

# Stereoselective reactions of $\alpha$ -(arylsulfonyl)cyclohexyl carbanions

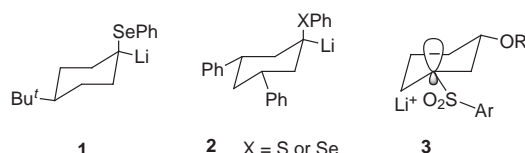
Michiko Tanaka, Mai Nakatani and Morio Asaoka\*

Department of Chemical and Biological Sciences, Faculty of Science,  
Japan Women's University, Mejirodai 2-8-1 Bunkyo-ku, Tokyo 112-0015, Japan

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The reactions of  $\alpha$ -arylsulfonyl carbanions generated from 3-hydroxy- and 3-alkoxy-1-(arylsulfonyl)cyclohexane with some electrophiles are suggested to proceed with inversion of configuration of the carbanionic centers.

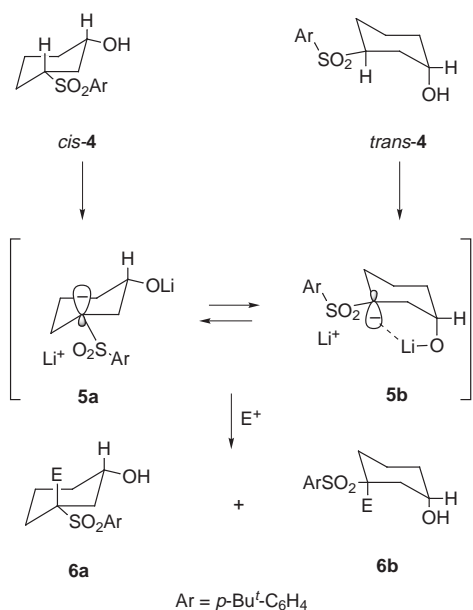
Recently, the configurational stability and stereochemical reaction tendencies of  $\alpha$ -heterosubstituted  $sp^3$  carbanions have been widely studied.<sup>1–5</sup>  $\alpha$ -Heterosubstituted cyclohexyllithium compounds such as phenylseleno- and phenylthio- compounds **1** and **2** have already been examined.<sup>6–8</sup> In this communication,



we will report the stereochemical features of the reaction of  $\alpha$ -sulfonylcyclohexyl carbanion **3**.

Non-benzylic type  $\alpha$ -sulfonyl carbanions are suggested to have pyramidalized structures and the counter cation is bound to the oxygens of the sulfonyl group, not to the carbanionic centers.<sup>9,10</sup> We envisioned controlling the stereochemistry of  $\alpha$ -sulfonylcyclohexyl carbanion **3** by using chelating, stereo-electronic, and purely steric effects.

First, we examined the generation of the dianion of 3-hydroxy-1-(arylsulfonyl)cyclohexane **4** (Scheme 1). Treatment



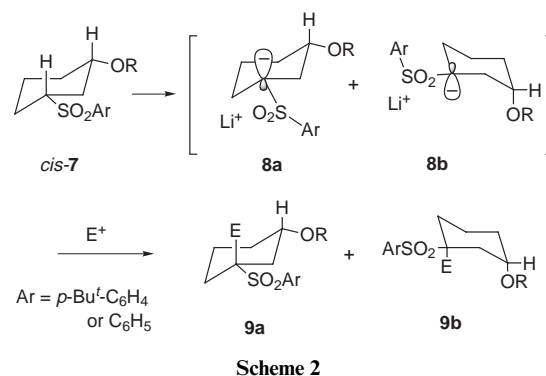
Scheme 1

of *trans*-**4** in THF with 2.5 equivalents of  $Bu^tLi$  at  $-78^\circ C$  for 1 h and subsequent quenching with  $D_2O$  gave **6b** ( $E = D$ ) exclusively (Table 1, entry 1). Starting from *cis*-**4**, a 4:96 mixture of **6a** and **6b** ( $E = D$ ) was obtained under the same conditions (entry 2). Consequently, dianion **5a** isomerizes on the time scale at  $-78^\circ C$  to give the thermodynamically more stable

chelated dianion **5b**. An experiment to trap the dianion **5a** as its silylated derivative, *i.e.* dianion generation from *cis*-**4** in the presence of chlorotrimethylsilane, resulted in failure due to the low reactivity of **5a,b**.

