

# Steric Course of the Electrophilic Substitution of a Lithiocarbanion Generated from (*S,E*)-1-Phenylbut-2-en-1-yl Diisopropylcarbamate and Solvent Effects

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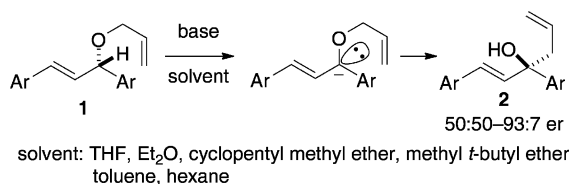
**Keywords:** Reaction mechanisms / Reactive intermediates / Electrophilic substitution / Solvent effects / Carbanions

The effects of electrophiles and solvents on the stereochemistry of electrophilic substitution of a lithiocarbanion generated from (*S,E*)-1-phenylbut-2-en-1-yl diisopropylcarbamate were examined using various acids and carbon electrophiles. The

stereochemical outcomes were influenced by the relative ability of the electrophiles and solvents to coordinate to lithium.

## Introduction

We have recently shown that the configurational stability of chiral carbanions<sup>[1]</sup> is greatly affected by the choice of solvent and additive. This was demonstrated by taking advantage of the [2,3]-Wittig rearrangement of the 1,3-diphenyl-1-propenyloxy-2-propen-1-yl carbanion and its derivatives **1**, in which the stability of the intermediate was estimated on the basis of the extent of chirality transfer to the products **2** (Scheme 1).<sup>[2]</sup> It is noteworthy that reactions performed in tetrahydrofuran (THF), one of the most common solvents for carbanion reactions, resulted in complete racemization under all conditions; this is in sharp contrast to the results obtained in other ethereal and hydrocarbon solvents, where 67:33 to 93:7 enantiomeric ratios were observed. We also proposed that the dependence of the configurational stability of chiral carbanions on the solvent reflects the ratio of contact ion pair (CIP) and solvent separated ion pair (SIP) that is associated with their solvated structures.



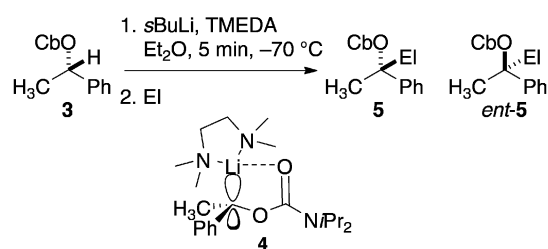
Scheme 1. Trapping of a chiral carbanion by [2,3]-Wittig rearrangement.

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To gain further insight into the generality of the solvent effects, we became interested in defining the stereochemical pathway (retention or inversion) of the intermolecular reaction of chiral organolithiums with an electrophile in various solvents. Regarding the stereochemistry of electrophilic substitution with relatively configurationally stable benzyl lithium compounds, considerable stereochemical divergence has been observed that apparently depends on the electrophile used (Scheme 2).<sup>[3]</sup> Whereas reactions of a lithio-derivative of **3**, generated by *s*BuLi in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) with protic acids, aldehydes, ketones, and esters, occurred with retention to give **5**, reactions with alkyl, silyl, and stannyl halides occurred with inversion to give *ent*-**5**. To rationalize these results, the authors hypothesized that electrophiles that are pre-complexed with a lithium cation, such as carbonyl compounds, prefer attack from the same side as the lithium (retention), whereas electrophiles with less ability to coordinate and with low-lying LUMO, such as alkyl halides, preferentially attack from the opposite side, which has increased electron density because of the partially flattened nature of the carbanion **4**.



Scheme 2. Intermolecular reaction of chiral organolithiums with an electrophile.

