Homogeneous Catalysis

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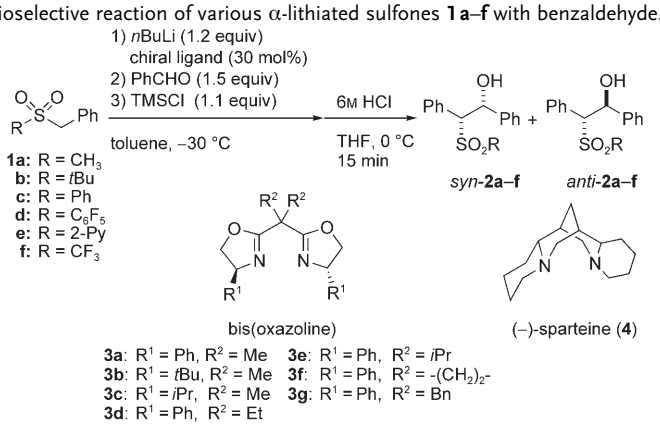
Highly Enantioselective Reactions of α-Sulfonyl Carbanions of Trifluoromethyl Sulfones**

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** (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 enantiose-

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



3a: R^1 = Ph, R^2 = Me **3e**: R^1 = Ph, R^2 = *i*Pr
3b: R^1 = *t*Bu, R^2 = Me **3f**: R^1 = Ph, R^2 = -$(CH_2)_2$-
3c: R^1 = *i*Pr, R^2 = Me **3g**: R^1 = Ph, R^2 = Bn
3d: R^1 = Ph, R^2 = Et

Entry	1	Chiral ligand	Product	Yield[a] [%]	d.r.[b] *syn*:*anti*	e.r.[c] *syn*	e.r.[c] *anti*
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[i]
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 ^{19}F NMR analysis. [b] Determined by ^{1}H 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. [i] 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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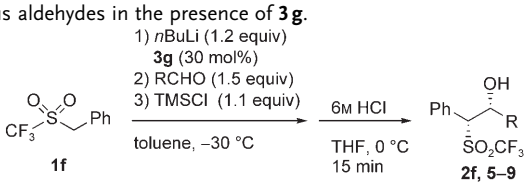
lectivity with bis(oxazoline)-Ph **3a** (Table 1, entry 6), whereas bis(oxazoline)-*t*Bu **3b**, -*i*Pr **3c**, and (−)-sparteine (**4**) gave lower enantioselectivity but exclusive formation of *syn*-**2f** (Table 1, entries 7–9). Other solvents such as cumene, Et_2O, or THF did not improve the enantioselectivity. 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).

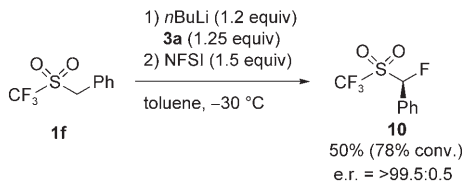
Table 2: Enantioselective reaction of trifluoromethyl sulfone **1f** with various aldehydes in the presence of **3g**.



Entry	R	Product	Yield[a,b] [%]	d.r.[c] *syn:anti*	e.r.[d] *syn*
1[e]	Ph	**2f**	74 (87)	96:4	97:3
2	*p*-$CH_3C_6H_4$	**5**	70 (84)	97:3	97:3
3	*p*-$MeOC_6H_4$	**6**	57 (91)	97:3	99:1
4	*p*-ClC_6H_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]	*p*-ClC_6H_4	**7**	16 (18)[g]	90:10	99:1

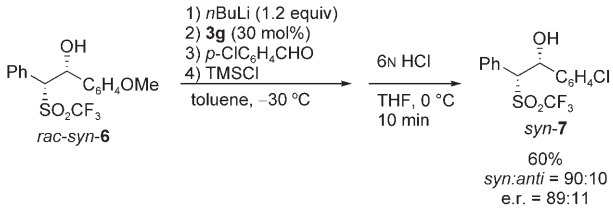
[a] Yield of isolated product. [b] Yield in parenthesis is the conversion yield. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase. [e] **3g** (10 mol%) was used. [f] *p*-ClC_6H_4CHO (0.2 equiv) was used. [g] Based on **1f**.

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–σ* 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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[9] We assume the catalytic pathway is as follows: The first-formed dynamic thermodynamic-controlled α-lithiated sulfone-bis(oxazoline) complexes are transformed, together with regeneration of bis(oxazoline), to an enantioenriched dimer or oligomer of the α-lithiated sulfone which reacts with an aldehyde to yield the enantioenriched product. In fact, we observed the precipitation of the complex out of the reaction mixture before the addition of an aldehyde, and confirmed that the precipitates mainly consist of the dimer of the sulfonyl carbanions by ESI mass spectrometry. The dimeric structure has been reported by Gais and coworkers, see Ref. [6a]; see also the Supporting Information.

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[14] It is well known that the configurational stability of α-sulfonyl carbanions depends upon the magnitude of the n–σ*(C_{CF3}-S) interaction, which is enhanced by the electron-withdrawing group attached to the sulfonyl group, see Refs. [6a,d].

