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Catalytic and Highly Enantioselective Reactions of α-Sulfonyl Carbanions with Chiral Bis(oxazoline)s

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Abstract: The enantioselective reactions of lithiated benzyl trifluoromethyl sulfones with a substoichiometric amount of a bis(oxazoline) and various aldehydes is disclosed. The products were formed with excellent diastereo- and enantioselectivities. Fluorination of the sulfone with *N*-fluorobenzenesulfonimide and a stoichiometric amount of a bis(oxazoline) gave products with extremely high enantioselectivities (up to 99% *ee*; *ee* = enantiomeric excess). The enantioselective reaction was confirmed to proceed through a dynamic thermodynamic resolution pathway.

Keywords: asymmetric synthesis · carbanions · catalysis · chirality · enantioselectivity

Introduction

Carbon–carbon bond formation by using α-sulfonyl carbanions has been extensively studied because carbanions can be easily formed α to sulfonyl groups due to their high acidity. These α-sulfonyl carbanions can then easily react with various electrophiles.[1] Therefore, reactions of α-sulfonyl carbanions have been applied in the syntheses of a number of natural products.[2] Furthermore, sulfones with chirality at the α position are known to show biological activity, for example, the antiglaucoma activity of dorzolamide[3] and the γ-secretase inhibitor for Alzheimer's disease.[4] On the other hand, chiral sulfonyl analogues of carbonyl derivatives are gaining an increasingly important role in medicinal chemistry because the structural and electronic properties of the chiral sulfonyl group mimic the carbonyl moiety in the transition state,[5] and thus the catalytic asymmetric preparation of enantiomerically pure sulfonyl derivatives is in high demand. However, only a little attention has been paid to the enantioselective reactions of α-sulfonyl carbanions, which is probably due to the difficulties in obtaining high enantioselectivities for these reactions.[6,7] Pioneering research on the highly enantioselective reactions of α-sulfonyl carbanions derived from allyl sulfones by using a chiral diamino alcohol and Grignard reagents has been reported by Akiyama and co-workers (up to 80% *ee* obtained; *ee* = enatiomeric excess).[6a] Simpkins has reported the enantioselective deprotonation of sulfonyl compounds by using camphor-derived chiral lithium amides in an in situ trap reaction with TMSCl (TMS = trimethylsilyl).[6b] Although these pioneering reports anticipated a possible method for improving the enantioselectivities of these reactions, there have been no reports that utilise α-lithiated sulfones to challenge these difficulties. Recently, we communicated the first highly enantioselective reactions of α-lithiated sulfones with various electrophiles by using a stoichiometric or a substoichiometric amount of a chiral bis(oxazoline).[8,9] Herein, we focus on a detailed study of the enantioselective reactions of α-lithiated sulfones and a systematic study of this type of asymmetric synthesis.

Results

Initially, we examined the enantioselective reactions of various α-lithiated sulfones **1a–e**, such as methyl **1a**, *t*Bu **1b**, phenyl **1c**, pentafluorophenyl **1d**, and 2-pyridyl benzyl **1e** sulfones, with benzaldehyde (Table 1). Sulfones **1a–e** were treated with *n*BuLi (1.2 equiv) and bis(oxazoline)-Ph **3a**

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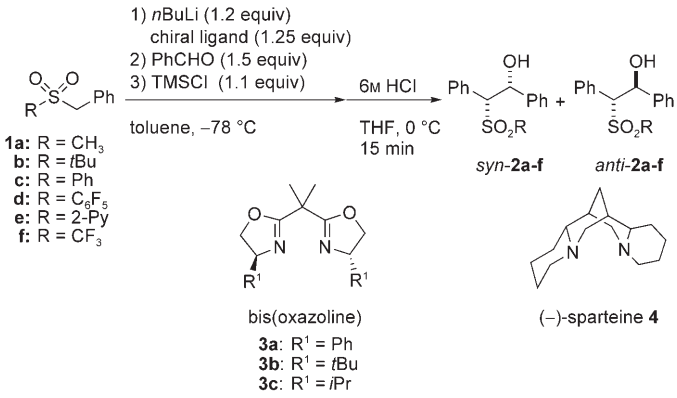
Table 1. Enantioselective reactions of various α-lithiated sulfones **1a–f** with benzaldehyde



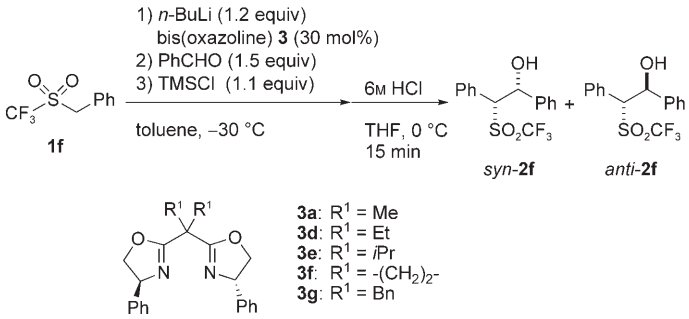
Entry	1	Chiral ligand	2	Yield[a] [%]	dr[b] *syn*/*anti*	er[c] *syn*	er[c] *anti*
1	**1a**	**3a**	**2a**	19[d]	50:50	55:45	51:49
2	**1b**	**3a**	**2b**	71[d]	64:36	65:35	61:39
3	**1c**	**3a**	**2c**	83[d]	68:32	66:34	71:29
4	**1d**	**3a**	**2d**	72	86:14	62:38	87:13
5	**1e**	**3a**	**2e**	66[d]	61:39	52:48	54:46
6	**1f**	**3a**	**2f**	56(56[d])	>98:2	85:15	–
7	**1f**	**3b**	**2f**	55	>98:2	71:29	–
8	**1f**	**3c**	**2f**	58	>98:2	50:50	–
9	**1f**	**4**	**2f**	31	>98:2	51:49	–
10[e]	**1f**	**3a**	**2f**	42	>98:2	70:30	–
11[f]	**1f**	**3a**	**2f**	45	>98:2	69:31	–
12[g]	**1f**	**3a**	**2f**	30	>98:2	51:49	–
13[h]	**1f**	**3a**	**2f**	65	95:5	86:14	nd[j]
14[i]	**1f**	**3a**	**2f**	87	95:5	94:6	nd[j]

