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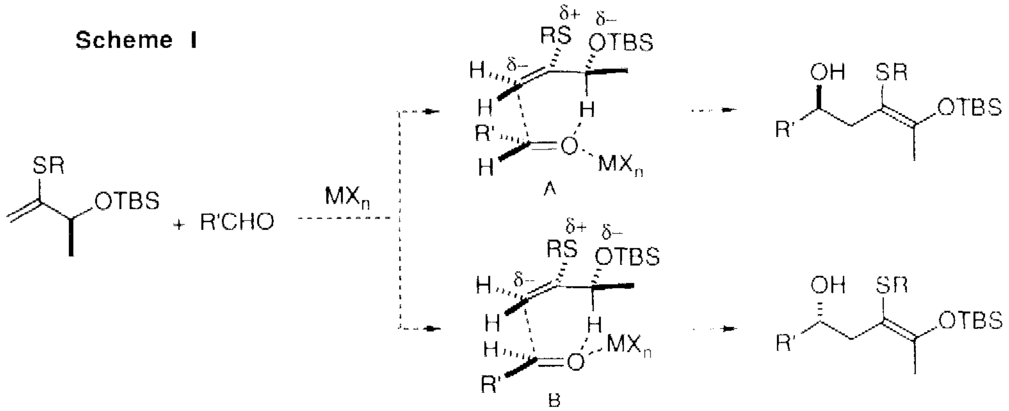
ENE REACTION OF 2-(ALKYLTHIO)ALLYL SILYL ETHER INVOLVING A CHIRALITY TRANSFER.

Keiji Tanino, Hisashi Shoda, Takashi Nakamura, and Isao Kuwajima*
Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

Abstract: A highly enantio-selective ene reaction was developed on the bases of chirality transfer. Under the influence of Me_2AlCl, the reactions of various aldehydes with (*S*)-3-(*tert*-butyldimethylsiloxy)-2-(ethylthio)-1-butene which was easily prepared from (*S*)-ethyl lactate afforded the optically active adducts in high ee.

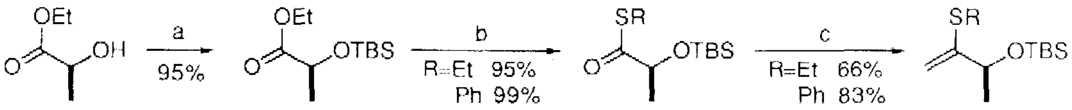
Preparation of enantiomerically pure substances via a chirality transfer[1] from readily available chiral substrates has been emerging as a useful tool in organic synthesis. In the previous paper,[2] we reported the ene reaction[3] of 2-(alkylthio)allyl silyl ethers which proceeds with various types of aldehydes accompanying with an efficient *threo* as well as Z geometry control. These stereoselectivities may be explained by assuming the transition state involving the dipole attractive interaction between SR and OTBS groups as shown in Scheme I.

Scheme I



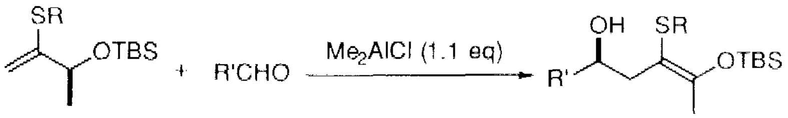
The fixed conformation of this transition state model[4] led us to examine the chirality transfer via ene reaction of optically active 2-(alkylthio)allyl silyl ethers. This paper describes a highly enantio-selective ene reaction giving optically active γ-hydroxy ketone derivatives. The optically pure enes (*S*)-**1a** and (*S*)-**1b** were easily prepared in three steps as shown in Scheme II. Thus, commercially available (*S*)-ethyl lactate was silylated and then converted to the thiol esters by the reaction with Me_2AlSR.[5] Treatment of the resulting thiol esters with Tebbe reagent[6] afforded the desired optically pure (*S*)-3-(*tert*-butyldimethylsiloxy)-2-(alkylthio)-1-butenes.[7] Under the influence of Me_2AlCl (1.1eq), the reactions of these enes with various aldehydes readily proceeded to afford the corresponding ene adducts in good yields. The enantiomeric excess of the product was determined by HPLC analysis after conversion to the (*R*)-MTPA ester of either β-hydroxy ester[8] or γ-hydroxy ketone.[9] The results were summarized in Table I.