Strohmman and co-workers also showed that the coordinating ability of a solvent to a lithium center plays a signifi-

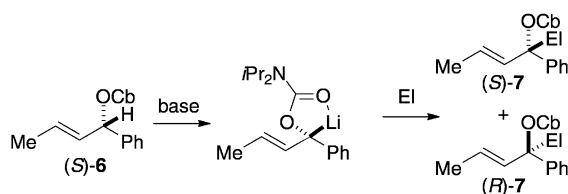
cant role in determining the stereochemical course of an electrophilic substitution reaction of a diastereomerically enriched benzyllithium compound.<sup>[4]</sup> Recently, Aggarwal and co-workers reported that lithiated carbamates underwent electrophilic substitution with boranes in the opposite sense of the stereochemical preferences; the reaction depended on the steric bulk of diamine additives such as TMEDA and sparteine, which were complexed to lithiated carbamates.<sup>[5]</sup>

On the basis of these studies, we decided to examine the stereochemical course of the reaction of (*S*)-**6** (Scheme 3) with a variety of electrophiles, and to study the influence of solvent upon it. In the reaction, an enantiopure carbanion can be generated under conditions in which it is free of a diamine ligand owing to its enhanced kinetic acidity, and the reaction with an electrophile can be conducted without introducing a possible diastereofacial bias. On the basis of our previous experience,<sup>[6]</sup> we felt that even if a double bond is introduced at the  $\alpha$ -position of the carbanion in **3**, which can cause more planarization, the enantiomeric purity would not be lost before trapping by an electrophile. Consequently, it would provide a better probe with which to inves-

tigate the stereochemical course of the reaction and the effects of solvent upon it.

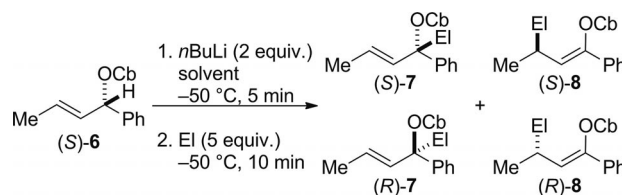
## Results

We first conducted the reaction of (*S*)-**6**, prepared from 1-phenyl-2-butenol by using Sharpless' kinetic resolution, with a carbon electrophile. When (*S*)-**6** was treated with *n*BuLi (2 equiv.) in THF at  $-50^{\circ}\text{C}$  for 5 min followed by addition of benzyl bromide (BnBr; 5 equiv.) and the reaction was stirred at the same temperature for 10 min, benzylated product **7a** was obtained in 72% yield with inversion of configuration (ret./inv. = 10:90) together with *anti*-S<sub>E'</sub>-type product **8** in 21% yield in a 30:70 ratio of (*S*)-**8** to (*R*)-**8**<sup>[7]</sup> (Table 1, entry 1). In the other four solvent systems (Table 1, entries 4, 7, 10, and 13), almost the same stereochemical outcomes were observed. Addition of 2 equiv. of TMEDA proved to have little effect on the stereochemical outcome of the reaction (Table 1, entries 2, 5, 8, 11, and 14). Although the reactions with ethyl cyanoformate also proceeded with marked preference for stereoinversion, the ratio of the retention product increased in solvents other than THF and *N*-methylmorpholine (NMM) in comparison with those for BnBr (Table 1, entries 9, 12, and 15), and the corresponding S<sub>E'</sub>-type product was not detected. The greater configurational stability of the lithiocarbanion of (*S*)-**6** than expected on the basis of results reported by Hoppe, and the intrinsically higher kinetic acidity of (*S*)-**6**,<sup>[8]</sup> makes the system shown in Scheme 3 an appropriate probe with which to examine the effects of electrophiles and



Scheme 3. Reaction of lithiocarbanion (*S*)-**6** with an electrophile.

Table 1. Reaction of lithiocarbanion (*S*)-**6** with a carbon electrophile (EI).



