Steric Protection of the Selenium Atom of the Episelenonium Ion Intermediate To Prevent both the Racemization of the Chiral Carbon and the Selenophilic Attack of Carbon Nucleophiles

Akio Toshimitsu,* Katsuhiro Nakano, Takao Mukai, and Kohei Tamao

Institute for Chemical Research, Kyoto University Uji, Kyoto 611, Japan

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Organic reactions *via* the three-membered cyclic episelenonium ion intermediate have been widely used in organic syntheses.[1] Still, two basic drawbacks of the episelenonium ion intermediate remain to be solved. Thus, in the episelenonium ion intermediate bearing a phenyl group on the selenium atom, (1) a chiral carbon present in the three-membered ring racemizes quite readily during reactions,[2] and (2) carbon nucleophiles such as ketene silyl acetals attack the selenium atom selectively rather than the carbon atom to give no carbon−carbon bond formation products.[3] We describe herein that these drawbacks are both overcome by the steric protection of the selenium atom by the 2,4,6-tri-*tert*-butylphenyl (TTBP) group.

Our strategy is based on our observation that the rate of racemization of the chiral carbon in the episelenonium ion intermediate is highly dependent on the concentration of the substrates in the Ritter-type reaction. Thus, in the acid-induced reaction in acetonitrile[4] of the chiral alcohol **1b**[5] bearing the *o*-(trifluoromethyl)phenylseleno group on the adjacent carbon atom (Scheme 1), the enantiomeric excesses[6] of the product amide **3b** are better in the reactions at lower concentrations, as shown in Table 1. The data in Table 1 also show that the reverse addition,[7] namely, addition of the alcohol **1b** to a solution of acid in acetonitrile, affords the amide **3b** of better enantiomeric excesses than does the normal addition, that is, addition of a solution of acid to a solution of **1b** in acetonitrile. It should be noted that while in the normal addition procedure episelenonium ion intermediates **2** are formed in the presence of unreacted starting material **1b**, in the reverse addition all starting materials are converted into the episelenonium ions as added, which must react with acetonitrile to form the amides. These results reveal that the racemization does not occur during the formation of the episelenonium ion intermediate *via* the bimolecular reaction of the arylseleno-substituted alcohol and the acid and during its reaction with nitrile but would be induced by selenophilic attack on the selenium atom of the episelenonium ion intermediate by the excess arylseleno-substituted alcohol.[8] This hypothesis prompted us to prove that the racemization is suppressed by the steric protection of the selenium atom from selenophilic attack.

Scheme 1

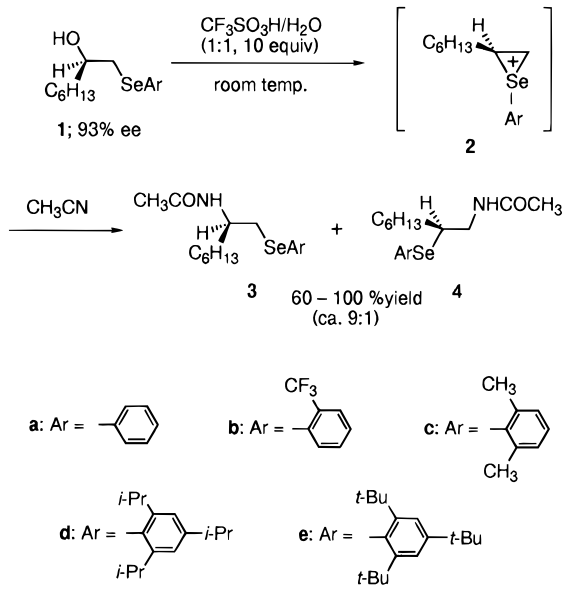

Table 1. Effect of the Concentrations of the Alcohol **1b** on the Stereospecificity for the Formation of **3b** *via* **2b**[a]

	stereospecificity, %[b]	
conc, mol/L	normal addn[c]	reverse addn[d]
0.1	9[e]	41
0.004	45	91
0.001	75	98

[a] Carried out using **1b** (0.1 mmol) and a mixture of CF_3SO_3H and H_2O (1 mmol, 1:1 by molar ratio) in acetonitrile at ambient temperature. [b] Defined as follows: stereospecificity % = ((% ee of **3**) × 100)/(% ee of **1**). [c] The solution of the acid was added to the solution of **1b**. [d] The solution of **1b** was added to the solution of the acid. [e] A stoichiometric amount (0.1 mmol) of CF_3SO_3H and H_2O was used.

