Stereoselective Cyclopropanation Reactions

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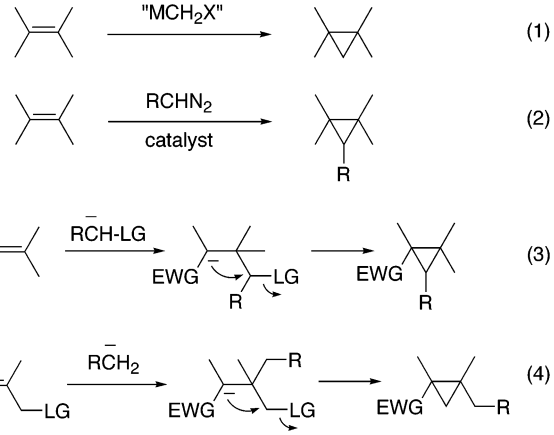
Contents

I. Introduction

Organic chemists have always been fascinated by the cyclopropane subunit.[1] The smallest cycloalkane is found as a basic structural element in a wide range of naturally occurring compounds.[2] Moreover, many cyclopropane-containing unnatural products have been prepared to test the bonding features of this class of highly strained cycloalkanes[3] and to study enzyme mechanism or inhibition.[4] Cyclopropanes have also been used as versatile synthetic intermediates in the synthesis of more functionalized cycloalkanes[5,6] and acyclic compounds.[7] In recent years, most of the synthetic efforts have focused on the enantioselective synthesis of cyclopropanes.[8] This has remained a challenge ever since it was found that the members of the pyrethroid class of compounds were effective insecticides.[9] New and more efficient methods for the preparation of these entities in enantiomerically pure form are still evolving, and this review will focus mainly on the new methods that have appeared in the literature since 1989. It will elaborate on only three types of stereoselective cyclopropanation reactions from olefins: the halomethylmetal-mediated cyclopropanation reactions (eq 1), the transition metal-catalyzed decomposition of diazo compounds (eq 2), and the nucleophilic addition−ring closure sequence (eqs 3 and 4). These three processes will be examined in the context of diastereo- and enantiocontrol. In the last section of the review, other methods commonly used to make chiral, nonracemic cyclopropanes will be briefly outlined.



II. Halomethylmetal (Zn, Sm, Al)-Mediated Cyclopropanation Reactions

A. Introduction

The observation that diiodomethane reacts with zinc to give an iodomethylzinc species was first reported in 1929 by Emschwiller.[10] However, about 30 years later, Simmons and Smith[11] were the first

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Hélène Lebel received her B.Sc. degree in biochemistry from the Université Laval in 1993. She performed graduate studies in organic chemistry in the Chemistry Department of the Université de Montréal under the supervision of Professor André B. Charette as a 1967 Science and Engineering NSERC fellow, during which she worked on stereoselective cyclopropanation reactions. In 1998, she joined the research group of Professor Eric Jacobsen at Harvard University as a NSERC postdoctoral fellow, where she completed the total enantioselective synthesis of taurospongin A. She started her academic career in 1999 in the Chemistry Department of the Université de Montréal as an assistant professor. Her research activities involve the development of new transition metals containing catalysts that mediate fundamentally interesting and useful organic reactions. She recently developed a new olefination reaction via the transition metal-catalyzed synthesis of salt-free phosphorus ylides.

Jean-François Marcoux received a B.Sc. degree in chemistry from Sherbrooke University, Canada, and went to Université de Montréal as a NSERC and FCAR predoctoral fellow, where he received his Ph.D. degree in 1996. His graduate work, directed toward the development of chiral auxiliaries and catalysts for the stereoselective Simmons–Smith cyclopropanation of olefins, was carried out under the mentorship of Professor André B. Charette. He then joined the laboratory of Professor Stephen Buchwald at MIT, Massachusetts, as a NSERC postdoctoral fellow. There he was involved in the development of practical catalysts for the palladium- and copper-catalyzed formation of aromatic amines and ethers. He currently is a Research Fellow in the department of Process Research at Merck & Co., Inc., Rahway, NJ.

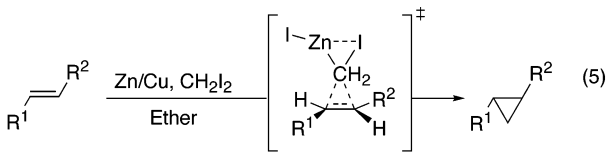
to appreciate that this reagent ($IZnCH_2I$) could be used for the stereospecific conversion of alkenes to cyclopropanes (eqs 5 and 6).[12] The cyclopropanation reactions using these reagents are characteristically stereospecific, proceeding through a "butterfly-type" transition structure.[13]

One major advantage of the reaction is its excellent chemoselectivity, since it is applicable to a variety of olefins and compatible with several functional groups such as enamines, enol ethers, esters, ketones, etc. (vide infra). Simmons and Smith's seminal studies

Carmela Molinaro received her B.Sc. degree in biochemistry at the Université de Montréal in 1996 and stayed to study for her M.Sc. and Ph.D. degree in organic chemistry (2002) with Professor André B. Charette. She has worked on the characterization of zinc cyclopropanating reagents and the development of catalysts for the enantioselective cyclopropanation reaction using these reagents. She has since joined the research group of Professor Timothy F. Jamison at the Massachusetts Institute of Technology as a FCAR postdoctoral fellow and is working on nickel-catalyzed coupling reactions.

André B. Charette received his Ph.D. (1987) from the University of Rochester under the supervision of Robert K. Boeckman, Jr., where he completed the total synthesis of the ionophore calcimycin. He then joined the research group of David A. Evans at Harvard University as a NSERC postdoctoral fellow, where he worked on the total synthesis of bryostatin. Since 1992, he has been professor at the Université de Montréal, and he is currently the holder of the NSERC/Merck Frosst/Boehringer Ingelheim Research Chair on Stereoselective Drug Synthesis at the Université de Montréal. He has received a number of awards, including the Eli Lilly Grantee Award, an Alfred P. Sloan Research Fellowship, the Astra Pharma Award, the Merck Frosst Centre for Therapeutic Research Award, a Steacie Fellowship, and the Rutherford Medal. His research interests are in the area of stereoselective synthesis of organic compounds.

were quickly followed by the development of several alternative methods to prepare related $ZnCH_2X$ species or to activate the zinc metal.[14]



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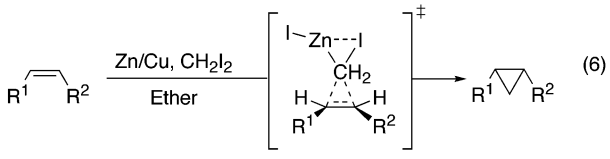


(6)

Table 1. Important Methods for the Preparation of Cyclopropanating Reagents

reactants (ref)	reagent
Oxidative Addition	
Zn/activator, XCH_2I (14)	$IZnCH_2X$ (X = Cl, I)
Sm/activator, CH_2I_2 (28)	$ISmCH_2I$
Alkyl Exchange	
Et_2Zn, CH_2I_2 (16)	$EtZnCH_2I$ or $Zn(CH_2I)_2$
EtZnI, CH_2I_2 (19,22a)	$IZnCH_2I$
CF_3COOH, Et_2Zn, CH_2I_2 (23)	$CF_3COOZnCH_2I$
2,4,6-$Cl_3C_6H_2OH$, Et_2Zn, CH_2I_2 (24)	2,4,6-$Cl_3C_6H_2OZnCH_2I$
$C_4F_9C(O)OCH_2I$, Et_2Zn, $h\nu$ (26)	$C_4F_9C(O)OCH_2ZnEt$
R_3Al, CH_2I_2 (30)	R_2AlCH_2I
Nucleophilic Displacement	
ZnX_2, CH_2N_2 (15)	$XZnCH_2X$
ZnX_2, CH_2N_2 (1:2) (15)	$Zn(CH_2I)_2$

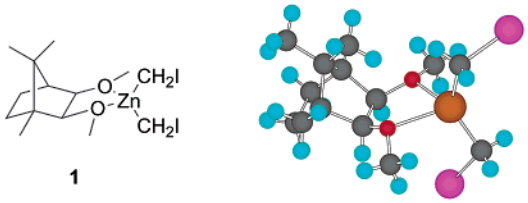


Figure 1. Chem3D representation of the X-ray crystal structure of the bis(iodomethyl)zinc·diether complex.

Shortly after Simmons and Smith's seminal publication, Wittig[15] reported that treatment of zinc iodide with either 1 or 2 equiv of diazomethane was an alternative method to prepare $IZnCH_2I$ or the analogous bis(iodomethyl)zinc reagent ($Zn(CH_2I)_2$). In 1966, Furukawa and co-workers[16] found that a similar reactive species could be prepared by substituting a Zn/Cu couple with $ZnEt_2$, to presumably form $EtZnCH_2I$. Denmark has further elaborated on the reactivity profile of $Zn(CH_2X)_2$ (X = I, Cl), prepared from 1 equiv of $ZnEt_2$ and 2 equiv of XCH_2I (X = I, Cl), showing that it is sometimes advantageous to use the more reactive bis(chloromethyl)zinc with deactivated alkenes.[17] This procedure was found to be particularly useful in the cyclopropanation of iodo-substituted alkenes.[18] Another very good and underused method for preparing $IZnCH_2I$ involves treatment of EtZnI with CH_2I_2.[19] This method is particularly suitable for the large-scale preparation of $IZnCH_2I$, since it avoids the use of Et_2Zn.

These reports were followed by the discovery of several new halomethylmetal reagents that are also very effective cyclopropanating reagents with unique properties and reactivities. Table 1 gives an overview of some preparative methods to generate these reagents.

The structures of these halomethylmetal reagents have been the subject of several postulates over the years, but it is only recently that X-ray crystal structures of some of them have become available. The complexes of $Zn(CH_2I)_2$, $Zn(CH_2Cl)_2$, and $IZnCH_2I$, with several ligands, have been characterized both in solution and in the solid state by Denmark[20] and Charette[21] (Figures 1−3).

Conversely, Furukawa's reagent, "$EtZnCH_2I$", has been characterized by solution NMR,[22] but its structure has not yet been determined in the solid state.

Finally, two very effective reagents were reported recently for the cyclopropanation of unfunctionalized alkenes. Iodomethylzinc trifluoroacetate, which is

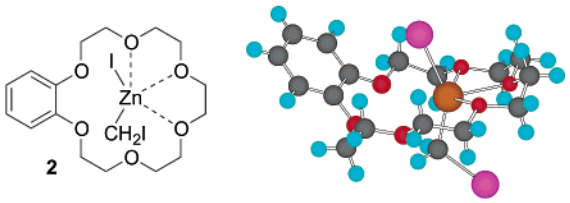


Figure 2. Chem3D representation of the X-ray crystal structure of the benzo-18-crown-6·$IZnCH_2I$ complex.

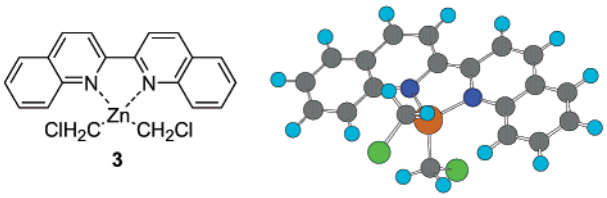


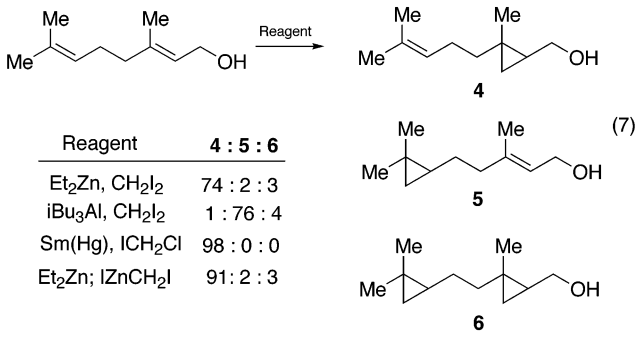
Figure 3. Chem3D representation of the X-ray crystal structure of the bis(quinoline)·$Zn(CH_2I)_2$ complex.

prepared by mixing equimolar amounts of trifluoroacetic acid, diethylzinc, and diiodomethane, cyclopropanates alkenes very effectively.[23] Substituted iodomethylzinc aryloxides are also very effective reagents for the cyclopropanation of unfunctionalized alkenes.[24]

Several other structures of zinc carbenoids, such as those of $MeOZnCH_2I$[25] and $(PhC(O)OCH_2)_2Zn$,[26] were recently resolved, but these reagents are quite unreactive toward alkenes unless they are activated (vide infra).

In general, the classical Simmons−Smith reagent in ether has been used in 90% of the zinc-mediated cyclopropanation reactions. However, the use of the Furukawa version, involving diethylzinc, is preferred when less nucleophilic alkenes need to be converted to their corresponding cyclopropanes, since noncomplexing solvents are better suited (higher electrophilicity of the reagent in noncomplexing solvents). These conditions are also experimentally quite practical, since both diethylzinc and CH_2I_2 are commercially available and can be used without purification. The other zinc reagents have been used sporadically in specific cases.

Other cyclopropanating reagents of the proposed general structure "MCH_2X" have also been prepared, but they have not been characterized as well as their zinc counterparts.[27] For example, the use of a samarium/mercury amalgam in conjunction with CH_2I_2 to generate samarium carbenoids was reported by Molander.[28,29] The analogous R_2AlCH_2I reagent, which displays a unique reactivity that complements that of the zinc- and samarium-mediated cyclopropanation reaction, was discovered by Yamamoto.[30] The synthetic utility of these reagents is clearly illustrated by the chemoselectivity observed in the cyclopropanation of geraniol (eq 7). The allylic alcohol group can be cyclopropanated in the presence of an isolated olefin with zinc- or samarium-derived reagents. Conversely, the isolated olefinic group can be converted into the corresponding cyclopropane, with outstanding chemoselectivity, with the aluminum reagent. Optimization of the reaction conditions has shown that zinc-based reagents could also be effectively used to achieve good chemoselectivities in that reaction.[31] However, a chemoselective cyclopro-



Reagent	4 : 5 : 6
Et_2Zn, CH_2I_2	74 : 2 : 3
iBu_3Al, CH_2I_2	1 : 76 : 4
Sm(Hg), ICH_2Cl	98 : 0 : 0
Et_2Zn; $IZnCH_2I$	91 : 2 : 3

panation at the allylic ether position is observed with all three types of reagents if the benzyl-protected geraniol is submitted to these conditions.

Prior coordination of the zinc or samarium reagent with the hydroxy group or the corresponding metal alkoxide to direct the addition of methylene to the neighboring alkene, to enhance the rate of the reaction, has been used extensively to control the stereochemical outcome of the cyclopropanation reactions. Along with steric effects, it has been the main controlling element for the high stereocontrol in these reactions. The following sections summarize the recent advances in hetereoatom-directed and nondirected stereoselective cyclopropanation reactions.

B. Relative Diastereoselection

1. Cyclic Alkenes

Simmons was the first to observe that the cyclopropanation of 1-(*o*-methoxyphenyl)-1-propene gave a higher yield of the cyclopropane than that of the related meta and *para* isomers.[11] He suggested that coordination between the ether oxygen and the reagent, prior to the methylene delivery, was involved. Winstein also observed that proximal hydroxyl groups could "direct" the delivery of the methylene group.[32] Since these observations, simple cycloalkenols have served as model substrates for kinetic studies, and transition-state models have recently been proposed for these directed processes.[33] The cyclopropanations of five-, six-, and seven-membered-ring 1-cycloalken-3-ols generally produce very good *syn*:*anti* ratios with Simmons−Smith's, Furukawa's, and Molander's reagents (Table 2).[34] Sometimes, reasonably good *syn* selectivities are observed with dihalocarbenes under phase-transfer conditions (Table 2, entry 5).[35]

A reversal of selectivity is observed with the analogous eight- or nine-membered ring. This can be explained on the basis of simple conformational analysis of the ground state. 2-Cycloocten-1-ol prefers to adopt a chair−boat conformation, in which the bulky hydroxyl group occupies the equatorial orientation (eq 8).[28,34a]

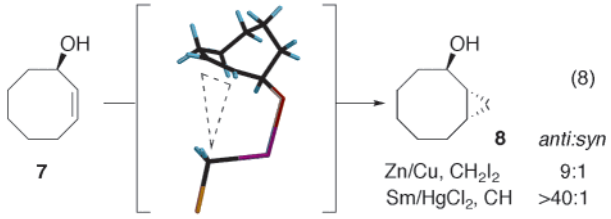
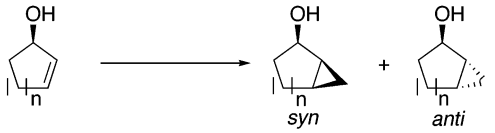
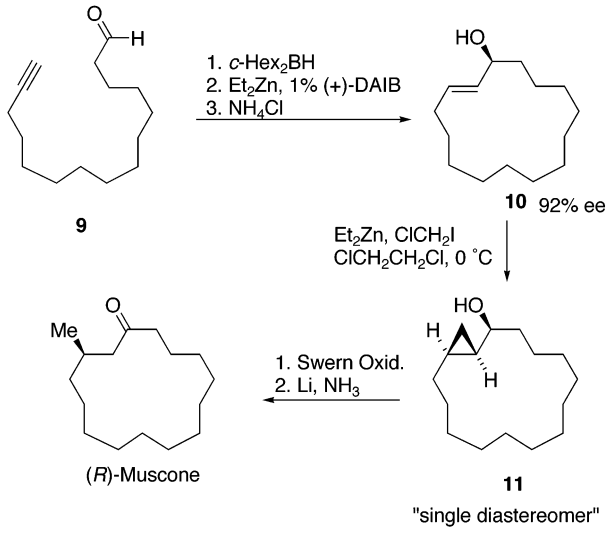


Table 2. Diastereoselective Cyclopropanation of Simple 2-Cycloalken-1-ols



entry (ref)	reagent	diastereoselectivity (*syn*:*anti*) $n = 1$	$n = 2$	$n = 3$
1 (34a)	Zn/Cu	>99:1	>99:1	90:10
2 (16)	Et_2Zn, CH_2I_2 (1:2)		>99:1	
3 (16)	Et_2Zn, $ClCH_2I$ (1:2)		>99:1	
4 (28)	Sm/Hg, CH_2I_2		>99:1	>97:3
5 (34d)	$CHCl_3$, $BnEt_3NCl$, NaOH		91:9	

Scheme 1. Oppolzer's Muscone Synthesis



An elegant synthesis of (*R*)-muscone, that features a diastereoselective cyclopropanation of a macrocyclic (*E*)-allylic alcohol **10**, was reported by Oppolzer (Scheme 1).[36] The hydroxyl-directed cyclopropanation was achieved with complete diastereocontrol to produce the corresponding cyclopropane. The stereochemical outcome of this reaction is best explained by the model shown in Figure 4, which is based on the minimization of the A(1,3) strain and is similar to that proposed for acyclic, chiral allylic alcohols (vide infra).

Recent additional examples of stereocontrol in the cyclopropanation of functionalized cycloalkenol de-

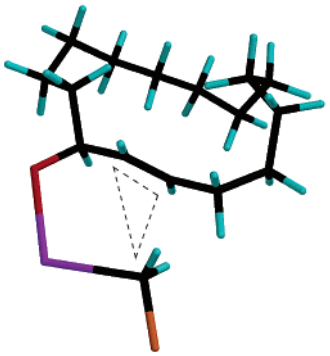
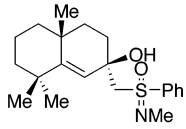
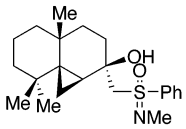
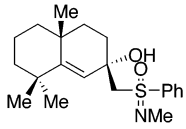
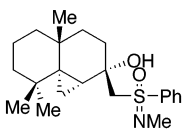
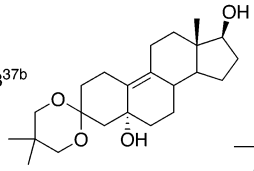
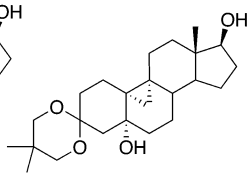
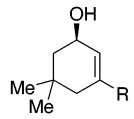
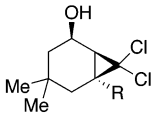
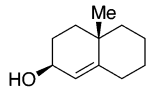
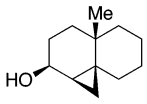
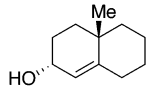
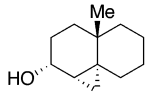
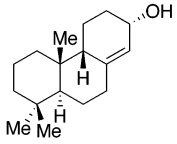
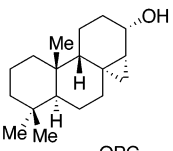
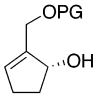
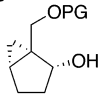
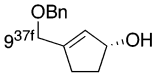
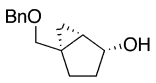
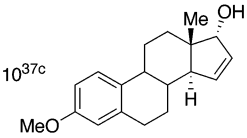
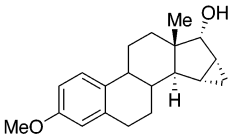
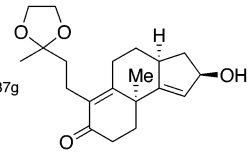
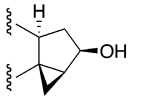
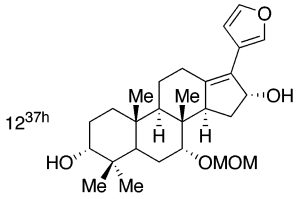
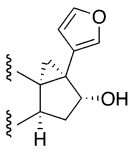
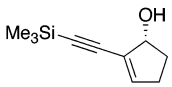
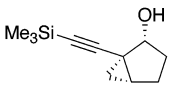
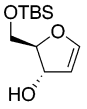
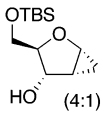
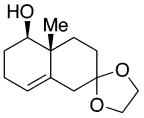
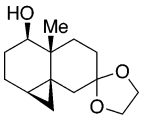
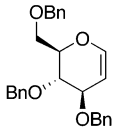
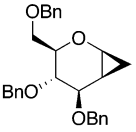
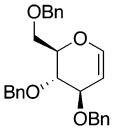
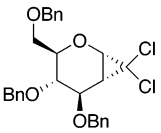
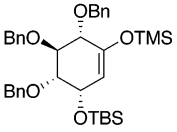
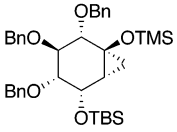
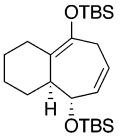
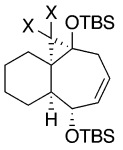
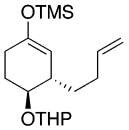
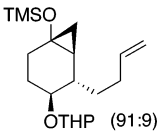


Figure 4. Transition-state model for the cyclopropanation of the 15-membered-ring alkenol leading to the *syn* isomer.