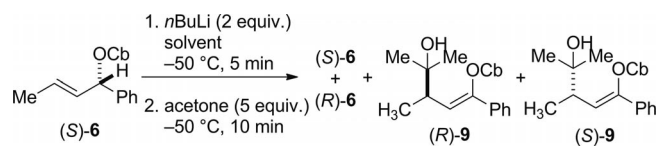
Entry	Solvent <sup>[a]</sup>	EI	TMEDA equiv.	( <i>S</i> )- and ( <i>R</i> )- <b>7</b> <sup>[b]</sup> Yield [%]	ret./inv.	( <i>S</i> )- and ( <i>R</i> )- <b>8</b> <sup>[b]</sup> Yield [%]	<i>S</i> / <i>R</i>
1	THF	BnBr	—	72	10:90	21	30:70
2	THF	BnBr	2	77	7:93	15	25:75
3	THF	NCCO <sub>2</sub> Et	—	72	3:97	0	—
4	NMM	BnBr	—	64	0:100	23	16:84
5	NMM	BnBr	2	59	0:100	32	6:94
6	NMM	NCCO <sub>2</sub> Et	—	57	0:100	0	—
7	Et <sub>2</sub> O	BnBr	—	56	1:99	31	9:91
8	Et <sub>2</sub> O	BnBr	2	59	1:99	30	7:93
9	Et <sub>2</sub> O	NCCO <sub>2</sub> Et	—	21	12:88	0	—
10	CPME	BnBr	—	45	4:96	45	8:92
11	CPME	BnBr	2	51	1:99	39	5:95
12	CPME	NCCO <sub>2</sub> Et	—	55	13:87	0	—
13	MTBE	BnBr	—	54	4:96	33	8:92
14	MTBE	BnBr	2	62	0:100	37	5:95
15	MTBE	NCCO <sub>2</sub> Et	—	76	15:85	0	—

[a] *N*-methylmorpholine (NMM), CPME (cyclopentyl methyl ether), MTBE (methyl *tert*-butyl ether). [b] **7a**: EI = Bn, **7b**: EI = CO<sub>2</sub>Et, **8**: EI = Bn.

solvents on the stereochemical course of the electrophilic substitution.

In the reaction with acetone, the organolithium showed distinctly different behavior toward the trapping agent, depending on the solvent used (Table 2). Whereas the reactions in THF and NMM afforded *syn*-S<sub>E'</sub>-type product **9**<sup>[9]</sup> exclusively, in other solvents, particularly diethyl ether, compound (*S*)-**6** protonated with retention of configuration, and was obtained in marked preference to (*R*)-**6**. Acetone was indicated as the proton source because no benzylated products were detected upon the addition of BnBr after treatment with acetone.

Table 2. Reaction of lithiocarbanion (*S*)-**6** with acetone.

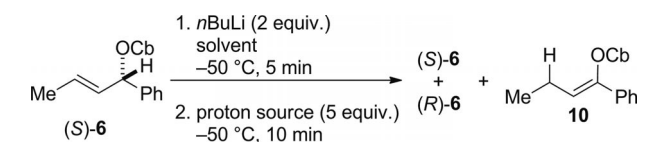


Entry	Solvent	( <i>S</i> )- and ( <i>R</i> )- <b>6</b> Yield [%]	( <i>R</i> )- and ( <i>S</i> )- <b>9</b> ret./inv.	( <i>R</i> )- and ( <i>S</i> )- <b>9</b> Yield [%]	<i>R/S</i>
1	THF	0	—	80	87:13
2	NMM	0	—	82	97:3
3	Et <sub>2</sub> O	74	96:4	21	89:11
4	CPME	58	95:5	36	71:29
6	MTBE	32	92:8	60	94:6

Because the results described above indicate that the use of 2 equiv. of *n*BuLi at  $-50\text{ }^{\circ}\text{C}$  for 5 min is sufficient to allow complete deprotonation<sup>[10]</sup> and that racemization arising from planarization prior to the addition of an electrophile occurs only to a negligible extent under the reaction conditions, we then examined the deprotonation/protonation reactions of (*S*)-**6** using two classes of protonating agent: oxygen acids (MeOH and CF<sub>3</sub>COOH) and carbon acids [diethyl malonate (*pK<sub>a</sub>* 13) and cyclopentadiene (*pK<sub>a</sub>* 16)]. The results are shown in Table 3. With prolongation of the reaction time prior to the addition of an electrophile, a noticeable increase in the extent of racemization was not observed any of the cases, except for the reactions in THF, in which a gradual loss of the enantiomeric purity occurred in time, and almost complete loss was observed after 60 min (Table 3, entries 1–4).

