Asymmetric Ylide Reactions: Epoxidation, Cyclopropanation, Aziridination, Olefination, and Rearrangement†

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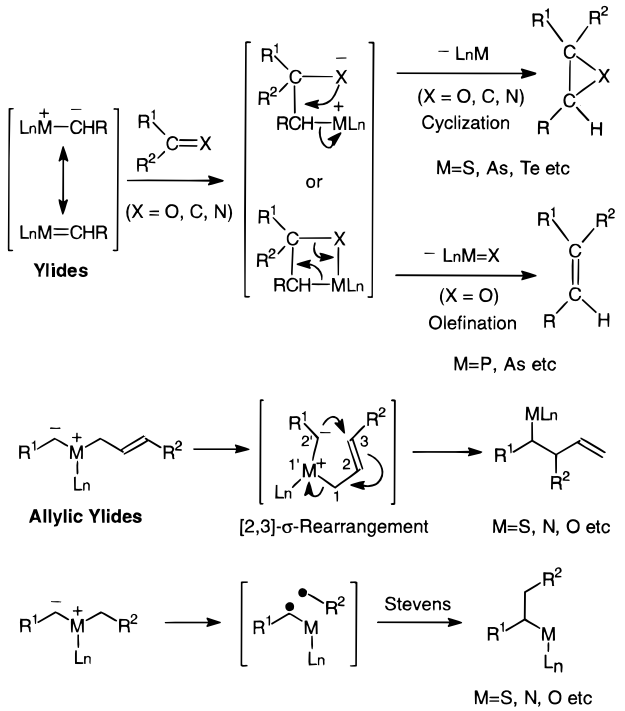
I. Introduction

Although the first ylide appeared as early as the 1900s, the recognition of these structurally interesting compounds as synthetically useful reagents was only realized after the birth of Wittig reaction in 1953.[1] Since then, the chemistry of ylides grew rapidly and they have now become powerful and versatile synthetic tools in the arsenal of organic chemists. In addition to the synthetically important phosphonium[2] and sulfonium[3] ylides, ylides of other heteroatoms,[4] namely ammonium,[5] azomethine,[6] pyridinium,[7] nitrile,[8] aminosulfoxonium,[9] thiophenium,[10] thiocarbonyl,[6c,6f] carbonyl,[8,11] As,[12] Sb,[12a,b,13] Bi,[12a,b] Se,[14] Te,[14a,15] Ge,[16] Sn,[16] and I[17] have been developed and reviewed in recent years.

An ylide can be viewed as a special carbanion, which bears a neighboring positively charged heteroatom. Ylides undergo three types of reactions: olefination, cyclization to a three-membered ring (epoxidation, cyclopropanation or aziridination), and rearrangement reactions ([2,3]-σ-rearrangement or Stevens rearrangement) as shown in Scheme 1. The reaction of an ylide with an electrophilic carbon atom of a C=X (X = O, C, N) bond (carbonyl compounds,

Scheme 1



† Dedicated to Professor Yao-Zeng Huang on the occasion of his 85th birthday and for his significant contributions to the ylide chemistry.

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Li-Xin Dai was born in Beijing, China, in 1924. He received his B.A. from Zhejiang University in 1947. He has been assistant professor, associate professor, and full professor of Shanghai Institute of Organic Chemistry (SIOC) since 1953 and was elected as a Member of Chinese Academy of Sciences in 1993. He is now the Vice President of the Academic Committee of SIOC and the President of the Academic Committee of Laboratory of Organometallic Chemistry, Chinese Academy of Sciences. His research interests are focusing on synthetic methodology and asymmetric synthesis.

Michael acceptors or imines) gives a betaine or oxetane intermediate. From this intermediate, elimination of the heteroatom-containing group can occur in either one of two different modes resulting in cyclization or olefination.

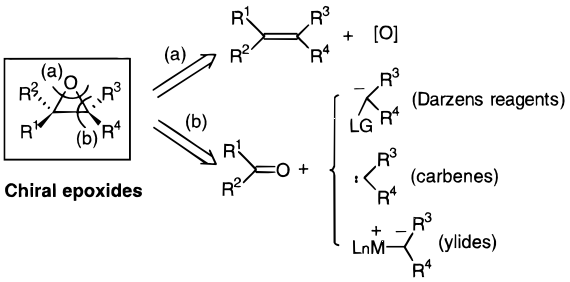
The exploration of asymmetric ylide reactions using a chiral ylide or a chiral C═X compound began in the early 1960s, and many results have been reported in the field of asymmetric reactions via an ylide route over the last 30 years. Although several related summaries were documented in specialized areas, like cyclopropanation,[9,18] epoxidation,[9] and [2,3]-σ-rearrangement,[19] a comprehensive review on asymmetric ylide reaction has not appeared yet. The present review aims to summarize the recent work in the field of asymmetric ylide reactions, with respect to epoxidations, cyclopropanations, aziridinations, [2,3]-σ-rearrangements, and olefinations.

Varinder Kumar Aggarwal was born in Kalianpur (a small village in the state of Punjab) in North India in 1961 and emigrated to the United Kingdom in 1963. He received his B.A. (1983) and Ph.D. (1986) from Cambridge University, the latter under the guidance of Dr. Stuart Warren. He was subsequently awarded a Harkness Fellowship and carried out postdoctoral work with Professor Gilbert Stork at Columbia University, NY (1986–1988). He returned to a lectureship at Bath University and in 1991 moved to Sheffield University where he is currently Reader in Chemistry. His research interests are in synthetic organic chemistry and asymmetric synthesis.

II. Asymmetric Epoxidations

The notable biological significance[20] and various chemical transformations[21] of nonracemic epoxides make them one of the most useful synthetic intermediates.[22] They can be prepared by either enantioselective oxidation of a prochiral C═C bond (route a) or by enantioselective alkylidenation of a prochiral C═O bond, such as via an ylide, carbene, or a Darzens reaction (route b) (Scheme 2). Although the

Scheme 2

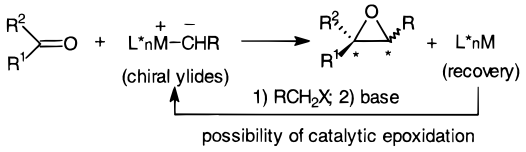


oxidation method has proved overwhelmingly successful,[23] the structural requirements of the substrates are a limiting prerequisite: the Sharpless asymmetric epoxidation[23a] requires allylic alcohols; the Jacobsen method[23b] only works well with *cis* double bonds; and the dioxirane method good for some *trans* olefins.[23c–e] The ylide route provides an alternative nonoxidative approach to prepare optically active epoxides and many results have appeared in recent years. These will be discussed in two parts: reagent-controlled and substrate-controlled ylide asymmetric epoxidations.

A. Reagent-Controlled Asymmetric Epoxidations

The reaction of a chiral ylide reagent with an achiral aldehyde or ketone will give a chiral epoxide with the recovery of chiral ylide precursor, which can usually be reconverted into the ylide reagent (Scheme

Scheme 3

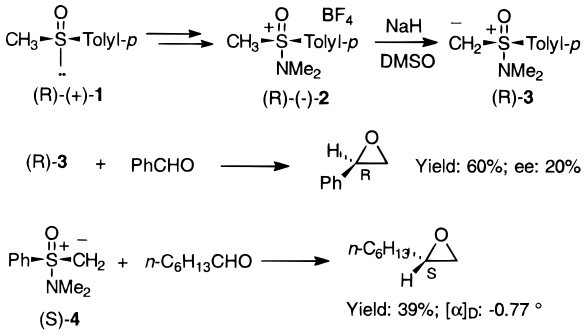


3). The intermediates used in asymmetric epoxidation include sulfonium, aminosulfoxonium, and arsonium ylides. Most work has centered around the use of sulfonium ylides and excellent results have been obtained when these intermediates were used.

1. Chiral Aminosulfoxonium Ylides

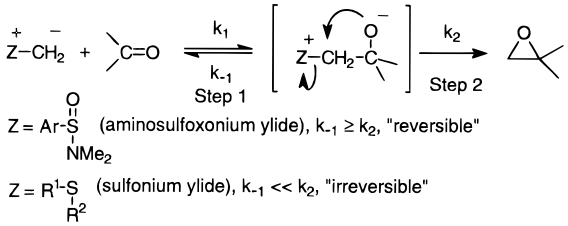
A. W. Johnson[24] first showed that the sulfonium ylides could be used to prepare oxiranes. While it is questionable whether tetrahedral sulfonium ylides can racemize,[25,26] there is no dispute about the configurational stability of aminosulfoxonium ylides. Carl Johnson first prepared enantiomerically pure ylide (*R*)-(−)-**3** starting from sulfoxide (*R*)-(+)-**1** and when reacted with benzaldehyde gave (*R*)-styrene oxide in 20% ee (Scheme 4).[9,27−30] Reaction of ylide

Scheme 4



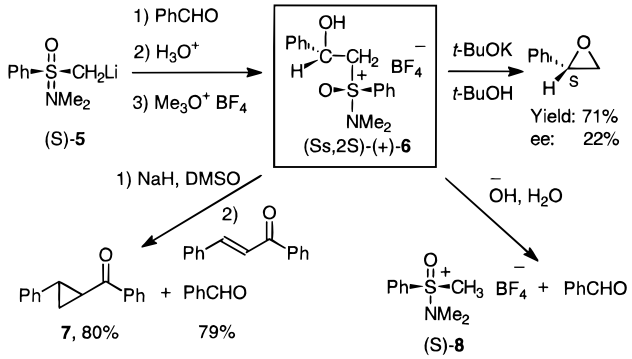
4 with heptaldehyde gave the corresponding epoxide with opposite enantioselectivity as expected.[27,28] The mechanism of epoxidation was investigated. Assuming a two-step mechanism for epoxidation, ylides can react reversibly or irreversibly with carbonyl compounds (step 1) prior to irreversible ring closure (step 2) (Scheme 5). To probe whether ylide additions to

Scheme 5

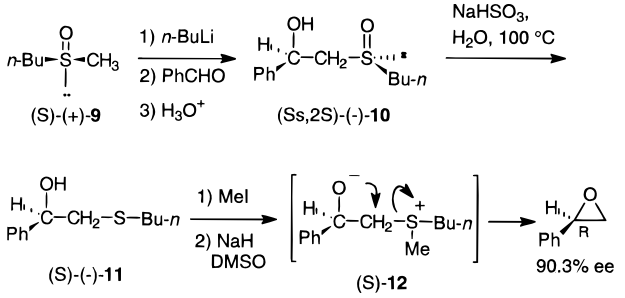


carbonyl compounds were reversible or not, Johnson prepared sulfonium salt **6** (Scheme 6) and sulfide **11** (Scheme 7) in diastereo- and enantiomerically pure form.[29,30] Treatment of **6** with base gave styrene oxide with 22% ee. As this is the same value as that expected from direct addition of ylide (*R*)-(−)-**3** to benzaldehyde, this indicated that the intermediate betaine from aminosulfoxonium ylides was formed reversibly. This was confirmed by deprotonating **6** with base in the presence of chalcone. Only the

Scheme 6



Scheme 7



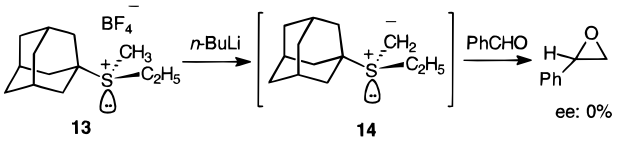
cyclopropane was formed. In contrast, treatment of sulfide **11** with MeI followed by base gave styrene oxide in 90% ee. As alkylation of sulfide **11** gave a mixture of diastereomers; reverse betaine formation would have produced a mixture of enantiomeric ylides which could not have produced such high levels of enantiomeric excess. It was therefore concluded that the intermediate betaine from sulfonium ylides was formed irreversibly.

Although asymmetric epoxidations using aminosulfoxonium ylides have not been extensively explored, the work shown above demonstrated for the first time that nonracemic epoxides could be obtained via chiral ylides.

2. Chiral Sulfonium Ylides

The relative ease of preparation and versatility in epoxidation reactions of chiral sulfonium ylides make them the more useful ones than aminosulfoxonium ylides in the preparation of nonracemic epoxides. Sulfonium salts and their corresponding ylides are tetrahedral and are thus capable of exhibiting optical activity.[25,26] Sulfonium salts can racemize by inversion (and other mechanisms), but the barrier is relatively high and requires elevated temperature.[26] Sulfonium ylides are known to racemize more readily,[25d] but at the temperatures required for racemization they may also decompose.[26d] Trost showed that ylide **14** was configurationally stable under the reaction conditions required for epoxidation as deprotonation of **13** followed by treatment with HBF_4 gave back **13** with identical optical rotation (Scheme 8).[31] Under the same conditions but quenching the ylide with PhCHO gave styrene oxide but with 0% ee.[31] This was the first attempt to use chiral sulfonium ylides for asymmetric epoxidation, and its failure probably resulted in the limited activity in this area over the subsequent 16 years. The failure was probably due to the poor selectivity

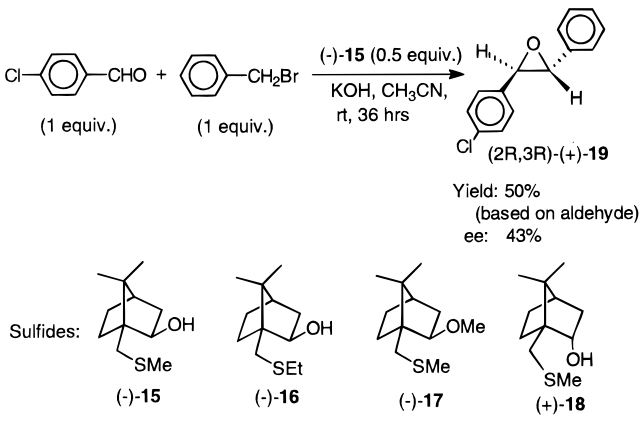
Scheme 8



often observed in reactions of sulfonium methylides with carbonyl compounds (see later). Had Trost attempted to use sulfonium benzylides, asymmetric epoxidation using chiral sulfur ylides may have taken off much earlier.

In 1989, Furukawa's group reported the first successful example of the use of chiral sulfonium ylides for asymmetric epoxidation (Scheme 9).[32] Chiral

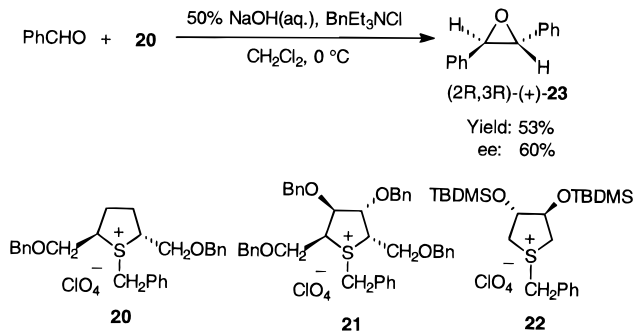
Scheme 9



sulfides (−)-**15**, (−)-**16**, (−)-**17**, and (+)-**18**, which were derived from (+)-10-camphorsulfonic acid, were employed to mediate the reaction of aldehyde and benzyl bromide in the presence of base through the *in situ* formation of sulfonium salts and their corresponding ylides, and *trans*-stilbene oxide (**19**) was obtained in up to 47% ee. The use of substoichiometric amounts of sulfides also gave epoxide but in low yield. Interestingly, sulfide (−)-**17** which is simply the methoxy ether of (−)-**15** gave the opposite enantiomer of stilbene oxide (3*S*,2*S*) compared to (−)-**15** itself.

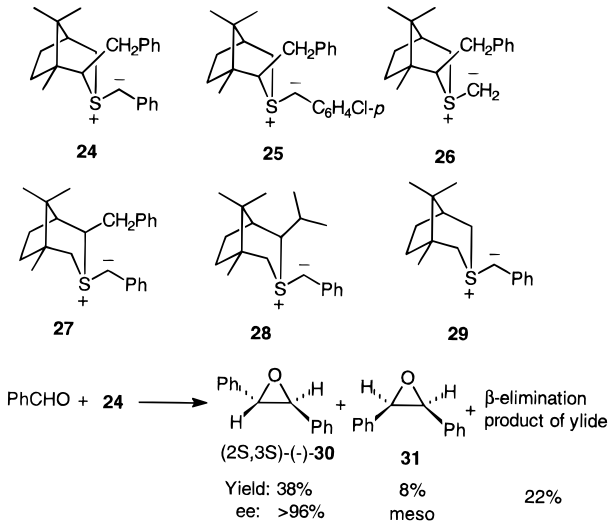
The low level of asymmetric induction may result from formation of a diastereomeric mixture of chiral sulfonium salts, which will react with different and possibly opposite selectivity. The use of C_2-symmetric sulfides was envisaged to overcome this problem. Thus, Durst[33,34] prepared three C_2-symmetric sulfonium salts **20**−**22** to prepare nonracemic diaryloxiranes (Scheme 10). Under phase-transfer

Scheme 10



and low-temperature conditions, (2*R*,3*R*)-*trans*-diaryloxiranes were prepared in good yields, and up to 83% ee for 4-nitrobenzaldehyde was obtained. The presence of oxygenated groups at the 2- and 5-positions may be important. Higher asymmetric induction in epoxidation was reported by the same group[35a,34] using (1*R*,3*S*)-(+)-camphoric acid-derived sulfonium ylides **24**−**29** (Scheme 11). Although they

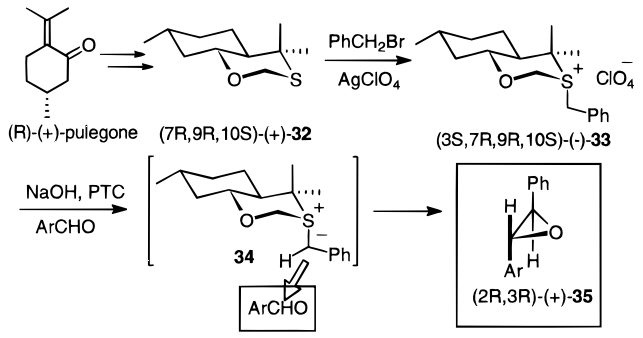
Scheme 11



are prepared from non-C_2 symmetric sulfides, alkylation yielded a single diastereomeric sulfonium salt. From a single diastereomeric sulfonium salt, only one ylide isomer having a defined configuration at sulfur is formed. High enantioselectivity was reported for benzylidene transfer (**24** gave up to 96% ee[35b] but only low enantioselectivity for methylene transfer (**26** gave up to 4% ee) in less than 50% yields. The epoxidations of aliphatic aldehydes and a ketone with chiral sulfonium ylides were also demonstrated.

Durst claimed that in order to ensure high sulfur nucleophilicity, the sulfide should be devoid of other electronegative heteroatoms. However, a very successful asymmetric epoxidation with chiral oxathiane-derived sulfonium ylides was reported by Solladié-Cavallo (Scheme 12).[36−39] For aromatic aldehydes,

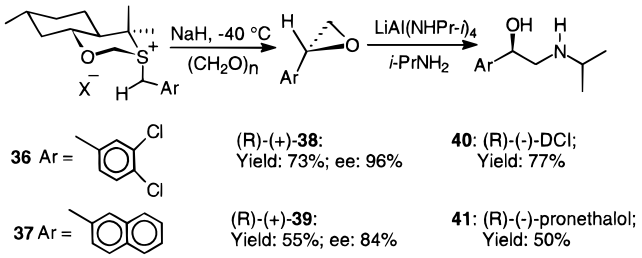
Scheme 12



up to 100% ee were obtained in reasonable yields. The X-ray analysis of sulfonium salt **33** showed that unusually, alkylation of the axial lone pair had occurred.[37] This is the first example of a six-membered sulfonium salt having the third axial group at sulfur. This was explained by the 1,3-anomeric effect: the equatorial lone pair may overlap

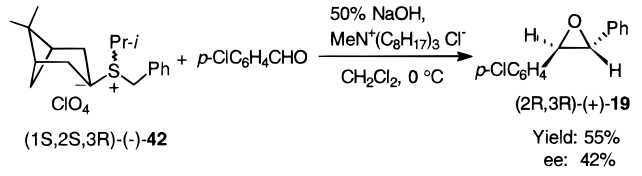
with σ^* of the C−O bond and so be less nucleophilic than the axial lone pair. There is an alternative steric argument with the consideration of gauche interaction with a neighboring methyl group may also operate. This asymmetric ylide epoxidation method has been successfully applied in the synthesis of two (*R*)-*β*-adrenergic compounds **40** and **41** (Scheme 13).[38] Recently, a two-step process for the preparation of (2*R*,3*R*)-*trans*-diaryloxiranes of >99% ee was also reported by the same group.[39]

Scheme 13



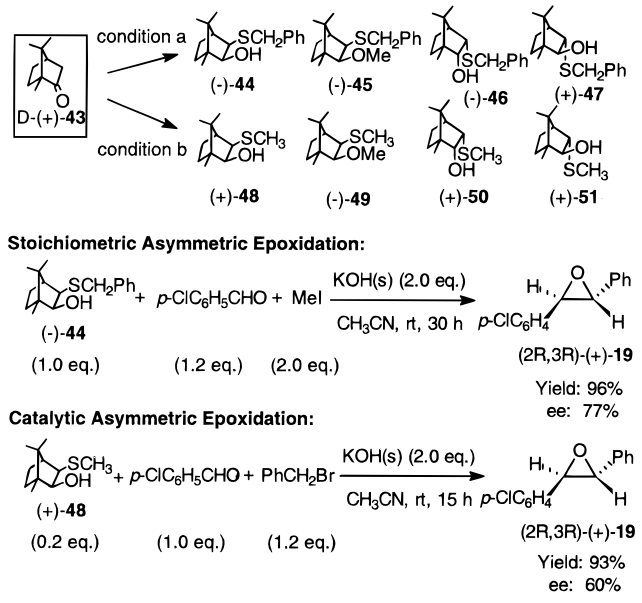
Aggarwal[40] reported an asymmetric epoxidation using sulfonium salt (−)-**42**-derived ylides, where the S atom was situated outside the ring system (Scheme 14). The ee values were lower than those reported by Durst and Solladié-Cavallo's systems.

