Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

Asymmetric Synthesis of Biologically Interesting Compounds Utilizing Chiral Sulfoxides

Hauro Matsuyama[a]
[a] Department of Chemistry, Graduate School of Science, Tokyo Metropolitan University, Tokyo, Japan

To cite this Article Matsuyama, Hauro(1999) 'Asymmetric Synthesis of Biologically Interesting Compounds Utilizing Chiral Sulfoxides', Journal of Sulfur Chemistry, 22: 1, 85 — 121
To link to this Article: DOI: 10.1080/01961779908047955
URL: http://dx.doi.org/10.1080/01961779908047955

Sulfur Reports, 1999, Vol. 22, pp. 85–121
Reprints available directly from the publisher
Photocopying permitted by license only

ASYMMETRIC SYNTHESIS OF BIOLOGICALLY INTERESTING COMPOUNDS UTILIZING CHIRAL SULFOXIDES

HARUO MATSUYAMA

Department of Chemistry, Graduate School of Science, Tokyo Metropolitan University, Minami-ohsawa, Hachioji, Tokyo 192-0397, Japan

(Received 23 November 1998)

An overview of recent studies on asymmetric synthesis of biologically interesting compounds utilizing chiral sulfoxides is described. The reaction mechanism of some asymmetric syntheses is also discussed.

Keywords: Asymmetric synthesis; chiral auxiliaries; chiral sulfoxides

CONTENTS

1. INTRODUCTION

This short review concentrates mainly on the utility of chiral sulfoxides in asymmetric syntheses of biologically interesting compounds. The main advantage of sulfoxides over other sulfur functions such as sulfides and sulfones is indeed their chirality. The efficacy of a sulfoxide in diastereoselective auxiliary-induced reactions is mainly due to the steric and stereoelectronic differences existing between the substituents of the stereogenic sulfur atom: a lone electron pair, an oxygen, and two different carbon ligands, which are able to differentiate the diastereotopic faces of a proximal or even of a remote reaction center. Sulfoxides are chiral groups which are easy to introduce and easy to remove and which give high asymmetric induction in many reactions.[1,2]

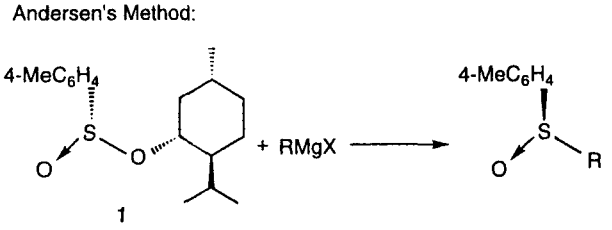
The oxygen atom of a sulfoxide can be coordinated to a metal ion or a proton, and electronic and steric repulsions between nucleophiles and the substituents of a sulfoxide are also expected. The sulfinyl group acts as an electron-withdrawing group and activates a carbon–carbon double bond for conjugate addition and stabilizes the corresponding α-carbanion. To date, a large number of asymmetric syntheses using chiral sulfoxides[3–7] have been investigated in a wide range of reactions such as the reduction of β-keto sulfoxides,[7] the Michael addition of nucleophiles to activated α,β-unsaturated sulfoxides,[8] C–C bond formation using sulfoxide-stabilized carbanions,[4,9–11] or the Diels–Alder reaction of vinyl sulfoxides.[7]

2. SYNTHESIS OF CHIRAL SULFOXIDES

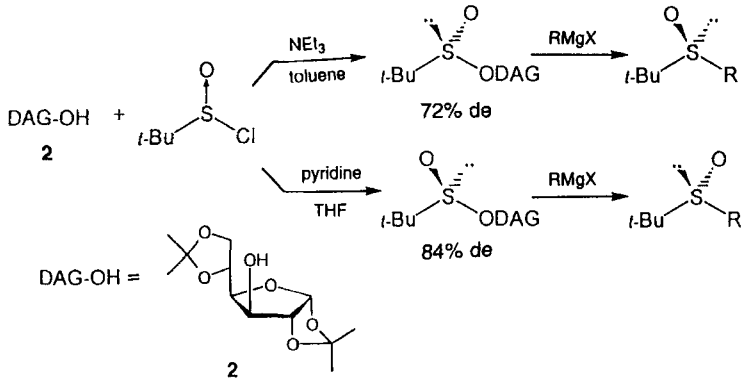
Several methods are presently available to obtain optically active sulfoxides: optical resolution, asymmetric oxidation, and asymmetric synthesis. The best way to prepare large quantities of optically active

sulfoxides, the Andersen method (= substitution at the sulfur atom of (*S*)-menthyl *p*-toluenesulfinate **1** with an appropriate organometallic reagent), is favored since it has the advantage that the substitution takes place with 100% inversion of configuration (Scheme 1).[12]

In addition, (*S*)-menthyl *p*-toluenesulfinate **1** is commercially available.[13] The selectivity in the formation of chiral epimeric alkane- and arenesulfinates is greatly enhanced by using D-glucose diacetonide **2**[14] in the sulfinyl chloride esterification. Either sulfur epimer could be obtained as the major diastereomer by changing the base present in this esterification step. Further chromatographic separation permitted their obtention in optically pure form. In an Andersen-type synthesis these sulfinyl transfer agents allow the obtention of enantiomerically pure sulfoxides of both absolute configurations. This agent overcame one of the limitations of the Andersen method by opening access to sulfoxides with substituents different from the *p*-tolyl group (Scheme 2). Unequal



SCHEME 1

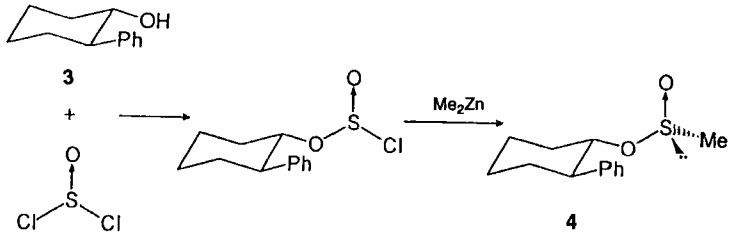


SCHEME 2

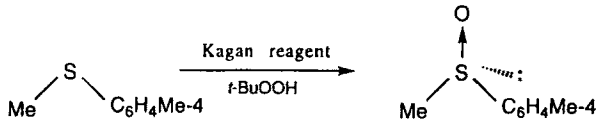
amounts of diastereomeric sulfinates (4–10 : 1) were also obtained in the reactions of (1*S*,2*R*)-*trans*-2-phenylcyclohexanol **3**[15] with an excess of an arene- or alkanesulfinyl chloride. An improved asymmetric synthesis of (*SR*)-*trans*-2-phenylcyclohexyl methanesulfinate **4**[16] has been achieved by reaction of the corresponding chlorosulfinate with dimethylzinc (Scheme 3).

Optically active sulfoxides can also be prepared by asymmetric oxidation of sulfides. The first examples of asymmetric oxidation of sulfides to sulfoxides were independently reported by Pitchen *et al.*[17] and Di Furia *et al.*[18] in 1984 in the shape of a modified Sharpless epoxidation, H_2O/Ti(OPr-*i*)$_4$/diethyl tartrate/*t*-BuOOH (Scheme 4). Further development of this methodology[19] led to an increase in the optical purity of the resulting sulfoxide by replacing the original oxidant by cumene hydroperoxide. In these conditions aryl methyl sulfoxides could be obtained in 86–90% ee. More general are the applications of the stoichiometric chiral oxidizing reagents described by Davis *et al.*[20] The enantiopure (camphorsulfonyl)oxaziridines and their 8,8-dichloro derivatives, which are available as both enantiomers, gave ee's ranging from 84% to 96%.

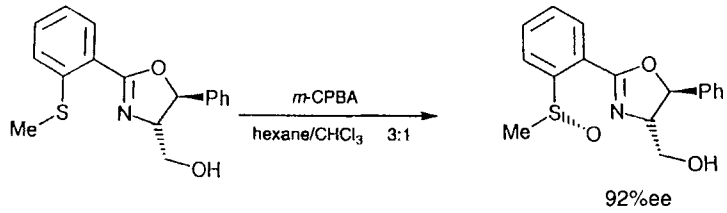
Several papers have also reported the asymmetric oxidation of chiral sulfides having a structure derived from camphor and heterocycles (Scheme 4).[21] Optically active vinyl sulfoxides can be prepared by the Andersen synthesis, using (−)-menthyl (−)-(*S*)-*p*-toluenesulfinate **1** and vinyl Grignards,[22,23] or by the Wittig–Horner procedure, using carbonyl compounds and the anion of dimethyl (*R*)-*p*-toluenesulfinylmethanephosphonate, easily made from the corresponding menthyl sulfinate.[24] However, the applicability of the former method depends on the availability of stereochemically pure 1-alkenyl halides for



SCHEME 3



Kagan reagent: $Ti(OPr^i)_4/(R,R)$-diethyl tartrate/H_2O 1:2:1



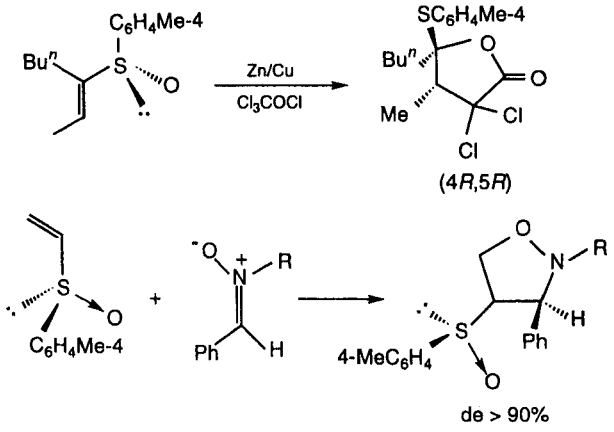
SCHEME 4

preparing the Grignard reagents and the latter usually leads to a mixture of (*E*)- and (*Z*)-vinyl sulfoxides. Therefore, it is sometimes easier to prepare the corresponding alkynyl sulfoxide by the Andersen method from alkynyl Grignards and then reduce stereospecifically the triple bond to a *trans* double bond with DIBAL or a *cis* double bond by catalytic hydrogenation using a Wilkinson catalyst.[25]

Vinyl sulfoxides have been used successfully in several Michael-type asymmetric syntheses. One typical example is given by the asymmetric synthesis of (−)-methyl jasmonate.[26] The CD rings of steroids have been synthesized by the same method in high enantioneric purity.[27] Vinylic sulfoxides have also been used in asymmetric Diels–Alder reactions.[28] A very high diastereoselectivity was observed with optically active sulfinylacrylates. Vinyl sulfoxides can undergo an additive Pummerer rearrangement when treated with trichloroacetyl chloride and a zinc/copper couple in refluxing ether to give an optically pure γ-butyrolactone.[29] Vinyl sulfoxides also exhibit high chiral induction in the 1,3-dipolar cycloadditions to typical nitrones (Scheme 5).[30]

3. REACTIONS OF SULFOXIDE-STABILIZED CARBANIONS

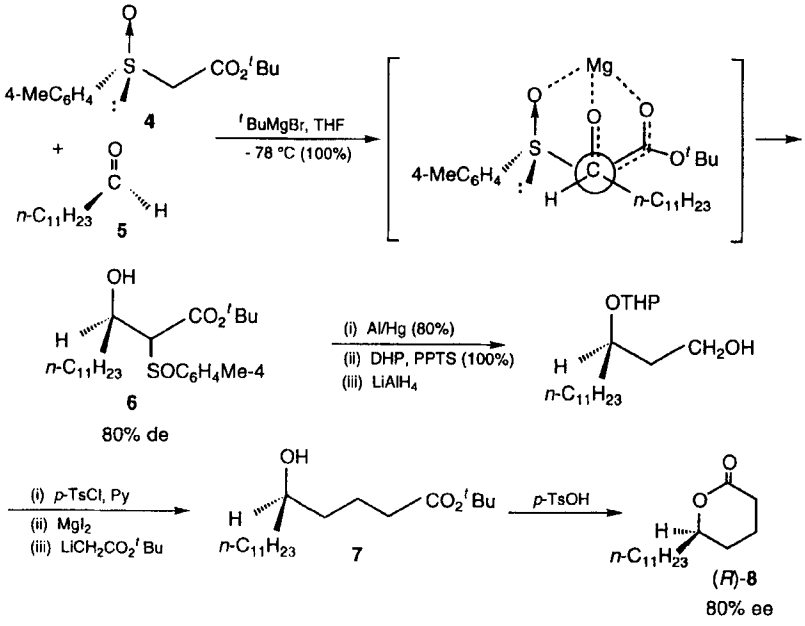
In the first attempts to use a chiral α-sulfinyl ester enolate as donor in Michael additions to α,β-unsaturated esters only low selectivities were observed.[31]



SCHEME 5

Condensations of α-sulfinyl carbanions with aldehydes provide a useful method for generating 1,2-asymmetry as well as for the construction of 1,3-asymmetric relationships in acyclic systems. If optically active sulfoxides such as methyl *p*-tolyl sulfoxide give a poor diastereoselectivity when such an α-sulfinyl carbanion is added to a carbonyl, the presence of another function such as ester, sulfide or amide, which has a chelating effect in the transition state, makes optically active α-sulfinyl esters, sulfides or amides very useful in asymmetric aldol-type condensation.