In contrast to the results obtained with carbon electrophiles, protonation with oxygen acids proceeded with essentially complete retention of configuration.<sup>[11]</sup> In solvents other than THF, slight increases in the ratio of inversion were observed by changing the electrophile from MeOH to CF<sub>3</sub>COOH, which has less effective coordination to the lithium cation (Table 3, entries 5–8 and 10–13). In the case of carbon acids, the two agents gave contrasting results. The reactions with diethyl malonate, which is capable of pre-coordinating to the lithium cation, in acyclic ether solvents, afforded **6** with almost complete retention of configuration (Table 3, entries 16–18). In contrast, the reaction with cyclopentadiene, which does not have a coordinating atom, led to a striking increase in the amount of stereoinversion product (*R*)-**6** (Table 3, entries 19–23).

Table 3. Reaction of lithiocarbanion (*S*)-**6** with a protonating agent.

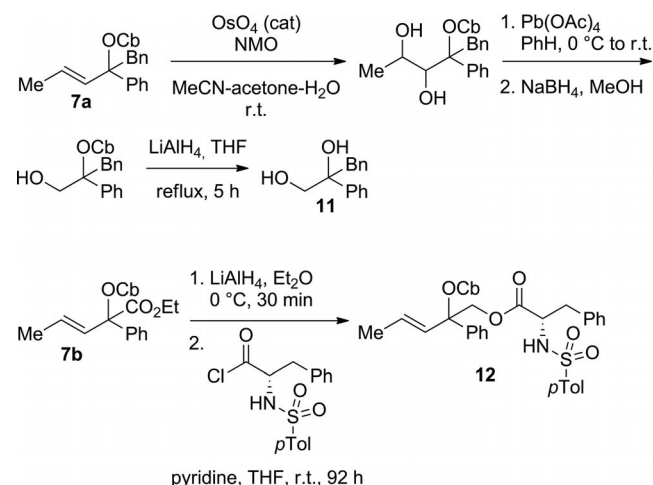


Entry	Solvent	Proton source	Time [min]	( <i>S</i> )- and ( <i>R</i> )- <b>6</b> Yield [%]	( <i>S</i> )- and ( <i>R</i> )- <b>6</b> ret./inv.	<b>10</b> Yield [%]
1	THF	MeOH	5	43	86:14	39
2	THF	MeOH	15	47	75:25	39
3	THF	MeOH	30	45	60:40	35
4	THF	MeOH	60	38	52:48	25
5	NMM	MeOH	5 <sup>[a]</sup>	45	100:0	36
6	Et <sub>2</sub> O	MeOH	5 <sup>[a]</sup>	81	99:1	12
7	CPME	MeOH	5 <sup>[a]</sup>	77	100:0	15
8	MTBE	MeOH	5 <sup>[a]</sup>	48	99:1	40
9	THF	CF <sub>3</sub> COOH	5	51	90:10	36
10	NMM	CF <sub>3</sub> COOH	5	57	85:15	28
11	Et <sub>2</sub> O	CF <sub>3</sub> COOH	5	86	94:6	—
12	CPME	CF <sub>3</sub> COOH	5	93	96:4	—
13	MTBE	CF <sub>3</sub> COOH	5	90	94:6	3
14	THF	diethyl malonate	5	0	—	75
15	NMM	diethyl malonate	5	0	—	75
16	Et <sub>2</sub> O	diethyl malonate	5	65	98:2	26
17	CPME	diethyl malonate	5	42	97:3	34
18	MTBE	diethyl malonate	5	47	98:2	33
19	THF	cyclopentadiene	5	54	38:62	41
20	NMM	cyclopentadiene	5	47	65:35	32
21	Et <sub>2</sub> O	cyclopentadiene	5	53	71:29	28
22	CPME	cyclopentadiene	5	37	53:47	32
23	MTBE	cyclopentadiene	5	41	46:54	36

[a] Upon addition of MeOH after 15 min, the ratio remained unchanged.

## Determination of Absolute Configuration

Benzylated compound **7a** was converted into known diol **11**<sup>[12]</sup> through a three-step sequence involving dihydroxylation, oxidative cleavage of the diol by Pb(OAc)<sub>4</sub> followed by reductive workup, and removal of the carbamoyl group by treatment with LiAlH<sub>4</sub> (Scheme 4); the product showed



Scheme 4. Determination of absolute configurations of **7**.