Table 3. Selected Examples of Diastereoselective Cyclopropanation of Cyclic Alkenes

Entry[ref.]	Starting Material	Major Product (ratio)	Conditions (Yield)
1[37a]			$Zn(Ag)$ CH_2I_2 (80%)
2[37a]			$Zn(Ag)$ CH_2I_2 (76%)
3[37b]			no yield no reagent (1 isomer)
4[37c]			$NaOH$, $BnNEt_3Cl$ $CHCl_3$ R = Me (71%) R = Bu (73%)
5[37c]			Zn, CH_2I_2 DME, sonication (68%)
6[37c]			Zn, CH_2I_2 DME, sonication (82%)
7[37d]			Sm(Hg), ICH_2Cl, (88%)
8[37e]			Et_2Zn, CH_2I_2 (80%) PG = MEM (6:1) PG = H (6:1)
9[37f]			$Sm/HgCl_2$ ICH_2Cl, THF (100%)
10[37c]			Zn/Cu, CH_2I_2 (81%)
11[37g]			Zn/Cu, CH_2I_2 (66%)
12[37h]			Zn/Ag, CH_2I_2 (61%)
13[37i]			$Sm/HgCl_2$ ICH_2Cl, (77%)
14[37j]			$ZnEt_2$, CH_2I_2 toluene (41%) (4:1)
15[37k]			Zn/Cu, CH_2I_2 Ether, reflux (68%)
16[37l]			CH_2I_2, Zn, CuCl, AcCl, Et_2O (89%) or $ZnEt_2$, CH_2I_2, (92%)
17[37l]			$CHCl_3$, 50% aq. NaOH, $BnEt_3NCl$ (cat.) (84%)
18[37p]			Et_2Zn, CH_2I_2 $PhCH_3$, 0 °C (>32%)
19[37q]			$ZnEt_2$, CH_2I_2 Benzene, Δ (X = H, 75%)
20[37q]			Cl_3CCO_2Et NaOMe (X = Cl, 99%)
21[37r]			$ZnEt_2$, CH_2I_2 Et_2O, reflux (87%) (91:9)

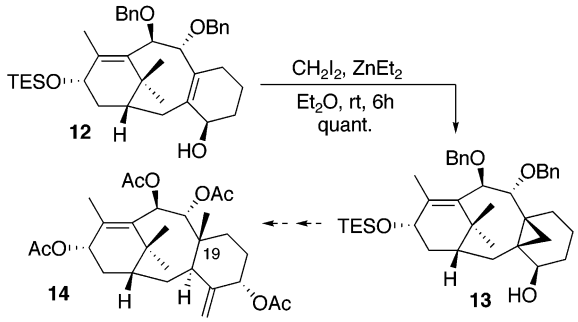
rivatives are presented in Table 3.[37] This collection of examples shows the compatibility of a variety of functional groups under the cyclopropanation conditions, especially when an alcohol or a basic group is present to direct the methylenation.

Much of the early work in this area has involved substrates deprived of functionality that could potentially compete for the reagent complexation. More recently, Johnson[37a] has shown, in his approach to enantiomerically pure cyclopropyl ketones, that β-hy-

droxysulfoximines derived from cyclic enones could undergo reaction to produce the cyclopropane *syn* to the hydroxy group (Table 3, entries 1 and 2). This is one of the first examples in which two relatively basic groups (hydroxyl and sulfoximines) can compete for the group-assisted methylene delivery.

Some examples of stereocontrol in the cyclopropanation of functionalized cyclohexenol are presented in Table 3 (entries 3−7). In addition, this reaction has been cleverly used recently to install the C19 methyl group of taxusin (Scheme 2).[38]

Scheme 2. Introduction of C19 of Taxusin

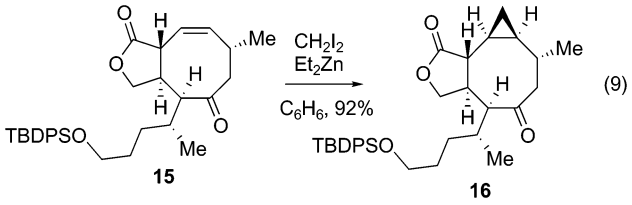


The directed cyclopropanation of functionalized cyclopentenol (Table 3, entries 8−14) is also fairly common. A key building block of 1,25-dihydroxyvitamin D_3 was accessible by a stereoselective cyclopropanation of a diol or the corresponding monoprotected diol (Table 3, entries 8−9).

Interestingly, the protecting groups used had little impact on the level of stereocontrol in that reaction, and similar selectivities were observed if the secondary alcohol was protected as a *tert*-butylsilyl (TBS) ether. The directed cyclopropanation has been widely used to introduce angular methyl groups on steroid-type skeletons (Table 3, entries 10−12).

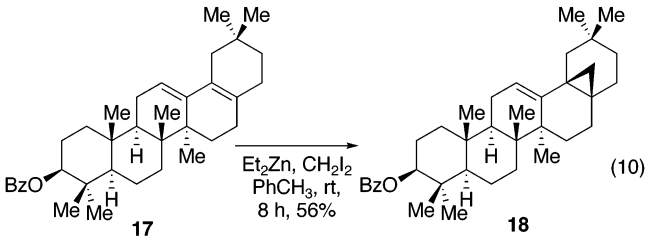
The synthesis of cyclopropanated sugars, involving a directed cyclopropanation of glucal derivatives, was recently reported by two groups. The stereochemistry of the allylic benzyl ether group was the controlling element in these reactions. The *syn* isomer was obtained as the major product with halomethylzinc reagents, whereas the *anti* isomer could be prepared by a multistep sequence involving a phase-transfer dichlorocarbene cyclopropanation (Table 3, entries 16−18). These examples, and those shown in entries 19 and 21 of Table 3, clearly show that a benzyl ether and a THP group can also be used as a good directing group in these reactions. The cyclopropanation of the fused [5.4.0] shown in entry 20 (Table 3) produced the cyclopropane *syn* to the OTBS group. It is not clear whether the silyl ether exerts any directing effect in this case, since the analogous dichlorocarbene reaction also produced the *syn* isomer.

In the absence of a directing group, the cyclopropanation of cyclic olefins is generally subjected to steric effects. The level of stereochemical induction is usually very high, and the sense can be predicted on the basis of the prevailing ground-state conformation of the starting olefin. Some recent examples are shown in eqs 9 and 10. The stereoselective cyclopropanation of **15** is directed to the more accessible β face to produce **16**, a key intermediate in the synthesis of (+)-acetoxycrenulide, as a single isomer (eq 9).[39]



(9)

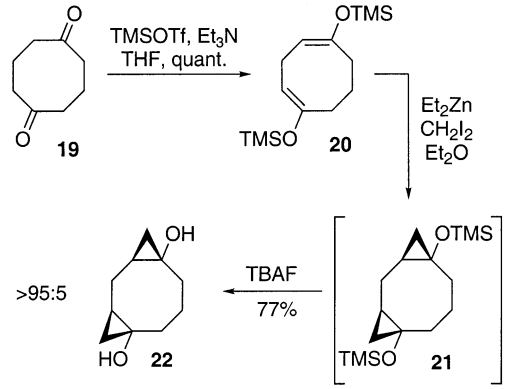
The stereoselective cyclopropanation allowed the introduction of an oxygenated angular methyl group at the C(17) in Corey's β-amyrin total synthesis.[40] The selective methylenation of **17** to form **18** is striking, since the analogous reaction using dibromocarbene adds exclusively to the 12,13-double bond of **17** (eq 10).



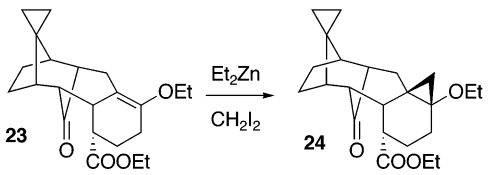
(10)

Schreiber and co-workers reported that the bis-(trimethylsilyl)enol ether **20** can be efficiently cyclopropanated, with excellent stereocontrol, with Furukawa's reagent (Scheme 3).[41] The cyclopropanation proceeded to produce the *syn*-dicyclopropane **22**, with excellent yield and stereocontrol (>15:1).

Scheme 3. Schreiber's Bis-Cyclopropanation



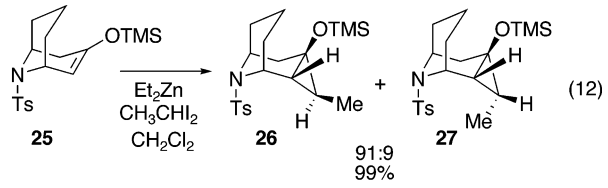
The cyclopropanation of **23** leads to only one diastereomer, **24**, in which the cyclopropanation occurs *anti* to the ester and to the ketone group (eq 11).[42]



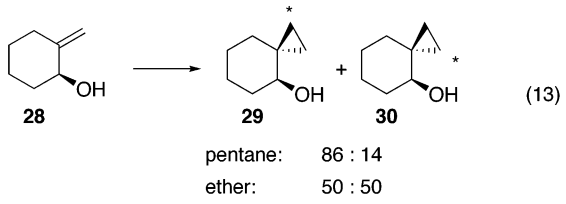
(11)

In the course of the asymmetric synthesis of (−)-pinidine, Momose has reported a highly diastereoselective cyclopropanation reaction of silyl enol ether

25 with the reagent derived from 1,1-diiodoethane and diethylzinc (eq 12).[43,44] The level of induction was highly dependent on the nature of the nitrogen protecting group.



An interesting cyclopropanation of an exocyclic olefin was reported by Ronald (eq 13).[45] The cyclopropanation of 2-methylenecyclohexanol using $^{13}CH_2I_2$ in pentane produced the isotopically labeled *syn* isomer in an 86:14 ratio. The same reaction carried out in ether afforded a 50:50 mixture.

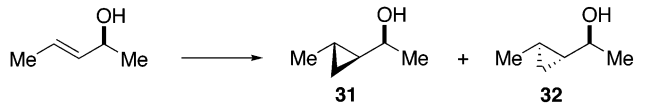


2. Acyclic Alkenes

The stereoselective cyclopropanation of a chiral, acyclic allylic alcohol using the Simmons−Smith reagent (Zn−Cu, CH_2I_2) was first reported by Pereyre and co-workers[46] in 1978. They observed that very high *syn* selectivities (>200:1) were obtained with (*Z*)-disubstituted olefins, but the analogous reaction on (*E*)-disubstituted olefins gave modest ratios (<2:1) (vide infra).

Charette has shown that the nature of the Zn carbenoid used in these reactions is very important for obtaining high diastereoselectivities, especially with (*E*)-disubstituted olefins.[47] The cyclopropanation of (*E*)-3-penten-2-ol, one of the substrate that produces the lowest diastereomeric ratios under Pereyre's conditions,[46] served as a model substrate to highlight the efficiency of each reagent with (*E*)-olefins (Table 4). The classical Simmons−Smith conditions used by Pereyre ($IZnCH_2I$ from Zn/Cu, CH_2I_2) or $Zn(CH_2I)_2$ generally gave lower diastereomeric ratios. Conversely, the use of an excess (5 equiv) of Furukawa's reagent ($EtZnCH_2I$ prepared from a 1:1 mixture of Et_2Zn and CH_2I_2) in CH_2Cl_2 produced the highest selectivities to date, favoring the *syn* isomer **31** with this substrate. The choice of the solvent in these various processes is certainly a very important issue for optimizing the diastereoselectivities. For example, the ratio drops to 2:1 if ether is used as the solvent with Furukawa's conditions. Interestingly, the samarium-derived reagent led to the formation of the *anti* isomer as the major product with this substrate (Table 4, entry 5). From these data, $EtZnCH_2I$ clearly appears to be the most general reagent to access the *syn* isomer with (*E*)-disubstituted olefins.

Table 4. Cyclopropanation of (*E*)-3-Penten-2-ol[47]

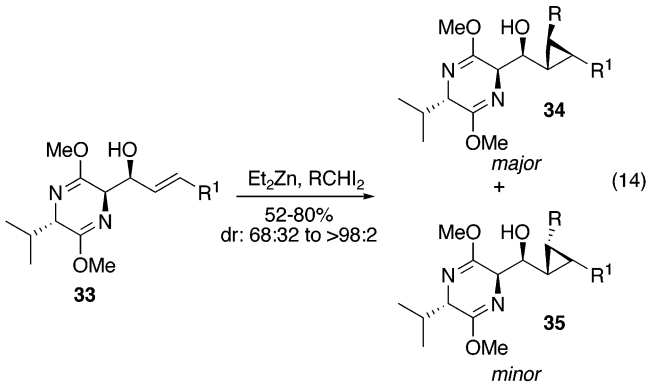


conditions	ratio **31:32**
Zn/Cu, CH_2I_2, ether	56:44[46]
Et_2Zn, CH_2I_2 (1:1), CH_2Cl_2	86:14
Et_2Zn, CH_2I_2 (1:1), ether	67:33
$Zn(CH_2I)_2$, CH_2Cl_2	67:33
Sm(Hg), CH_2I_2, THF	25:75

The selectivities obtained in the cyclopropanation of other simple (*E*)-disubstituted chiral allylic alcohols with these various reagents are shown in Table 5.[48] The general trends described above are maintained with more complex systems. The Simmons−Smith reagent (Table 5, entries 1−3) and the samarium-derived reagent (Table 5, entries 11−18) generally give lower diastereoselectivities than the excess $EtZnCH_2I$ (Table 5, entries 4−10). It is also clear that stereoelectronic effects play an important role in these reactions. For example, the substitution of a methyl group (Table 5, entry 12) by a trifluoromethyl group (Table 5, entry 19) with the samarium reagent led to a spectacular increase of the *syn* selectivity. Lautens and Delanghe have shown that this reaction can be extended to silyl-substituted olefins (Table 5, entries 21−26).[48e,f]

These trends are also followed with more complex systems that contain other basic groups that could have affected the stereochemical outcome of the reaction. For example, a high *syn* selectivity was also reported by Schöllkopf for the cyclopropanation of the bislactim ethers **33** with Et_2Zn/CH_2I_2 (eq 14, R = H).[49]

The cyclopropanation of these bislactim ethers was also reported to occur when alkyl- or aryl-substituted carbenoids of type CHR or CHAr were used (eq 14, R = Me, Ph).[50] Although the facial selectivity of the attack on the alkene was very high, the stereochemistry of the third substituent could not be completely controlled.



The cyclopropanation of (*Z*)-disubstituted chiral allylic alcohols is uniformly good, and high *syn* selectivities are observed (eq 15).[51] In addition to the iodomethylmetal-derived reagents, dichlorocarbene also reacts with secondary allylic alcohols, to form a major diastereomeric cyclopropane with *cis*-alkenes.

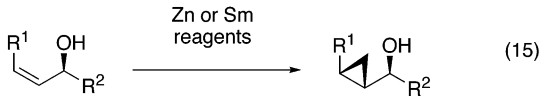


Table 5. Cyclopropanation of Chiral, Acyclic Allylic Alcohols: (*E*)-Disubstituted Alkenes

entry	substrate R^1	substrate R^2	conditions	products	yield (%)	ref
1	Me	Me	Zn/Cu, CH_2I_2, ether	57:43	nr[a]	46
2	Et	Me	Zn/Cu, CH_2I_2, ether	63:37	nr	46
3	*t*-Bu	Me	Zn/Cu, CH_2I_2, ether	67:33	nr	46
4	Me	Me	Et_2Zn, CH_2I_2, CH_2Cl_2	86:14	75	47
5	Ph	Me	Et_2Zn, CH_2I_2, CH_2Cl_2	88:12	86	47
6	Ph	Et	Et_2Zn, CH_2I_2, CH_2Cl_2	>98:2	97	47
7	Ph	Et	Et_2Zn, CH_2I_2, CH_2Cl_2	>98:2	87	47
8	Ph	Bu	Et_2Zn, CH_2I_2, CH_2Cl_2	>98:2	98	47
9	Ph	*i*-Pr	Et_2Zn, CH_2I_2, CH_2Cl_2	>98:2	97	47
10	Ph	*t*-Bu	Et_2Zn, CH_2I_2, CH_2Cl_2	>98:2	84	47
11	Me	Me	Sm(Hg), CH_2I_2, THF	25:75	>95	47
12	Ph	Me	Sm(Hg), CH_2I_2, THF	14:86	98	28
13	Ph	Bu	Sm(Hg), CH_2I_2, THF	42:58	99	28
14	Ph	*i*-Pr	Sm(Hg), CH_2I_2, THF	>98:2	88	28
15	Ph	*t*-Bu	Sm(Hg), CH_2I_2, THF	>98:2	76	28
16	*t*-Bu	Me	Sm(Hg), CH_2I_2, THF	15:84	98	28
17	*t*-Bu	*i*-Pr	Sm(Hg), CH_2I_2, THF	>98:2	46	28
18	Bu	*i*-Pr	Sm(Hg), $ClCH_2I$, THF	83:17	93	28
19	Ph	CF_3	Sm(Hg), CH_2I_2, THF	>98:2	87	48d
20	*n*-C_6H_{13}	CF_3	Sm(Hg), CH_2I_2, THF	>98:2	92	48d
21	TMS	*c*-hexyl	Sm(Hg), CH_2I_2, THF	98:2	81	48e,f
22	TMS	Pr	Sm(Hg), CH_2I_2, THF	43:57	84	48e,f
23	TMS	Me	Sm(Hg), CH_2I_2, THF	9:91	76	48e,f
24	Bu	*c*-hexyl	Sm(Hg), CH_2I_2, THF	95:5	73	48e,f
25	Bu	*i*-Pr	Sm(Hg), CH_2I_2, THF	85:15	85	48e,f
26	Bu	Pr	Sm(Hg), CH_2I_2, THF	60:40	94	48e,f
27	Me	Me	$BnEt_3NCl$, $CHCl_3$, NaOH	89:11	68	34d

[a] Not reported. [b] Formation of the 1,1-dichlorocyclopropane.

Table 6. Cyclopropanation of Chiral, Acyclic Allylic Alcohols: Trisubstituted Alkenes

entry	substrate R^1	substrate R^2	substrate R^3	substrate R^4	conditions	products	yield (%)	ref
1	Et	I	H	Me	Et_2Zn, $ClCH_2I$, $(CH_2Cl)_2$	>98:2	86	52a
2	Ph	H	Me	Me	Et_2Zn, CH_2I_2, CH_2Cl_2	97:3	95	47
3	Ph	H	Me	Me	Sm(Hg), $ClCH_2I$, THF	50:50	>95	47
4	$Me_2C{=}CH(CH_2)_2{-}$	Me	H	Me	Sm(Hg), $ClCH_2I$, THF	>98:2	98	28
5	Me	$Me_2C{=}CH(CH_2)_2{-}$	H	Me	Sm(Hg), $ClCH_2I$, THF	>98:2	98	28
6	Bu_3Sn	Bu	H	*c*-hexyl	Sm(Hg), CH_2I_2, THF	>98:2	75	48e,f
7	Bu_3Sn	Bu	H	Me	Sm(Hg), CH_2I_2, THF	>98:2	76	48e,f
8	Bu_3Sn	Bu	H	*c*-hexyl	Sm(Hg), CH_2I_2, THF	>98:2	70	48e,f
9	Bu	$SnBu_3$	H	*c*-hexyl	Sm(Hg), CH_2I_2, THF	>98:2	63	48e,f
10	Bu	$SnBu_3$	H	*i*-Pr	Sm(Hg), CH_2I_2, THF	>98:2	89	48e,f
11	Bu	$SnBu_3$	H	Pr	Sm(Hg), CH_2I_2, THF	>98:2	77	48e,f
12	Bu	$SnBu_3$	H	Me	Sm(Hg), CH_2I_2, THF	>98:2	81	48e,f
13	TMS	$SnBu_3$	H	*c*-hexyl	Sm(Hg), CH_2I_2, THF	>98:2	80	48e,f
14	TMS	$SnBu_3$	H	*c*-hexyl	Et_2Zn, $ClCH_2I$, DCE	>98:2	80	48e,f
15	TMS	$SnBu_3$	H	Pr	Sm(Hg), CH_2I_2, THF	>98:2	67	48e,f
16	TMS	$SnBu_3$	H	Me	Sm(Hg), CH_2I_2, THF	>98:2	85	48e,f
17	$SnBu_3$	$SnBu_3$	H	*c*-hexyl	Sm(Hg), CH_2I_2, THF	>98:2	71	48e,f
18	$SnBu_3$	$SnBu_3$	H	*c*-hexyl	Et_2Zn, CH_2I_2, CH_2Cl_2	>98:2	92	48e,f
19	$SnBu_3$	H	$SnMe_3$	Me	Sm(Hg), CH_2I_2, THF	>98:2	26	52e
20	TMS	H	$SnMe_3$	Me	Sm(Hg), CH_2I_2, THF	>98:2	40	52e
21	H	H	Me	Me	$BnEt_3NCl$, $CHCl_3$, NaOH	50:50[a]	53	34d
22	Me	Me	H	Me	$BnEt_3NCl$, $CHCl_3$, NaOH	96:4	77	34d

[a] Formation of the 1,1-dichlorocyclopropane.

The cyclopropanation of trisubstituted alkenes leads to only one diastereomer when a (*Z*)-substituent is present at the R^2 position, regardless of whether zinc- or samarium-based reagents are used (Table 6).[52]

The stereochemical outcome of these reactions can be qualitatively predicted by assuming an oxygen group-assisted delivery of the reagent from a conformation in which the minimization of the A(1,3) strain is the predominant controlling element.[53] It is clear

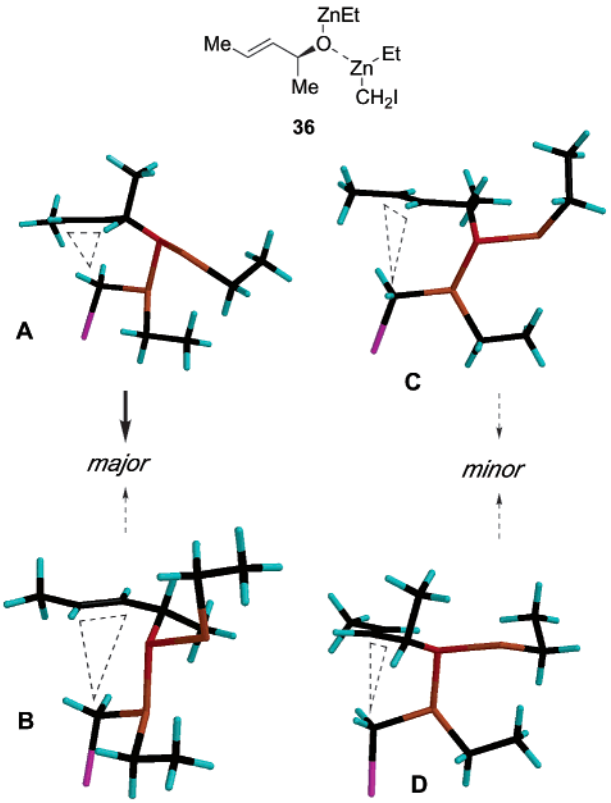


Figure 5. Transition-state models for the cyclopropanation involving zinc reagents.