Scheme 14



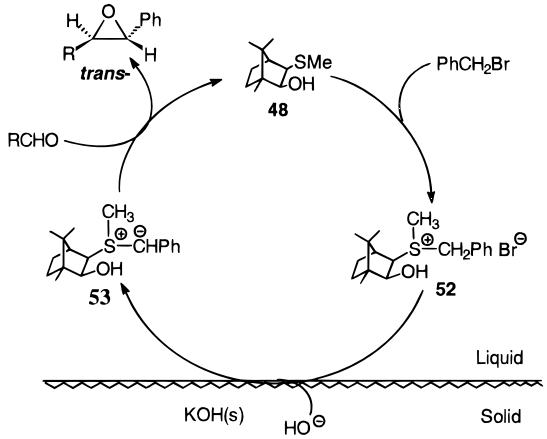
An efficient stoichiometric and a catalytic epoxidations have been developed recently in Dai's group (Scheme 15).[41] From the same starting material

Scheme 15



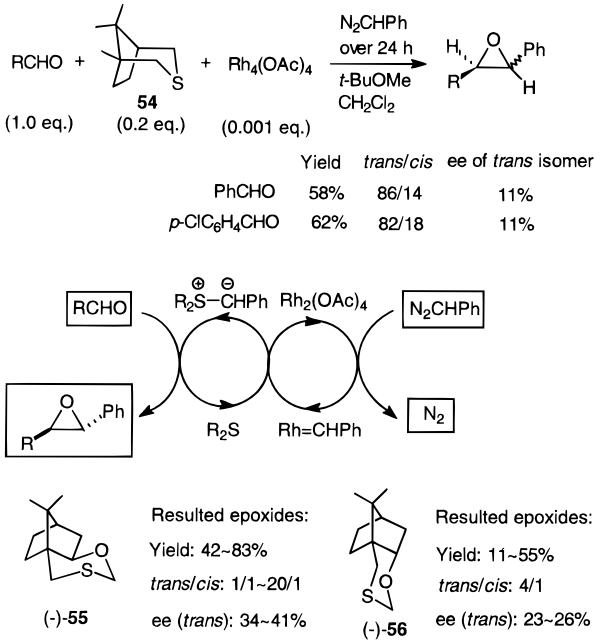
D-(+)-camphor (**43**), chiral sulfides in which the sulfur atom was situated outside the ring and oriented at *exo* (**44**, **45**, **48**, **49**) or *endo* (**46**, **47**, **50**, **51**) were prepared and used in a one-pot asymmetric ylide epoxidations. Epoxides with opposite asymmetric induction were obtained using either *exo* or *endo* sulfides. When benzylated sulfides **44**−**47** were used for asymmetric benzylidene transfer, a stoichiometric epoxidation was realized with high ee and *trans* isomer was obtained exclusively. A catalytic version of this reaction was also achieved by employing methylated sulfides **48**−**51**. As high yields and enantioselectivities were obtained, this reaction may be regarded as a good example of catalytic asymmetric epoxidation via an ylide route. The mechanism of this catalytic epoxidation reaction was proposed (Scheme 16).

Scheme 16

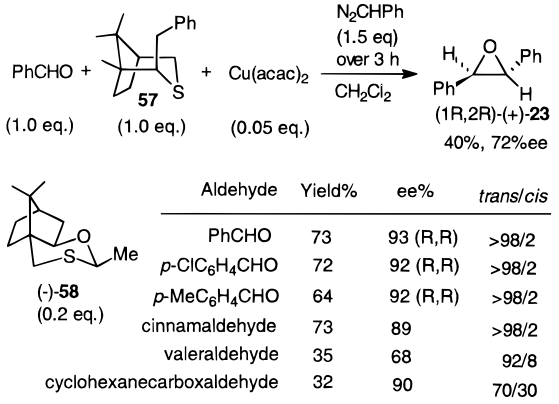


To render the ylide epoxidation more synthetically useful, the catalytic mode has been the target of many groups. It is probable that the formation of the sulfonium salt in the catalytic cycle is rate-determining, and it is essential that this is fast. However, in most cases, the formation of sulfonium salts usually requires a silver salt, like $AgBF_4$ and $AgClO_4$. Only in a few examples, the formation of sulfonium salts through the direct reaction of the corresponding sulfide and halide had no problem. Some sulfonium salts could not be prepared even in the presence of silver salt.[34] Fortunately, an alternative method for ylide formation, i.e., by the reaction of carbenes or carbenoids with heteroatom lone pairs, is available.[4] This idea has been used in asymmetric epoxidation by Aggarwal and co-workers,[42,43] who have developed a one-pot catalytic asymmetric epoxidation process by generation of a sulfonium ylide *in situ* (Scheme 17). In this process, the sulfonium ylide was formed directly from the reaction of chiral sulfide **54** and phenyl diazomethane, catalyzed by rhodium acetate. However, only very low ee values were obtained. Better asymmetric induction was achieved when oxathianes **55** and **56** were used.[43] Recently, very encouraging results were reported by the same group (Scheme 18).[44a] Aggarwal reported that while the more hindered chiral sulfide **57** did not give epoxide under $Rh_2(OAc)_4$ catalysis, using $Cu(acac)_2$ a reasonable yield and good enantioselectivity of stilbene oxide was obtained.[44a] This suggested that $Cu(acac)_2$ was a superior catalyst compared to $Rh_2(OAc)_4$ in the formation of sulfur ylides from hindered sulfides. Very high levels of asymmetric induction was finally realized using thioacetal (−)-**58** which simply possesses one additional methyl

Scheme 17



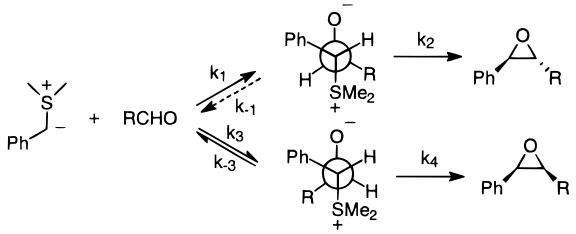
Scheme 18



group more than (−)-**55**. The enantioselectivities are greater than 90% for aromatic aldehydes but slightly lower for α,β-unsaturated aldehydes. However, the lower yields and diastereoselectivity for aliphatic aldehydes limits the scope of the process. Nevertheless, this method of ylide formation solves the problem of slow alkylation reactions of sulfides used in the more conventional epoxidation process.

The origin of the *cis*/*trans* selectivity in reactions of benzyl sulfonium ylides with aldehydes and in particular whether reactions are under kinetic or thermodynamic control have been studied.[44b] From independent generation of single diastereomers of betaine intermediates and carrying out ring closure and cross-over experiments it was found that epoxide formation was essentially under kinetic control. The *trans*-epoxide was derived from irreversible formation of the *anti*-betaine in polar or nonpolar solvent ($k_2 > k_{-1}$) but the *cis*-epoxide was derived from reversible formation of the *syn* betaine ($k_{-3} > k_4$) (Scheme 19). The higher *trans* selectivity observed in reactions involving aromatic aldehydes compared to aliphatic aldehydes was due to greater reversibility in the formation of the *syn*-betaine. The higher *trans* selectivity observed in reactions of benzaldehyde with ylides derived from (−)-**58** compared to **54** again is a

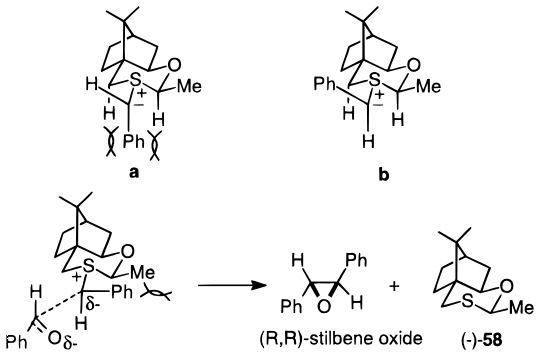
Scheme 19



result of even greater reversibility in the formation of the *syn* betaine ($k_{-3} \gg k_4$). The degree of reversibility was highly solvent dependent and increased in more polar solvents. As the *trans*-epoxide was formed from irreversible formation of the *anti*-betaine it was concluded that nonbonded interactions in the transition state for betaine formation were important.

Having determined that reactions of benzyl sulfonium ylides were essentially under kinetic control it became possible to provide a mechanistic rationale for the high asymmetric induction observed in reactions involving sulfide (−)-**58**. The ylide can adopt two conformations **a** or **b** in which the filled orbital on the ylide carbon is perpendicular to the lone pair on sulfur (Scheme 20).[25a,c,f,g] However, ylide **a** suffers

Scheme 20

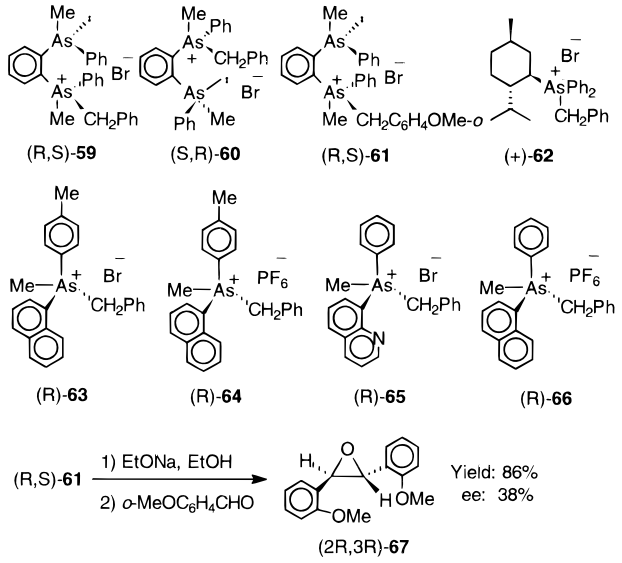


from 1,3-diaxial interactions of the phenyl group with the axial H's and so **b** is preferred. The aldehyde can attack either face of ylide **b** but the equatorial methyl group hinders *Si* face attack and hence *Re* face is preferred. Since the *trans*-epoxide is obtained this dictates the orientation of the aldehyde as it approaches the *Re* face of the ylide and gives rise to the (R,R)-epoxide.

3. Chiral Arsonium Ylides

Compared with those of sulfonium ylides, the use of chiral arsonium ylides in the asymmetric ylide epoxidation has received less attention. Wild's two papers[45,46] represent the only examples. Optically pure arsonium salts **59**−**61** and **63**−**66**, which were obtained from the resolution of the corresponding racemates and (−)-menthol-derived **62**, have been used for asymmetric benzylidene transfer (Scheme 21). These ylide reactions proceeded via a similar mechanism to the sulfonium ylides. The highest ee value of 38% (for compound **67**) was obtained in these epoxidations.

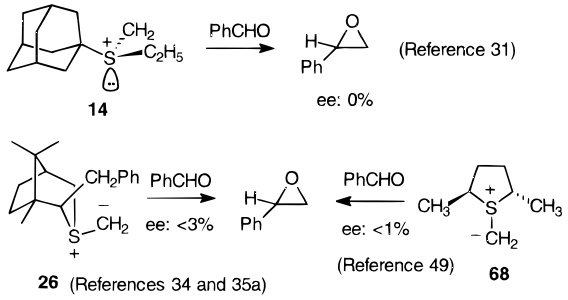
Scheme 21



4. Other Related Reagents

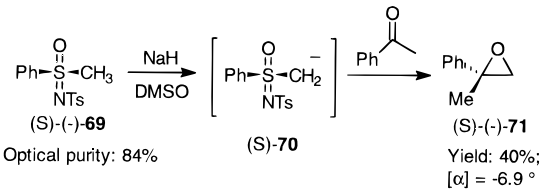
Optically active styrene oxide of high ee from the reaction of benzaldehyde and dimethylsulfonium methylide in the presence of chiral phase-transfer catalysts was reported by Hiyama and colleagues.[47] The high ee values (up to 97%) are noteworthy. Even using the well-established Jacobsen asymmetric epoxidation,[48] the preparation of styrene oxide in high ee is still a challenge. Moreover, the asymmetric methylene transfer from chiral sulfonium ylides to C=O bonds has not been successful to date (Scheme 22).[31,34,35a,49] Unfortunately, Hiyama's work was questioned and considered incorrect five years later.[50]

Scheme 22

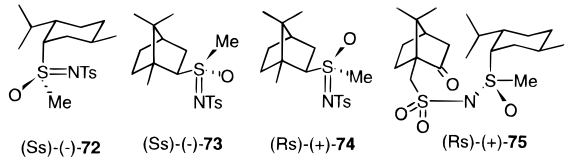


As mentioned above, monosubstituted or 2,2-disubstituted optically active oxiranes are difficult to prepare by asymmetric methylene transfer from chiral sulfonium ylides. Fortunately, several other methods have been documented. Asymmetric methylene transfer from chiral sulfoximine anions to C=O bonds was first demonstrated by Johnson et al.[51] Optically active (*S*)-(−)-2-methyl-2-phenyloxirane (**71**) was successfully prepared by the reaction of (*S*)-**70** and acetophenone (Scheme 23). This reaction was revisited by Soman and co-workers[52,53] 20 years later (Scheme 24). They used (−)-menthol and D-(+)-camphor-derived sulfoximines **72**−**75** in asymmetric methylene transfer, and obtained 2,2-disubstituted oxiranes in up to 86% ee. They investigated the influence of chirality at sulfur and the nature of the group on nitrogen on the asymmetric induction of the epoxidation process. By changing the chirality at

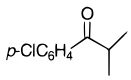
Scheme 23



Scheme 24



The ee values of epoxides from the reaction of sulfoximines and C=O bonds.

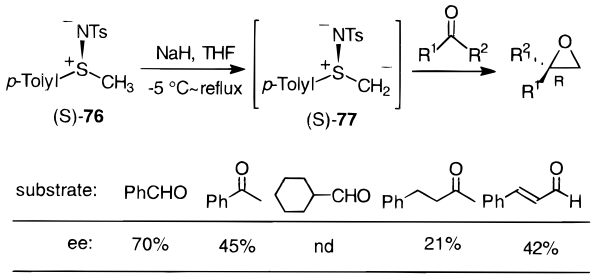
Aldehydes	(Ss)-(-)-72*	(Ss)-(-)-73	(Rs)-(+)-74	(Rs)-(+)-75
PhCHO	66.2%, (R)-(+)-	28.6%, (S)-(-)-	28.5%, (S)-(-)-	61.0%, (S)-(-)-
p-ClC$_6$H$_4$CHO	55.8%, (R)-(+)-	21.7%, (S)-(-)-	18.6, (S)-(-)-	49.9%, (S)-(-)-
	82.3%, (-)-	nd, (-)-	56.9%, (+)-	86.1%, (+)-
	86.0%, (-)-	58.1%, (-)-	68.2%, (+)-	81.2%, (+)-

* The oxiranes, obtained from (Rs)-(+)-**72**, showed [α] nearly equal in magnitude, but opposite in sign to those of oxiranes from (Ss)-(-)-**72**.

sulfur (**73** *vs* **74**) they obtained similar levels of asymmetric induction in reactions with aldehydes but opposite selectivity in reactions with ketones. Changing the substituent on nitrogen made little difference to the asymmetric induction observed (**75** *vs* **72**). These results showed that the chirality on the carbon substituent was the most important factor in determining the outcome of the epoxidation process. Changing chirality at sulfur had a mixed effect.

The first asymmetric methylene transfer from chiral sulfimides to C=O bonds was recently reported by Taylor et al. (Scheme 25).[54] Anion **77**, formed by deprotonation of sulfimide (*S*)-**76**, reacted smoothly with aldehydes and ketones to give (*R*)-epoxides in 21−70% ee.

Scheme 25



Although there are only a few reports on the preparation of optically active epoxides by asymmetric methylene transfer from chiral sulfoximines and sulfimides, the examples illustrated provide a good complement to the sulfonium ylide approach.

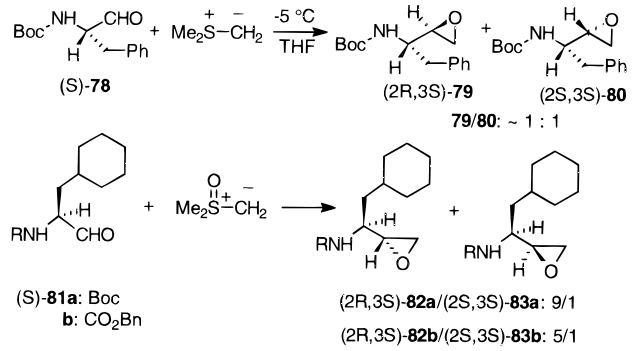
B. Substrate-Controlled Asymmetric Epoxidations

The reaction of a chiral carbonyl compound and an achiral ylide is another direct method to prepare

optically active epoxides. This constitutes the substrate-controlled asymmetric ylide epoxidations. Some synthetically useful epoxidation methods involving the reaction of easily available chiral substrates, like amino aldehydes, sugar derivatives, carbohydrates, etc., and sulfonium or sulfoxonium ylides have been developed.

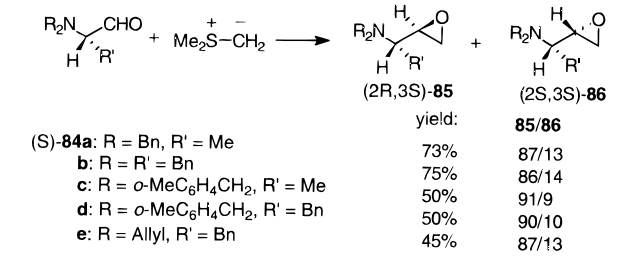
In the synthesis of hydroxyethylene dipeptide isosteres, Evans[55] found that a ~1:1 mixture of diastereomers of chiral aminoalkyl epoxides **79** and **80** were obtained in the reaction of Boc-L-phenylalanine-derived amino aldehyde (*S*)-**78** and dimethylsulfonium methylide (Scheme 26). Using the same ylide

Scheme 26



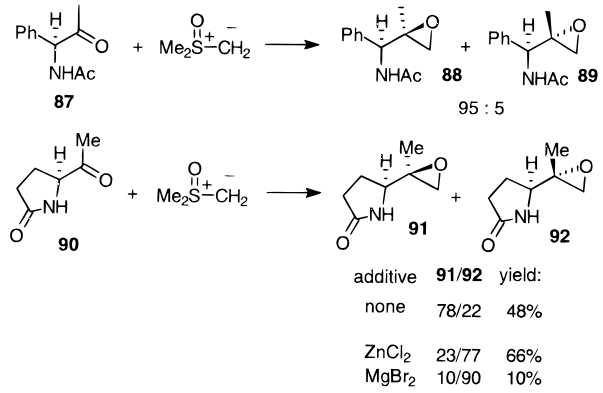
with aldehyde **81a** gave a 1:1 mixture of **82a**:**83a**.[56] However, much better stereoselectivity was achieved in reactions of dimethylsulfoxonium methylide with protected cyclohexyl-L-alaninals (*S*)-**81a**[56] and (*S*)-**81b**.[57] The produced epoxyamines **82a** and **82b** have been applied to the synthesis of human renin inhibitors. The reaction of dimethylsulfonium methylide with α-amino aldehydes bearing different protecting groups (compare **84** and **78**) has been studied by Reetz (Scheme 27).[58a] In contrast to Evans' results,[55]

Scheme 27



high diastereoselectivity was obtained in reactions of α-amino aldehydes (**84**) although some degree of racemization upon scale up has been reported (up to 80%) due to the strongly basic conditions required for ylide formation.[58b,c] Using triphenylarsonium methylide instead of sulfonium ylide, even greater asymmetric induction (95:5) was observed. The stereoselectivity of the reaction of α-amino ketones and dimethylsulfoxonium methylide has also been studied.[59] A 95:5 diastereomeric mixture of **88** and **89** was afforded when ketone **87** was submitted to this ylide epoxidation (Scheme 28). Interesting salt effects have also been observed in the epoxidation of cyclic amino ketone **90**. The diastereomer ratio was reversed by the presence of $ZnCl_2$ or $MgBr_2$, probably

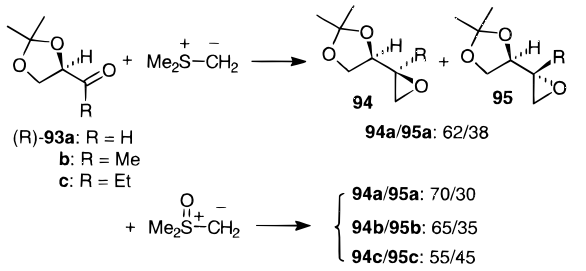
Scheme 28



as a result of chelation of the ketone and amide groups with the metal.

