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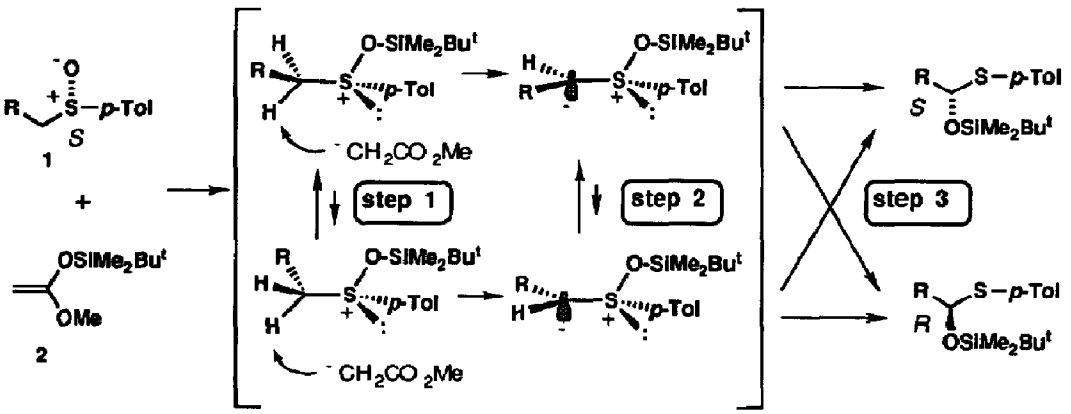
ENANTIOSELECTIVE PUMMERER-TYPE REARRANGEMENT BY REACTION OF *O*-SILYLATED KETENE ACETAL WITH ENANTIOPURE α-SUBSTITUTED SULFOXIDES

Yasuyuki Kita*, Norio Shibata, Seiji Fukui, and Shigekazu Fujita

Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565, Japan

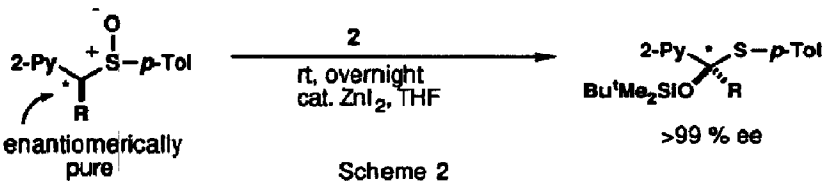
Abstract: Chiral non-racemic α-substituted sulfoxides were reacted with *O*-silylated ketene acetal in the presence of a catalytic amount of ZnI_2 in THF to give chiral non-racemic α-siloxysulfides in >99% ee. This is the highest enantioselectivity reported to date for the Pummerer reaction.

Although the asymmetric Pummerer rearrangement is of significant importance due to the stereogenicity transfer from optically active sulfoxides to the α-carbon of the sulfur, the extent of asymmetric induction in acyclic systems was quite low,[1] probably due to the formation of a sulfurane intermediate with the generated acetate anion. The enantioselectivity was considerably improved by the addition of 1,3-dicyclohexylcarbodiimide (DCC) as an effective acetate anion scavenger, but the chemical yield significantly decreased.[2] Recently, we reported the first highly enantioselective silicon-induced Pummerer-type rearrangement in acyclic chiral non-racemic sulfoxides (**1**) using *O*-methyl-*O*-*tert*-butyldimethylsilyl ketene acetal (**2**), which gave chiral non-racemic α-siloxysulfides under mild conditions in high yield.[3] The extent of asymmetric transformation, however, never exceeded 90% ee. To develop the optimal asymmetric transformation of **1**, it is quite important to determine in which step(s) racemization occurs (Scheme 1).



Scheme 1

Very recently, we have shown that the silicon-induced Pummerer rearrangement of **1** proceeded with highly diastereoselective deprotonation of the α-methylene proton in step 1 and *anti* elimination of the siloxy group in step 2 using the detailed deuterium-labeling experiment.[4] We describe here a highly selective Pummerer rearrangement of chiral non-racemic sulfoxides (Scheme 2).