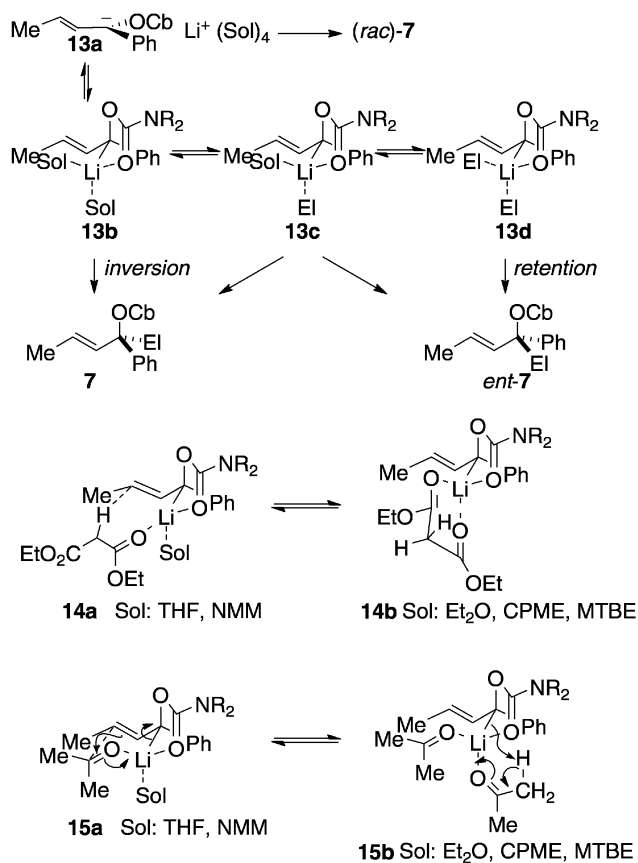
*S* absolute configuration. The absolute configuration of **7b** (El = CO<sub>2</sub>Et) was determined by X-ray crystallographic analysis after derivatization into **12**.

## Discussion

A basic premise applied throughout this study is that the organolithium derived from (*S*)-**6** is configurationally more stable than expected, in other words, little or no racemization occurs under the reaction conditions (−50 °C, 5 min). This premise is based on results obtained from the reactions with carbon electrophiles (Table 1, entries 3, 4, 7, 10, and 13). Therefore, enantiomeric ratios obtained in the protonation reactions should directly show that the electrophilic substitution in the organolithiums occurs with either retention or inversion of configuration.

As a general trend, reactions with a proton source and a carbon electrophile occur with retention and inversion of configuration, respectively. This can be understood by invoking the precoordination of the proton sources to the lithium atom, as suggested by Hoppe.<sup>[3]</sup> Moreover, attack by carbon electrophiles can occur from the less-hindered and uncoordinated backside of the molecule, in which the electron density increases because of the partially flattened nature of the carbanion. To explain the change in enantiomeric ratio observed when the solvent and electrophile were changed, we propose a stereochemical pathway that involves equilibrium between a solvent-separated ion pair **13a** and contact ion pairs **13b–d** (Scheme 5).

The contact ion pairs differ in the number of solvent molecules coordinated to the lithium atom, which should be determined by the balance of the coordinating ability of a solvent and an electrophile to a lithium atom. Thus, the lithium atom in **13**, generated by deprotonation of (*S*)-**6**, has two vacant coordination sites that can be occupied by a solvent and/or an electrophile molecule in a ratio that depends on their coordinating ability. In a strong electron-donating solvent such as THF, however, a solvent separated ion pair **13a** might exist in some ratio even in the presence of a strong coordinating carbamoyloxy group. We previously reported that the order of the coordinating ability of solvents to a lithium atom in organolithium derivatives lacking a strong coordinating carbamoyloxy group is THF > NMM > Et<sub>2</sub>O > CPME > MTBE, and that THF can drive the conversion of a contact ion pair into a separated ion pair.<sup>[2]</sup> This result can explain the racemization through planarization that occurs during the course of the reaction in THF (Table 3, entries 2–4), which was not observed in other solvents. In the reaction with electrophiles that are able to precoordinate to the lithium atom, as either the ability of the substrate to coordinate increases or the ability of the solvent decreases, the equilibrium among **13a–d** shifts to favor **13d**. This speculative hypothesis can explain the following observations: (1) the reaction with ethyl cyanoformate, which is capable of precoordination to a lithium atom, gives an increased ratio of the retentive product relative to that of BnBr; (2) the relative amount of retention