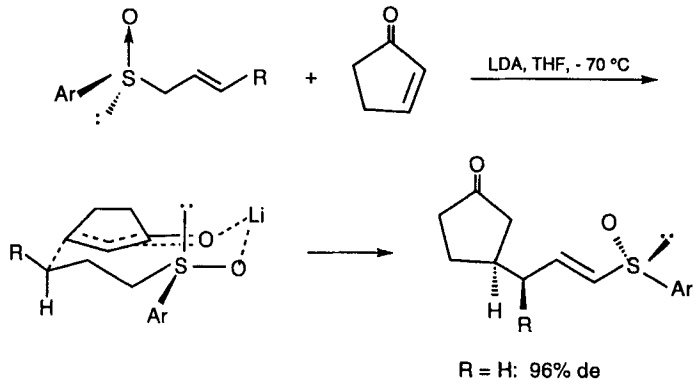
A significant improvement of the diastereoselection was observed with the introduction of a *tert*-butyl ester group on the α-carbon. The aldol-type condensation of (*R*)-*tert*-butyl 2-(*p*-tolylsulfinyl)acetate **4** (Scheme 6) with aldehyde **5** or with ketones in the presence of *tert*-butylmagnesium bromide gave a good yield (74–90%) and moderate to good diastereoselection (up to 95%).[31] When long-chain aliphatic aldehydes were used, an easy approach to the asymmetric synthesis of insect pheromone lactones such as **8** was reported (Scheme 6). The adduct **6** resulting from the aldol-type condensation of **4** with dodecanal **5** was desulfurized, protected, and transformed into the seco-ester **7** whose cyclization led to the natural δ-lactone (*R*)-8 with 80% ee.



SCHEME 6

This value corresponds to the diastereoselectivity achieved in the condensation step and was explained assuming the evolution of the system through a rigid chelated transition state in which the enolate approaches the *si* face of the aldehyde from its less hindered face which supports the lone electron pair of the sulfoxide. This methodology was applied by Corey *et al.* to create the C-3 stereogenic carbinol of the antitumor agent maytansine.[31f]

The diastereoselective addition of chiral allylsulfinyl anions to cyclic enones has been investigated in terms of its diastereoselectivity and mechanism (working with racemic material).[32] For example, the lithiated allylic sulfoxide reacts with 2-cyclopentenone in a highly diastereoselective mannner yielding an adduct which can be converted to the optically active keto acid (Scheme 7). Application of this methodology allows the synthesis of cyclopentanoid natural products like (+)-hirsutene.[32]



SCHEME 7

4. CONJUGATE ADDITIONS TO α,β-UNSATURATED SULFINYL COMPOUNDS

4.1. C–C Bond Formation

The first asymmetric Michael addition of an enolate ion to acyclic α,β-unsaturated sulfoxides was reported in 1973 to proceed with 60% asymmetric induction.[33]

Posner and his coworkers have developed a highly useful methodology based on the conjugate addition of carbon nucleophiles to homochiral α,β-unsaturated α-arylsulfinyl carbonyl compounds. While acyclic derivatives only give moderate results,[34] the strength of this method is in the case of cyclic systems.

More general results were obtained in conjugate additions to cyclic α,β-unsaturated keto sulfoxides. Thus, 2-(*p*-tolylsulfinyl) cyclopentenone (Figure 1) underwent very efficiently conjugate addition of different organometallic reagents, the resulting diastereoselectivity being dependent on the nature of the reagent and the reaction conditions.[35] The best results were obtained with Grignard reagents in the presence of $ZnBr_2$. (*R*)-3-Methylcyclopentanone **14** was generated in 87% ee when the enone sulfoxide (*S*) was treated with $ZnBr_2$ prior to the addition of methylmagnesium iodide, after desulfurization of the resultant conjugate adduct **13** (Table I, entry 1). The observed diastereoselectivity was explained by assuming the formation of a chelate **A** with $ZnBr_2$

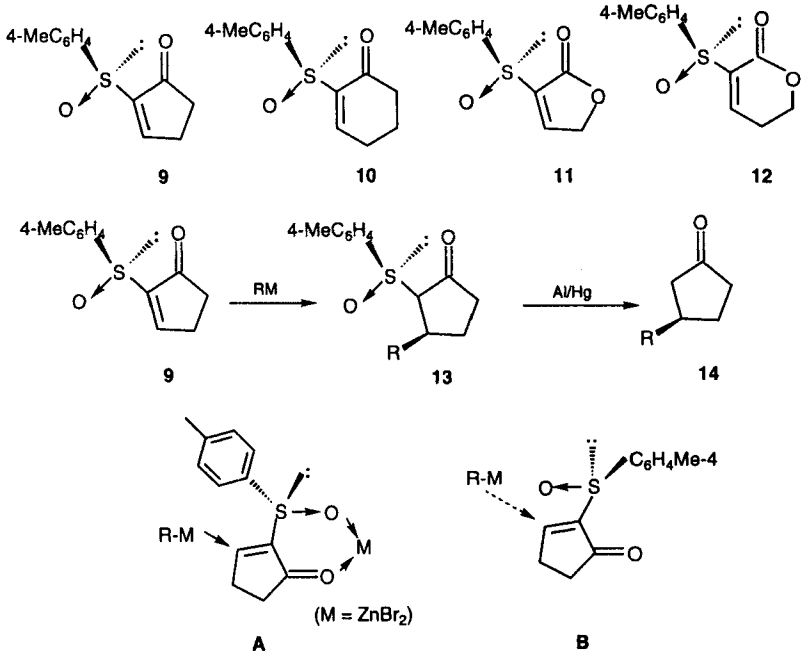


FIGURE 1

TABLE I Synthesis of cyclic β-substituted carbonyl compounds **14** via addition of organometallic reagents to unsaturated sulfoxides **9** or **10**, followed by desulfurization of the intermediates **13** (Figure 1)

Entry	*Sulfoxide*	*R–M*	*R*	Yield/%	ee *of* **14** (%)
1	**9**	$ZnBr_2$/MeMgBr	Me	89	87
2	**9**	MeTi(*i*-PrO)$_3$	Me	90	90
3	**9**	MeMgCl	Me	91	95–100
4	**10**	$ZnBr_2$/MeMgBr	Me	95	62
5	**10**	MeTi(*i*-PrO)$_3$	Me	85	86
6	**9**	$ZnBr_2$/EtMgBr	Et	90	80
7	**9**	EtTi(*i*-PrO)$_3$	Et	67	>98
8	**9**	$ZnBr_2$/vinylMgBr	vinyl	75	92
9	**9**	$ZnBr_2$/PhMgBr	Ph	70	>98
10	**9**	2-naphthylMgBr	2-naphthyl	90	>98

where the organometallic approach takes place from the less-hindered *re* face of the enone.[35,36] In contrast, dialkylmagnesiums[37] and dialkylcuprates[38] afford products with an absolute configuration opposite to that obtained with other reagents. This in turn can be rationalized

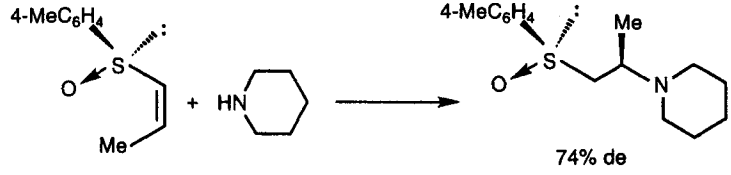
as the result of an attack on the non-chelated substrate molecule, which should prefer the conformation shown in **B** (Figure 1). Ester enolates may also be added as donors to these substrates (attack in the non-chelate addition mode),[39] especially with α-substituted derivatives leading to an extraordinarily high level of asymmetric induction in some cases.

Several applications in total syntheses exemplify the value of this methodology; 11-oxoequilenine methyl ether,[34,35] (+)-α-cuparenone,[38] (−)-podorhizone,[40] (−)-methyl jasmonate,[41] (+)-estrone methyl ether,[42] and so-called (+)-A-factor[43] were all prepared in high enantiomeric purity. Other applications constitute preparations of 2-alkylchroman-4-ones, and of 3-vinylcyclopentanones, highly valuable intermediates for steroid total synthesis.[35,36]

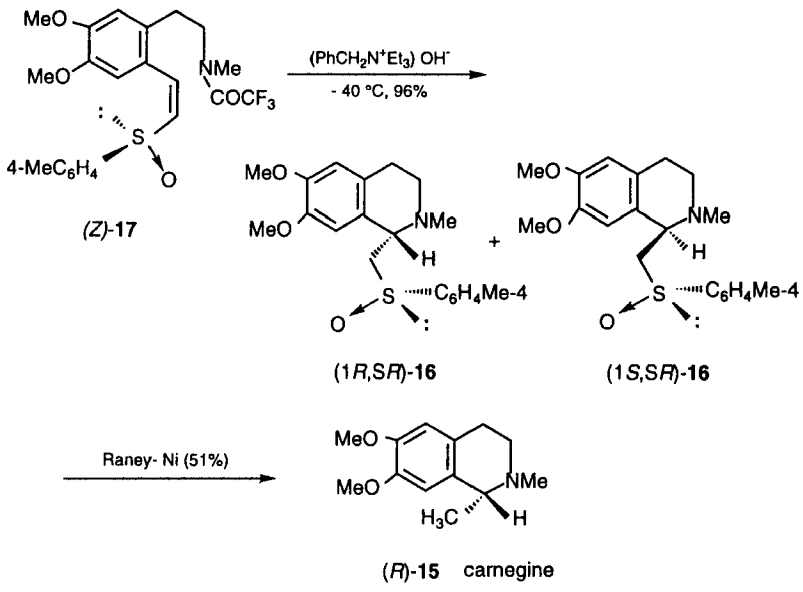
4.2. C–N Bond Formation

Although Abott *et al.* reported the asymmetric conjugate addition of a cyclic amine to vinyl sulfoxide in 1971, this intermolecular reaction has not been further applied to natural products synthesis, probably due to the low reactivity of these simple Michael acceptors (Scheme 8).[44]

The intramolecular version, which takes place at low temperature and with higher reaction rates,[45,46] was used in alkaloid synthesis although the asymmetric induction was not as high as that achieved in other sulfinyl-induced processes. The total synthesis of (*R*)-carnegine (**15**, Scheme 9) reported by Pyne[46,47] was based on the formation of the tetrahydroisoquinoline system **16** upon cyclization of the (*Z*)-vinyl sulfoxide **17** in basic conditions. Although the major diastereomer (1*R*,*SR*)-**16** was formed with only 68% de, the excellent yield of this



SCHEME 8

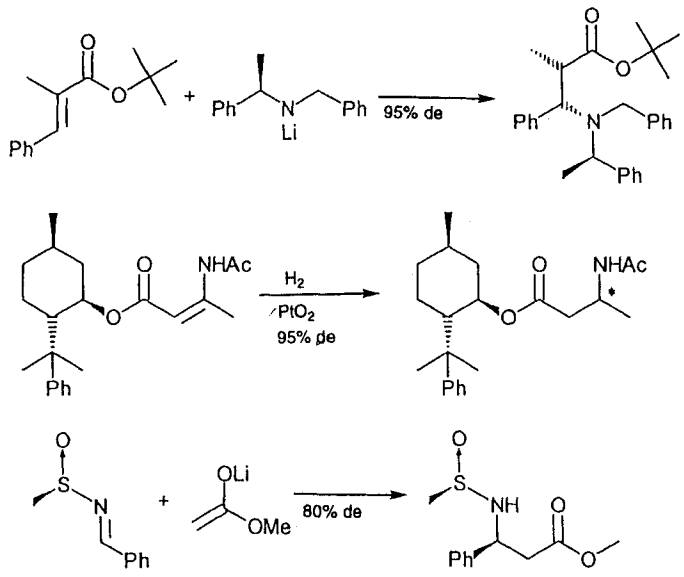


SCHEME 9

intramolecular addition (96%) allowed its isolation in 78% yield. Desulfurization of (1*R*,*SR*)-**16** gave the alkaloid carnegine (*R*)-**15**.