[a] Conversion yield determined by ^{19}F NMR analysis. [b] The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopic analysis. [c] The enatiomeric ratio (er) was determined by chiral HPLC analysis. [d] Isolated yield. [e] In cumene. [f] In Et_2O. [g] In THF. [h] The reaction was carried out at −90 °C. [i] At −30 °C. [j] nd = not determined

(1.25 equiv) in toluene for 1 h and subsequently with benzaldehyde (1.5 equiv). TMSCl was added to suppress the retro-aldol-type reaction by trimethylsilylation of the formed alkoxides. Most of the reactions gave high yields of a diastereomeric mixture of the *syn* and *anti* isomers of the products **2a–e**, in which each isomer was found to have low enantioselectivity (entries 1–5). On the other hand, trifluoromethyl sulfones,[10] which are known to have unusual configurational stability[11] were allowed to react at −78 °C under similar reaction conditions with a stoichiometric amount of a bis(oxazoline) and the *syn* isomer (*syn*-**2f**) was formed exclusively (entry 6). The reaction of lithiated **1f** with bis(oxazoline)-*t*Bu **3b** afforded *syn*-**2f** with a slightly lower enantioselectivity than that obtained from the reaction with bis(oxazoline)-Ph **3a** (entry 7), whereas the reaction with bis(oxazoline)-*i*Pr **3c** or (−)-sparteine (**4**) gave racemic **2f** (entries 8 and 9). The reaction of lithiated **1f** with **3a** in other solvents, such as cumene, Et_2O, and THF, afforded the product **2f** with a lower enantioselectivity than that obtained in toluene (entries 10–12). The best enantioselectivity was obtained when the reaction was carried out at −30 °C in toluene with **3a** (entry 14).

Furthermore, we were pleased to find that the reaction of **1f** proceeded with a substoichiometric amount of **3** (Table 2). Thus, the reaction of **1f** was performed with

Table 2. Catalyst loading of the bis(oxazoline) ligands for the reaction of **1f** with benzaldehyde.



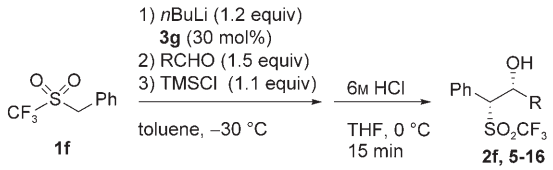
Entry	Chiral ligand	**3** [mol%]	Yield[a] [%]	dr[b] *syn*/*anti*	er[c] *syn*
1	**3a**	30	84	93:7	87:13
2	**3d**	30	81	93:7	96:4
3	**3e**	30	74	91:9	97:3
4	**3f**	30	76	90:10	93:7
5	**3g**	30	87	96:4	97:3
6	**3g**	10	87	96:4	97:3
7	**3g**	5	81	96:4	95:5
8	**3g**	2	86	95:5	96:4
9	**3g**	1	77	96:4	90:10

[a] Conversion yield determined by ^{19}F NMR spectroscopic analysis. [b] Determined by ^{1}H NMR spectroscopic analysis. [c] Determined by chiral HPLC analysis.

30 mol% of **3a** at −30 °C to give *syn*-**2f** as a major product in high yield and with slightly lower enantioselectivity than that obtained by using a stoichiometric amount of **3a** (entry 1). To improve the enantioselectivity, we optimized the bridging group of the bis(oxazoline) ligand. Several bis(oxazoline) derivatives **3d–g** also showed excellent results (entries 2–5). Even 10 or 5 mol% of dibenzyl bis(oxazoline) derivative **3g** worked well and produced a good yield and excellent enantiomeric ratio (entries 6 and 7). Notably, 2 mol% of **3g** was found to show even higher enantioselectivity, although the reaction by using 1 mol% of **3g** gave **2f** with slightly lower enantioselectivity (entries 8 and 9). In general, enantioselective reactions of carbanions α to heteroatoms prepared from a substoichiometric amount of a chiral ligand and a stoichiometric amount of alkyllithium species afforded adducts derived from the reaction of aldehydes with alkyllithium species as major products. Recently, O'Brien and co-workers have overcome this difficulty by using a substoichiometric amount of (−)-**4** and a stoichiometric amount of an achiral ligand; however, an achiral ligand is inevitably used to regenerate the chiral ligand.[12a,b] It should be noted that our enantioselective reaction proceeds in a catalytic manner without any additives.

Table 3 shows the results of the reaction of sulfone **1f** with various aldehydes in the presence of a substoichiometric amount of **3g**. The reaction of **1f** with various aromatic

Table 3. Enantioselective reaction of trifluoromethyl sulfone **1f** with various aldehydes in the presence of **3g**.



