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Highly diastereoselective and thermodynamically controlled nucleophilic addition of α-fluoro-α-phenylthio-α-phenylsulfonylmethane (FTSM) to aldehydes

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This manuscript is dedicated to Professor Steve Davies in celebration of his career of innovative research, and with gratitude for his service to Tetrahedron Asymmetry.

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ABSTRACT

A thermodynamically controlled and reversible nucleophilic addition of a monofluorinated sulfone, α-fluoro-α-phenylthio-α-phenylsulfonylmethane (FTSM), to aldehydes has been developed, which allows the efficient synthesis of β-fluorinated carbinols with high diastereoselectivity. Control experiments showed that the fluorine substitution not only promotes the addition process, but also improves the diastereoselectivity.

1. Introduction

Fluoroalkylation is a direct approach to introduce structurally diverse fluorinated moieties into organic molecules, and has been frequently used in the synthesis of fluorine-containing target molecules [1–6]. However, compared with trifluoromethylation and difluoroalkylation, monofluoroalkylation is more intriguing due to the need for controlling stereochemistry of the fluorinated carbon centers associated with the incorporation of the monofluoroalkyl groups. In recent years, much attention has been paid to the asymmetric construction of fluorine-bearing carbon stereogenic centers through monofluoroalkylation approaches [7].

Our group has focused on the development of sulfur-based fluoroalkylation reagents and methods by tackling the negative fluorine effect in nucleophilic fluoroalkylation reactions [8–10]. During our investigation on the monofluoromethylation of aldehydes and ketones with fluoromethyl phenyl sulfone ($PhSO_2CH_2F$) in the presence of a base at low temperature [11–13], we noticed that the irreversible, kinetically controlled addition of the fluorinated carbanion $PhSO_2CHF^-$ to carbonyls proceeds with very low diastereoselectivity albeit in high yields (Scheme 1a) [12,13]. Although the addition reaction is reversible at elevated temperatures, the low thermal stability of $PhSO_2CHF^-$ precludes further formation of the thermodynamically more stable diastereoisomer [12,13]. It is interesting to note that when a fluoromethyl sulfoximine was used instead of $PhSO_2CH_2F$, a similar irreversible and kinetically controlled addition of $PhS(O)(NTBS)CHF^-$ to both aldehydes and ketones could afford the adducts with excellent diastereoselectivity, implying high relative stereoselectivity at the carbinol carbon and fluorinated carbon centers (Scheme 1b) [14]. Obviously, the bulky sulfonimidoyl group is superior to the sulfonyl group in controlling the stereoselectivity under kinetically controlled conditions.

Previously, Shibata and co-workers and our group independently disclosed the use of fluorobis(phenylsulfonyl)methane

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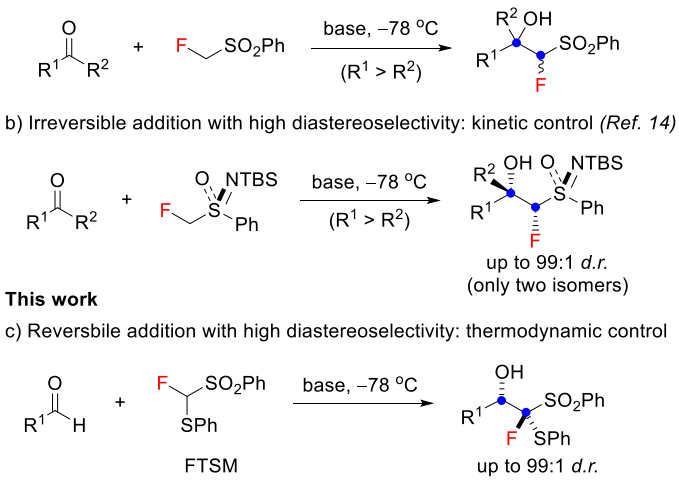


Scheme 1. Diastereoselective nucleophilic monofluoromethylation of carbonyl compounds with fluorinated sulfones and sulfoximines.

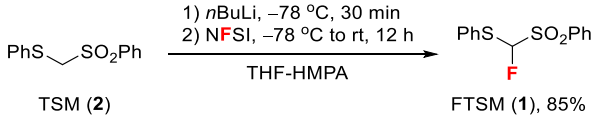
[FBSM, $(PhSO_2)_2CFH$] as a fluoromethide equivalent for nucleophilic monofluoromethylation [15,16], and we also showed that the highly reversible addition of $(PhSO_2)_2CF^-$ to aldehydes could be tamed by stabilizing the carbinolate intermediate through both strong Li–O coordination and control of the reaction at low temperature [17]. In this context, we envisioned that a highly diastereoselective monofluoromethylation of carbonyl compounds with a monofluorinated sulfone should be accessible through a thermodynamically controlled process, providing that the addition of the corresponding prochiral carbanion to carbonyl groups is reversible at low temperature. Herein, we report the highly diastereoselective nucleophilic addition of α-fluoro-α-phenylthio-α-phenylsulfonylmethane (FTSM) to aldehydes under mild conditions (Scheme 1c), proceeding through a thermodynamically controlled and reversible addition of the corresponding fluorinated carbanion to a carbonyl group.

2. Results and discussion

α-Fluoro-α-phenylthio-α-phenylsulfonylmethane (FTSM) (**1**) was previously prepared *via* electrochemical monofluorination of α-phenylthio-α-phenylsulfonylmethane (TSM) (**2**) in moderate yield [18]. As an alternative method, we developed an efficient synthesis of FTSM using electrophilic fluorination of TSM (**2**) with *N*-fluorobenzenesulfonimide (NFSI) (Scheme 2).

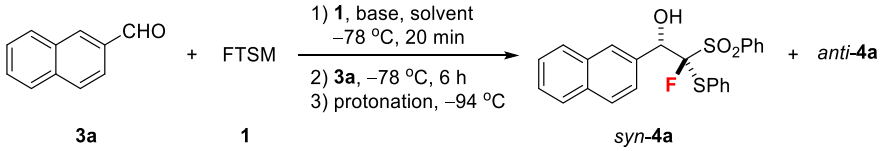
With FTSM (**1**) in hand, we set out to study its nucleophilic addition to aldehydes by choosing 2-naphthaldehyde (**3a**) as a model substrate (Table 1). According to our previous results with FBSM [17], we initially added lithium hexamethyldisilazide (LiHMDS) into a CH_2Cl_2 solution of FTSM (**1**) at −78 °C. After 20 min, aldehyde **3a** was added and the mixture was stirred at the same temperature for 6 h, followed by quenching with trifluoroacetic acid at −94 °C. However, the adduct **4a** was formed in only 45% yield with very low diastereoselectivity as determined by ^{19}F NMR spectroscopy (Table 1, entry 1). The use of NaHMDS instead of LiHMDS afforded adduct **4a** with somewhat improved diastereoselectivity, albeit in much lower yield (Table 1, entry 2). Gratifyingly, when the base was switched to KHMDS, adduct **4a** was formed in 85% yield with 99:1 diastereoselectivity (Table 1, entry 3). With KHMDS as the optimal base, screening of the solvents showed that THF, toluene, and diethyl ether were inferior to CH_2Cl_2 (Table 1, entries 4–6). In the case of THF, the use of hexamethylphosphoramide (HMPA) as the co-solvent significantly improved the yield, albeit a little lower than the highest yield (Table 1, entry 7). Of note is that in this reaction the metal—oxygen coordination contributes little to the stabilization of the alcoholate intermediate, probably due to the reduced steric hindrance of FTSM compared to FBSM (see Table 1, entry 4 *vs* entry 7). When the quenching of the reaction was performed at −78 °C instead of −94 °C, the yield of **4a** decreased significantly (Table 1, entry 9). When saturated NH_4Cl solution or concentrated hydrochloric acid was used to quench the reaction, product **4a** was formed in rather low yield even when the quenching was conducted at −98 °C (Table 1, entries 10 and 11). The addition of FTSM (**1**) to **3a** under Barbier-type reaction conditions decreased the yield of adduct **4a** to some extent, probably due to the competitive reaction between KHMDS and **3a** to form the aldimine (Table 1, entry 12) [19].

