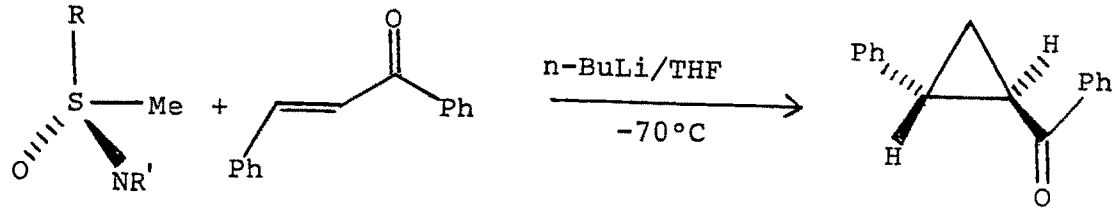
CHAPTER V

ASYMMETRIC CYCLOPROPANATION OF BENZYLIDENE ACETOPHENONE USING CHIRAL S-NEOMENTHYL AND S-EXO-2-BORNYL SULFOXIMINES

A. INTRODUCTION

Chiral three membered ring compounds such as oxiranes[1], cyclopropanes[2] and aziridines[3] are very important classes of organic compounds from the point of view of their biological activity as well as of their synthetic utility. In the previous chapters we have elaborated on the use of methylene transfer (MT) reactions for the asymmetric synthesis of oxiranes. In this chapter we describe the use of the same chiral sulfoximines for the asymmetric synthesis of trans-1-benzoyl-2-phenyl cyclopropane in high diastereomeric excess (de) from (E)-benzylidene acetophenone.



B. SYNTHESIS OF CHIRAL CYCLOPROPANES - BRIEF REVIEW

Cyclopropane group is present in a large number of naturally occuring isoprenoids[4] (mono-, sesqui-, di- and triterpenes), Steroidal alkaloids[4], marine natural products[5], certain amino acid derivatives[6], a few fatty acids (e.g. Sterculic acid[4]) and in a few well known and widely used synthetic drugs

(e.g. ciprofloxacin, cisplatin etc.). Many have one or more chiral centres and are optically active. Incorporation of cyclopropane ring in the synthesis of variety of compounds have appealed to many as great challenges in synthetic organic chemistry.

With the growing realization that among bioactive racemates, only one isomer may be pharmacologically beneficial and its antipode could even be dangerous (e.g. thalidomide), the more towards synthesis of single isomers in drugs and agrochemicals have gained importance during the last two decades. This has been accentuted by pressures from government regulatory agencies. Efforts towards the asymmetric incorporation of cyclopropane ring in a variety of bioactive compounds are part of this overall movement.

From the point of view of the extent of synthetic efforts, wide usage, and, economic significance, the most important cyclopropanoids are pyrethroid insecticides. Worldwide consumption of naturally occuring pyrethrins, synthetic products such as (S)-bioallethrin and the more photostable synthetics such as biophenothrin, cypermethrin and deltamethrin is estimated[7] to be worth over US $ 1.7 billions (1993). Most of these insecticides are esters of substituted cyclopropane carboxylic acids possessing two or more stereogenic centres and sold as mixtures of optical isomers. (S)-Bioallethrin and deltamethrin

are the two major synthetic insecticides sold as pure enantiomers. The methods employed for the manufacture of these pure enantiomers illustrate two conventional ways of synthesis of chiral cyclopropanes. They are :

(1) By resolution of racemates

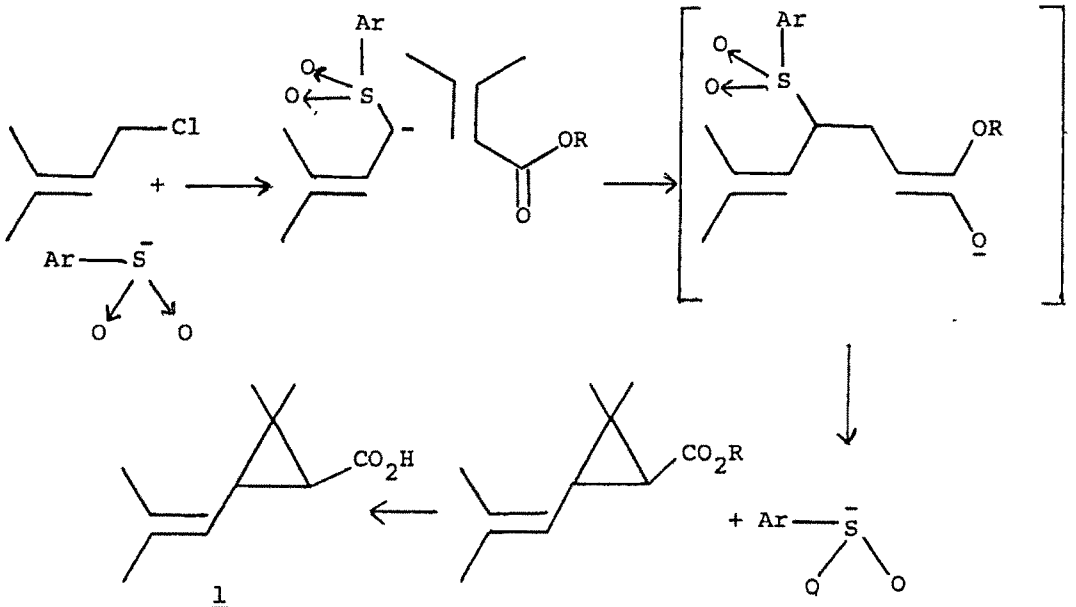
(2) By the use of chiral starting materials