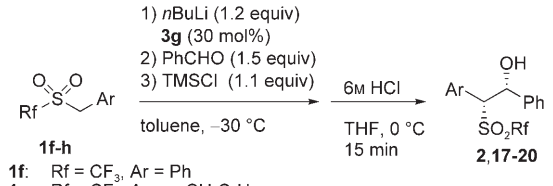
Entry	R	Product	Yield[a] [%]	dr[b] *syn/anti*	er[c] *syn*
1[d]	Ph	**2f**	87	96: 4	97: 3
2	*p*-$CH_3C_6H_4$	**5**	84	97: 3	97: 3
3	*o*-$CH_3C_6H_4$	**6**	88	97: 3	98: 2
4	2,4-$(CH_3)_2C_6H_3$	**7**	71	98: 2	99: 1
5	*p*-$MeOC_6H_4$	**8**	91	97: 3	99: 1
6	*p*-ClC_6H_4	**9**	85	90:10	92: 8
7	*o*-ClC_6H_4	**10**	87	84:16	91: 9
8	*p*-FC_6H_4	**11**	96	91: 9	96: 4
9	1-Naphthyl	**12**	80	98: 2	98: 2
10[d]	2-Naphthyl	**13**	80	94: 6	98: 2
11	2-Furyl	**14**	58	93: 7	95: 5
12	2-Thienyl	**15**	95	97: 3	96: 4
13	PhCH=CH−	**16**	94	86:16	99: 1

[a] Conversion yield. [b] Determined by ^{1}H NMR spectroscopic analysis. [c] Determined by chiral HPLC analysis. [d] Bis(oxazoline) **3g** (10 mol%) was used.

aldehydes gave products **5–16** with excellent diastereo- and enantioselectivities (entries 1–13).

Table 4 shows the results of the reaction of various fluoroalkyl sulfones **1f–j** with benzaldehyde in the presence of a

Table 4. Enantioselective reaction of various trifluoromethyl sulfones **1f–j** with benzaldehyde in the presence of **3g**.



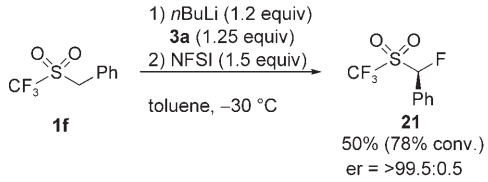
1f: Rf = CF_3, Ar = Ph
1g: Rf = CF_3, Ar = *p*-$CH_3C_6H_4$
1h: Rf = CF_3, Ar = *p*-$MeOC_6H_4$
1i: Rf = CF_3, Ar = *p*-ClC_6H_4
1j: Rf = $CF_3(CF_2)_3$-, Ar = Ph

Entry	Sulfone	Product	Yield[a,b] [%]	dr[c] *syn/anti*	er[d] *syn*
1	**1f**	**2f**	87 (74)	96:4	97:3
2	**1g**	**17**	75 (60)	94:6	97:3
3	**1h**	**18**	73 (55)	93:7	82:18
4	**1i**	**19**	90 (64)	97:3	98:2
5	**1j**	**20**	94 (38)	>98:2	98:2

[a] Conversion yield. [b] Yield in parenthesis is the isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by chiral HPLC analysis.

substoichiometric amount of **3g**. These reactions also gave the products **2f** and **17–20** with excellent diastereo- and enantioselectivities (entries 1–5).

α-Fluorinated sulfur compounds can also serve as useful synthetic intermediates for the synthesis of fluorinated molecules[13] and precursors of bioactive compounds.[14] Therefore, we tried to prepare optically active α-fluorobenzyl sulfones. Although the reaction of lithiated **1f** and bis(oxazoline)-Ph **2a** with Selectfluor as a fluorination reagent afforded a trace amount of the product **21**, the reaction with NFSI (*N*-fluorobenzenesulfonimide) afforded **21** in moderate yield with excellent enantioselectivity (99% *ee*; Scheme 1).

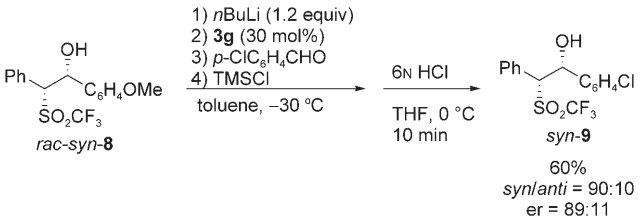


Scheme 1. Enantioselective fluorination of lithiated **1f**.

The absolute configuration of **21** was determined to be *R* by X-ray crystallographic analysis. These results are the first examples of highly enantioselective reactions of α-lithiated sulfones with various electrophiles.

Discussion

Kinetic test for the reaction and proposed reaction mechanism: To understand the enantioselective reactions of α-lithiated sulfones, the enantiodetermining step was studied by the use of a kinetic test for the reaction. First, *rac-syn*-**8** was treated with 1.2 equivalents of *n*BuLi to give the racemic α-sulfonyl carbanion of **1f** through the retroaldol-type reaction. Carbanion **1f** was then allowed to react with *p*-chlorobenzaldehyde after the addition of 30 mol% of **3g** (Scheme 2). The reaction afforded *syn*-**9** with high enantio-

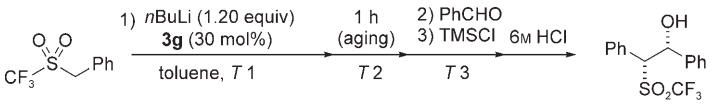


Scheme 2. Enantioselective reaction of the racemic carbanion of **1f**.

selectivity. Considering the apparent formation of the racemic α-sulfonyl carbanion in the reaction, the result shows that the enantiodetermining step is not at the deprotonation stage.