Using the optimized reaction conditions (Table 1, entry 3), we then investigated the substrate scope of this diastereoselective nucleophilic monofluoromethylation reaction between FTSM (**1**) and aldehydes **3** (Table 2). A variety of structurally diverse aldehydes could react with FTSM to give the adducts **4** in good to excellent yields with high diastereoselectivity (Table 2, entries 1–17). The reaction of less sterically demanding 2-naphthaldehyde and 1-naphthaldehyde proceeded smoothly in 80% and 83% yield, respectively (Table 2, entries 1 and 2). Various functional groups such as methyl, methoxy, chloro, bromo, and fluoro groups were well tolerated (Table 2, entries 4–10). In addition to the *para*-substituted benzaldehydes, the *meta*-substituted ones could also react smoothly to give the corresponding products (Table 2, entries 11–13). α,β-Unsaturated aldehydes were also amenable to the reaction, as demonstrated by the formation of the carbonyl addition product **4n** in 60% yield with 99:1 diastereoselectivity (Table 2, entry 14). Heterocyclic aldehyde 5-methylthiophene-2-



Scheme 2. Preparation of FTSM *via* electrophilic fluorination.

Table 1
Optimization of the nucleophilic addition of FTSM to aldehyde **3a**.[a]



3a **1** *syn*-**4a**

Entry	Base	Solvent	Protonation conditions	Yield (%)[b]	syn/anti[b]
1	LiHMDS	CH_2Cl_2	CF_3CO_2H	45	43:57
2	NaHMDS	CH_2Cl_2	CF_3CO_2H	24	33:67
3	KHMDS	CH_2Cl_2	CF_3CO_2H	85	99:1
4	KHMDS	THF	CF_3CO_2H	74	99:1
5	KHMDS	$PhCH_3$	CF_3CO_2H	28	99:1
6	KHMDS	Et_2O	CF_3CO_2H	58	99:1
7	KHMDS	THF-HMPA (3:1, v/v)	CF_3CO_2H	84	99:1
8	KHMDS	CH_2Cl_2-HMPA (5:1, v/v)	CF_3CO_2H	65	99:1
9[c]	KHMDS	CH_2Cl_2	CF_3CO_2H	72	99:1
10	KHMDS	CH_2Cl_2	sat. NH_4Cl aq.	0	–
11	KHMDS	CH_2Cl_2	conc. HCl	38	96:4
12[d]	KHMDS	CH_2Cl_2	CF_3CO_2H	78	99:1

[a] Reagents and conditions: FTSM (**1**) (0.2 mmol) in solvent was treated with base (1.2 equiv, 1.0 M in THF) at −78 °C for 20 min, then aldehyde **3a** (1.2 equiv) was added and the mixture was stirred for an additional 6 h. Finally, the reaction was cooled to −94 °C, and quenched with a proton source.
[b] The yield and *syn*/*anti* ratio were determined by ^{19}F NMR analysis of the crude product **4**. The yield refers to the total yield of *syn*-**4a** and *anti*-**4a**.
[c] The protonation was carried out at −78 °C.
[d] KHMDS was added to a mixture of FTSM (**1**) and **3a**.

carbaldehyde could be transformed to adduct **4o** in good yield with high diastereoselectivity (Table 2, entry 15). Aliphatic aldehydes such as isobutyraldehyde and pivalaldehyde could also react with FTSM smoothly (Table 2, entries 16 and 17). However, the reaction is sensitive towards the steric hindrance and the electronic nature of the aromatic aldehydes. Sterically hindered aldehydes (Table 2, entries 18–22) and electron-deficient aldehydes (Table 2, entries 23–25) significantly decreased the yield and/or diastereoselectivity. The relative configuration of the major diastereoisomer **4i** was determined by X-ray single crystal structure analysis [20], and the configurations of the other products were assigned by comparison of their ^{19}F NMR data with those of **4i** (Fig. 1).

To shed light on the high diastereoselectivity of the current nucleophilic monofluoromethylation, we investigated the interconversion between the two diastereomers. The minor diastereomer *anti*-**4d** was obtained by *in-situ* trapping of the alcoholate intermediate with acetic anhydride followed by column separation and acidic hydrolysis (Scheme 3a). The analytically pure *anti*-**4d** and *syn*-**4d** were separately dissolved in CH_2Cl_2 and treated with KHMDS at −78 °C. After 6 h, the reaction was quenched with trifluoroacetic acid at −94 °C (Scheme 2b). In the former case, *anti*-**4d** was completely consumed and transformed to *syn*-**4d** and FTSM, while in the latter case, large amounts of *syn*-**4d** still remained, with the formation of FTSM in less than 10% yield. These results indicated that the addition reaction of FTSM to aldehydes is a reversible process, and the *anti*-diastereomer of the alcoholate **4**-K could be transformed to the thermodynamically more stable *syn*-diastereomer through a retro-addition reaction (Scheme 4). As depicted in the Newman projections, though sterically more crowded, *syn*-**4**-K is thermodynamically more stable, presumably due to the significantly decreased electrostatic repulsion between the fluorine atom and the negatively charged oxygen atom.

Furthermore, to demonstrate the unique role of fluorine substitution, we examined the nucleophilic addition reaction of α-chloro-α-phenylthio-α-phenylsulfonylmethane (CTSM) (**5**) and α-phenylthio-α-phenylsulfonylmethane (TSM) (**2**) to 2-naphthaldehyde (Scheme 5). Under the optimized conditions for the reaction of FTSM, the anion of CTSM failed to react with 2-naphthaldehyde and the starting material CTSM was recovered in 80% yield. Although TSM could react with 2-naphthaldehyde to give the adduct **7** in 80% yield, the diastereoselectivity was low (58:42 *d.r.*). It is clear that the electronegative fluorine atom plays an important role in improving the diastereoselectivity.

Finally, to show the potential value of our monofluoromethylation reaction in organic synthesis, the *syn*-**4a** adduct was stereoselectively transformed to the deoxyfluorination product **8** in 72% yield with a diastereomeric ratio of 95:5. Upon the treatment with LiHMDS in THF at −78 °C for 6 h, compound **8** was converted to 1,2-difluorinated alkene **9** in 52% yield with 96:4 *Z*/*E* stereoselectivity (Scheme 6).

3. Conclusion

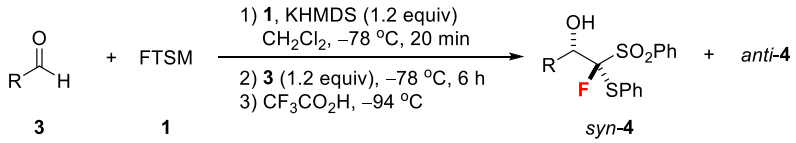
In conclusion, we have developed a thermodynamically controlled and reversible nucleophilic addition of α-fluoro-α-phenylthio-α-phenylsulfonylmethane (FTSM) to aldehydes, which allows the efficient synthesis of β-fluorinated carbinols with high diastereoselectivity. Mechanistic investigations showed that the fluorine substitution plays important roles in promoting the addition process and enhancing the diastereoselectivity. Further studies on monofluoromethylation with FTSM are currently underway in our laboratory.

4. Experimental

4.1. General

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. Anhydrous Et_2O, THF and toluene were freshly distilled over sodium. Anhydrous HMPA and CH_2Cl_2 were distilled over CaH_2. Melting points were measured on an electrothermal digital melting point apparatus and were not corrected. ^1H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a 500 MHz, 400 MHz or 300 MHz NMR spectrometer. ^1H NMR chemical shifts were determined relative to internal $(CH_3)_4Si$ (TMS) at δ 0.0 or to the signal of a residual

Table 2
Nucleophilic addition of FTSM to various aldehydes[a].



