred for 3 h. Then 5 mL of a saturated aqueous solution of NH_4Cl was added. The resulting mixture was gradually warmed to room temperature and extracted with EtOAc (10 mL × 3). The combined organic solution was dried over Na_2SO_4. After the removal of volatile solvents under vacuum, the residue was further purified by column chromatography on silica gel to give product **5a** (81 mg).

*4.3.1. (Rs,1S,3R)-N-((E)-3-hydroxy-1,5-diphenyl-3-(trifluoromethyl)pent-4-enyl)-tert-butane sulfinamide (**5a**)*

White solid, yield 96%; mp 153–155 °C; FT-IR (KBr, cm^{-1}): ν 3285, 3163, 2960, 2929, 1494, 1456, 1367, 1285, 1255, 1180, 1147, 1028; ^1H NMR ($CDCl_3$): δ 7.26–7.37 (m, 10H), 7.08 (d, *J* = 15.6 Hz, 1H), 6.16 (d, *J* = 15.6 Hz, 1H), 5.44 (s, 1H), 4.95–5.01 (m, 1H), 4.51 (d, *J* = 3.9 Hz, 1H), 2.53 (dd, J_1 = 15.0 Hz, J_2 = 3.9 Hz, 1H), 2.36 (dd, J_1 = 15.0 Hz, J_2 = 9.0 Hz, 1H), 1.10 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −80.84 (s, 3F); EI MS (*m/z*, %): 369 (M^+-^{t}Bu + 1, 10.59), 320 (12.61), 201 (100.00); Anal. Calcd. for $C_{22}H_{26}F_3NO_2S$: C, 62.10; H, 6.16; N, 3.29. Found: C, 62.36; H, 6.38; N, 2.98.

*4.4. Reduction of **3a** with Catecholborane*

To a solution of **3a** (60 mg, 0.14 mmol) in 2 mL THF was slowly added Catecholborane (0.75 mL, 0.75 mmol, 1.0 M solution in THF) and the resulting solution was stirred for 24 h at −10 °C. To the reaction mixture was added 1.5 mL of MeOH and 2.0 mL of a saturated solution of sodium potassium tartrate. The resulting mixture was stirred for 1 h, washed with 5 mL of brine, and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic solution was dried over Na_2SO_4. After the removal of volatile solvents under vacuum, the residue was further purified by column chromatography on silica gel to give product **5b** (45 mg) (16 mg of **3a** was recovered).

*4.4.1. (Rs,1R,3R)-N-((E)-3-hydroxy-1,5-diphenyl-3-(trifluoromethyl)pent-4-enyl)-tert-butane sulfinamide (**5b**)*

White solid, yield 99%; FT-IR (KBr, cm^{-1}): ν 3227, 2981, 2928, 1425, 1369, 1285, 1263, 1178, 1136, 1076, 1027; ^1H NMR ($CDCl_3$): δ 7.44–7.47 (m, 2H), 7.29–7.39 (m, 8H), 7.13 (d, *J* = 15.6 Hz, 1H), 6.18 (d, *J* = 15.6 Hz, 1H), 5.79 (s, 1H), 4.62-4.70 (m, 1H), 4.40 (d, *J* = 4.2 Hz, 1H), 3.04 (dd, J_1 = 14.3 Hz, J_2 = 12.0 Hz, 1H), 2.38 (d, *J* = 14.3 Hz, 1H), 1.16 (s, 9H); ^{19}F NMR ($CDCl_3$): δ −82.04 (s, 3F); EI MS (*m/z*, %): 320 (M^+-^{t}Bu-SO, 6.32), 201 (100.00); HRMS (MALDI) calcd. for $C_{22}H_{26}F_3NO_2SNa^{+1}$ [M^++Na]: 448.1529; Found: 448.1537.

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