A number of β-amino acids have been isolated in free form and show interesting pharmacological properties.[48] These β-amino acids can be cyclized to β-lactams,[49] a well-known class of potentially biologically active substances which occur in nature.[50] Recently some reports of asymmetric syntheses of β-amino acids were published (Scheme 10).[51]

Macrocyclic lactams containing the biogenetic bases spermine and spermidine represent a new class of polyamine alkaloids which have a β-amino acid framework and are of particular interest as synthetic targets in view of the broad biological activity, for instance as antibiotics and antihypertensives.[52,53] Kaseda *et al.*[54] and Ishihara *et al.*[55] synthesized the 13-membered lactam (*S*)-(+)-dihydroperiphylline starting from an (*S*)-(−)-β-amino acid (Figure 2). Asymmetric induction in the conjugate addition of nitrogen nucleophiles to chiral vinyl sulfoxides has proven to be a useful methodology for the synthesis of chiral compounds.[56] Pyne *et al.* have developed an asymmetric synthesis of chiral β-amino sulfoxides by conjugate addition of amines to chiral vinyl sulfoxides.[57] Davis *et al.* reported the enantioselective



SCHEME 10

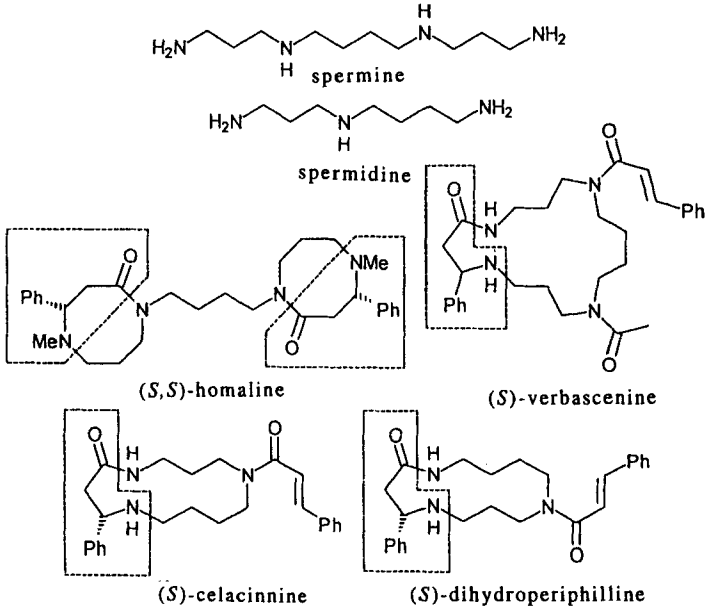


FIGURE 2

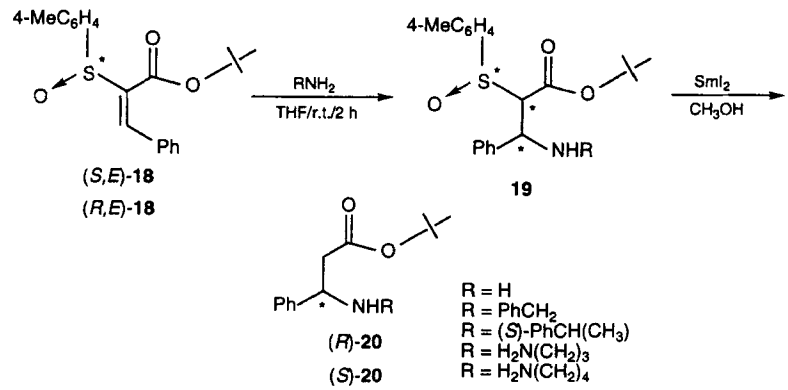
synthesis of β-amino acids by addition of enolates to chiral sulfinimines (Scheme 10).[58]

We have investigated the synthesis of β-amino esters by conjugate addition of nitrogen nucleophiles to chiral vinyl sulfoxides.[59] The optically pure vinyl sulfoxides (*S*)- and (*R*)-**18** were synthesized from (*S*)-and (*R*)-*tert*-butyl *p*-tolylsulfinylacetates.[60]

Addition of the carbanion derived from *tert*-butyl *p*-tolylsulfinylacetate to benzaldehyde, followed by treatment with acetyl chloride and pyridine in ether, gave optically active (*E*)-**18**. The conjugate addition of nitrogen nucleophiles to the chiral vinyl sulfoxides **18** affords the corresponding chiral β-amino acid derivatives, which are important building blocks for the synthesis of biologically active polyamine alkaloids (Scheme 11).

The conjugate addition of ammonia to the chiral vinyl sulfoxides (*R*)-**18** and (*S*)-**18**, followed by successive reduction of the *p*-tolylsulfinyl group of the adducts **19** with SmI_2 proceeded smoothly at room temperature in THF to give (*S*)-(−)- and (*R*)-(+)-*tert*-butyl β-amino-β-phenylpropionate **20** in 68% yield with good optical purity (74% and 81% ee), respectively. In the reaction of (*R*)-**18** and (*S*)-**18** with benzylamine in THF at room temperature the stereoselectivity was moderate (52% ee) (Scheme 11, Table II).[59]

On the basis of the stereochemistry of the (*S*)-β-amino ester obtained from (*R*,*E*)-**18**, the mechanism of the asymmetric conjugate addition of nitrogen nucleophiles to **18** can be explained as follows. The structure of



SCHEME 11

TABLE II Conjugate addition of nitrogen nucleophiles to vinyl sulfoxides **18**

Entry	*Sulfoxide* **18**	*Nitrogen nucleophile*	*Products* **20**		
			Yield/%	ee (%)	(*R*/*S*)
1	*S*	NH_3	68	81	*R*
2	*R*	NH_3	68	74	*S*
3	*S*	$C_6H_5CH_2NH_2$	41	49	*R*
4	*R*	$C_6H_5CH_2NH_2$	45	52	*S*
5	*S*	(*S*)-$C_6H_5CH(CH_3)NH_2$	37	17	*R*,*S*
6	*R*	(*S*)-$C_6H_5CH(CH_3)NH_2$	83	62	*S*,*S*
7	*S*	$H_2N(CH_2)_3NH_2$	89	67	*R*
8	*R*	$H_2N(CH_2)_3NH_2$	79	62	*S*
9	*S*	$H_2N(CH_2)_4NH_2$	67	58	*R*
10	*R*	$H_2N(CH_2)_4NH_2$	64	89	*S*

(*R*,*E*)-**18** was determined by X-ray analysis as shown in Figure 3. The oxygen of the sulfinyl group lies near the plane of the carbon–carbon double bond and the phenyl group. The *p*-tolyl group on the sulfur atom lies below the plane and the bulky *tert*-butoxy group of the ester is also placed below the plane. Therefore, the front side of the plane shown in Figure 3 is less sterically crowded and the nitrogen nucleophiles can easily attack the β-carbon atom of the double bond of (*R*,*E*)-**18** from the front side of the plane (*re*-face). Thus, the reaction of (*R*,*E*)-**18** with an amine affords the (*S*)-β-amino ester, and the reaction of (*S*,*E*)-**18** with the same amine gave the (*R*)-β-amino ester.

We have investigated the conjugate addition reaction of 6- and 5-membered cyclic hydrazines such as piperidazine **21** and pyrazolidine **24** to chiral vinyl sulfoxides and could synthesize the corresponding chiral 9- and 8-membered lactams with high optical purity (up to 95% ee). The asymmetric synthesis of a 13-membered lactam alkaloid, celacinnine,[61] and of an 8-membered lactam alkaloid, homaline,[60] have been accomplished by this method.

The 9-membered lactam **23** is a key intermediate in the total synthesis of the natural 13-membered polyamine alkaloid, celacinnine.[62] In the reactions of (*R*)-**18** and (*S*)-**18** with the 6-membered cyclic hydrazine piperidazine **21**, in the presence of potassium *tert*-butoxide in THF at room temperature, the conjugate addition–cyclization proceeded stereoselectively and (*S*)-**22** and (*R*)-**22** were obtained in 73% and 75% yield and high enantiomeric purity (95% ee), respectively (Scheme 12 and Figure 4). The reductive cleavage of the N–N bond of

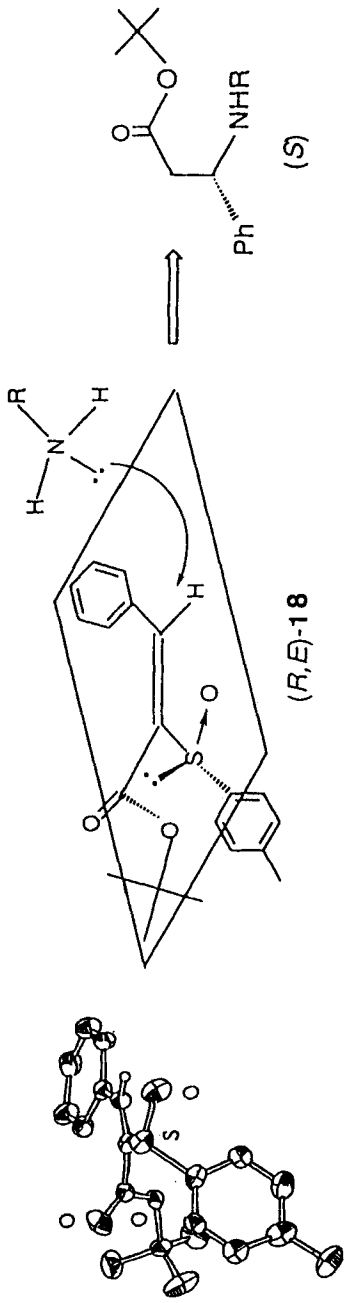
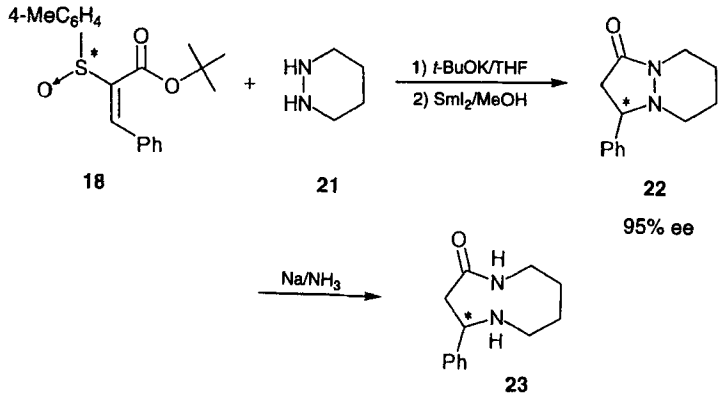


FIGURE 3



SCHEME 12

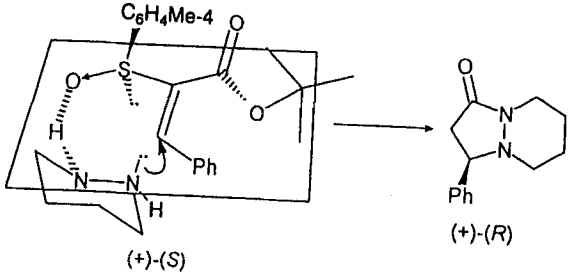
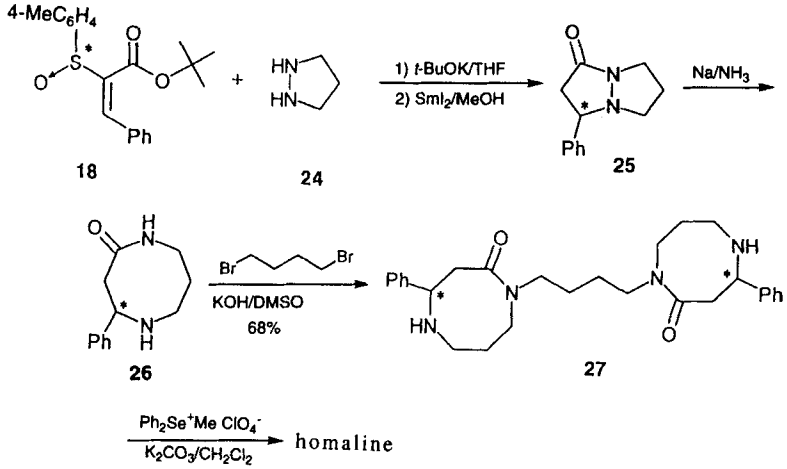


FIGURE 4

enantiomerically pure (*S*)-**22** with sodium (3 equiv.) in liquid ammonia gave the 9-membered azalactam (*S*)-**23**, 97% ee, in 87% yield (Scheme 12). Starting from the optically pure 9-membered lactam **23**, the synthesis of (*S*)-(−)-celacinnine was accomplished by the ring-expansion method.[63,64]

Both (*S*)- and (*R*)-4-phenyl-1,5-diazacyclooctan-2-one **26** have been synthesized stereoselectively with good optical purity (82–87% ee) by the asymmetric conjugate addition of pyrazolidine **24** to the optically active vinyl sulfoxides, *tert*-butyl (*E*)-2-[(*R*)- and (*S*)-*p*-tolylsulfinyl] cinnamate **18**, respectively. Starting from the enantiomerically pure 8-membered lactam **26**, a synthesis of optically active homaline has been achieved (Scheme 13).[60]



SCHEME 13

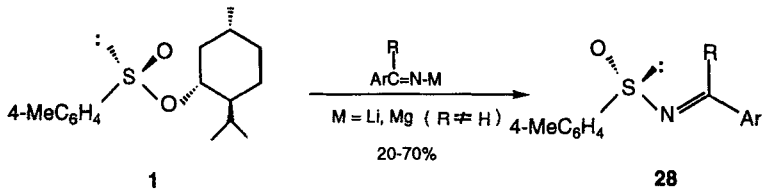
4.3. Asymmetric Additions to Sulfinimines

Asymmetric oxidation of the sulfenimines **29** affords the sulfinimines **30** (88–90% ee) which are chiral ammonia imine synthons and useful in the enantioselective synthesis of β-amino acids and α-hydroxy-β-amino acids such as the C-13 side chain of taxol (2*R*,3*S*).[65]

Annuniata *et al.*[66] and Hua[67] have prepared enantiopure examples of **28** by reaction of metalloketimines, synthesized by treatment of benzonitrile with Grignard and lithium reagents, with (−)-menthyl (*S*)-*p*-toluenesulfinate **1**. However, this "Andersen-type" procedure is limited to the preparation of alkyl aryl sulfinimines **28** (R ≠ H) (Scheme 14).

