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# THE FIRST HIGHLY ASYMMETRIC PUMMERER-TYPE REACTION IN CHIRAL ACYCLIC SULFOXIDES: CHEMISTRY OF *O*-SILYLATED KETENE ACETALS

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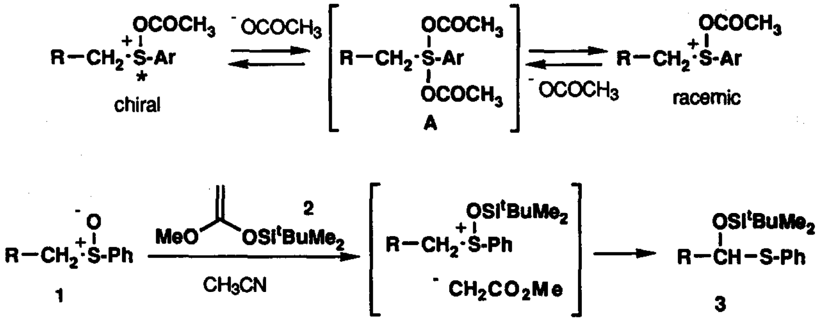
*Key words:* Pummerer reaction, *O*-silylated ketene acetals, chiral sulfoxides, acyclic, asymmetric

*Abstract:* The chiral sulfoxides (4) were reacted with *O*-silylated ketene acetal (2) in acetonitrile to give the corresponding α-siloxysulfides (5) in high degree of stereochemistry and high yields.

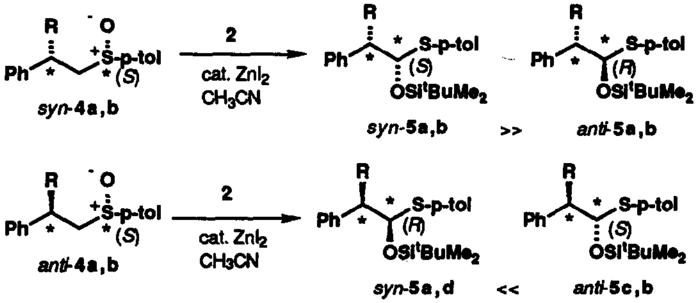
It is an attractive area of study to perform the asymmetric induction with self-immolative[1a)] or self-reproduction[1b)] on simple compounds, which have only one chiral center, without racemization. The stereoselective Pummerer reaction[2)] of optically active sulfoxides is one of the self-immolative-type asymmetric inductions and is quite of interest because it would provide a means for the synthesis of chiral α-substituted sulfides, and has attracted considerable attention from both synthetic and mechanistic points of view.[3)] In fact, the chirality transfer from sulfur of chiral sulfoxides to α-carbon of sulfur has been reported in recent investigations.[4, 5)] The yields of enantiomeric excess, however, were quite low in acyclic sulfoxides.[4b-e,g,h)] This was probably due to the formation of the sulfurane intermediate (A) by the reaction of the generated acetate anion. Several years ago, we reported a novel silicon induced Pummerer-type reaction of sulfoxides (1) using *O*-methyl-*O*-*tert*-butyldimethylsilyl ketene acetal (2), which gave α-siloxy sulfides (3) under mild conditions[6)] (Scheme 1) and applied this method to a novel and effective intramolecular Pummerer-type cyclization reaction of ω-amidosulfoxides to α-thio-*N*-heterocycles involving 4- to 7-membered α-thiolactams.[7)] We now report the first highly asymmetric induction of chiral acyclic sulfoxides (4) leading to chiral α-siloxysulfides (5) in high yields using our silicon induced Pummerer-type reaction.



Scheme 1

*Syn* and *anti*-β-substituted (*S*s)-sulfoxides (**4a**,[8] **b** ) were reacted with **2** in the presence of a catalytic amount of zinc iodide in acetonitrile to give the corresponding α-siloxysulfides (**5a**, **b**). The results are summarized in Table 1 and the ratio of *syn*/*anti* was determined by $^1$H NMR.[9] All reactions proceeded under mild conditions with high chemical yields, and a remarkably high degree of stereospecificity. Surprisingly, an extremely high retention occurred in both β-siloxy and β-alkyl substituted sulfoxides.[10]

**Table 1. Asymmetric Silicon-Induced Pummerer-Type Reactions**

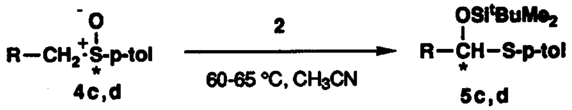


| Sulfoxide [a] | R | Condition | Yield (%) | *Syn* : *Anti* | $[\alpha]_D^{24}$ (*c*, $CHCl_3$) | Nomal Pummerer *syn* : *anti* |
|---|---|---|---|---|---|---|
| *syn*-**4a** [b] | $OSi^tBuMe_2$ | 0°C, 1h - r.t. 1h | 75 | 88 : 12 | -17.5 (1.16) (pure *syn*) | 80 : 20 [f] |
| *anti*-**4a** [b] | $OSi^tBuMe_2$ | 0°C, 4h - r.t. 3h | 82 | 4 : 96 | -7.4 (1.75) (pure *anti*) | 80 : 20 [f] |
| *syn*-**4b** [c] | Me | r.t. overnight | 45 [d] | 90 : 10 | -66.9 (0.639) | 57 : 43 (or 43 : 57) [g] |
| *anti*-**4b** [c] | Me | r.t. overnight | 56 [e] | 24 : 76 | +95.0 (1.75) | 57 : 43 (or 43 : 57) [g] |