I. CONVENTIONAL METHODS OF SYNTHESIS OF CHIRAL CYCLOPROPANOIDS

1) Resolution of racemates

Michael addition of S-aryl-S-(3-methyl)-2-butene with 3,3-dimethyl acrylic ester followed by a 1,3-elimination to form the cyclopropane ring (Scheme 1) resulted almost exclusively in the methyl ester of racemic trans-chrysanthemic acid. The free acid, 1 was then resolved into (1R)-trans and (1S)-trans-chrysanthemic acids with base. (1R)-trans-chrysanthemic acid is esterified with chiral alcohols to give active products like (S)-bioallethrin and (S)-bioresmethrin.

The unwanted epimer, (1S)-trans-chrysanthemic acid was esterified and epimerised to (1R)-cis-ester which on ozonolysis gave (1R)-cis caronaldehydic acid, 2 (Scheme 2), critical intermediate required for deltamethrin, 3. The utilization of both epimers made the whole process economically attractive and pure enantiomers of both (S)-bio-allethrin and deltamethrin are being manufactured using this process[8].



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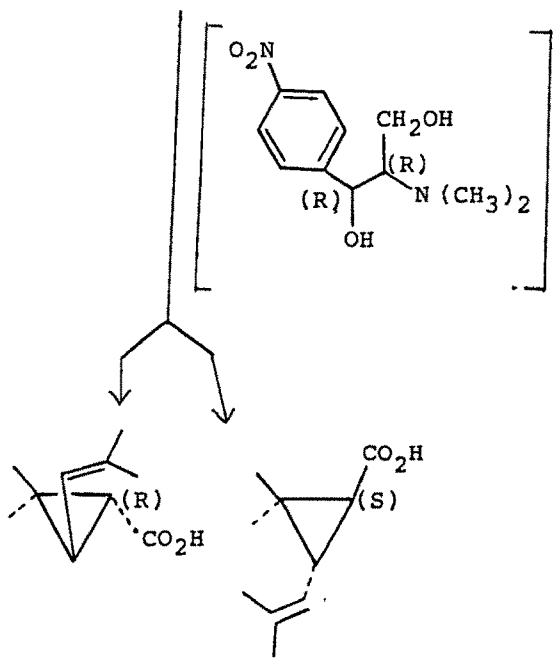
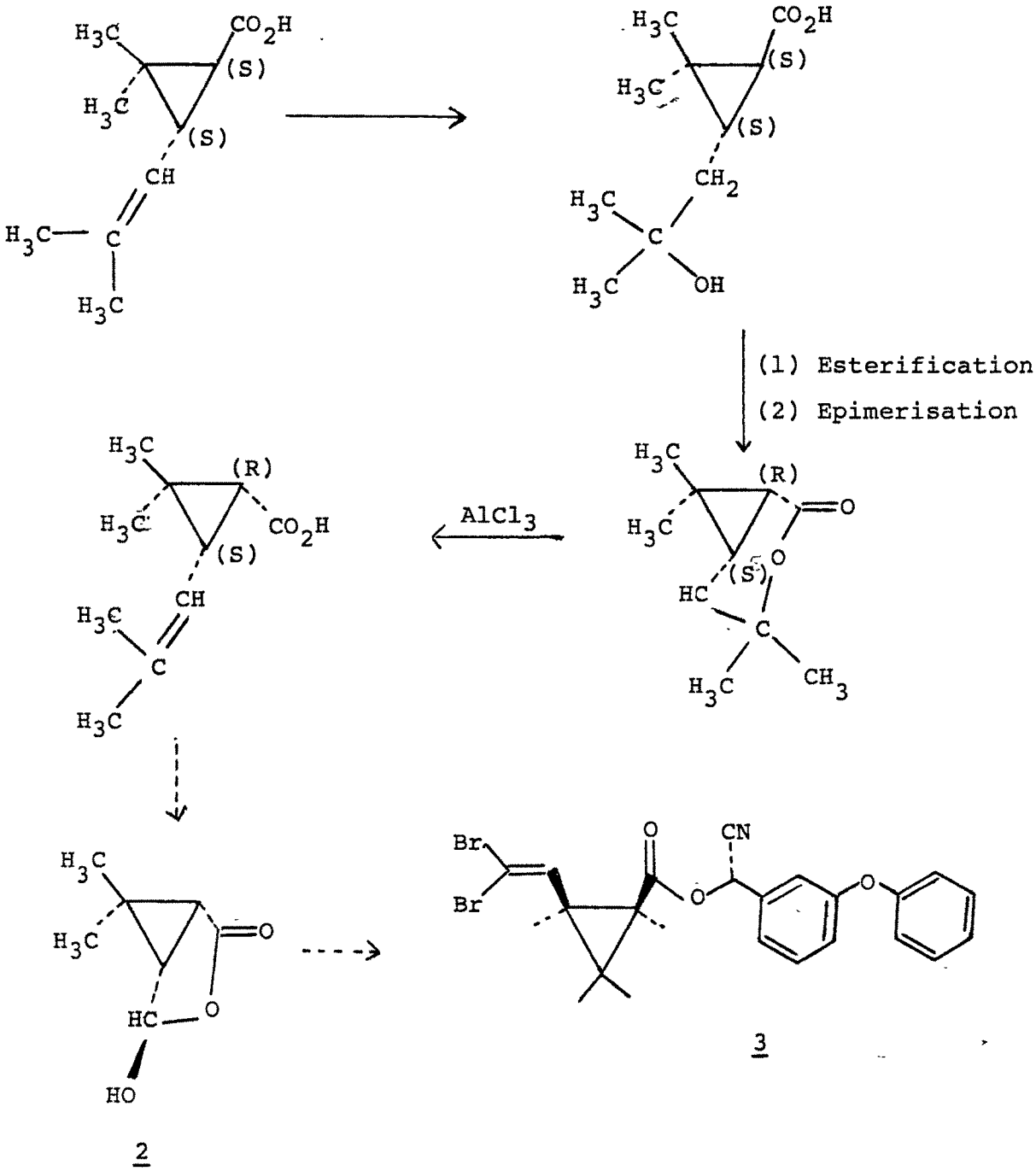


