

A NOVEL AND USEFUL SYNTHETIC WAY TO CHIRAL α -SULFINYL CYCLIC
KETONES BY THE ACID-CATALYZED REACTION OF ENOL SILYL
ETHERS OF CYCLIC KETONES WITH CHIRAL SULFINATES

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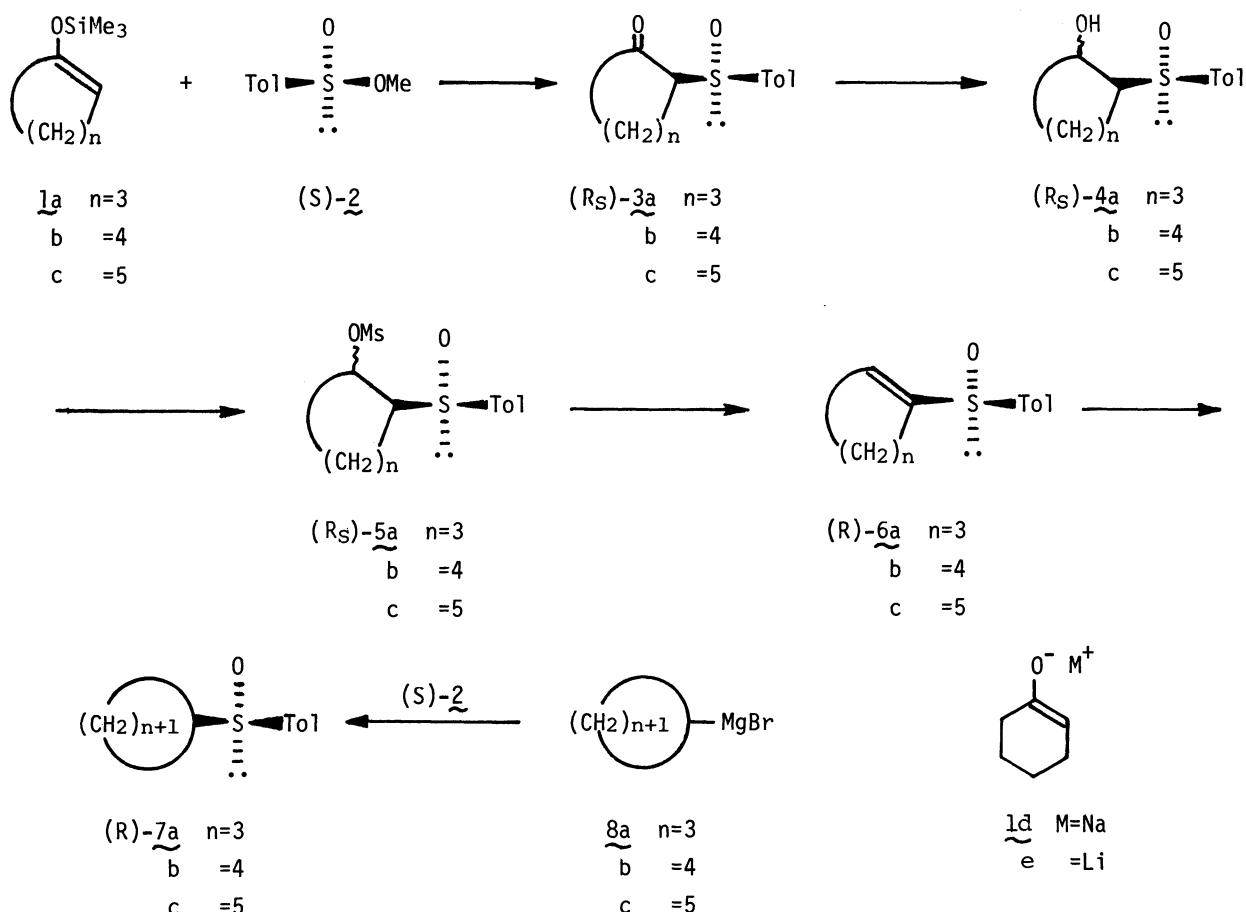
The acid-catalyzed reactions of enol silyl ethers of cyclic ketones with chiral sulfinic esters provided a new and general entry to optically active α -sulfinyl ketones. Reaction of the enol silyl ether of cyclohexanone with methyl (S)-p-toluenesulfinate in the presence of boron trifluoride etherate (2.0 equiv.) produced (R_S)-2-p-toluenesulfinylcyclohexanone with inversion of configuration in 98.3% stereospecificity at the sulfur atom. This method was applicable smoothly to enol silyl ethers of other cyclic ketones with high stereospecificity.

