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Asymmetric Carbon-Carbon Bond Formations by the Reaction of "Chiral Episulfonium Ions" with Enol Silyl Ethers

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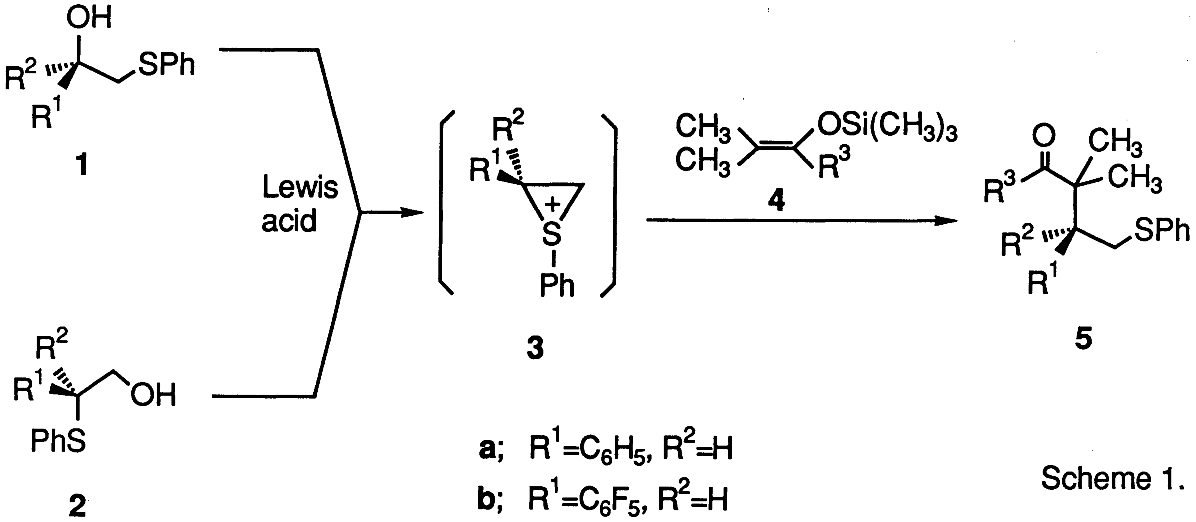
Carbonyl compounds having asymmetric carbon center at β position and phenylthio group on γ carbon were produced by the reaction of optically active 2-hydroxyalkyl phenyl sulfides with enol silyl ethers in the presence of Lewis acid through "chiral episulfonium ions".

In the previous paper we reported that the treatment of chiral alcohol having phenylthio group on β carbon atom with trifluoromethanesulfonic acid in acetonitrile resulted in the replacement of the hydroxyl group by acetamido group with retention of configuration through the anchimeric assistance of the phenylthio group; i.e., that the intermediate "chiral episulfonium ions" (episulfonium ion with asymmetric carbon atom in the ring) did not racemize during the reaction.[1)] In view of the importance of asymmetric carbon-carbon bond forming reactions, we tried the reaction of the "chiral episulfonium ions" with carbon nucleophiles. After several screenings we found that the combination of Lewis acid such as titanium tetrachloride or boron trifluoride with enol silyl ethers of carbonyl compounds in nonpolar solvents[2)] works well for the generation of "chiral episulfonium ions" from chiral 2-hydroxyalkyl phenyl sulfides and also for the subsequent carbon-carbon bond forming reactions without loss of optical purity. This reaction resulted in the substitution of hydroxyl group by carbon atom α to the carbonyl group with retention of configuration. This reaction provides another example of the usefulness of "chiral episulfonium ions" in asymmetric synthesis.

In a typical procedure, titanium tetrachloride (2 mmol) was added to a solution of (1*R*)-1-phenyl-2-(phenylthio)ethanol (**1 a**) (1 mmol) and 2,4-dimethyl-3-[(trimethylsilyl)oxy]-2-pentene (**4**;

R^3=i-Pr) (4 mmol) in dichloromethane (4 ml) under nitrogen atmosphere and the resulting mixture was stirred at ambient temperature for 2 h. After the usual workup, (5*S*)-2,4,4-trimethyl-5-phenyl-6-(phenylthio)-3-hexanone (**5 a**; R^3=i-Pr) was isolated in 92% yield by column chromatography (Scheme 1). Optical purity of this compound was confirmed to be 100% e.e. by liquid chromatographic analysis using chiral column (Daicel, Chiralcel OD), indicating that the "chiral episulfonium ion" (**3 a**) did not racemize during the reaction. Absolute configuration of **5 a** (R^3= i-Pr) was supposed to be *S* from the consideration of the reaction mechanism (double inversion; note that a priority sequence of the groups has changed by the replacement of hydroxyl group by carbon atom). The results are summarized in Table 1 using various 2-hydroxyalkyl phenyl sulfides and enol silyl ethers. Generally titanium tetrachloride gave satisfactory results. But, in a few cases, boron trifluoride gave bettter results with respect to chemical yields of **5** (for example, compare Run 10 to 9). The role of Lewis acids may be ascribed to the interaction with oxygen atom of hydroxyl group to generate the "chiral episulfonium ion", but possibility of the rate enhancement by the formation of reactive metal enolates from enol silyl ethers can not be excluded. Decrease in optical purity during the reaction (partial racemization of the "chiral episulfonium ion") was not observed except for three cases (Runs 5, 11, and 13). In two cases out of the three, we succeeded to suppress the partial racemization by carrying out the reactions at lower temperatures