Scheme 2

Since we learned that the deprotonation step of the α-methylene protons plays a significant role in the stereoselectivity, we selected the compounds (3, 4) which have two stereogenic centers: the α-carbon and sulfur atom. The starting chiral non-racemic 3, 4 were easily prepared in stereoselective form using the reported method.[5] Surprisingly, a high stereogenicity transfer was observed in the reaction of 3 and 4 with 2. Thus, treatment of (C_SS_S)-(-)-*anti*-3, 4 with 2 in the presence of a catalytic amount of ZnI_2 in THF[6] gave enantiomerically pure α-siloxysulfide (*R*-6, 7),[7, 8] and the reaction of (C_SS_R)-(-)-*syn*-3, 4 with 2 gave pure *R*-6, 7[7, 8] respectively (Table 1, runs 1-4). Interestingly, the stereochemistry of sulfoxide had no effect on the configuration of the product. The introduction of a stereogenic center α to a sulfoxide dramatically improved the enantioselectivity from 88% ee to >99% ee.

This high stereocontrol of the reaction is explained as follows: In both isomers ((-)-*anti*-3, 4, (-)-*syn*-3, 4), the deprotonation step is completely controlled and the deprotonated hydrogen has the *anti*-periplanar orientation with S-O bond. The deprotonation step of the α-methylene proton proceeds via an E2-type elimination to give the ylide intermediates A and B.[9] The siloxy anion then rearranged on the same face of the S-O group. This results suggest that the rotational step of ylide (step 2, i.e. between A and A', B and B') is not the racemization step (Fig. 1) and at least the racemization must have occurred in the deprotonation step[10] (step 1).

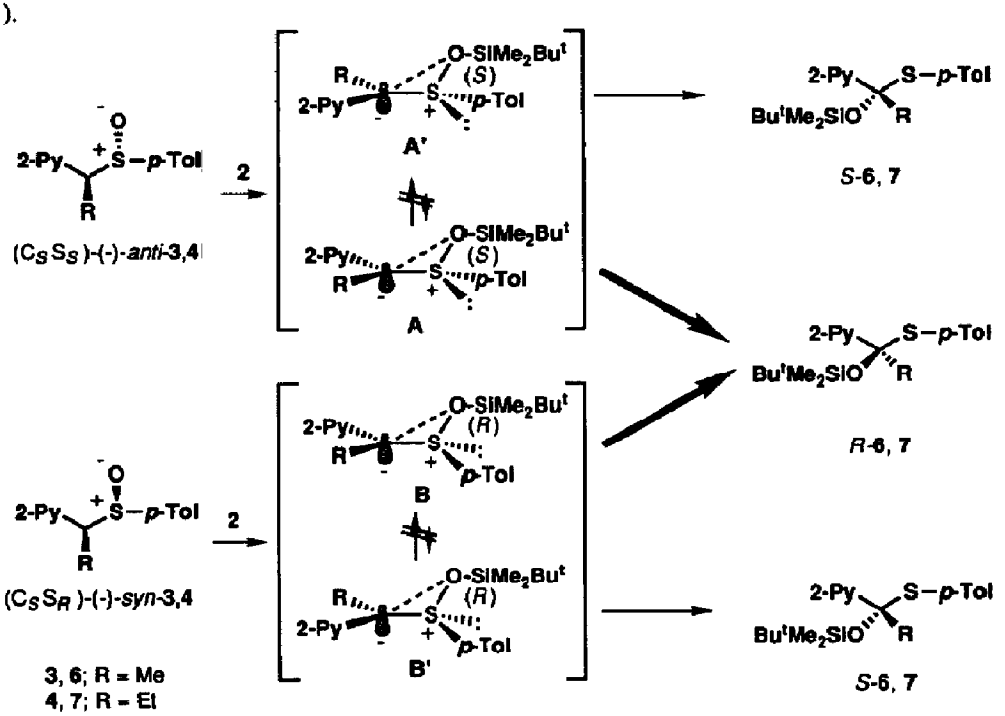
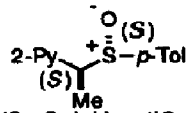
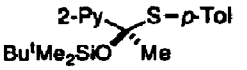
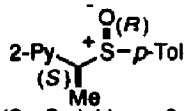
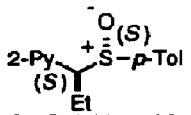
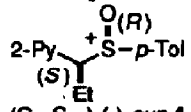
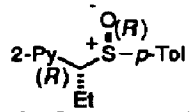
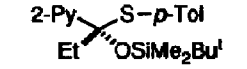
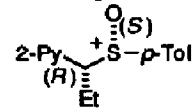
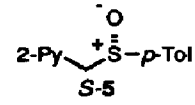
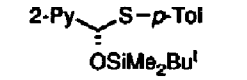
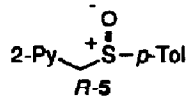
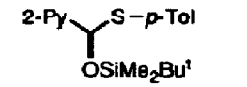