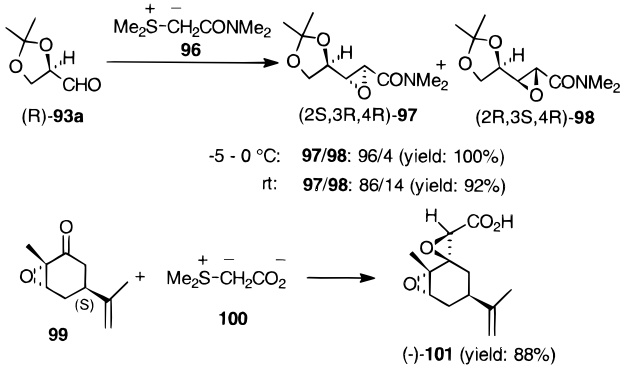
Reducing sugars and their derivatives represent a large type of easily accessible and cheap chiral staring materials and have been extensively utilized in organic synthesis. The ylide epoxidation with sugar-derived substrates has been investigated. The epoxidation of 2,3-*O*-isopropylidene-D-glyceraldehyde **93a** and its homologues **93b** and **93c** with dimethylsulfonium methylide and dimethylsulfoxonium methylide was reported by Anthonsen and co-workers (Scheme 29).[60,61] Diastereoisomerical epoxides **94**

Scheme 29



and **95** were obtained in moderate yields and de values. Much higher diastereocontrol has been achieved in the reaction of the stabilized sulfonium ylide **96** and aldehyde **93a** and other monosaccharide derivatives (Scheme 30).[62,63a] 2,3-Epoxy amides with

Scheme 30

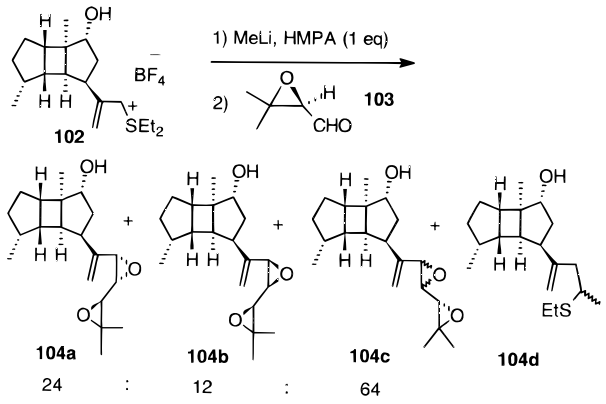


up to 92% de in favor of the *anti* adduct **97** was obtained. However, such high diastereoselectivity was not seen in reactions of other aldoses and ketoses. Recently, the above reaction has been conducted under two phase conditions.[63b] A similar dimethylthetin anion **100** was used for the diaste-

reocontrolled construction of glycidic acid (−)-**101**, which was further transformed into an important intermediate for the synthesis of 1α-hydroxylated vitamin D.[64] The reaction of amido-substituted stabilized sulfonium ylides with common aldehydes is noteworthy since the corresponding ester-substituted stabilized sulfonium ylides can only react with reactive aldehydes.[65]

The reaction of optically pure aldehyde **103** with allylic sulfonium ylide produced from salt **102**, gave (+)-Spatol (**104a**) in low yield and low stereoselectivity (Scheme 31).[66] The vinyl epoxide structural

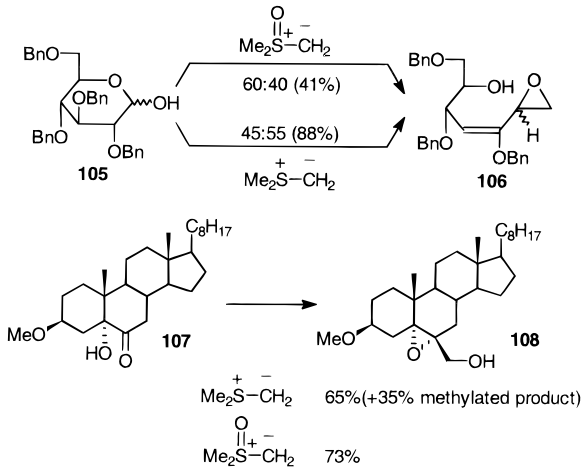
Scheme 31



unit is not usually prepared using an allylic sulfonium ylide, as the reaction is usually accompanied by a sigmatropic rearrangement.

A series of protected reducing sugars have been epoxidized by dimethylsulfonium methylide and dimethylsulfoxonium methylide (Scheme 32).[67] Un-

Scheme 32



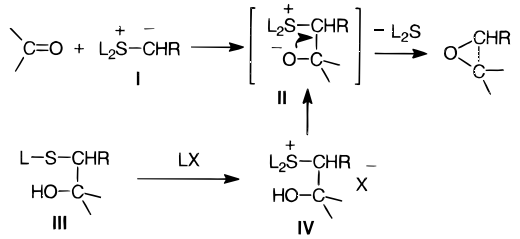
saturated hydroxy epoxides were formed as a mixture of diastereomers. The methylene group has also been transferred to the C=O bond in cholestanone (**107**) with good diastereocontrol, but hydroxy epoxide **108** was furnished by an intramolecular Payne rearrangement of the original epoxidation product.[68]

Dimethylsulfonium methylide and dimethylsulfoxonium methylide are both easily prepared reagents in common use for constructing an epoxy unit from chiral carbonyl compounds and many examples have been documented. Only a few examples have been discussed here.

C. Related Reactions

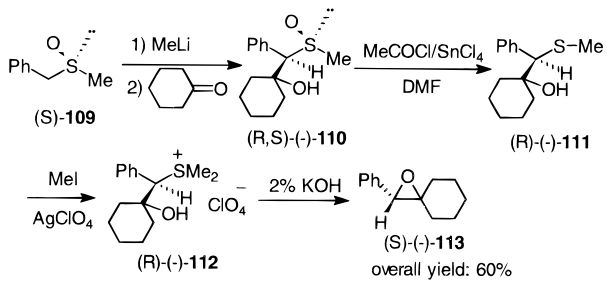
The ylide epoxidation is thought to proceed via a two-step mechanism, as illustrated in Scheme 33 and Scheme 5 (section II.A.-1). A zwitterionic intermediate (betaine) **II** is involved and is normally formed by the addition of an ylide to a C=O bond, but can also be produced by the deprotonation of the β-hydroxyl sulfonium salt **IV**, which is conveniently prepared from β-hydroxyl sulfide **III**. Furthermore, it is possible to upgrade the optically purity of **IV** by recrystallization and thus epoxides with very high ee may be prepared in this way. There are many examples of epoxide synthesis using this strategy and some examples are discussed.

Scheme 33



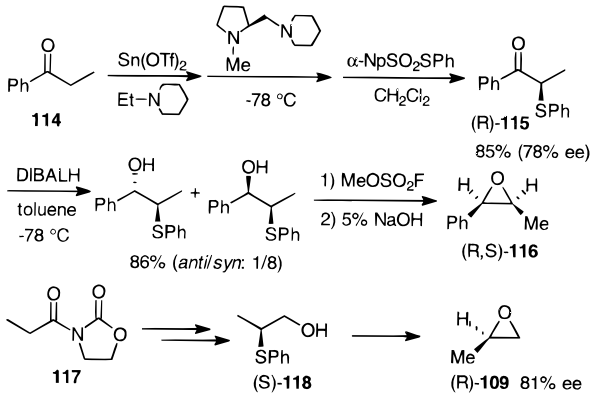
As early as 1971, a multistep sequence for preparation of chiral oxirane (*S*)-(−)-**113** was reported by Durst (Scheme 34).[69] β-Hydroxyl sulfoxide (*R,S*)-

Scheme 34



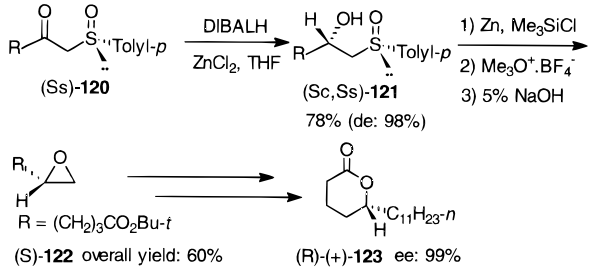
(−)-**110**, which was obtained by the reaction of cyclohexanone with the carbanion of (*S*)-**109**, was reduced to give chiral β-hydroxyl sulfide (*R*)-(−)-**111**. It was then (*S*)-alkylated and recrystallized to give optically pure sulfonium salt (*R*)-(−)-**112**. Upon treatment with a base, epoxide (*S*)-(−)-**113** was furnished in fair overall yield although it was not possible at the time to determine its optical purity. Such a sequence had been ingeniously employed to investigate the mechanism of ylide epoxidation (please see above) by Johnson.[29,30] Later, several methods were established for preparing the key intermediate β-hydroxyl sulfides in this sequence. Pirkle[70] used a chromatographic method to separate the carbamate diastereomers of the corresponding β-hydroxyl sulfides. By this approach, epoxides in 100% ee were prepared. Furia[71] adopted the enantioselective oxidation of protected racemic β-hydroxy thioethers with modified Sharpless reagent to obtain optically active β-hydroxyl sulfides. Mukaiyama[72] utilized the asymmetric sulfenylation of ketones and oxazolidones to obtain chiral sulfides, which were then reduced to the required β-hydroxyl sulfides and transformed into nonracemic epoxides (Scheme 35). Diastereocon-

Scheme 35



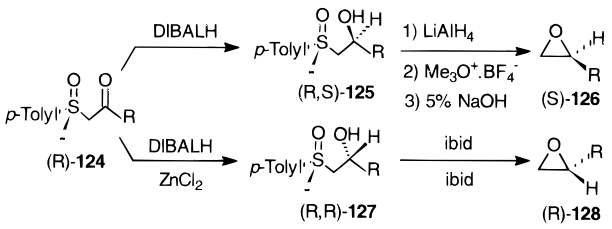
trolled reduction of easily available chiral β-keto sulfoxides is a very important entry to chiral epoxides. A route based on such strategy had been adopted by Kosugi[73] in the synthesis of pheromone (*R*)-(+)-**123** (Scheme 36). Furthermore, Solladié[74]

Scheme 36



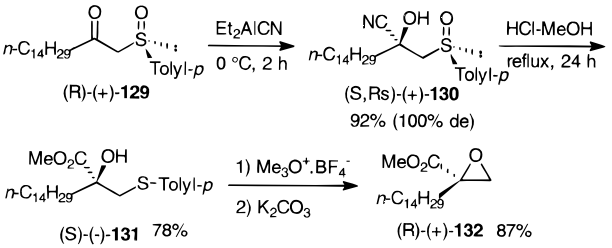
found that either diastereomer of β-hydroxy sulfoxides could be easily prepared in very high de (90−95%) by reduction of β-keto sulfoxides with DIBALH or DIBALH/$ZnCl_2$ (Scheme 37). These results were

Scheme 37



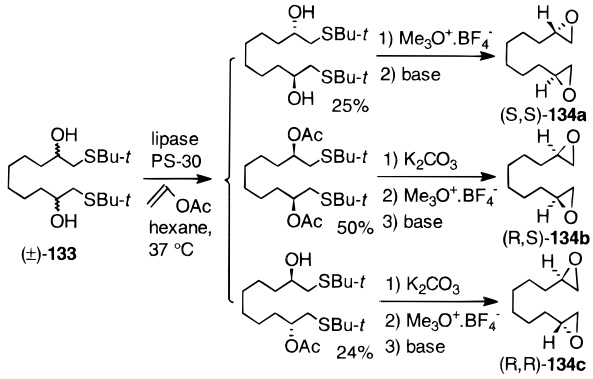
used to prepare both enantiomers of monosubstituted oxiranes in very high ee. By the addition of chiral β-keto sulfoxides with cyanide and further transformations, 2-alkylglycidic acid derivatives (1,1-disubstituted epoxides) could be prepared. This approach had been applied in the synthesis of methyl (*R*)-(+)-palmoxirate (*R*)-(+)-**132** (Scheme 38).[75]

Scheme 38



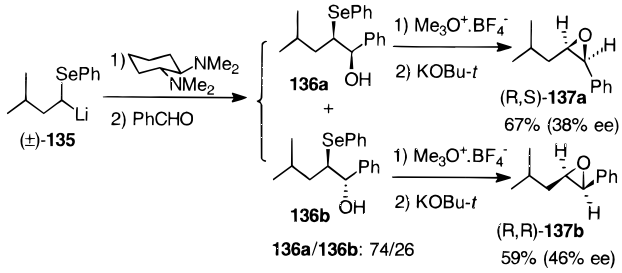
Very recently, an enzyme-mediated synthesis of optically pure α,ω-diepoxides via β-hydroxyl sulfides was reported by Hoye (Scheme 39).[76] Racemic β,β'-dihydroxyalkyl dithioethers **133** were resolved by a transesterification reaction catalyzed by lipase PS-30 to give chiral β-hydroxy sulfides, which were further transformed into enantiomerically pure α,ω-diepoxides.

Scheme 39



Optically active epoxides prepared from β-hydroxy selenides have also been reported. Chiral diamine chelated α-(phenylseleno)isopentyllithium **135** reacted with benzaldehyde to form β-hydroxy selenides **136a** and **136b** in a ratio of 74:26 (Scheme 40). Each diastereomer was smoothly transformed into the corresponding optically active epoxide with moderate ee.[77]

Scheme 40



III. Asymmetric Cyclopropanations

Like nonracemic epoxides, chiral cyclopropanes are an important class of strained small ring compounds. They can undergo a variety of chemical transformations to give many useful intermediates, and the cyclopropyl group is also found as a basic structural unit in a wide range of naturally occurring compounds both in plants and in microorganisms.[78] The development of an important class of photodegradable and low mammalian-toxic insecticides, namely the pyrethroids made the stereocontrolled synthesis of substituted cyclopropanes an important goal. This directly led to the birth of various asymmetric strategies. Besides resolution of their racemates, a number of synthetic methods, including asymmetric Simmons−Smith reaction, metal-catalyzed reaction of diazo compounds with olefins, and asymmetric ylide cyclopropanation, have been used for preparing optically active cyclopropanes, some of which are new industrial processes.[78c,79] Several recent reviews on the asymmetric cyclopropanations are available,[78]

thus, only asymmetric ylide cyclopropanations will be discussed here.

Many results on the asymmetric ylide cyclopropanation have been documented, and this work can be divided into two categories: reagent-controlled and substrate-controlled processes. Such classification will be adopted in the following discussions.

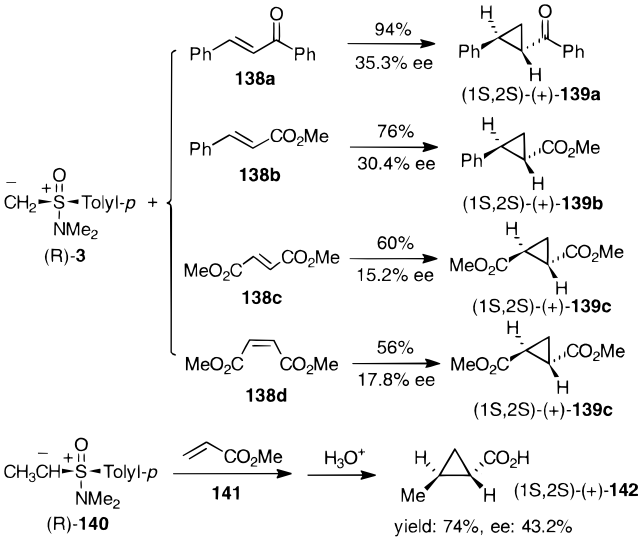
A. Reagent-Controlled Asymmetric Cyclopropanations

The ylide cyclopropanation is one of the earliest developed and extensively studied ylide reactions. Its asymmetric version was reported as early as 1960s. Over the last 30 years, homochiral aminosulfoxonium ylides, sulfonium ylides, sulfoxonium ylides, and arsonium ylides have been used in the chiral reagent-controlled asymmetric cyclopropanations.

1. Chiral Aminosulfoxonium Ylides

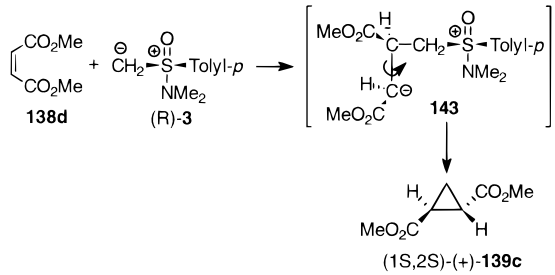
Asymmetric methylene transfer from chiral aminosulfoxonium ylides to C=C bonds was first investigated by Johnson and co-workers (Scheme 41).[9,27−30]

Scheme 41



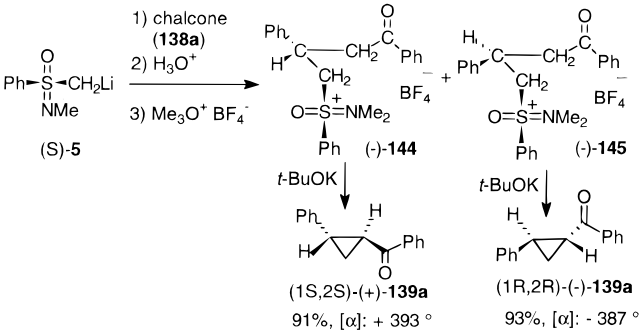
Optically active disubstituted cyclopropanes were obtained in moderate yields and up to 35% ee by the reaction of chiral ylide (*R*)-**3** with α,*β*-unsaturated ketones, esters, and unsaturated diesters. Ethylene could also be successfully transferred to C=C bonds with *p*-tolyl(dimethylamino)sulfoxonium ethylide (*R*)-**140**. It is interesting to note that the same product (**139c**) was obtained with dimethyl fumarate **138c** as was obtained with dimethyl maleate **138d**. These results provided evidence for an intermediate betaine in the cyclopropanation reaction. The production of *trans*-cyclopropane in the case of dimethyl maleate **138d** was believed to occur through rotation about a single bond of the betaine adduct **143**, which has sufficient lifetime for the change of conformation (Scheme 42). This indicates that like ylide epoxidation, ylide cyclopropanation also involves a two-step mechanism (please see Scheme 5, section II.A.-1). If cyclopropanation did indeed occur by a two-step mechanism, then under certain conditions, ylide addition to electrophilic olefins could be a reversible

Scheme 42



process. This was confirmed by control experiments as dimethyl maleate **138d** isomerized to dimethyl fumarate **138c**.[27] However, the high optical purity of cyclopropane (1*S*,2*S*)-(+)-**139a** and its enantiomer (1*R*,2*R*)-(−)-**139a** obtained from the corresponding optically pure salt (−)-**144** and (−)-**145** respectively indicates that for collapse of their betaine precursors $k_2 \gg k_{-1}$ for the specific conditions used (Scheme 43).[29,30]

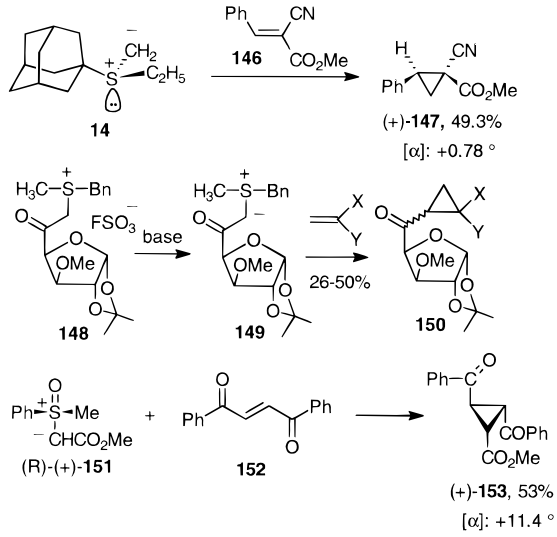
Scheme 43



2. Other Ylides and Related Reagents

The use of other chiral ylides in asymmetric cyclopropanations has been reported. Chiral sulfonium ylide **14** reacted with an α,*β*-unsaturated ester **146** to give optically active cyclopropane (+)-**147** in 49% yield (Scheme 44).[31] The sugar-derived stabilized

Scheme 44

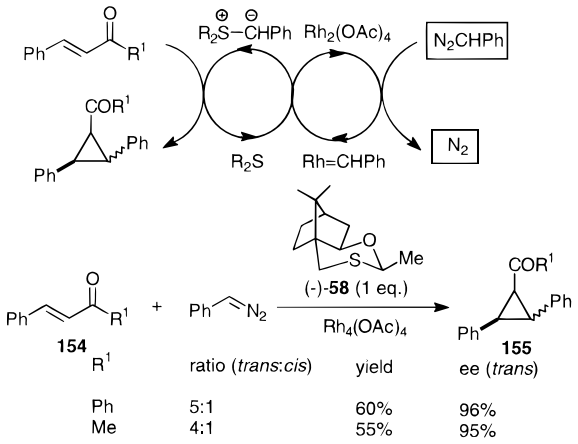


sulfonium ylide **149** was reacted with a range of Michael acceptors, like acrylonitrile, acrolein, and diethyl methylenemalonate, to give cyclopropanes

150 in 26−50% yields and 6/4−7/3 isomer ratios.[80] In the synthesis of optically active oxosulfonium ylides by the reaction of sulfoximines with diazomalonate in the presence of a Cu salt, Oae[81] showed that cyclopropanation of dibenzoylethylene **152** with chiral oxosulfonium ylide (*R*)-(+)-**151** was possible. Optically active methyl 2,3-dibenzoylcyclopropanecarboxylate **153** was formed in 53% yield.

Aggarwal has recently applied the successful catalytic asymmetric epoxidation process to cyclopropanation by substituting the aldehyde for an α,β-unsaturated carbonyl compound **154** (Scheme 45).[44c]

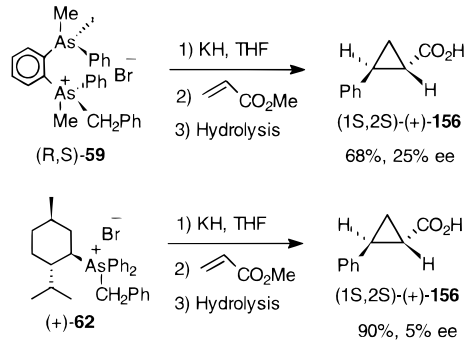
Scheme 45



As the sulfonium ylides are semistabilized, cyclopropanation rather than epoxidation occurred with α,β-unsaturated ketones. Very high enantioselectivities were achieved in the cyclopropanation process although diastereoselectivities were only moderate. It should be noted that the greater reactivity of the carbonyl group of α,β-unsaturated aldehydes resulted in the expected epoxidation.[44a]

Two examples of asymmetric cyclopropanation with chiral arsonium benzylides were reported by Wild and co-worker (Scheme 46).[46] Arsonium ylides, gen-

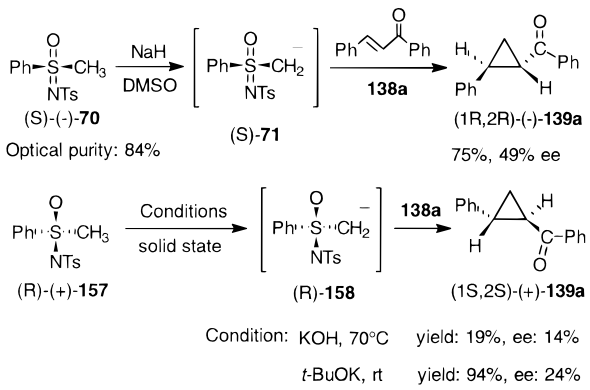
Scheme 46



erated from optically active arsonium salts (*R*,*S*)-**59** and (+)-**62**, reacted smoothly with methyl acrylate to furnish (1*S*,2*S*)-(+)-2-phenylcyclopropanecarboxylic acid **156** in 25% and 5% ee respectively after hydrolysis.