Entry	R	3	4	Yield, *syn*-**4** (%)[b]	*syn*/*anti*[c]
1	2-naphthyl	**3a**	**4a**	82 (79)[d]	99:1
2	1-naphthyl	**3b**	**4b**	83	99:1
3	Ph	**3c**	**4c**	71	99:1
4	4-Me-C_6H_4	**3d**	**4d**	86	99:1
5	4-*i*Pr-C_6H_4	**3e**	**4e**	86	99:1
6	4-MeO-C_6H_4	**3f**	**4f**	69	99:1
7	4-Ph-C_6H_4	**3g**	**4g**	80	96:4
8	4-Cl-C_6H_4	**3h**	**4h**	84	98:2
9	4-Br-C_6H_4	**3i**	**4i**	91	96:4
10	4-F-C_6H_4	**3j**	**4j**	80	99:1
11	3-Me-C_6H_4	**3k**	**4k**	78	99:1
12	3-PhO-C_6H_4	**3l**	**4l**	75	94:6
13	3,4-Me-C_6H_3	**3m**	**4m**	73	99:1
14	(*E*)-PhCH = CH	**3n**	**4n**	60	99:1
15	5-Me-2-thiophenyl	**3o**	**4o**	80	99:1
16	*i*Bu	**3p**	**4p**	83	97:3
17	*t*Bu	**3q**	**4q**	83	99:1
18	2,5-MeO-C_6H_3	**3r**	**4r**	79	87:13
19	9-anthracenyl	**3s**	**4s**	34[e]	99:1
20	2-Br-C_6H_4	**3t**	**4t**	58[e]	61:39
21	2-MeO-C_6H_4	**3u**	**4u**	26[e]	99:1
22	4-Me-5-thiazolyl	**3v**	**4v**	20[e]	99:1
23	4-CF_3-C_6H_4	**3w**	**4w**	17[e]	72:28
24	4-NO_2-C_6H_4	**3x**	**4x**	13[e]	39:61
25	3-pyridyl	**3y**	**4y**	37[e]	88:12

[a] Reagents and conditions: FTSM (**1**) (0.2 mmol) in CH_2Cl_2 was treated with KHMDS (0.24 mmol, 1.0 M in THF) at −78 °C for 20 min, then aldehyde **3** (0.24 mmol) was added and the mixture was stirred for an additional 6 h. Finally, the reaction was cooled to −94 °C, and quenched with CF_3CO_2H.
[b] Isolated yield.
[c] The *syn*/*anti* ratio was determined by ^{19}F NMR analysis of the crude product.
[d] The isolated yield of the reaction on 2.0 mmol scale is given in parentheses.
[e] The yield refers to the total yield of the two isomers as determined by ^{19}F NMR analysis of the crude product.

protonated solvent: $CDCl_3$ at δ 7.26. ^{13}C NMR chemical shifts were determined relative to internal TMS at δ 0.0. ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ at δ 0.0. Mass spectra were obtained on a mass spectrometer. High-resolution mass data were recorded on a high-resolution mass spectrometer in the EI, ESI or MALDI mode. IR spectra were recorded on an FT-IR spectrometer.

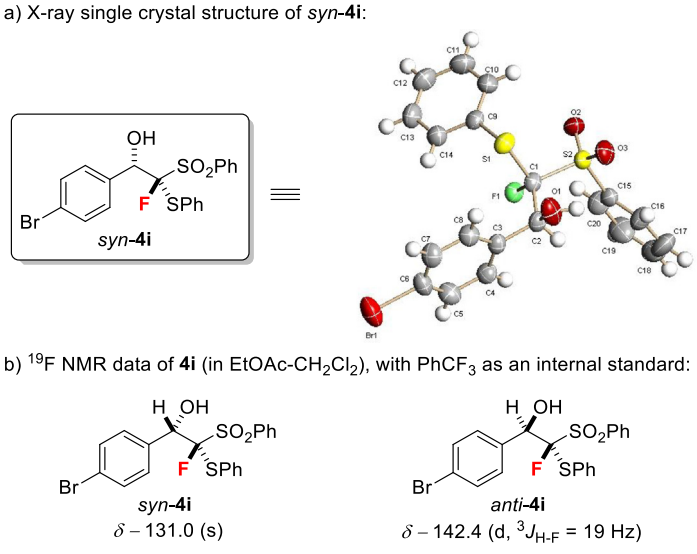
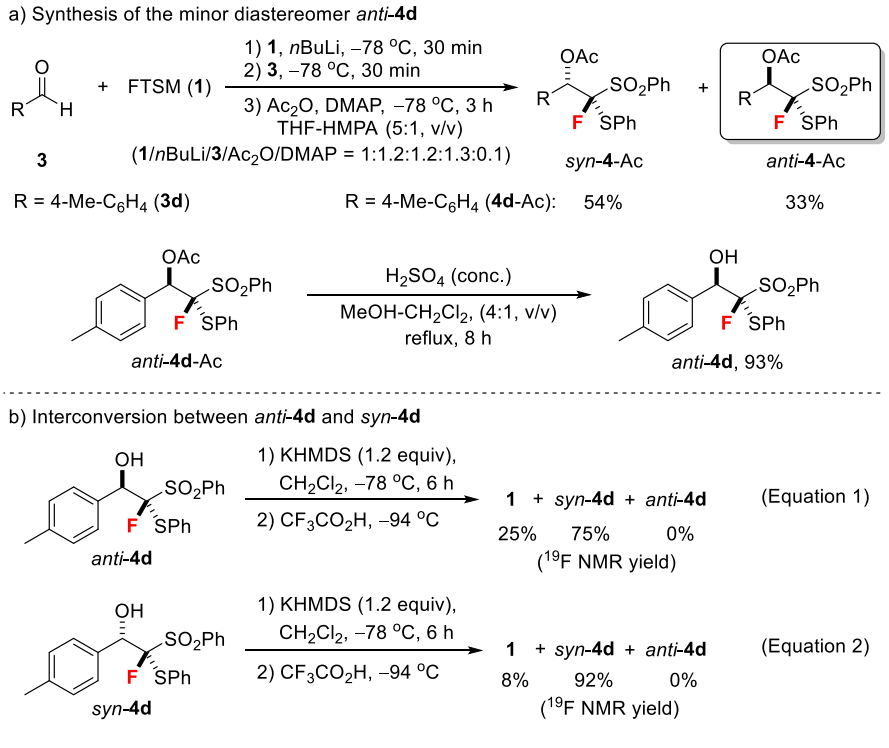
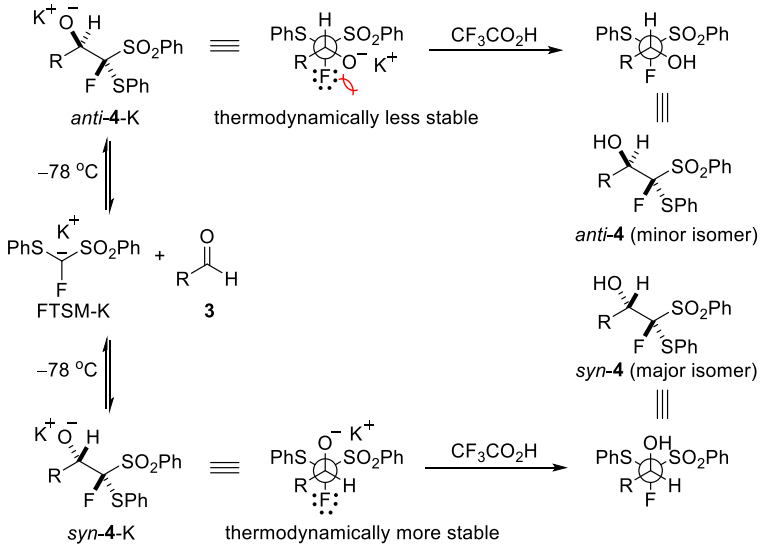


Fig. 1. X-ray single crystal structure of *syn*-**4i** and ^{19}F NMR data of crude **4i**.



Scheme 3. Synthesi of *anti*-**4d** and interconversion between *anti*-**4d** and *syn*-**4d**.

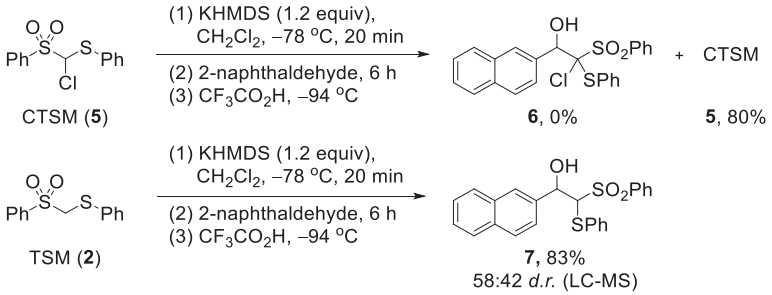


Scheme 4. Mechanistic consideration of the addition reaction.