Allylation products of **5a,b** with allyl bromide could not be detected even after 17 h at  $-78^\circ C$ . Allylation with 2 equivalents of allyl bromide in THF at  $-30$  to  $20^\circ C$  for 4 h gave a 63:37 mixture of **6a,b** ( $E = \text{allyl}$ ) in 33% yield. The ratio and the yield were improved by carrying out the reaction in hexane–toluene at  $50^\circ C$  for 13 h (Table 1, entry 4) or in ether (entry 5) at room temperature for 13 h. Similarly, cinnamyl bromide, methyl iodide and dimethyl disulfide gave **6a** predominantly (entries 6–8).<sup>†‡</sup> If the product distribution obtained by  $D_2O$  quenching reflects the distribution of **5a** and **5b**, then reaction with allyl bromide, cinnamyl bromide, methyl iodide and dimethyl disulfide proceeded with inversion of configuration of the carbanionic center.

In the case of the hydroxy group protected derivative **7**, the sterically more stable anion **8a** is expected to be preferable since chelation like **5b** is impossible (Scheme 2). Thus, we examined



Scheme 2

carbanion formation and the subsequent reaction of *cis*-**7** ( $R = \text{PhCH}_2$  or TBDMS), and totally different stereoselectivity was observed.

Generation of the corresponding carbanion from *cis*-**7** was carried out by treatment with 1.3–1.5 equivalents of  $n-BuLi$  at  $-78^\circ C$  for 1 h. In reactions with  $D_2O$  at  $-78^\circ C$ , both benzyl and *tert*-butyldimethylsilyl (TBDMS) protected compounds *cis*-**7** gave almost a 1:1 mixture of diastereoisomers **9a,b** ( $E = D$ ) (Table 2, entries 1 and 2).

In contrast to the dianion **5**, monoanion **8** ( $R = \text{TBDMS}$ ) reacted with allyl bromide smoothly at  $-78^\circ C$  to give allylated product **9b** ( $E = \text{allyl}$ ,  $R = \text{TBDMS}$ ) selectively (Table 2, entries 3 and 4).<sup>§</sup> Similarly, a high diastereoselectivity was observed in the reaction with cinnamyl bromide (entry 5)<sup>§</sup> and benzyl bromide (entry 6). However, reversal of stereoselectivity was observed in the reaction with dimethyl disulfide (entry 7).<sup>§</sup> Almost no selectivity was observed in the reaction with methyl iodide (entry 8).

Although the reasons for the above outcome have not yet been clearly established, we might assume that the mode of the  $S_E$  reaction, *i.e.* inversion or retention of the configuration at the carbanionic centers is related to the reactivity of both the carbanion and the electrophile. One of the plausible mechanisms for the above results at this stage is as follows. In the

**Table 1** Reaction of dianions **5a,b** with some electrophiles

Entry	<b>4</b>	Electrophile	Solvent	Temp (°C)	t/h	Yield (%) <sup>a</sup> <b>6a</b> + <b>6b</b>	Ratio <sup>a</sup> <b>6a</b> : <b>6b</b>
1	<i>trans</i> - <b>4</b>	D <sub>2</sub> O	THF	-78	0.5	98	0:100
2	<i>cis</i> - <b>4</b>	D <sub>2</sub> O	THF	-78	0.5	96 (92 <sup>b</sup> )	4:96
3	<i>cis</i> - <b>4</b>	allyl-Br	THF	-30 to 20	4	33	63:37
4	<i>cis</i> - <b>4</b>	allyl-Br	hexane-toluene	50	13	59	84:16
5	<i>cis</i> - <b>4</b>	allyl-Br	Et <sub>2</sub> O	rt	13	90 (84 <sup>b</sup> )	80:20
6	<i>cis</i> - <b>4</b>	cinnamyl-Br	Et <sub>2</sub> O	35	16	92	73:27
7	<i>cis</i> - <b>4</b>	MeI	Et <sub>2</sub> O	rt	2	83 <sup>b,c</sup>	84:16
8	<i>cis</i> - <b>4</b>	(MeS) <sub>2</sub>	Et <sub>2</sub> O	rt	2	54 <sup>b</sup>	72:28

<sup>a</sup> The yields and the ratios were determined by 400 MHz NMR. <sup>b</sup> Isolated yield. <sup>c</sup> Contaminated with a small amount of unidentified product.