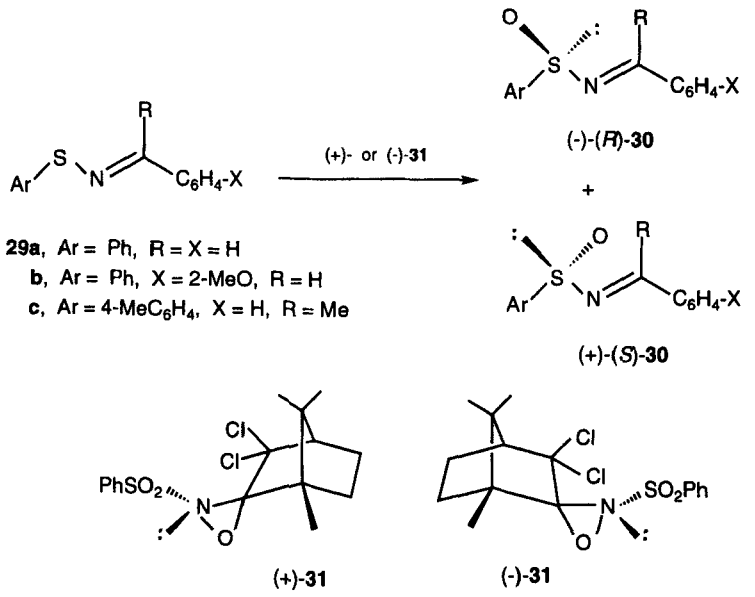
Davis *et al.* have developed a new method for the synthesis of non-racemic sulfinimines in both enantiomeric forms, which avoids this limitation. This methodology involves the asymmetric oxidation of the sulfenimines **29** with (+)- or (−)-*N*-(phenylsulfonyl)(3,3-dichloro-camphoryl)oxaziridine **31** (Scheme 15).[65]

The oxidations were carried out by addition of 1.0 equiv. of (+)- or (−)-**31** to the appropriate sulfenimine **29** in CCl_4. After the oxidation was complete, as determined by TLC, the sulfinimines **30** were isolated by flash chromatography in 85–95% yield and 88–90% ee. Crystallization from *n*-hexane improved the ee's to >97%.



1 28

SCHEME 14

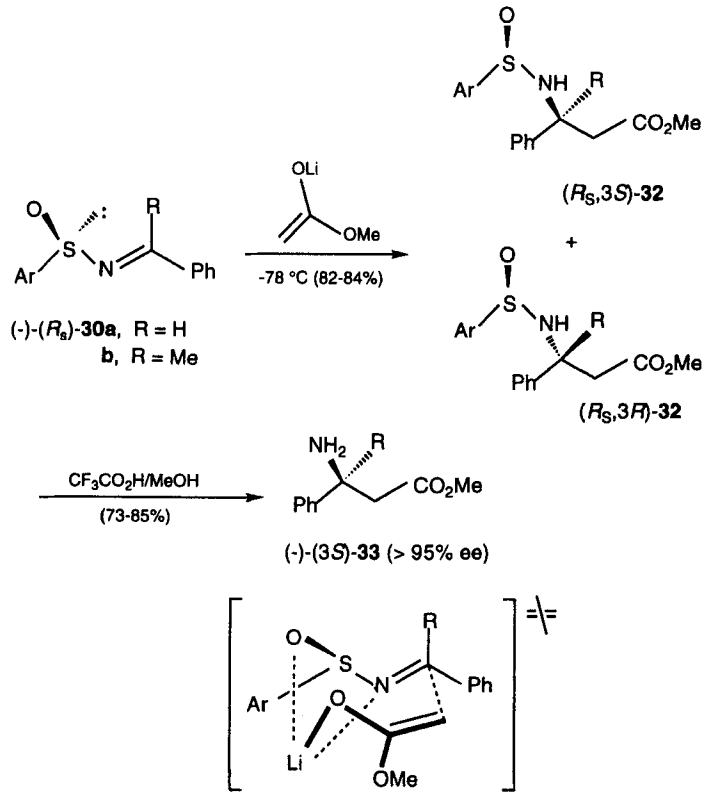


SCHEME 15

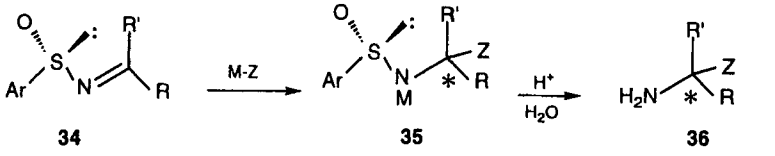
A more general approach to β-amino acids, essential intermediates in organic synthesis, is the addition of enolates to chiral sulfinimines. Addition of 1.5 equiv. of the lithium enolate of methyl acetate (LDA, methyl acetate) to the enantiopure (R_S)-**30a** and (R_S)-**30b** gave the sulfinamides **32a** and **32b**, respectively. The sulfinamide **32a** was obtained as a 90 : 10 mixture of diastereoisomers by flash chromatography and on crystallization from *n*-hexane it afforded (R_S,3*S*)-**32a** diastereomerically pure in 74% isolated yield. The sulfinamide (R_S,3*S*)-**32b** was obtained diastereomerically pure in 90% yield. Significantly, the enolization of the sulfinimine **30b** does not compete with the enolate addition to the C=N double bond. The absolute configurations of the

new amino stereocenters in **32a** and **32b** were determined by hydrolysis, without epimerization, to the β-amino acid (3*S*)-**33a** and (3*S*)-**33b** with 4 equiv. of CF_3CO_2H/MeOH. A Zimmerman–Traxler-type 6-membered transition state TS favoring the approach of the enolate from the *Si*-face of **30** is consistent with these results (Scheme 16).

The sulfinimines **34** are chiral ammonia imine building blocks because addition of the organometallic reagent (M–Z) to the C=N bond affords the sulfinamide **35**, which upon hydrolytic cleavage furnishes the primary amine **36** containing a new stereogenic center (Scheme 17). The application of **34**, derived from aliphatic and aromatic aldehydes and ketones, in highly diastereoselective asymmetric syntheses of amines,[68–70] α-amino acids,[71] β-amino acids,[65,69,72]



SCHEME 16



34 **35** **36**

sulfinimine sulfinamide primary amine

SCHEME 17

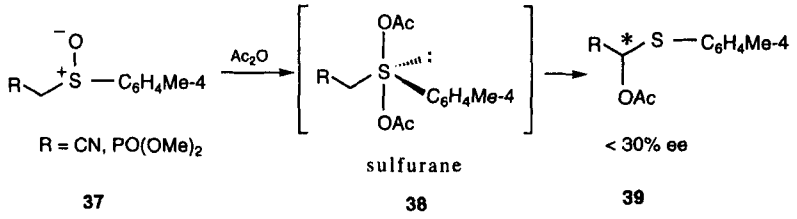
β-amino phosphonic acids,[73] the taxol C-13 side chain[65] and its fluorinated analog,[74] 2-arylpyrrolines,[75] *N*-sulfinyl-*cis*-aziridine-2-carboxylic acids,[76] and β-hydroxy α-amino acids,[77] has recently been reported. Davis *et al.* reported new information on the mechanism, general scope, and efficiency of the asymmetric synthesis of the sulfinimines **34** (R′ = H) from aliphatic and aromatic aldehydes.[78]

5. PUMMERER REARRANGEMENTS

The asymmetric Pummerer reaction of chiral, non-racemic sulfoxides,[79] a self-immolative-type asymmetric induction, is of significant interest, since it allows the synthesis of enantiomerically pure α-substituted sulfides.[80] The intramolecular version of the asymmetric Pummerer-type reaction is especially useful for the synthesis of optically active heterocyclic compounds.[81,82] In the late 1970s, the first asymmetric Pummerer reaction of chiral, non-racemic acyclic sulfoxides was independently reported by Numata and Oae[83] and by Mikolajczyk *et al.* (Scheme 18).[84] The extent of asymmetric transformation, however, never exceeded 30% ee, probably owing to the formation of a sulfurane intermediate **38** by reaction with the acetate anion generated *in situ*. Although the stereochemistry was improved up to 70% ee by the addition of 1,3-dicyclohexylcarbodiimide (DCC) as an effective scavenger of acetic acid, the chemical yield decreased to 10%.[85]

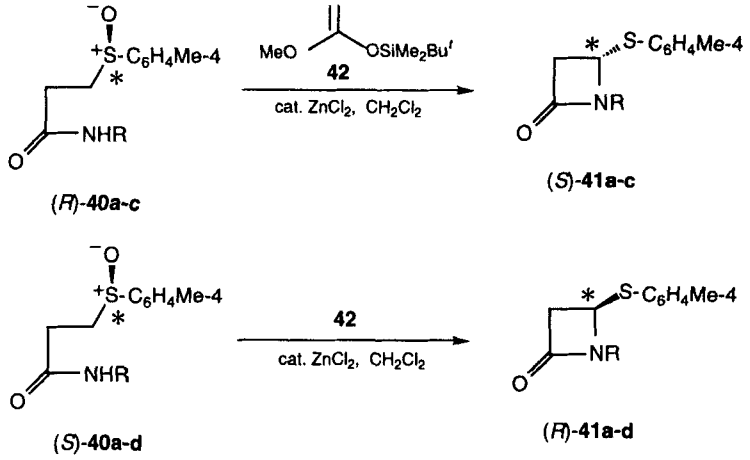
A highly asymmetric Pummerer-type cyclization of chiral, non-racemic β-amido sulfoxides to enantiomerically enriched β-lactams (80–85% ee) has been developed (Scheme 19, Table III).[86]

The (*S*)- and (*R*)-sulfoxides (*S*)-**40a–d** and (*R*)-**40a–c** have been treated with *O*-methyl-*O*-*tert*-butyldimethylsilyl ketene acetal **42** in the presence of a catalytic amount of zinc chloride in methylene dichloride



37 38 39

SCHEME 18



SCHEME 19

TABLE III Asymmetric Pummerer-type cyclization of chiral, non-racemic sulfoxides **40** with **42**

Sulfoxide **40**	*R*	*Conditions*	**41**	% ee (% *yield*)
(*S*)-**40a**	CH(Me)Ph	0 °C, 1 d	(*R*)-**41a**	60 (72)
(*S*)-**40a**	CH(Me)Ph	0 °C, 3 d	(*R*)-**41a**	82 (96)
(*R*)-**40a**	CH(Me)Ph	0 °C, 3 d	(*S*)-**41a**	85 (89)
(*S*)-**40b**	CH_2Ph	5 °C, 6 d	(*R*)-**41b**	80 (54)
(*R*)-**40b**	CH_2Ph	5 °C, 6 d	(*S*)-**41b**	82 (54)
(*S*)-**40c**	$CHPh_2$	15 °C, 2 d	(*R*)-**41c**	80 (84)
(*R*)-**40c**	$CHPh_2$	15 °C, 2 d	(*S*)-**41c**	83 (90)
(*S*)-**40d**	$CH_2C_6H_4Br_2$	5 °C, 7 d	(*R*)-**41d**	83 (59)

to give predominantly the corresponding (4*R*)- and (4*S*)-β-lactams (*R*)-**41a–d** and (*S*)-**41a–c** in more than 80% ee. These results show that the stereoinduction is governed by the absolute configuration of the sulfoxide. Optically pure (*R*)- and (*S*)-**41c** were readily obtained by simple recrystallization in about 60% yield.