Much attention has been given to organic synthesis with organosulfur groups; especially to asymmetric synthesis with chiral sulfur compounds.¹⁾ Among them, α -sulfinyl ketones have proved to be versatile synthetic intermediates in organic synthesis²⁾ and an α -sulfinyl ketone having chirality on the sulfur atom is one of the most valuable starting chiral sources for asymmetric synthesis.³⁾ Chiral α -sulfinyl acyclic ketones have been easily obtainable from optically active sulfoxides and carboxylic esters.^{3,4)} However, there has been reported no general method for preparation of chiral α -sulfinyl cyclic ketones, since reaction of sodium or lithium enolates of cyclic ketones with chiral sulfinites gave α -sulfinyl ketones retaining the optical activity only partially.

We wish to communicate herein a novel and highly efficient method for preparation of chiral α -sulfinyl cyclic ketones by the acid-catalyzed reaction⁵⁾ of enol silyl ethers of cyclic ketones with chiral sulfinites.

Reaction of the enol silyl ether 1b⁶⁾ with methyl (S)-p-toluenesulfinate (2)⁷⁾ (93.4% e.e.) in tetrahydrofuran (THF) at 0 °C for 14 h in the presence of boron

trifluoride etherate (2.0 equiv.) gave 2-(*R_S*)-p-toluenesulfinylcyclohexanone (*3b*) in 95% yield with 91.8% e.e. at the sulfur atom. The absolute configuration of the sulfur atom in *3b* and the stereospecificity on the sulfur atom in the above reaction were determined by chemical correlation to the authentic cyclohexyl p-tolyl sulfoxide (*7b*) in the following way. Reduction of (+)-*3b*, obtained from *1b* and (*S*)-*2* (93.4% e.e.) as described above, with NaBH₄ followed by mesylation with methanesulfonyl chloride in pyridine produced a mesylate *5b* in a quantitative yield. Treatment of the resulting mesylate *5b* with potassium t-butoxide in dimethyl sulfoxide at room temperature for 2 h afforded (+)-1-cyclohexenyl p-tolyl sulfoxide (*6b*)⁸⁾ in 65% yield with an optical rotation of $[\alpha]_D^{24} +70.1^\circ$ (*c* 2.01, EtOH). Reduction of the sulfoxide *6b* obtained with LiAlH₄ in THF at 0 °C for 2.5 h gave (+)-*7b* in 40% yield ($[\alpha]_D^{23} +170.6^\circ$ (*c* 1.77, EtOH)). The reaction of (*S*)-*2* (82.9% e.e.) with cyclohexylmagnesium bromide (*8b*) led to the authentic sulfoxide (*R*)-(+)-*7b* in 80% yield with inversion of configuration, having an optical rotation of $[\alpha]_D^{19} +154.1^\circ$ (*c* 2.18, EtOH). The optical rotation of the optically pure sulfoxide *7b* was calculated to be 185.9° (EtOH), based on the enantiomeric excess of (*S*)-*2* used.



Thus, by this chemical correlation and calculation, the absolute configuration of the sulfur atom in 3b and the stereospecificity on the sulfur atom in the reaction of 1b with (S)-2 were unequivocally determined to be (R_S)-3b and 98.3%.

The titanium tetrachloride or tin tetrachloride-catalyzed reactions of 1b with (S)-2 in dichloromethane at 0 °C for 30 or 40 h gave (R_S)-3b in low yields (42 or 40%) with rather low stereospecificity (74.9 or 80.0%).