We also studied the temperature dependence of the enantioselectivity in the reaction of α-lithiated **1f** with benzaldehyde (Table 5). The reaction with benzaldehyde at −95°C showed slightly lower enantioselectivity relative to the reaction performed at −78°C. A solution of the α-carbanion of **1f**, prepared at −95°C, was warmed to −78°C. The reaction mixture was stirred for 1 h at that temperature, and was then recooled to −95°C before the addition of benzalde-

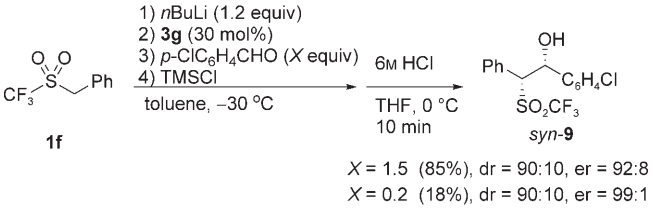
Table 5. Temperature dependence of the enantioselective reaction of **1f** with benzaldehyde.



T_1 [°C]	T_2 [°C]	T_3 [°C]	Yield [%]	*syn*/*anti*	er *syn*
−95	−95	−95	65	95:5	86:14
−78	−78	−78	67	97:3	93:7
−95	−78	−95	60	95:5	92:8
−30	−78	−78	42	97:3	96:4
−30	−30	−30	87	96:4	97:3

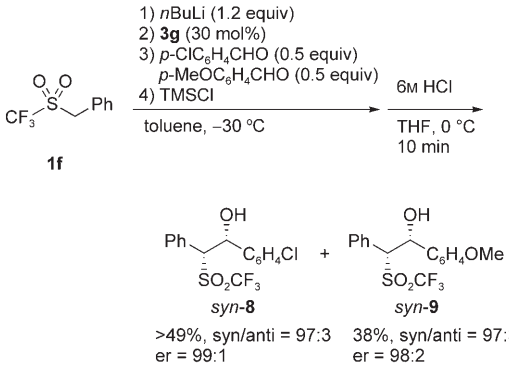
hyde. The product **2f** was found to have an enantiomeric ratio similar to that obtained in the reaction at −78 °C, but higher than that at −95 °C. When the first deprotonation step was carried out at −30 °C and the subsequent reaction with benzaldehyde at −78 °C, *syn*-**2f** was obtained with high enantioselectivity.

Furthermore, we carried out the modified Hoffman test by using a deficient amount of an electrophile. The reaction of lithiated **1f** with a deficient amount of *p*-chlorobenzaldehyde afforded **9** with almost complete enantioselectivity, which is even higher than the 92:8 enantiomeric ratio obtained in the reaction with a stoichiometric amount of *p*-chlorobenzaldehyde (Scheme 3).



Scheme 3. Enantioselective reaction of lithiated **1f** with a deficient amount of *p*-chlorobenzaldehyde.

In addition, we also examined a novel kinetic test for the enantioselective reaction of lithiated **1f** by using a substoichiometric amount of **3g** with a mixture of *p*-chlorobenzaldehyde and *p*-methoxybenzaldehyde to give two products *syn*-**8** and *syn*-**9** (Scheme 4). As described in Scheme 2, *p*-chlorobenzaldehyde is more reactive towards lithiated **1f** than *p*-methoxybenzaldehyde, and thus, *syn*-**8** was produced in higher yield than *syn*-**9**. It should be noted that *syn*-**8** was formed with a higher enantioselectivity than that obtained in the reaction with 1.2 equivalents of chlorobenzaldehyde (Table 3, entry 6; er = 92:8). On the other hand, the reaction with *p*-methoxybenzaldehyde gave *syn*-**9** with a lower enantioselectivity than that obtained in the reaction with 1.2 equivalents of *p*-methoxybenzaldehyde (Table 3, entry 5; er = 99:1). All these results support the dynamic thermodynamic resolution pathway, because the enantioselectivity for both *syn*-**8** and *syn*-**9** should not be different from that ob-

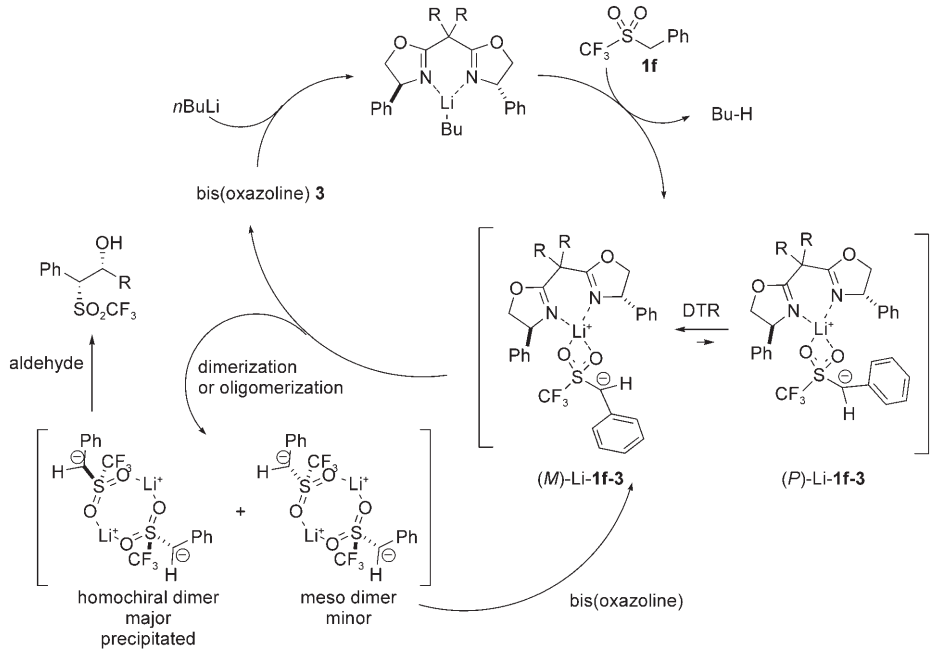


Scheme 4. Enantioselective reaction of lithiated **1f** with a mixture of electrophiles.

tained with a stoichiometric amount of an electrophile if the reaction proceeds through a dynamic kinetic resolution pathway.