The following mechanism is proposed to explain the results with an analysis of the transition state of the reaction of (*S*)-**40** with **42** (Figure 5). Silylation of (*S*)-**40** with **42** affords an intermediate **A** which may then yield the chiral pseudoisothiazolone derivative **B** through axial attack of the amido anion generated by abstraction with the ester anion and elimination of the siloxy ligand. The hydrogen neighboring the sulfur atom is then removed by the siloxy anion and the amido ligand then undergoes a 1, 2 rearrangement from the α-face to give the β-lactam (*R*)-**41**. The usefulness of the chiral, non-racemic 4-tolylthio-β-lactams **41a–d** has been shown by their conversion into the key intermediate for the optically pure carbapenem antibiotic (+)-*PS*-5.[86]

Mechanistic studies of a Pummerer-type reaction in acyclic and rigid cyclic sulfoxides induced by ketene *tert*-butyldimethylsilyl methyl acetal have been carried out.[87]

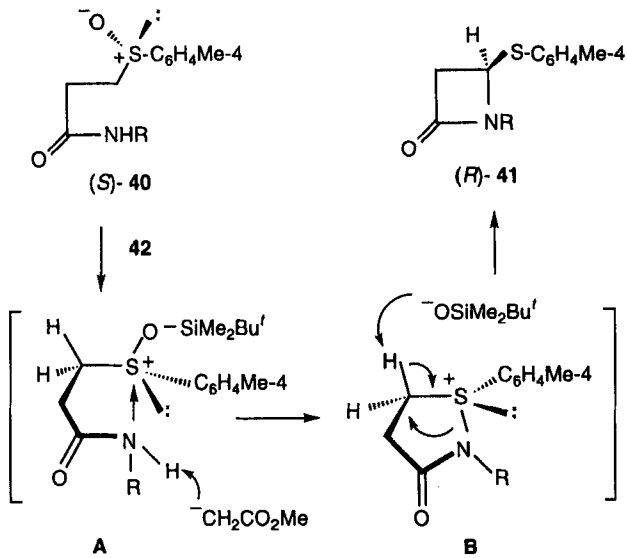


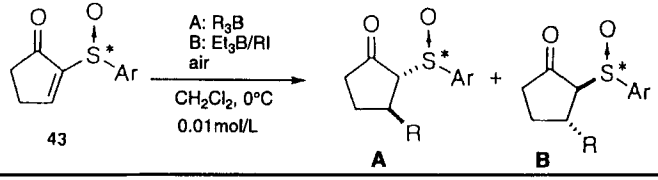
FIGURE 5

6. RADICAL ADDITIONS TO C=C BONDS

Radical-mediated asymmetric reactions have been extensively studied.[88] The addition of radicals to prochiral alkenes bearing a chiral center[89] or a chiral auxiliary[90] is an important radical-mediated asymmetric process. Toru *et al.* envisaged the diastereofacial control of the alkene face β with respect to the carbonyl group by a chiral sulfoxide auxiliary and have reported highly diastereoselective radical β-additions to 2-(arylsulfinyl)-2-cyclopentenones.[91] A carbonyl α to the sulfinyl group can lock the conformation as well as enhance the reactivity toward alkyl radicals, where the sulfur–oxygen and the carbonyl bond would be arranged in an antiperiplanar orientation.[92]

The addition of alkyl radicals to 2-cyclopentenones **43** and to 2-cyclohexenones with chiral bulky arylsulfinyl groups showed excellent diastereoselectivity (Table IV).[93] Performance of the radical addition in the presence of a Lewis acid reversed the stereoselectivity. Both diastereoisomers could be prepared with complete diastereoselectivity in radical β-addition reactions to (*S*)-2-[(2,4,6-trimethylphenyl)sulfinyl]-2-cyclopentenone in the presence and absence of Lewis acid. Since

TABLE IV Radical β-addition to 2-(arylsulfinyl)-2-cyclopentenones **43**



43 **A** **B**

Entry	*Enone*	*Method*	*R*	*Yield* (%)	*Ratio* **A** : **B**
1	**43a**	A	Et	98	57 : 43
2	**43a**	B	*i*-Pr	97	59 : 41
3	**43a**	B	*t*-Bu	96	67 : 33
4	**43b**	B	*t*-Bu	91	38 : 62
5	**43c**	A	Et	98	> 98 : < 2
6	**43c**	B	*i*-Pr	99	> 98 : < 2
7	**43c**	B	*c*-Hex	87	> 98 : < 2
8	**43c**	B	*t*-Bu	97	> 98 : < 2
9	**43d**	A	Et	94	94 : 6
10	**43d**	B	*i*-Pr	99	> 98 : < 2
11	**43d**	B	*c*-Hex	89	> 98 : < 2
12	**43d**	B	*t*-Bu	99	> 98 : 2

43a: (*S*), Ar = 4-MeC_6H_4. **43b**: (*S*), Ar = 3,5-di-*tert*-butyl-4-methoxyphenyl. **43c**: (*S*), Ar = 2,4,6-triisopropylphenyl. **43d**: (*S*), Ar = 2,4,6-trimethylphenyl.

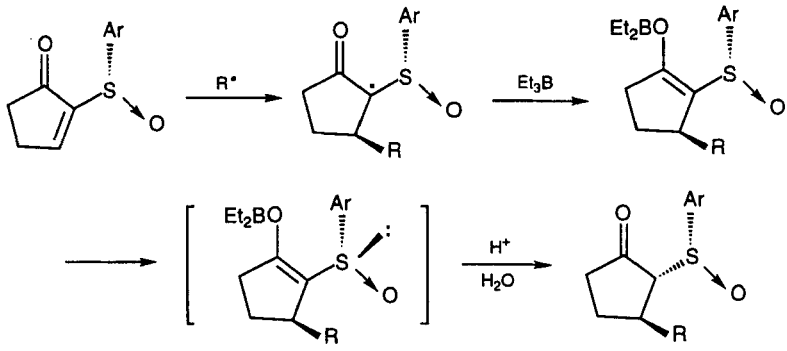


FIGURE 6

the sulfinyl group can be readily removed, these reactions provide a preparative method for chiral 3-alkyl-1-cyclopentanones and -cyclohexanones (Figure 6). The reaction of (*S*,*E*)-3-(*p*-tolylsulfinyl)pent-3-en-2-one with isopropyl radicals, generated from isopropyl iodide and triethylborane, gives a non-stereoselective addition product and an unexpected α-(arylthio)enone which is formed through a radical addition and subsequent Pummerer-type rearrangement.[94]

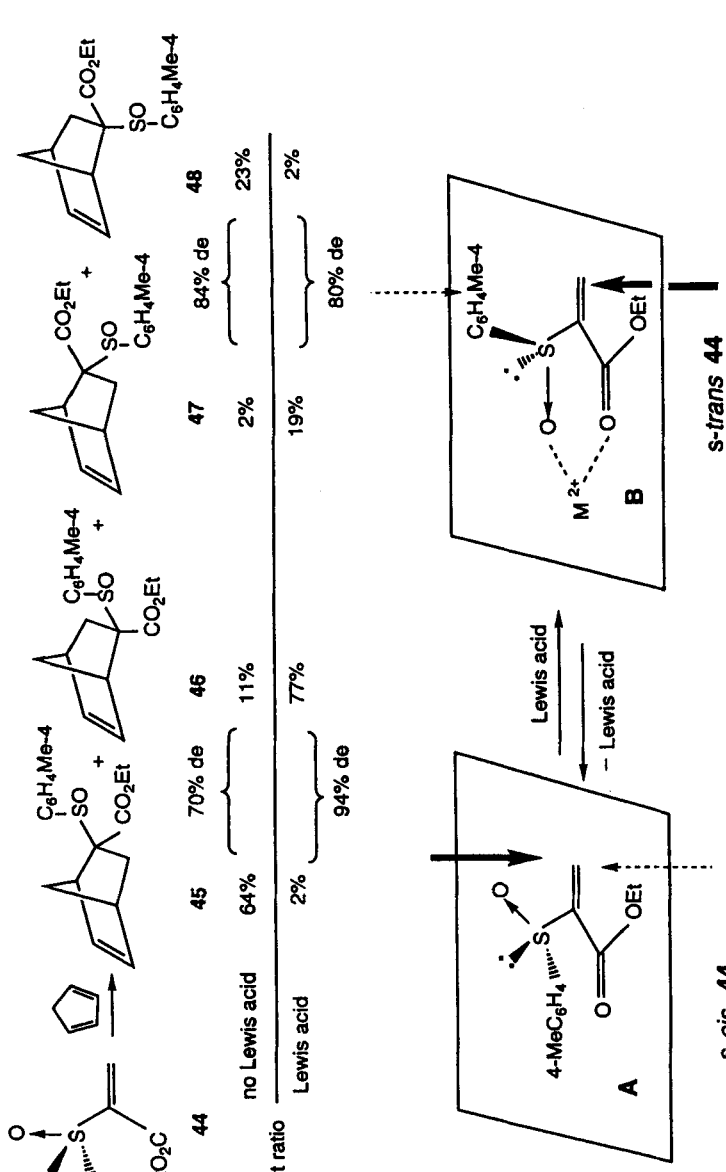
7. CYCLOADDITION REACTIONS

If the dienophile is activated by an optically active sulfoxide group, then the cycloaddition may occur with high diastereoselectivity. In recent years examples of Diels–Alder reactions of optically active sulfinyl dienophiles have been reported. The first report is by Maignan *et al.*[95] who utilized (+)-(*R*)-*p*-tolyl vinyl sulfoxide and cyclopentadiene. They showed the existence of four diastereomers and a poor stereoselectivity (*endo*/*exo* 2 and facial selectivity 2–4), probably due to the lack of dienophile reactivity which requires heating and favors thermodynamic control of the process. Subsequent efforts focused on the design of sulfinyl dienophiles bearing additional electron-withdrawing groups on the double bond such as ketones,[96] esters,[97,98] and sulfones.[97] Although the cycloadditions of these doubly activated dienophiles still proceeded with low *endo*/*exo* selectivity, a serious improvement of the facial selectivity was achieved in both cases. Koizumi *et al.*[98] have

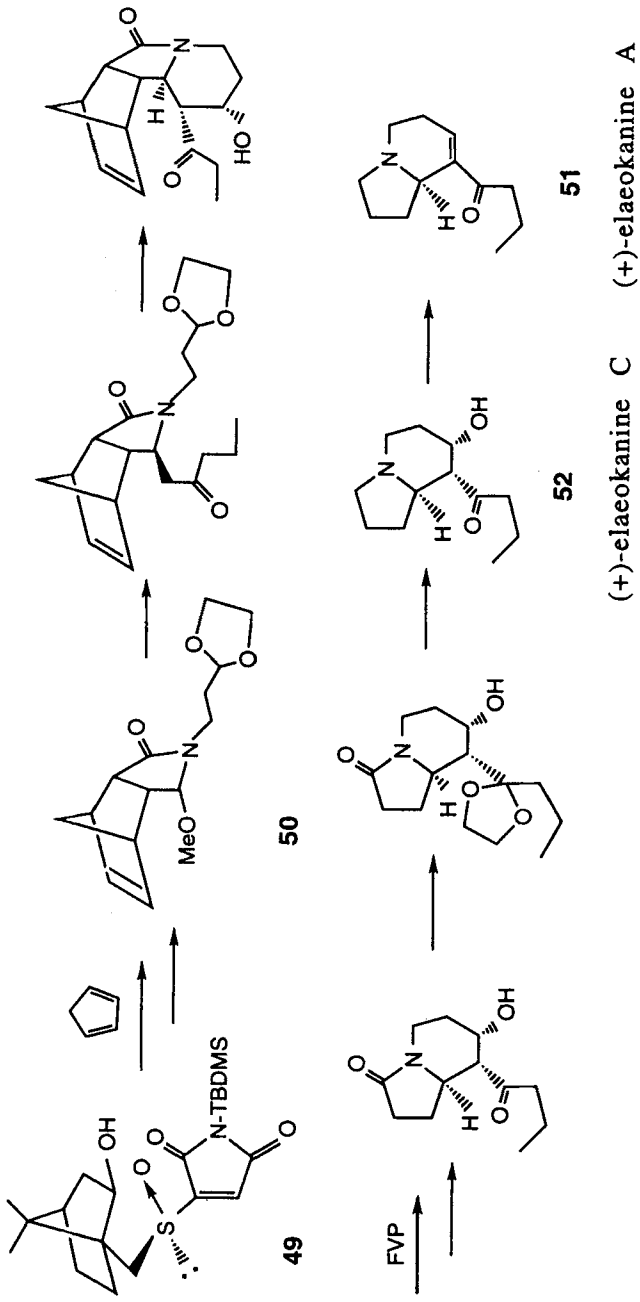
shown that the presence of $ZnCl_2$ in the reaction of ethyl 2-(*p*-tolylsulfinyl)acrylate with cyclopentadiene only slightly changes the *endo*/*exo* ratio but produces a significant increase of the facial selectivity yielding adducts of opposite configuration with respect to those formed in thermal conditions (Scheme 20). Without a Lewis acid, the reaction of **44** and cyclopentadiene affords the adducts **45** and **48** as the major *exo*- and *endo*-sulfinyl products. This can be reasonably explained by assuming that cyclopentadiene would attack the less hindered face of the more stable conformer **A** of **44**, resulting in the formation of the two major products **45** and **48**. On the other hand, in the presence of a Lewis acid ($ZnCl_2$), the two major adducts **46** and **47** are obtained. The chelation of S–O and C=O with the Lewis acid in the dienophile **44** should freeze the rotation around the bond between C=C and S–O, resulting in the favorable conformer **B**. The *exo*- and *endo*-sulfinyl adducts **46** and **47** are thus obtained as the major products. The adducts resulting from the reaction between (−)-(*Z*,*R*)-ethyl 2-methyl-3-(*p*-tolylsulfinyl) propenoate and cyclopentadiene under thermal conditions have been used to prepare santalene-type sesquiterpenes.[99,100]

