

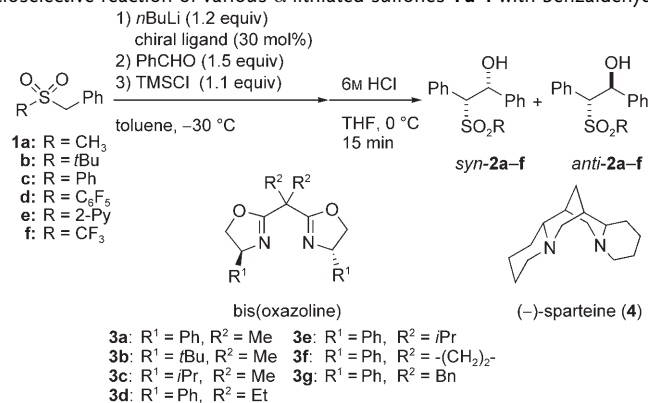
Highly Enantioselective Reactions of α -Sulfonyl Carbanions of Trifluoromethyl Sulfones**

Shuichi Nakamura,* Norimune Hirata, Takeshi Kita, Ryusuke Yamada, Daisuke Nakane, Norio Shibata, and Takeshi Toru*

The formation of carbon–carbon bonds by using readily generated α -sulfonyl carbanions^[1] and their applications to the synthesis of natural products^[2] have been extensively studied. Sulfones having chirality at the α position are known to show biological activity, for example, dorzolamide has antiglaucoma activity,^[3] but little attention has been paid to the enantioselective reaction of α -sulfonyl carbanions,^[4] probably because of the difficulty in obtaining high enantioselectivity. However, there are a few precedents: the enantioselective reaction of α -lithio sulfones derived from an allyl sulfone using a chiral amino alcohol as a chiral ligand^[4a] and by using chiral lithium amides.^[4b] However, the enantioselectivities reported in these reports are unsatisfactory. Herein we report the first highly and catalytic enantioselective reaction of α -lithiated sulfones.^[5]

We first attempted the enantioselective reaction of α -carbanions of various benzyl sulfones, for example, methyl, *t*Bu, phenyl, pentafluorophenyl, and 2-pyridyl benzyl sulfones **1a–e**, respectively (Table 1). The benzyl sulfones were treated with *n*BuLi (1.2 equiv) and bis(oxazoline)-phenyl **3a**

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



Entry	1	Chiral ligand	Product	Yield ^[a] [%]	d.r. ^[b] <i>syn:anti</i>	e.r. ^[c] <i>syn</i>	e.r. ^[c] <i>anti</i>
1 ^[d]	1a	3a	2a	19 ^[e]	50:50	55:45	51:49
2 ^[d]	1b	3a	2b	71 ^[e]	64:36	65:35	61:39
3 ^[d]	1c	3a	2c	83 ^[e]	68:32	66:34	71:29
4 ^[d]	1d	3a	2d	72	86:14	62:38	57:43
5 ^[d]	1e	3a	2e	66 ^[e]	61:39	52:48	54:46
6 ^[d]	1f	3a	2f	56(56 ^[e])	> 98:2	85:15	
7 ^[d]	1f	3b	2f	55	> 98:2	71:29	
8 ^[d]	1f	3c	2f	58	> 98:2	50:50	
9 ^[d]	1f	4	2f	31	> 98:2	51:49	
10 ^[f]	1f	3a	2f	87	95:5	94:6	nd ^[j]
11	1f	3a	2f	84	93:7	87:13	nd
12	1f	3d	2f	74	93:7	97:3	nd
13	1f	3e	2f	74	92:8	97:3	nd
14	1f	3f	2f	76	90:10	93:7	nd
15	1f	3g	2f	87	96:4	97:3	nd
16 ^[g]	1f	3g	2f	87	96:4	97:3	nd
17 ^[h]	1f	3g	2f	44	95:5	95:5	nd

[a] Conversion yield determined by ¹⁹F NMR analysis. [b] Determined by ¹H NMR analysis. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction was carried out at –78 °C with 125 mol% **3**. [e] Yield of isolated product. [f] **3a** (125 mol%) was used. [g] **3g** (10 mol%) was used. [h] **3g** (2 mol%) was used. [j] Not determined.

[*] Prof. S. Nakamura, N. Hirata, T. Kita, R. Yamada, D. Nakane, Prof. N. Shibata, Prof. T. Toru
Department of Applied Chemistry
Graduate School of Engineering
Nagoya Institute of Technology
Gokiso, Showa-ku, Nagoya 466-8555 (Japan)
Fax: (+81) 52-735-5442
E-mail: snakamur@nitech.ac.jp
toru@nitech.ac.jp

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(1.25 equiv) in toluene and subsequently with benzaldehyde. Trimethylsilyl chloride (TMSCl) was added for the trimethylsilylation of the formed alkoxide, thereby suppressing the retro-aldol-type reaction. Most of the reactions gave high yields of a diastereomeric mixture of the *syn* and *anti* isomers of the products **2a–e**, with each isomer having low enantioselectivity. Trifluoromethyl sulfones are known to have unusual configurational stability.^[6] Indeed, when benzyl trifluoromethyl sulfone **1f** was allowed to react with a stoichiometric amount of the bis(oxazoline)s at –78 °C under similar reaction conditions, the *syn*-**2f** was formed exclusively. This *syn* isomer was obtained in high enantioselectivity.