All these results show that the reaction of **1f** in the presence of a substoichiometric amount of **3g** proceeds through a dynamic thermodynamic resolution pathway.[15] To the best of our knowledge, this is the first report of a catalytic enantioselective reaction of a carbanion α to a heteroatom that proceeds by dynamic thermodynamic resolution. The highly enantio- and diastereoselective reactions of lithiated trifluoromethyl sulfones can be ascribed to the high configurational stability of the carbanion, which is caused by the large n–σ* interaction. Gais and co-workers have reported that the racemization barrier of lithiated trifluoromethyl sulfone (16.0–17.3 kcal mol^{-1}) is larger than that of α-lithio phenyl or *tert*-butyl sulfones (9.6–13.0 kcal mol^{-1}), that is, that an electron withdrawing group, such as a trifluoromethyl group, in α-sulfonyl carbanions enhances their configurational stability.[11,16] Based on the configurational stability of α-sulfonyl carbanions, the plausible catalytic reaction pathway is as follows (Scheme 5): Bis(oxazoline) and *n*BuLi form a chiral organolithium species, which reacts with sulfone **1f** to afford a mixture of the diastereomeric complexes (*M*)-Li–**1f**–**3** and (*P*)-Li–**1f**–**3**. The thermodynamically more stable α-lithiated sulfone–bis(oxazoline) complex (*M*)-Li–**1f**–**3** is transformed into enantioenriched dimers or oligomers of the α-lithiated sulfone with simultaneous regeneration of bis(oxazoline) **3**. The dimer or oligomers react with an aldehyde to yield the enantioenriched product.

Confirmation of formation of the dimer species: In the proposed reaction mechanism in Scheme 5, the key step of the catalytic cycle is the transformation of the (*M*)-Li–**1f**–**3** complex into a homochiral dimer with regeneration of bis(oxazoline) **3**. In fact, we observed precipitation of the complex in the reaction mixture prior to the addition of the aldehyde, the precipitates being redissolved in the reaction mixture on the addition of the aldehyde, and the formation of the dimer of lithiated **1f** was confirmed by ESIMS of the reaction mixture (calcd for $C_{16}H_{12}F_6O_4S_2Li_2$: 460; found: 460, Figure 1).[17]



Scheme 5. Catalytic cycle for the enantioselective reaction for **1f** when using a substoichiometric amount of **3**.

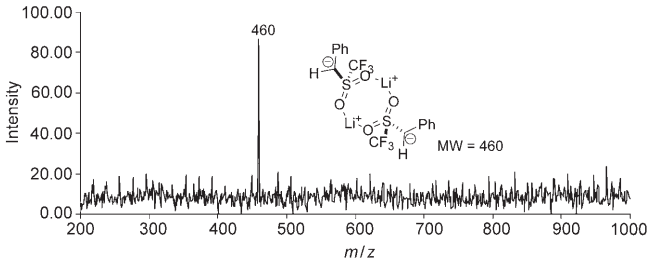


Figure 1. ESIMS of the reaction mixture.

Furthermore, in the ^{19}F NMR spectrum of the reaction mixture, prepared from **1f**, 0.3 equivalents of **3g**, and 1.2 equivalents of *n*BuLi in [D_8]toluene at −30 °C, one major signal and three minor signals are shown (Figure 2a). One of the minor signals at $\delta = -72.0$ ppm was assigned to the sulfone **1f** by examination of the spectra of the reaction mixture mixed with **1f** (Figure 2b,c). Although we were not able to clearly assign the two other minor signals at around $\delta = -80$ ppm, which are possibly due to the **1f**–**3g** complex, it was definitely shown that non-lithiated **1f** was not observed as a major species after lithiation with an even less than stoichiometric amount of **3g**, and almost only one species (>90%), which produced the signal at $\delta = -73.9$ ppm, was formed in the reaction mixture before the addition of the aldehyde. When combining these NMR spectral and ESIMS data, it is reasonable to conclude that **1f** is transformed into the enantioenriched dimeric lithiated **1f** through the sulfone–bis(oxazoline) complex (*M*)-Li–**1f**–**3**.