Indeed, among several arylseleno groups examined, the alcohol bearing 2,4,6-tri-*tert*-butylphenylseleno (TTBPSe) group[9,10] **1e** has been found to afford the amide **3e**[6] without loss of optical purity; 2,6-xylyl (**1c**) and 2,4,6-triisopropylphenyl (**1d**) groups (28% and 33% stereospecificity)[11] were far less effective than the TTBP group. Worthy of note is that the TTBP group allows the reaction to proceed with complete stereospecificity even at higher concentration (0.1 mol/L) favorable for racemization. This result clearly shows that the bulky TTBPSe group prevents completely the racemization of the chiral carbon in the episelenonium ion intermediate, thus providing strong evidence for our hypothesis.

In addition to prevention of the racemization, the steric protection by the TTBP group of the selenium atom has been

(1) For recent examples, see (a) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1726. (b) Fujita, K.; Murata, K.; Iwaoka, M.; Tomoda, S. *J. Chem. Soc., Chem. Commun.* **1995**, 1641. (c) Déziel, R.; Malenfant, E. *J. Org. Chem.* **1995**, *60*, 4660. (d) Lipshutz, B. H.; Gross, T. *J. Org. Chem.* **1995**, *60*, 3572. (e) Fukuzawa, S.; Kasugahara, Y.; Uemura, S. *Tetrahedron Lett.* **1994**, *35*, 9403. (f) Déziel, R.; Goulet, S.; Grenier, L.; Bordeleau, J.; Bernier, J. *J. Org. Chem.* **1993**, *58*, 3619. (g) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L.; Santi, C. *J. Chem. Soc., Chem. Commun.* **1993**, 637. (h) Kang, S. H.; Lee, S. B. *Tetrahedron Lett.* **1993**, *34*, 1955. (i) Mihelich, E. D.; Hite, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7318. (j) Lipshutz, B. H.; Barton, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 1084. (k) Mihelich, E. D. *J. Am. Chem. Soc.* **1990**, *112*, 8995 and references cited therein.

(2) Toshimitsu, A.; Ito, M.; Uemura, S. *J. Chem. Soc., Chem. Commun.*, **1989**, 530. For the epimerization of the chiral ring carbon in a diastereomeric episelenonium ion intermediate, see ref 1k.

(3) Alexander, R. P.; Paterson, I. *Tetrahedron Lett.* **1983**, *24*, 5911. Successful examples of the carbon−carbon bond formation *via* the episelenonium ion intermediate have been limited to certain intramolecular reactions using olefins as a carbon nucleophile: (a) Toshimitsu, A.; Kusumoto, M.; Tanimoto, S. *Bull. Inst. Chem. Res., Kyoto Univ.* **1992**, *70*, 270. (b) Ley, S. V.; Lygo, B.; Morins, H.; Morton, J. A. *J. Chem. Soc., Chem. Commun.* **1982**, 1251. (c) Toshimitsu, A.; Uemura, S.; Okano, M. *J. Chem. Soc., Chem. Commun.* **1982**, 87. (d) Kametani, T.; Kurobe, H.; Nemoto, H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1085, and references cited therein.

(4) Toshimitsu, A.; Hayashi, G.; Terao, K.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 343.

(5) The chiral alcohols were prepared by the ring opening of chiral oxiranes by sodium areneselenolates, generated by the reaction of diaryl diselenide with $NaBH_4$.

(6) The enantiomeric excesses of **3a**−**e** were determined by HPLC analyses using chiral columns (Chiralcel OD (Daicel) for **3a**, **3b**, and **3e** and Chiralpak AD (Daicel) for **3c** and **3d**).

(7) Total yields and isomer ratios were not affected by the mode of the addition.

(8) The precise mechanism of this reaction has not yet been clarified.

(9) Rundel, W. *Chem. Ber.* **1968**, *101*, 2956. du Mont, W. W.; Kubiniok, S.; Peters, K.; von Schnering,H.-G. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 780.

(10) Pearson, D. E.; Frazer, M. G.; Frazer, V. S.; Washburn, L. C. *Synthesis* **1976**, 621.

(11) These reactions were carried out at the concentration of 0.001 mol/L using the reverse addition.