a; R^1=C_6H_5, R^2=H
b; R^1=C_6F_5, R^2=H
c; R^1=n-C_5H_{11}, R^2=CH_3
d; R^1=n-$C_{10}H_{21}$, R^2=H

Scheme 1.

Table 1. Optical Purity and Chemical Yield of Carbonyl Compound (5)a)

Run	Substrate(% e.e.)		Lewis acid (equiv.)		Temp ℃	Time h	R^3	Product	Yieldb) %	(% e.e.)
1	**1a**	(100)	$TiCl_4$	(2)	r.t.	13	OEt	**5a**	89	(99)c)
2	**1a**	(100)	$TiCl_4$	(2)	r.t.	15	Ph	**5a**	68	(99)d)
3	**1a**	(100)	$TiCl_4$	(2)	r.t.	2	i-Pr	**5a**	92	(100)e)
4	**2a**	(100)	$TiCl_4$	(2)	r.t.	12	OEt	**5a**	89	(99)c)
5	**2a**	(100)	$TiCl_4$	(2)	r.t.	16	Ph	**5a**	70	(84)d)
6	**2a**	(100)	$TiCl_4$	(2)	0	19	Ph	**5a**	84	(99)d)
7	**2a**	(100)	$TiCl_4$	(2)	r.t.	2	i-Pr	**5a**	96	(100)e)
8	**1b**	(97)	$TiCl_4$	(2)	r.t.	3	i-Pr	**5b**	63	(97)f)
9	**2b**	(97)	$TiCl_4$	(2)	r.t.	6	i-Pr	**5b**	26	(96)f)
10	**2b**	(97)	$BF_3{\bullet}OEt_2$	(5)	r.t.	24	i-Pr	**5b**	41	(97)f)
11	**1c**	(86)	$TiCl_4$	(2)	r.t.	6	OEt	**5c**	71	(83)e)
12	**1d**g)	(86)	$BF_3{\bullet}OEt_2$	(5)	r.t.	42	OEt	**5d**h)	54	(85)i)
13	**1d**g)	(86)	$BF_3{\bullet}OEt_2$	(5)	reflux	19	OEt	**5d**h)	68	(81)i)

a) Carried out using 2-hydroxyalkyl phenyl sulfide (1 mmol) and enol silyl ether (4 mmol) in CH_2Cl_2 (4-5 ml). b) Isolated yield by column chromatography. c) Determined by the integral of the N M R spectrum of the methoxy(trifluoromethyl)phenylacetic acid ester of the reduced alcohol. d) Determined by liquid chromatography using chiral column (Daicel, Chiralpak AS). e) Determined by liquid chromatography using chiral column (Daicel, Chiralcel OD). f) Oxidized to the sulfone and analyzed by liquid chromatography using chiral column (Daicel, Chiralpak AD). g) CH_2Cl_2 (10 ml). h) Contains ca. 25% of its regioisomer, namely ethyl 2,2-dimethyl-4-(phenylthio)tetradecanoate, the enantiomeric excess of which was not determined. i) Reduced to the alcohol and analyzed by liquid chromatography using chiral column (Daicel, Chiralcel OD).

(Runs 6 and 12). In the liquid chromatographic analyses using chiral columns, we found that the derivation to the more polar molecules was advantageous for the separation of the peaks of enantioisomers. Thus, the reduction of **5d** (R^3=OEt) to the corresponding alcohol or the oxidation of **5b** (R^3=i-Pr) to the sulfone made the separation possible and this enabled us to estimate their enantiomeric excesses (Runs 8-10, 12,and 13).

The products of the present reaction are carbonyl compounds (**5**) having asymmetric carbon center at β position and phenylthio group on γ carbon. Further transformations are possible on the carbonyl group and also on the carbon atom bearing phenylthio group. As exemplified by **5c**, we succeeded to construct asymmetric quaternary carbon center with four carbon-carbon bonds which attracted much interest in recent years.3) Thus, various asymmetric compounds of current interest may be produced from **5** and our progress along this line will be reported in due course.

We thank Nippon Mining Co., Ltd. for donating (*R*)-styrene oxide, (*R*)-2,3,4,5,6-pentafluorostyrene oxide, (*R*)-1,2-epoxydodecane, and (*R*)-2-methyl-1,2-epoxyheptane.

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