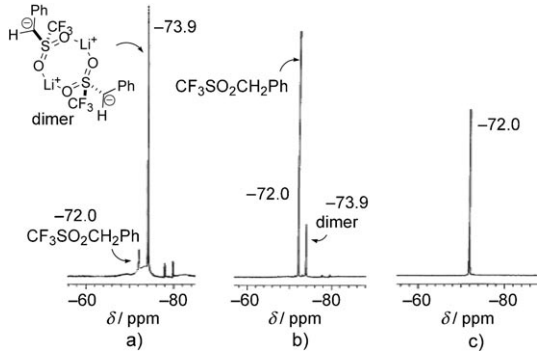


Figure 2. ^{19}F NMR spectra for the lithiated **1f** when using a substoichiometric amount of **3g**. a) reaction mixture; b) reaction mixture and $CF_3SO_2CH_2Ph$; c) $CF_3SO_2CH_2Ph$

Origin of the enantioselectivity: To elucidate the origin of the enantioselectivity, we next estimated the activation energy for the deprotonation of both prochiral methylene protons and the stability of diastereomeric complexes between α-sulfonyl carbanion **1f** and bis(oxazoline) **3** by MO calculations by using Gaussian 03 HF/3-21+G* or 6-31+G* methods.[18] Structures were first optimized by using a semiempirical method (MOPAC93/PM3) and then fully optimized at the HF/3-21+G* or 6-31+G* level of theory.[19] The relative energies of the transition-state structures are depicted in Figure 3a. To simplify the calculation, bis(oxazoline)-Ph **1a** and MeLi were used for the optimization of the transition-states TS-**1**(pro-*S*) (TS = transition state) and TS-**2**(pro-*R*). Because the acidity of the protons in sulfone **1f** is increased by the n–σ* interaction, it is preferably deprotonated and one of the sulfonyl oxygen atoms, pro-*S* sulfonyl oxygen, is preferably coordinated to lithium together with two bis(oxazoline) nitrogen atoms and a methyl group in TS-**1** and TS-**2**.[20] As a result, the pro-*S* proton was found to be slightly more reactive towards deprotonation by the Box **3a**/MeLi complex than the pro-*R* proton; this is probably due to destabilization of transition-state TS-**2** by steric repulsion of the two phenyl groups. Therefore, the (*M*)-Li–**1f**–**3a** complex is formed kinetically through TS-**2**; however, the energy difference between TS-**1** and TS-**2** is not very large. This calculated result is in good agreement with the reaction of **1f** at −95 °C, in which *syn*-**2f** is kinetically formed with a slightly lower enantioselectivity (Scheme 3; er = 86:14) than that obtained in the reaction at −78 and −30 °C. We next estimated the optimized structures of lithiated diastereomeric complex (Li–**1f**–**3a**), which is closely re-

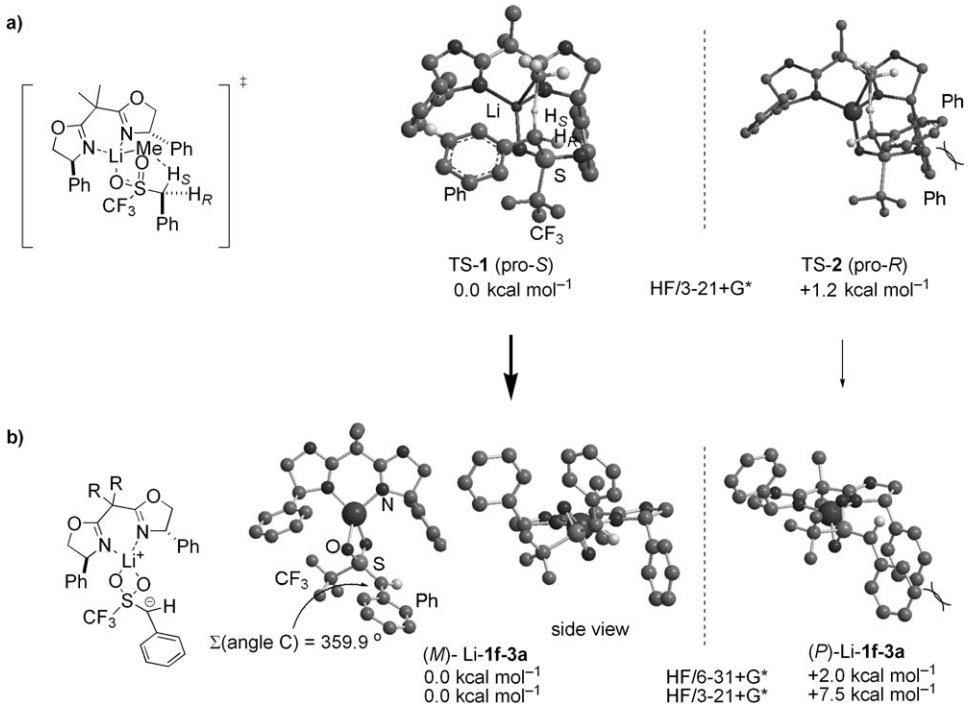


Figure 3. a) Structures in the transition state for deprotonation and b) the optimized structures of Li–**1f**–**3a**.

lated to the determination of enantioselectivity in the dynamic thermodynamic resolution pathway (Figure 3b). Calculation of the stability of Li–**1f**–**3a** showed that the (*M*)-Li–**1f**–**3a** complex is more stable than the (*P*)-Li–**1f**–**3a** complex because of steric repulsion between the two phenyl groups. The results of the calculations show that the lithium atoms are coordinated to two nitrogen atoms of bis(oxazoline) **3a** and two oxygen atoms of the sulfonyl group, but not with the anionic carbon atom. These calculated structures are in good agreement with the findings with regard to the structural aspects of α-lithiated sulfones.[21] Since the sum of bond angles of the carbanionic carbon atom is about 360°, the carbanionic carbon atom nearly attains sp^2 hybridization, in which the molecule may lose the stereogenic center. However, this is not the case: the stereochemistry induced on removal of one of the prochiral protons is maintained by the axial chirality around the S–C bond in the α-sulfonyl carbanion, which indicates that the enantioselective reaction of the α-sulfonyl carbanion of **1f** proceeds through dynamic axial chirality.[11,22]