Scheme II



a) TBSCl, imidazole b) Me_2AlSR c) Cp_2TiCl_2, Me_3Al

Table I



1a: R=Et
1b: R=Ph

entry	ene	R'	solvent	conditions		yield (%)	ee (%)
1	(*S*)-**1 a**	C_6H_{13}	toluene	-78°C	1h	82	86 (*R*)
2	"	"	hexane	-78°C	5h	78	94 (*R*)
3	"	Ph	CH_2Cl_2	-78°C	2h	96	96 (*S*)
4	"	"	toluene	-78°C	3h	91	96 (*S*)
5	"	*o*-$CH_3C_6H_4$	"	-78°C	19h	93	97 (*S*)
6	"	*o*-$CH_3OC_6H_4$	CH_2Cl_2	-78°C	7h	80	91 (*S*)
7	"	*o*-$TBSOC_6H_4$	"	-78°C	12h	91	99 (*S*)
8	"	2-furyl	toluene	-46°C	2h	76	86 (*S*)
9	"	PhCH=CH	"	-23°C	8h	70	90 (*S*)
10	(*S*)-**1 b**	Ph	CH_2Cl_2	-40°C	2h	98	80 (*S*)
11	"	"	toluene	-40°C	5h	95	86 (*S*)

Typical procedure: A mixture of (*S*)-**1 a** or (*S*)-**1 b** (0.50 mmol) and aldehyde (0.50 mmol) in 2 mL of solvent was treated with 1M Me_2AlCl solution in hexane (0.55 ml). After stirring for several hours, a mixture of triethylamine (0.25 mL) and water (0.50 mL) was added. Usual work up followed by column chromatographic purification gave the desired product.

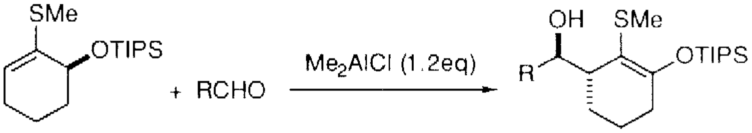
Several characteristic features of the reaction have been noted: (1) The ene with *S* configuration attacks the carbonyl group of an aldehyde from the *si*-face.[10] This selectivity would indicate that the transition state A in Scheme I is preferred to the transition state B which includes steric repulsion between OTBS group and Lewis acid. (2) Higher selectivity is observed in the reaction of ethylthio ether **1a** than that of phenylthio ether **1b**[11] (entries 3 and 10). (3) A role of the reaction solvent is also quite important[11]: Use of non-polar solvent such as hexane is preferable (entry 2). On such a case where a precipitate of the Lewis acid-aldehyde complex is formed, toluene is a solvent of second choice.

Effects of *o*-substituents on ee have also been examined by using *o*-substituted benzaldehydes. *o*-Tolualdehyde gave the ene adduct with comparatively high ee, but the reaction of 2-furaldehyde resulted in decrease of ee. Further, ee was slightly decreased in the reaction of *o*-anisaldehyde, whereas use of *o*-TBSO substituted benzaldehyde gave the almost enantiomerically pure ene adduct, a useful precursor for optically active anthracyclines.[12] (entries 5, 6 and 7). Coordination of more basic methoxy oxygen to Lewis acid may be responsible for decrease of ee.[13]

Though crotonaldehyde underwent a hetero Diels-Alder reaction predominantly,[14] cinnamaldehyde afforded the ene adduct in good yield (entry 9).