lectivity with bis(oxazoline)-Ph **3a** (Table 1, entry 6), whereas bis(oxazoline)-*i*Bu **3b**, -*i*Pr **3c**, and (–)-sparteine (**4**) gave lower enantioselectivity but exclusive formation of *syn*-**2f** (Table 1, entries 7–9). Other solvents such as cumene, Et₂O, or THF did not improve the enantioselectivity. The best enantioselectivity was obtained when the reaction was carried out at –30 °C in toluene using **3d** (Table 1, entry 10).^[7] Furthermore, we were pleased to find that the reaction of **1f** proceeded with a substoichiometric amount of **3a**. Thus, the reaction of **1f** was performed with 30 mol % of **3a** at –30 °C to give *syn*-**2f** as the major product in high yield and with high enantioselectivity (Table 1, entry 11). Several bis(oxazoline) derivatives also showed excellent results (Table 1, entries 12–15). Even 10 mol % of the dibenzyl bis(oxazoline) derivative **3g** worked well (Table 1, entry 16). Notably, 2 mol % of **3g** was found to show even higher enantioselectivity (Table 1, entry 17). O'Brien and co-workers have reported an asymmetric deprotonation of a methylene proton α to amino and oxy groups in the presence of a substoichiometric amount of (–)-sparteine to give products with high enantioselectivity, with an achiral ligand used to regenerate the BuLi/(–)-sparteine complex.^[8] Interestingly, our enantioselective reaction proceeded in a catalytic manner without any additives.^[9]

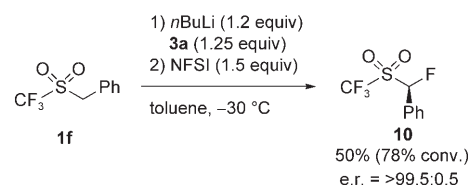
The reaction of **1f** with various aromatic aldehydes such as *p*-tolualdehyde, *p*-methoxybenzaldehyde, *p*-chlorobenzaldehyde, 2-naphthaldehyde, and 2-furaldehyde in the presence of **3g** gave the products **5–9** with excellent diastereoselectivities and high enantioselectivities (Table 2, entries 1–6).

Table 2: Enantioselective reaction of trifluoromethyl sulfone **1f** with various aldehydes in the presence of **3g**.

Entry	R	Product	Yield ^[a,b] [%]	d.r. ^[c] <i>syn:anti</i>	e.r. ^[d] <i>syn</i>
1 ^[e]	Ph	2f	74 (87)	96:4	97:3
2	<i>p</i> -CH ₃ C ₆ H ₄	5	70 (84)	97:3	97:3
3	<i>p</i> -MeOC ₆ H ₄	6	57 (91)	97:3	99:1
4	<i>p</i> -ClC ₆ H ₄	7	66 (85)	90:10	92:8
5 ^[e]	2-naphthyl	8	54 (80)	94:6	98:2
6	2-furyl	9	35 (58)	93:7	95:5
7 ^[f]	<i>p</i> -ClC ₆ H ₄	7	16 (18) ^[g]	90:10	99:1

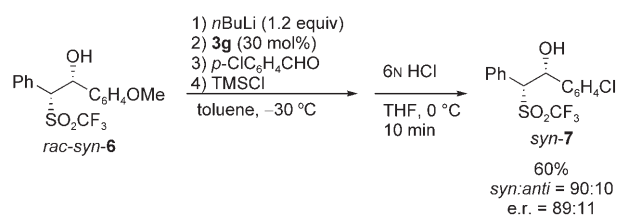
[a] Yield of isolated product. [b] Yield in parenthesis is the conversion yield. [c] Determined by ¹H NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase. [e] **3g** (10 mol %) was used. [f] *p*-ClC₆H₄CHO (0.2 equiv) was used. [g] Based on **1f**.

α -Fluorinated sulfur compounds can also serve as synthetic intermediates or precursors for the synthesis of fluorinated molecules^[10] and bioactive compounds.^[11] We further studied the preparation of optically active α -fluorobenzyl sulfones. Fluorination of **1f** with *N*-fluorobenzensulfonimide (NFSI) with 1.25 equivalents of **3a** afforded (*R*)-**10** exclusively in moderate yield (Scheme 1).^[12]



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

To define the enantiodetermining step in the enantioselective reaction of α -lithiated sulfones, we studied the reaction of the racemic product *syn*-**6** (*rac-syn*-**6**) by treating it with 1.2 equivalents of *n*BuLi and a substoichiometric amount of **3g** to cause the retro-aldol-type reaction and then subsequent reaction with *p*-chlorobenzaldehyde (Scheme 2).



Scheme 2. Enantioselective reaction of the racemic carbanion.

It was found that *syn*-**7** was obtained with high enantioselectivity. Furthermore, the reaction of lithiated **1f** with a deficient amount of benzaldehyde afforded **2f** with complete enantioselectivity (compare entries 4 and 7 in Table 2). These results show that the reaction of **1f** proceeds through a dynamic thermodynamic resolution pathway.^[9,13] The highly enantio- and diastereoselective reaction of lithiated trifluoromethylsulfone can be ascribed to high configurational stability of the carbanion as a result of the large $n-\sigma^*$ interaction.^[14]

In summary, we have disclosed the first highly enantioselective reactions of carbanions α to the sulfonyl group using bis(oxazoline) derivatives. The reaction of lithiated **1f** proceeds through a dynamic thermodynamic resolution pathway. Furthermore, the success of the catalytic reaction is surprising, considering that a stoichiometric amount of butyllithium is used. To the best of knowledge, this is the first report for the catalytic enantioselective reaction through a dynamic thermodynamic resolution. This novel reaction should provide insight for the development of enantioselective reactions of carbanions. A detailed study of the reaction mechanism is currently under investigation and will be reported in due course.

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