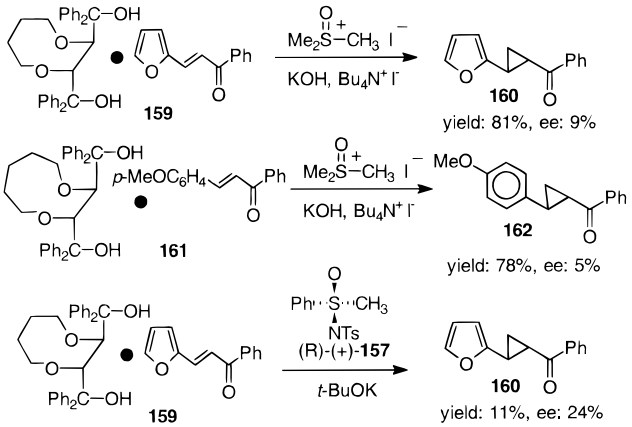
The asymmetric transfer of methylene from chiral sulfoximine derived anions to C=C bonds is another useful way to prepare optically active cyclopropanes. Cyclopropane (1*R*,2*R*)-(−)-**139a** was obtained in 75% yield and 49%ee by Johnson[51] through the reaction of sulfoximine anion (*S*)-**71** with chalcone. This reaction was reinvestigated by Toda[82] in the solid state. When sulfoximine (*R*)-(+)-**157**, chalcone and KOH or *t*-BuOK were heated in the solid state, cyclopropanation product (1*S*,2*S*)-(+)-**139a** was furnished in 14% and 24% ee, respectively (Scheme 47).

Scheme 47



The reaction was also carried out as an inclusion crystal of α,β-unsaturated ketones with the optically active host compound. Treatment of 1:1 inclusion complexes **159** or **161** with trimethylsulfoxonium iodide and KOH in the presence of the phase-transfer reagent Bu_4NI gave nonracemic cyclopropanes **160** and **162** in 9% and 5% ee respectively (Scheme 48).

Scheme 48



When chiral sulfoximine (*R*)-(+)-**157** was used (double asymmetric induction), the ee of **160** was improved to 24%, but the yield was only 11%.

B. Substrate-Controlled Asymmetric Cyclopropanations

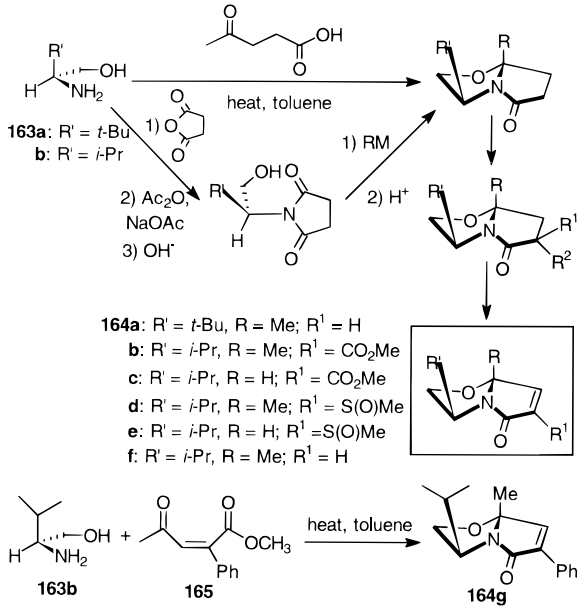
Substrate-controlled ylide asymmetric cyclopropanation refers to the reaction of chiral α,β-unsaturated compounds (Michael acceptors) with achiral ylides to give optically active cyclopropanes. Chiral α,β-unsaturated compounds used in such reaction have included amino acid-derived bicyclic γ-lactams, tartaric acid and sugar-derived α,β-unsaturated esters. Sulfonium ylides, sulfoxonium ylides, and phosphonium ylides have been employed as the ylide reagents.

1. Chiral α,β-Unsaturated Bicyclic γ-Lactams

Chiral α,β-unsaturated bicyclic γ-lactams **164** (4-oxa-1-azabicyclo[3.3.0]nonanone), the so called "Mey-

ers lactams", are a commercially available[83] class of easily accessible chiral amino alcohol-based Michael acceptors. They can be prepared from L-valinol (**163b**) and L-*tert*-leucinol (**163a**) by cyclodehydration and introduction of unsaturation (Scheme 49).[84,85]

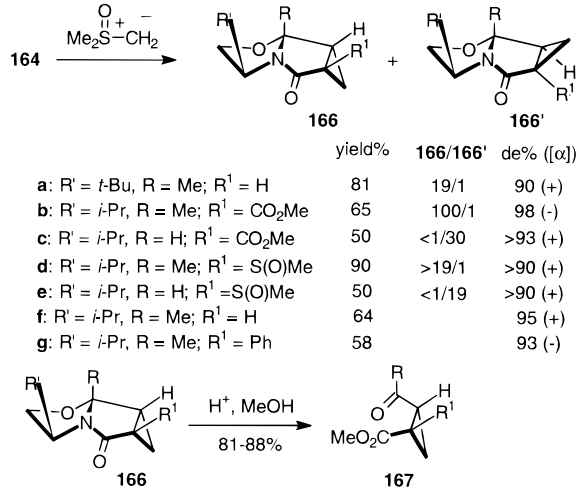
Scheme 49



The α-phenyl unsaturated lactam **164g** has also been prepared by direct heating of L-valinol and the unsaturated keto ester **165** in toluene.[85]

In the past few years, many synthetic methods based on **164** have been developed by Meyers' group.[85,86] Among these methods, the diastereoselective cyclopropanation of **164** with ylide reagents constitutes an important class.[85−88] The reaction of various chiral α,β-unsaturated bicyclic γ-lactams **164** with dimethylsulfoxonium methylide, gave chiral cyclopropanes **166** or **166′** with high diastereoselectivity (Scheme 50). It is interesting to note that a

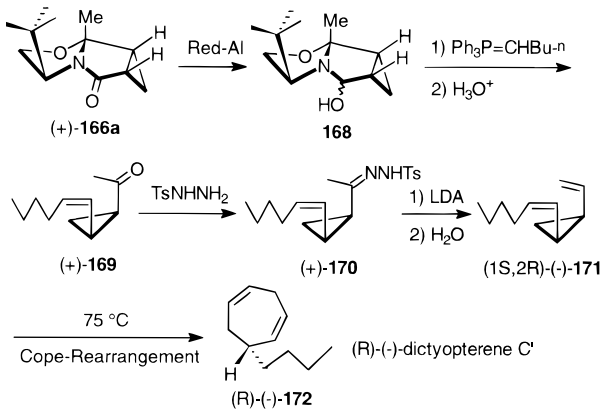
Scheme 50



	yield%	166/166'	de% ([α])
a: R' = *t*-Bu, R = Me; R^1 = H	81	19/1	90 (+)
b: R' = *i*-Pr, R = Me; R^1 = CO_2Me	65	100/1	98 (-)
c: R' = *i*-Pr, R = H; R^1 = CO_2Me	50	<1/30	>93 (+)
d: R' = *i*-Pr, R = Me; R^1 = S(O)Me	90	>19/1	>90 (+)
e: R' = *i*-Pr, R = H; R^1 =S(O)Me	50	<1/19	>90 (+)
f: R' = *i*-Pr, R = Me; R^1 = H	64		95 (+)
g: R' = *i*-Pr, R = Me; R^1 = Ph	58		93 (-)

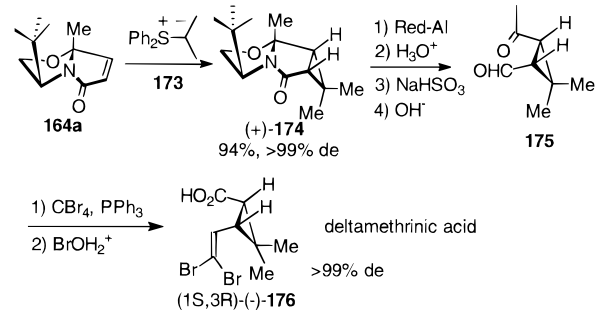
simple change of angular substituent (*R*) in the lactam from methyl to hydrogen leads to a complete reversal in *endo*−*exo* (**166**/**166′**) selectivity. Cyclopropanes **166**/**166**' could be easily hydrolyzed to give chiral cyclopropyl keto esters **167** which could be further elaborated for synthesis. By a sequence of reduction−olefination−hydrolysis, chiral vinylcyclopropane (+)-**169** was obtained and further transformed into physiologically active (*R*)-(−)-dictyopterene C' (**172**) (Scheme 51). The cyclopropanation

Scheme 51



of **164a** with diphenylsulfonium isopropylidene **173** furnished *gem*-dimethyl cyclopropyl adduct (+)-**174** in 94% yield and >99% de value (Scheme 52). The

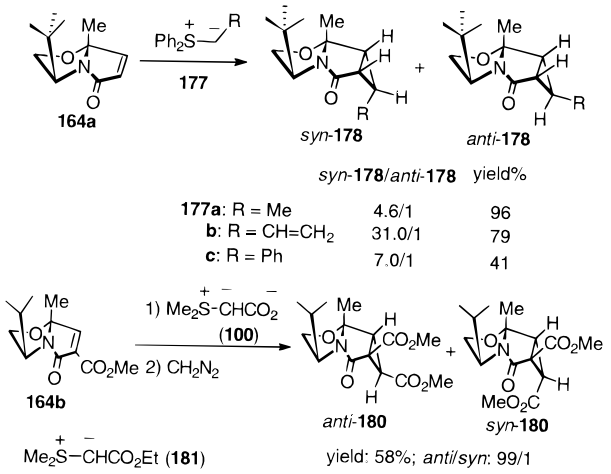
Scheme 52



immediate precursor of deltamethrin (one of the pyrethroid insecticides in wide commercial use), deltamethiric acid (1*S*,3*R*)-(−)-**176** was efficiently prepared in several steps from chiral cyclopropane (+)-**174**. The above examples demonstrate the usefulness of vinylcyclopropanes and methodology devised by the Meyers' group. This cyclopropanation methodology was extended to the preparation of optically pure 1,2,3-trisubstituted cyclopropanes by the same group.[88] When unstabilized (**177a**) and semi-stabilized (**177b** and **177c**) sulfonium ylides were used, *syn*-cyclopropanes **178** were the major isomer (Scheme 53). However, when dimethylthetin anion **100** (dimethylsulfuranylidene acetate) was used as the ylide reagent, *anti*-**180** became the main product. Stabilized ylide **181** showed no selectivity in the cyclopropanation, and gave a 1:1 mixture of *anti*-**180** and *syn*-**180**.

Chiral α,β-unsaturated bicyclic γ-lactams can be smoothly cyclopropanated by dimethylsulfoxonium methylide and various sulfonium ylides. The stereochemical control in such a system has proven very successful in some cases, and many enantiomerically pure cyclopropane derivatives can be prepared by this method.

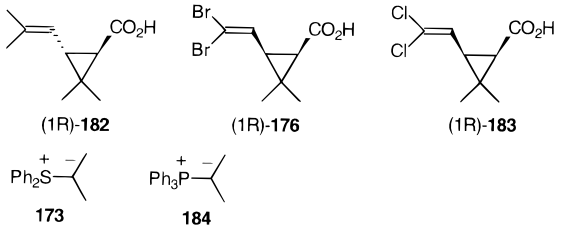
Scheme 53



2. L-Tartaric Acid- and D-Glyceraldehyde-Derived α,β-Unsaturated Esters

The great commercial demand for pyrethroid insecticides, which are both safe to mammals and biodegradable, has fueled the search for cheap and convenient synthetic routes to the important intermediates *trans*-chrysanthemic acid (**182**) and its dihalogeno *cis* analogues **176** (deltamethrinic acid) and **183** (cypermethrinic acid) (Scheme 54).[89] The

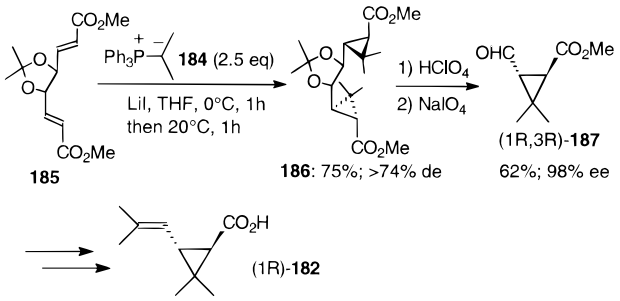
Scheme 54



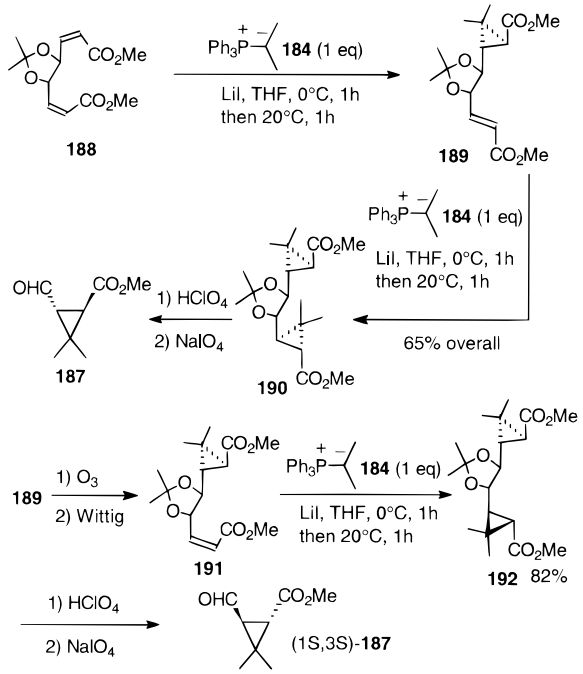
gem-dimethyl cyclopropyl unit in these acids can be incorporated by the reaction of chiral α,β-unsaturated compounds and a phosphonium isopropylide or a sulfonium isopropylide. Much work has been done through such a strategy by using isopropylidenetriphenylphosphorane (**184**)[90−92] and isopropylidenediphenylsulfurane (**173**)[90,91b,92a,93] in Krief's laboratory over the past 20 years.

From cheap chiral starting materials L-tartaric acid and D-glyceraldehyde, various α,β-unsaturated esters have been prepared and cyclopropanated with phosphonium ylide **184** and sulfonium ylide **173**.[90,91] When L-tartaric acid-derived *E*,*E*-diester **185** was treated with isopropylidenetriphenylphosphorane (**184**), diadduct **186** was obtained in 74% de which was upgraded to 100% de by crystallization and was further converted into (1*R*,3*R*)-hemicaronic aldehyde (**187**) and *trans*-chrysanthemic acid (**182**) in 98% ee (Scheme 55). However, when *Z*,*Z*-diester **188** was used as the Michael acceptor, with 1.0 equiv of ylide reagent, monoadduct **189** was formed (Scheme 56). In this product, the configuration of the double bond had changed from *Z* to *E*, and the configuration of the cyclopropane moiety was opposite to that obtained from the *trans*-alkene. Treatment of **189** with another equivalent of **184** gave diadduct **190** in 65% overall yield. As the two cyclopropanes in **190** had opposite configuration, the hemicaronic aldehyde **187**

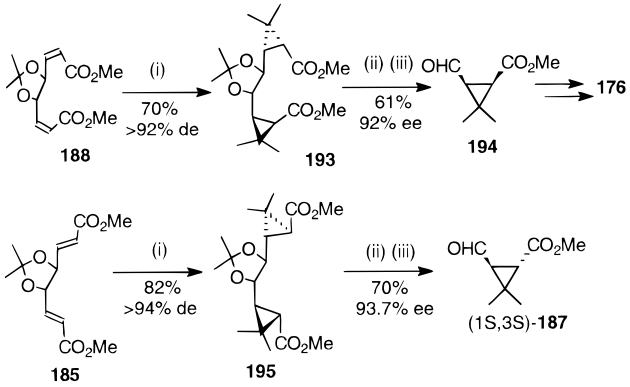
Scheme 55



Scheme 56



Scheme 57



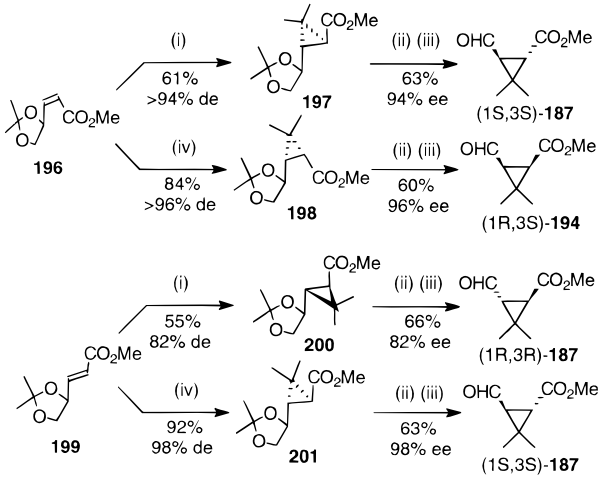
Conditions: (i) isopropylidenediphenylsulfurane (3 eq, **173**), DME, -78 °C, 0.3 h then -60 °C to -50 °C, 0.7 h then -50 °C to 20 °C; (ii) 2N $HClO_4$(6 eq), THF, 20 °C, 6 h; (iii) $NaIO_4$(1.5 eq), MeOH, PH 7.2, 20 °C, 1 h.

derived from it was essentially racemic. However, if the *E* double bond in **189** was converted into a *Z* double bond, the enantiomer (1*S*,3*S*)-**187** was furnished by the same process.

Unlike the cyclopropanation with phosphonium ylide **184**, the cyclopropanation of diesters **185** and **188** with sulfonium ylide **173** was completely stereocontrolled (Scheme 57).[91b] With both **185** and **188**, bis-cyclopropanes were stereospecifically obtained in high diastereomeric excess. Thus using *Z*,*Z*-diester **188**, *cis*-hemicaronic aldehyde (**194**) could be pre-

pared; *E*,*E*-diester **185** afforded *trans*-(1*S*,3*S*)-**187**. Different stereochemical results were also observed in the cyclopropanation of D-glyceraldehyde-derived *Z*- and *E*- α,β-unsaturated esters **196** and **199** with phosphonium ylide **184** and sulfonium ylide **173** (Scheme 58). Using these methods, both enantio-

Scheme 58



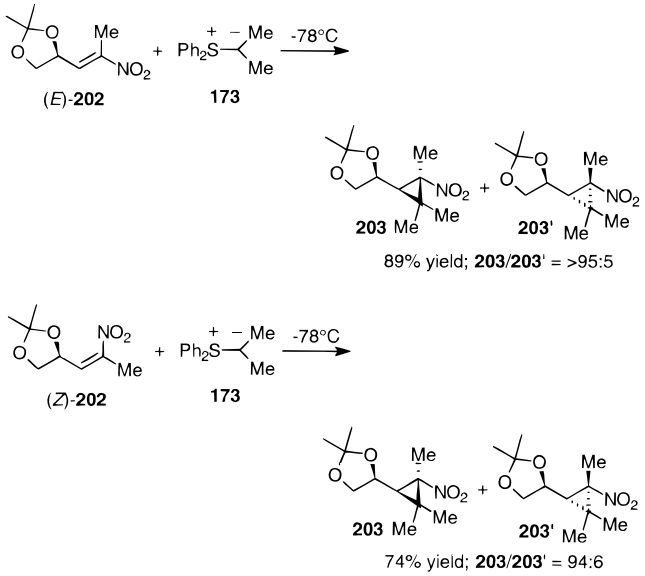
Conditions: (i) $Ph_3P{=}C(Me)_2$(**184**, 1.5 eq), LiI, THF, 0°C, 1 h then 20°C, 1 h; (ii) 2N $HClO_4$(4 eq), THF, 20°C, 6 h; (iii) $NaIO_4$(1.5 eq), MeOH, PH 7.2, 20°C, 1h;(iv) $Ph_2S{=}C(Me)_2$(**173**), DME, -78°C 0.2h, -78°C to -50°C, 0.7h, -50°C to 20°C, 0.3h.

merically pure *trans*-hemicaronic aldehydes **187** and *cis*-hemicaronic aldehydes (1*R*,3*S*)-**194** were efficiently prepared with very high diastereocontrol. A similar enantioselective preparation of (1*R*,3*R*)-**187** by the cyclopropanation of **199** with **184** was also reported by Mulzer[94a] as early as 1983.

Obviously, the substrate-controlled asymmetric cyclopropanation of L-tartaric acid- and D-glyceraldehyde-derived α,β-unsaturated compounds with phosphonium or sulfonium isopropylides provides a very promising entry to optically active pyrethroid insecticides. Fluorinated pyrethroid derivatives have been synthesized very recently by this strategy.[94b]

Very recently, the ylide cyclopropanation of D-glyceraldehyde-derived nitroolefins have been reported (Scheme 59).[95] Optically active nitrocyclopropane **203** was obtained in high de through the

Scheme 59

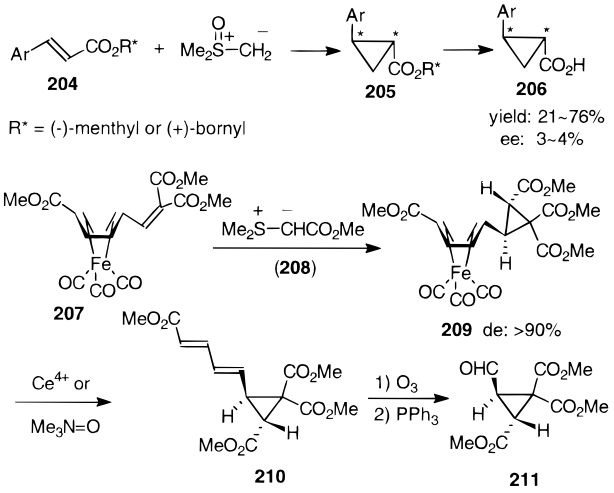


reaction of (*E*)- and (*Z*)-**202** with sulfonium ylide **173**. The ratio of diastereomers was not dependent on the olefin geometry.