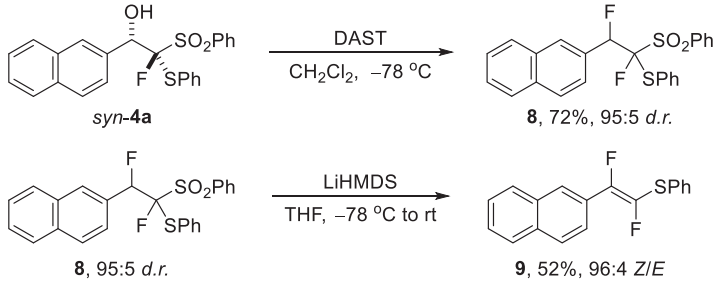
*4.2. Synthesis of α-fluoro-α-phenylthio-α-phenylsulfonylmethane (FTSM) (**1**)*

Under N_2 atmosphere, to a solution of α-phenylthio-α-phenylsulfonylmethane (TSM) (**2**) (4.19 g, 15.84 mmol) and hexaphosphoramide (HMPA) (1.90 mL) in anhydrous THF (54 mL) at −78 °C, was added *n*-butyllithium (4.3 mL, 2.5 M in hexane, 10.75 mmol). After stirring at −78 °C for 30 min, *N*-fluorobenzenesulfonimide (NFSI) (3.39 g, 10.75 mmol) was added in one portion at −78 °C. The resulted mixture was stirred at −78 °C for 20 min, then allowed to warm to room temperature and stirred for 12 h. The reaction was carefully quenched with a saturated aqueous solution of NH_4Cl, and the mixture was extracted with ethyl acetate (EtOAc) for three times. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, evaporated under vacuum, and finally purified by flash column chromatography on silica gel with petroleum ether/EtOAc (14:1, v/v) as eluent to afford FTSM (**1**) as pale yellow solid (2.57 g, 85% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, J = 7.8 Hz, 2H), 7.74 (t, J = 7.2 Hz, 1H), 7.64–7.57 (m, 4H), 7.43–7.33 (m, 3H), 6.21 (d, J = 51.0 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −144.7 (d, J = 53 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.9, 134.7, 133.84, 133.81, 129.75, 129.66, 129.5, 129.2, 110.6 (d, J = 264 Hz). MS (ESI, m/z): 305.0 ($[M + Na]^+$). The ^{1}H, ^{19}F, and ^{13}C NMR data are consistent



Scheme 5. Nucleophilic addition of CTSM and TSM to 2-naphthaldehyde.



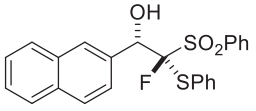
Scheme 6. Further transformation of adduct **4a.**

with a previous report [18].

4.3. General procedures for the nucleophilic addition of FTSM (**1**) to aldehydes **3**

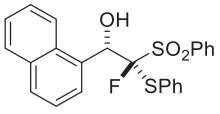
Under N_2 atmosphere, to the solution of FTSM (**1**) (57 mg, 0.2 mmol) in CH_2Cl_2 (1.2 mL) at −78 °C was slowly added KHMDS (0.24 mL, 1.0 M in THF, 0.24 mmol). After stirring at −78 °C for 20 min, a solution of aldehyde **3** (0.24 mmol) in CH_2Cl_2 (0.4 mL) was added. The reaction mixture was stirred at −78 °C for 6 h, quenched with CF_3CO_2H (0.5 mL) at −94 °C, diluted with H_2O (5 mL), and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel with petroleum ether/EtOAc (form 10:1 to 3:1, v/v) as eluent to afford the major isomer *syn*-**4**.

4.3.1. (1S*,2R*)-2-fluoro-1-(naphthalen-2-yl)-2-(phenylsulfonyl)-2-(phenylthio)ethan-1-ol (syn-**4a**)



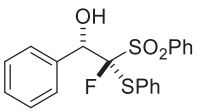
72 mg, 82% yield (0.2 mmol scale); 694 mg, 79% yield (2.0 mmol scale). White solid. M.p.: 176–177 °C. IR (KBr): 3506, 3057, 1602, 1580, 1508, 1471, 1446, 1439, 1320, 1311, 1227, 1145, 1079 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.92–7.81 (m, 5H), 7.69 (t, J = 7.5 Hz, 1H), 7.58–7.47 (m, 5H), 7.14 (t, J = 7.5 Hz, 1H), 6.94 (t, J = 7.8 Hz, 2H), 6.80 (d, J = 7.5 Hz, 2H), 5.70 (s, 1H), 3.79 (br. dd, J = 1.5 Hz, J = 3.0 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −130.3 (s, 1F). ^{13}C NMR (100 MHz, DMSO-d_6): δ 136.0, 135.4, 124.8, 134.7, 132.8, 132.2, 130.6, 129.4, 129.0, 128.4, 128.0, 127.4, 127.0, 126.3, 126.2, 125.8, 125.5 (d, J = 5 Hz), 114.0 (d, J = 268 Hz), 72.2 (d, J = 25 Hz) (there was an overlap of two aromatic carbons). MS (ESI, m/z): 456.2 ($[M + NH_4]^+$). HRMS (ESI, m/z): Calcd. for $C_{24}H_{19}FNaO_3S_2^+$ ($[M + Na]^+$): 461.0652; Found: 411.0664.

4.3.2. (1S*,2R*)-2-fluoro-1-(naphthalen-1-yl)-2-(phenylsulfonyl)-2-(phenylthio)ethan-1-ol (syn-**4b**)



73 mg, 83% yield. White solid. M.p.: 176–177 °C. IR (KBr): 3497, 3050, 1596, 1584, 1510, 1474, 1448, 1440, 1326, 1308, 1293, 1209, 1168, 1151, 1091, 1083 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J = 7.2 Hz, 1H), 7.95 (d, J = 8.1 Hz, 2H), 7.88 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.63–7.52 (m, 3H), 7.43–7.38 (m, 1H), 7.25 (d, J = 4.2 Hz, 2H), 7.12 (t, J = 7.5 Hz, 1H), 6.94 (t, J = 7.5 Hz, 2H), 6.81 (d, J = 7.8 Hz, 2H), 6.48 (s, 1H), 3.76 (d, J = 1.5 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −129.9 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.7, 134.8, 133.9, 133.1, 131.7, 130.8, 130.7, 129.5, 129.3, 129.2, 128.6, 128.2, 127.2, 126.1, 125.3, 125.2 (d, J = 5 Hz), 125.0, 122.7 (d, J = 4 Hz), 114.7 (d, J = 277 Hz), 68.1 (d, J = 21 Hz). MS (ESI, m/z): 456.1 ($[M + NH_4]^+$). E.A. calcd. for $C_{24}H_{19}FO_3S_2$: C, 65.73; H, 4.37. Found: C: 65.75; H: 4.47.

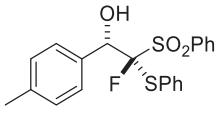
4.3.3. (1S*,2R*)-2-fluoro-1-phenyl-2-(phenylsulfonyl)-2-(phenylthio)ethan-1-ol (syn-**4c**)



55 mg, 71% yield. White solid. M.p.: 149–150 °C. IR (KBr): 3449, 3068, 1601, 1582, 1493, 1476, 1446, 1359, 1320, 1309, 1248, 1147,

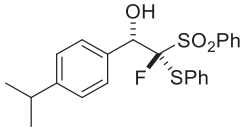
1095 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, J = 6.9 Hz, 2H), 7.68 (t, J = 6 Hz, 1H), 7.54–7.48 (m, 4H), 7.38–7.36 (m, 3H), 7.1 (t, J = 6 Hz, 1H), 7.03–6.98 (m, 2H), 6.80 (d, J = 7.2 Hz, 2H), 5.54 (s, 1H), 3.69 (d, J = 2.7 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −130.8 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 134.9, 134.7, 134.0, 130.6, 129.4, 129.0, 128.8, 128.4 (d, J = 3 Hz), 128.2, 127.7, 125.2 (d, J = 6 Hz), 113.3 (d, J = 274 Hz), 72.8 (d, J = 22 Hz). MS (ESI, *m/z*): 406.1 ($[M + NH_4]^+$). HRMS (ESI, *m/z*): Calcd. for $C_{20}H_{17}FNaO_3S_2^+$ ($[M + Na]^+$): 411.0495; Found: 411.0509.

4.3.4. (1S,2R*)-2-fluoro-2-(phenylsulfonyl)-2-(phenylthio)-1-(p-tolyl)ethan-1-ol (syn-**4d**)*



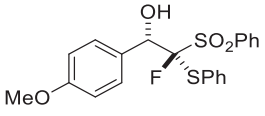
69 mg, 86% yield. White solid. M.p.: 132–133 °C. IR (KBr): 3495, 3065, 1612, 1583, 1513, 1476, 1448, 1442, 1332, 1314, 1288, 1196, 1149, 1070 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J = 7.2 Hz, 2H), 7.68 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 7.21–7.16 (m, 3H), 7.02 (t, J = 7.8 Hz, 2H), 6.86 (d, J = 7.8 Hz, 2H), 5.49 (s, 1H), 3.66 (s, 1H), 2.37 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −131.5 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 136.6, 134.6, 134.1, 131.9, 130.5, 129.3, 128.9, 128.5, 128.2, 128.2, 125.3 (d, J = 4 Hz), 113.6 (d, J = 274 Hz), 72.8 (d, J = 21 Hz), 21.2. MS (ESI, *m/z*): 420.1 ($[M + NH_4]^+$). Elem. Anal. Calcd. for $C_{21}H_{19}FO_3S_2$: C, 62.66; H, 4.76. Found: C: 62.51; H: 4.98.