Use of conformationally rigid ene such as cyclic one effected the transfer of chirality more efficiently. The requisite 6-membered allylic ether (*S*)-**1c** was prepared[15] from (*S*)-2-bromo-2-cyclohexenol which is obtained by enantioselective reduction of 2-bromocyclohexenone.[16] In the reactions with aldehydes (*S*)-**1c** induced almost complete chirality transfer (from 83% ee to 83% ee). In the reaction with aliphatic aldehyde, *threo* and *erythro* adducts were formed in 85:15 ratio. These could be easily separated by column chromatography and each of them has been identified as (*R*)- and (*S*)-alcohol of 83% ee.[17] The reaction with aromatic aldehyde exclusively afforded *threo* alcohol.

Table II



(*S*)-**1c**
83% ee

R	solvent	conditions	yield (%)	ratio *threo:erythro*	ee (%)
C_6H_{13}	hexane	-23°C 5h	94	85:15	83 *
Ph	toluene	-23°C 2h	94	>99:1	83 (*S*)
$CH_3CH{=}CH$	toluene	-23°C 5h ~ 0°C 17h	82	97: 3	82 (*S*)

* Each of *threo* and *erythro* isomers has (*R*)- and (*S*)- configuration respectively.

Consequently, the present method is the first practically useful example of ene reaction with chirality transfer. The applicability to a wide variety of aldehydes and the utility of the products may make it one of the most powerful method for optically active γ-hydroxy carbonyl compounds. We are currently investigating on application to the enantioselective synthesis of biologically active natural products.

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References

(1) (a) Hill, R. K. Chirality Transfer via Sigmatropic Rearrangements. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, p 503. Chirality transfer via ene reaction: (b) Hill, R. K.; Rabinovitz, M. *J. Am. Chem. Soc.* **1964**, *86*, 965.

(2) Tanino, K.; Nakamura, T.; Kuwajima, I. *Tetrahedron Lett.* **1990**, *31*, 2165.

(3) Ene reactions. For reviews, see: (a) Hoffmann, H. M. R.; *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (b) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. (c) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. (d) Dubac, J.; Laporterie, A. *Chem. Rew.* **1987**, *87*, 319.

(4) The calculation study on the transition state of an ene reaction of propene with formaldehyde: Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 6947.

(5) (a) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 5829. (b) Hatch, R. P.; Weinreb, S. M. *J. Org. Chem.* **1977**, *42*, 3960.

(6) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270.

(7) The NMR analysis of the (*R*)-MTPA esters obtained from the enes through desilylation and esterification showed no evidence of racemization.

(8) Ozonolysis of the ene adducts followed by oxidation with mCPBA in absolute ethanol afforded the β-hydroxy esters.

(9) The ene adducts were desilylated by TBAF and were desulfurized by Raney-Ni to give the γ-hydroxy ketones. When the ene adduct of cinnamaldehyde was treated as above, 7-phenyl-5-hydroxy-2-heptanone was obtained through hydrogenation of the double bond.

(10) The absolute configuration of the adducts were determined by the specific rotation of the corresponding β-hydroxy esters.[8]

(11) It is noteworthy that similar effects on diastereo-selectivity were observed in the *threo* selective ene reactions of (*E*)-2-(alkylthio)-2-butenyl silyl ether.[2]

(12) Adachi, A.; Tanino, K.; Kuwajima, I. to be published.

(13) It is reported that aluminum reagents form chelates with α- or β-alkoxy aldehydes: (a) Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556. (b) Mikami, K; Loh, T.-P.; Nakai, T. *Tetrahedron Asymmetry* **1990**, *1*, 13.

(14) Hetero Diels-Alder reactions of alkenyl sulfides with α,β-unsaturated carbonyl compounds: Boger, D. L.; Weinreb, S. M. In *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; Chapter 7, p 167.

(15) (*S*)-2-Bromo-2-cyclohexenol was protected by a silyl group, then the bromide was converted to the sulfide through a lithiation with *tert*-butyllithium followed by addition of dimethyldisulfide.

(16) Corey, E. J.; Chen, C.-P.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5547.

(17) The products were converted to the (*R*)-MTPA esters, and the enantiomeric excess were determined by HPLC analysis.

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