3. Other Chiral α,β-Unsaturated Compounds

A chiral auxiliary-induced asymmetric cyclopropanation was reported by Nozaki[96] as early as 1966. When (−)-menthol- or (+)-borneol-derived α,β-unsaturated esters **204** were treated with dimethylsulfoxonium methylide, optically active **205**, could be obtained but in very low ee (Scheme 60). These could

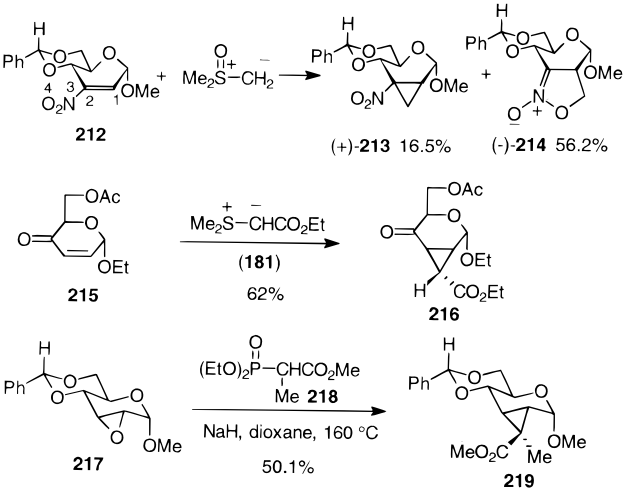
Scheme 60



then be hydrolyzed to the corresponding acid **206**. High asymmetric induction has been achieved in the cyclopropanation of planar chiral Michael acceptors. On treatment of chiral α,β-unsaturated ester **207** with stabilized sulfonium ylide **208**, optically active cyclopropane **209** was obtained in >90% de.[97] This was then conveniently transformed into the chiral electrophilic cyclopropane **211**.

Both cyclopropane (**213**) and isoxazoline *N*-oxide (**214**) have been obtained in the reaction of unsaturated nitro sugar **212** with dimethylsulfoxonium methylide (Scheme 61).[98−100] These two products were

Scheme 61

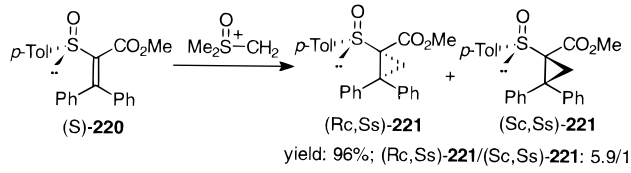


formed respectively by equatorial 1,2- and axial 1,4-additions to the nitroolefin. However, when using stabilized sulfonium ylide **181**, only isoxazoline *N*-

oxide and a new ylide containing the sugar moiety were produced. No cyclopropane was found. Unlike the unsaturated nitro sugar, α-D-*allo*-pyranoside **215** reacted smoothly with ylide **181** to give the α-D-pyranoside **216** in 62% yield.[101] In the synthesis of (+)- and (−)-chrysanthemum dicarboxylic acids, the Wadsworth−Emmons cyclopropanation of anhydro sugar **217** was used.[101] Cyclopropane adduct **219** was obtained in 50.1% yield.

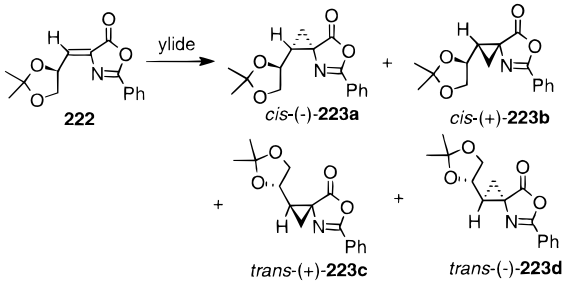
The first use of a chiral vinyl sulfoxide in the asymmetric ylide cyclopropanation was demonstrated by Hamdouchi.[102] When (*S*)-**220** was reacted with dimethylsulfoxonium methylide, optically active (R_c,S_s)-**221** and (S_c,S_s)-**221** were obtained as a 5.9:1 mixture in 96% yield (Scheme 62).

Scheme 62



An asymmetric cyclopropanation of a chiral oxazolone with ylides appeared in 1995.[103] When a specially designed oxazolone **222**, with unsaturation at C_4, was treated with dimethylsulfoxonium methylide under various conditions, a mixture of *cis* (**223a** and **223b**) and *trans* (**223c** and **223d**) cyclopropanes were obtained (Scheme 63). With aminosulfoxonium

Scheme 63

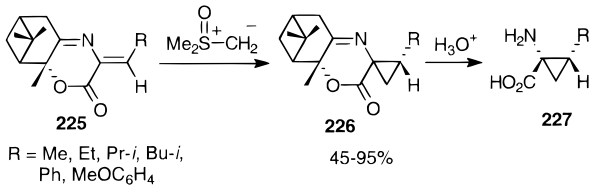


ylide	Conditions	*cis*/*trans*	dr of *cis* (**223a**/**223b**)	dr of *trans* (**223c**/**223d**)
$Me_2S^+-CH_2^-$	CH_2Cl_2,-20 °C	52/48	94/6	98/2
	toluene,-20 °C	70/30	85/15	97/3
	DMF,-20 °C	35/65	61/39	81/19
$Ph-S^+(NEt_2)-CH_2^-$ (**224**)	CH_2Cl_2,-20 °C	53/47	74/26	91/9
	toluene,-20 °C	62/38	87/13	98/2
	DMF,-20 °C	73/27	80/20	86/14

ylide **224**, similar selectivity was achieved. Generally, the de of the *trans* cyclopropanes were better than the *cis* products. These products are useful in preparing 2-substituted 1-aminocyclopropanecarboxylic acids.

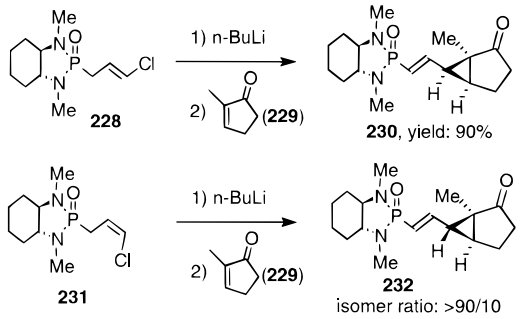
The (1*R*,2*R*,5*R*)-2-hydroxypinan-3-one-based dehydroamino acid derivatives **225** could be smoothly cyclopropanated by dimethylsulfoxonium methylide to give cyclopropanes **226** as a single diastereomer in 45−95% yields (Scheme 64).[104] Compounds **226** were easily converted by acidic hydrolysis into a class of biologically important amino acids 2-alkyl-1-aminocyclopropane-1-carboxylic acids (**227**).

Scheme 64



Recently, a novel asymmetric cyclopropanation of α,β-unsaturated compounds with the anions of *trans*-chloroallyl phosphonamide **228** and *cis*-chloroallyl phosphonamide **231** was reported by Hanessian and co-workers.[105a] Very high diastereomeric ratios were obtained. When *trans*-chloroallyl phosphonamide **228** was used, the *endo*,*endo* isomer **230** was predominantly produced (Scheme 65). However, in the

Scheme 65



case of *cis*-(chloroallyl)phosphonamide **231**, the *exo*,*endo* isomer **232** became the main product. Using this approach, diversely functionalized cyclopropanes of high enantiomeric purity could be prepared.

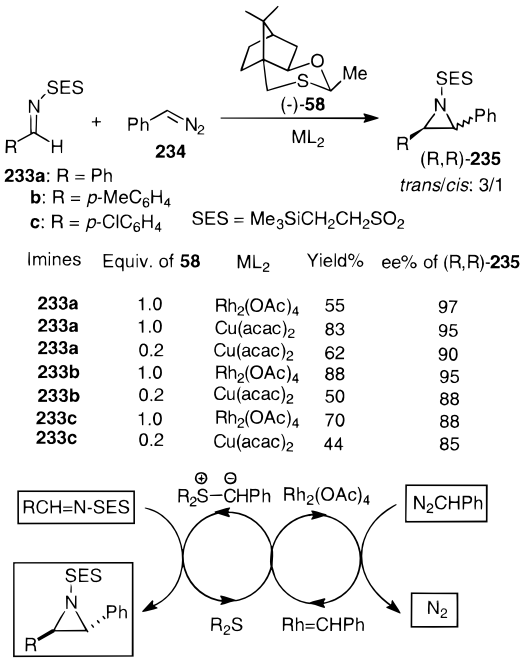
IV. Asymmetric Aziridinations

In sharp contrast to ylide epoxidation and cyclopropanation, the ylide aziridination reaction remains rather undeveloped. This may be rationalized by the relatively low reactivity of common *N*-alkyl- or *N*-aryl imines to nucleophilic attack by ylide reagents compared to carbonyl compounds (for epoxidation) and α,β-unsaturated compounds (for cyclopropanation). Reported ylide addition to C=N bond is almost exclusively methylene transfer. One very recent work successfully realized the transfer of an allylide to a C=N bond by using the reactive *N*-sulfonylimines as the substrates for preparing *C*-vinylaziridnes.[106a−d] Moreover, the asymmetric ylide aziridination has been even less explored.[106e] There are only two reports of reagent-controlled asymmetric aziridination: one from Aggarwal's group and the second from Li and Dai's laboratories. For chiral substrate-controlled aziridination, there are three papers. These results will be presented herein.

A. Reagent-Controlled Asymmetric Aziridinations

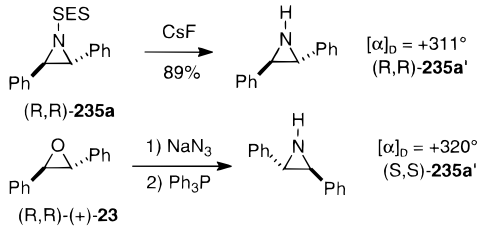
As mentioned above, the reagent-controlled asymmetric ylide aziridination remains rather unexplored in the literature. It was not until very recently that a catalytic asymmetric ylide aziridination was reported by Aggarwal and co-workers.[107] On the basis of their successful experiences in the catalytic ylide epoxidation,[42,43] an aza variant has been developed

Scheme 66



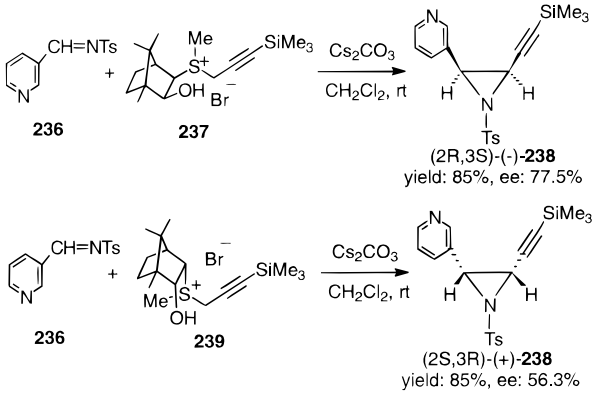
(Scheme 66). The chiral sulfonium benzylide was generated *in situ* from sulfide (−)-**58** and benzylcarbene (generated by the decomposition of phenyl diazomethane **234** with metal catalysts) and trapped by *N*-sulfonylimines **233** to form optically active aziridines (*R,R*)-**235** in high enantioselectivity. A mechanism similar to the corresponding epoxidation reaction (see the epoxidation section)[42,43] has been suggested. The SES group was easily removed using CsF and the absolute stereochemistry of the product aziridine was determined by correlation (Scheme 67).[107]

Scheme 67



Dai's group have studied the reactions of allylic sulfonium, arsonium, and telluronium ylides with *N*-sulfonylimines and obtained vinylaziridines but with low diastereoselectivity.[106a−d] As such, asymmetric versions of the same reactions have not been examined. However, we recently found that aziridination of exclusive cisoid selectivity could be achieved using silylated dimethylsulfonium propargylide instead of allylic sulfonium ylides. On the basis of these results, asymmetric aziridination with moderate to high ee was successfully realized using the corresponding chiral ylides.[108] For example, when Cs_2CO_3/CH_2Cl_2 was used as the base/solvent system, *N*-tosylimine **236** reacted smoothly with the ylide generated *in situ* from chiral sulfonium salt **237** (prepared from the direct reaction of chiral sulfide (+)-**48** and 3-(trimethylsilyl)propargyl bromide in acetone) to give optically active acetylenylaziridine (2*R*,3*S*)-(−)-**238** in 85% yield and 77.5% ee value (Scheme 68). Interestingly, we found, that, similar

Scheme 68



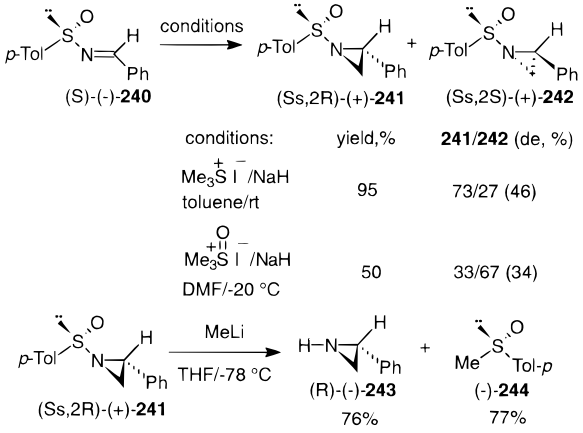
to the asymmetric epoxidation,[41] opposite asymmetric induction was achieved using the same chiral starting material D-camphor-derived ligands with an *endo* orientated sulfur-containing group, sulfonium salt **239**.

In all reactions, the *cis* isomers are the only products. This reaction works well with various *N*-sulfonylimines, including aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldimines as well as aliphatic ketimines. Such a broad substrate span is noteworthy compared with other asymmetric aziridination reactions. Although the ee values of the products are not high enough (up to 85%), they can be easily upgraded by recrystallization in suitable solvents. For instance, the ee of (2*R*,3*S*)-(−)-**238** can be upgraded from 77.5% to 99.1% by single recrystallization from *n*-hexane in a yield of 52%. The ylide precursor sulfides can be recovered in generally >80% yield after completion of the aziridination reaction, and reused, although the present reaction is stoichiometric.

B. Substrate-Controlled Asymmetric Aziridinations

Three similar examples appeared in the literature for the preparation of optically active aziridines by transferring the methylene group of achiral ylide reagents to chiral sulfinimines.[109,110] A diastereomeric mixture of 1,2-disubstituted (+)-**241** and (+)-**242** was obtained from the reaction of (*S*)-(+)-*N*-*p*-tolylsulfinyl phenylamine **240** and dimethylsulfonium methylide or dimethylsulfoxonium methylide under various conditions in moderate yields and low de's.[109a] The best result was achieved using dimethylsulfonium methylide, generated from the deprotonation of trimethylsulfonium iodide with NaH in toluene, giving 46% de with the preferential production of (S_s,2*R*)-(+)-**241** (Scheme 69). Opposite diastereoselectivities were obtained using dimethylsulfonium methylide and dimethylsulfoxonium methylide, i.e., the former favors the production of (S_s,2*R*)-(+)-**241** and the latter forms (S_s,2*S*)-(+)-**242**. The stereoselectivity of this reaction has recently been significantly improved using *tert*-butylsulfinylimines instead of *p*-tolylsulfinylimines as the substrates.[109b]

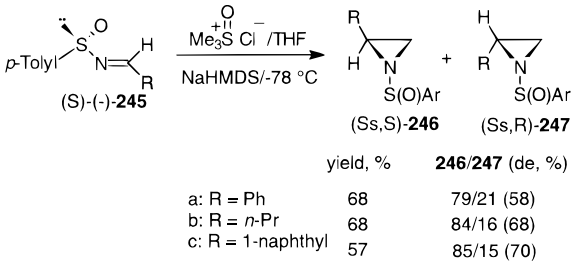
Scheme 69



The product **241** can be easily deprotected to produce the known compound (*R*)-(−)-**243** by treatment with MeLi in dry THF, and therefore the absolute configuration of **241** could be assigned. However, Davis[110] claimed later that the configurations of the products were incorrectly assigned.

Almost at the same time, Davis[110] reported their results of the aziridination of chiral sulfinimines (*S*)-(−)-**245** with dimethylsulfoxonium methylide under different conditions (Scheme 70). Higher de values

Scheme 70



(up to 70%) were achieved using the base NaHMDS. They found that the base NaHMDS was better than NaH. This reaction was also applied to aliphatic imine **245b**.

As shown above, the ylide aziridination reaction provides a possible route to optically active aziridines although only a few reports have been documented to date. No doubt this area will continue to expand in the future.

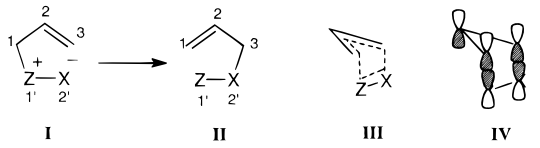
V. Asymmetric Rearrangements

In addition to cyclization reactions, ylide rearrangement reactions are another important feature of sulfonium, ammonium, selenonium, and oxonium ylides. Several excellent summary articles on the [2,3]-σ-rearrangements,[19,111a−e] Stevens rearrangements,[111e] and Pummerer rearrangement[111f] are available, and some asymmetric reactions have also been discussed in these articles. Therefore, in this section, asymmetric ylide rearrangements with emphasis on recent advances will be presented.

A. [2,3]-σ-Rearrangements

The [2,3]-σ-rearrangement is the most important rearrangement involving an ylide intermediate. It is an orbital symmetry-allowed process and is expected to take place in a concerted suprafacial mode involving an envelope transition state **III** (Scheme 71), which may be viewed as a bis-homoaromatic

Scheme 71

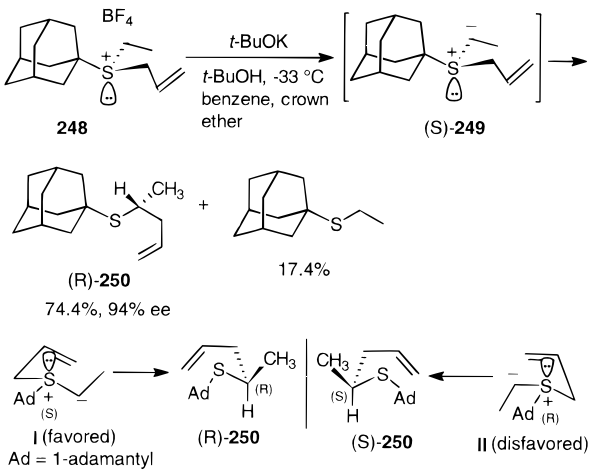


system.[111c,112,113] Due to the concerted mechanism, high regio-, diastereo- and enantioselectivities are usually achieved in the [2,3]-σ-rearrangement. Thus, such rearrangement has been extensively studied and used in organic synthesis after the generalization of this reaction by some initial work from Baldwin and others groups.[114] Herein, the asymmetric [2,3]-σ-rearrangements of sulfonium and ammonium allylides and propargylides will be summarized with emphasis on recent developments.

1. Allylic and Propargylic Sulfonium and Oxonium Ylides

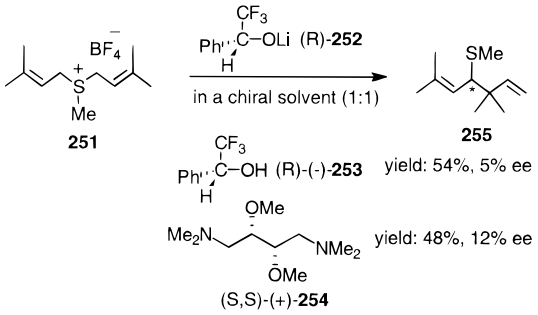
The [2,3]-σ-rearrangement of allylic sulfonium ylides is the most extensively studied and applied reaction. The sulfur-mediated ring expansion in the preparation of medium and large ring sulfides is an example.[111b] The first successful asymmetric [2,3]-σ-rearrangement involving sulfonium ylides appeared in the early 1970s from Trost's laboratory.[31] On treatment of the resolved optically active sulfonium salt **248**, nonracemic (*R*)-**250** was obtained in 94% ee via an [2,3]-σ-rearrangement of allylic ylide **249**, in which the chiral information has been transferred from sulfur to carbon with excellent control (Scheme 72). The authors suggested a concerted mechanism

Scheme 72



via a favored folded envelope transition state **I**. The absolute configuration of the sulfur center in salt **248** was deduced as *S* by comparison with the known configuration of the product **250**. The same group reported another way to generate the chiral sulfur center and further undergo asymmetric rearrangement (Scheme 73).[115] By deprotonation of diallylic sulfonium salt **251** with a chiral base (*R*)-**252** in a

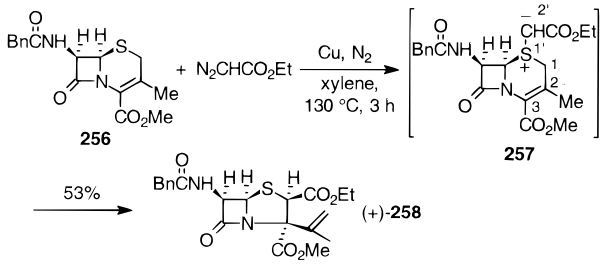
Scheme 73



chiral solvent **253** or **254**, the *in situ* produced ylide rearranged immediately into artemisia methyl thioether **255** in 5−12% ee. A chiral solvent is necessary for obtaining significant ee values. For example, in an achiral solvent THF, the rearrangement product obtained by the deprotonation of **251** with chiral lithium 1-(−)-menthoxide or *n*-butyllithium sparteine showed 0% ee.