Calculation of the racemization barrier of the carbanion–diamine complexes confirmed the configurational stability of (*M*)-Li–**1f**–**3a**. It is known that the racemization rate of the α-sulfonyl carbanion is in accord with the rotational barrier around the C–S bond.[11] The ground state of the (*M*)-Li–**1f**–**3a** complex and the transition-state TS-Li–**1f**–**3a** for rotation around the C–S bond were calculated (Figure 4). The activation energy for the rotational barrier around the C–S bond was estimated to be 16.8 and 17.5 kcal mol^{-1} by the HF/3-21+G* and HF/6-31+G* methods, respectively. The half-life of rotation around the S–C_α bond in Li–**1f**–**3a** was calculated as 1000 h at −78 °C from the activation energy of 17.5 kcal mol^{-1}. The high activation energy of the rotational barrier around the S–C_{CF3} bond in the trifluoromethylsulfonyl carbanion was attributed to an increase of the n–σ* overlap caused by the lower energy σ* orbital of the S–C_{CF3} bond.[11] The (*M*)-Li–**1f**–**3a** complex shows that the S–C_{CF3} bond is conformationally arranged at the position parallel to the lone pair orbital of the carbanion (the dihedral angle of the

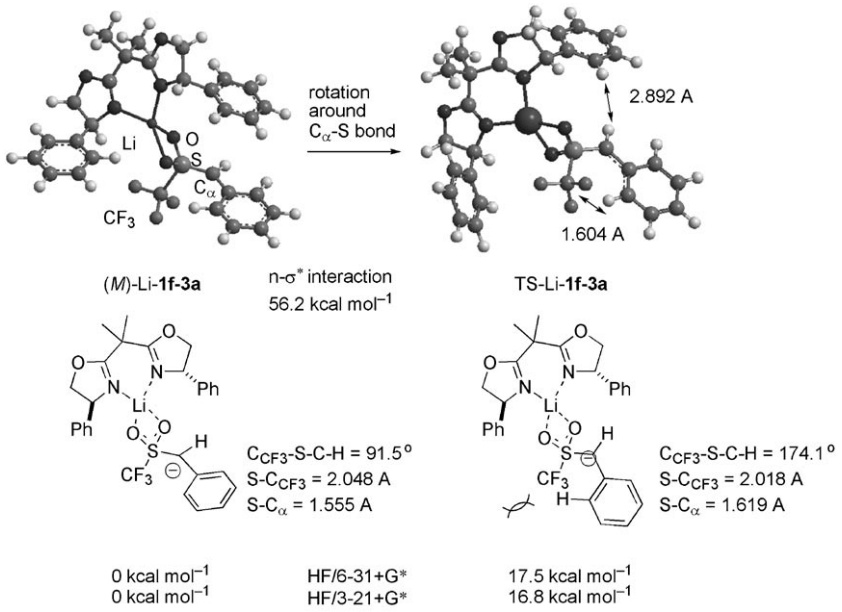
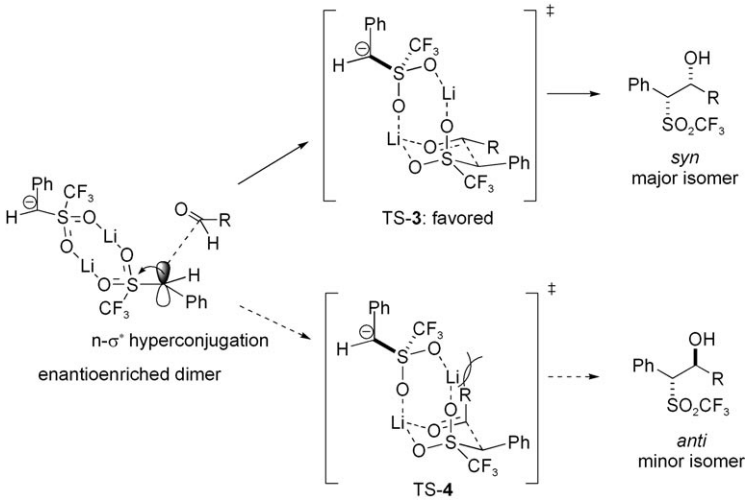


Figure 4. Structures and relative energies of optimized structure and transition state of **Li**–**1f** with bis(oxazoline)-Ph **2a**.

C_{CF3}-S-C_α–H bond in the (*M*)-Li–**1f**–**3a** complex is 91.5°) due to stabilization by the n–σ* negative hyperconjugation between the lone pair and σ* orbital of the C_{CF3}–S bond,[11] which was estimated to be 56.2 kcal mol^{-1} by NBO analysis.[23,24] On the other hand, the dihedral angle of the C_{CF3}-S-C_α–H bond in the TS-Li–**1f**–**3a** complex was 174.1°. The strong n–σ* negative hyperconjugation in (*M*)-Li–**1f**–**3a** causes a longer S–C_{CF3} bond and a shorter S–C_α bond in the (*M*)-Li–**1f**–**3a** complex than that in the TS-Li–**1f**–**3a**. Therefore, the high configurational stability of the α-sulfonyl carbanion derived from trifluoromethyl sulfone is enough to transfer the chirality of the carbanion to the axial chirality around the S–C_α bond in the α-sulfonyl carbanion complex. Thus, finally, the dimer or the oligomer of Li–**1f** complexes is formed from the (*M*)-Li–**1f**–**2a** complex.[25]

Origin of the diastereoselectivity: In the reaction of the dimer or the oligomer of lithiated **1f** with an electrophile such as an aldehyde, the electrophile approaches the carbanionic center, avoiding any steric interaction with the CF_3 group to form the expected products with retention of configuration in a S_E2_{Ret} reaction manner[26] (Scheme 6). The



Scheme 6. Proposed transition state for the reaction of [(*S*)-Li–**1f**]$_2$ with benzaldehyde.

syn isomer is formed exclusively through the boat form of the six-membered transition-state TS-**3** from the dimer of the α-sulfonyl carbanion, which is more stable than TS-**4** due to the 1,3-diaxial steric repulsion between the aldehyde substituent and the sulfonyl oxygen atom. It should be noted that the reaction afforded the products with high *syn* selectivity, in contrast to the low diastereoselectivities (50:50–86:14)[27] generally obtained in the reactions of various α-sulfonyl carbanions with aldehydes, which is probably due to the lower stabilization energy arising from n–σ* negative hyperconjugation.