4.3.5. (1S,2R*)-2-fluoro-1-(4-isopropylphenyl)-2-(phenylsulfonyl)-2-(phenylthio)ethan-1-ol (syn-**4e**)*



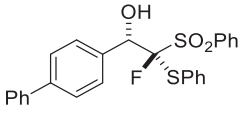
74 mg, 86% yield. White solid. M.p.: 143–144 °C. IR (KBr): 3495, 3059, 2959, 1699, 1475, 1447, 1315, 1241, 1149, 1081 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, J = 7.8 Hz, 2H), 7.69 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.26–7.15 (m, 3H), 6.99 (t, J = 7.5 Hz, 2H), 6.75 (d, J = 7. 5Hz, 2H), 5.52 (s, 1H), 3.60 (s, 1H), 2.93 (t, J = 6.9 Hz, 1H), 1.26 (d, J = 6.9 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −130.7 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 136.7, 134.8, 134.3, 132.3, 130.8, 129.4, 129.1, 128.5 (d, J = 6 Hz), 128.3, 126.0, 125.5 (d, J = 6 Hz), 113.5 (d, J = 205 Hz), 72.8 (d, J = 16 Hz), 34.0, 24.0 (d, J = 3 Hz). MS (ESI, *m/z*): 453.0 ($[M + Na]^+$). HRMS (ESI, *m/z*): Calcd. for $C_{23}H_{23}FNaO_3S_2^+$ ($[M + Na]^+$): 453.0965; Found: 453.0968.

4.3.6. (1S,2R*)-2-fluoro-1-(4-methoxyphenyl)-2-(phenylsulfonyl)-2-(phenylthio)ethan-1-ol (syn-**4f**)*



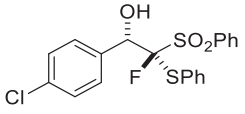
58 mg, 69% yield. White solid. M.p.: 151–152 °C. IR (KBr): 3493, 2837, 1609, 1583, 1512, 1466, 1442, 1330, 1303, 1251, 1176, 1147 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, J = 6.6 Hz, 2H), 7.66 (d, J = 7.5 H, 1H), 7.54–7.40 (m, 4H), 7.28–6.90 (m, 7H), 5.48 (s, 1H), 3.84 (s, 3H), 3.06 (s, 1H). ^{19}F ^{NMR} (282 MHz, $CDCl_3$): δ −130.7 (s, 1F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 136.7, 134.7, 134.1, 130.6, 129.63, 129.4, 129.0, 128.3, 126.9, 125.3 (d, J = 5 Hz), 113.5 (d, J = 274 Hz), 113.2, 72.6 (d, J = 22 Hz), 55.2. MS (ESI, *m/z*): 436.1 ($[M + NH_4]^+$). HRMS (ESI, *m/z*): Calcd. for $C_{21}H_{19}FNaO_4S_2^+$ ($[M + Na]^+$): 441.0601; Found: 441.0603.

4.3.7. (1S,2R*)-1-([1,1′-Biphenyl]-4-yl)-2-fluoro-2-(phenylsulfonyl)-2-(phenylthio)ethan-1-ol (syn-**4g**)*



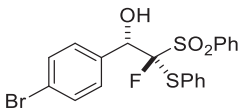
74 mg, 80% yield. White solid. M.p.: 140–141 °C. IR (KBr): 3474, 3060, 1486, 1448, 1308, 1151, 1074 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, J = 7.8 Hz, 2H), 7.70 (t, J = 6.9 Hz, 1H), 7.64–7.59 (m, 4H), 7.55–7.44 (m, 6H), 7.36 (t, J = 7.5 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.00 (t, J = 7.5 Hz, 2H), 6.83 (d, J = 7.8 Hz, 2H), 5.59 (s, 1H), 3.72 (s, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −131.6 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 140.7, 136.8, 134.8, 134.2, 134.0, 130.8, 129.5, 129.1, 129.0, 128.9, 128.4, 127.6, 127.2, 126.6, 125.4 (d, J = 3 Hz), 113.6 (d, J = 204 Hz), 72.9 (d, J = 16 Hz). MS (ESI, *m/z*): 487.1 ($[M + Na]^+$). HRMS (ESI, *m/z*): Calcd. for $C_{26}H_{21}FNaO_3S_2^+$ ($[M + Na]^+$): 487.0808; Found: 487.0816.

4.3.8. (1S,2R*)-1-(4-Chlorophenyl)-2-fluoro-2-(phenylsulfonyl)-2-(phenylthio)ethan-1-ol (syn-**4h**)*



71 mg, 84% yield. White solid. M.p.: 171–172 °C. IR (KBr): 3504, 3063, 1587, 1490, 1472, 1449, 1441, 1401, 1312, 1295, 1283, 1231, 1150, 1085 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 7.8 Hz, 2H), 7.70 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.42–7.33 (m, 4H), 7.21 (t, J = 7.5 Hz, 1H), 7.04 (t, J = 7.5 Hz, 2H), 6.81 (d, J = 7.8 Hz, 2H), 5.51 (d, J = 1.8 Hz, 1H), 3.75 (d, J = 1.2 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −132.0 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.7, 134.9, 134.8, 133.9, 133.4, 130.7, 129.8, 129.5, 129.1, 128.4, 128.0, 125.0 (d, J = 5 Hz), 113.2 (d, J = 274 Hz), 72.3 (d, J = 22 Hz). MS (ESI, *m/z*): 445.2 ($[M + Na]^+$). HRMS (ESI, *m/z*): Calcd. for $C_{20}H_{16}ClFNaO_3S_2^+$ ($[M + Na]^+$): 445.0106; Found: 445.0127.

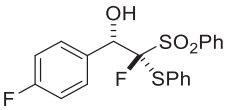
4.3.9. (1S,2R*)-1-(4-Bromophenyl)-2-fluoro-2-(phenylsulfonyl)-2-(phenylthio)ethan-1-ol (syn-**4i**)*



85 mg, 91% yield. White solid. M.p.: 171–172 °C. IR (KBr): 3502, 3060, 1587, 1486, 1472, 1448, 1441, 1398, 1311, 1229, 1150, 1010 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 7.8 Hz, 2H), 7.70 (t, J = 7.5 Hz, 1H), 7.54–7.48 (m, 4H), 7.34 (d, J = 7.8 Hz, 2H), 7.21 (t, J = 7.5 Hz, 1H), 7.03 (t, J = 7.8 Hz, 2H), 6.82 (d, J = 7.8 Hz, 2H), 5.49 (s, 1H), 3.73 (s, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −131.2 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.3, 134.9, 133.9, 133.8, 130.9, 130.6,

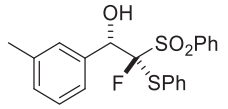
130.0 (d, J = 3 Hz), 129.5, [129].1, 128.4, 124.9 (d, J = 5 Hz), 123.0, 113.1 (d, J = 275 Hz), 72.4 (d, J = 21 Hz). MS (ESI, *m/z*): 489.3 ([M + Na]$^+$). HRMS (ESI, *m/z*): Calcd. For $C_{20}H_{16}BrFNaO_3S_2^+$ ([M +Na]$^+$): 488.9601; Found: 488.9620.