The ability of cyclic sulfides to undergo ring expansions and ring contractions via [2,3]-σ-rearrangements have been exploited in synthesis.[111b] It has been used to rebuild the skeleton of certain antibiotics and a good example is the conversion of cephalosporin to penicillin (Scheme 74).[116] On heating the

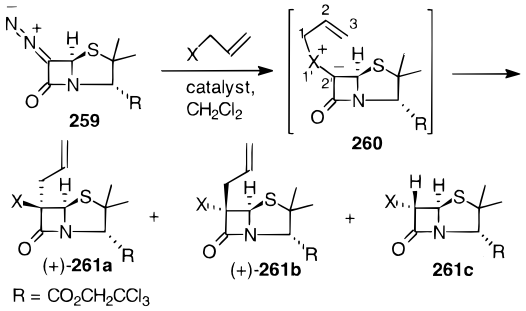
Scheme 74



cephalosporin compound **256** with ethyl diazoacetate in the presence of Cu powder, the penam compound (+)-**258** was afforded in 53% yield as a single isomer through [2,3]-σ-rearrangement of ylide **257**. The high stereoselectivity of this rearrangement is understandable because of the high selectivity in ylide formation. However, such high stereoselectivity has not been achieved in reactions with penicillanates. The reaction of 6-diazopenicillanate (**259**) with allylic sulfides or selenides in the presence of a catalyst gave a complex mixture, the major product being (+)-**261a**, formed by the rearrangement of ylide **260** (Scheme 75).[117−119] The copper catalyst gave higher yields of the desired 6,6-disubstituted penicillanates and no 6α-monosubstituted product **261c** was formed. Sulfides appeared to give better diastereoselectivity than selenides. When using allyl bromide, even a halogen ylide could be formed and transformed immediately into unstable **262** by a [2,3]-σ-rearrangement. Compound **262** was reduced *in situ* using Bu_3SnH to 6β-allylpenicillanate **263** (Scheme 76). However, this reaction failed in the case of a oxonium ylide **264**. Only complex products were obtained.

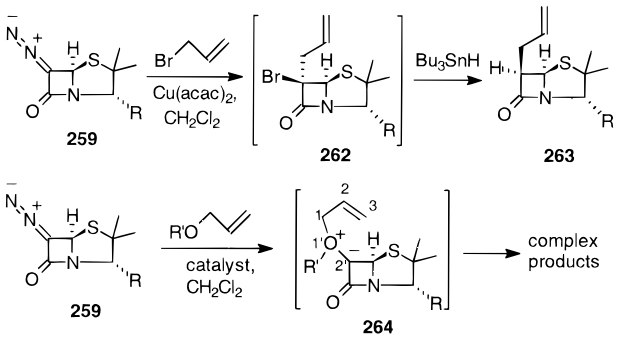
The [2,3]-σ-rearrangement in a thioxanone-based chiral template system was reported by Kurth (Scheme 77).[120,121] From L-valine, chiral allylthio diazo compound **266** was prepared via **265**. It was

Scheme 75

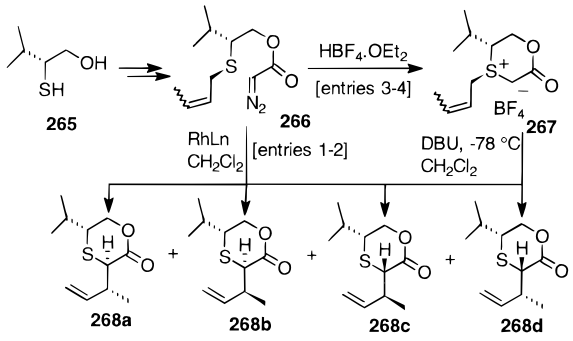


X =	Catalyst	Yield (**261a** + **261b**)	**261a**/**261b**	Yield (**261c**)
PhS	$BF_3{\cdot}Et_2O$	47%	56/44	5%
MeS	$BF_3{\cdot}Et_2O$	49%	80/20	16%
PhSe	$BF_3{\cdot}Et_2O$	48%	66/34	15%
PhS	$Cu(acac)_2$	65%	87/13	0
MeS	$Cu(acac)_2$	60%	80/20	0
PhSe	$Cu(acac)_2$	64%	50/50	0

Scheme 76



Scheme 77

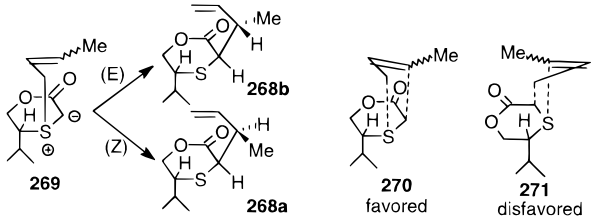


entry	yield:	**268a**/**268b**/**268c**/**268d**
1 (*Z*-**266**)	35%	84 / 8 / 7 / 1
2 (*E*-**266**)	28%	10 / 83 / 2 / 5
3 (*Z*-**266**)	66%	94 / 4 / 2 / trace
4 (*E*-**266**)	64%	4 / 93 / 1 / 2

then converted to the corresponding allylic sulfonium ylide either by direct intramolecular trapping of the Rh−carbene by the S atom or by a two-step process via sulfonium salt **267**. The ylide rearranged to give a mixture of **268a**, **268b**, **268c**, and **268d**. When using *Z*-**266** or *E*-**266**, compounds **268a** or **268b**, respectively, were predominantly formed. Better yields and diastereoselectivity were achieved in the two-step process (entries 3 and 4 in Scheme 77). The different stereoselectivity obtained when using *Z*- or *E*-**266** has been qualitatively rationalized by Wu and Houk who proposed transition states for the reaction.[113] The transition structure with the *endo* six-membered ring, **270**, is favored over the transition structure with the *exo* six-membered ring, **271**,

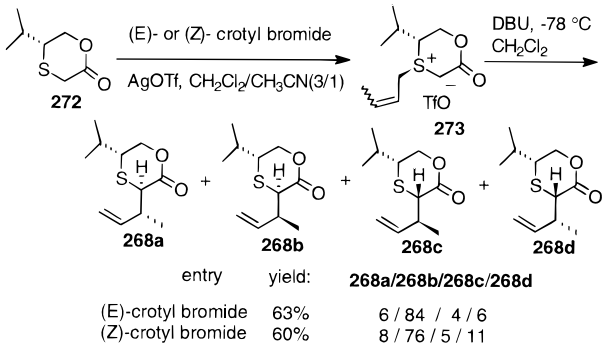
leading to a large preference for **268b** from the *E* reactant and **268a** from the *Z* reactant (Scheme 78).

Scheme 78



In a similar two-step process, compound *E*-**268b** was always the major product when either *E*- or *Z*-crotyl bromide was used (Scheme 79).[121] These

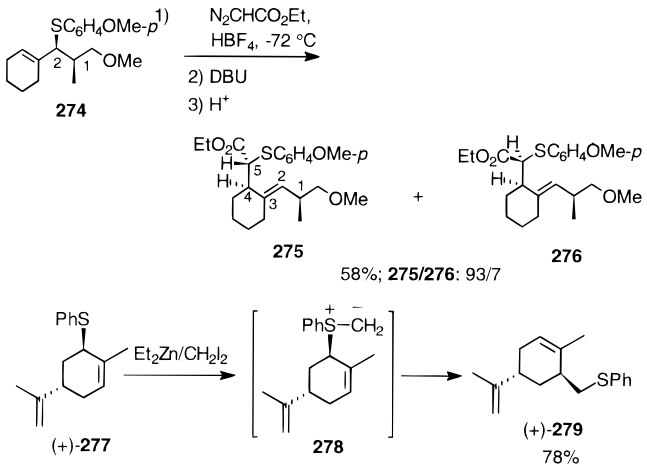
Scheme 79



results suggest that the presence of silver triflate causes olefin isomerization so that both *E*- and *Z*-crotyl bromide give predominantly *E*-**268b**. Compound **268** can be conveniently transformed into *Cβ*-chiral pent-4-enoic acids with the recovery of the chiral auxiliary **265**.

The stereochemistry in the [2,3]-*σ*-rearrangement of open-chain sulfonium ylides was investigated by Warren.[122] Reaction of sulfide **274** (in this compound, S on the open chain, but the allylic system is still a part of a ring) with ethyl diazoacetate and acid followed by treatment with DBU gave the rearrangement products **275** and **276** in 58% yield and 93/7 diastereomeric ratio (Scheme 80). The original 1,2-

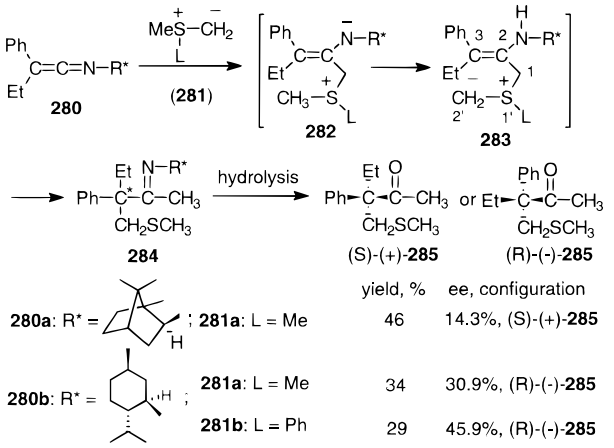
Scheme 80



syn relationship was completely transferred to the newly formed 1,4-*syn* relationship. The 4,5-*anti* relationship is favored and may be explained by using Wu and Houk's envelope transition structure.[113] Complete control of the enantioselectivity was realized in a similar system based on *cis*-carveol-derived sulfide (+)-**277**.[123] Ylide **278**, from the reaction of (+)-**277** and a Zn−carbenoid, rearranges into (+)-**279** in 78% yield as a single diastereomer.

Several publications[124−126] from Hiroi's laboratory demonstrated the [2,3]-*σ*-rearrangement of chiral ketenimine-derived sulfonium ylides. Sulfonium ylide **281a** or **281b** was first added to chiral ketenimine **280** to form a zwitterionic intermediate **282** (Scheme 81). Due to the strong basicity of the negatively

Scheme 81



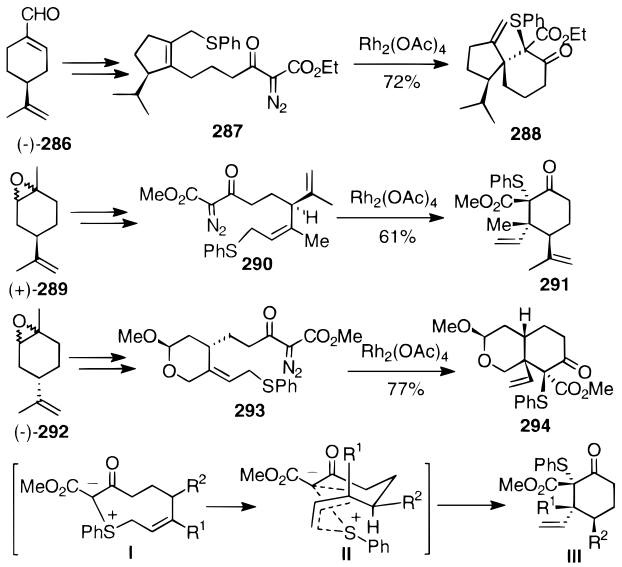
	yield, %	ee, configuration
281a: L = Me	46	14.3%, (S)-(+)-**285**
281a: L = Me	34	30.9%, (R)-(-)-**285**
281b: L = Ph	29	45.9%, (R)-(-)-**285**

charged nitrogen and the acidity of the α-hydrogens adjacent to the positively charged sulfur atom, an intramolecular H transfer occurred to give the allylic sulfonium ylide **283** which rearranged to chiral imine **284**. Upon hydrolysis, chiral ketone (*S*)-(+)-**285** or (*R*)-(−)-**285** was obtained in low to moderate ee. Higher ee was obtained using prochiral sulfonium ylide **281b**. By choosing isobornyl or menthyl as the chiral auxiliary, ketones with opposite configuration were obtained.

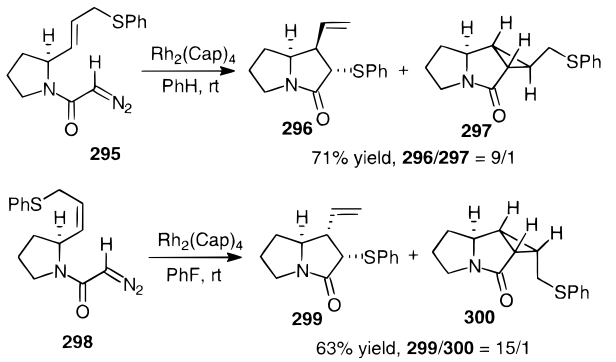
Complete stereocontrol in the [2,3]-*σ*-rearrangement of nine-membered allylic sulfonium ylides was realized by Kido and Kato recently.[127−130] From (−)-perillaldehyde (−)-**286** and (+)- or (−)-limonene oxide **289** and **292**, sulfides **287**, **290**, and **293** were first prepared (Scheme 82). In the presence of Rh catalyst, allylic sulfonium ylides were formed *in situ* by intramolecular carbene capture and they rearranged to compounds **288**, **291**, and **294** as single diastereomers. Compound **288** has been used for the preparation of (+)-acorenone B[127] and **291** and **294** are versatile intermediates for enantioselective synthesis of elemanoid sesquiterpenes. To explain the high stereoselectivity, the authors proposed a nine-membered transition state **II**, which consists of two fused rings, i.e., a chair-like six-membered ring and a five-membered ring.

Very recently, a competition experiment involving intramolecular carbene cyclopropanation and [2,3]-*σ*-rearrangement was reported by McMills et al.[131] In proline-derived systems **295** and **298**, the carbenes, produced by metal-catalyzed decomposition of the diazo groups, can either be trapped intramolecu-

Scheme 82



Scheme 83

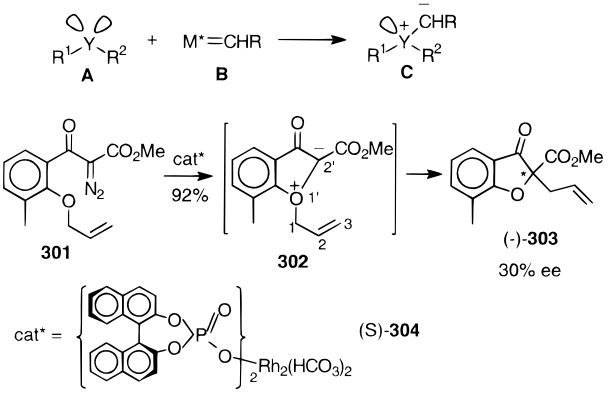


larly by the double bond to form cyclopropanes or by the sulfide to form allylic sulfonium ylides which would undergo [2,3]-σ-rearrangement (Scheme 83). The authors found that under most conditions, the cyclopropanes **297** and **300** were the major products, but under the conditions indicated, the rearrangement products **296** and **299** were predominantly formed.

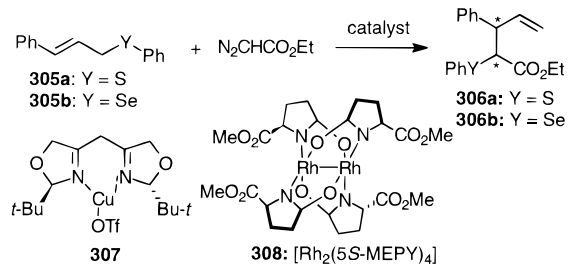
Chiral ylides **C** can be produced by the direct reaction of chiral metal carbenes or carbenoids with prochiral ylide precursors, derived from sulfides, selenides, ethers, or other heteroatom reagents. Surprisingly, such protocol was not realized until 1992 when it was applied in the [2,3]-σ-rearrangement of oxonium allylides.[132] The carbene, generated by the decomposition of diazo allylic ether **301** with chiral rhodium catalyst (*S*)-**304**, was trapped by the ethereal oxygen to form an oxonium ylide **302**. It then underwent the [2,3]-σ-rearrangement to produce compound (−)-**303** in 30% ee (Scheme 84). The stereochemical information was successfully transferred from the catalyst to the ylide.

A similar example involving the production of chiral chalcogen ylides was disclosed by Uemura.[133] Aryl cinnamyl chalcogenides **305a** and **305b** were reacted with ethyl diazoacetate and chiral copper(I) **307** or rhodium(II) **308** (Doyle's catalyst) catalysts, to give the corresponding ylides which underwent an asymmetric [2,3]-σ-rearrangement (Scheme 85). These

Scheme 84



Scheme 85

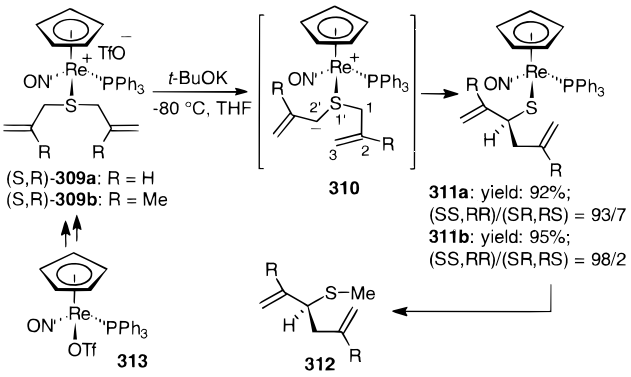


Chalcogen	Catalyst	Condition	Yield, % of **306**	Diastereomeric ratio (ee, %/ee, %)
305a	**307**	toluene, 0 °C, 24 h	41	65/35 (20/14)
305b	**307**	$CHCl_3$, 0 °C, 24 h	71	66/34 (22/32)
305a	**308**	CH_2Cl_2, 40 °C, 20 h	49	60/40 (18/17)
305b	**308**	CH_2Cl_2, 40 °C, 20 h	65	58/42 (25/41)

reactions gave a diastereoisomeric mixture of ethyl 2-(arylchalcogeno)-3-phenylpent-4-enoates in up to 41% ee.

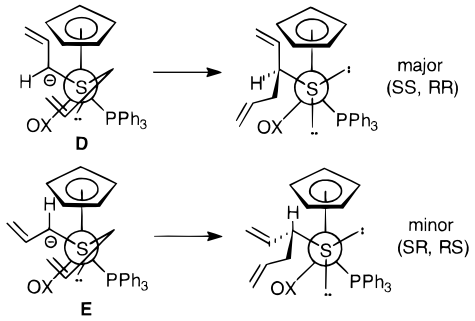
The use of chiral metal complexes in the asymmetric ylide [2,3]-σ-rearrangement was recently achieved by Gladysz (Scheme 86).[19,134] An easily

Scheme 86



resolved and recycled organorhenium chiral auxiliary was successfully attached to allylic sulfonium salts **309**. Upon treatment with a base, ylide **310** was produced and rearranged to give sulfides **311a** or **311b** in excellent yields and high enantiomeric excess. When the BF_4^- salt of enantiomerically pure (*S*)-**309b** was used, the slightly higher diastereoselectivity was obtained compared to the TfO^- salt of (*S*,*R*)-**309b**, ratio of (*S*,*S*):(*S*,*R*) = 99.5:0.5. The stereochemical outcome can be rationalized in light of conformations **D** and **E** of the ylide intermediates

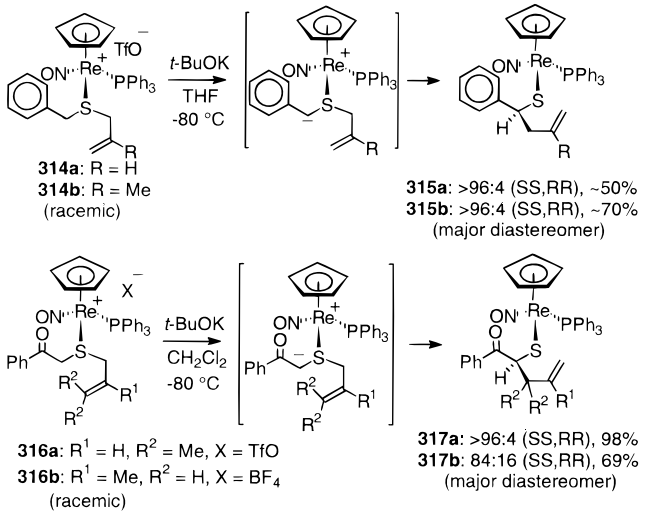
Scheme 87



(Scheme 87).[135b] From favored conformation **D**, the (*SS*,*RR*) diastereomer was exclusively formed. The thiolate ligands **312** in **311** can be decomplexed with the recovery of the chiral auxiliary **313** in several steps with retention of configuration in the product and auxiliary.

The above rhenium-based asymmetric rearrangement has later been extended to other thiolate ligands[135a] and other metals.[135b] Besides diallyl sulfide complexes, rearrangements of dibenzyl (will be discussed in section V.B), benzyl allyl, and allyl β-keto sulfide complexes of the chiral Re Lewis acids have also been examined by Gladysz (Scheme 88).[135a]

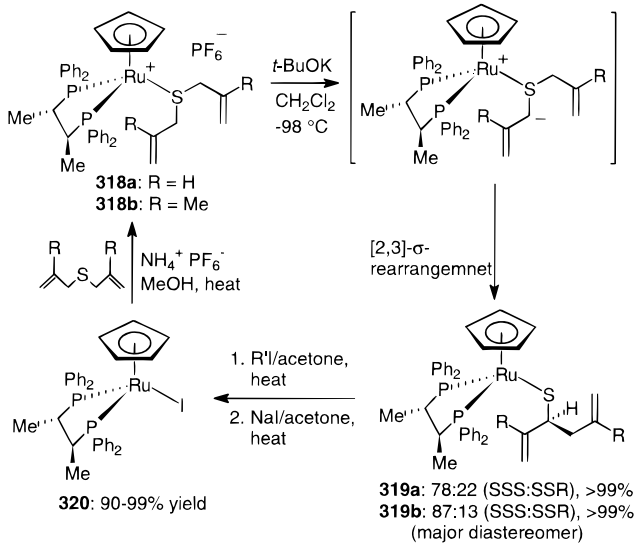
Scheme 88



On treatment with *t*-BuOK, benzyl allyl sulfide complexes **314a** or **314b** produced rearranged products **315a** or **315b** diastereospecifically in moderate yields along with other products. Similarly, the allyl β-keto sulfide complexes **316a** or **316b** could also undergo the [2,3]-σ-rearrangement to produce **317a** or **317b** in high de. These products could all be smoothly decomplexed to give corresponding thioethers with recovery of the Lewis acid auxiliaries.