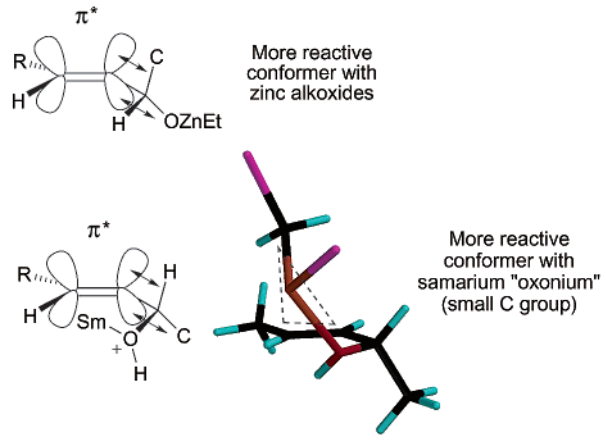
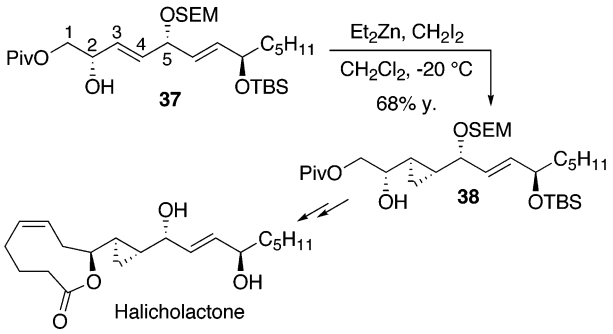


Figure 6. Reactive conformers: zinc vs samarium.

Scheme 4. Regio- and Stereoselective Cyclopropanation of Allylic Alcohol 37



that other important factors should be taken into account in order to explain the level of induction. The nature of the carbenoid reagent used is extremely important. The acidity and the bulkiness of the reagent ($EtZnCH_2I$ vs $Zn(CH_2I)_2$ vs $IZnCH_2I$) appear to be very important in some cases. These differences are evident in the cyclopropanation of (*E*)-3-penten-2-ol, for which the diastereoselectivities go from 1:3 to 6:1 (*syn*:*anti*), depending on the reaction conditions (Table 5, entry 2 vs 5). Four possible transition-state models for this reaction are depicted in Figure 5.

It was shown that, under Furukawa's conditions, the methylene delivery occurs from complex **36**. Unfavorable nonbonded interactions, arising from the bulky zinc alkoxide substituent, are present in three staggered transition structures, **B**, **C**, and **D**. It is possible that the increase of the steric bulk of the alkoxide under certain conditions is a significant feature to increase the energy difference between **A** and (**C**, **D**).

The fact that the samarium reagent leads to the *anti* isomer as the major adduct with this substrate is an indication that a different conformer is involved in the cyclopropanation reaction. One possible assumption is that the deprotonation does not occur with the samarium reagent and the most reactive conformer is the one in which the C−O(H)Sm is orthogonal to the π-system, to maximize the nucleophilicity of the alkene (Figure 6). Methylene delivery from the face away from the alkyl group would then lead to the *anti* isomer.

Even in the presence of other proximal basic groups, the cyclopropanation is still directed by a zinc alkoxide moiety, as shown by Takemoto and coworkers in the asymmetric total synthesis of halicholactone.[54] The regio- and stereoselective cyclopropanation of allylic alcohol **37** produces **38** in 68% yield as a single product in the presence of an equimolar quantity of diiodomethane and diethylzinc (Scheme 4). In comparison, the corresponding acetonide at C-1 and C-2 was ineffective for the delivery of the methylene. In addition, the cyclopropanation did not proceed when the SEM protection group at C-5 was replaced by a TBS moiety.

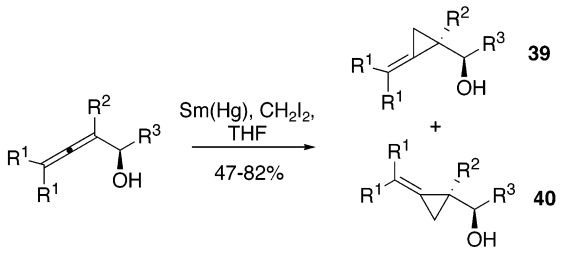
Lautens and Delanghe have reported a highly regioselective cyclopropanation of α-allenic alcohols using a samarium carbenoid that provided a variety of methylene- and alkylidenecyclopropane carbinols in good yields (Table 7).[55]

The diastereoselectivities vary from 33:67 to 98:2, depending upon the substitutents on the carbinol side chain and on the substitution of the allene. The use of the samarium reagent was essential to optimize the regioselectivity of this process and to minimize the formation of spiropentane carbinols.

The outside Houk model[56] was used by Molander[28] and Lautens[55] to explain the sense and level of the diastereoselection in the samarium−carbenoid reactions. The transition-state model **A** was postulated to be the predominant one, with large R^3 (Figure 7).

The diastereoselective cyclopropanation of allylic ethers using Furukawa's reagent has been systematically investigated by Charette with simple systems (Table 8).[57] Both the steric hindrance of the substituents and the nature of the protecting group were found to be pivotal elements for obtaining high selectivities and for determining the sense of induc-

Table 7. Diastereoselective Cyclopropanation of Allenic Alcohols[55]



R^1	R^2	R^3	ratio **39:40**	yield (%)
H	H	*t*-Bu	98:2	57
H	H	*c*-hexyl	90:10	82[a]
H	H	*i*-Pr	80:20	67
H	H	heptyl	46:54	73
Pr	H	*c*-hexyl	63:37	70[a]
H	Me	*c*-hexyl	89:11	66
H	Me	heptyl	33:67	52
H	OMe	*c*-hexyl	98:2	47
H	OMe	heptyl	93:7	59

[a] $ClCH_2I$ was used instead of CH_2I_2.

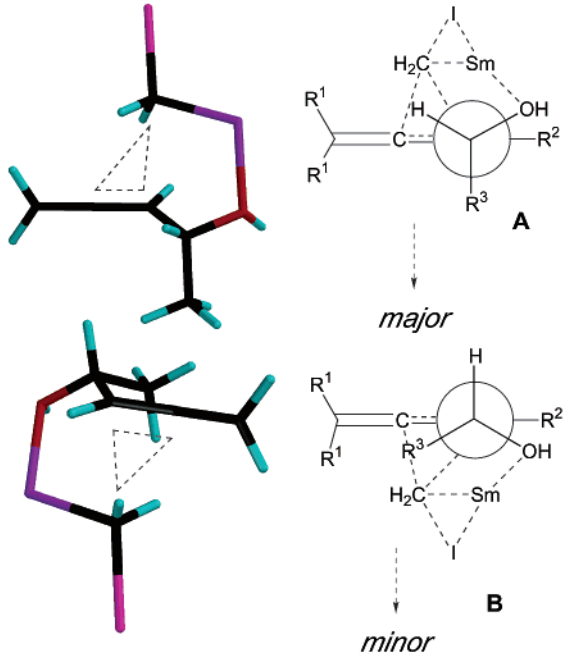


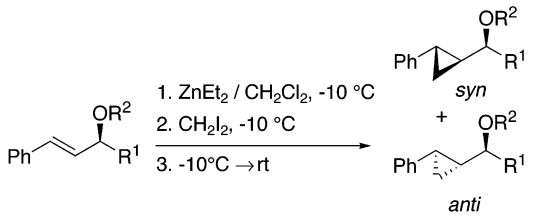
Figure 7. Diastereoselective cyclopropanation of allenic alcohols.

tion. First, the sense of induction inverts as the steric bulk of the substituent on the carbinol side chain increases (Table 8, entries 1−3). Second, increasing the steric bulk of the protecting group decreases the *syn* selectivity (Table 8, entries 1 vs 4, 2 vs 5, and 3 vs 6).

Furthermore, these data clearly show that the use of simple A(1,3) strain arguments is not sufficient to explain the diastereoselection in these reactions. The size of the protective group was shown to play a very important role in these reactions. Synthetically useful *anti* diastereoselectivities were obtained when the benzyl ether was replaced by a more hindered silyl ether (Table 9).[58]

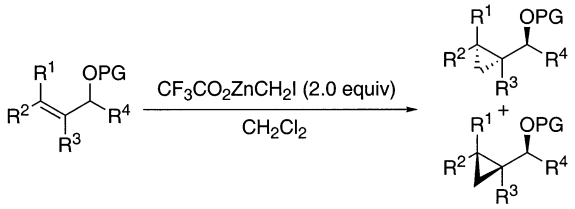
However, in these cases, Shi's reagent ($CF_3COOZnCH_2I$) had to be used for optimal selectivities

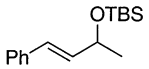
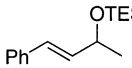
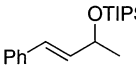
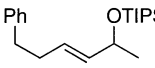
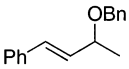
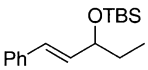
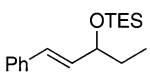
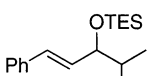
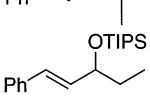
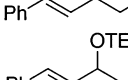
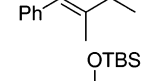
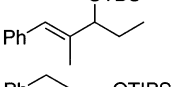
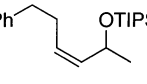
Table 8. Diastereoselective Cyclopropanation of Allylic Ethers[57]



entry	R^1	R^2	yield (%)	ratio *syn/anti*
1	Me	Bn	94	10:90
2	Et	Bn	97	33:67
3	*i*-Pr	Bn	82	95:5
4	Me	Me	95	39:61
5	Et	Me	93	77:23
6	*i*-Pr	Me	94	98:2

Table 9. Cyclopropanation of Silyl-Protected Allylic Alcohols[58]



Entry	Substrate	Yield (%)	*anti* : *syn*
1		86	98 : 2
2		87	> 99 : 1
3		88	> 99 : 1
4		84	96 : 4
5		80	94 : 6
6		85	97 : 3
7		87	97 : 3
8		78	70 : 30
9		88	98 : 2
10		88	> 99 : 1
11		88	99 : 1
12		52	97 : 3
13		89	25 : 75

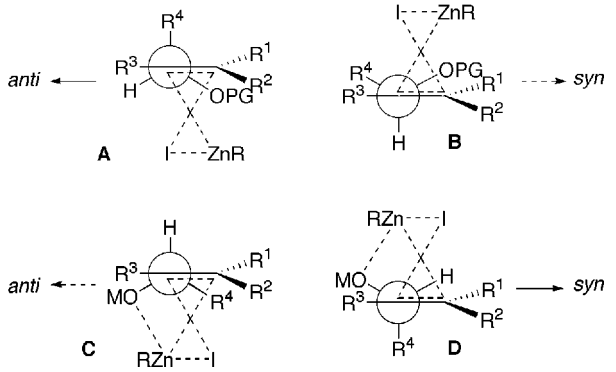
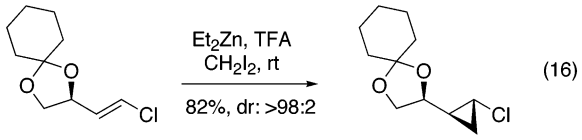


Figure 8. Transition structures for the cyclopropanation of silyl-protected allylic alcohols.

and conversions. Of the two possible transition structures **A** and **B**, **A** appears to be the most plausible one, on the basis of the work of Gung, who has established that the eclipsed conformer (C—O, C═C) is more highly populated when a bulky protective group is present on the alcohol.[59] Furthermore, it is expected, on the basis of stereoelectronic arguments, that the eclipsed conformation will also be the most reactive when the oxygen is complexed with the reagent (Figure 8).

Furthermore, the *anti* selectivity seems to be quite substrate dependent, since the reaction of the chloro-substituted alkene led to the *syn* diastereomer (eq 16).[60] This elegant use of diastereocontrol led to the efficient synthesis of the chlorocyclopropane unit of callipeltoside A.[61]



(16)

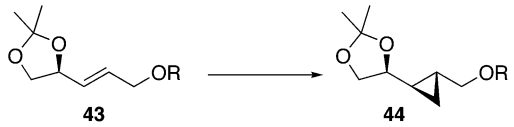
The diastereoselective cyclopropanations of (*E*)- and (*Z*)-allylic alcohols derived from 2,3-*O*-isopropylideneglyceraldehyde (**41** and **43**) have been the subject of several investigations, since the products are precursors to cyclopropyl carbocyclic nucleosides, which are potential chemotherapeutic agents (Tables 10[62] and 11[63]). With both isomers, the nature of the protecting group was found to be extremely important for obtaining high yields and high levels of stereocontrol.

Table 10. Diastereoselectivity of the Cyclopropanation of 41 as a Function of the Protective Group[62]

41 42

entry	R	conditions	yield (%)	ratio *syn*:*anti*
1	H	Et_2Zn (2), $ClCH_2I$ (4) $(CH_2Cl)_2$	70	77:33
2	H	Et_2Zn (5), CH_2I_2 (10) CH_2Cl_2	61	58:42
3	Bn		94	84:16
4	MOM		86	92:8
5	TBDPS		84	100:0

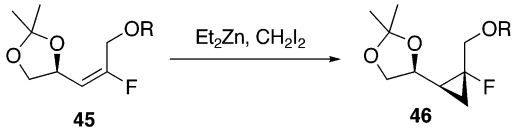
Table 11. Diastereoselectivity of the Cyclopropanation of 43 as a Function of the Protective Group[63]



43 44

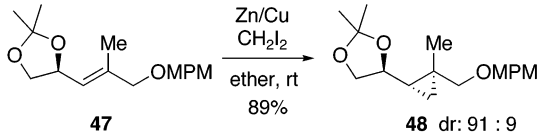
entry	R	conditions	yield (%)	ratio *syn*:*anti*
1	Bn	Et_2Zn (5), CH_2I_2 (10) CH_2Cl_2	quant.	68:32
2	MOM		86	82:18
3	TBDPS		90	100:0

The analogous fluoro derivative **45** could also be converted into the corresponding *syn* cyclopropane **46** (dr >99:1) in 73% yield upon treatment with Et_2Zn/CH_2I_2 in CH_2Cl_2, but the reaction required 8 days (eq 17).[64]



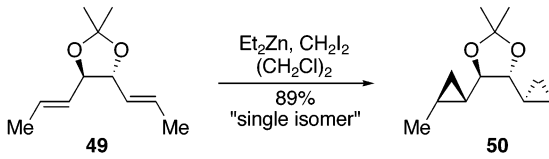
45 46 (17)

Quite interestingly, Kodama independently reported a related reaction in the total synthesis of (+)-bicyclohumulenone, in which the cyclopropanation of allyl alcohol derivative **47** proceeded with the opposite diastereofacial selectivity (eq 18).[65] The discrepancies between the two results may be a consequence of the difference of solvent (ether vs CH_2Cl_2) and reagent ($IZnCH_2I$ vs $EtZnCH_2I$).

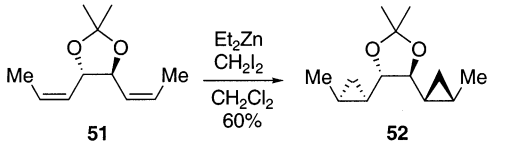


47 48 dr: 91 : 9 (18)

In a model study related to the total synthesis of FR-900848, Barrett has shown that a double asymmetric Simmons—Smith cyclopropanation of the (*E*)-bis(olefin) **49** could be used to successfully prepare (1*S*,2*S*)-(*E*)-1,2-bis[2-methylcyclopropyl]ethene with excellent stereocontrol (eq 19).[66] The analogous (*Z*)-bis(olefin) **51** reacted in a similar fashion to produce bis(cyclopropane) **52** as a single diastereomer (eq 20).[67]

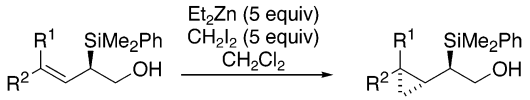


49 50 (19)



51 52 (20)

Table 12. Diastereoselective Cyclopropanation of Homoallylic Alcohols[69]



entry	R^1	R^2	yield (%)	ds
1	H	Ph	88	93:7
2	H	*n*-C_5H_{11}	83	>98:2
3	*n*-C_5H_{11}	H	71	>98:2
4	Me	Ph	79	>98:2

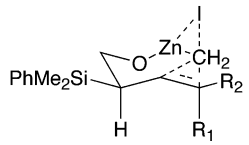
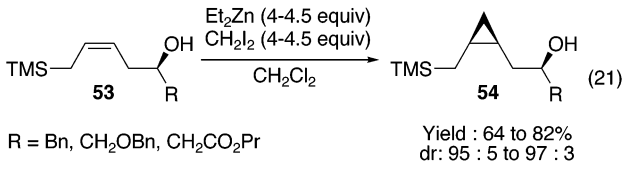


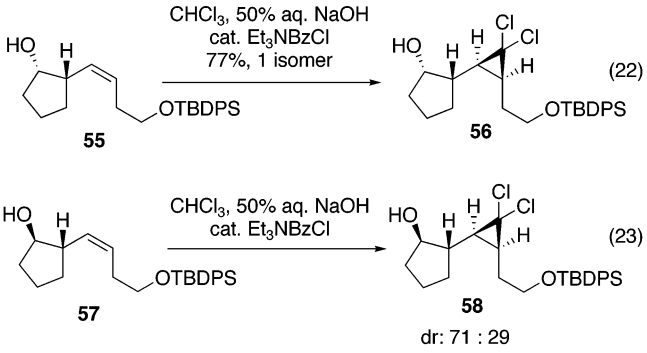
Figure 9. Chairlike transition structure for the cyclopropanation of homoallylic alcohols.

The stereoselective cyclopropanation of homoallylic alcohols has been used with moderate success. For example, the cyclopropanation of (*Z*)-5-hydroxy-2-alkenylsilanes **53** occurs with very a high level of stereochemical induction (eq 21).[68] This is one of the few acyclic homoallylic alcohols in which the cyclopropanation produces a good level of control.



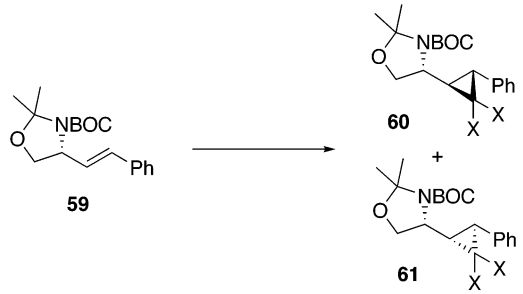
Landais has shown that the cyclopropanation of 2-silyl-3-alkenols occurred with very high 1,2-stereocontrol to produce the *anti* isomer irrespective of the geometry of the starting olefin (Table 12).[69] A chairlike transition state, as shown in Figure 9, has been proposed to explain the high diastereoselectivity of this transformation.

Addition of dichlorocarbene to **55** led to the exclusive formation of **56** (eq 22).[70] Conversely, cyclopropanation of **57** produced a 71:29 mixture of diastereomers under the same conditions (eq 23). The



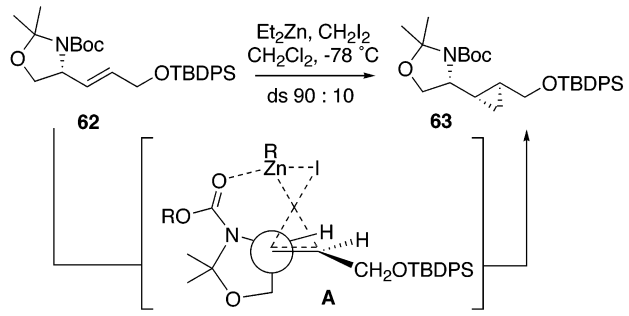
exclusive formation of **56** can be rationalized by considering that the carbene delivery is hydroxy-assisted on the most stable alkene conformation (minimization of the A(1,3) allylic strain). The lower stereoselectivity with **57** was explained by the fact

Table 13. Cyclopropanation of Chiral Allylic Amines[71]



entry	conditions	ratio **60:61**
1	Et_2Zn, CH_2I_2 Et_2O, reflux, 5 h (50%)	75:25 (X = H)
2	$CHBr_3$, NaOH TEBAC, rt, 2 d (87%)	85:15 (X= Br)

Scheme 5. Diastereoselective Cyclopropanation of Chiral Allylic Amine 62



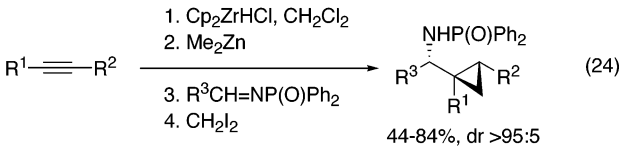
that the spacial relationship between the hydroxy group and the alkene is not optimal for a directed reaction.

The cyclopropanation of chiral protected allylic amine **59** produced the *anti* isomer **60** with good selectivity (Table 13).[71] The analogous dibromocyclopropanation of *tert*-butyl-2,2-dimethyl-4-(2′-phenylvinyl)-3-oxazolidinecarboxylates afforded good diastereomeric ratios of dibromocyclopropanes (Table 13, entry 2). In both cases, unassisted delivery of the carbene from the least hindered face of the olefin in its most stable ground state conformation can be invoked to predict the stereochemical outcome of these reactions.

Quite intriguingly, the cyclopropanation of **62** led to the opposite diastereomer (Scheme 5).[72]

The change to a noncoordinating solvent may be responsible for the participation of the amide butyloxycarbonyl (Boc) group in the delivery of the reagent.

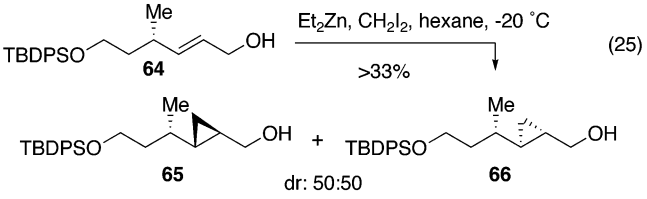
An interesting *anti*-selective cyclopropanation has been reported by Wipf (eq 24).[73] Hydrozirconation of



an alkyne, followed by the addition of the vinylzinc intermediate to the *N*-phosphinoylimine, led to a chiral allylic amine, which was cyclopropanated to give the *anti* isomer with outstanding diastereocon-

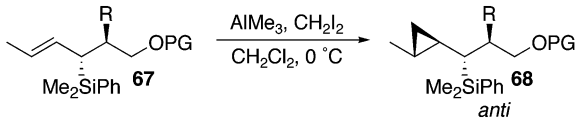
trol. This is the first example that demonstrates that a methylzinc amide can undergo an alkyl exchange reaction with diiodomethane to generate the reactive iodomethylzinc amide.

The stereocontrol in the cyclopropanation of acyclic alkenes, in which the basic group that directed the reagent is not on a stereogenic center, is usually not very high. For example, the cyclopropanation of **64** led to equal amounts of both diastereomers of **65** and **66** (eq 25).[74]



If, however, the stereocenter at the allylic position bears a bulky dimethylphenylsilyl group, reasonably good diastereoselectivities can be observed (Table 14).[75] The level of stereochemical induction depends

Table 14. Cyclopropanation of Chiral Allylsilanes[75]

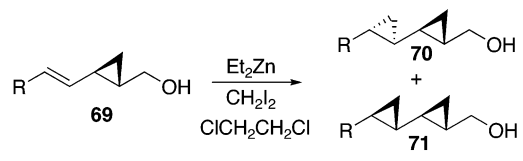


entry	R	PG	yield (%)	ratio *anti*:*syn*
1	H	H	79	75:25
2	Me	H	81	95:5
3	Bn	H	67	86:14
4	H	TBDPS	67	60:40

on the nature of the groups on the chain and on the protecting groups. It is interesting to know that both the zinc- and samarium-derived reagents failed to produce the desired product.