(1R)-trans-1 (1S)-trans-1

Scheme 1



Scheme 2

2) Use of chiral starting materials

(+)-3-Carene, 4 is a cheap, commercially available monoterpene hydrocarbon present in Indian terpentine oil to the extent of about 60%. This molecule contains a cyclopropane ring and breaking up the rest of the molecule could give rise to (1R)-cis-caronaldehydic acid, 2, the intermediate from which deltamethrin is manufactured. A process for this crucial intermediate starting from (+)-3-carene has been developed in our laboratory[9] and is given in scheme 3.

II. ASYMMETRIC SYNTHESIS

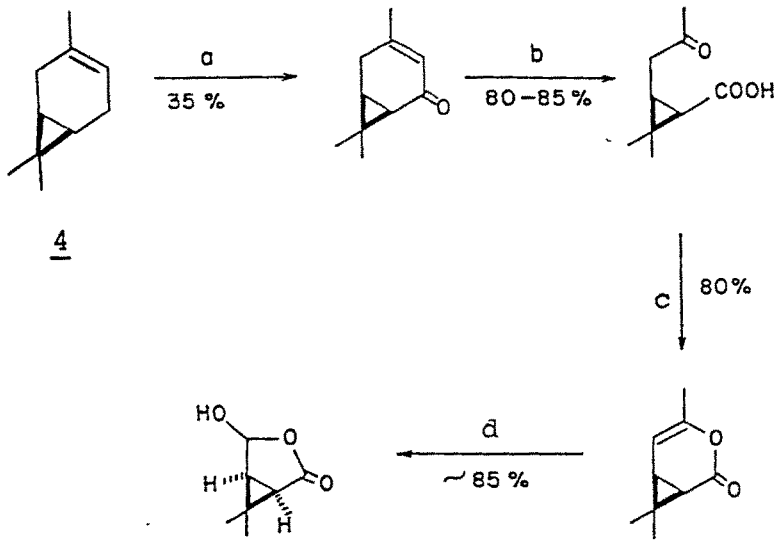
There are two widely used reactions for the incorporation of a cyclopropane ring in simple or complex molecules. These are :

(1) Simmons - Smith cyclopropanation

(2) Addition to olefins of carbenes from metal catalysed decomposition of diazoacetic esters

(1) Simmons - Smith cyclopropanation

This procedure involves the treatment of the olefin with CH_2I_2 and Zn-Cu couple to give cyclopropane. Asymmetric induction is achieved mostly by attaching a chiral auxiliary on the functional group adjacent to alkene double bond. For example[10], α,β -unsaturated aldehyde acetal, 5, prepared from crotonaldehyde and (S,S)-tartaric acid on reaction with diethylzinc and methylene iodide at $-25^{o}C$ gave cyclopropane carboxaldehyde acetal, 6 with 94% diastereomeric excess (de).