[a] *syn*-**4a**: $[\alpha]_D^{23}$= -129 (*c*=1.08, $CHCl_3$); *anti*-**4a**: $[\alpha]_D^{23}$= -176 (*c*=1.06, $CHCl_3$); *syn*-**4b** (92% d.e.): $[\alpha]_D^{24}$= -64.8 (*c*=1.24, $CHCl_3$); *anti*-**4b** (93% d.e.): $[\alpha]_D^{24}$= -335 (*c*=0.74, $CHCl_3$). [b] **4a** was prepared according to the reported procedure[8]. [c] The configuration of the phenethylcarbon of **4b**, which was prepared from α-lithio (*S*)-methyl *p*-tolyl sulfoxide and phenethyl bromide and HPLC separation, was determined from the conversion to the known aldehyde [12] using the reported method [13]. [d] 53% of unreacted *syn*-**4b** was recovered. [e] 38% of unreacted *anti*-**4b** was recovered. [f] Normal Pummerer reaction of *syn* and *anti*-**4a** with hot acetic anhydride gave the same ratio of diastereomeric acetoxy sulfide. The predominant formation of *syn*-isomer is predicted by Felkin-Anh model of the well-documented thionium ion intermediate. The details will be published in the full paper. [g] S-Ph sulfoxide was used. See reference 9a.

In order to ascertain the effect of the sulfoxide itself, we next examined the reaction of sulfoxides (**4c**, **d**) having one chiral center on sulfur atom with **2**. Known chiral sulfoxides (**4c**, **d** ) [4g] were reacted with **2** in the absence of a catalyst in acetonitrile to give the corresponding chiral α-siloxysulfides (**5c**, **d**). In both cases, the optical purity and chemical yield of the Pummerer adducts were greater than the Oae's approach[4e, g] (Table 2).

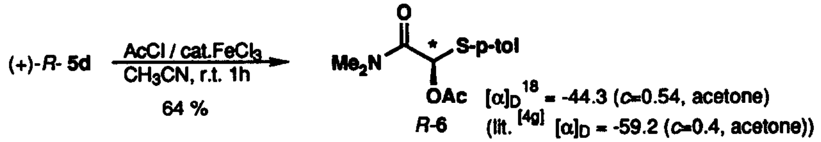
**Table 2. Asymmetric Silicon-Induced Pummerer-Type Reactions**



| Sulfoxide [a] | R | Condition | % E.e. [b] (% Yield [c]) | $[\alpha]_D^{18}$ (c, acetone) | Configuration | Oae's approach [d] % E.e. (% yield) |
|---|---|---|---|---|---|---|
| *S*-4c | $CO_2Et$ | 4h | 87 (75) | +35.8 (0.46) | *S* [f] | |
| *R*-4c | $CO_2Et$ | 4h | 86 [e] (72) | -34.8 (0.67) | *R* [f] | 70 (10) |
| *S*-4d | $CONMe_2$ | 12h | 88 (65) | -28.9 (1.4) | *S* | |
| *R*-4d | $CONMe_2$ | 12h | 88 [e] (69) | +28.8 (1.23) | *R* | 65 (35) |

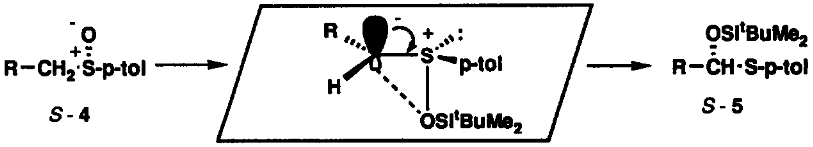
[a] *S*-4c: $[\alpha]_D^{20} = -189$ (c=1.80, acetone); *R*-4c: $[\alpha]_D^{20} = +195$ (c= 0.97, acetone); *S*-4d: $[\alpha]_D^{19} = -187$ (c=1.24, acetone); *R*-4d: $[\alpha]_D^{18} = +192$ (c= 0.83, acetone). [b] Determined by $^1$H-NMR with $Eu(hfc)_3$. [c] Isolated yield. [d] See reference 4e, g. [e] E.e. value was calculated on the basis of the other e.e. value determined with the shift reagent. [f] The stereochemistry of 5c was tentatively assigned from the similarity of the shift patterns in $^1$H-NMR by addition of $Eu(hfc)_3$ to those of 5d.

The stereochemistry of the newly generated chiral center of **5d** was determined by the conversion to the known sulfide (*R*-**6**)$^{4g, 11)}$ (Scheme 2).



Scheme 2

While the detail of the mechanism remains unknown, the asymmetric induction of chiral sulfoxides is explained as follows: The initial silicon transfer from **2** to the sulfoxides (**4**) and subsequent abstruction of α-hydrogen by a generated ester enolate anion would give the intermediate (**B**), which then rearranges via 3-membered (sliding mode) cyclic route within the ylide molecules. Then a siloxy anion attacks at the same face of the starting sulfoxides (Fig. 1).



B

Fig. 1

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9. The relative stereochemistry of diastereomeric $\alpha$-siloxysulfides was determined by the Heathcock's method. According to the definition, the molecules exist predominantly in conformations having the two hydrogens *anti* and the aryl group causes an upfield shift of the $^1$H NMR resonance of the group gauche to it on the vicinal stereocenter. Therefore, the resonance of the *t*-butyl group of *anti*-isomers occurs at a substantially higher field than that of *syn*-isomers. For precedents, see: a) Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 5966; b) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *ibid.* **1984**, *49*, 4219; c) Heathcock, C. H.; Lampe, J. *ibid.* **1983**, *48*, 4330.
10. Contrary to these findings, normal Pummerer reaction of both *syn* and *anti*-**4a**, **b** with acetic (or trifluoracetic) anhydride gave the same ratio of diastereomeric acetoxy (or trifluoracetoxy) sulfides. See Table 1.
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