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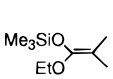
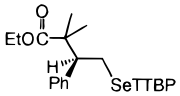
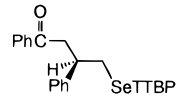
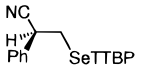
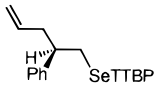
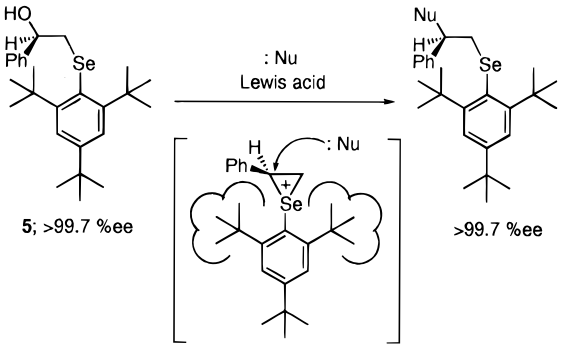
Table 2. Yields and Enantiomeric Excesses of the Products by the Reaction of the Chiral Alcohol **5** with Carbon Nucleophiles[a]

carbon nucleophile	Lewis acid	temp.	time	product[b]		yield[c]	enantiomeric excess[d]
	$TiCl_4$	− 78 °C → r.t.	2 h		**6**	95%	>99.7 %ee
	$BF_3{\bullet}OEt_2$	0 °C	8 h		**7**	84%	>99.7 %ee
Me_3SiCN	$SnCl_4$	r.t.	2 h		**8**	88%	>98 %ee[e]
	$TiCl_4$	− 78 °C → r.t.	2 h		**9**	85%	>99.7 %ee[f]

[a] Carried out using **5** (0.5 mmol), carbon nucleophile (2.0 mmol), and Lewis acid (1.0 mmol) in dichloromethane (5.0 mL). [b] SeTTBP denotes the 2,4,6-tri-*tert*-butylphenyl group. [c] Isolated yield by column chromatography. Regioisomers of **6**−**9** were not detected among the products. [d] Determined by HPLC analyses using chiral columns, Chiralcel OD (Daicel) for **6** and Chiralpak AD (Daicel) for **7**. It is confirmed that 99.7% is the lower limit of the enantiomeric excess in the case where the other enantiomer was not detected. [e] The cyanide **8** was reduced to the corresponding amine by aluminum hydride followed by the acylation to afford the acetamide. The enantiomeric excess of this amide was 98% as determined by Chiralcel OD (Daicel). A slight loss of the % ee might be due to the partial racemization during the reduction under basic conditions. [f] The olefin **9** was derived to the primary alcohol *via* hydroboration ($BH_3{\cdot}$THF/oxidation), Chiralpak AD (Daicel).

Scheme 2



found to prevent the selenophilic attack of the carbon nucleophiles, allowing selective carbon−carbon bond formation in a stereospecific manner, as shown in Scheme 2. Thus, chiral alcohol **5** bearing the TTBPSe group on the adjacent carbon atom reacts with carbon nucleophiles such as alkenyl silyl ethers, trimethylsilyl cyanide, and allyltrimethylsilane in the presence of Lewis acid to afford the carbon−carbon bond formation products **6**−**9** in satisfactory yields without loss of optical purity, as summarized in Table 2. No carbon−selenium bond formation product was formed in all cases, except only one case where allyltrimethylsilane afforded a trace amount (1.5% yield) of allyl 2,4,6-tri-*tert*-butylphenyl selenide as a byproduct.

Finally, we present an example to demonstrate that steric protection of the selenium atom by the TTBP group does not interfere with the removal of the selenium group from the chiral products thus obtained. When the ketone **7** bearing the TTBPSe group on the γ carbon atom was treated with tributyltin hydride in the presence of AIBN, the replacement of the selenium group by a hydrogen atom proceeded smoothly to afford the chiral ketone **10** in excellent yield without loss of the optical purity (Scheme 3).

Scheme 3

Steric protection by the TTBP group of selenium atom of the episelenonium ion intermediate has been shown to effectively prevent the attack of nucleophiles on the selenium atom. The result is to suppress the racemization of the chiral carbon and to afford the carbon−carbon bond formation products selectively.[12] We have now developed a new methodology for chiral transformation *via* the episelenonium ion intermediate especially in the synthetically important carbon−carbon bond forming reactions.

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Supporting Information Available: Typical experimental procedures and characterization of all new compounds (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering informations and Internet access intructions.

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(12) In addition to the steric protection, an electron-withdrawing effect of the substituent(s) seems to contribute to prevent the racemization. Thus, we have found that while the steric protection by the 2,6-bis(trifluoromethyl)phenyl group on the selenium group is insufficient to prevent the selenophilic attack by carbon nucleophiles, the Ritter-type reaction proceeds stereospecifically without loss of the optical purity. Further study is now in progress in our laboratory to clarify the origin of the electronic effect.