4.3.10. (1S,2R*)-2-fluoro-1-(4-fluorophenyl)-2-(phenylsulfonyl)-2-(phenylthio)ethan-1-ol (syn-**4j**)*



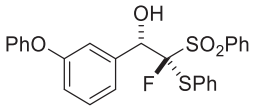
65 mg, 80% yield. White solid. M.p.: 137–138 °C. IR (KBr): 3505 (br), 3070, 1902, 1605, 1581, 1509, 1473, 1448, 1308, 1224, 1149 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, J = 8.1 Hz, 2H), 7.70 (t, J = 7.2 Hz, 1H), 7.55–7.43 (m, 4H), 7.21 (t, J = 7.5 Hz, 1H), 7.09–7.00 (m, 4H), 6.80 (d, J = 7.5 Hz, 2H), 5.53 (s, 1H), 3.73 (s, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −112.5 (s, 1F), −131.2 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0 (d, J = 247 Hz), 136.6, 134.8, 133.9, 130.7, 130.6, 130.2 (dd, J = 8 Hz, 2 Hz), [129].5, 129.0, 128.3, 125.0 (d, J = 4 Hz), 114.7 (d, J = 22 Hz), 113.2 (d, J = 274 Hz), 72.3 (d, J = 22 Hz). MS (ESI, *m/z*): 429.2 ([M + Na]$^+$). Elem. Anal. Calcd. For $C_{20}H_{16}F_2O_3S_2$: C, 59.10; H, 3.97. Found: C, 59.31; H, 4.09.

4.3.11. (1S,2R*)-2-fluoro-2-(phenylsulfonyl)-2-(phenylthio)-1-(m-tolyl)ethan-1-ol (syn-**4k**)*



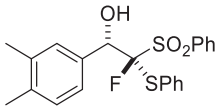
62.4 mg, 78% yield. White solid. M.p.: 101–102 °C. IR (KBr): 3513, 3063, 1580, 1447, 1310, 1234, 1144, 1103 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, J = 8.1 Hz, 2H), 7.97 (t, J = 7.5 Hz, 1H), 7.80 (t, J = 7.5 Hz, 2H), 7.58–7.53 (m, 3H), 7.51–7.45 (m, 2H), 7.31 (t, J = 7.8 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 5.79 (s, 1H), 3.94 (s, 1H), 2.65 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −130.5 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 136.8, 134.9, 134.8, 134.3, 130.8, 129.7, 129.5, 129.1, 128.4, 127.8, 125.6 (d, J = 2 Hz), 125.5 (d, J = 4 Hz), 113.7 (d, J = 275 Hz), 73.1 (d, J = 22 Hz), 21.5, there was an overlap [of] two aromatic carbons. MS (ESI, *m/z*): 425.0 ([M + Na]$^+$). HRMS (ESI, *m/z*): Calcd. for $C_{21}H_{19}FNaO_3S_2^+$ ([M + Na]$^+$): 425.0652; Found: 425.0672.

4.3.12. (1S,2R*)-2-fluoro-1-(3-phenoxyphenyl)-2-(phenylsulfonyl)-2-(phenylthio)ethan-1-ol (syn-**4l**)*



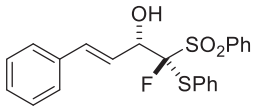
72 mg, 75% yield. White solid. M.p.: 122–123 °C. IR (KBr): 3533, 3059, 1582, 1447, 1292, 1242, 1160, 957 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 7.5 Hz, 2H), 7.69 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.37–7.18 (m, 6H), 7.10–7.01 (m, 4H), 6.96 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.1 Hz, 2H), 5.51 (s, 1H), 3.69 (s, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −131.7 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 156.7, 137.0, 136.8, 134.9, 134.1, 130.8, 129.8, 129.6, 129.1, 128.4, 125.3, 123.5, 123.3, 119.6, 119.42, 119.39, 118.6, 113.4 (d, J = 271 Hz), 72.6 (d, J = 22 Hz). MS (ESI, *m/z*): 503.0 ([M + Na]$^+$). HRMS (ESI, *m/z*): Calcd. for $C_{26}H_{21}FNaO_4S_2^+$ ([M + Na]$^+$): 503.0757; Found: 503.0766.

4.3.13. (1S,2R*)-1-(3,4-Dimethylphenyl)-2-fluoro-2-(phenylsulfonyl)-2-(phenylthio)ethan-1-ol (syn-**4m**)*



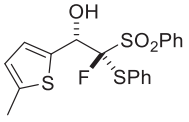
61 mg, 73% yield. White solid. M.p.: 136–137 °C. IR (KBr): 3508, 3058, 1584, 1448, 1308, 1148, 1081 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J = 7.5 Hz, 2H), 7.66 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.26–7.10 (m, 5H), 7.05–6.88 (m, 3H), 5.45 (s, 1H), 3.59 (s, 1H), 2.27 (s, 3H), 2.25 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −130.5 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4, 136.7, 136.1, 134.7, 134.5, 132.4, 130.7, 129.5, 129.4, 129.2, 129.0, 128.4, 125.9, 125.7, 114.1 (d, J = 273 Hz), 73.0 (d, J = 22 Hz), 19.8, 19.6. MS (ESI, *m/z*): 439.0 ([M + Na]$^+$). HRMS (ESI, *m/z*): Calcd. for $C_{22}H_{21}FNaO_3S_2^+$ ([M + Na]$^+$): 439.0808; Found: 439.0818.

4.3.14. (1R,2S*,E)-1-fluoro-4-phenyl-1-(phenylsulfonyl)-1-(phenylthio)but-3-en-2-ol (syn-**4n**)*



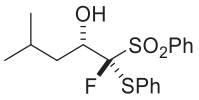
50 mg, 60% yield. White solid. M.p.: 176–177 °C. IR (KBr): 3501, 3059, 1582, 1448, 1306, 1269, 1149, 1081, 966 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, J = 7.8 Hz, 2H), 7.69 (t, J = 7.5 Hz, 1H), 7.[52] (t, J = 7.8 Hz, 2H), 7.39–7.26 (m, 8H), 7.18 (t, J = 7.8 Hz, 2H), 6.74 (d, J = 15.6 Hz, 1H), 6.30 (dd, J = 15.6 Hz, 1H), 4.97 (s, 1H), 3.44 (s, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −130.0 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 136.1, 134.9, 134.8, 134.6, 130.7, 129.9, 129.1, 128.8, 128.6, 128.3, 126.9, 125.7, 122.9, 114.4 (d, J = 279 Hz), 73.1 (d, J = 23 Hz). MS (ESI, *m/z*): 437.0 ([M + Na]$^+$). HRMS (ESI, *m/z*): Calcd. for $C_{22}H_{19}FNaO_3S_2^+$ ([M + Na]$^+$): 437.0652; Found: 437.0672.

4.3.15. (1S,2R*)-2-fluoro-1-(5-methylthiophen-2-yl)-2-(phenylsulfonyl)-2-(phenylthio)ethan-1-ol (syn-**4o**)*



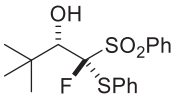
66 mg, 80% yield. White solid. M.p.: 166–167 °C. IR (KBr): 3467, 3067, 2920, 1581, 1448, 1147, 1040, 1019 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, J = 7.8 Hz, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.26–7.22 (m, 1H), 7.13–7.09 (m, 4H), 6.89 (d, J = 3 Hz, 1H), 6.66 (s, 1H), 5.67 (s, 1H), 3.70 (s, 1H), 2.49 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −130.6 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 136.8, 135.1, 134.8, 134.3, 130.6, 129.6, 129.1, 128.5, 128.0, 125.5 (d, J = 3 Hz), 124.6, 113.3 (d, J = 273 Hz), 71.0 (d, J = 22 Hz), 15.4. MS (ESI, *m/z*): 426.0 ([M + NH_4]$^+$). HRMS (MALDI, *m/z*): Calcd. for $C_{19}H_{17}FNaO_3S_3^+$ ([M + Na]$^+$): 431.0216; Found: 431.0226.

4.3.16. (1R,2S*)-1-fluoro-4-methyl-1-(phenylsulfonyl)-1-(phenylthio)pentan-2-ol (syn-**4p**)*



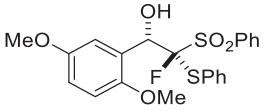
61 mg, 83% yield. White solid. M.p.: 85–87 °C. IR (KBr): 3521, 2947, 1582, 1447, 1306, 1292, 1151, 1021 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, J = 8.1 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.35 (t, J = 7.8 Hz 3H), 7.21 (t, J = 7.5 Hz, 2H), 4.34 (d, J = 9.3 Hz, 1H), 3.14 (s, 1H), 1.94–1.84 (m, 2H), 1.59–1.54 (m, 1H), 0.96 (d, J = 6.3 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −131.5 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 134.7, 134.6, 130.5, 129.7, 129.0, 128.7, 125.9 (d, J = 3 Hz), 115.4 (d, J = 274 Hz), 70.6 (d, J = 21 Hz), 39.5, 24.4, 23.6, 21.3. MS (ESI, *m/z*): 391.0 ($[M + Na]^+$). HRMS (ESI, *m/z*): Calcd. for $C_{18}H_{21}FNaO_3S_2^+$ ($[M + Na]^+$): 391.0808; Found: 391.0813.