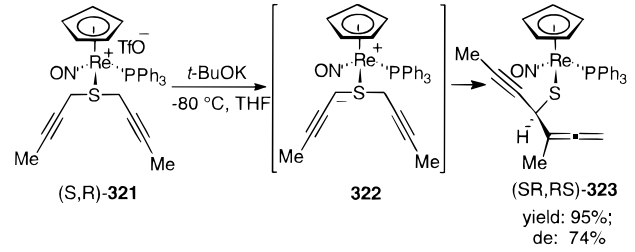
Rearrangement of ylides from diallyl sulfide complexes of chiral iron Lewis acids provided an environment that is approximately isosteric with corresponding Re analogs. The diastereoselectivities obtained were not higher than those of the latter. However, in the rearrangement of chiral diphosphine-derived ruthenium complexes (**318a** and **318b**), slightly higher diastereoselectivities were achieved (Scheme 89).[135b] Compared to the rhenium-based rearrangement, the most significant aspects of the present reaction is the efficient recycle protocol. The thiolate ligand is easily detatched in a one-flask alkylation/substitution sequence (R′I/NaI, from **319** to **320**), and it allows the starting ruthenium diallyl sulfide complex to be regenerated in a single step. In addition, all yields are essentially quantitative.

Scheme 89



The asymmetric rearrangement of metal Lewis acid complexes also works well with the propargylic ylide (*S*,*R*)-**321**. Chiral allene (*SR*,*RS*)-**323** was obtained in 95% yield and 74% de through the [2,3]-σ-rearrangement of ylide **322** (Scheme 90). This

Scheme 90

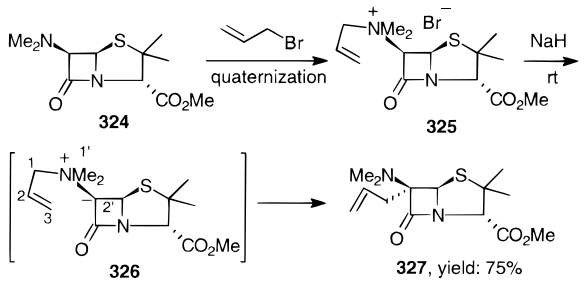


example may also represent the only asymmetric version of the [2,3]-σ-rearrangement involving propargylic ylides although this type of rearrangement has been explored very early.[136] The above examples showed for the first time that a [2,3]-σ-rearrangement has been effected in a metal coordination sphere.

2. Allylic Ammonium Ylides

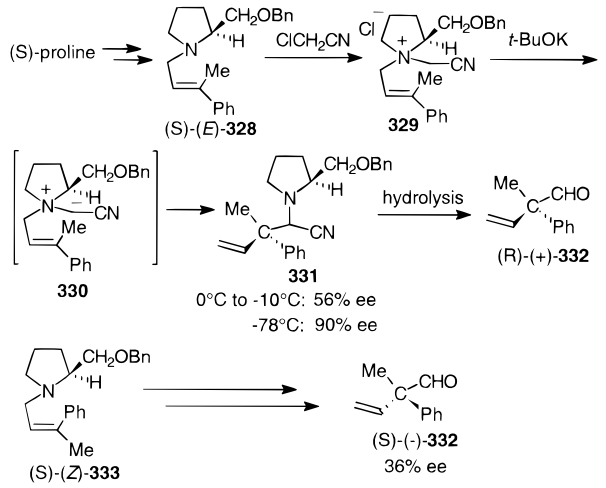
Like allylic sulfonium ylides, allylic ammonium ylides can also undergo the [2,3]-σ-rearrangement. The asymmetric version of this process was examined at an early stage. One example is the *C*-6 alkylation of a penicillin in the early 1970s by Kaiser and Baldwin.[137] On treatment of penicillin ammonium salt **325** with NaH in DMF−benzene, methyl 6-α-allyl-6-β-*N*,*N*-dimethylaminopenicillanate (**327**) was obtained stereoselectively in 75% yield by rearrangement of ammonium allylide **326** (Scheme 91).

Scheme 91



An asymmetric [2,3]-σ-rearrangement involving amino acid-derived chiral allylic ammonium ylides was later reported by Hiroi (Scheme 92).[138] Chiral

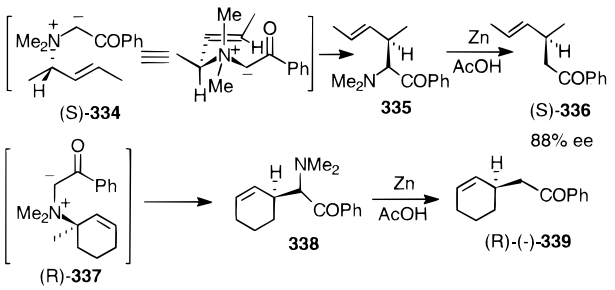
Scheme 92



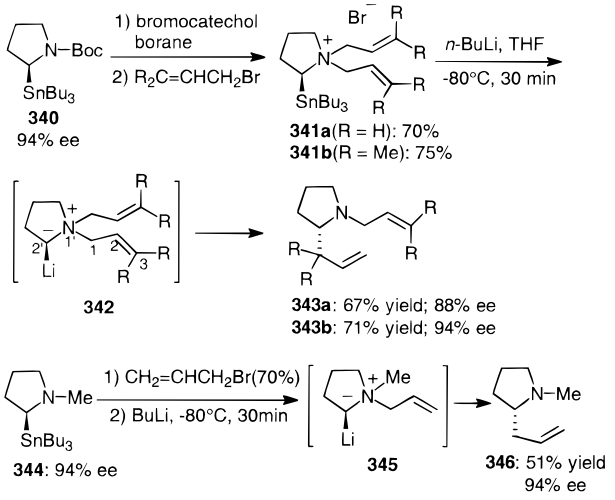
allylic amine (*S*)-(*E*)-**328** was synthesized and quaternized with cyanomethyl chloride to give **329**. Treatment of this ammonium salt with base afforded compound **331**, which was transformed into aldehyde (*R*)-(+)-**332** by hydrolysis, in 56−90% ee. When the *Z*-allylic amine **333** was used instead of corresponding *E* isomer **328**, aldehyde **332** with *S* configuration was furnished. These results show that the configuration of the double bond in the allylic ylides influences the stereochemistry of the rearrangement product. A detailed investigation illustrated that both the original chiral center and the double-bond configuration in ammonium allylides affect the stereochemical outcome of reactions which occur via an envelope transition state.[111a] An (*S*)-(*E*) starting material (**334**) usually leads to an (*S*)-(*E*) product (**336**), whereas the use of an (*R*)-(*Z*) substrate (**337**) in which the alkene is constrained in a ring gives the (*R*)-(*Z*) product (**339**) (Scheme 93).

An excellent example for chirality transfer in the [2,3]-σ-rearrangement of ammonium ylides was recently demonstrated by Gawley (Scheme 94).[139] The organostannane **340** was converted to the diallyl quaternary ammonium salts **341a** and **341b** in reasonable yields. Ammonium ylides **342**, with the chirality at the ylidic carbon atom were produced by transmetalation with *n*-BuLi, and rearranged into products **343a** or **343b** in high yields and high ee. Similarly, monoallylic ylide **345** was rearranged into **346** with complete transfer of the chirality. Complete inversion of stereochemistry at the metal bearing

Scheme 93



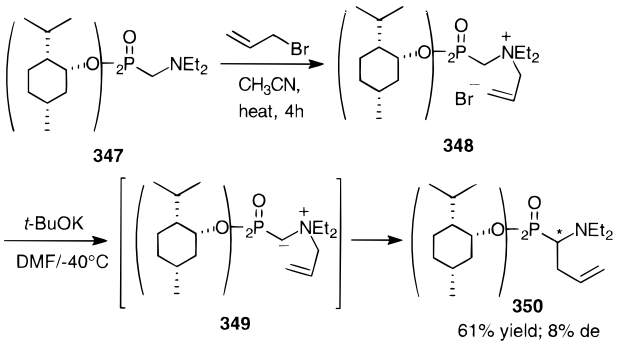
Scheme 94



carbon atom was observed in these reactions, which is analogous to the Still−Wittig rearrangement. The faithful transfer of chirality from the ylidic carbon is noteworthy. They also demonstrated that the rate of the [2,3]-σ-rearrangement of a monoallylated substrate (i.e., a tertiary amine not a ammonium salt) was much slower and was in competition with the [1,2]-rearrangement resulting in low chirality transfer. The ylide [2,3]-σ-rearrangement is more facile than the anion reaction.

A very recent asymmetric [2,3]-σ-rearrangement involving chiral ammonium ylide was reported by Collignon.[140] Dimenthylphosphonyl-stabilized allylic ammonium ylide **349** rearranged to **350** in only 8% diastereomeric excess (Scheme 95). The low selectiv-

Scheme 95



ity is a consequence of the chiral group being too far from the reaction center.

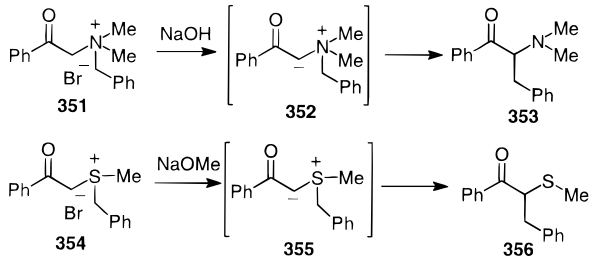
B. Other Rearrangements

It is known that in addition to [2,3]-σ-rearrangements, ylides can undergo several other rearrange-

ments, for example, Stevens rearrangements and Sommelet rearrangements. The Pummerer rearrangement also occurs via an ylide-like intermediate. The asymmetric versions of these rearrangements will be discussed.

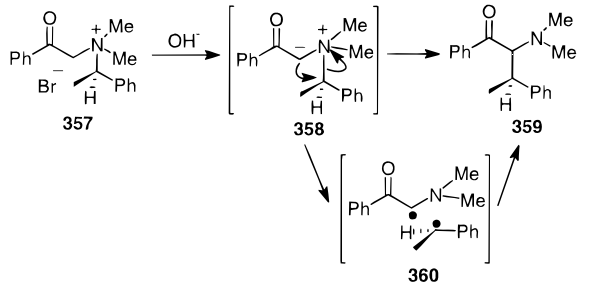
The Stevens rearrangement is an early-known ylide rearrangement, which was discovered in 1928 by Stevens (Scheme 96).[141] Its asymmetric version

Scheme 96



was also investigated along with the mechanism of the [1,2]-allyl migration. Kenyon[142] first showed that the migrating group retained its configuration during the course of the rearrangement of optically active ammonium ylide **358** (Scheme 97). Wittig[143] and

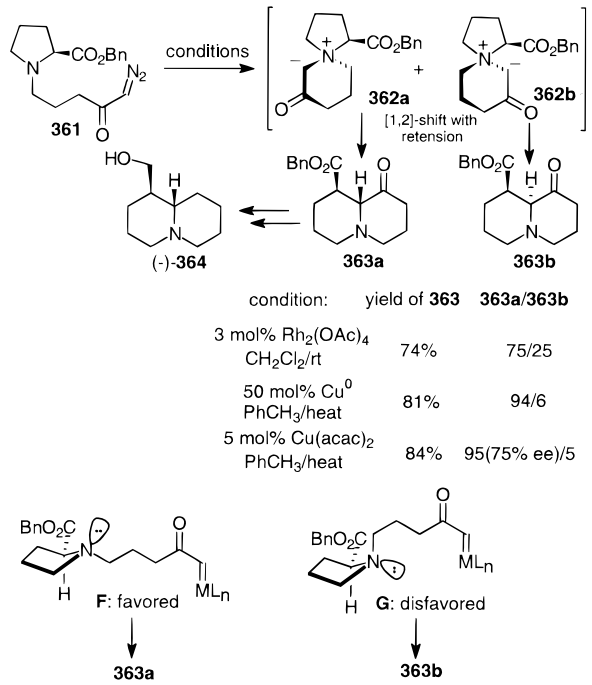
Scheme 97



Hauser[144] then proposed a concerted intramolecular displacement of the migrating group by the ylidic carbon of **358** for this reaction. A high degree of retention of configuration is usually observed and so led to the proposal that the mechanism of the reaction was concerted. However, according to the Woodward−Hoffmann rules of conservation of orbital symmetry,[112] the 1,2-alkyl migration reaction of an ylide is a symmetry-forbidden process. The concerted mechanism was therefore questioned. Ollis[145,146] carried out a series of elegant experiments and by careful analysis, they were able to show that the Stevens rearrangement proceeded by a radical pair intermediate **360**. These radicals recombine rapidly before they have time to diffuse out of the solvent cage. This reaction therefore exhibits a very high degree of intramolecularity and is highly stereoselective when the reaction is carried out at low temperature and in viscous solvent. Many asymmetric Stevens rearrangements have been reported. An excellent review,[111e] which contains most of the early asymmetric work, is now available. There are also some other early examples on the enantioselective Stevens rearrangement and its applications in penicillin chemistry,[147a−c] in the synthesis of pyrrolizidine alkaloids[147d] and 6-amidocarbapenem antibiotics,[147e] and in the sugar chemistry.[148]

A recent asymmetric Stevens rearrangement and its application in the synthesis of (−)-epilupinine was disclosed by West (Scheme 98).[149] Monocyclic diazo

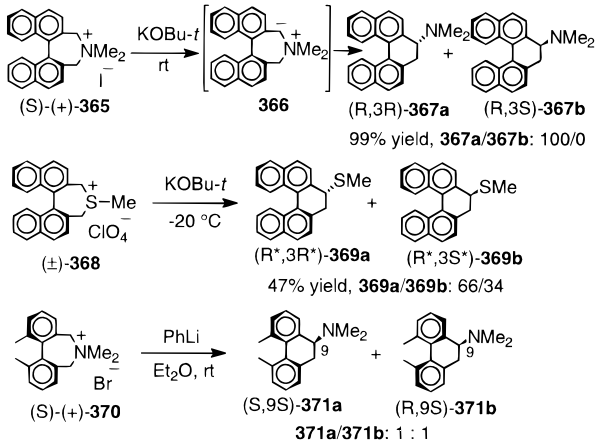
Scheme 98



ketone **361**, which was prepared from proline benzyl ester, was converted into diastereomeric ammonium ylides **362a** and **362b** upon treatment with Rh or Cu catalysts. These ylides readily underwent the Stevens [1,2]-shift with retention of configuration to furnish bicyclic compounds **363a** and **363b** in high diastereoselectivity with **363a** being the major product formed via the more favored conformation **F**. Compound **363a** was easily transformed into (−)-epilupinine ((−)-**364**) in several steps.

The transfer of axial chirality to central chirality by the Stevens rearrangement has been investigated by Zavada.[150] When axially twisted dihydroazepinium salt (*S*)-(+)-**365** was treated with *t*-BuOK at room temperature, amine **367a** was obtained as the sole product in quantitative yield through the Stevens rearrangement of ammonium ylide **366** (Scheme 99). Contrary to the complete transfer of axial chirality to central chirality in the ammonium ylide system,

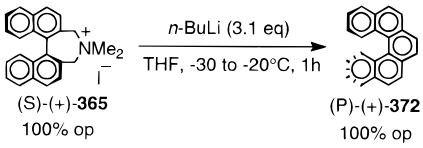
Scheme 99



the Stevens rearrangement with corresponding sulfonium ylide, derived from racemic dihydrothiepinium salt **368** exhibited only low diastereoselectivity.

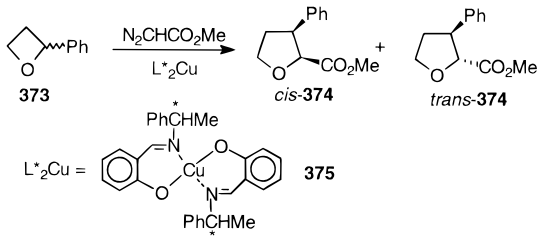
Interestingly, the Stevens rearrangement of an analogous biphenyl-substituted dihydroazepinium salt (*S*)-(+)-**370**-derived ammonium ylide yielded two diastereomers, **371a** and **371b** in a 1:1 ratio. Compounds **371a** and **371b** interconverted rapidly under the rearrangement conditions.[151] For the different stereochemical outcomes at the nitrogen bearing chiral center in these analogous systems, a mechanistic dichotomy in the rearrangement of the biaryl azepinium and thiepinium ylides was suggested. The first mechanism transfers the biaryl chirality with configurational retention (**370** to **371**), whereas the other occurs with inversion (**366** to **367a**). An explanation was suggested in terms of competition between suprafacial (concerted) and antarafacial (nonconcerted) mechanism. This rearrangement has been applied to an asymmetric synthesis of chiral pentahelicene (P)-(+)-**372** in 100% optical purity (Scheme 100).

Scheme 100



The asymmetric Stevens rearrangement of oxonium ylides has also been described.[152−155] In 1968, Nozaki et al[152] demonstrated a preparation of tetrahydrofuran derivatives **374** by the Stevens rearrangement of oxonium ylides, produced by the reaction of oxetane **373** with methyl diazoacetate in the presence of chiral salicylaldimine−Cu complexes (Scheme 101). Although the optical purity of the

Scheme 101

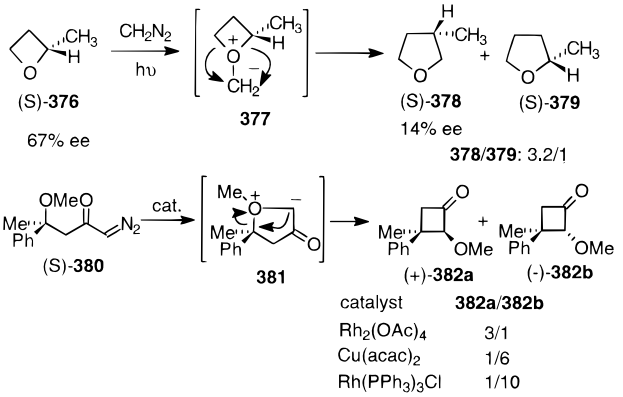


products was not determined at that time, this still represents a very early example of the asymmetric Stevens rearrangement of oxonium ylides.

When diazomethane was photolyzed in the presence of oxetane (*S*)-**376**, 3- and 2-methyltetrahydrofuran (*S*)-**378** and (*S*)-**379** were obtained via oxonium ylide **377** in a ratio of 3.2:1 with 21% net retention of configuration for the former (Scheme 102).[153] The preferential migration of the tertiary carbon is in accordance with the radical-pair mechanism. Higher selectivity, up to 10:1, was achieved in the rearrangement of chiral oxonium ylide **381**.[154]

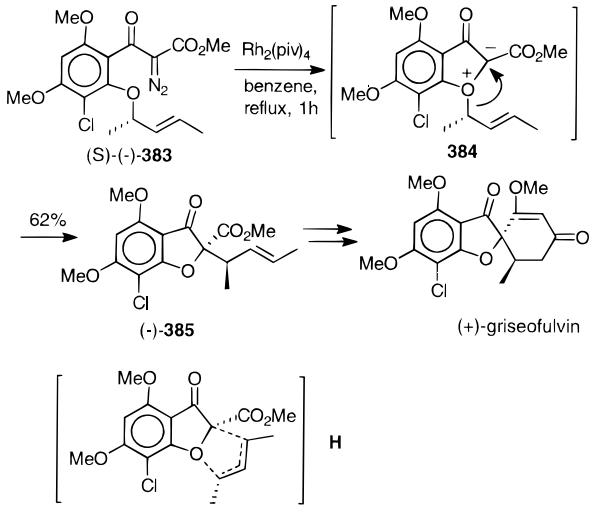
The asymmetric Stevens rearrangement of oxonium ylides has been successfully utilized in the synthesis of naturally occurring (+)-griseofulvin by

Scheme 102



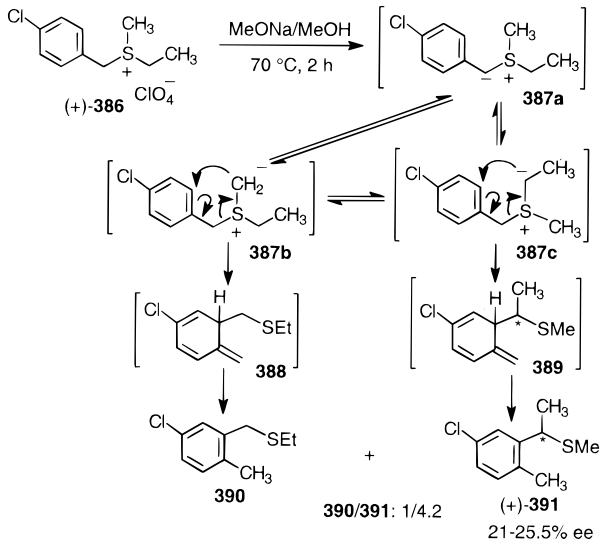
Pirrung (Scheme 103).[155] The Rh-catalyzed decomposition of diazo compound (*S*)-(−)-**383** led to the formation of allylic oxonium ylide **384** by intramolecular carbene capture. The subsequent Stevens rearrangement of **384** gave (−)-**385** as single diastereomer in 62% yield, which was subsequently transformed into (+)-griseofulvin. The stereochemistry of this rearrangement was rationalized in terms of a transition-state model **H**. This resembles an oxabicyclo[3.3.0]octane ring system, with the key stereochemistry-defining methyl group located on the convex face.