The chiral α-sulfinyl maleimides **49** can be synthesized in excellent yields from *N*-substituted maleimides and 10-mercaptoisoborneol in a 3-step sequence.[98] The maleimides **49** have been found to be quite reactive toward Diels–Alder dienes. In the presence of $ZnCl_2$ the reaction proceeds with high diastereoselectivity (99 : < 0.5) to produce the adduct. In contrast, in the absence of a Lewis acid, the diastereoselectivity (27 : 73) is low, and the other adduct is obtained as the major product. In no case are the *endo*-sulfinyl adducts obtained. The application of this methodology has culminated in the enantioselective synthesis of bicyclic alkaloids. Starting with the adduct **50** derived from the Lewis acid-promoted Diels–Alder reaction of *N*-TBDMS-maleimide **49** with cyclopentadiene, Arai *et al.* have succeeded in the enantioselective synthesis of (+)-elaeokanine A **51** and (+)-elaeokanine C **52** via flash vacuum pyrolysis (FVP) (Scheme 21).[102]

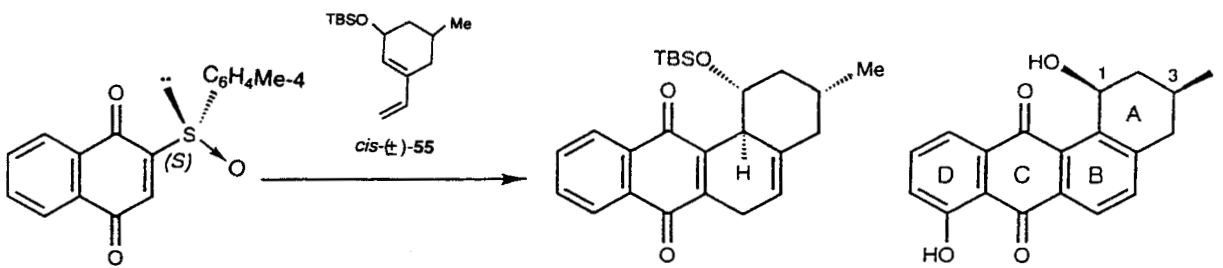
Angucyclines are a large group of naturally occurring quinones of microbial origin which display a broad range of biological activities. This family of antibiotics shares a benz[*a*]anthracene framework of decaketide origin, as well as a methyl group at C3 and an oxygen functionality at C1. An example of angucyclinone antibiotics is (+)-emycin A **53** (Scheme 22). Carreno and co-workers have studied the



SCHEME 20



SCHEME 21



(+)-54 (+)-56 >97% ee (+)-53 (+)-emycin A

SCHEME 22

dienophilic behavior of enantiomerically pure sulfinyl quinones, and found a high ability of the sulfoxides to control the regiochemistry, *endo* selectivity, and π-facial selectivity of cycloadditions with a wide range of dienes.[103] The homochiral sulfinyl quinone **54** is used to discriminate between both faces of a racemic vinylcyclohexene with a bulky alkoxy substituent at the allylic position. Generation of three stereogenic centers in the angular tetracyclic framework of **56** is possible starting from the enantiomerically pure naphthoquinone **54** and the substituted racemic vinylcyclohexene **55**. The product **56** is formed in a one-pot domino reaction comprising Diels–Alder cycloaddition and pyrolytic elimination from the sulfoxide. The key step is the kinetic resolution of the racemic diene (Scheme 22).

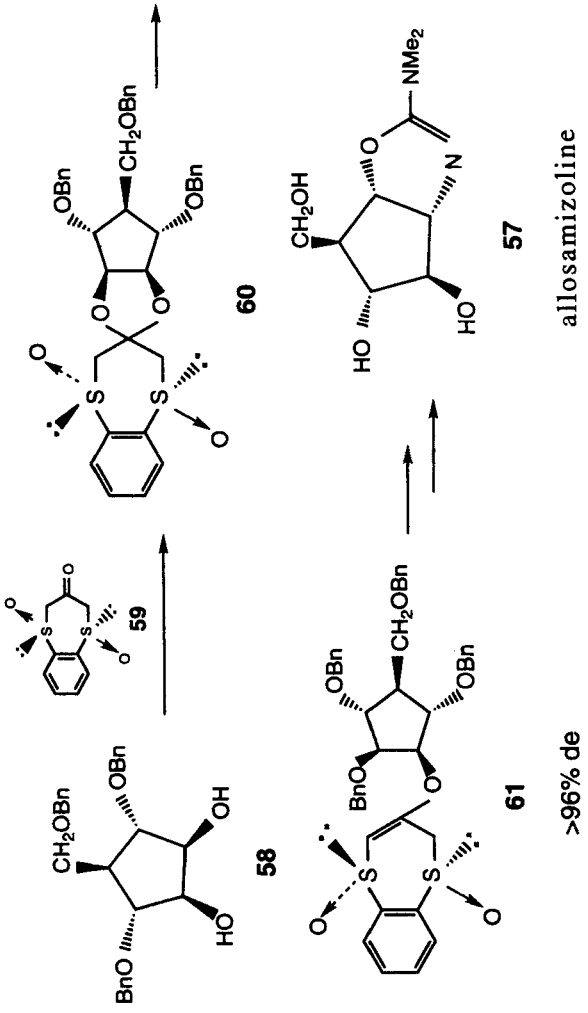
8. STEREOCHEMICAL CONTROL IN OTHER TRANSFORMATIONS

A synthesis of (−)-allosamizoline **57**, a highly potent chitinase inhibitor, has been accomplished via asymmetric desymmetrization of the *meso*-cyclopentitol **58** using the C_2-symmetric bis-sulfoxides **59** as chiral auxiliary.[104]

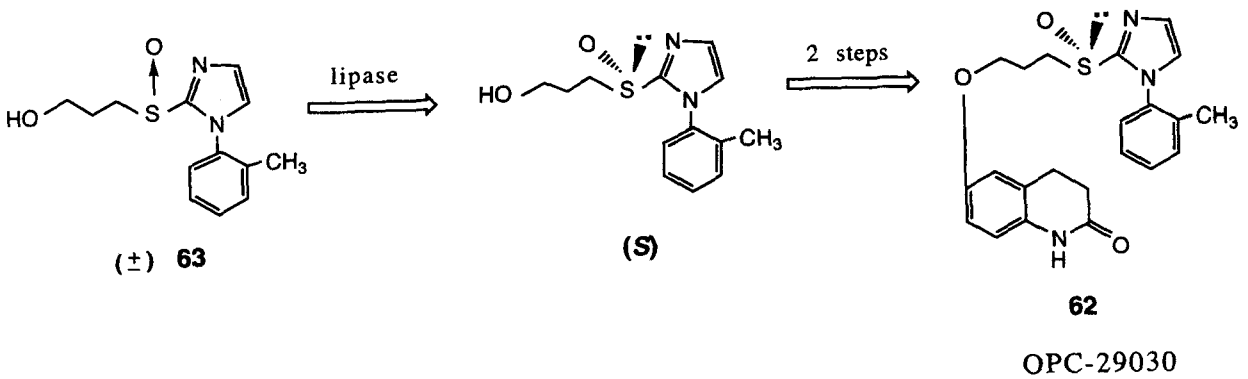
Acetalization of the monosilyl ether of **58** with the (*R*,*R*)-bis-sulfoxide **59**[105] in the presence of TMSOTf proceeds in good yield to give the acetal **60**. On treatment of **60** with KHMDS, followed by benzylation, an acetal cleavage reaction proceeds with high diastereoselectivity (> 96% de) to give the benzyl ether **61**. Then the chiral auxiliary is readily removed by hydrolysis with dilute hydrochloric acid (Scheme 23).

The sulfinyl derivative (*S*)-(+)-3,4-dihydro-6-[3-(1-*o*-tolyl-2-imidazoyl)sulfinylpropoxyl]-2(1*H*)-quinolinone (OPC-29030, **62**)[106] is a new platelet aggregation inhibitor which inhibits the release of (*S*)-12-hydroxyeicosatetraenoic acid (12-HETE) from platelets, and is now under clinical trial. Enzyme-catalyzed processes are some of the most useful synthetic technologies for the preparation of optically active compounds from a racemate. Morita *et al.* have reported the first lipase-catalyzed kinetic resolution of (+)-**63** with a sulfinyl group remote from the reacting site (Scheme 24).[106]

The diastereoselective hydrocyanation of enantiomerically pure *p*-tolylsulfinylacetaldehyde and 2-*p*-tolylsulfinylpropanal with Et_2AlCN



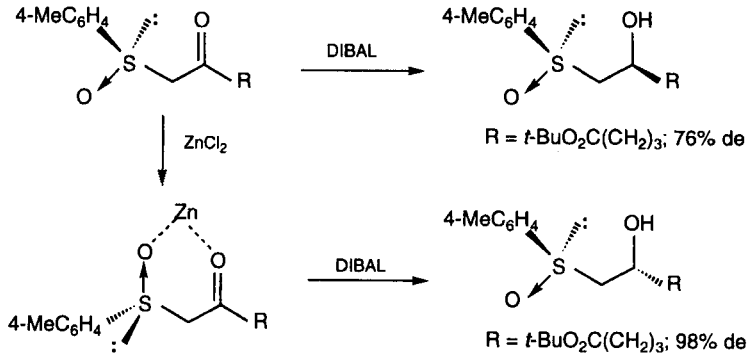
SCHEME 23



SCHEME 24

catalyzed by $ZnBr_2$ has been reported.[107] The sulfur configuration controls the stereochemical course of the reaction. Hydrolysis of the resulting cyanohydrins and further desulfurization yields the corresponding α-hydroxyamides in high ee's (90%).

One of the most versatile methods to obtain enantiomerically pure secondary methyl carbinols involves the reduction of the corresponding enantiomerically pure β-keto sulfoxides with DIBALH or DIBALH/$ZnCl_2$,[108] followed by hydrogenolysis of the carbon–sulfur bond of the resulting β-hydroxy sulfoxides (Scheme 25). The scope of this methodology has recently been extended by Barros *et al.*[109] to the synthesis of other secondary alcohols, using α-alkyl-β-keto sulfoxides as starting compounds. The high stereoselectivity observed in DIBALH reduction has been related to the ability of the aluminum to associate with the unshared electron pair at the sulfinyl group prior to the intramolecular hydride attack.[110] Therefore, it could be expected that the presence in the same molecule of other groups able to compete with the sulfinyl group for association with the metal would have significant negative influence on the stereoselectivity. In order to expand the scope of Solladié's methodology to highly functionalized substrates, the influence of different groups had to be evaluated. In this context several papers concerning the reduction of β-keto sulfoxides bearing additional alkoxy,[111] keto,[112] ester,[113] hydroxyl[114] and carboxylic[115] groups have been published, which demonstrates the predominant role of the sulfinyl group in the stereoselectivity.



SCHEME 25

Recently, many optically active tricoordinate organoselenium and tellurium compounds have been synthesized. Some asymmetric reactions via optically active selenoxides and telluroxides as key intermediates have been developed.[116]

9. CONCLUSIONS

The sulfoxides act as chiral inducers in the reactions mentioned giving good to excellent asymmetric inductions. The key to the success is related to the steric and electronic differences between the substituents at sulfur as well as to the conformational behavior of the sulfinyl group which is able to react in a rigid conformation. The presence in the reaction medium of metal atoms in the reagents or in an added catalyst, which may undergo a bonding interaction with the sulfinyl oxygen, could dramatically modify the nature of the reactive conformation, in many cases being able to achieve products of opposite configuration from a common starting material by changing the reaction conditions.