Conclusion

We have disclosed the first highly enantioselective reactions of configurationally stable α-sulfonyl carbanions derived from trifluoromethyl sulfone **1f** by using bis(oxazoline)s as chiral ligands. The reaction of lithiated **1f** proceeded through a dynamic thermodynamic resolution pathway. It should be noted that a highly enantioselective reaction can be achieved with a substoichiometric amount of a chiral ligand and a stoichiometric amount of butyllithium. To the best of our knowledge, this is the first report of a catalytic version of an enantioselective reaction that was found to proceed through dynamic thermodynamic resolution. A detailed survey of the catalytic pathway on the basis of stereoscopic features and MO calculations elucidated a novel catalytic reaction mechanism involving a dimeric or a less likely oligomeric lithiated species as an intermediate, which enables the enantioselective catalytic cycle. The dimerization mechanism of lithiated species opens the door for a catalytic enantioselective dynamic thermodynamic resolution pathway. The present novel reaction may provide insight into the development of enantioselective reactions for carbanions.

Experimental Section

General methods: All reactions were performed in oven-dried glassware under a positive pressure of nitrogen. Solvents were transferred by syringe and were introduced into the reaction vessels through a rubber septum. All of the reactions were monitored by TLC carried out on 0.25 mm Merck silica gel (60-F254). The TLC plates were visualized with UV light and 7% phosphomolybdic acid or panisaldehyde in ethanol/heat. Column chromatography was carried out on a column packed with silica gel 60N spherical neutral size 63–210μm. The ^{1}H (200 MHz), ^{19}F (188 MHz), and ^{13}C NMR (50.3 MHz) spectra for solutions in $CDCl_3$ were recorded on a Varian Gemini-200. Chemical shifts (δ) are expressed in ppm downfield from internal TMS or $CHCl_3$. HPLC analyses were performed on a JASCO PU-2080 Plus or Shimadzu LC-2010A HT by using a 4.6×250 mm CHIRALPAK AD-H or OJ-H, CHIRALCEL OD-H, or CHIRALPAK AS-H column. Mass spectra were recorded on a Shimadzu GCMS-QP5050A. Optical rotations were measured on a HORIBA SEPA-300. IR spectra were recorded on a JASCO FTIR 200 spectrometer.

General procedure for the enantioselective reaction of α-sulfonyl carbanions with bis(oxazoline)s: 1,2-Diphenyl-2-(trifluoromethylsulfonyl)ethanol (2f): *n*BuLi (0.11 mL, 0.142 mmol) was added to a solution of bis(oxazoline) **3g** (17.3 mg, 0.035 mmol) and sulfone **1f** (26.5 mg, 0.118 mmol) in toluene (1.5 mL) at −30°C and the solution was stirred for 1 h at this temperature. Benzaldehyde (0.018 mL, 0.177 mmol) was then added. After stirring for 5 min, TMSCl (0.017 mL, 0.13 mmol) was added and the mixture was stirred for an additional 12 h. Aqueous NH_4Cl was added to the reaction mixture and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give silylated **2f**. Silylated **2f** was treated with aqueous HCl (6 mol L^{-1}) to give the crude, which was purified by column chromatography (silica gel 15 g, hexane/ethyl acetate 90:10) to give *syn*-**2f** (28.4 mg, 74%; 94% *ee*). The enantiomeric ratio was determined by HPLC analysis by using chiralpak AD-H.

Compound syn-***2f***: $[\alpha]_D^{26}=+1.03$ ($c=0.59$ in $CHCl_3$, 90% *ee*); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=2.90$ (br s, 1H), 4.75 (d, $J=9.8$ Hz, 1H), 5.59 (d, $J=9.8$ Hz, 1H), 7.11–7.26 ppm (m, 10H); ^{13}C NMR (50.3 MHz, $CDCl_3$):

δ = 74.0, 75.1, 116.4, 122.9, 126.7, 126.9, 128.0, 128.2, 128.5, 129.5, 130.0, 138.5 ppm; ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -73.3$ ppm; IR (KBr) $\tilde{\nu}$ = 3538, 3067, 3035, 2924, 2853, 2359, 1716, 1493, 1455, 1346, 1296, 1203, 1105, 1053, 1034, 917, 857, 802, 763, 698, 651, 632, 620 cm^{-1}; EIMS *m/z* (%) 330 (12) [M^+], 197 (14), 165 (22), 107, (100), 91 (77), 79 (83); HPLC (CHIRALPAK AD-H hexane/*i*PrOH 95:5, flow rate = 1.0 mL min^{-1}), t_R 15.7 (minor) and 17.8 (major) min. *anti*-**2f**; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.80 (brs, 1H), 4.46 (d, J = 7.2 Hz, 1H), 5.99 (s, 1H), 6.99–7.43 ppm (m, 10H); ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -74.4$ ppm (s).

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