The cyclopropanation of (*E*)-vinylcyclopropane proceeds with surprisingly high induction. Barrett and Tustin have found that the cyclopropanation of various vinylcyclopropanes **69** produced the *anti* isomer as the major product (Table 15).[76]

Table 15. Synthesis of Bis(cyclopropane) Derivatives[76]



entry	R	yield (%)	ratio **70**:**71**
1	Ph	80	83:17
2	Me	68	83:17
3	*i*-Pr	72	86:14
4	C_6H_{11}	78	88:12
5	$TBDPSOCH_2$	72	>95:5

The major products in all the cases presented above can be predicted on the basis of the minimization of the A(1,3) allylic strain.

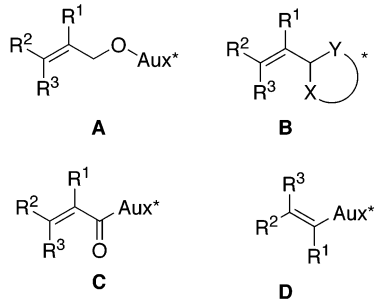


Figure 10. Various classes of chiral auxiliaries.

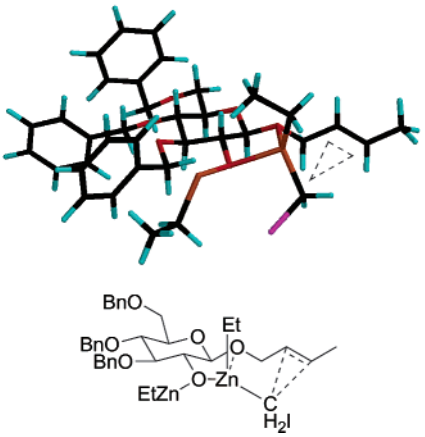


Figure 11. Transition-state model for the cyclopropanation involving the glucose-derived chiral auxiliary.

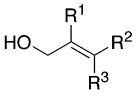
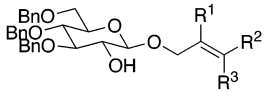
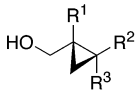
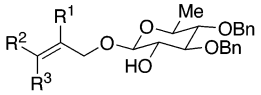
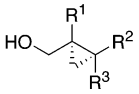
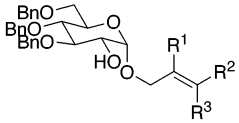
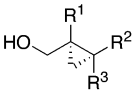
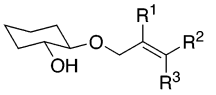
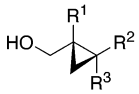
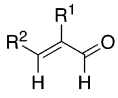
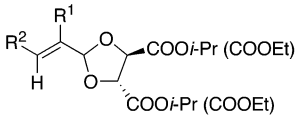
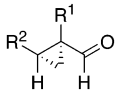
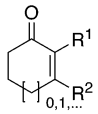
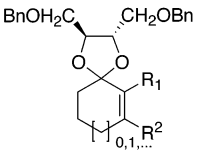
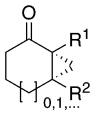
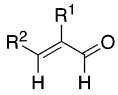
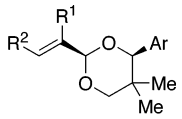
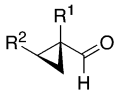
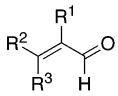
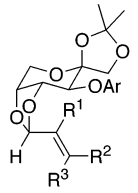
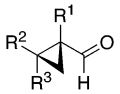
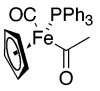
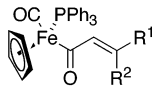
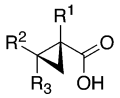
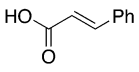
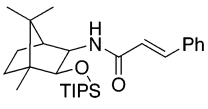
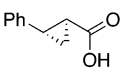
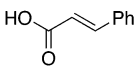
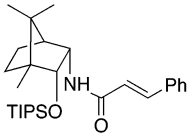
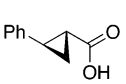
C. Chiral Auxiliaries

A number of auxiliary-based approaches have been reported, and many of them offer the advantage of producing enantiomerically pure cyclopropyl derivatives after the cleavage of the auxiliary. The different chiral auxiliaries that have been developed for the reaction with the various halomethylmetal reagents are emcompassed in four general classes. Chiral allylic ethers (**A**), acetals (**B**), α,β-unsaturated carbonyl derivatives (**C**),[77] and enamines and enol ethers (**D**) have been successfully studied for these reactions (Figure 10).

The chiral auxiliaries in each class are shown in Table 16.[78] Carbohydrate-derived chiral auxiliaries[79] have produced extremely high diastereoselectivities in the cyclopropanation reaction involving substrates of type **A** (Table 16, entries 1−3).[78a−c] It is believed that the chiral auxiliary acts as a bidentate ligand to complex to the zinc reagent (Figure 11). This postulate has given rise to the simpler auxiliary derived from 1,2-cyclohexanediol (Table 16, entry 4).[78d] Cleavage of the chiral auxiliary is then accomplished by a ring contraction reaction (glucose-derived auxiliary) or by a three-step sequence involving conversion of the alcohol into an iodide and reductive elimination of the cyclopropylmethanol moiety upon treatment with BuLi.

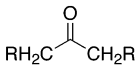
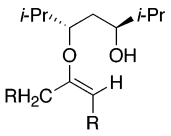
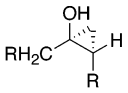
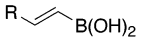
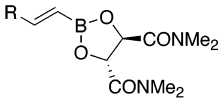
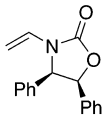
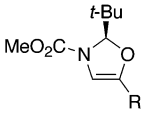
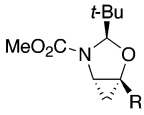
A number of acetal-derived auxiliaries have been studied for this reaction (Table 16, entries 5−8). The most efficient auxiliaries are derived from tartaric acid. Diisopropyl tartrate has been particularly effective with (*E*)-disubstituted and -trisubstituted acyclic substrates (Table 16, entry 5),[78e,f] whereas di-*O*-benzylthreitol undergoes efficient and diastereo-

Table 16. Chiral Auxiliaries for Halomethylzinc-Mediated Cyclopropanation

Entry	Starting Material	Chiral auxiliary	Conditions	Yield (%ds)	Product of cleavage	Ref.
Class A						
1			Et_2Zn (10 equiv) CH_2I_2 (10 equiv) Toluene	≥95% (≥98%)		78a,b
2			Et_2Zn (10 equiv) CH_2I_2 (10 equiv) Toluene	>95% (≥98%)		78a,b
3			Et_2Zn (10 equiv) CH_2I_2 (10 equiv) *t*-BuOMe	83-93% (92-94%)		78c
4			Et_2Zn (3 equiv) $ClCH_2I$ (3 equiv) Toluene	90-98% (≥93%)		78d
Class B						
5			Et_2Zn (5 equiv) CH_2I_2 (10 equiv) Hexane	50-95% (93-97%)		78e,f
6			Zn/Cu (≥6 equiv) CH_2I_2 (3 equiv) Ether	54-99% (88-95%)		78g-i
7			Et_2Zn (3-5 equiv) CH_2I_2 (6-10 equiv) Toluene	34-67% (66-92%)		78j
8			Et_2Zn (5 equiv) CH_2I_2 (10 equiv) $(CH_2Cl)_2$	45-90% (21-81%)		78k
Class C						
9			Et_3Al (4 equiv) CH_2I_2 (4 equiv) Toluene	49-86% (94-97%)		78l-m
10			Et_2Zn (3 equiv) CH_2I_2 (5 equiv) L-(+)-Diethyltartrate (0.5 equiv) CH_2Cl_2	62% (99%)		78n
11			Et_2Zn (3 equiv) CH_2I_2 (5 equiv) L-(+)-Diethytartrate (0.5 equiv) CH_2Cl_2	56% (99%)		78n

selective cyclopropanation with cyclic substrates (Table 16, entry 6).[78g,h] Both auxiliaries are readily cleaved under acidic conditions to produce the corresponding cyclopropyl ketone or aldehyde.[80,81] The configuration of the cyclopropane can be rationalized by the models shown in Figure 12. In the case of 2-cycloalken-1-ones, studies support a mechanistic model that involves preferential chelation of the reagent by the least sterically hindered dioxolane oxygen atom proximal to the alkene (Figure 12, model

Table 16 (Continued)

Entry	Starting Material	Chiral auxiliary	Conditions	Yield (%ds)	Product of cleavage	Ref.
Class D						
12			Et_2Zn (7.5 equiv) CH_2I_2 (10 equiv) Ether	57-80% (99%)		78o-r
13			Zn/Cu (excess) CH_2I_2 (3 equiv) Ether	46-67% (94-97%)		78s
14	$MeCH(OMe)_2$		Et_2Zn (3 equiv) $CHFI_2$ (3 equiv) DME (3 equiv) CH_2Cl_2	76% (30%)		78t-u
15			Et_2Zn CH_2I_2 Ether	52-83% (>98%)		78v-w

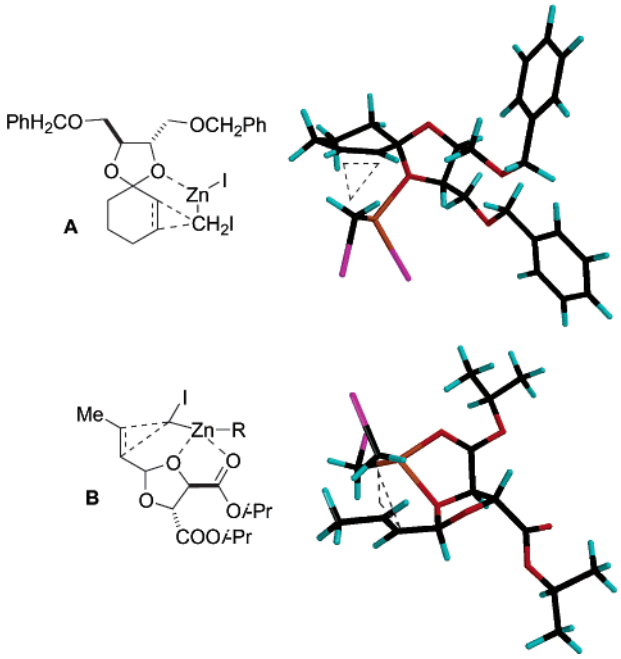


Figure 12. Transition-state model with tartaric acid-derived auxiliaries.

A).[82] Mash has also reported that the auxiliary derived from dihydrobenzoin is even superior to the tartrate-derived ligand with cyclic enones,[82a] but attempts to use it with acyclic systems did not produce high ratios.[83,84] This is consistent with the fact that bidentate chelation by the chiral auxiliary is not favored in this case, since the reaction is done in a complexing solvent (ether). Quite interestingly, the sense of induction in Yamamoto's acyclic system is opposite to that found in the cyclic system. This can be accounted for by assuming that the chiral auxiliary acts as a bidentate ligand under Yamamoto's conditions ($Zn(CH_2I)_2$, hexane). Precomplexation of the reagent by the dioxolane oxygen and the carboxyl oxygen leads to the model **B** shown in Figure 12.[85]

Other chiral auxiliaries in this class include the one derived from 1-aryl-2,2-dimethyl-1,3-propanediols (Table 16, entry 7)[78j] and D-fructose (Table 16, entry 8),[78k] but their installation leads to diastereomers that need to be separated, and the selectivities observed are much more modest than those presented above.

The use of chiral α,*β*-unsaturated ester, amide, or other derivatives is not very common for this reaction, since the electrophilic nature of these reagents often precludes the cyclopropanation reaction with these substrates.[86] The asymmetric synthesis of (*Z*)- and (*E*)-disubstituted and -trisubstituted cyclopropanecarboxylic acid derivatives was achieved via a stereoselective electrophilic methylene transfer to α,*β*-unsaturated acyl ligands bound to the iron chiral auxiliary (Table 16, entry 9).[78l,m] It was proposed that the olefinic bond adopts a conformation approximately orthogonal to the acyl group, thus increasing its nucleophilicity. The aluminum-derived reagent was superior with this auxiliary. The *exo*- and *endo*-3-amino-2-hydroxybornane-derived auxiliaries were also effective only with the hydroxy group protected as a triisopropylsilyl ether (Table 16, entries 10 and 11).[78n] Furthermore, the addition of diethyl tartrate was necessary to increase the yield of the cyclopropane product. Unfortunately, only one example (cinnamic acid) was reported.

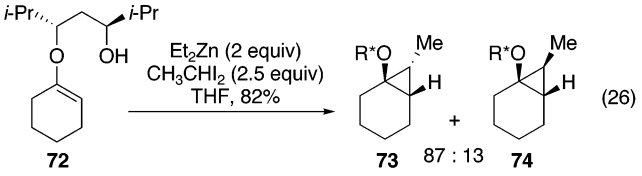
The last class of auxiliaries is shown in entries 12−14 of Table 16. These compounds allow preparation of enantiomerically enriched cyclopropyl alcohols and amines. The highly nucleophilic enol ethers derived from ketones react smoothly with bis(iodomethyl)-zinc to produce cyclopropyl ethers with outstanding diastereoselectivities (Table 16, entry 12).[78o−r] The destructive cleavage of the auxiliary produced cyclopropanol derivatives (1, PCC; 2, K_2CO_3).[87] Imai has shown that 1-alkenylboronic esters bearing the tetramethyltartaramide group underwent highly diastereoselective cyclopropanation reactions to produce

2-substituted cyclopropanols after oxidation (H_2O_2, $KHCO_3$) (Table 16, entry 13).[78s,88]

The diastereoselective cyclopropanation of chiral 3-vinyl-2-oxazolidinone with zinc monofluorocarbenoid produced the corresponding 2-fluorocyclopropylamine with modest selectivities (Table 16, entry 14).[78t−u] This derivative, which has also been prepared by resolution, is a key intermediate in the synthesis of DU-6859, a quinolonecarboxylic acid exhibiting antibacterial activity and little side effects.[89]

Seebach has also used a chiral dihydrooxazole, readily obtained from (*S*)-serine or (*S*)-threonine, to generate the corresponding cyclopropane with perfect stereocontrol (Table 16, entry 15).[78v,w]

Very little work has been reported on the use of more complex diiodoalkane as precursors to more substituted haloalkylzinc reagents. Sugimura has reported that his chiral auxiliary was effective at producing one major diastereomer from this reaction (eq 26).[90]



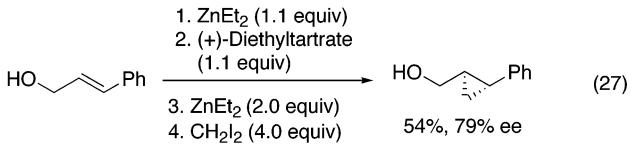
(26)

D. Stoichiometric Chiral Ligands

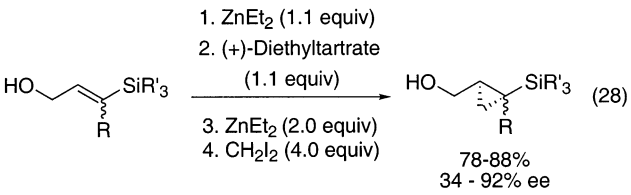
The first attempts to control the absolute stereochemistry in the cyclopropanation of substrates by adding external chiral ligands were reported in 1968. Inouye and co-workers found that very low yields (≤15%) and enantiomeric excesses (≤3.4%) were obtained if a mixture of (−)-menthol and $IZnCH_2I$ was added to α,β-unsaturated esters.[91] Furukawa and co-workers also had very little success when they added L-leucine as a coadditive in the cyclopropanation of vinyl ethers.[44c] Denmark also found that modest enantioselectivities were observed in the enantioselective cyclopropanation of cinnamyl alcohol using (1*R*,2*S*)-*N*-methylephedrine-modified halomethylzinc reagent.[92]

The first practical stoichiometric system for the enantioselective cyclopropanation of allylic alcohol was reported by Fujisawa and co-workers.[93] They showed that moderate levels of enantioselection (70−81% ee) were observed if a stoichiometric amount of diethyl tartrate (DET) was added to a mixture of the allylic alcohol, diethylzinc, and diiodomethane (eq 27). They have also shown that this system is slightly more efficient in the cyclopropanation of silicon-substituted allylic alcohols (eq 28).

A major breakthrough in this area occurred when it was found that a simple bifunctional, chiral, nonracemic ligand containing both acidic (different than zinc) and basic sites would allow simultaneous chelation of the acidic halomethylzinc reagent and the basic zinc alkoxide. The dioxaborolane **75**, prepared from the commercially available *N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide and butylboronic acid, was an efficient chiral controller for that reaction (Table 17).[94]

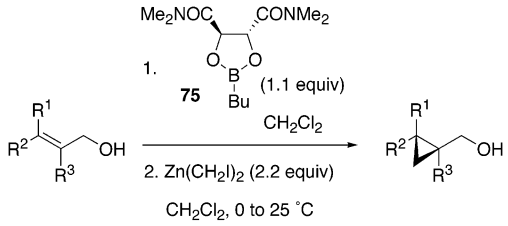


(27)



(28)

Table 17. Enantioselective Cyclopropanation with Dioxaborolane Ligand 75[94]



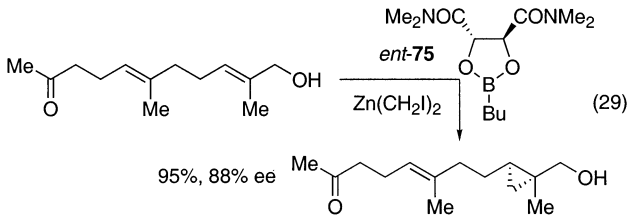
R^1	R^2	R^3	yield (%)	ee (%)
H	Ph	H	95	94
H	3-MeOPh	H	>98	93
H	Pr	H	80	93
H	$PhCH_2CH_2$	H	90	94
H	$BnOCH_2$	H	87	94
H	Bu_3Sn	H	88	90
H	I	H	83	90
Bu_3Sn	H	H	73	90
I	H	H	90	93
Et	H	H	90	93
$TBDPSOCH_2$	H	H	93	91
$BnOCH_2$	H	H	93	91
Me	Me	H	85	94
H	Ph	Me	96	85
H	Et	CH_2OTIPS	>98	89
Me	Me	CH_2OTIPS	85	88

The corresponding substituted cyclopropylmethanols of a variety of allylic alcohols are produced with excellent enantioselectivities (85−94% ee) when a mixture of the alcohol and ligand **75** is added to the preformed halomethylzinc reagent. The reaction proceeds well with *cis*- and *trans*-disubstituted allylic alcohols as well as with tetra-disubstituted ones. Some trisubstituted allylic alcohols are converted to the corresponding cyclopropane with high enantiomeric excess, but others are problematic. One example is 1-cyclohexenylmethanol, which is converted to the corresponding cyclopropane in good yield (84%) but with low enantiomeric excess (60%).

Since this methodology is one of the most efficient known to date for the preparation of enantiomerically enriched substituted cyclopropylmethanols, it is not surprising to see that it has been used in the enantioselective cyclopropanation of important chiral building blocks for natural product synthesis, such as 3-tributylstannyl-2-propen-1-ol,[95] 3-iodo-2-propen-1-ol,[96] 2-chloro-2-propen-1-ol,[97] and allenylic alcohols.[98]

Charette has also shown that the reaction could be used in the case of polyenes. Excellent regioselectivity favoring the allylic alcohol is observed in the

cases where the substrate contains more than one double bond (eq 29).[99]

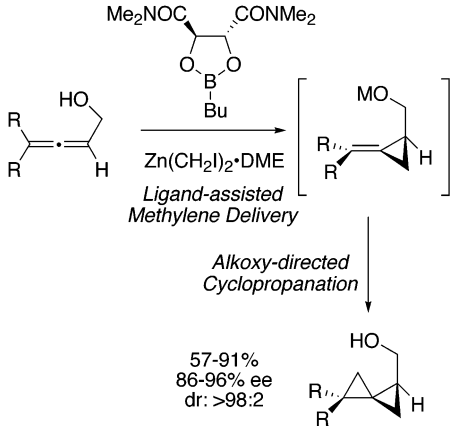


(29)

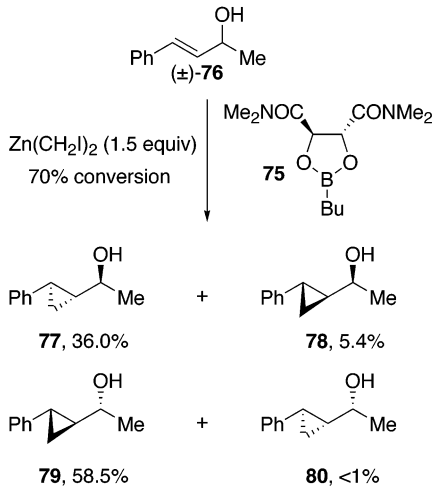
The enantioselective cyclopropanation reaction using the dioxaborolane-derived ligand is quite general and practical. Accordingly, it has been used to elaborate the chiral cyclopropanes subunits of curacin A,[100] FR-900848,[101] U-106305,[102] epothilone analogues,[103] and doliculide.[104]

The same reaction conditions were also applied to the enantio- and diastereoselective cyclopropanation of allenic alcohols, which led to enantiomerically enriched spiropentane derivatives (Scheme 6).[98]

Scheme 6. Cyclopropanation of Allenic Alcohols

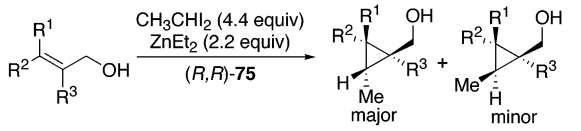


It is not possible to use this reaction to carry out kinetic resolution of chiral, racemic allylic alcohols. For example, when racemic **76** is cyclopropanated with zinc reagents in the presence of the chiral ligand, both enantiomers react at about the same rate, and they both lead mainly to the *anti* isomers (eq 30). Even though this method can be used to convert an enantiomerically pure chiral allylic alcohol to the *anti*-cyclopropyl derivative, it is probably more



(30)

Table 18. Preparation of 1,2,3-Substituted Cyclopropanes[106]

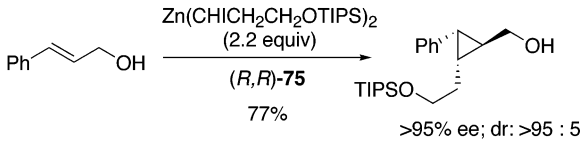


Entry	Allyl alcohol	dr	ee (%)	Yield (%)
1	Ph, OH	98:2	98	96
2	Ph, OH, Me	94:6	90	83
3	BnO, OH	>98:2	94	80
4	Et, OH	96:4	94	87
5	OH	97:3	90	84
6	*n*-Pr, OH	92:8	93	80

practical to simply cyclopropanate its corresponding silyl ether, which gives also the *anti* isomer with an excellent *anti*:*syn* ratio (vide supra).[105]

The chiral dioxaborolane-derived ligand was recently used to synthesize 1,2,3-substituted cyclopropanes (Table 18).[106] High diastereoselectivities and enantioselectivities were recorded when a variety of allylic alcohols were treated with the reagent formed by mixing 1,1-diiodoethane and diethylzinc. This reaction constitutes the first practical stereoselective synthesis of 1,2,3-substituted cyclopropanes using zinc-derived reagents.[107]

It was also shown that functionalized 1,1-diiodoalkanes can be used in this reaction (eq 31).