Fig. 1

Table 1 Asymmetric Pummerer-type Rearrangement by *O*-Silylated Ketene Acetal[a]

Run	Sulfoxide[b]	$[\alpha]_D$ ($CHCl_3$)	Product	Yield (%)	$[\alpha]_D$ (cyclohexane)	Ee (%)[c]
1	 (C*S* S*S*)-(-)-*anti*-**3**	-235	 *R*-**6**	70	-23.3 (c = 1.2)	>99
2	 (C*S* S*R*)-(-)-*syn*-**3**	-23.6	*R*-**6**	49	-22.6 (c = 0.9)	>99
3	 (C*S* S*S*)-(-)-*anti*-**4**	-276	 *R*-**7**	61	-54.1 (c = 0.6)	>99
4	 (C*S* S*R*)-(-)-*syn*-**4**	-138	*R*-**7**	72	-54.0 (c = 1.2)	>99
5	 (C*R* S*R*)-(+)-*anti*-**4**	+277	 *S*-**7**	57	+56.2 (c = 1.1)	>99
6	 (C*R* S*S*)-(+)-*syn*-**4**	+138	*S*-**7**	75	+54.1 (c = 1.6)	>99
7	 *S*-**5**	-251	 *S*-**8**	64 66[d]	-28.8 (acetone, c = 0.9) -30.2 (acetone, c = 0.5)	79 83
8	 *R*-**5**	+251	 *R*-**8**	61[d]	+29.6 (acetone, c = 1.0)	82

a. All reactions were carried out in THF.
b. Starting sulfoxides (3-5) were prepared by reported methods.
c. Ee values were determined by ^{1}H-NMR ($CDCl_3$ and C_6D_6) with Eu(hfc)$_3$.
d. Reactions were carried out in MeCN.

In conclusion, the deprotonation step (step 1) is the most important step for high enantiomeric purity and an optimal asymmetric Pummerer reaction of chiral non-racemic acyclic sulfoxides was accomplished to control the step 1.

References and Notes

1. Pummerer, R. *Chem. Ber.* **1909**, *42*, 2282; Pummerer, R. *Ibid.* **1910**, *43*, 1401. Reviews, see: a) Oae, S.; Numata, T. "The Pummerer Type of Reactions," in "*Isotopes in Organic Chemistry*," ed. by Buncel, E.; Lee, C. C. Elsevier, New York, **1980**, Vol. 5. Chapter 2; b) Lucchi, O. D.; Miotti, U.; Modena, G. *Organic Reactions*, **1990**, *40*, 157.

