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ASYMMETRIC SULFENYLATION OF KETONES WITH CHIRAL SULFENAMIDES

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Asymmetric sulfenylations of 4-alkylcyclohexanones (6a,b) with chiral sulfenamides (1-5) were achieved in the presence of a catalytic amount of triethylamine hydrochloride to give 4-alkyl-2-phenylthiocyclohexanones (7a,b), which were transformed into optically active 4-alkyl-2-phenylthiocyclohexenes (10a,b) and 3-alkylcyclohexanones (11a,b) in fairly good chemical and optical yields. The influences of chiral sulfenamides and the reaction conditions on this asymmetric induction are described.

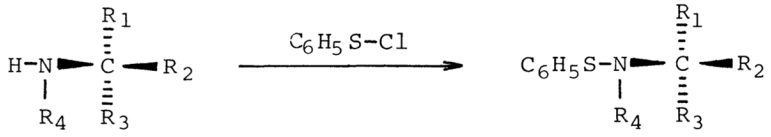
A number of new asymmetric synthetic reactions[1] have been devised in recent years for the preparation of chiral biologically active compounds, in which the interest lies mainly in the pharmaceutical area. And also recent synthetic efforts have revealed that organo-sulfur groups have a wide synthetic utility for the introduction of functionality into a molecule.[2]

We wish to demonstrate herein a potential utility of chiral sulfenamides for asymmetric organic syntheses.

In general, sulfenamides could be used for sulfenylation of active methylene compounds such as acetoacetic esters and malonic esters.[3] However, a detailed examination has not been made for sulfenylation of ketones with sulfenamides.

We attempted the asymmetric sulfenylation of ketones with several kinds of chiral sulfenamides under various reaction conditions.

Chiral sulfenamides (1-5) were prepared in good yields, as shown in Table I, from optically active primary or secondary amines and phenylsulfenyl chloride with triethylamine in THF at -10°-0°C for 1.5 h or with butyllithium in THF at -78°C for 1.5 h. No racemization was observed in these preparations, which was comfirmed



1-5

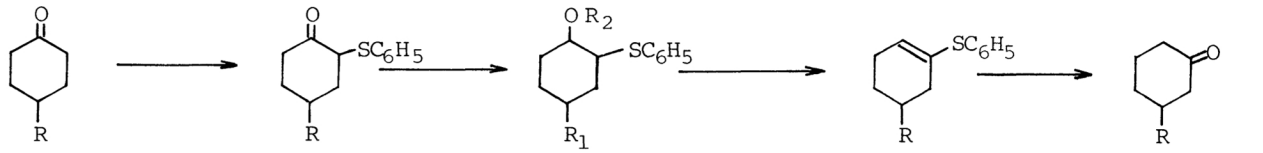
Table I. Yields and Physical Properties of Chiral Phenylsulfenamides (1-5)

	R_1	R_2	R_3	R_4	Bp[a] [Mp] (°C)	$[\alpha]_D^{20}$ (MeOH)	Yield (%)
1	C_6H_5	H	CH_3	H	140	-128.6°	88[b] 77[c]
2	$C_{10}H_7$ (α)	H	CH_3	H	160	-63.7°	72[b]
3	$CO_2C_2H_5$	H	CH_3	H	122	-124.4°	100[b]
4	$CO_2C_2H_5$	H	$C_6H_5CH_2$	H	160	-71.6°	84[b]
5a	CO_2CH_3	H	$-(CH_2)_3-$		128	-135.3°	97[b]
5b	$CO_2C_2H_5$	H	$-(CH_2)_3-$		140	-128.6°	98[b]
5c	CO_2t-Bu	H	$-(CH_2)_3-$		[56-57]	-118.4°	95[b]

a) Boiling points were described at the temperature of oil bath under 1 mmHg.
b) In the presence of triethylamine in THF at -10°-0°C for 1.5 h.
c) Employing butyllithium as a base in THF at -78°C for 1.5 h.

by the measurements of the optical rotations of the recovered amines, obtained from the chiral sulfenamides by treatment with trifluoroacetic acid.

Sulfenylations of 4-alkylcyclohexanones (6) were carried out with (S)-(-)-N-phenylthio-α-phenethylamine (1) in the presence of a catalytic amount of triethylamine hydrochloride (7% molar ratio) to give diastereomeric mixtures of α-phenylthio ketones (7) in the yields given in Tables II and III. Reaction of 6 with 1 without a catalytic amount of triethylamine hydrochloride resulted in extremely low



6a R=t-Bu b =CH_3 7a R=t-Bu b =CH_3 8a R_1=t-Bu, R_2=H b =CH_3, =H 9a R_1=t-Bu, R_2=Ms b =CH_3 =Ms 10a R=t-Bu b =CH_3 11a R=t-Bu b =CH_3

Table II. Asymmetric Induction in the Sulfenylation of 6a with (S)-(-)-1

Solvent	Asymmetric Sulfenylation Reaction Temp. (°C)	Reaction Time h	Yield of 7a (%)	(S)-(-)-10a $[\alpha]_D^{20}$ (MeOH)	Optical Yield (%)
C_6H_6	80	7	83	-31.8°	30
	65	14	60	-52.3°	50
CCl_4	77	4.5	80	-38.2°	36
	65	14	57	-48.3°	46
$CHCl_3$	62	14	63	-17.4°	17
	55	55	63	-37.0°	35
THF	66	14	47	-23.6°	22

product yield (5 %).