(31)

In all the previous reactions involving the dioxaborolane ligand, the absolute stereochemistry of the cyclopropane is consistent with the model shown in Figure 13, in which the reaction proceeds via three distinct steps.

First, the zinc reagent deprotonates the alcohol to generate the zinc alkoxide. Second, the zinc alkoxide reacts with the dioxaborolane ligand in an irrevers-

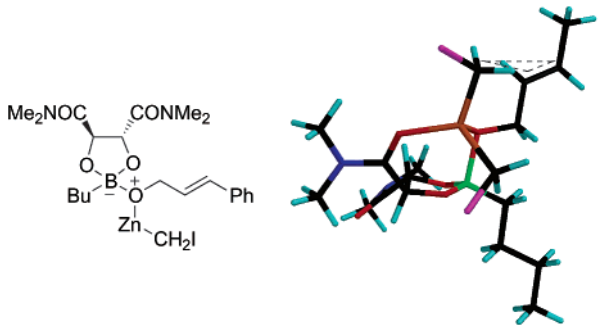
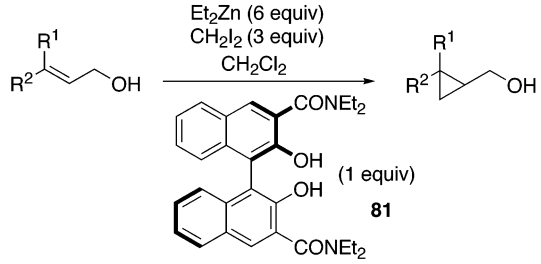


Figure 13. Transition structure for the cyclopropanation with chiral ligand **75**.

Table 19. Enantioselective Cyclopropanation Mediated by 81[108]



Entry	Substrate	Yield (%)	% ee
1	*p*-MeOC$_6$H$_4$	78	94
2	*p*-ClC$_6$H$_4$	50	90
3	Ph	65	89
4	TrO	64	88
5	TBDPSO	59	87
6	TrO	34	65

ible fashion to generate the tetracoordinated boron intermediate, which then undergoes an "amide-directed" cyclopropanation reaction on the most stable conformation of the allylic ether chain.

Recently, Katsuki and co-workers have found that *N*,*N*,*N*′,*N*′-tetraethyl-1,1′-bi-2-naphthol-3,3′-dicarboxamide (**81**), a ligand that is prepared in four steps from binaphthol, can be used for the enantioselective cyclopropanation of allylic alcohols (Table 19).[108] The scope of the reaction seems somewhat limited, since only (*E*)-substituted allylic alcohols can be converted into the corresponding cyclopropanes with reasonably good yields and enantioselectivities. Furthermore, a significantly large excess of diethylzinc is required (enantiomeric excess and yield drop dramatically if less than 6 equiv of diethylzinc is used).

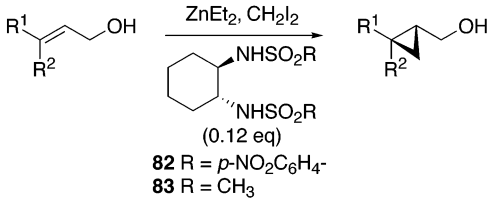
E. Chiral Catalysts

A few catalytic systems have been reported for the enantioselective cyclopropanation of allylic alcohols. Kobayashi and co-workers[109] were the first to report that the Simmons−Smith cyclopropanation reaction could be significantly accelerated by the addition of a chiral Lewis acid. They found that unprecedently good enantioselectivities were observed if the C_2-symmetric chiral disulfonamide ligand **82** was added in catalytic amounts to the zinc-mediated cyclopropanation of allylic alcohols (Table 20).

Consistently high enantioselectivities were obtained with 3-substituted *cis*- and *trans*-allylic alcohols. This method has also been extended to the enantioselective cyclopropanation of vinyl silanes and stannanes (Table 20, entries 8−11).[110] Equally high enantioselectivities were obtained if the zinc-derived Lewis acid was replaced by the analogous aluminum catalyst.[111]

Denmark has published an in-depth study of this reaction and highlighted the effect of the many variables to optimize the enantiomeric excesses of the

Table 20. Asymmetric Cyclopropanation of Allylic Alcohols with Chiral Disulfonamide Catalysts[109−112]



			ee (%); yield (%)	
entry	R^1	R^2	catalyst **82**	catalyst **83**
1	Ph	H	76; 82	89; 92[a]
2	H	Ph	75; 71	81; 81
3	$PhCH_2CH_2$	H	82; 100	89; 88[a]
4	$BnOCH_2$	H	36; 70	
5	$TrOCH_2$	H	80; 86	
6	H	$BnOCH_2$	13; 36	
7	H	$TrOCH_2$	65; 77	
8	Bu_3Sn	H	86; 94	
9	Me_2PhSi	H	81; 83	
10	H	Bu_3Sn	66; 75	
11	H	Me_2PhSi	59; 67	
12	H	$PhCH_2CH_2$	72; 93	72; 93

[a] In situ generation of ZnI_2.

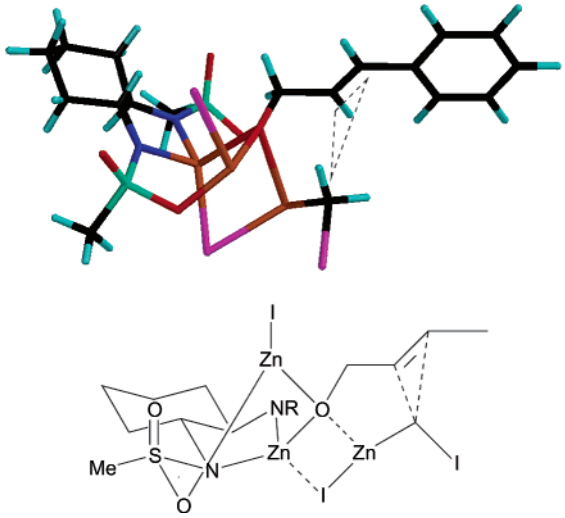


Figure 14. Transition structure for the cyclopropanation with **83**.

product. He has shown that the rate and selectivity of the catalytic enantioselective cyclopropanation of cinnamyl alcohol utilizing bis(iodomethyl)zinc and the bis(sulfonamide) **83** are greatly dependent on the order of addition of the reagents.[112] The independent preformation of the ethylzinc alkoxide and bis(iodomethyl)zinc was found to be crucial. The reaction displayed autocatalytic behavior, which was shown to be due to the generation of zinc iodide. This and other observations have led to the proposed transition-state assembly, in which three zinc atoms are involved in the methylene delivery process (Figure 14).

These optimized conditions, using the dimethylsulfonamide ligand **83** derived from *trans*-cyclohexanediamine, led to the formation of the cyclopropanes with consistently higher enantioselectivities (Figure 15). The enantioselective cyclopropanation of tri- and tetrasubstituted olefins is generally not as effective.

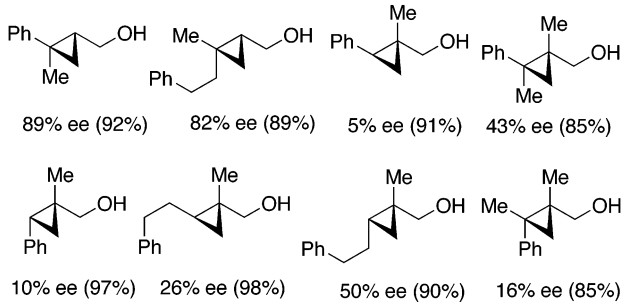
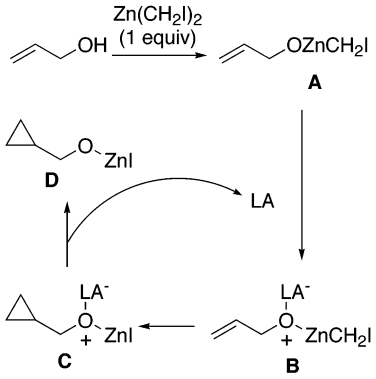


Figure 15. Enantiomeric excesses (yield) for the cyclopropanation with **83**.

Scheme 7. Proposed Catalytic Cycle



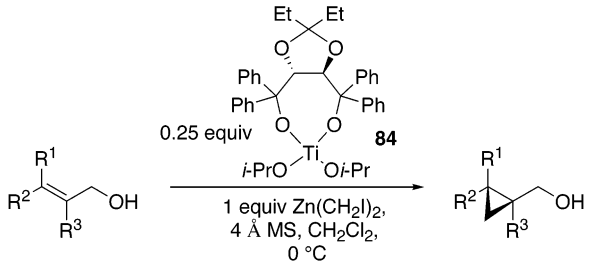
Charette and Brochu have reported an alternative protocol for the Lewis acid-catalyzed cyclopropanation reaction of allylic alcohols, in which the uncatalyzed process is minimized.[113] The addition of $Zn(CH_2I)_2$ (1 equiv) to an allylic alcohol (1 equiv) produced the iodomethylzinc alkoxide (Scheme 7). These species are typically not good methylene-transfer agents unless a Lewis acid is added. Several achiral Lewis acids were effective in inducing the cyclopropanation. In addition, the use of the titanium taddolate produced the corresponding cyclopropane derived from aryl-substituted allylic alcohols in up to 92% ee.

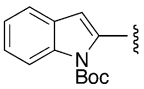
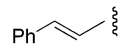
This substoichiometric system is particularly effective with aryl-substituted allylic alcohols,[114] but the cyclopropanation of alkyl-substituted allylic alcohols still needs to be improved.

The Kobayashi/Denmark system is, so far, superior with some alkyl-substituted allylic alcohols. However, it is clear from the results presented in this section that a chiral catalyst for the haloalkylzinc-derived cyclopropanation of greater scope and selectivity would still be welcome.

It is apparent that significant advances have been made toward the development of an efficient catalytic, asymmetric cyclopropanation using zinc-derived reagents, namely with regard to the understanding of how to achieve significant ligand-accelerated reaction. However, the search for better catalysts to increase the scope of the reaction and to improve the enantioselectivities is still among the top research priorities in this area. At this time, the enantioselective cyclopropanation reaction of allylic alcohols using the stoichiometric dioxaborolane chiral ligand is probably still the most reliable method to generate cyclopropylmethanol derivatives in high enantioselectivities.

Table 21. Cyclopropanation Catalyzed by Ti-Taddolate 84[114]



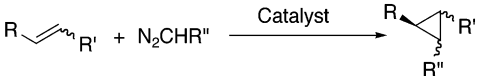
Entry	R^1	R^2	R^3	ee % (Yield %)
1	H	Ph	H	92 (85)
2	Ph	H	H	72 (62)
3	Me	Ph	H	88 (80)
4	H	Ph	Me	50 (80)
5	H	3,5-$Me_2C_6H_3$	H	92 (86)
6	H	2-Napht	H	92 (81)
7	H	1-Napht	H	84 (80)
8	H	4-$MeOC_6H_4$	H	92 (90)
9	H	4-ClC_6H_4	H	82 (81)
10	H	Pr	H	74 (68)
11	Pr	H	H	48 (87)
12	H	$PhCH_2CH_2$	H	60 (63)
13	H	Cyclohexyl	H	56 (60)
14	Me	Me	H	72 (89)
15	H		H	88 (73)
16	H		H	84 (86)
17	H		H	86 (75)

Finally, the use of new zinc-based systems for the enantioselective cyclopropanation of unfunctionalized alkenes or those deprived of proximal functionalities that could assist in the reagent delivery is still elusive.

III. Transition Metal-Catalyzed Decomposition of Diazoalkanes

A. Introduction

The cyclopropanation of olefins using the transition metal-catalyzed decomposition of diazoalkanes is one of the most extensively studied reactions of the organic chemist's arsenal (eq 32).[115]



(32)

Both inter- and intramolecular versions of this reaction have been developed and exploited in synthesis. The nature of the starting diazo reagent, as well as the type of the reaction to be carried out (inter- vs intramolecular), plays a key role in the appropriate selection of the most efficient catalyst for a given transformation. In light of this, this section of the review will be divided into inter- and intramolecular cyclopropanation reactions, and, within

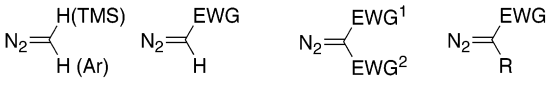


Figure 16. Common diazoalkane precursors.

each section, each class of diazo precursor will be reviewed separately. The emphasis will be placed on the most efficient catalyst to use with a given diazo starting material, and the scope of the reaction will be presented. The diazo precursors **85**−**88** will be divided according to their electronic properties, as shown in Figure 16. It is important to emphasize that, because of the large body of data available on this topic, only the most effective catalytic systems will be reviewed. In the part B of this section, the intramolecular version of the reaction will be reviewed. Again, only the optimal catalysts for a given substrate will be highlighted.

B. Intermolecular Cyclopropanation

1. Diazomethane

The simplest diazoalkane, diazomethane (CH_2N_2), has been used in cyclopropanation reactions, along with its more stable trimethylsilyl analogue ($TMSCHN_2$)[116] and phenyldiazomethane ($PhCHN_2$).[117] Although a large number of metal salts interact with diazomethane (Ni, Pd, Cu, Fe, Co, Ru, Zn, U, Os),[118] palladium salts[119] are very effective at decomposing diazomethane in the presence of an alkene to lead to cyclopropane formation.[120] Mechanistically, it is possible that the palladium(II) catalyst precursor is initially reduced to palladium(0) by diazomethane, since some palladium(0) complexes, such as the palladium dibenzylideneacetone complex ($Pd_2(dba)_3$), are effective catalysts.[121] A subsequent reaction with diazomethane would generate the palladium carbene (eq 33).[122] In some other cases, the formation of a palladium halomethyl complex has been demonstrated, but these species are apparently not good cyclopropanating agents[123,124] (eq 34).

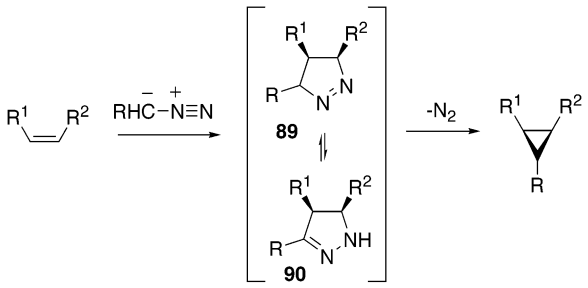
$$Pd_2(dba)_3 \xrightarrow{CH_2N_2} \text{“}L_nPd{=}CH_2\text{”} + N_2 \qquad (33)$$

$$(PPh_3)_2PdCl_2 \xrightarrow{CH_2N_2} (PPh_3)_2Pd(CH_2Cl)Cl + N_2 \qquad (34)$$

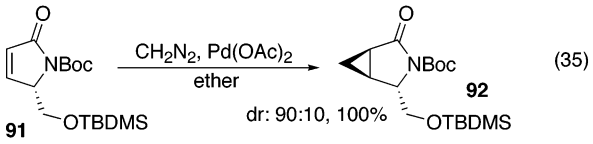
We have also included in this section the cyclopropanation of alkenes via a 1,3-dipolar cycloaddition (Scheme 8). The pyrazolines **89** and **90**, resulting from the 1,3-dipolar cycloaddition, are sometimes not stable and decompose directly to the cyclopropane, but heat or photolysis has also been used to induce N_2 extrusion. This reaction has been extensively used in the cyclopropanation of chiral alkenes, and it will be briefly reviewed below.

The Pd-catalyzed cyclopropanation of chiral cyclic alkenes usually proceeds with good diastereocontrol when sterically demanding groups are present near the olefin. For example, the lactam **91** and lactone **93** produced cyclopropane **92** and **94** in 90:10 and

Scheme 8. 1,3-Dipolar Cycloaddition of Diazo Compounds



86:14 diastereomeric ratios, respectively (eqs 35 and 36).[125]



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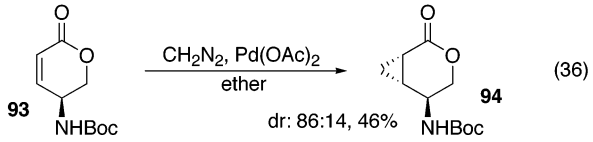
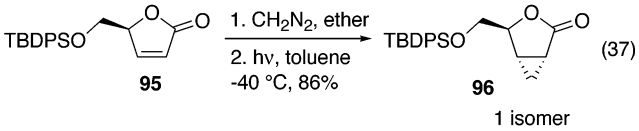


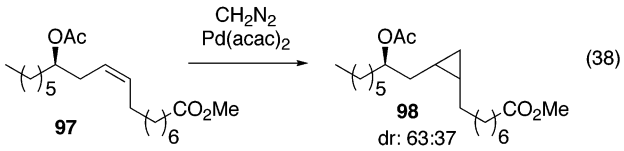
(36)

It should be pointed out that it is also possible to get similar levels of diastereocontrol by 1,3-dipolar cycloadition with diazomethane. The reaction of **95** with diazomethane in the absence of a catalyst leads to only one isomer after nitrogen extrusion (eq 37).[126]



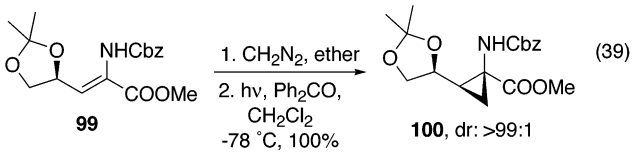
(37)

The cyclopropanations of chiral acyclic alkenes usually do not proceed with a high level of stereocontrol unless a bulky chiral auxiliary is used (vide infra). For example, the cyclopropanation of ricinolic acid derivative **97** does not proceed with an acceptable level of stereocontrol (eq 38).[127]



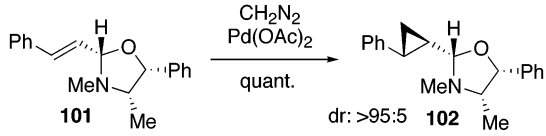
(38)

The 1,3-dipolar cycloaddition of diazomethane to chiral acyclic alkenes has been studied quite extensively.[128] For example, treatment of the dehydroaminopentenoate **99**, derived from 2,3-*O*-isopropylideneglyceraldehyde, with diazomethane produced the corresponding pyrazoline, which, upon irradiation, led to cyclopropane **100** as a single isomer (eq 39).[129,130]



(39)

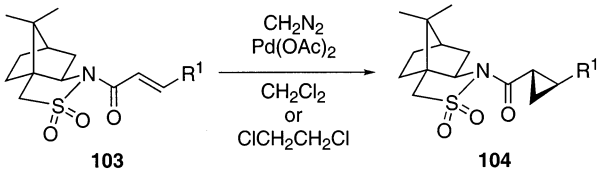
A number of chiral auxiliaries have been developed for the cyclopropanation of acyclic alkenes. An ephedrine-derived auxiliary was shown to be quite effective in these reactions (eq 40).[131] Cinnamaldehyde,



upon treatment with ephedrine, produced oxazolidine **101** as a single diastereomer. The cyclopropanation of **101** gave **102** as a single diastereomer. Cleavage of the auxiliary was accomplished with silica gel. Unfortunately, this auxiliary has been tested only with cinnamaldehyde.

Oppolzer's chiral sultam has also been used as a chiral auxiliary for this transformation (Table 22).[132]

Table 22. Chiral Sultam 103 as Chiral Auxiliary[133]



R^1	yield (%)	dr
Ph	73	93:7
2-$MeOC_6H_4$	73	96:4
3-$MeOC_6H_4$	63	86:14
3,4,5-$(MeO)_3C_6H_2$	62	83:17
4-NCC_6H_4	29	80:20
2-MeO-5-FC_6H_3	46	90:10
2-RC_6H_4[a]	11	81:19
2-thienyl	71	94:6
4-Br-2-thienyl	59	84:16
2-furyl	67	88:12
ferrocenyl	76	91:9
Me	72	95:5
decyl	62	92:8

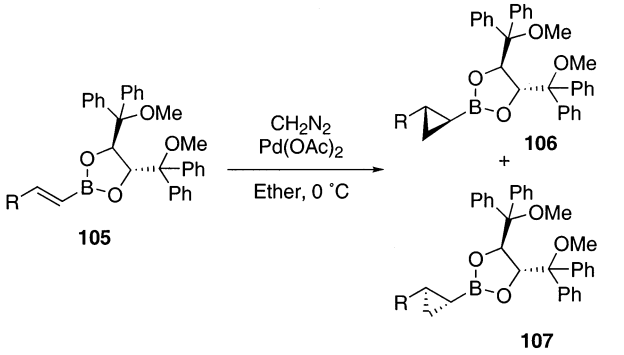
[a] R = 2-methyl-1,3-dioxolan-2-yl.

Although, in many examples, the diastereomeric excesses are quite modest, the diastereomeric products could be recrystallized to remove the minor isomer (96 → 99.5% de).[133]

In an extensive study to generate enantiomerically pure substituted cyclopropylboronic acids that are suitable for palladium-catalyzed cross-coupling, Pietruszka has examined the cyclopropanation reaction of vinylboronate esters bearing various chiral auxiliaries.[134] The most successful auxiliary was that derived from 1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol, and several derivatives of **105** were cyclopropanated with good diastereoselectivities (Table 23). A major advantage of this approach is that diastereomeric products could be separated by chromatography. However, the formation of the cyclopropylboronic acid could be achieved only through an LAH treatment, followed by hydrolysis of the resulting borohydride.[134f]

The cyclopropanations of the corresponding *cis* isomer of **105** were tested, but the diastereoselectivities were significantly lower (65:35 to 87:13).[134g]

Table 23. Cyclopropanation of Vinylboronate Esters 105[134]



R	yield (%)	dr
Pent	99	93:7
Bu	98	89:11
t-Bu	95	87:13
Ph	93	86:14
$TIPSO(CH_2)_3$	89	95:5
$TBSOCH_2$	90	70:30

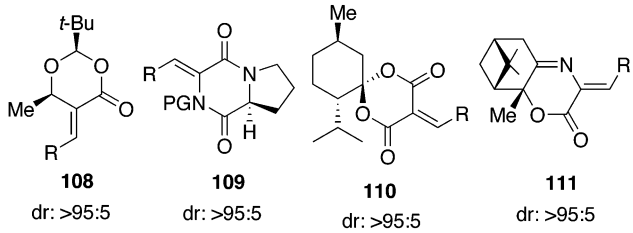
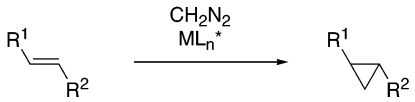


Figure 17. Chiral auxiliaries for the 1,3-dipolar cycloaddition of diazomethane.[135]

Chiral auxiliaries that allow control of the facial selectivity of the 1,3-dipolar cycloaddition of diazomethane have also been developed for specific substrates. Some representative examples are shown in Figure 17.[135] The problem with this approach often resides in the stereoselective preparation of the alkene precursor or of the photoinduced nitrogen extrusion, which could lead to a diastereomeric mixture under some reaction conditions.