2. Acyclic Sulfoxides: a) Numata, T.; Oae, S. *Tetrahedron Lett.* **1977**, 1337; b) Numata, T.; Itoh, O.; Oae, S. *Chem. Lett.* **1977**, 909; c) Mikolajczyk, M.; Zatorski, A.; Grzejszczak, S.; Costisella, B.; Midura, W. *J. Org. Chem.* **1978**, *43*, 2518; d) Numata, T.; Itoh, O.; Oae, S. *Tetrahedron Lett.* **1979**, 1869; e) Numata, T.; Itoh, O.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 257. Cyclic sulfoxides: f) McCormick, J. E.; McElhinney, R. S. *Chem. Commun.* **1969**, 171; g) Glue, S.; Kay, I. T.; Kipps, M. R. *ibid.* **1970**, 1158. Cyclization: h) Stridsberg, B.; Allenmark, S. *Acta Chem. Scand.* **1974**, *B28*, 591; i) Idem *ibid.* **1976**, *B30*, 219; j) Wolfe, S.; Kazmaier, P. M.; Auski, H. *Can. J. Chem.* **1979**, *57*, 2404; k) Kaneko, T.; Okamoto, Y.; Hatada, K. *J. Chem. Soc. Chem. Commun.* **1987**, 1511.

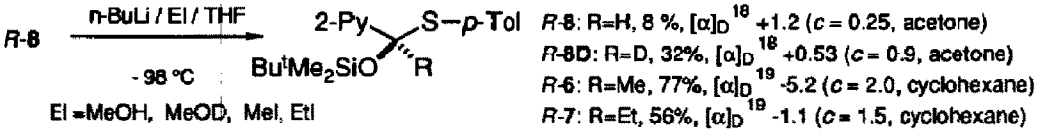
3. Kita, Y.; Shibata, N.; Yoshida, N. *Tetrahedron Lett.* **1993**, *34*, 4063.

4. Kita, Y.; Shibata, N.; Yoshida, N. ; Fukui, S.; Fujimori, C. *Tetrahedron Lett.* **1994**, *35*, 2569.

5. Furukawa, N.; Hosono, E.; Fujihara, H.; Ogawa, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 461.

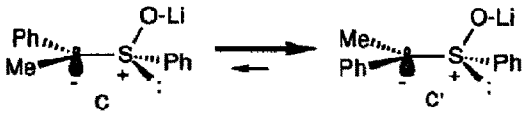
6. The reaction in MeCN gave slightly lower selectivities of **6**, **7**.

7. The configuration of the produced quaternary carbon was determined from the following chemical procedures. The protonation of the α-lithiocarbanion of *R*-**8** with MeOH and MeOD to *R*-**8** and *R*-**8D** suggested that the electrophilic substitution proceeds with retention of configuration.[8] The lithiation of *R*-**8** and subsequent alkylation then gave *R*-**6**, **7** with retention of configuration.



8. Alkylation of the heteroatom substituted organolithium compounds, Aggarwall, V. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 175; Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1422.

9. In the case of the α-lithiocarbanion of *syn*- and *anti*-phenethyl phenylsulfoxides, the larger substitutes in conformation C sterically avoid unfavorable interactions and are rapidly rotated into the more stable conformer C' and the phenyl rings are oriented trans to one another.; Marsch, M.; Massa, W.; Harms, K.; Baum, G.; Boche, G. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1011; Boche, G. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 277.



In our silicon-induced Pummerer reaction, if the rotation step of ylide (step 2) is the racemization step, the produced **6**, **7** should have the opposite sign of the [α]$_D$ value from (-)-*anti*-**3**, **4** and (-)-*syn*-**3**, **4**.

10. As expected, the extent of asymmetric induction of the chiral sulfoxides (*S*-and *R*-**5**), which have two α-protons never exceeded 83 % (Table 1, runs 7 and 8). The absolute stereochemistry of **8** was tentatively assigned from references 3 and 4.

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