**Table 2** Reaction of **8a,b** with some electrophiles

Entry	Ar <sup>a</sup>	R	Electrophile	Solvent	Temp (°C)	t/h	Yield (%) <sup>b</sup> <b>9a</b> + <b>9b</b>	Ratio <sup>b</sup> <b>9a</b> : <b>9b</b>
1	A	PhCH <sub>2</sub>	D <sub>2</sub> O	THF	-78	0.5	91	44:56
2	B	TBDMS	D <sub>2</sub> O	THF	-78	0.5	82	46:53
3	B	TBDMS	allyl-Br	THF	-78	1.5	78	12:88
4	B	TBDMS	allyl-Br	Et <sub>2</sub> O	-78	1.5	92	7:93
5	B	TBDMS	cinnamyl-Br	Et <sub>2</sub> O	-78 to -40	18.0	77	5:95
6	B	TBDMS	PhCH <sub>2</sub> Br	Et <sub>2</sub> O	-78 to rt	14.0	43	2:98
7	B	TBDMS	(MeS) <sub>2</sub>	Et <sub>2</sub> O	-78	0.25	89 <sup>c</sup>	86:14
8	B	TBDMS	MeI	Et <sub>2</sub> O	-78	1.0	90	54:46

<sup>a</sup> A = Ph, B = *p*-Bu<sup>t</sup>-C<sub>6</sub>H<sub>5</sub>. <sup>b</sup> Yields and ratios were determined by 400 MHz NMR. <sup>c</sup> Isolated yield.

former case (**5**→**6**) the reaction of the less reactive dianion **5b** with D<sub>2</sub>O proceeded with retention of configuration of the carbanionic center,<sup>¶</sup> while with allyl bromide, cinnamyl bromide, methyl iodide and dimethyl disulfide the configuration inverted. In the latter case (**8**→**9**), the much more reactive monoanion **8a** reacted with D<sub>2</sub>O<sup>¶</sup> and MeI with almost equal degrees of retention and inversion, and reacted with less reactive electrophiles such as allyl bromide, benzyl bromide and cinnamyl bromide with inversion of configuration.

Further investigations using acyclic systems is currently underway.

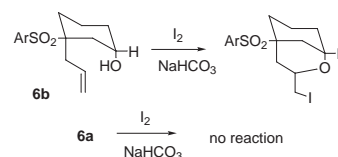
## Experimental

### Typical procedure for the reaction of *cis*-**4**

To a solution of *cis*-**4** (148 mg, 0.5 mmol) in Et<sub>2</sub>O (5 cm<sup>3</sup>) was added Bu<sup>n</sup>Li (2.5 mmol) at -20 °C. After 2 h stirring allyl bromide (242 mg, 2 mmol) was added. The resulting mixture was warmed to room temperature and stirred for 13 h. After quenching with aq. NH<sub>4</sub>Cl, the reaction mixture was extracted with AcOEt. The organic layer was dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The diastereomeric ratio of the products **6a**:**6b** was determined by <sup>1</sup>H NMR (400 MHz) analysis of the crude mixture. The analytically pure samples of the diastereomers [hexane-AcOEt (1:1 v/v): **6a** (E = allyl), *R<sub>f</sub>* 0.43; **6b** (E = allyl), *R<sub>f</sub>* 0.53] were obtained by flash column chromatography on silica gel with hexane-AcOEt [4:1-2:1 v/v] as eluent.

## Notes and references

† The stereochemistry of the products was assigned by the chemical shifts of the protons *α* to the hydroxy group. The structures of the allylated products were further confirmed by the chemical transformation as shown below (Scheme 3):

**Scheme 3**

‡ A similar chelating effect was reported in the reaction of an sp<sup>2</sup>-like carbanion: T. Kato, S. Marumoto, T. Sato and I. Kuwajima, *Synlett*, 1990, 671.

§ The stereochemistry of **9a,b** was determined by conversion to **6a,b**.

¶ During D<sub>2</sub>O quenching, there may be some scrambling. However the influence on the product distribution seems to be small since protonation with AcOH also showed a similar selectivity.

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