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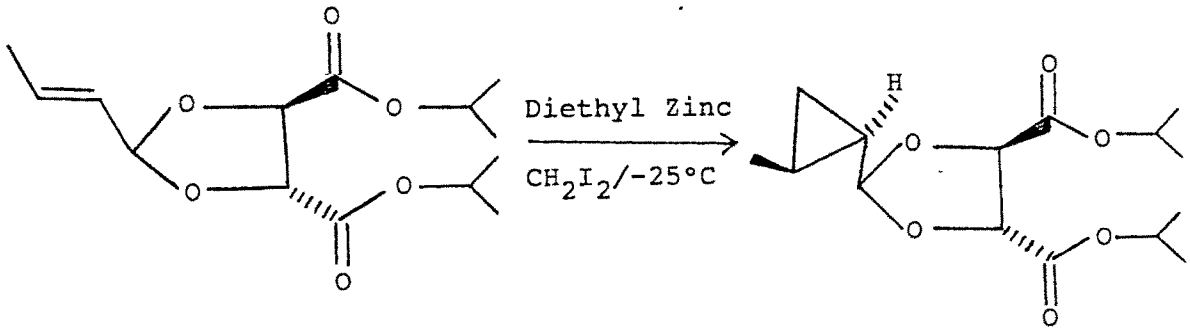
Reagents : a) O_2, Co^{++}; b) O_3, Na_2SO_3; c) Ac_2O, H^+;
d) O_3, Me_2S

Scheme 3



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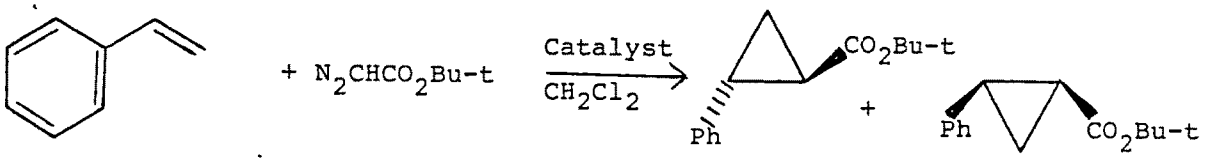
Other syntheses where excellent ee was achieved are reaction of enol ethers[11] of cycloalkanones and optically active 2,6-dimethyl-3,5-heptanediol (ee, over 95%) with Simmons-Smith reagents, 1-alkenyl boronic esters[12] (ee, 84%) etc.

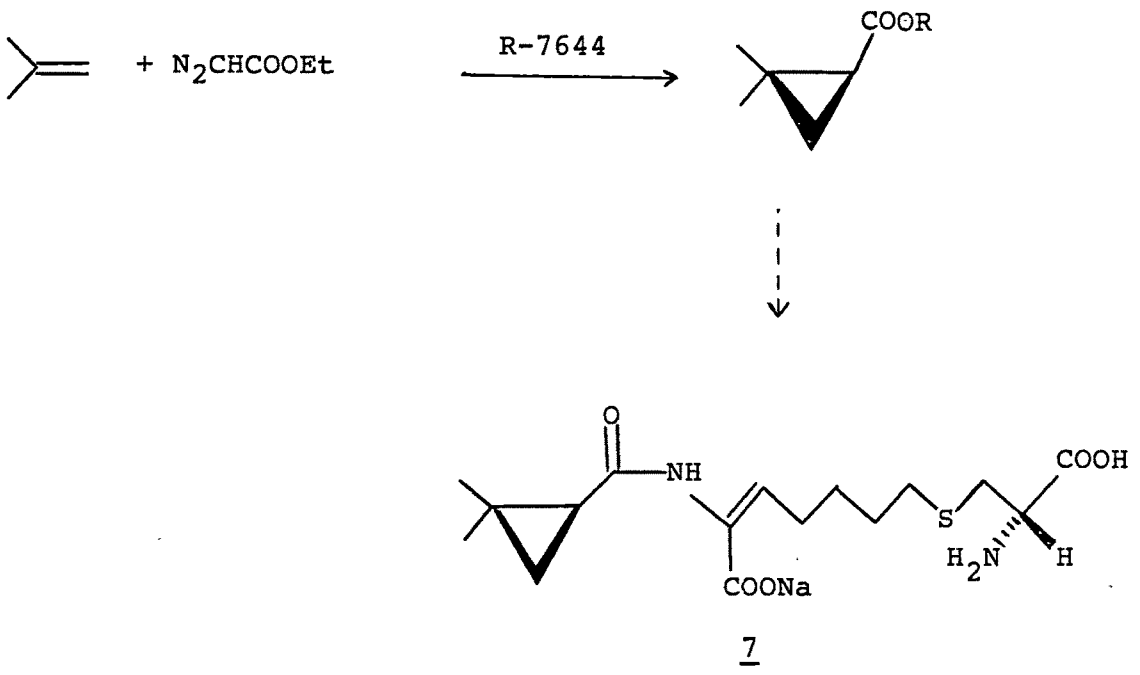
(2) Addition to olefins of carbene from metal catalysed decomposition of diazoacetic esters

This conventional method of synthesis of achiral cyclopropanes has been modified with the use of organomettalic complexes containing chiral ligands as catalyst for the decomposition of diazoacetic esters to give chiral cylopropanes. For example, cyclopropanation of styrene[13] with about 77% ee has been achieved by the use of copper complexes of optically active C-2 symmetric bipyridines.