Reactions of sodium or lithium enolates of ketones with chiral sulfinates provided α -sulfinyl ketones with exceedingly low stereospecificity. The reactions of the sodium enolate 1d, prepared from cyclohexanone with sodium hydride, with (S)-2 in THF at 0 °C for 5 h gave (R_S)-3b in 93% yield with 12.5% stereospecificity on the sulfur atom. Similarly, the treatment of the lithium enolate 1e, obtained from cyclohexanone and lithium diisopropylamide (LDA), with (S)-2 in THF at 0 °C for 5 h resulted in the formation of (S_S)-3b (92% yield) with much lower stereospecificity (8.7%). The stereochemistry in these reactions was determined by the chemical correlation in the same sequences as mentioned above and the results obtained are summarized in Table 1.

The acid-catalyzed reactions of the enol silyl ethers 1a and 1c of other cyclic ketones with (S)-2 were carried out in the same way, using boron trifluoride etherate, titanium tetrachloride, and tin tetrachloride as acidic catalysts. The absolute configurations of the sulfur atoms of the products 3a and 3c in the above reactions were determined, by the same sequence as described earlier, to be (R_S)-3a and -3c in all cases. The stereospecificities on the sulfur atoms in the transformation of (S)-2 into 3a and 3c were obtained in the same manner as mentioned above, by converting the products 3a,c into the corresponding chiral sulfoxides 7a,c and the results are listed in Table 1.

Consequently, it should be concluded that the boron trifluoride etherate-catalyzed sulfinylation of enol silyl ethers was the most efficient and useful method for the preparation of chiral α -sulfinyl cyclic ketones, in terms of the chemical yields and the stereospecificity.

We are now on a way to applying this novel method for the development of new asymmetric synthetic reactions utilizing chiral organosulfur groups.

Table 1. Studies on Synthesis of Chiral α -Sulfinyl Cyclic Ketones $\underline{3a-c}$

\underline{l}	Acids	Reaction conditions for preparation of $\underline{3a-c}$	Yields/% of $\underline{3a-c}$	Abs.config. of S in $\underline{3a-c}$	$\underline{7a-c}$ [α] _D (EtOH)	$\underline{7a-c}$ e.e.(%) ^d	Stereospecificity in $\underline{l} \rightarrow \underline{3}$ (%)	
1a	$\text{BF}_3 \cdot \text{OEt}_2$ ^{a)}	85.2	12	90	R	+135.6°	73.0	85.7
1a	TiCl_4 ^{a)}	84.6	40	26	R	+99.4°	53.5	63.2
1a	SnCl_4 ^{a)}	89.9	58	15	R	+91.2°	49.1	54.6
1b	$\text{BF}_3 \cdot \text{OEt}_2$ ^{a)}	93.4	14	95	R	+170.6°	91.8	98.3
1b	TiCl_4 ^{a)}	74.8	30	42	R	+104.1°	56.0	74.9
1b	SnCl_4 ^{a)}	74.8	40	40	R	+111.2°	59.8	80.0
1c	$\text{BF}_3 \cdot \text{OEt}_2$ ^{a)}	89.2	14	93	R	+109.8°	80.7	90.5
1c	TiCl_4 ^{a)}	84.6	40	39	R	+82.7°	60.8	71.9
1c	SnCl_4 ^{a)}	89.9	50	22	R	+72.7°	53.4	59.4
1d	-	75.3	5	93 ^{b)}	R	+17.5°	9.4	12.5
1e	-	75.3	5	92 ^{c)}	S	-12.3°	6.6	8.7

a) Reacted in dichloromethane in the presence of boron trifluoride etherate (2.0 equiv.), titanium tetrachloride (3.0 equiv.), or tin tetrachloride (3.0 equiv.).

b) Reacted in THF, using \underline{l}_d derived from cyclohexanone and sodium hydride.

c) Reacted in THF, using \underline{l}_e derived from cyclohexanone and LDA.

d) The optical rotations of optically pure $\underline{3a-c}$ obtained by the reaction of the optically pure (S)- $\underline{2}$ with Grignard reagents $\underline{8a-c}$; (R)- $\underline{7a}$: [α]_D+185.8°(EtOH); (R)- $\underline{7b}$: [α]_D+185.9°(EtOH); (R)- $\underline{7c}$: [α]_D+136.1°(EtOH).

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