REFERENCES

[1] K. Mislow and J. Siegel, *J. Am. Chem. Soc.* **106**, 3319 (1984).
[2] G. Solladié, *Synthesis* **1981**, 185.
[3] K. K. Andersen, *The Chemistry of Sulfone and Sulfoxides*, S. Patai, Z. Rappoport and C. J. M. Stirling, Eds. (John Wiley & Sons, New York, 1988), Chapter 3, pp. 56–94.
[4] A. J. Walker, *Tetrahedron: Asymmetry* **3**, 961 (1992).
[5] G. Solladié, *Comprehensive Organic Synthesis*, B. M. Trost and I. Fleming, Eds. (Pergamon, Oxford, 1991), Vol. 6, Chapter 3, pp. 148–170.
[6] G. Kresze, *Methoden der Organischen Chemie* (Houben-Weyl), D. Klamann, Ed. (Georg Thieme Verlag, Stuttgart, 1985), pp. 669–886.
[7] G. Solladié and M. C. Carreno, *Organosulfur Chemistry. Synthetic Aspects*, P. C. B. Page, Ed. (Academic Press, New York, 1995), Chapter 1, pp. 1–47.
[8] G. H. Posner, *The Chemistry of Sulfones and Sulfoxides*, S. Patai, Z. Rappoport and C. J. M. Stirling, Eds. (John Wiley & Sons, New York, 1988), Chapter 16, pp. 823–849; G. H. Posner, *Acc. Chem. Res.* **20**, 72 (1987); G. H. Posner, *Asymmetric Synthesis*, J. D. Morrison, Ed. (Academic, New York, 1983), Vol. 2, pp. 225–241.
[9] G. Solladié, *Asymmetric Synthesis*, J. D. Morrison, Ed. (Academic, New York, 1983), Vol. 2, pp. 157–199.
[10] M. Cinquini, F. Cozzi and F. Montanari, *Organic Sulfur Chemistry, Theoretical and Experimental Advances*, F. Bernardi, G. Csizmadia and A. Mangini, Eds. (Elsevier, Amsterdam, 1985).
[11] D. H. Hua, *Advances in Carbanion Chemistry*, V. Snieckus, Ed. (JAI Press, London, 1992), Vol. 1, p. 249.
[12] K. K. Andersen, *Tetrahedron Lett.* **1962**, 93; K. K. Andersen, W. Gaffield, N. E. Papanikolau, J. W. Foley and R. I. Perkins, *J. Am. Chem. Soc.* **86**, 5637 (1964);

K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons and A. L. Ternay, Jr., *J. Am. Chem. Soc.* **87**, 1968 (1965).
[13] For an improved method for the preparation, see: G. Solladié, J. Hutt and A. Girardin, *Synthesis* **1987**, 173.
[14] I. Fernandez, J. M. Llera and F. Alcudia, *Tetrahedron Lett.* **32**, 7229 (1991); I. Fernandez, N. Khiar, J. M. Llera and F. Alcudia, *J. Org. Chem.* **57**, 6789 (1992); I. Fernandez, N. Khiar and F. Alcudia, *Tetrahedron Lett.* **37**, 5719 (1994).
[15] J. K. Whitesell and M.-S. Wong, *J. Org. Chem.* **56**, 4552 (1991).
[16] J. K. Whitesell and M.-S. Wong, *J. Org. Chem.* **59**, 597 (1994).
[17] P. Pitchen, F. E. Dunach, N. N. Deshmukh and H. B. Kagan, *J. Am. Chem. Soc.* **106**, 8188 (1984).
[18] F. Di Furia, G. Modena and R. Seraglia, *Synthesis* **1984**, 325.
[19] (a) S. H. Zhao, O. Samuel and H. B. Kagan, *Tetrahedron* **43**, 5135 (1987); (b) H. B. Kagan and F. Rebiere, *Synlett* **1990**, 643.
[20] (a) F. A. Davis, R. T. Reddy and M. C. Weismiller, *J. Am. Chem. Soc.* **111**, 5964 (1989); F. A. Davis, R. T. Reddy, W. Han and P. J. Carroll, *J. Am. Chem. Soc.* **114**, 1428 (1992).
[21] Y. Arai, K. Hayashi and T. Koizumi, *Tetrahedron Lett*, **29**, 6143 (1988); J. F. Bower and J. M. Williams, *Tetrahedron Lett.* **35**, 7111 (1994); O. de Lucchi, C. Marchioro, B. Valle and G. Modena, *J. Chem. Commun., Chem. Commun.* **1985**, 878.
[22] D. J. Abott, S. Colonna and C. J. M. Stirling, *J. Chem. Soc. (D)* **1971**, 471.
[23] G. H. Posner and P. W. Tang, *J. Org. Chem.* **43**, 4131 (1978).
[24] M. Mikolajczyk, W. Midura, S. Grzejszczak, A. Zatorski and A. Chefzynska, *J. Org. Chem.* **43**, 473 (1978).
[25] H. Kosugi, M. Kitaoka, K. Tagami and H. Uda, *Chem. Lett.* **1985**, 805; H. Kosugi, M. Kitaoka, K. Tagaimi, A. Takahashi and H. Uda, *J. Org. Chem.* **52**, 1978 (1987).
[26] G. H. Posner and E. Asirvatham, *J. Org. Chem.* **50**, 2589 (1985).
[27] G. H. Posner and C. Switzer, *J. Am. Chem. Soc.* **108**, 1239 (1986).
[28] (a) C. Maignan and R. A. Raphael, *Tetrahedron* **39**, 3245 (1983); (b) T. Koizumi, I. Hakamada and E. Yoshii, *Tetrahedron Lett.* **25**, 87 (1984); (c) C. Maignan, A. Guessous and F. Rouessac, *Tetrahedron Lett.* **25**, 1727 (1984); (d) Y. Arai, S. Kuwayama, Y. Takeuchi and T. Koizumi, *Tetrahedron Lett.* **26**, 6205 (1985); (e) H. Takayama, A. Iyobe and T. Koizumi, *J. Chem. Soc., Chem. Commun.* **1986**, 771; (f) C. Maignan, A. Guessous and F. Rouessac, *Tetrahedron Lett.* **27**, 2603 (1986).
[29] J. P. Marino and A. D. Perez, *J. Am. Chem. Soc.* **106**, 7643 (1984); J. P. Marino and R. Fernandez, *Tetrahedron Lett.* **26**, 5381 (1985).
[30] T. Koizumi, H. Hirai and E. Yoshii, *J. Org. Chem.* **47**, 4004 (1982).
[31] (a) C. Mioskowski and G. Solladié, *J. Chem. Soc., Chem. Commun.* **1977**, 162; (b) C. Mioskowski and G. Solladié, *Tetrahedron* **36**, 227 (1980); (c) G. Solladié and F. Matloubi-Moghadanm, *J. Org. Chem.* **47**, 91 (1982); (d) F. Matloubi and G. Solladié, *Tetrahedron Lett.* **1979**, 2141; (e) G. Solladié, *Synthesis* **1981**, 185; (f) E. J. Corey, L. O. Weigel, A. R. Chamberlin, H. Cho and D. H. Hua, *J. Am. Chem. Soc.* **102**, 6613 (1980).
[32] (a) M. R. Binns, O. L. Chai, R. K. Haynes, A. A. Katsifis, P. A. Schober and S. C. Vonwiller, *Tetrahedron Lett.* **26**, 1565 (1985); (b) D. H. Hua, G. Sinai-Zingde and S. Venkataraman, *J. Am. Chem. Soc.* **107**, 4088 (1985); (c) D. H. Hua, *J. Am. Chem. Soc.* **108**, 3835 (1986); (d) D. H. Hua, S. Venkataraman, R. A. Ostrander, G.-Z. Sinai, P. J. McCann, M. J. Coulter and M. R. Xu, *J. Org. Chem.* **53**, 507 (1988); (e) D. A. Hua, R. Chan-Yu-King and J. A. McKie, *J. Am. Chem. Soc.* **109**, 5026 (1987).
[33] G. Tsuchihashi, S. Mitamura, S. Inoue and K. Ogura, *Tetrahedron Lett.* **1973**, 323.
[34] G. H. Posner, J. P. Mallamo and K. Miura, *J. Am. Chem. Soc.* **103**, 2886 (1981).
[35] G. H. Posner, J. P. Mallamo, M. Hulce and L. L. Frye, *J. Am. Chem. Soc.* **104**, 4180 (1982).
[36] G. H. Posner, M. Hulce, J. P. Mallamo, S. A. Drexler and J. Clardy, *J. Org. Chem.* **46**, 5244 (1981).

[37] G. H. Posner and M. Hulce, *Tetrahedron Lett.* **25**, 379 (1984).
[38] G. H. Posner, T. P. Kogan and M. Hulce, *Tetrahedron* **40**, 1401 (1984).
[39] G. H. Posner, M. Weitzberg, T. G. Hamill, E. Asirvatham, H. Cun-Heng and J. Clardy, *Tetrahedron* **42**, 2919 (1986).
[40] G. H. Posner, T. P. Kogan, S. R. Haines and L. L. Frye, *Tetrahedron Lett.* **25**, 2627 (1984).
[41] G. Posner and E. Asirvatham, *J. Org. Chem.* **50**, 2589 (1985).
[42] G. H. Posner and C. Switzer, *J. Am. Chem. Soc.* **108**, 1239 (1986).
[43] G. H. Posner and M. Weitzberg, *Synth. Commun.* **17**, 611 (1987).
[44] D. J. Abott, S. Colona and C. J. M. Stirling, *J. Chem. Soc., Chem. Commun.* **1971**, 471; D. J. Abott, S. Colona and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 1* **1976**, 492.
[45] S. G. Pyne, *Tetrahedron Lett.* **28**, 4737 (1987).
[46] S. G. Pyne and S. L. Chapman, *J. Chem. Soc., Chem. Commun.* **1986**, 1688.
[47] S. G. Pyne, P. Bloem, S. L. Chapman, C. E. Dixon and R. Griffith, *J. Org. Chem.* **55**, 1086 (1990).
[48] (a) S. Shinagawa, T. Kanamaru, S. Harada, M. Asai and H. Okazaki, *J. Med. Chem.* **30**, 1458 (1987); (b) A. Bongini, G. Cardillo, M. Orena, G. Porzi and S. Sandri, *Tetrahedron* **43**, 4377 (1987); (c) N. Kawabata, Y. Inamoto, K. Sakane, T. Iwamoto and S. Hashimoto, *J. Antibiot.* **45**, 513 (1992); (d) H. Ohki, G. Cashiragi, L. Colombo, G. Rassu and P. Spanu, *J. Org. Chem.* **56**, 6523 (1991).
[49] For reports of the cyclization of β-amino acids to β-lactams, see: (a) N. Mayachi and M. Shibasaki, *J. Org. Chem.* **55**, 1975 (1990); (b) S. Kim, P. H. Lee and T. A. Lee, *J. Chem. Soc., Chem. Commun.* **1988**, 1242; (c) D. Tanner and P. Somfai, *Tetrahedron* **44**, 613 (1988); (d) T. Kunieda, T. Nagamatsu, T. Kiguchi and M. Hirobe, *Tetrahedron Lett.* **29**, 2203 (1988); (e) H. Huang, N. Iwasawa and T. Mukaiyama, *Chem. Lett.* **1984**, 1465.
[50] C. Gennari, I. Venturini, G. Gision and G. Schimperna, *Tetrahedron Lett.* **28**, 227 (1987), and references cited therein.
[51] D. C. Cole, *Tetrahedron* **50**, 9512 (1994).
[52] H. H. Wasserman and J. S. Wu, *Heterocycles* **17**, 581 (1982).
[53] S. Funayama, K. Yoshida, C. Konno and H. Hikino, *Tetrahedron Lett.* **21**, 1355 (1980), and references cited therein.
[54] T. Kaseda, T. Kikuchi and C. Kibayashi, *Tetrahedron Lett.* **30**, 4539 (1989).
[55] K. Ishihara, Y. Kuroki and H. Yamamoto, *Synlett.* **1995**, 41; Y. Kuroki, K. Ishihara, N. Hanaki, S. Ohara and H. Yamamoto, *Bull. Chem. Soc. Jpn.* **71**, 1221 (1998).
[56] M. C. Carreno, *Chem. Rev.* **95**, 1717 (1995).
[57] S. G. Pyne, P. Bloem and R. Griffith, *Tetrahedron*, **45**, 7013 (1989) and references cited thcrein.
[58] F. A. Davis, R. T. Reddy and R. E. Reddy, *J. Org. Chem.* **57**, 6387 (1992).
[59] H. Matsuyama, N. Itoh, M. Yoshida, N. Kamigata, S. Sasaki and M. Iyoda, *Chem. Lett.* **1997**, 375.
[60] N. Itoh, H. Matsuyama, M. Yoshida, N. Kamigata and M. Iyoda, *Bull. Chem. Soc. Jpn.* **68**, 3121 (1995).
[61] For the isolation of (−)-celacinnine: S. M. Kupchan, H. P. J. Hintz, R. M. Smith, A. Karim, M. W. Cass, W. A. Court and M. Yatagai, *J. Org. Chem.* **42**, 3669 (1977); For the synthesis of a racemic 13-membered spermidine alkaloid: B. F. Tawil, A. Guggisberg and M. Hesse, *Tetrahedron* **48**, 3775 (1992).
[62] (a) H. H. Wasserman, R. P. Robinson and H. Matsuyama, *Tetrahedron Lett.* **21**, 3493 (1980); (b) H. Matsuyama, M. Kobayashi and H. H. Wasserman, *Heterocycles* **26**, 85 (1987); (c) H. Matsuyama, N. Itoh and N. Kamigata, *Chem. Lett.* **1990**, 1547.
[63] N. Itoh, H. Matsuyama, M. Yoshida, N. Kamigata and M. Iyoda, *Heterocycles* **41**, 415 (1995).
[64] H. Matsuyama, N. Itoh, M. Yoshida and M. Iyoda, *Phosphorus, Sulfur, Silicon* **120&121**, 475 (1977).