Other catalysts used are Co(III)-salen complexes[14] (ee, 69-75%), chiral dirhodium catalysts[15] (ee, 84-94%), bis oxazoline copper complexes[16] etc.

On an industrial scale, asymmetric cyclopropanation has been achieved[17] in the decomposition of ethyl diazoacetate in isobutylene in the presence of the dimeric copper catalyst R-7644 giving 2,2-dimethyl cyclopropane-1-carboxylic acid. This is the key intermediate in Sumitomo's industrial process for cilastatin, 7, a drug useful in treatment of urinary tract infection (in combination with imipenim).



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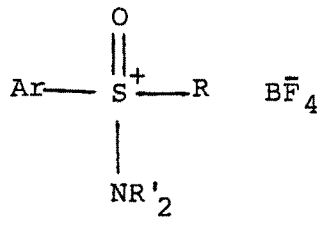
III. ASYMMETRIC METHYLENE TRANSFER REACTIONS

The most characteristic reaction of sulfur ylides is the transfer of alkylidene group across electrophilic double bonds like -C=O, -C=C and -C=N resulting in the formation of three membered ring compounds such as oxiranes, cyclopropanes and aziridines respectively.

Johnson and co-workers reported the use of optically active (dialkyl amino) aryloxosulfonium alkylide, 8 as asymmetric nycleophilic alkylidene transfer reagents[18]. These ylides react with α,β-unsaturated carbonyl compounds to give non-racemic cyclopropanes with optical purities ranging from 7-43%.



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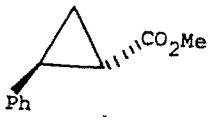
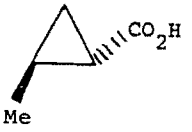
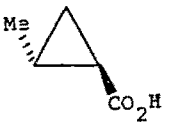
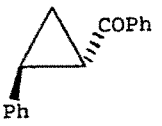
Where,

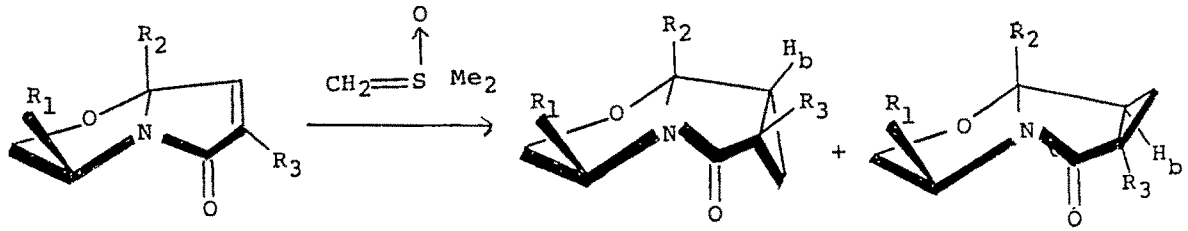
8	Ar	R	R'	Abs.Config. at Sulfur
a	Tol	Me	Me	(R)
b	Tol	Et	Me	(R)
c	Ph	Me	Me	(S)
d	2-Mesityl	Me	Me	(R)

Representative examples of asymmetric induction by these ylides are given in Table 1.

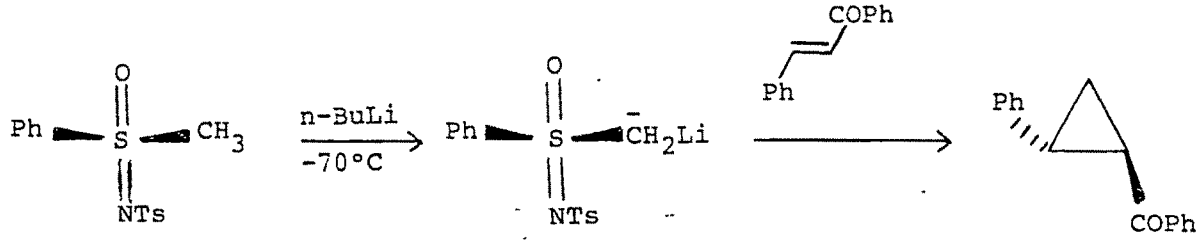
Table 1 : Asymmetric Synthesis of Cyclopropane derivatives using Oxosulfonium Ylides

Sr. No.	Substrate	Oxosulfonium Salt	Product	Abs. Config.	Optical purity (%)
1.	trans-Methyl cinnamate	8a		(1S,2S)	30.4
2.	Methyl acrylate	8b		(1S,2S)	43.2
3.	trans-Methyl crotonate	8c		(1R,2R)	11.9
4.	trans-Benzal acetophenone	8d		(1R,2R)	36.5
5.	trans Benzal acetophenone	8a		(1S,2S)	35.3

Transfer[19] of a methylene group from achiral trimethyl sulfoxonium ylide to a C=C double bond forming part of chiral bicyclic lactams and reduction of lactam group led to cyclopropane derivative with 90-98% ee.