4.3.17. (1R,2S*)-1-fluoro-3,3-dimethyl-1-(phenylsulfonyl)-1-(phenylthio)butan-2-ol (syn-**4q**)*



61 mg, 83% yield. White solid. M.p.: 80–82 °C. IR (KBr): 3500, 2994, 2954, 1448, 1327, 1144, 1080, 1028 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, J = 8.1 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.52 (d, J = 7.8 Hz, 4H), 7.31 (t, J = 7.5 Hz, 1H), 7.20 (t, J = 7.8 Hz, 2H), 4.05 (d, J = 3.9 Hz, 1H), 3.12 (d, J = 3.9 Hz, 1H), 1.07 (s, 9H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −131.6 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.8, 134.5, 134.3, 130.5 (d, J = 1.5 Hz), 129.4, 128.9, 128.4, 127.2 (d, J = 4 Hz), 118.0 (d, J = 281 Hz), 76.5 (d, J = 18 Hz), 36.8, 27.4 (d, J = 4 Hz). MS (ESI, *m/z*): 391.0 ($[M + Na]^+$). HRMS (ESI, *m/z*): Calcd. for $C_{18}H_{21}FNaO_3S_2^+$ ($[M + Na]^+$): 391.0808; Found: 391.0820.

4.3.18. (1S,2R*)-1-(2,5-Dimethoxyphenyl)-2-fluoro-2-(phenylsulfonyl)-2-(phenylthio)ethan-1-ol (syn-**4r**)*

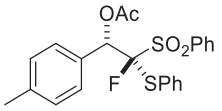


71 mg, 79% yield. White solid. M.p.: 161–162 °C. IR (KBr): 3478, 2931, 1499, 1311, 1217, 1147, 1048 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, J = 8.1 Hz, 2H), 7.71 (t, J = 7.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 2H), 7.39 (d, J = 3.0 Hz, 1H), 7.30 (d, J = 9.0 Hz, 3H), 7.17 (t, J = 7.5 Hz, 2H), 6.86 (dd, J = 3 Hz, 9.0 Hz, 1H), 6.70 (d, J = 9.0 Hz, 1H), 5.80 (d, J = 3.0 Hz, 1H), 3.82 (s, 3H), 3.70 (t, J = 1.5 Hz, 1H), 3.34 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −133.2 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 151.7, 137.4, 134.4, 130.8, 129.6, 128.9, 128.4, 125.9 (d, J = 4 Hz), 124.2, 115.5, 114.8, 114.6 (d, J = 275 Hz), 111.6, 67.6 (d, J = 22 Hz), 55.93, 55.90 (there was an overlap two aromatic carbons). MS (ESI, *m/z*): 471.1 ($[M + Na]^+$). HRMS (ESI, *m/z*): Calcd. for $C_{22}H_{21}FNaO_5S_2^+$ ($[M + Na]^+$): 471.0707; Found: 471.0713.

*4.4. Synthesis of syn-**4d**-Ac and anti-**4d**-Ac*

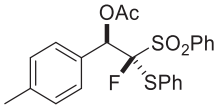
Under N_2 atmosphere, to a solution of FTSM (**1**) (141 mg, 0.5 mmol) in THF-HMPA (2.25 mL/0.45 mL) at −78 °C was slowly added *n*BuLi (0.39 mL, 1.6 M in hexane, 0.6 mmol). After 30 min, a solution of 4-methylbenzaldehyde (72 mg, 0.6 mmol) in THF (0.2 mL) was added. After another 30 min, acetic anhydride (0.07 mL, 0.7 mmol) and DMAP (7 mg, 0.05 mmol) were added, and then the reaction was continued at −78 °C for 3 h. Finally, the reaction mixture was treated with pH 7.0 phosphate buffer (5 mL) at the same temperature, and extracted with EtOAc for three times. The organic phases were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was subjected to silica gel column chromatography using petroleum ether-EtOAc (12:1, v/v) as eluent to give *syn*-**4d**-Ac (120 mg, 54%) and *anti*-**4d**-Ac (73 mg, 33%).

4.4.1. (1S,2R*)-2-fluoro-2-(phenylsulfonyl)-2-(phenylthio)-1-(p-tolyl)ethyl acetate (syn-**4d**-Ac)*



White solid. M.p.: 186–187 °C. IR (KBr): 3065, 1755, 1582, 1514, 1474, 1440, 1324, 1224 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): ä 7.87–7.84 (m, 2H), 7.69–7.63 (m, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.28–7.22 (m, 3H), 7.14–7.06 (m, 6H), 6.43 (d, J = 4.5 Hz, 1H), 2.35 (s, 3H), 2.21 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): ä −132.9 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): ä 168.4, 139.2, 137.0, 134.41, 134.37, 130.8, 130.1, 129.6, 128.8, 128.7, 128.4, 128.3, 125.3 (d, J = 5 Hz), 112.1 (d, J = 268 Hz), 72.7 (d, J = 27 Hz), 21.2, 20.8. MS (ESI, *m/z*): 467.1 ($[M + Na]^+$). Elem. Anal. calcd. for $C_{23}H_{21}FO_4S_2$: C, 62.14; H, 4.76. Found: C, 61.84; H, 4.45.

4.4.2. (1R,2R*)-2-fluoro-2-(phenylsulfonyl)-2-(phenylthio)-1-(p-tolyl)ethyl acetate (anti-**4d**-Ac)*



White solid. M.p.: 152–153 °C. IR (KBr): 1752, 1614, 1581, 1475, 1440, 1325, 1224, 1158 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): ä 7.92 (d, J = 8.1 Hz, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.2 Hz, 2H), 7.40 (d, J = 7.8 Hz, 2H), 7.30–7.25 (m, 1H), 7.18–7.09 (m, 4H), 6.96 (d, J = 7.8 Hz, 2H), 6.47 (d, J = 19.8 Hz, 1H), 2.36 (s, 3H), 1.78 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): ä −140.7 (d, J = 16.4 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): ä 168.3, 139.2, 136.52, 136.47, 134.2, 130.5, 130.3, 129.7, 129.4, 128.7, 128.6, 128.4, 125.4 (d, J = 4 Hz), 114.0 (d, J = 280 Hz), 74.5 (d, J = 18 Hz), 21.1, 20.5. MS (ESI, *m/z*): 467.1 ($[M + Na]^+$). Elem. Anal. calcd. for $C_{23}H_{21}FO_4S_2$: C, 62.14; H, 4.76. Found: C, 61.95; H, 4.93.

*4.5. Hydrolysis of anti-**4d**-Ac to prepare (1R*,2R*)-2-fuoro-2-(phenylsulfonyl)-2-(phenylthio)-1-(p-tolyl)ethan-1-ol (anti-**4d**)*

To a solution of *anti*-**4d**-Ac (89 mg, 0.2 mmol) in MeOH-CH_2Cl_2 (0.8 mL/0.2 mL) at 0 °C was added concentrated H_2SO_4 (0.02 mL, 0.4 mmol). Then the mixture was heated at reflux for 8 h. After cooling to room temperature, the mixture was quenched with H_2O, and extracted with EtOAc. The organic phase was subsequently washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was subjected to silica gel column chromatography using petroleum

ether-EtOAc (8:1, v/v) as eluent to give *anti*-**4d** (75 mg, 93%). (The complete hydrolysis of *syn*-**4d**-Ac under the same conditions needs 24 h)

White solid. M.p.: 132–133 °C. IR (KBr): 3474, 3062, 2872, 1612, 1580, 1511, 1475, 1444, 1376, 1320, 1309, 1286, 1152, 1116 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 8.4 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.33 (d, J = 7.2 Hz, 2H), 7.21 (t, J = 7.5 Hz, 1H), 7.11 (d, J = 8.1 Hz, 2H), 7.03 (t, J = 7.5 Hz, 2H), 6.84 (d, J = 7.8 Hz, 2H), 5.40 (dd, J = 4.5 Hz, J = 18.6 Hz, 1H), 3.89 (d, J = 4.2 Hz, 1H), 2.35 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −142.1 (d, J = 20.3 Hz, 1F). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 136.2 (d, J = 1.7 Hz), 135.2, 134.3, 133.1, 130.5, 129.5, 128.7, 128.6, 128.5, 128.4, 125.6 (d, J = 3 Hz), 115.2 (d, J = 282 Hz), 75.1 (d, J = 20 Hz), 21.1. MS (ESI, m/z): 420.4 ($[M + NH_4]^+$). HRMS (ESI, m/z): Calcd. for $C_{21}H_{19}FNaO_3S_2^+$ ($[M + Na]^+$): 425.0652; Found: 425.0665.