[65] F. A. Davis, T. R. Reddy and R. E. Reddy, *J. Org. Chem.* **57**, 6387 (1992).
[66] R. Annuniata, M. Cinquini and F. Cozzi, *J. Chem. Soc., Perkin Trans. 1* **1982**, 339.
[67] D. H. Hua, S. W. Miao, J. S. Chen and S. Iguchi, *J. Org. Chem.* **56**, 4 (1991).
[68] R. Annuniata, M. Cinquini and F. Cozzi, *J. Chem. Soc., Perkin Trans. 1* **1982**, 339.
[69] D. H. Hua, S. W. Miao, J. S. Chen and S. Iguchi, *J. Org. Chem.* **56**, 4 (1991).
[70] (a) D. R. J. Hose, M. F. Hahon, K. C. Molloy, T. Raynham and M. Wills, *J. Chem. Soc., Perkin Trans. 1* **1996**, 691; (b) T.-K. Yang, R.-Y. Chen, D.-S. Lee, W.-S. Peng, A.-Q. Mi and T.-T. Jong, *J. Org. Chem.* **59**, 914 (1994).
[71] (a) F. A. Davis, P. S. Portonovo, R. E. Reddy and Y.-H. Chiu, *J. Org. Chem.* **61**, 440 (1996); (b) D. H. Hua, N. Lagneau, H. Wang and J. Chen, *Tetrahedron: Asymmetry* **6**, 349 (1995).
[72] J. Jiang, K. K. Schumacher, M. M. Joullie, F. A. Davis and R. E. Reddy, *Tetrahedron Lett.* **35**, 2121 (1994).
[73] M. Mikolajczyk, P. Lyzwa, J. Drabowicz, M. W. Wieczorek and J. Blaszczyk, *J. Chem. Soc., Chem. Commun.* **1996**, 1503.
[74] F. A. Davis and R. E. Reddy, *Tetrahedron: Asymmetry* **5**, 955 (1994).
[75] T. Balasubramanian and A. Hassner, *Tetrahedron Lett.* **37**, 5755 (1996).
[76] (a) F. A. Davis, P. Zhou and G. V. Reddy, *J. Org. Chem.* **59**, 3243 (1994); (b) F. A. Davis and P. Zhou, *Tetrahedron Lett.* **35**, 7525 (1994).
[77] F. A. Davis and G. V. Reddy, *Tetrahedron Lett.* **37**, 4349 (1996).
[78] F. A. Davis, R. E. Reddy, J. M. Szewczyk, G. V. Reddy, P. S. Portonovo, H. Zhang, D. Fanelli, R. T. Reddy, P. Zhou and P. J. Carroll, *J. Org. Chem.* **62**, 2555 (1997); F. A. Davis, R. E. Reddy, J. M. Szewczyk and P. S. Portonovo, *Tetrahedron Lett.* **34**, 6229 (1993).
[79] Asymmetric Pummeer rearrangement: J. P. Marino and A. D. Perez, *J. Am. Chem. Soc.* **106**, 7643 (1984); T. Numata, O. Itoh, T. Yoshimura and S. Oae, *Bull. Chem. Soc. Jpn.* **56**, 257 (1983); O. Itoh, T. Numata, T. Yoshimura and S. Oae, *Bull. Chem. Soc. Jpn.* **56**, 266 (1983).
[80] Reviews, see: (a) S. Oae and T. Numata, *The Pummerer type of reactions, in Isotopes in Organic Chemistry*, E. Buncel and C. C. Lee Eds. (Elsevier, New York, 1980), Vol. 5, Chapter 2; (b) O. D. Lucchi, U. Miotti and G. Modena, *Org. React.* **40**, 157 (1990).
[81] T. Kaneko, Y. Okamoto and K. Hatada, *J. Chem. Soc., Chem. Commun.* **1987**, 1511.
[82] Y. Kita, O. Tamura, T. Miki, H. Tono and N. Tamura, *Tetrahedron Lett.* **30**, 729 (1989).
[83] T. Numata and S. Oae, *Tetrahedron Lett.* **1977**, 1337; T. Numata, O. Itoh and S. Oae, *Chem. Lett.* **1977**, 909.
[84] M. Mikolajczyk, A. Zatorski, S. Grzejszczak, B. Costissella and W. Midura, *J. Org. Chem.* **43**, 2518 (1978).
[85] T. Numata, O. Itoh and S. Oae, *Tetrahedron Lett.* **1979**, 1869; T. Numata, O. Itoh, T. Yoshimura and S. Oae, *Bull. Chem. Soc. Jpn.* **56**, 257 (1983).
[86] Y. Kita, N. Shibata, N. Kawano, T. Tohjo, C. Fujimori, K. Matsumoto and S. Fujita, *J. Chem. Soc., Perkin Trans. 1* **1995**, 2405.
[87] Y. Kita, N. Shibata, N. Yoshida, N. Kawano, C. Fujimori, N. Yoshikawa and S. Fujita, *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2829.
[88] (a) D. P. Curran, N. A. Porter and B. Giese, *Stereochemistry of Radical Reactions;* (VCH, Weinheim, 1995); (b) W. Smadja, *Synlett* **1994**, 1; (c) N. A. Porter, B. Giese and D. P. Curran, *Acc. Chem. Res.* **24**, 296 (1991).
[89] (a) M. Roth, W. Damm and B. Giese, *Tetrahedron Lett.* **37**, 351 (1996); (b) H. Urabe, K. Yamashita, K. Suzuki, K. Kobayashi and F. Sato, *J. Org. Chem.* **60**, 3576 (1995); (c) E. P. Kundig, L.-H. Xu and P. Romanens, *Tetrahedron Lett.* **36**, 4047 (1995).
[90] (a) N. A. Porter, I. J. Rosenstein, R. A. Breyer, J. D. Bruhnke, W.-X. Wu and A. T. McPhail, *J. Am. Chem. Soc.* **114**, 7664 (1992); (b) N. A. Porter, D. M. Scott, I. J. Rosenstein, B. Giese, A. Veit and H.G. Zeitz, *J. Am. Chem. Soc.* **113**, 1791 (1991); (c) R. Vassen, J. Runsink and H.-D. Scharf, *Chem. Ber.* **119**, 3492 (1986); (d) N. Hoffmann, *Tetrahedron: Asymmetry* **5**, 879 (1994).

[91] (a) T. Toru, Y. Watanabe, N. Mase, M. Tsusaka, T. Hayakawa and Y. Ueno, *Pure Appl. Chem.* **68**, 711 (1996); (b) T. Toru, Y. Watanabe, M. Tsusaka and Y. Ueno, *J. Am. Chem. Soc.* **115**, 10464 (1993).
[92] B. M. Trost, T. N. Salzmann and K. Hiroi, *J. Am. Chem. Soc.* **98**, 4887 (1976).
[93] N. Mase, Y. Watanabe, Y. Ueno and T. Toru, *J. Org. Chem.* **62**, 7794 (1997).
[94] N. Mase, Y. Watanabe, Y. Ueno and T. Toru, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1613.
[95] C. Maignan and R. A. Raphael, *Tetrahedron* **39**, 3245 (1983).
[96] C. Maignan, A. Guessous and F. Rouessac, *Tetrahedron Lett.* **27**, 2603 (1986).
[97] O. De Lucchi, V. Lucchini, G. Valle and G. Modena, *J. Chem. Soc., Chem. Commun.* **1985**, 878; O. De Lucchi, V. Lucchini, C. Marchioro and G. Modena, *J. Org. Chem.* **51**, 1457 (1986).
[98] T. Koizumi, I. Hakamada and E. Yoshii, *Tetrahedron Lett.* **25**, 87 (1984); Y. Arai, S. Kuwayama, Y. Takeuchi and T. Koizumi, *Tetrahedron Lett.* **26**, 6205 (1985).
[99] Y. Arai, M. Yamamoto and T. Koizumi, *Chem. Lett.* **1986**, 1225; Y. Arai, M. Yamamoto and T. Koizumi, *Bull. Chem. Soc. Jpn.* **61**, 467 (1988).
[100] Y. Arai and T. Koizumi, *Sulfur Rep.* **15**, 41 (1993).
[101] Y. Arai, T. Kontani and T. Koizumi, *Chem. Lett.* **1991**, 2135.
[102] Y. Arai, T. Kontani and T. Koizumi, *Tetrahedron: Asymmetry* **3**, 535 (1992).
[103] M. C. Carreno, A. Urbano and J. Fischer, *Angew. Chem. Int. Ed. Engl.* **36**, 1621 (1997).
[104] M. Maezaki, A. Sakamoto, T. Tanaka and C. Iwata, *Tetrahedron: Asymmetry* **9**, 179 (1998).
[105] N. Maezaki, A. Sakamoto, M. Soejima, I. Sakamoto, Y.-X. Li, T. Tanaka, H. Ohishi, K. Sakaguchi and C. Iwata, *Tetrahedron: Asymmetry* **7**, 2787 (1996).
[106] S. Morita, J. Matsubara, K. Otsubo, K. Kitano, T. Ohtani, Y. Kawano and M. Uchida, *Tetrahedron: Asymmetry* **8**, 3707 (1997).
[107] M. M. C. Garcia, J. L. G. Ruano, A. M. M. Castro, J. H. R. Ramos and I. Fernandez, *Tetrahedron: Asymmetry* **9**, 859 (1998).
[108] H. Kosugi, H. Konta and H. Uda, *J. Chem. Soc., Chem. Commun.* **1985**, 211; G. Solladié, G. Demailly and C. Greck, *Tetrahedron Lett.* **26**, 435 (1985); G. Solladié, G. Demailly and C. Greck, *J. Org. Chem.* **50**, 1552 (1985); G. Solladié, C. Frechou, G. Demally and C. Greck, *J. Org. Chem.* **51**, 1912 (1986); G. Solladié, A. Rubio, M. C. Carreno and J. L. G. Ruano, *Tetrahedron: Asymmetry*, **1**, 187 (1990).
[109] (a) D. Barros, M. C. Carreno, J. L. G. Ruano and M. C. Maestro, *Tetrahedron Lett.* **33**, 2733 (1992); (b) J. L. G. Ruano, *Phosphorus, Sulfur, Silicon* **74**, 233 (1993).
[110] C. Carreno, J. L. G. Ruano, A.M. Martin, C. Pedregal, J. H. Rodriguez, A. Rubio, J. Sanchez and G. Solladié, *J. Org. Chem.* **55**, 2120 (1990).
[111] (a) G. Solladié and A. Almario, *Tetrahedron Lett.* **36**, 1973 (1994); (b) J. L. G. Ruano, M. C. Maestro and F. S. Sancho, *Tetrahedron: Asymmetry* **6**, 2299 (1995); (c) J. L. G. Ruano, M. C. Maestro, D. Barros and A. M. Gonzalez-Vadillo, *Tetrahedron: Asymmetry* **7**, 1819 (1996).
[112] G. Solladié and N. Chiatou, *Bull. Soc. Chim. Fr.* **131**, 575 (1994).
[113] (a) G. Solladié and A. Almario, *Tetrahedron Lett.* **33**, 2477 (1992); (b) G. Solladié, N. Hauser, J. L. G. Ruano, J. Adrio, M. C. Carreno and A. Tito, *Tetrahedron Lett.* **35**, 5297 (1994).
[114] J. L. Garcia Ruano, A. M. Gonzalez-Vadillo and M. C. Maestro, *Tetrahedron: Asymmetry* **8**, 3283 (1997).
[115] J. L. Garcia Ruano, A. Fuerte and M. C. Maestro, *Tetrahedron: Asymmetry* **5**, 1443 (1994).
[116] For a review, see: T. Shimizu and N. Kamigata, *Org. Prep. Proc. Int.* **29**, 603 (1977).