Asymmetric methylene transfer reactions to electrophilic alkenes(e.g. Phenyl conjugated α,β-unsaturated ketones) resulting in the formation of cyclopropane derivatives using chiral sulfoximines having its stereogenicity on sulfur atom gave moderate enantiomeric excess. The lithio derivative of (R)-S-methyl-S-phenyl-N-tosyl sulfoximine 9 was reacted with benzylidene acetophenone to give a 75% yield of (1R,2R)-trans-1-benzoyl-2-phenyl cyclopropane, 10 with 49% de[20].



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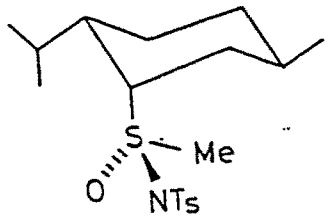
C. PRESENT WORK

In chapter II, III and IV, we have described the preparation of certain chiral sulfoximines and how they were used as methylene transfer reagents to react with carbonyl compounds giving rise to chiral oxiranes with upto 86% ee. We felt that these same sulfoximines should react with α,β-unsaturated carbonyl compounds to give chiral cyclopropyl ketones with good ee. As we have seen in the brief review above, so far, the maximum ee reported[20] in such methylene transfer reaction is 49%. This was achieved with chiral sulfoximines in which the stereogenicity is confined to sulfur atom only.

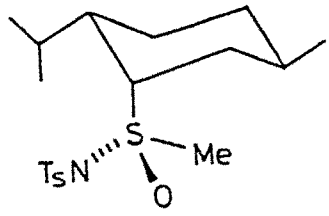
We chose trans-benzylidene acetophenone as a model substrate for these studies as the prospective product from this reaction is a well characterised cyclopropanoide with known optical rotation. Also, results of earlier studies[18,20] on asymmetric cyclopropanation carried out on this substrate could be used for comparative evaluation.

D. RESULTS AND DISCUSSIONS

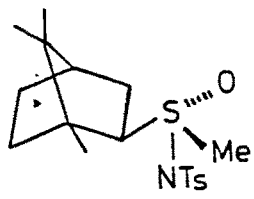
(E)-Benzylidene acetophenone (trans chalcone, 11; m.p.55-57°C) was prepared by the aldol condensation of benzaldehyde with acetophenone[21]. The preparation of chiral sulfoximines 12-16 has been described in chapter II-IV.



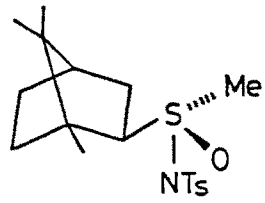
(S_S)-12



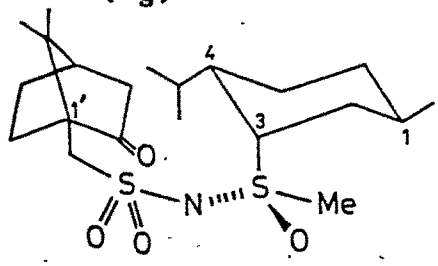
(R_S)-13



(S_S)-14



(R_S)-15



(R_S)-16

The lithio derivative of sulfoximine was prepared by treating it with n-butyl lithium in THF at -70°C. To the carbanion formed was added (E)-benzylidene acetophenone, 11 in THF and after stirring at -70°C for 30 minutes the mixture was allowed to attain room temperature. Work up followed by chromatographic purification gave pure 1-benzoyl-2-phenyl cyclopropane in 65-91% yield. The diastereomeric excess determined through measurment of optical rotation, varied from 66-85%. The results are given in Table 2.