To determine the enantiomeric purity of the newly formed asymmetric center at C4 position, another asymmetric center at C2 was eliminated by the following sequence. 4-t-Butyl-2-phenylthiocyclohexanol (8a) prepared by $NaBH_4$ reduction of 7a thus obtained was mesylated and followed by demesylation with t-BuOK in DMSO to give (-)-4-t-butyl-2-phenylthiocyclohexene (10a) in 67 % overall yield from 7a.[4] (-)-10a ($[\alpha]_D^{20}$-31.0° (c 0.63, MeOH) was hydrolyzed by treatment with mercuric chloride in a refluxing solution of CH_3CN-H_2O (3:1) to afford (-)-3-t-butylcyclohexanone (11a) ($[\alpha]_D^{20}$-7.4° (c 0.45, $CHCl_3$). Since optically pure (S)-(-)-11a was reported to have $[\alpha]_D^{24.5}$-25.0°($CHCl_3$),[5] the optical rotation of optically pure (-)-10a was calculated to be $[\alpha]_D^{20}$-105° (MeOH) and its absolute configuration was determined to be (S)-(-)-10a.

Solvent effects on this asymmetric induction reaction with 1 were demonstrated in Table II, which indicates that the sulfenylation in refluxing benzene provided the best chemical yield (83 %) of 7a and the reaction at 65° in benzene resulted in the highest optical yield of 10a.

Sulfenylation of 4-methylcyclohexanone (6b) with 1 was carried out at the reaction conditions given in Table III and the same sequence as described above gave (-)-4-methyl-2-phenylthiocyclohexene (10b) as shown in Table III. The optical rotation of optically pure (-)-10b and its absolute configuration were determined to be (S)-(-)-10b ($[\alpha]_D^{20}$-96° (MeOH)), by conversion of (-)-10b ($[\alpha]_D^{20}$-40.1° (c 1.3, MeOH)) obtained into (-)-3-methylcyclohexanone (11b) ($[\alpha]_D^{25}$-4.0° (c 1.1, MeOH)), since optically pure (S)-(-)-11b was reported to have $[\alpha]_D^{25}$-9.6° (MeOH).[5b]

Table III. Asymmetric Induction in the sulfenylation of 6b with (S)-(-)-1

Solvent	Asymmetric Sulfenylation			(S)-(-)-10b	
	Reaction Temp.(°C)	Reaction Time h	Yield of 7b (%)	$[\alpha]_D^{20}$(MeOH)	Optical Yield (%)
C_6H_6	80	5	77	-42.4°	44
	65	14	47	-52.9°	55
CCl_4	77	4	64	-43.2°	45
	65	20	49	-51.3°	53

Effects of other chiral amino components on sulfenylation of 6a were studied in the same way by employing chiral sulfenamides (2-5) and the results were summarized in Table IV, which indicates that N-phenylthio-α-naphthylethylamine (2) was the most effective sulfenamide on these asymmetric induction reactions.

Table IV. Asymmetric Induction in the Sulfenylation of 6a with Chiral Sulfenamides

Chiral Sulfenamides	Asymmetric Sulfenylation of 6a Solvent	Reaction Temp. (°C)	Reaction Time h	Yield of 7a (%)	10a $[\alpha]_D^{20}$(MeOH) (Abs. Confign.)	Optical Yield (%)
2	C_6H_6	80	10	80	-40.0° (S)	38
	C_6H_6	65	14	62	-66.7° (S)	64
	CCl_4	65	14	59	-65.0° (S)	62
3	C_6H_6	80	6	71	-3.8° (S)	4
	CCl_4	77	6	69	-2.7° (S)	3
4	C_6H_6	80	6	87	+12.7° (R)	12
	CCl_4	77	6	65	+7.1° (R)	7
5a	$CHCl_3$	62	5	84	-11.1° (S)	11
5b	$CHCl_3$	62	5	100	-18.0° (S)	17
	CCl_4	77	5	89	-16.7° (S)	16
	C_6H_6	80	5	85	-12.0° (S)	11
5c	$CHCl_3$	62	5	97	-28.4° (S)	27
	CCl_4	77	5	78	-21.7° (S)	21

We think this will be the first example of the asymmetric induction reactions with chiral sulfenamides.

Studies on the mechanism of this asymmetric induction and its synthetic application to other systems are now in progress.

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