An attractive approach to enantiomerically pure cyclopropane derivatives would be to introduce chiral ligands on the metal complex (eq 41) in the diazomethane-mediated cyclopropanation of alkenes. A

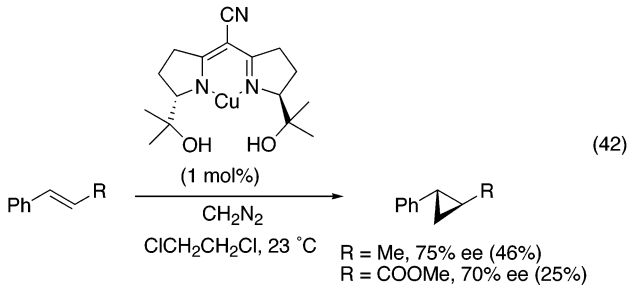


large number of chiral palladium complexes have been tested by Denmark and co-workers,[136] but, although all the catalysts were very active, no enantioselection was observed. It was concluded that either partial or complete decomplexation of the ligand was occurring during the course of the reaction.

The most efficient system known to date uses a copper-based catalyst, but the scope of the reaction has not been described (eq 42).[137]

2. Diazoalkanes Bearing an Electron-Withdrawing Group ($N_2CH(EWG)$)

The most exhaustively studied diazo reagents for intermolecular cyclopropanation reactions are the



(42)

α-diazoesters (**112**, Y = OR),[138] but several others, all containing one electron-withdrawing group (**113**−**116**),[139] have been used to prepare cyclopropanes (Figure 18). Simple α-diazoesters have been prepared

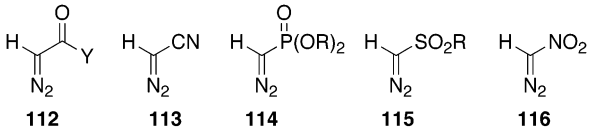


Figure 18. Most common diazo reagents.

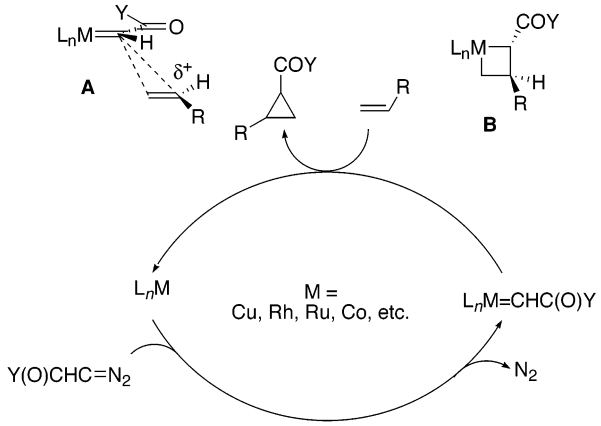
and reacted in situ in the presence of the metal catalyst and the alkene.[140]

A wide range of metal catalysts derived from Cu, Rh, Ru, Co, Fe, Os, Pd, Pt, Cr, and others have been reported to catalyze the diazo reagent decomposition.[141] Usually, Rh, Ru, Co, and Cu metal carbenes react faster with electron-rich alkenes, whereas Pd metal carbenes are optimal for electron-deficient alkenes.

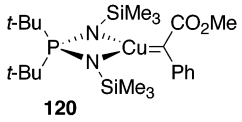
In most of these cases (Cu, Rh, Ru, Os), the mechanism of the transition metal-catalyzed decomposition of α-diazocarbonyl compounds is believed to initially proceed via the formation of a metal carbene complex (Scheme 9).[142]

Several stoichiometric carbenes derived from ruthenium[143] and osmium[144] have been prepared and characterized in solution and were shown to act as

Scheme 9. Catalytic Cycle for the Cyclopropanation



efficient catalysts for the cyclopropanation reaction. Nishiyama successfully obtained the X-ray crystal structure of a pybox ruthenium carbene **117** (Figure 19), which was shown to be an active cyclopropanating reagent under drastic conditions.[145] Porphyrin−ruthenium carbenes **118** and **119** have been isolated, and their X-ray crystal structures have been reported.[146] Although the copper carbenes have never been characterized by X-ray crystallography, a recent solution-state NMR study of carbene **120**[147] has been carried out and showed that the mechanistic picture is fully consistent with that proposed by Pfaltz and co-workers (vide infra).[148]



Recent calculations,[149] and isotope effect and Hammett studies,[150] have also been carried out on the copper(I)-catalyzed cyclopropanation of propene with

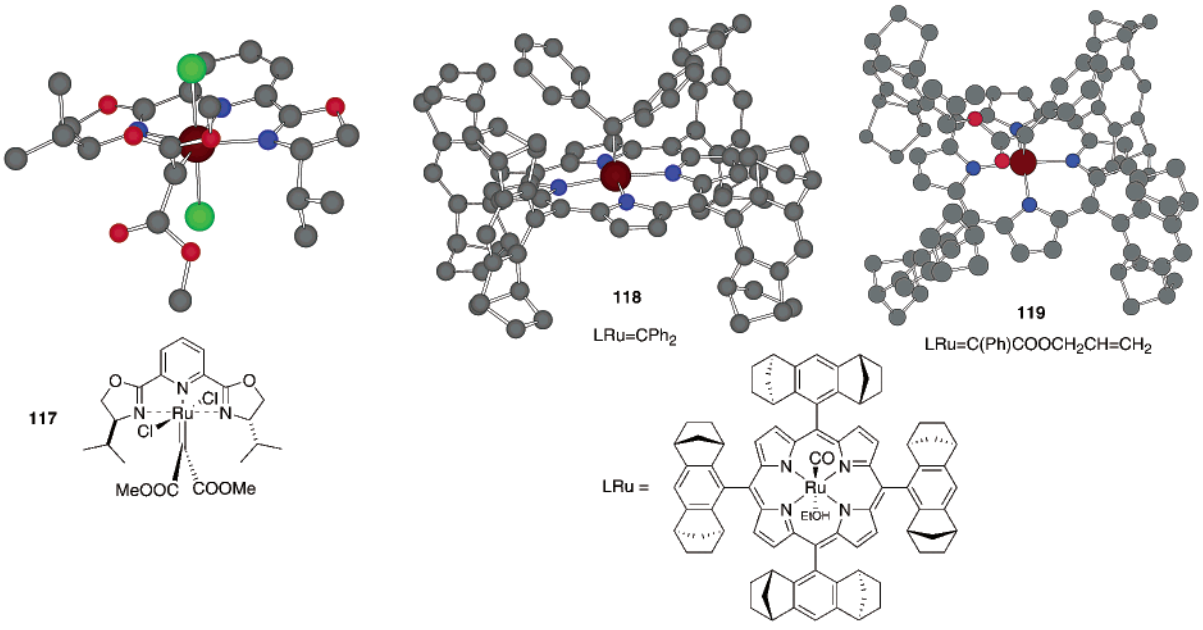


Figure 19. Chem3D representation of several X-ray crystal structures of ruthenium carbenes.

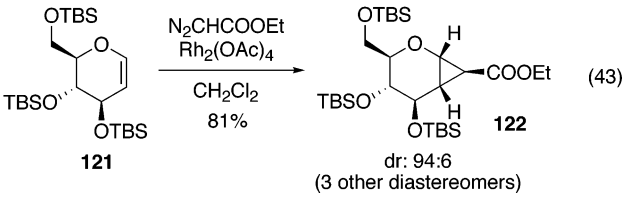
diazo compounds. Both studies support the addition of the very reactive metallacarbene intermediate in an early transition state to the substrate alkene in a concerted but strongly asynchronous pathway with substantial cationic character on one alkene carbon, represented by the transition structure **A** (and not metallacyclobutane **B** in Scheme 9).

It is important to point out that, although Cu(II) salts are often used as catalyst precursors, it has been demonstrated that Cu(I) salts are the catalytically active species in these reactions.[151] In a seminal work, Kochi has shown that CuOTf is one of the most effective catalysts.[152] Further evidence for the involvement of a Cu(I) species is provided by the observation that Cu(II) salts complexed with chiral ligands need to be preactivated for the reaction to proceed (DIBAL, substituted hydrazine, heat with diazo reagent).

As expected from the transition structure **A**, the diastereoselectivities favoring the *trans* isomer usually improve when the steric demand of the Y group increases. Doyle has shown that the rhodium-catalyzed decomposition of a very hindered α-diazoester (such as the 2,6-di-*tert*-butyl-4-methylphenyl ester) led to very high *trans*:*cis* ratios with monosubstituted alkenes.[153]

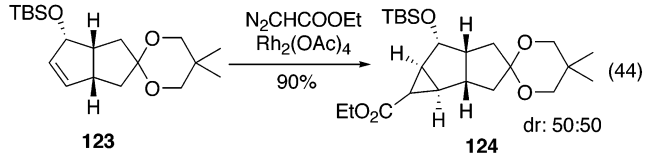
An alternative approach to metal carbenes is to substitute the diazo reagent with the corresponding iodonium ylide (PhI=CHCOOR) or sulfonium ylide (Ph_2S=CHCOOR), but these will not be discussed in this review.[154]

The reaction of ethyl diazoacetate with a chiral cyclic alkene usually proceeds well with reactive alkenes. For example, the TBS-protected D-glucal could be converted to the cyclopropyl derivative with almost complete stereocontrol when $Rh_2(OAc)_4$ was used as the catalyst (eq 43).[155] Other protected glycals reacted in a similar fashion.[156]



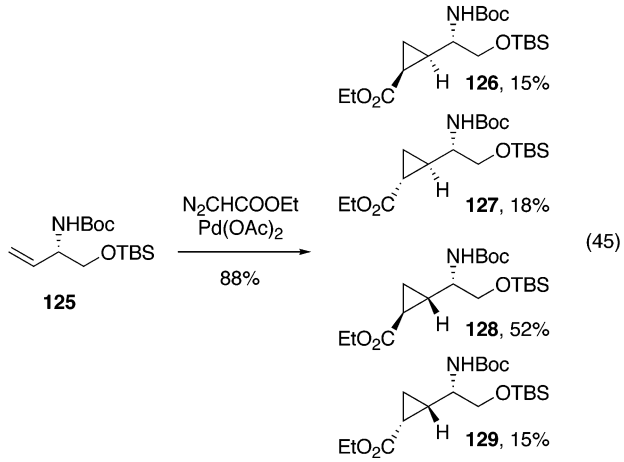
(43)

Although the facial selectivity in the reaction of relatively rigid systems is quite good, the relative stereocontrol for the stereogenic center bearing the ester group is sometimes quite modest (eq 44).[157]



(44)

Although there are some exceptions, the cyclopropanation of acyclic chiral alkenes leads to mixtures of stereoisomers. For example, a mixture of all four possible diastereomers was obtained when alkene **125** was treated with ethyl diazoacetate and palladium acetate (eq 45).[158]



(45)

The introduction of a chiral auxiliary on the diazo reagent has not been very successful. Some examples are shown in Figure 20, along with the diastereoselectivities observed for the cyclopropanation of styrene.[159]

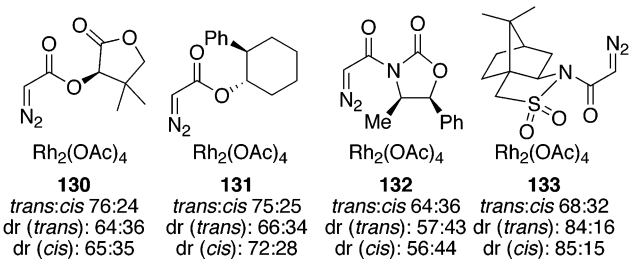
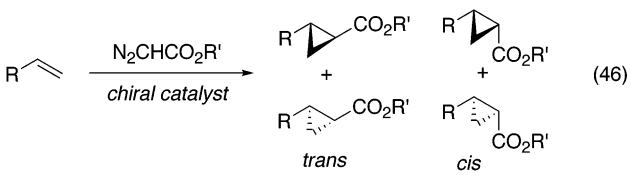


Figure 20. Chiral auxiliaries for the intermolecular cyclopropanation of styrene.

The decomposition of α-diazoesters by chiral transition metal complexes to cyclopropanate achiral alkenes in an intermolecular fashion is one of the most widely studied asymmetric processes, for which an incredibly large number of chiral complexes have been prepared and tested. This section of the review will focus only on the most effective chiral catalysts in terms of both enantio- and diastereoselectivity (eq 46).[160] The selection of the appropriate chiral catalyst for a given substrate depends on the nature of the starting alkene and on the appropriate choice of the starting diazoester (generally to maximize the *trans*:*cis* ratio).

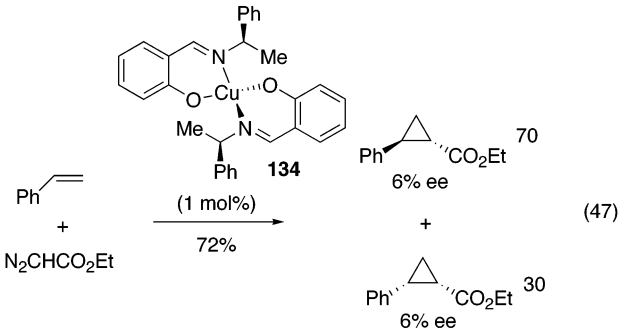


(46)

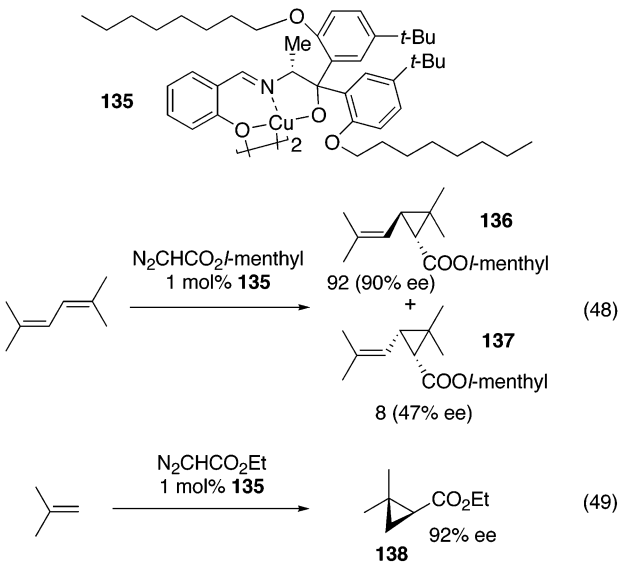
Some general conclusions can be drawn from the experimental data available. First, the most effective catalysts for the preparation of the *trans* isomer with the widest reaction scope are the copper-based catalysts. Rhodium-based catalysts are very effective, but they generally produce lower enantio- and diastereomeric ratios. For this reason, they have not been

used much in enantioselective, intermolecular cyclopropanation involving α-diazoesters, and they will be briefly reviewed.[161] Second, ruthenium-based catalysts are very efficient, but the scope is usually a bit narrower than that of the best copper-based ones. Finally, cobalt-based catalysts are usually used in *cis*-selective cyclopropanation reactions, but the ligands are usually structurally quite complex.

The first example of an enantioselective copper-based intermolecular cyclopropanation reaction was reported by Nozaki in 1966.[162] The copper-catalyzed decomposition of ethyl diazoacetate in the presence of an *N*-benzylethylamine-based chiral salicylaldimino complex **134** gave about 6% enantiomeric excess of the corresponding *cis*- and *trans*-cyclopropanecarboxylates (eq 47). Although the enantiomeric ratios were modest, this catalyst defined the basis for further ligand optimization.[163] This exercise led to catalyst **135**, which proved to be quite effective in the synthesis of chrysantemate esters (eq 48)[164] and the side chain of cilastatin (eq 49).



(47)



(48)

(49)

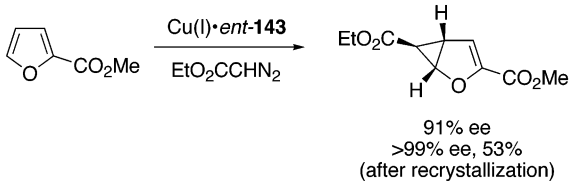
In the past four decades, several hundred chiral ligands have been synthesized and tested in copper-catalyzed processes. Some of the structural variations of the ligands include substituted salicylaldimines, semicorrins, bis(oxazolines), bipyridines, and others. Only a sample of the potentially most useful chiral ligands that provide high enantioselectivities will be discussed in the review. The best chiral ligands for the copper-catalyzed cyclopropanation are shown in Figure 21, and the diastereo- and enantioselectivities are provided for the cyclopropanation of styrene.[165]

In 1986, Pfaltz disclosed the novel semicorrin-type ligand **139**, which displayed unprecedented high enantioselectivities in cyclopropanation reactions.[166] These ligands, however, suffered from their relatively low Lewis acidity; therefore, low yields were observed with unactivated alkenes (such as 1-heptene). The facial selectivity observed is consistent with the model shown in Figure 22. The main discriminating stereochemical element is the steric interaction between the ester group and the semicorrin substituent upon pyramidalization of the carbene center.

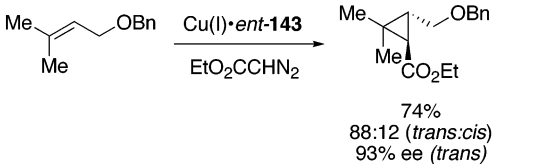
This disclosure was quickly followed by the development of numerous, even more effective ligands with broader scope. Many bis(oxazoline) and related bidentate ligands have been reported to be quite effective (**140**,[167] **141**,[168] **142**,[169] **145**,[170] **146**,[171] **147**,[172] **149**,[173] **155**[174]). The copper(I) complex of bis(oxazoline) **143**,[175] disclosed by Evans in the early 1990s, is still a standard to which new bis(oxazoline) ligands are compared. The reaction proceeds with high yield and enantioselectivities with mono- and 1,1-disubstituted alkenes (Table 24). Although the BHT ester is reluctant to undergo saponification,[153] reduction with $LiAlH_4$ provides the primary alcohol in good yield.

The stereochemical prediction of the bis(oxazoline) copper(I)-catalyzed cyclopropanation has been rationalized by Salvatella and García using DFT calculations (Figure 23).[149] The calculated relative energies are in good agreement with the experimental enantiomeric excesses as well as with the *cis*/*trans* ratio.

Catalyst Cu(I)·**143** had been used quite extensively in cyclopropanation reactions. For example, it is quite effective in the cyclopropanation of some acyclic (1,1-disubstituted) and cyclic silyl enol ethers (Figure 24),[176] of furans (eq 50),[177] of protected allylic alcohols (eq 51),[178] and of vinyl fluorides.[179]



(50)



(51)

Masamune has also developed bis(oxazoline) **144**,[180] which, surprisingly, is not efficient for styrene. However, this ligand turned out to be quite good in the Cu(I)·**144**-catalyzed cyclopropanation of trisubstituted and unsymmetrically 1,2-disubstituted alkenes. Some typical examples are shown in Figure 25.

Bipyridine-derived ligands (**151**,[181] **152**,[182]), as well as diamines (**148**,[183] **154**[184]), have also produced some good results in these reactions. Bisazaferrocene ligand **150**[185] gives very high enantioselectivities not

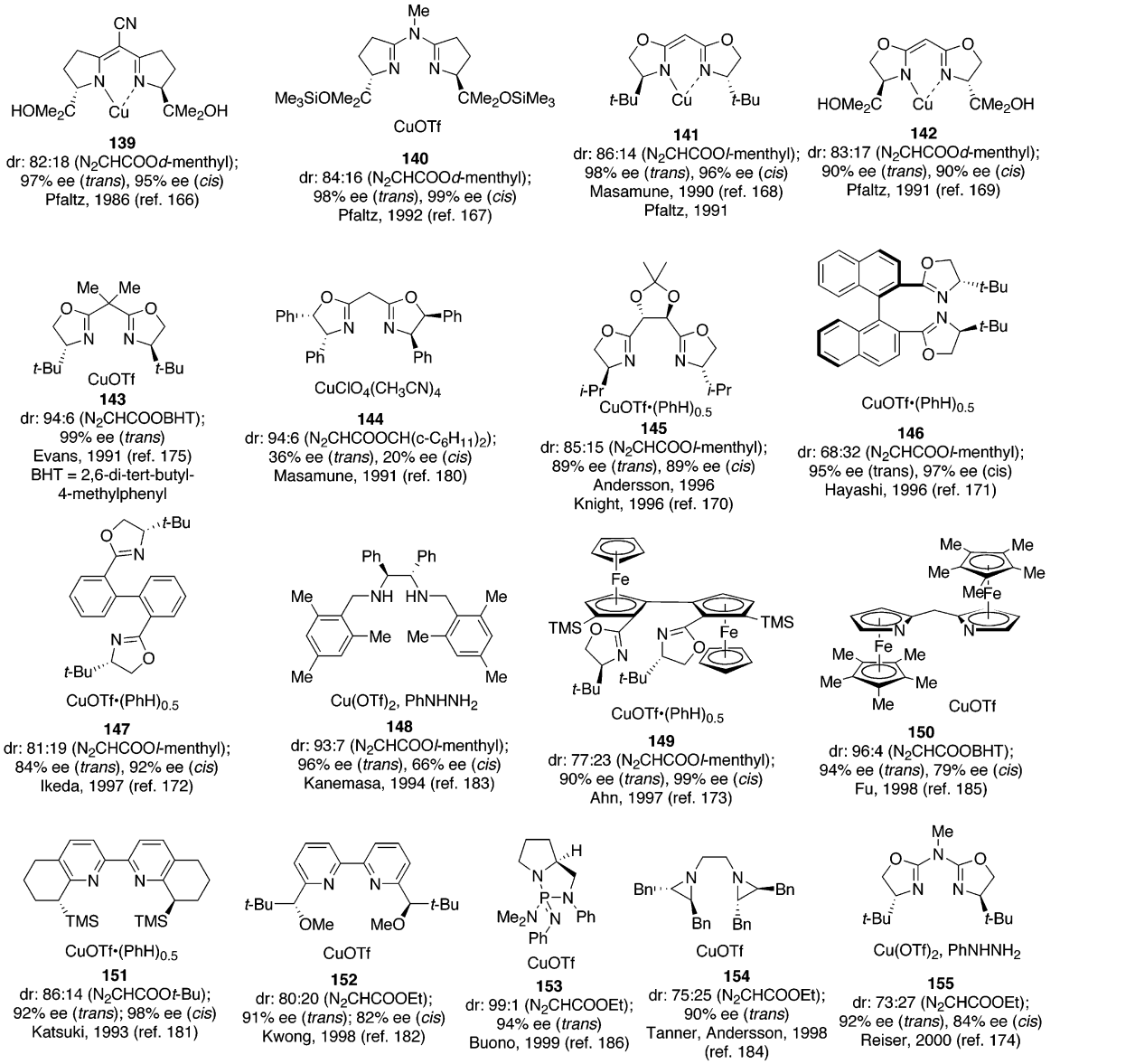
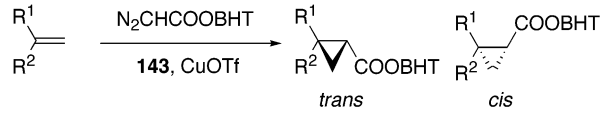


Figure 21. Chiral catalysts for the intermolecular Cu-catalyzed cyclopropanation and the diastereoselectivies and enantiomeric excesses observed for the cyclopropanation of styrene.