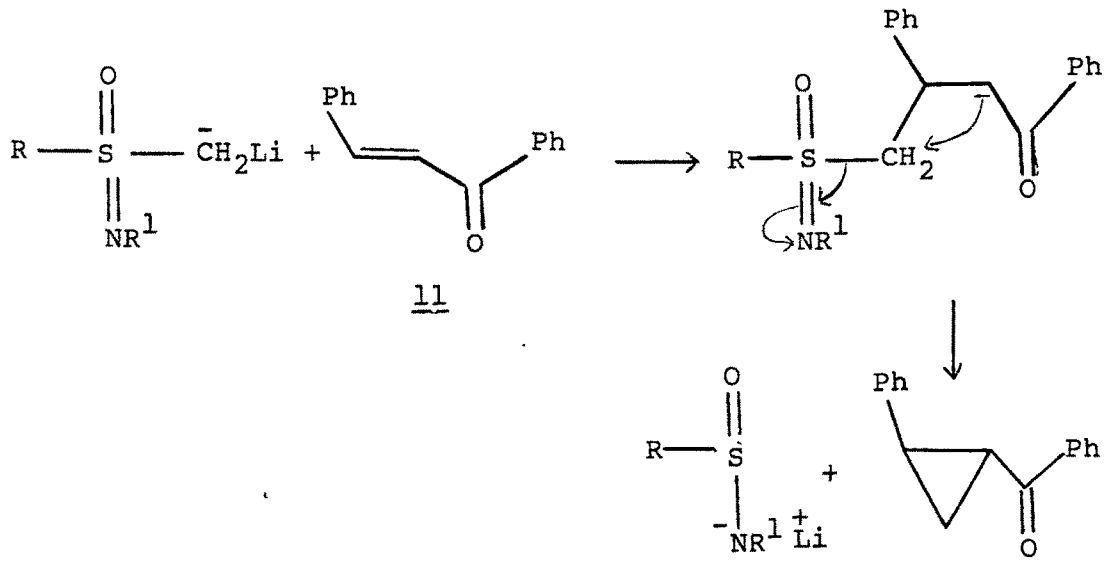
Table 2 : Preparation of 1-Benzoyl-2-Phenyl Cyclopropane with Sulfoximines 12-16

Sr. No.	Sulfoximine	1-Benzoyl-2-Phenyl Cyclopropane			
		Yield (%)	$[\alpha]_D$*	de# (%)	Abs. Config.
1.	(1R,3S,4S,S_S)-(-)-12	82.5	+282.5 (c,0.5,Ac)	72.5	(1S,2S) 17
2.	(1R,3S,4S,R_S)-(+)-13	77.8	-263.5 (c,0.8,Ac)	67.4	(1R,2R) 10
3.	(1R,S_S)-(-)-14	91.0	+277.0 (c,0.8,Ac)	71.0	(1S,2S) 17
4.	(1R,R_S)-(+)-15	85.0	-256.4 (c,0.58,Ac)	65.7	(1R,2R) 10
5.	(1R,3S,4S,1'S,R_S)-(+)-16	65.0	-330.81 (c,0.79,Ac)	84.8	(1R,2R) 10

* The reported[22] $[\alpha]$D for pure diastereomer 17 = + 390 (acetone)

\# The de were calculated by compairing the optical rotation with reported[22] value for the pure diastereomer.

The attack of sulfoximine carbanion on the electrophilic double bond of (E)-benzylidine acetophenone resulting finally in the cyclopropane derivative proceeds as follows (Scheme 4).



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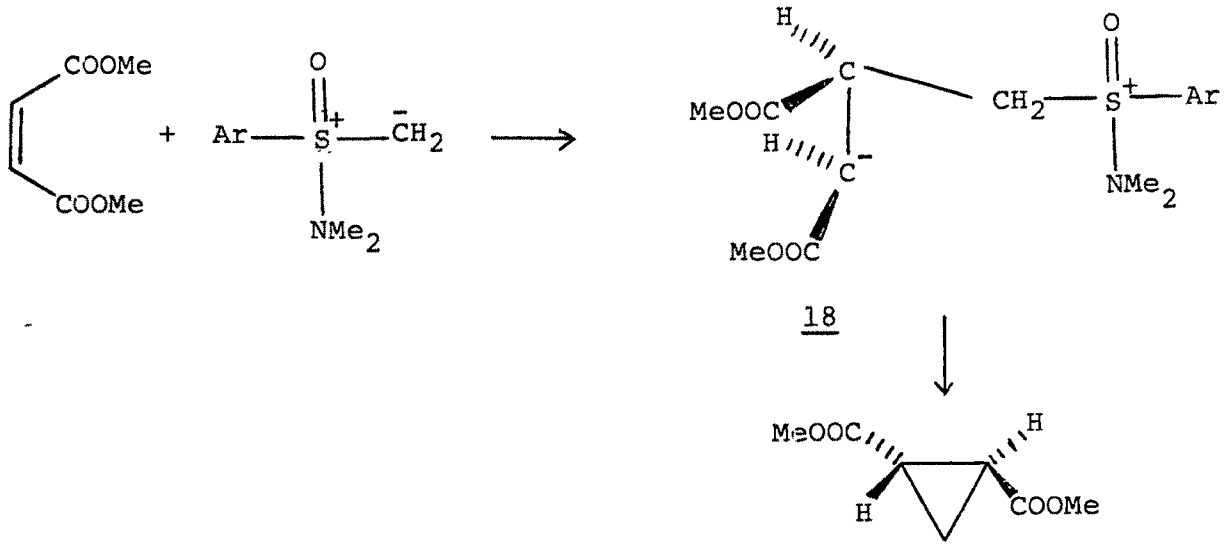
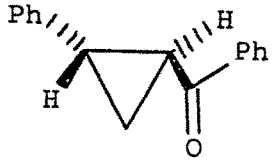
Scheme 4

The trans cyclopropane derivative was exclusive product in our experiments. Formation of other cyclopropanoid could not be detected. This is as we expacted, as it is known[18a] that regardless of the geometry of the olefinic substrate, the product formed is always trans. This has been proved in the case of dimethyl maleate (Scheme 5). Here, rotation about single bond of the betaine 18 occurs giving the thermodynamically more stable product[18a].