4.6. Synthesis of α-chloro-α-phenylthio-α-phenylsulfonylmethane (CTSM) (**5**)

Under N_2 atmosphere, to the solution of α-phenylthio-α-phenylsulfonylmethane (TSM) (**2**) (132 mg, 0.5 mmol) in CCl_4 (2 mL) at the 0 °C was slowly added NCS (68 mg, 0.5 mmol). The reaction was allowed to warm to the room temperature and stirred for 24 h. The reaction mixture was treated with H_2O (5 mL), extracted with CCl_4. The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was subjected to silica gel column chromatography to give CTSM (**5**) (81 mg, 61%).

White solid. M.p.: 156–158 °C. IR (KBr): 3062, 2957, 1583, 1479, 1441, 1331, 1154 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, J = 7.5 Hz, 2H), 7.73 (t, J = 7.2 Hz, 1H), 7.60 (d, J = 7.8 Hz, 4H), 7.42–7.33 (m, 3H), 5.74 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.94, 134.90, 134.7, 130.5, 130.1, 129.6, 129.2, 82.0 (there was an overlap of two aromatic carbons). MS (ESI, m/z): 316.0 ($[M + NH_4]^+$). HRMS (ESI, m/z): Calcd. For $C_{13}H_{11}ClNaO_2S_2^+$ ($[M + Na]^+$): 320.9781; Found: 320.9784.

4.7. Synthesis of 1-(naphthalen-2-yl)-2-(phenylsulfonyl)-2-(phenylthio)ethan-1-ol (**7**)

Prepared from α-phenylthio-α-phenylsulfonylmethane (TSM) (**2**) (53.0 mg, 0.2 mmol) and 2-naphthaldehyde (38.0 mg, 0.24 mmol) following the procedures for the synthesis of compound **4**. Eluted with petroleum ether/EtOAc (5:1, v/v). Compound **7** was obtained as a mixture of two diastereomers in a ratio of 58:42 (69 mg, 82%). The diastereomeric ratio was determined by LC-MS analysis.

White solid. ^1H NMR (300 MHz, $CDCl_3$) (for two diastereomers): δ 8.04 (d, J = 7.8 Hz, 2H), 7.91–7.44 (m, 10H), 7.03–6.94 (m, 1H), 6.78 (t, J = 7.2 Hz, 2H), 6.30 (d, J = 7.8 Hz, 2H), 6.14 (s, 0.42H), 5.46 (d, J = 9.0 Hz, 0.58 H), 4.61 (brs, 0.58 H), 4.39 (d, J = 9.0 Hz, 0.58 H), 4.31 (s, 0.42 H), 3.64 (brs, 0.42 H). ^{13}C NMR (100 MHz, $CDCl_3$) (for one diastereomer): δ 136.9, 136.5, 134.2, 133.2, 133.0, 132.3, 129.8, 129.0, 128.8, 128.3, 128.2, 128.0, 127.7, 126.4, 126.3, 126.0, 123.9, 81.8, 70.1. MS (ESI, m/z): 438.1 ($[M + NH_4]^+$). HRMS (ESI, m/z): Calcd. for $C_{24}H_{20}NaO_3S_2^+$ ($[M + Na]^+$): 443.0746; Found: 443.0751.

4.8. Synthesis of (1,2-difluoro-2-(naphthalen-2-yl)-1-(phenylsulfonyl)ethyl)(phenyl)sulfane (**8**)

Under N_2 atmosphere, to a solution of *syn*-**4a** (876 mg, 1.0 mmol) in CH_2Cl_2 (30 mL) at −78 °C was slowly added DAST (2.2 mmol). After stirring at −78 °C for 4 h, the reaction mixture was quenched with H_2O (40 mL), extracted with EtOAc for three times. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, evaporated under vacuum, and purified by column chromatography on silica gel with petroleum ether/EtOAc (5:1, v/v) to give **8** as a mixture of two diastereomers in a ratio of 95:5 (633 mg, 72%). The diastereomeric ratio was determined by ^{19}F NMR analysis.

White solid. Mp: 179–181 °C. IR (KBr): 3059, 1474, 1445, 1326, 1153, 1035. ^1H NMR (300 MHz, $CDCl_3$) (for the major diastereomer): δ 7.96 (d, J = 7.8 Hz, 2H), 7.89–7.80 (m, 4H), 7.66 (t, J = 7.5 Hz, 1H), 7.54–7.49 (m, 5H), 7.25–7.22 (m, 1H), 7.13–7.03 (m, 4H), 6.16 (dd, J = 43.8 Hz, 6.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) (for the major diastereomer): δ −146.3 (t, J = 19 Hz, 1F), −171.8 (dd, J = 43 Hz, 17 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) (for the major diastereomer): δ 137.1, 136.8, 134.4, 133.9, 132.6, 130.7, 130.1, 129.8 (d, J = 21 Hz), 129.4 (d, J = 6.5 Hz), 128.7, 128.6, 128.5, 128.0, 127.8, 127.2, 126.6, 125.4 (dd, J = 5 Hz, 2 Hz), 124.8 (d, J = 4 Hz), 114.3 (dd, J = 281 Hz, 23 Hz), 92.4 (dd, J = 189 Hz, 19 Hz). MS (ESI, m/z): 463.0 ($[M + Na]^+$). HRMS (ESI, m/z): Calcd. For $C_{24}H_{18}F_2NaO_2S_2^+$ ($[M + Na]^+$): 463.0608; Found: 463.0605.

4.9. Synthesis of (Z)-(1,2-difluoro-2-(naphthalen-2-yl) vinyl)(phenyl)sulfane (**9**)

Under N_2 atmosphere, to a solution of (1,2-difluoro-2-(naphthalen-2-yl)-1-(phenylsulfonyl)ethyl)(phenyl)sulfane (**8**) (440 mg, 1.0 mmol) in THF (10 mL) at −78 °C was slowly added LiHMDS (1.1 mL, 1.0 M in THF, 1.1 mmol). The reaction mixture was allowed to warm to room temperature in 6 h. After that, the reaction mixture was treated with H_2O (20 mL), and extracted with EtOAc for three times. The combined organic layer was dried over anhydrous Na_2SO_4, evaporated under vacuum, and purified by column chromatography on silica gel with petroleum ether to give **9** (152 mg, 52%). The Z/E ratio (96:4) was determined by ^{19}F NMR analysis.

Yellow oil. IR (KBr): 3060, 2925, 1583, 1479, 1441, 1119 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.84 (t, J = 8.4 Hz, 4H), 7.54–7.49 (m, 4H), 7.36–7.27 (m, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −125.4 (d, J = 140 Hz, 1F), −134.4 (d, J = 140 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9 (dd, J = 47 Hz, J = 236 Hz), 145.0 (dd, J = 288 Hz, 56 Hz), 133.7, 132.9, 132.0 (q, J = 4 Hz), 130.2, 129.7, 128.9, 128.4, 128.4, 127.9, 127.7, 127.5, 126.8, 126.5, 123.0 (dd, J = 9 Hz, 6 Hz). MS (EI, m/z, %): 298 (M^+, 4.4), 232 (40.6), 151 (100.0). HRMS (EI, m/z): Calcd. For $C_{18}H_{12}F_2S^+$ (M^+): 298.0622; Found: 298.0629.

Declaration of competing interest

Fluoroalkylation is a direct approach to introduce structurally diverse fluorinated moieties into organic molecules, and has been frequently used in the synthesis of fluorine-containing target molecules. In our submitted manuscript, we a thermodynamically controlled and reversible nucleophilic addition of a monofluorinated sulfone, that is, α-fluoro-α-phenylthio-α-phenylsulfonylmethane (FTSM), to aldehydes has been developed, which allows the efficient synthesis of β-fluorinated carbinols with high diastereoselectivity. Control experiments showed that the fluorine substitution not only promotes the addition process, but also improves the diastereoselectivity. We feel that this chemistry is of high interest to the broad readership of *Tetrahedron*.

Acknowledgments

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Science and Technology Program (No. 18JC1410601) is gratefully acknowledged.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2019.130877.

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[20] CCDC 1961387 (*syn*-**4i**) contains the supplementary crystallographic data for this paper.