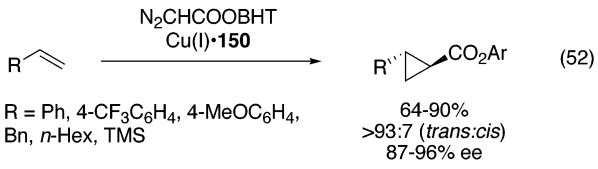
Table 24. Enantioselective Cyclopropanation with 143[a,175]



R^1	R^2	yield (%)	ratio *trans*:*cis*	ee *trans* (%)
Ph	H	85	94:6	99
$PhCH_2$	H		93:7	>99
Ph	Ph	70		>99
Me	Me	91		>99

[a] BHT = 2,6-di-*tert*-butyl-4-methylphenyl.

only with styrene but also with monosubstituted alkenes, including vinyltrimethylsilane (eq 52).



(52)

Most previously described catalytic systems require a bulky ester to maximize the *trans*:*cis* ratio. One exception to this is the catalyst generated by mixing the iminodiazaphospholidine ligand **153**[186] with a stoichiometric amount of CuOTf. Although the scope is limited to 1-aryl-substituted alkenes, the enantio- and diastereoselectivities observed with ethyl diazoacetate are impressive (Table 25).

In general, ruthenium carbenes bearing chiral ligands are less reactive than those derived from copper and rhodium. Most of them will efficiently convert aryl-substituted alkenes to their corresponding cyclopropane, but lower yields are observed with alkyl-substituted alkenes.

The most effective ruthenium-based chiral catalysts are shown in Figure 26. The first very effective system was reported in 1994 by Nishiyama. The pybox-*i*-Pr ligand reacts with $[RuCl_2(p\text{-cymene})]_2$ to generate a complex that is quite effective in cyclopropanation reactions. However, it is preferable to

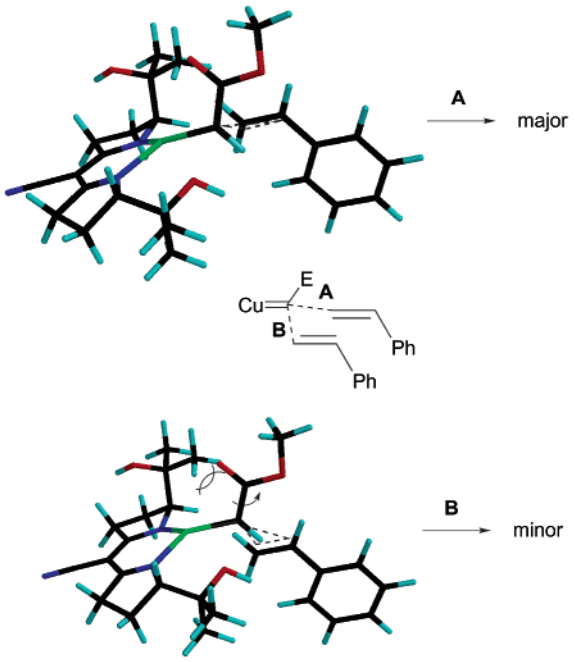


Figure 22. Preferred approach of the alkene for the cyclopropanation with **139**.

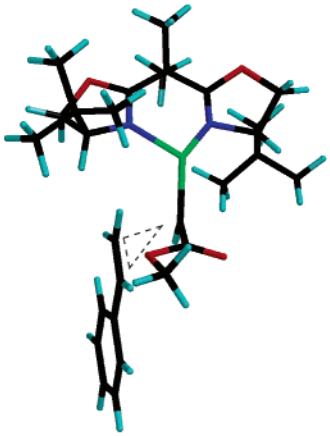
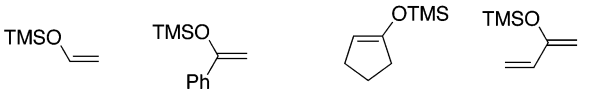


Figure 23. The proposed metallacyclobutane formed with **143**.

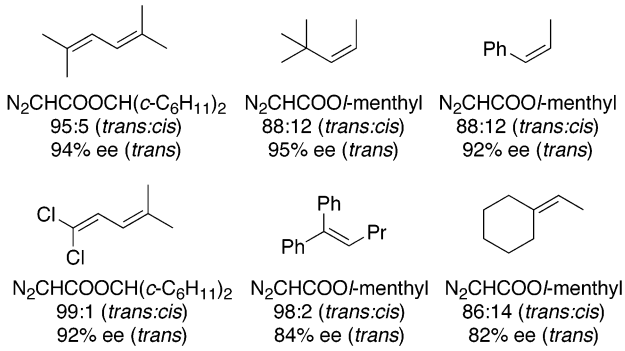


33:67 (*cis*:*trans*)	50:50 (*cis*:*trans*)	75:25 (*cis*:*trans*)	50:50 (*cis*:*trans*)
76% ee (*cis*)	95% ee (*cis*)	92% ee (*cis*)	>95% ee (*cis*)
73% ee (*trans*)	90% ee (*trans*)	87% ee (*trans*)	74% ee (*trans*)

Figure 24. Cyclopropanation of silyl enol ethers catalyzed by Cu(I)·**143**.

carry out the reaction under an ethylene atmosphere to generate complex **156**[187,188] (Figure 26), which can be purified by silica gel chromatography and is stable in solution. The cyclopropanation of aryl-substituted alkenes with this catalyst provides the corresponding cyclopropane in enantiomeric excesses ranging from 95 to 98%. It should be pointed out that the use of the L-menthyl diazoacetate produced slightly higher diastereo- and enantioselectivities compare to those observed with ethyl diazoacetate (eq 53).

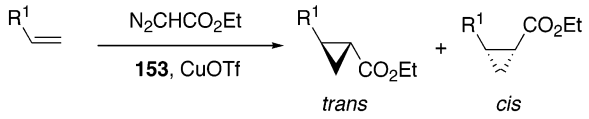
The sense of induction in these reactions is consistent with the model shown in Figure 27, in which



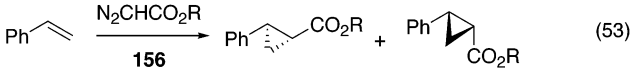
$N_2CHCOOCH(c\text{-}C_6H_{11})_2$	N_2CHCOO*l*-menthyl	N_2CHCOO*l*-menthyl
95:5 (*trans*:*cis*)	88:12 (*trans*:*cis*)	88:12 (*trans*:*cis*)
94% ee (*trans*)	95% ee (*trans*)	92% ee (*trans*)
$N_2CHCOOCH(c\text{-}C_6H_{11})_2$	N_2CHCOO*l*-menthyl	N_2CHCOO*l*-menthyl
99:1 (*trans*:*cis*)	98:2 (*trans*:*cis*)	86:14 (*trans*:*cis*)
92% ee (*trans*)	84% ee (*trans*)	82% ee (*trans*)

Figure 25. Cyclopropanation of alkene using Cu(I)·**144**.

Table 25. Cyclopropanation of Alkenes with Cu(I)·153[186]



R^1	yield (%)	ratio *trans*:*cis*	ee *trans* (%)
Ph	80	98:2	94
1-naphthyl	76	100:0	95
$PhCH_2$	71	98:2	12
$PhOCH_2$	78	83:17	34



(53)

R = Et; 91:9 (*trans*:*cis*), 89% ee (*trans*), 73%
R = *t*-Bu; 97:3 (*trans*:*cis*), 94% ee (*trans*), 65%
R = *l*-menthyl; 97:3 (*trans*:*cis*), 96% ee (*trans*), 83%

the alkene attacks in a geometry that puts the phenyl group away from the ester and isopropyl groups.

The pybox−Ru catalytic system is probably the most studied Ru-based catalyst for cyclopropanation reactions, and many structural variations of the ligand have been tested. Two interesting observations have been made. First, a remote stereoelectronic effect has been reported. Variable enantioselectivities are observed, depending on the nature of a substituent at the 4-position of the pyridine ring (**157**).[189]

Electron-donating substituents decrease the enantiomeric excess (84% ee for the cyclopropanation of styrene if X = NMe_2), and electron-withdrawing groups increase the enantiomeric excess significantly (X = CO_2Me, 97% ee). However, the *trans*:*cis* ratios were not affected by the substituents. The second interesting observation is that non-C_2-symmetric ligands are also quite effective in this reaction. For example, pybox-Ru **158** catalyzes the reaction quite nicely by producing the cyclopropane not only with high enantioselectivity but also with an improved diastereoselectivity.[190] It was reasoned that the removal of one of the oxazoline substituents created more space for the ester group in the chiral pocket.

Many other chiral ruthenium complexes were disclosed, and many proved to be very good catalysts. Ruthenium porphyrin **159**,[191] and the ruthenium chiral Schiff base complexes **162**[192] and **164**,[193] produce excellent level of enantio- and diastereocontrol. However, their synthesis is more tedious than that of the pybox system.

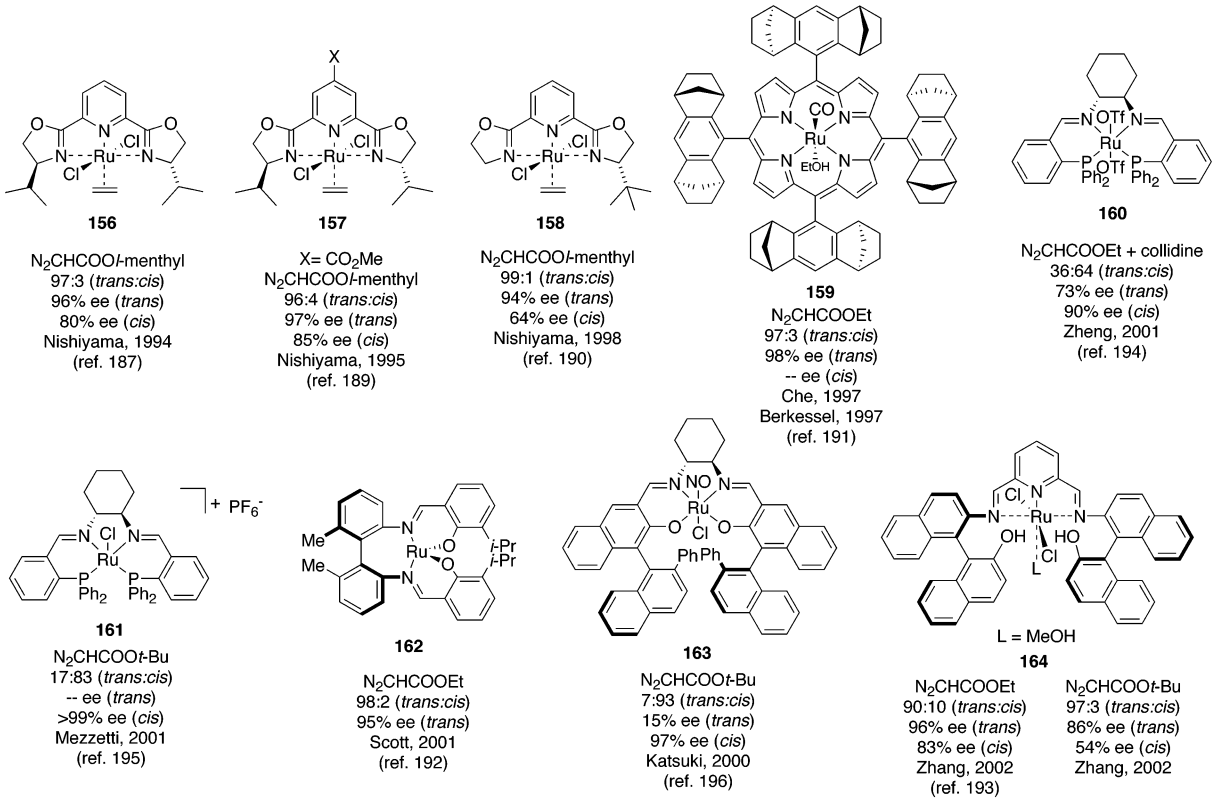


Figure 26. Ruthenium catalysts for the $N_2CHCOOR$-mediated cyclopropanation of alkenes.

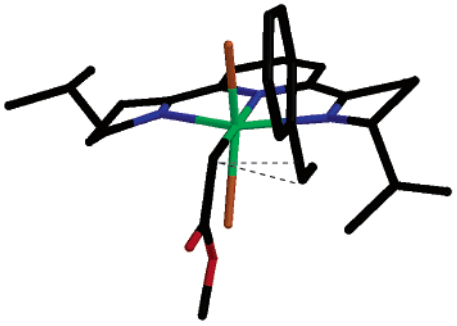
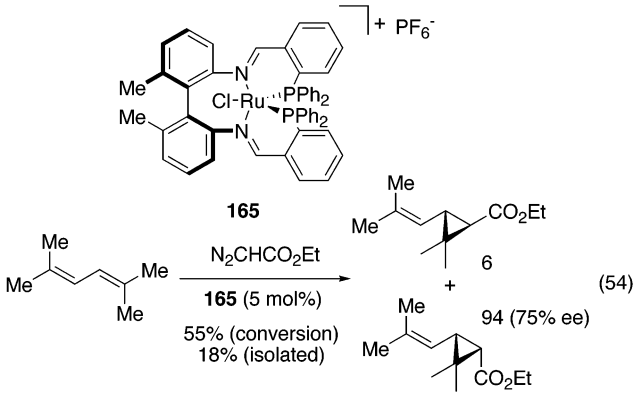


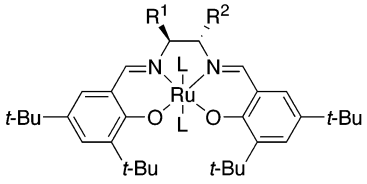
Figure 27. Transition-state model for the Ru·pybox cyclopropanation.

A few ruthenium-based systems displayed *cis* selectivity in the cyclopropanation reaction (**160**,[194] **161**, **163**). Among them, Mezzetti's **161**[195] and Katsuki's catalyst **163**[196] provide the highest *cis*:*trans* ratios. For example, Mezzetti's catalyst **165**[195] is effective for the cyclopropanation of 2,5-dimethyl-2,4-hexadiene, producing the *cis* isomer (eq 54).

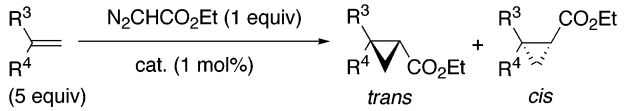


(54)

Table 26. Nguyen's Ruthenium(II)-Catalyzed Cyclopropanation[198]



166 L = pyridine; R^1,R^2 = -$(CH_2)_4$-
167 L = pyridine; R^1 = H, R^2 = Me
168 L = pyridine; R^1 = Ph, R^2 = Ph



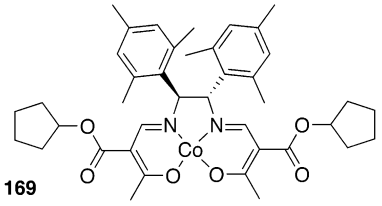
R^3	R^4	yield (%); (catalyst)	ratio *trans*:*cis*	ee *trans*; *cis* (%)
Ph	H	95; **168**	77:23	>99
COOMe	Me	95; **167**	>99:1	95
MeCH=CH	H	97; **168**	66:34	89; 90
OEt	H	80; **166**	80:20	69; 78
n-Pr	H	30; **166**	76:24	90; 18

Ruthenium salen complexes **166**−**168**,[197] in which two of the free coordinating sites are occupied by a pyridine ligand, were shown to give excellent enantiomeric excesses in the cyclopropanation of mono- or 1,1-disubstituted alkenes (Table 26).

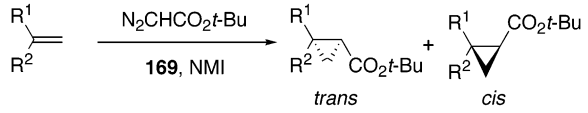
Cobalt complexes have been shown to be reactive catalysts for the α-diazoester decomposition, leading to a metal carbene that could convert alkenes to cyclopropanes. Although the early work in this area established that cobalt(II) complexes were catalytically active, the low level of diastereo- and enantio-

control limited their use in synthesis.[198] Recently, Yamada has shown that 3-oxobutylideneaminatocobalt(II) complexes, such as **169**, were quite effective in a *trans*-selective reaction (Table 27).[199] The addition of a catalytic amount of *N*-methylimidazole (NMI) increases the rate of the reaction as well as the enantioselectivity. The reaction is limited to aryl-substituted alkenes, and 1,1-disubstituted alkenes that are substituted with at least one aryl group are converted to the cyclopropane derivatives with low diastereocontrol. The diastereoselectivity in the cyclopropanation of styrene decreases to 83:17 if methyl diazoacetate is used.

Table 27. Yamada's Cobalt(II)-Catalyzed Cyclopropanation[199]

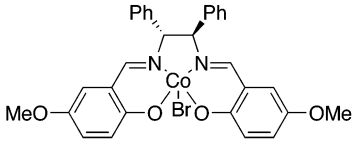


169



R^1	R^2	yield (%)	ratio *trans*:*cis*	ee (%)
Ph	H	99	91:9	96
4-ClC_6H_4	H	93	90:10	96
4-$MeOC_6H_4$	H	85	82:18	92
2-naphthyl	H	95	87:13	96
Ph	Me	47	47:53	99

Katsuki has developed a series of new ligands for *trans*- or *cis*-selective cyclopropanation reactions. The optimal *trans*-selective complex is the cobalt salen **170**.[200] It catalyzed the decomposition of *tert*-butyl diazoacetate in the presence of styrene to generate the *trans*-cyclopropane with an excellent diastereomeric ratio (96:4) and enantiomeric excess (93% ee).



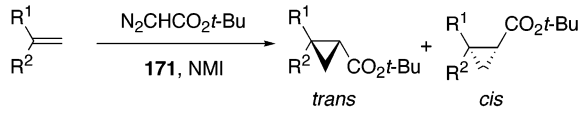
170

Katsuki has also designed *cis*-selective catalysts based on the salen scaffold.[201] Both diastereomeric complexes **171** and **172** were examined and, although similar enantio- and diastereoselectivities were observed with both of them, the rate of the reaction with **171** was significantly faster than that with **172**.

The reaction proceeded very well in the presence of NMI, but the scope is limited to aryl-substituted alkenes (Table 28). The role of the base is to occupy one additional coordination site on the catalyst.

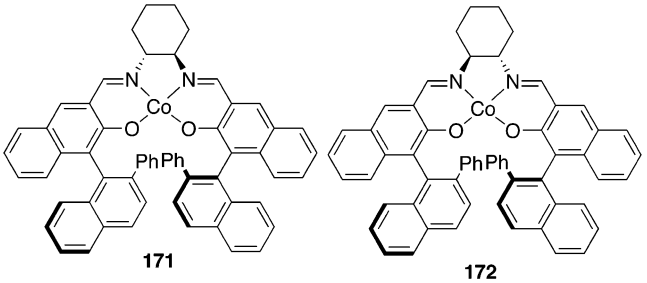
The following class of the rhodium-based catalysts has been extensively studied for the intermolecular cyclopropanation reaction of alkenes. For this reason, a large number of rhodium-based chiral complexes has been synthesized and tested in both inter- and intramolecular cyclopropanations (vide infra) as well as in C−H insertion reactions. Figure 28[202] surveys the wide range of chiral rhodium catalysts that have been prepared so far. There are two general classes: the dirhodium(II) carboxylates (**173**−**186**) and carboxamidates (**187**−**208**). Although the reactivity of the rhodium carbene that is generated when the catalyst reacts with an α-diazoester is not an issue, since most of them are very reactive, the level of diastereocontrol observed in intermolecular cyclopropanation reactions with α-diazoesters is problematic. As a general guideline, the level of diastereocontrol with rhodium carbenes does not match that observed with copper, ruthenium, or cobalt carbenes, even when sterically hindered α-diazoesters are used.[203] This important drawback has minimized the use of rhodium catalysts in intermolecular processes involving simple α-diazoesters.

Table 28. Katsuki's *cis*-Selective Cyclopropanation[200]



R^1	R^2	yield (%)[a]	ratio *cis*:*trans*	ee (%)
Ph	H	89	98:2	98
4-ClC_6H_4	H	85	97:3	96
4-$MeOC_6H_4$	H	84	97:3	95
2-Naphthyl	H	94	98:2	97
Ph	Me	39	83:17	99 (99)

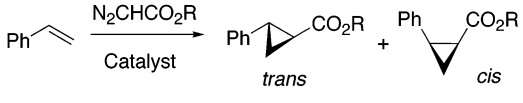
[a] Based on the diazoester reagent. Excess alkene (5 equiv) was used.



171 **172**

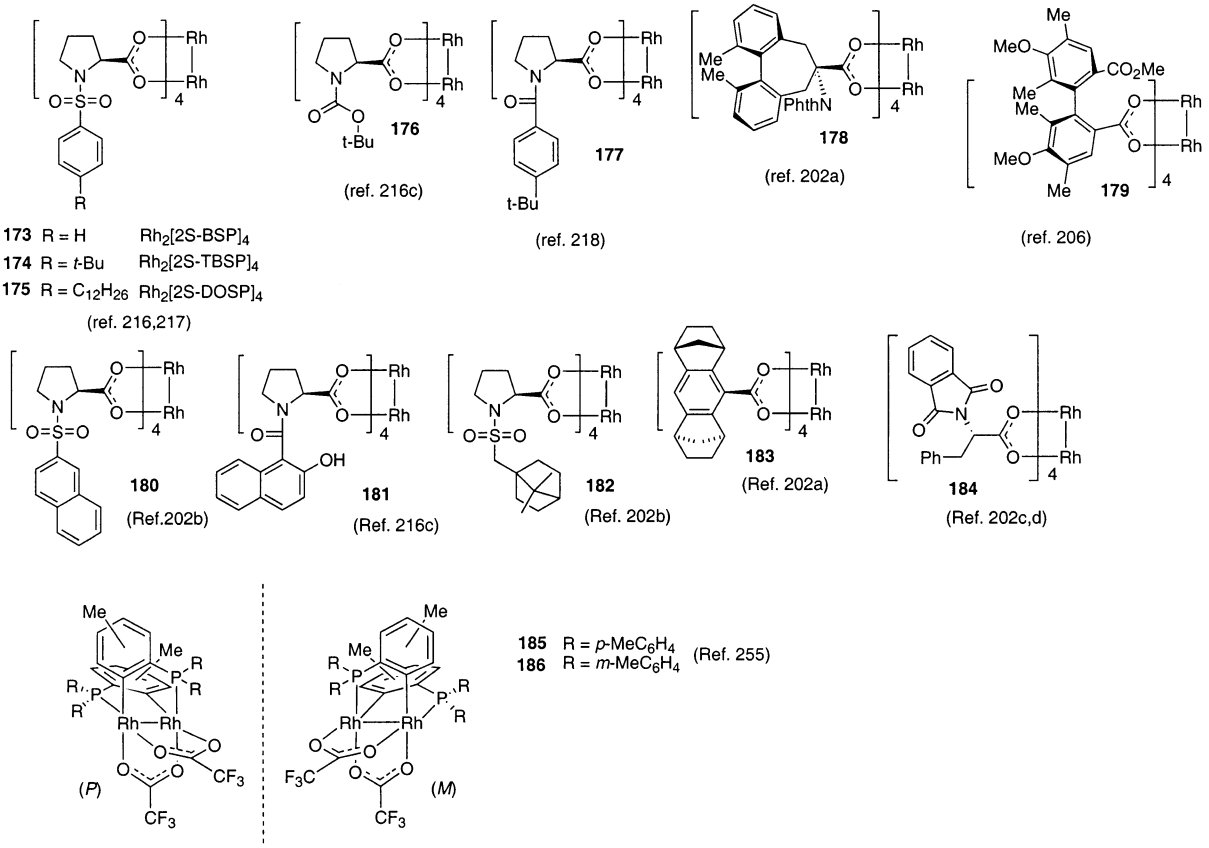
Some examples provided in Table 29[204−208] show that, although the level of enantioselection is sometimes excellent, the diastereocontrol is not very good.