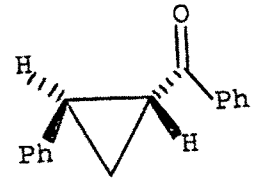


Scheme 5

The two diastereomers of trans-1-benzoyl-2-phenyl cyclopropane are (1S,2S)-(+)-17 and (1R,2R)-(-)-10.



(1S,2S)-(+)-17



(1R,2R)-(-)-10

Sulfoximines having (R) configuration at sulfur gave (1R,2R)-(-)-10 isomer in excess and the sulfoximines having (S) configuration at sulfur gave (1S,2S)-(+)-17 isomer in excess.

In the case of oxirane synthesis, we have found that chiral and achiral substituent on nitrogen of sulfoximine give rise to the same degree of asymmetric induction. However, in cyclopropanation camphor-10-sulfonyl derivative, 16 gave significantly improved de (85%) than the corresponding N-tosyl derivative, 13 (de, 67.4%).

Conclusion

As we have mentioned in the introduction, when methylene transfer reactions are carried out with chiral sulfoximine in which stereogenicity is confined to sulfur atom, the maximum de achieved in the asymmetric synthesis of trans-1-benzoyl-2-phenyl cyclopropane is 49%. By introducing chiral substituent on sulfur and nitrogen of the sulfoximine molecule, we have been able to achieve upto 85% de in the same reaction. In cyclopropanation, the absolute configuration at chiral sulfur of sulfoximine appears to be the guiding factor in deciding the absolute configuration of the cyclopropane derivative formed. It is hoped that another suitable chiral substituent on sulfur might lead to the cyclopropane derivative with 100% optical purity.

E. EXPERIMENTAL

General : Same as in chapter II. The optical rotations were measured at 25^{o}C in chloroform (unless otherwise stated) using JASCO DIP Model 371 digital polarimeter.

Tetrahydrofuran and diethyl ether were dried and distilled over lithium aluminium hydride. n-Butyllithium was prepared as per literature procedure[23].

General procedure for the preparation of (1S,2S)-(+)-1-benzoyl-2-phenyl cyclopropane, 17 or (1R,2R)-(-)-10 using chiral sulfoximines

A solution of optically pure epimer of S-neomenthyl or S-exo-2-bornyl sulfoximine (2.2 mmol) in dry THF (30-40 mL) was treated under strictly dry nitrogen atmosphere with 0.85M solution of n-butyl lithium (2.42 mmol) at -70^{o}C using a syringe through a rubber septum. After 15 minutes (a pale yellow solution), benzylidene acetophenone (11; 0.42 g, 2 mmol) in dry THF (2 mL) was added through syringe. The contents were stirred for 30 minutes at -70^{o}C and then slowly allowed to attain room temperature under stirring (8-12 h). The reaction was monitored by TLC (complete disappearance of chalcone spot). Solvent was removed under vacuo and the residue treated with saturated solution of ammonium chloride (10 mL), extracted with n-hexane

(20 mL x 5), the combined organic layer washed with water (10 mL x 2), dried on Na_2SO_4 and freed from solvent. The crude product was purified by column chromatography (25 g silica gel, eluent, n-hexane:EtOAc, 99:1) to give pure 1-benzoyl-2-phenyl cyclopropane, 17 or 10. The diastereomeric excess (de) in each case was determined by measuring its optical rotation and compairing it with reported value in the literature[22].

The asymmetric induction achieved in the cyclopropanation of trans-benzylidene acetophenone using five different optically pure sulfoximines, 12-16 are given in Table 2.

Preparation of (1S,2S)-(+)-17 using (1R-3S,4S,S_S)-(-)-S-methyl-S-neomenthyl-N-tosyl sulfoximine, (12)

A solution of sulfoximine, 12 (0.92 g, 2.2 mmol) in dry THF (30 mL) was treated with 0.85 M solution of n-BuLi (2.86 mL, 2.4 mmol) at -70°C. After 15 minutes, a solution of benzylidene acetophenone, (11; 0.42 g, 2 mmol) in dry THF (2 mL) was injected via syringe and stirred for 30 minutes. The contents were stirred and slowly allowed to reach room temperature (12h). After work up as described above, the crude product (0.61 g) was purified by column chromatography (25g silica gel, eluent, n-hexane : EtOAc, 99 : 1) to give (1S,2S)-(+)-1-benzoyl-2-phenyl cyclopropane, 17 (0.36g, 82.5% yield).

$[\alpha]_D$ +282.5 (c, 0.57, acetone)

Reported[22] $[\alpha]_D$ +390 (acetone)

de = 72.5 %

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