Scheme 103



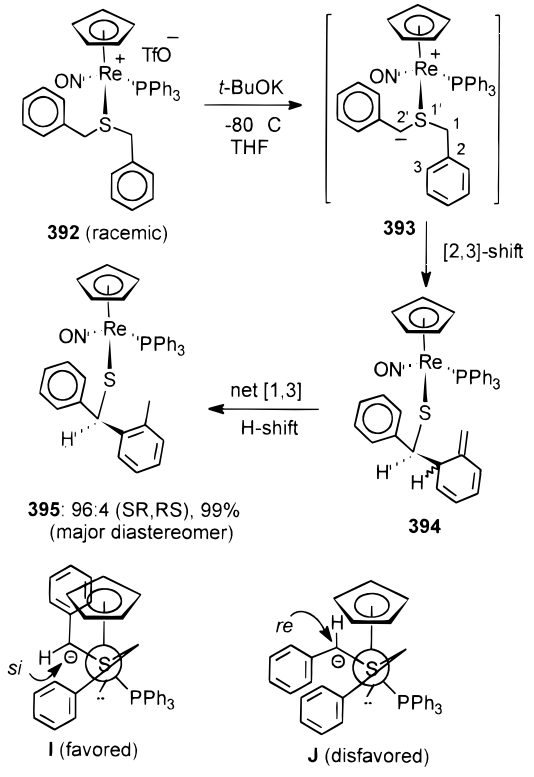
The Sommelet−Hauser rearrangement is another well-documented reaction of ylides and was discovered in 1937 by Sommelet.[156] An asymmetric version of this rearrangement was reported by Campbell and Darwish in 1976.[157] Treatment of the resolved chiral sulfonium salt (+)-**386** with base gave a mixture of sulfonium ylides **387a**, **387b**, and **387c** (Scheme 104). The latter two ylides underwent the intramolecular rearrangement to form **388** and **389**, which further rearranged to **390** and (+)-**391** in 1:4.2 ratio. The product **391** was obtained with only low ee (21−25.5%). Very high diastereoselectivity in Sommelet−Hauser rearrangement of dibenzyl sulfide complexes of a rhenium Lewis acid was achieved by Gladysz[135a] recently. Treatment of dibenzyl complex **392** with *t*-BuOK, product (*SR,RS*)-**395** was produced in 99% yield and 92% de through a [2,3]-σ-rearrangement

Scheme 104



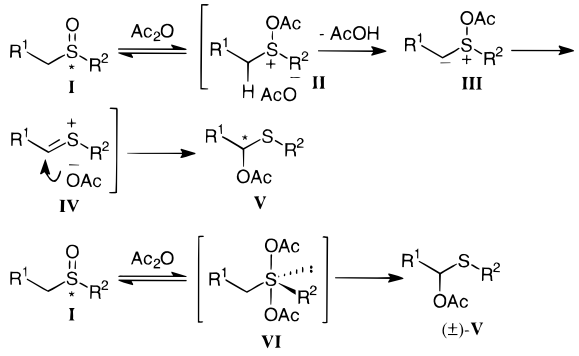
of ylide **393** and a net [1,3]-H shift (Scheme 105). The major diastereomer may come from the favored conformation **I** of ylide **393**. However, when the same complex **392** was treated by a stronger base MeLi (instead of *t*-BuOK), the [1,2]-shift product was afforded through the Stevens rearrangement.[135a]

Scheme 105



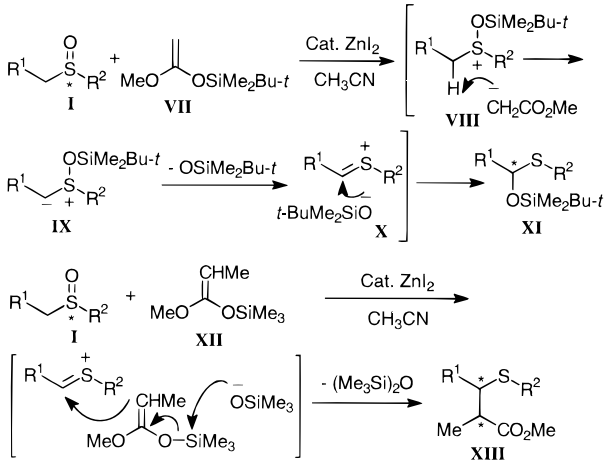
The sulfoxide-based Pummerer rearrangement (Scheme 106), discovered in 1909,[158] proceeds through an ylide-like intermediate **III**. It is clear that the chirality may be transferred from the sulfur center to a carbon center of the product (**V**) if a chiral sulfoxide is used. The ease of preparation of chiral sulfoxides provided an impetus for the development of an asymmetric version of this process. Several excellent reviews recorded most of the earlier asymmetric Pummerer rearrangements in detail.[159] However, only very low ee values (generally less than 30%) have ever been achieved in the traditional asymmetric Pummerer rearrangement (by the reaction of a sulfoxide and an acid anhydride), although 70% ee has been achieved under some special conditions.[160] The low selectivity is probably due to a competitive reaction via an achiral sulfurane intermediate **VI**, which leads to racemization of the chiral sulfoxides.

Scheme 106



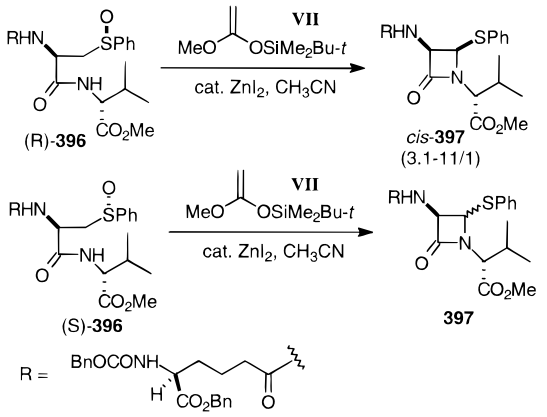
A great improvement in selectivity (higher than 80% in general) was achieved using *O*-silylated ketene acetals-induced Pummerer rearrangement by Kita's group (Scheme 107), and this work has recently been reviewed.[111f] The reaction of chiral sulfoxide **I** with *O*-silylated ketene acetal **VII** in the presence of catalytic amounts of ZnI_2 gave ylide intermediate **IX** which rearranged to give the α-siloxy substituted sulfide **XI** with ~99% ee. When *O*-silylated ketene acetal **XII** was used instead of **VII**, the *β*-sulfur substituted ester **XIII**, with two newly formed chiral centers, was obtained. The initiator for the asymmetric Pummerer rearrangement has also been extended to include ethoxyvinyl ester and α-acetoxy sulfide was obtained.[161]

Scheme 107



The *O*-silylated ketene acetal-induced asymmetric Pummerer rearrangement has been used to provide useful information on the first step in the biosynthesis of penicillin (Scheme 108).[162] The authors found that (*R*)-**396**, when treated with **VII**, gave the *cis*-*β*-lactams **397** predominantly, while (*S*)-**396** with **VII** gave a mixture of *cis*- and *trans*-**397**. The *cis*-*β*-lactams **397** were preferentially obtained from (*R*)-**396**, suggesting that the 3-amino-*β*-lactam moiety of

Scheme 108



naturally occurring penicillins has a *cis* orientation.

VI. Asymmetric Olefinations

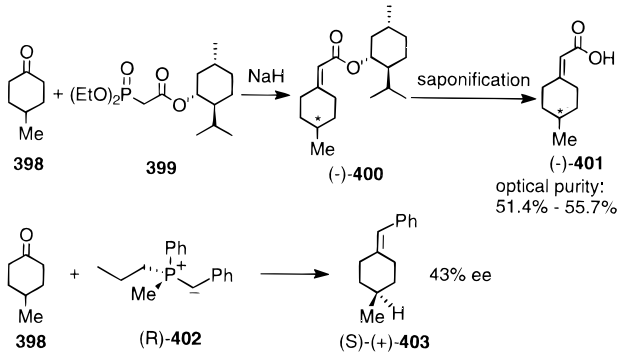
The Wittig-type olefination reaction is one of fundamental reactions of ylides.[1] The possibility of carrying out asymmetric version of such a reaction is not readily apparent as there are no new sp^3 stereocenters formed. However, asymmetric Wittig-type olefination reactions have been carried out by placing stereogenic centers adjacent to or near the reaction center. Three types of asymmetric Wittig-type reactions have been achieved: kinetic resolution of racemic carbonyl compounds, desymmetrization of ketones, and preparation of optically active allenes.

Due to the close relationship between the original Wittig olefination and other variants, e.g., Wittig−Horner and Horner−Wadsworth−Emmons (HWE) reaction, the olefination of carbonyl compounds with chiral phosphonium ylides, phosphonates, phosphonic bisamides, phosphine oxides, and other similar reagents to form olefins are all contained in this section and three topics, i.e., desymmetrization of ketones, kinetic resolution of racemic carbonyl compounds, and preparation of optically active allenes will be discussed. Because an excellent review on the asymmetric Wittig-type reactions, written by Rein and Reiser,[163a] has been published and two Chemtracts[163b,c] on the asymmetric olefination are also available, only a few typical examples on each topic will be discussed in this section.

A. Desymmetrization of Ketones

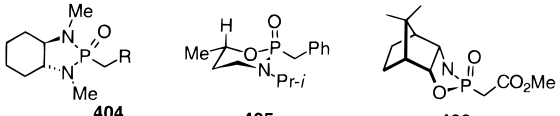
The reaction of a chiral phosphonium ylide or a related reagent with a 4-substituted cyclohexanone to give an axially dissymmetrical olefin is the earliest attempted asymmetric Wittig-type reaction. The first desymmetrization of 4-substituted cyclohexanones was reported in 1962.[164] In the presence of NaH, ketone **398** reacted with chiral phosphate **399** to give optically active alkene (−)-**400**, which was further saponified to produce the corresponding acid (−)-**401** in >50% optical purity (the result of the asymmetric induction was questioned, however[166a]) (Scheme 109). In order to improve the asymmetric induction, the first desymmetrization of ketones by the reaction of a chiral ylide reagent, with a stereo-

Scheme 109



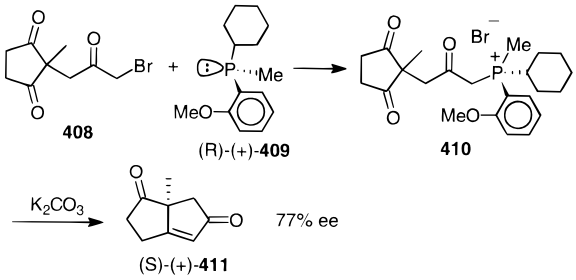
genic center on phosphorus, was realized by Bestmann.[165] The axially dissymmetrical alkene (*S*)-(+)-**403** was formed in 43% ee by the olefination of **398** with chiral phosphonium ylide (*R*)-**402**. Bestmann also tried this reaction with tropinone and pseudopelletierine. Very high ee values (>90%) have been achieved by Hanessian[166] and Denmark[167] using chiral phosphonic bisamide **404**, phosphonamidates **405** and **406**, respectively, in the desymmetrization of 4-substituted cyclohexanones (Scheme 110).

Scheme 110



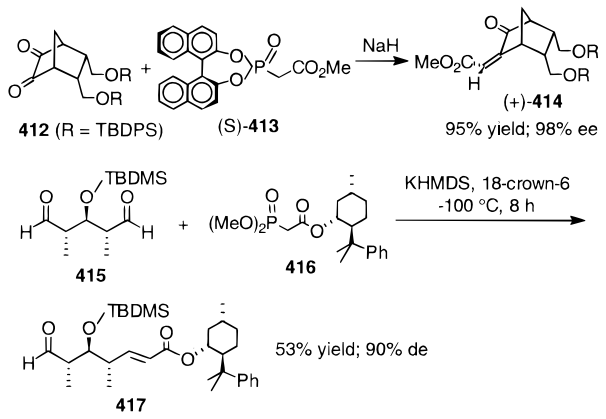
A strategy for desymmetrizing *meso*-triketone **408** by intramolecular Wittig olefination has been adopted by Trost and Curran[168] in the synthesis of cyclopentanoid natural products (Scheme 111). Bicyclic un-

Scheme 111

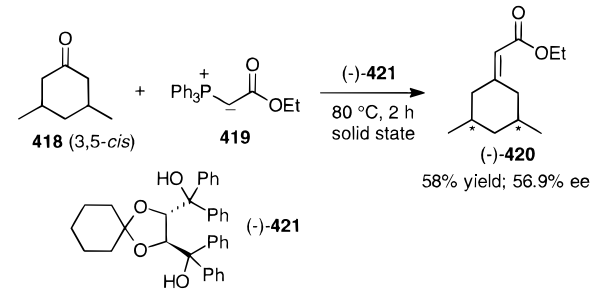


saturated diketone (*S*)-(+)-**411** was obtained in 77% ee by base treatment of phosphonium salt **410**. The desymmetrizations of *meso*-diketones[169] and *meso*-dialdehydes[170] by asymmetric Horner−Wadsworth−Emmons reaction were reported by both Fuji[169] and Rein.[170] Unsaturated ketone (+)-**414** and aldehyde **417** were obtained with high de or ee by the reaction of chiral phosphates (*S*)-**413** and **416** with the corresponding carbonyl compounds in the presence of base (Scheme 112). Desymmetrization was also realized by the reaction of an achiral ketone **418** with an achiral phosphonium ylide **419** in the presence of a chiral host (−)-**421** (Scheme 113).[171] This may provide opportunities for asymmetric catalytic ylide olefination.[163a] For other reports on ylide desymmetrization, the reader is directed to Rein and Reiser's review.[163a]

Scheme 112



Scheme 113

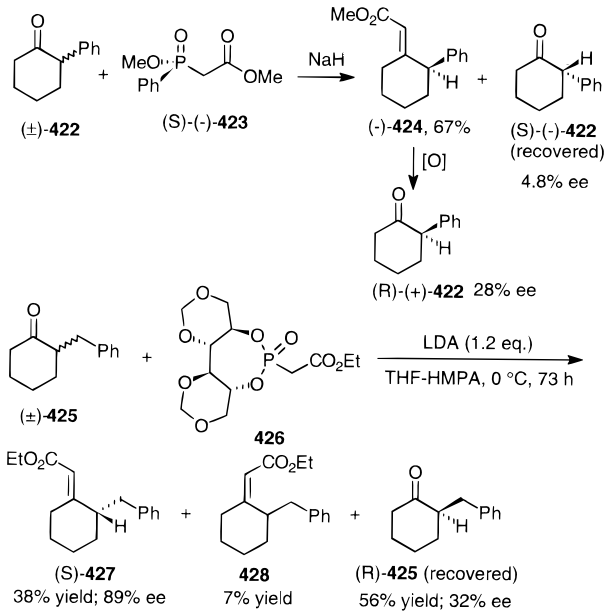


B. Kinetic and Dynamic Kinetic Resolutions of Racemic Carbonyl Compounds

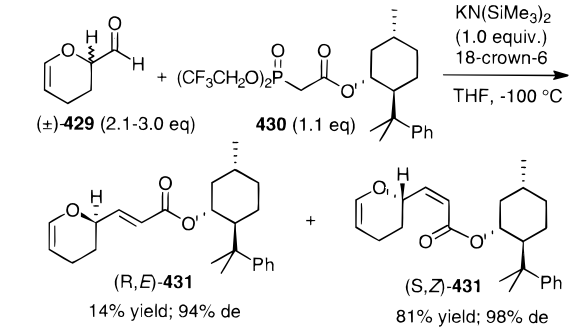
The idea of differentiating two enantiomers of a carbonyl compound, which contains one or more stereogenic centers adjacent to the carbonyl group, is readily apparent and easier to achieve than other asymmetric applications of the ylide olefination reaction. The first such attempt appeared as early as 1975.[172] When racemic α-phenylcyclohexanone **422** was treated with the anion of chiral phosphinate ester (*S*)-(−)-**423**, the olefination product (−)-**424** was obtained. The optically active starting ketone (*S*)-(-)-**422** was also recovered in 4.8% optical purity (Scheme 114). After oxidation, the olefinic product **424** could be converted back to the starting ketone, but with opposite absolute configuration compared to the recovered ketone (*S*)-(−)-**422**. Following this attempt, several other groups[166b,167b,173,174] reported their results on the kinetic resolution of racemic ketones. For example, Narasaka[174] used a mannitol-derived tricyclic chiral phosphate **426** to resolve racemic α-benzylcyclohexanone **425**. The starting ketone **425** was recovered in 32% ee (*R* configuration), together with the olefination product (*S*)-**427** and a small amount of **428**.

Compared with the kinetic resolution of ketones by ylide olefination, the resolution of corresponding racemic aldehydes has received less attention. The first example did not appear until 1994. In the resolution of Diels−Alder acrolein dimer, Rein and Reiser[175] achieved very high diastereoselectivity. For instance, when treated with the anion of chiral phosphate **430**, two enantiomers of racemic aldehyde **429** were efficiently separated by the formation of *E*- and *Z*-olefinic product (*R*)-(*E*)-**431** and (*S*)-(*Z*)-**431** in 94% and 98% de's, respectively (Scheme 115). At the same time, Furuta and Iwamura[176] reported a related kinetic resolution of amino aldehydes.

Scheme 114

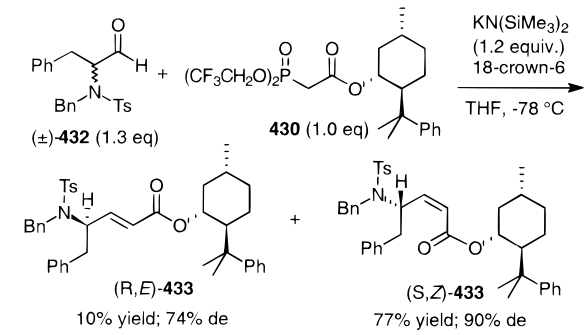


Scheme 115



By utilizing the easy equilibration (racemization) of the two enantiomers of α-amino aldehydes under basic conditions, Rein and Reiser[177] realized the first dynamic kinetic resolution of racemic α-amino aldehydes by asymmetric HWE olefination (Scheme 116).

Scheme 116



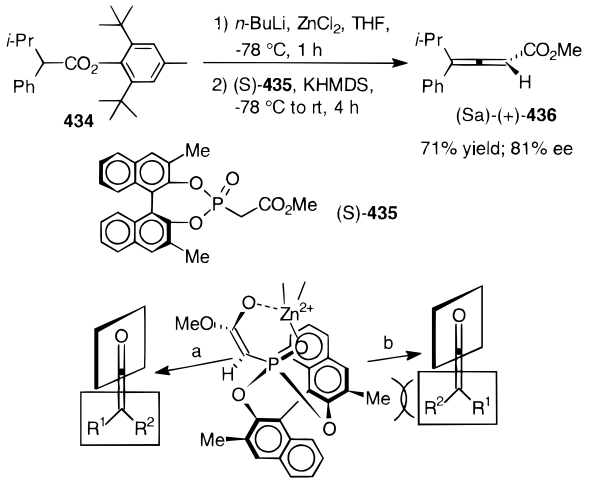
Under carefully controlled conditions, racemic protected amino aldehyde **432** was smoothly converted into *cis*-olefinic product (*S*)-(*Z*)-**433** in 77% yield and 90% de using chiral phosphate **430**. This was accompanied by a small amount of the *trans* isomer (*R*)-(*E*)-**433**. This represents a very successful example of complete conversion of a racemic aldehyde into an

olefin with good diastereoselectivity and is as good as classic kinetic resolution techniques.

C. Preparation of Chiral Allenes

The easy reaction of a carbonyl group in ketene with Wittig reagents or phosphate anions provides the possibility of assembling compounds with axial chirality. Such an idea was attempted at the beginning of the 1960s. Several attempts[172,176−180] have been well documented. However, the early attempts had limited success and only low ee values were reported. Not until very recently was a successful example disclosed by Fuji and co-workers.[181] On the basis of their one-pot procedure for the preparation of allenecarboxylates from the HWE olefination of ketenes produced *in situ*,[182] they developed an asymmetric version in the preparation of an allene by a Wittig-type reaction. Treatment of 2,6-di-*tert*-butyl-4-methylphenyl (BHT) ester **434** with base generated a ketene which was reacted with the anion of chiral phosphate (*S*)-**435** *in situ* to form optically active allene (+)-**436** in 71% yield and 81% ee (Scheme 117).

Scheme 117



The high enantioselectivity observed can be understood by consideration of the favorable chelated intermediate. Chelation of zinc to the phosphate produces a conformationally locked anion and the axially dissymmetrical binaphthyl group dictates the orientation of the approach of the electrophile from the less hindered *si* face of the reagent (route a). The enantiofacial selectivity was therefore well controlled. This paper may represent the best result, to date, for preparing chiral allenes by an asymmetric Wittig-type olefination.

VII. Concluding Remarks

Since the pioneering contributions from several famous groups, like C. R. Johnson, B. M. Trost, and H. J. Bestmann, the asymmetric ylide reactions have been extensively developed for about 30 years. During these years, many significant results in the field of asymmetric ylide reactions have been achieved. Some highly stereoselective processes have been developed, and several conceptually new ideas and new reagents have been presented and several new catalytic processes have been designed. The asymmetric variants have involved almost all types of ylide reactions, for example, cyclization, rearrangement and olefination, and many types of heteroatom ylides, i.e., O, S, Se, N, P, As, and their derivatives. However, there are still many problems which need to be solved before asymmetric ylide methodology becomes a really useful and powerful synthetic tool.

Among asymmetric cyclization reactions, epoxidation has received most attention and those methods provide a useful complement to asymmetric oxidation methods. The chiral oxathiane derivatives seem to be very promising reagents and lead to highly enantioselective epoxidations. The application of catalytic processes in epoxidation and aziridination not only conserves the relatively precious chiral reagents, but is also beneficial in solving difficulties in the preparation of sulfonium salt. Most studies of asymmetric cyclopropanation have centered on substrate-controlled processes. Reagent- and auxiliary-controlled reactions remain relatively undeveloped although some recent results seem most encouraging. More attention should be given to this area since such processes may be potentially useful for the preparation of insecticides. Comparatively, the asymmetric ylide aziridination is the least explored area. Several reports have very recently appeared. Due to the relatively low reactivity of ylides (compared with corresponding carbenes), only reactive *N*-sulfonyl and *N*-sulfinyl imines have been used. The development of more efficient methods for the activation of imines is necessary. The asymmetric ylide rearrangement has been well developed and many excellent results have been achieved and some of them have found synthetic applications. The use of chiral metal reagents (G. A. Gladysz's and R. E. Gawley's work) in asymmetric ylide rearrangement has improved the enantioselectivities. The application of chiral catalysts is still in its infancy. More efforts should be made on these catalytic asymmetric processes. For asymmetric ylide olefination, many exciting results have been achieved, especially in recent years, by the effort of S. Hanessian, S. E. Denmark, T. Rein, and O. Reiser. But some excellent and synthetically promising work, for example, the dynamic kinetic resolution of carbonyl compounds needs more work to make it practical.

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