Scheme 5. Stereochemical process of the reaction of (*S*)-**6** with an electrophile.

product formed is decreased by changing from MeOH to CF<sub>3</sub>COOH, and (3) the relative amount of inversion product formed increases markedly in the reaction with cyclopentadiene, which lacks the ability to coordinate to a lithium atom.

The results obtained with diethyl malonate and acetone, which are both able to coordinate strongly to lithium atoms, deserve brief comment because they show contrasting behavior depending on the solvent used. The fact that they function as electrophiles in an S<sub>E</sub>' fashion in THF and NMM can be understood by assuming that a solvent-dependent equilibrium exists between **14a** and **14b** and between **15a** and **15b**. Thus, in **14a** and **15a**, mainly in THF and NMM, the electrophiles coordinate to the lithium cation as a monodentate ligand due to the strong coordinating ability of the solvents. On the other hand, in the case of a less-coordinating solvent such as Et<sub>2</sub>O or a bulky ether solvent such as *i*PentOMe (CPME) or *t*BuOMe (MTBE), diethyl malonate can act as a bidentate ligand as shown in **14b** to give an S<sub>E</sub> protonation product in a retentive manner. In those solvents, acetone also becomes competitive with the solvents at the second vacant coordinating site owing to its strong coordinating ability and, as a consequence, can serve as a proton source as well as a carbon electrophile, as shown in **15b**.



## Conclusions

We have demonstrated that a lithiocarbanion generated by deprotonation between phenyl and alkenyl groups has a configurational stability that is sufficiently strong to be trapped without racemization by a proton source or a carbon electrophile at  $-50\text{ }^{\circ}\text{C}$  with the aid of a carbamoyloxy group and that the stereochemical outcomes are affected by changing the electrophile and solvent. The result can be understood in terms of the existence of an equilibrium involving a solvent-separated ion pair and three different kinds of contact ion pairs in which the ligand coordinated to the lithium atom differs.

## Experimental Section

**General Procedure for Electrophilic Substitution. Reaction of (S)-6 with BnBr in N-Methylmorpholine:** To a cooled ( $-50\text{ }^{\circ}\text{C}$ ) solution of (S)-6 (99:1 *er*, 50.7 mg, 0.184 mmol) in N-methylmorpholine (1.84 mL), was added a solution of *n*BuLi (2.32 M in hexane, 159  $\mu\text{L}$ , 0.368 mmol). The reaction mixture was stirred at the same temperature for 5 min, then a solution of benzyl bromide in N-methylmorpholine (2.0 M, 460  $\mu\text{L}$ , 0.920 mmol) was added dropwise. After stirring for 10 min, the reaction mixture was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (2 mL). The resulting mixture was extracted with  $\text{Et}_2\text{O}$  ( $2 \times 5\text{ mL}$ ), and the combined organic phases were washed with saturated brine (3 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel 10 g; hexane/AcOEt = 9:1) to give a mixture of 7 and 8 in a ratio of 1:0.36 (59.1 mg, 87%).

**Supporting Information** (see footnote on the first page of this article): Experimental procedures, spectroscopic data, and copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all new compounds.

## Acknowledgments

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- [7] The absolute configuration of 8 was determined by conversion into a known compound (see the Supporting Information for details).
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- [10] Addition of *n*BuLi to a solution of (S)-6a and BnBr (5 equiv.) at  $-50\text{ }^{\circ}\text{C}$  resulted in complete recovery of (S)-6a, suggesting that the rate of reaction of *n*BuLi with BnBr is much faster than that of deprotonation of (S)-6a under the conditions. Consequently, the possibility that deprotonation still occurs after addition of BnBr can be ruled out by the fact that (S)-6a is not recovered from the reaction.
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