Table 29. Rhodium-Catalyzed Enantioselective Cyclopropanation[204−208]



catalyst	R	yield (%)	ratio *trans*:*cis*	ee *trans*; *cis* (%)
185	Et	40	39:61	75; 87
202	*c*-Hex_2CH	81	46:54	66; >98
179	*d*-Menthyl	100	37:63	45; 99
187	*d*-Menthyl		57:43	24; 91
202	Et	62	31:69	52; 76

Dirhodium(II) Carboxylates



Dirhodium(II) Carboxamidates

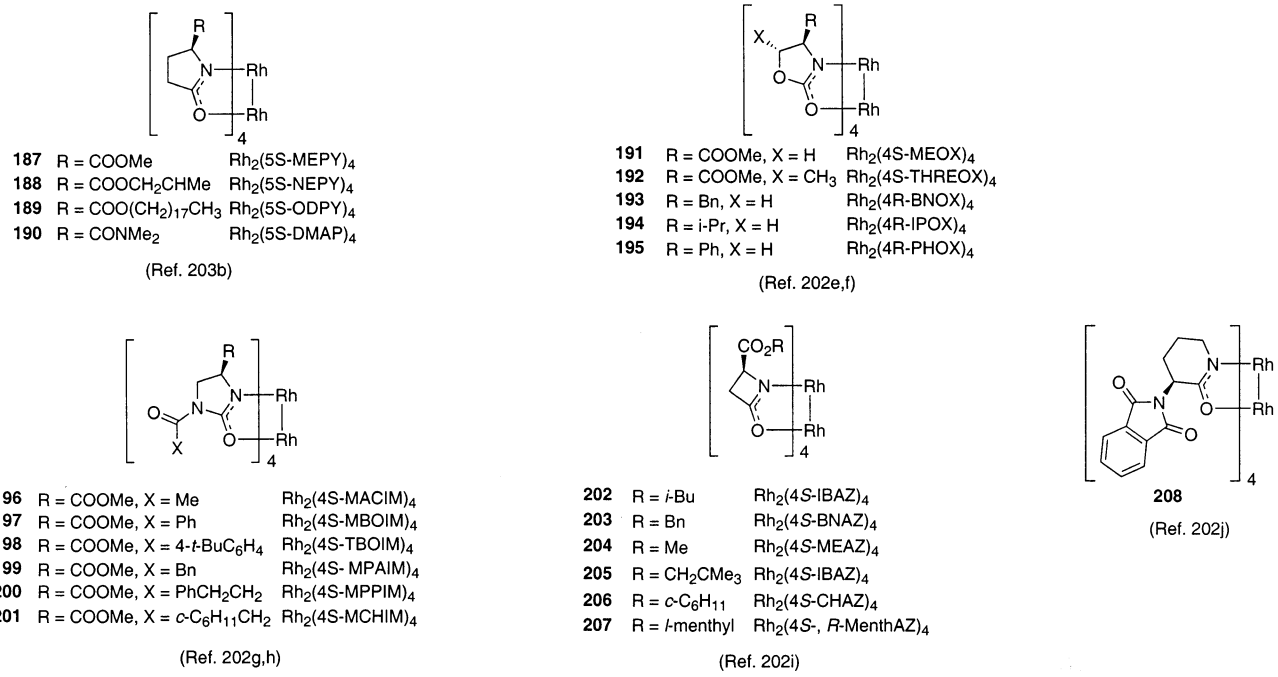
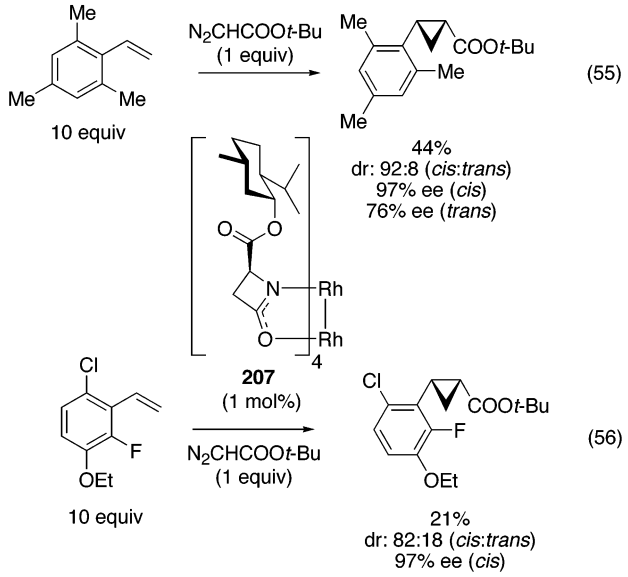


Figure 28. Most common chiral dirhodium catalysts for inter- and intramolecular cyclopropanations.

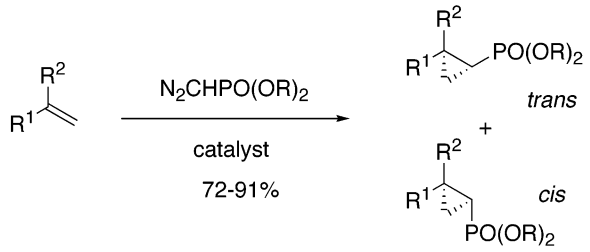
Doyle has recently reported that the novel L-menthyl ester-derived azetidine-ligated dirhodium catalyst **207**[209] led to good *cis* diasteroestereocontrol and excellent enantiocontrol in the cyclopropanation of substituted styrenes with *tert*-butyl diazoacetate (eqs 55 and 56). However, the low yield relative to the alkene makes this method not optimal for the cyclopropanation of complex substituted styrenes.

Very few other diazoalkanes bearing an electron-withdrawing group have been tested in the asym-



metric catalytic cyclopropanation reactions. One of them is the α-diazophosphonate reagent, which was used to make cyclopropylphosphonate derivatives. A large number of chiral catalysts were screened, and both bis(oxazoline)·Cu **143** and Nishiyama's ruthenium catalyst **156** gave satisfactory results (Table 30).[210]

Table 30. Enantioselective Cyclopropanation with α-Diazophosphonate Reagents

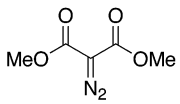


R^1	R^2	R	catalyst	ratio *trans*:*cis*	ee *trans* (%)
Ph	H	Me	**143**	86:14	93
Ph	H	Et	**143**	84:16	92
Ph	H	*i*-Pr	**143**	90:10	92
Ph	H	*i*-Pr	**156**	>98:2	96
4-$MeOC_6H_4$	H	*i*-Pr	**156**	>98:2	94
4-ClC_6H_4	H	*i*-Pr	**15**	>98:2	98
Ph	Me	*i*-Pr	**156**	88:12	95
1-styryl	H	*i*-Pr	**156**	95:5	90

As with the corresponding ester reagents, the best *trans*:*cis* ratios were observed with sterically more hindered phosphonate reagents.

3. Diazoalkanes Bearing Two Electron-Withdrawing Groups ($N_2C(EWG)_2$)

The diazoalkanes bearing two electron-withdrawing groups are substantially less reactive than those described above. For this reason, more active catalysts are required to generate the corresponding metal carbene intermediate. For example, styrene reacts with dimethyl diazomalonate (**209**) in the presence of $Rh_2(4S\text{-}MEAZ)_4$ (**204**) in 97% yield but in only 50% ee.[207] Similarly, styrene reacts with α-nitroester **210** in the presence of **184** in 41% ee (68% yield) and in the presence of **204** in 33% ee (76% yield).[211]



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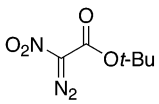
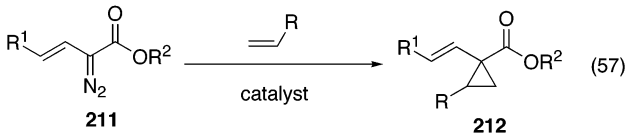


210

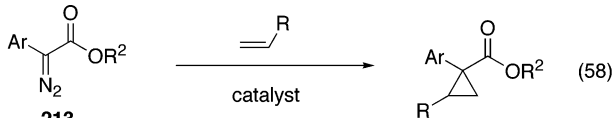
More reactive and enantiodiscriminating catalysts will have to be developed to increase the usefulness of this class of reagents. Furthermore, cyclopropane diesters are available in enantiomerically enriched form in a two-step process from the vinyl-substituted cyclopropane derivatives described in the following section.[212]

4. Aryl- and Vinyldiazoester Reagents

The last class of diazo reagents that has been widely used in asymmetric catalysis and in total synthesis is that of the aryl- and vinyl-substituted diazoester reagents **211** (eq 57) and **213** (eq 58).[213]



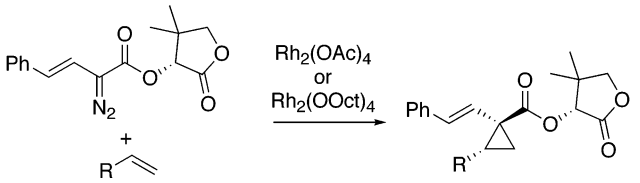
211 **212** (57)



213 **214** (58)

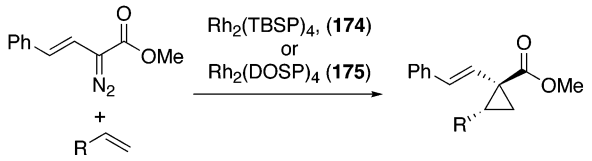
Early reports[214] established that rhodium complexes were the best catalysts for the decomposition of vinyldiazoesters in the presence of alkenes, to lead to the corresponding cyclopropane with a high level of diastereocontrol. The next major finding was the introduction of a simple chiral auxiliary on the ester moiety to generate an enantiomerically enriched product (Table 31).[215] It is quite remarkable that a single diastereomeric cyclopropane derivative is formed preferentially over the other three possible diastereomers.

Table 31. Chiral Auxiliary in the Cyclopropanation of Rhodium-Catalyzed Vinyldiazoester Decomposition



R	dr	yield (%)
Ph	98:2	84
4-ClC_6H_4	>98:2	92
4-$MeOC_6H_4$	>98:2	75
EtO	96:4	71
AcO	95:5	42

Table 32. Enantioselective, Catalytic Synthesis of Vinylcyclopropanes



R	catalyst	ee (%)	yield (%)
Ph	**175**	**98**	68
4-ClC_6H_4	**175**	>**97**	70
4-$MeOC_6H_4$	**175**	**90**	41
AcO	**175**	**95**	26
EtO	**175**	**93**	65
Bu	**174**	>**90**	63
Et	**174**	>**95**	65
i-Pr	**174**	**95**	58
Ph	**215**	**83**	52
Ph	**216**	**63**	>52
Ph	**217**	**98**	>52
Ph	**218**	**68**	>52

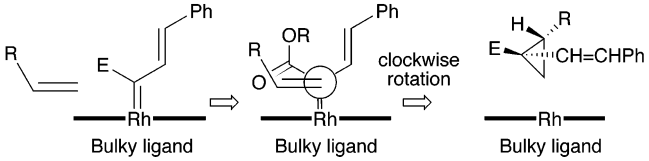


Figure 29. Diastereoselective rhodium-catalyzed cyclopropanation.

The next major breakthrough in this area was the substitution of a chiral auxiliary by chiral ligands on the catalyst. After an extensive catalyst screening, Davies has reported[216] that rhodium prolinate catalysts (**173** and **174**)[217] in nonpolar solvents were the most active ones for this substrate. After catalyst optimization, Davies has shown that $Rh_2(DOSP)_4$ (**175**) provides the highest enantiocontrol for many alkenes (Table 32).[218,219] Complete diastereocontrol is observed in these transformations. However, it should be pointed out that *trans*-disubstituted alkenes do not react under these conditions.

A model has been proposed to explain the diastereo- and enantiofacial selectivity using these rhodium catalysts.[218] The presence of an electron-withdrawing substituent (ester) and an electron-donating substituent (vinyl group) is crucial for high diastereoselectivity. Presumably, the approach by the alkene occurs on the side of the electron-withdrawing group, since metal carbenes lacking this combination of donor/acceptor functionality lead to much lower diastereoselectivities (Figure 29). In principle, the developing positive charge on the most substituted carbon can be stabilized by the oxygen lone pairs of the carboxyl group.

The most reactive flexible ligand arrangement in rhodium prolinate catalysts, responsible for the stereodiscriminating step, is believed to be the D_2-symmetric form.[220] Approach of the alkene from the most accessible trajectories in the orientation shown in Figure 30 correctly predicts the sense of induction in these reactions.

The assumption that the reactive catalyst conformer was that possessing a D_2 symmetry led Davies

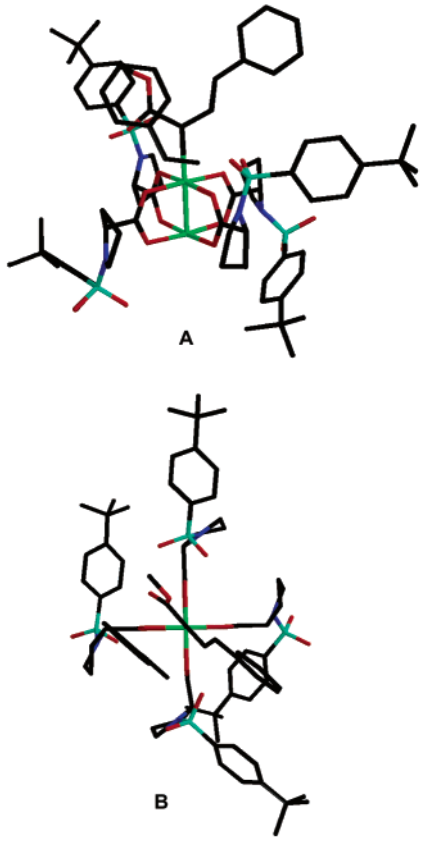
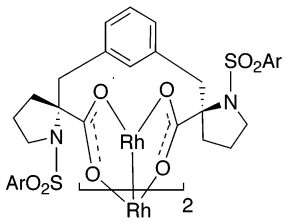


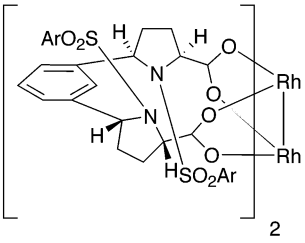
Figure 30. Enantioselective cyclopropanation catalyzed by **175**. (A) Side view; (B) top view.

to design new rhodium(II) dicarboxylates (**215**−**218**) with the prerequisite D_2 symmetry.[221]



Ar = *p*-*t*-BuC_6H_4

215



216, Ar = *p*-*t*-BuC_6H_4
217, Ar = 2,4,6-tri-*i*-PrC_6H_{12}
218, Ar = *p*-$C_{12}H_{25}C_6H_4$

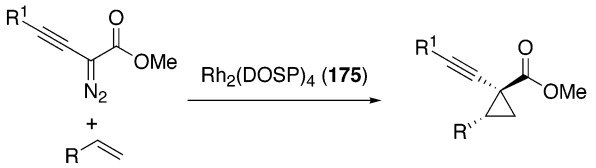
Three of them (**215**, **216**, and **218)** led to lower enantiomeric excesses than those observed with $Rh_2(DOSP)_4$ (**175**), but catalyst **217** was as effective as **175** (Table 32).

The Rh-catalyzed cyclopropanation of alkenes using vinyldiazoesters is synthetically quite useful, and applications of this methodology include an approach to cyclopropane α-amino acids,[222] to cyclopentenes,[223] to 8-oxabicyclo[3.2.1]octene,[224] to 2,3-dihydrofuran,[225] and to 1,4-cycloheptadienes.[226]

Davies has also extended this chemistry to alkynyldiazoacetates (Table 33), which are decomposed nicely with $Rh_2(DOSP)_4$ and lead to alkynyl-substituted cyclopropanes with good to excellent enantiomeric excesses.[227]

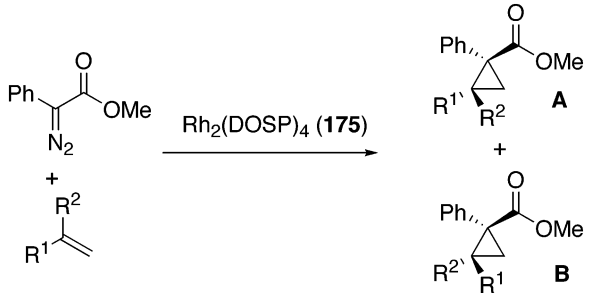
The Rh-catalyzed cyclopropanation of alkenes with aryldiazoester reagents follows the same trends as those found with the vinyl-substituted reagent.[228] In

Table 33. Cyclopropanation with Alkynyldiazoacetate



R^1	R	yield (%)	dr	ee (%)
Ph	Ph	68	92:8	89
Et	Ph	91	99:1	56
TMS	Ph	84	94:6	65
Ph	OBu	66	>97:3	87
Ph	OAc	61	>97:3	95

Table 34. Cyclopropanation Using Phenyldiazoesters

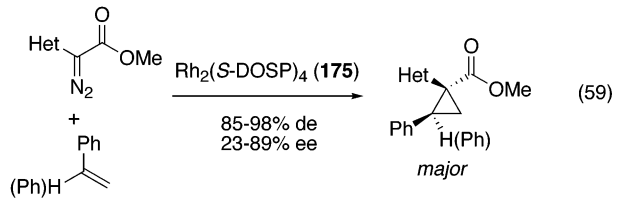


R^1	R^2	yield (%)	ratio **A**:**B**	ee **A** (%)	catalyst
Ph	H	90	98:2	87	**175**
Ph	Ph	83		97	**174**
Ph	Me	88	60:40	85 (81)	**174**
4-ClC_6H_4	H	84	98:2	85	**174**
4-$MeOC_6H_4$	H	82	98:2	88	**174**
Et	H	86	93:7	80	**175**

general, the most practical catalyst to use is Rh_2(DOSP)$_4$ (**175**) or Rh_2(TBSP)$_4$ (**174**).[229] Usually, very good enantio- and diastereocontrol is displayed in these reactions (Table 34).

Quite interestingly, this reaction has been extended to a solid-phase cyclopropanation between phenyldiazoacetate and a resin-bound alkene. The stereoselectivities are almost identical to those observed in solution.[230]

Davies has also extended this chemistry to a wide range of different heteroaryldiazoacetate reagents. Excellent enantio- and diastereoselectivities are usually observed for the Rh_2(DOSP)$_4$-catalyzed reaction with styrene or 1,1-diphenylethylene (eq 59).



(59)

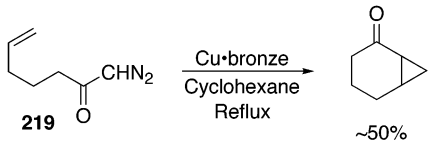
Het = thiophenyl-, furyl-, indolyl-, oxazolyl-, isoxazolyl-benzoxazolyl-, pyridinyl-.

C. Intramolecular Cyclopropanation

When both functionalities—the diazo unit and the alkene—are in the same molecule, an intramolecular cyclopropanation is possible in the presence of the appropriate catalyst, thus producing bicyclic products.[231] In contrast to the intermolecular reaction, only one diastereoisomer is obtained when forming five- or six-membered rings. However, it is important to consider the chemoselectivity, as, in some cases, the C−H insertion may become the major pathway.[232] Indeed, most of the successful systems involve cyclization of either γ,δ-unsaturated diazocarbonyl or δ,ϵ-unsaturated diazocarbonyl systems, leading to fused [3.1.0] or [4.1.0] bicyclic systems. It is also possible to form macrocycles using the intramolecular cyclopropanation reaction, but the diastereoselectivity becomes an issue. As for the intermolecular cyclopropanation with diazo reagents, this section is organized to present the best catalytic systems by focusing on the more recent disclosures, rather than being an exhaustive review of all the possible methods. Diazocarbonyl compounds in intramolecular processes can be divided in three major categories: diazoketones, diazoester, and diazoacetamide derivatives. Copper and rhodium catalysts are generally suitable, and their efficiency, especially for the enantiocontrol, will be compared for each class of substrates.

1. Diastereoselective Intramolecular Cyclopropanation of Chiral Substrates

The first intramolecular cyclization of an unsaturated diazocarbonyl compound that formed a cyclopropane unit was reported in 1961 by Stork and Ficini, when diazoketone substrate **219** was cyclized in the presence of a catalytic amount of copper (eq 60).[233]

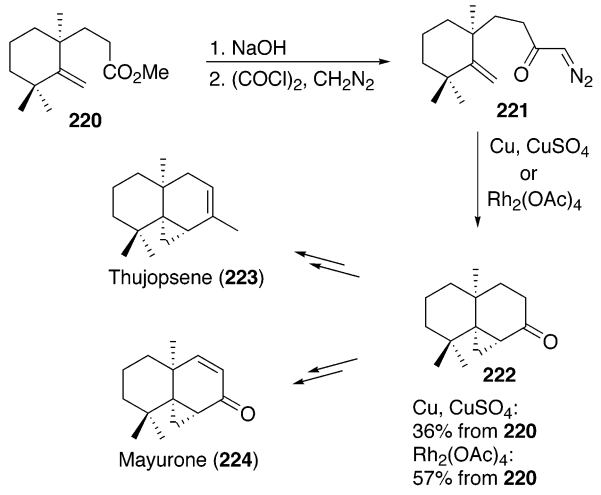


(60)

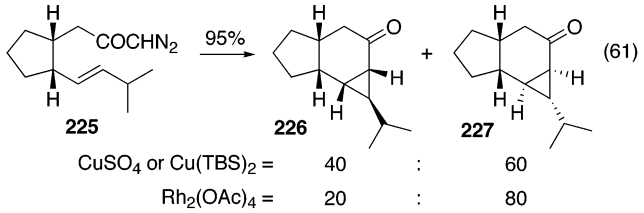
A variety of intramolecular cyclopropanation reactions of olefin-containing diazoketones have followed this seminal discovery. Initially, the reaction was catalyzed by heterogeneous copper catalysts such as copper powder, copper bronze, or cupric sulfate. These catalysts are still used today, although homogeneous copper and rhodium catalysts are more popular. This reaction has been widely used to synthesize terpenes.[234] With an appropriate chiral substrate, the cyclopropanation proceeds generally with complete stereocontrol, leading to the exclusive formation of one stereoisomeric bicyclic product. For instance, the cyclopropanation of diazoketone **221** in the presence of copper or rhodium catalyst led to the formation of bicyclic cyclopropane **222** as a single diastereoisomer (Scheme 10). Dihydromayurone **222**, that has been prepared using this strategy in both racemic[235] and enantiomerically pure[236] forms, was a useful chiral synthon for the preparation of sesquiterpenes such as thujopsene (**223**) and mayurone (**224**).

Sarkar has described the synthesis of the tricarbocyclic framework of oreodaphnenol using a highly diastereoselective rhodium-catalyzed intramolecular cyclopropanation.[237] Initial attempts to induce the

Scheme 10. Intramolecular Cyclopropanation as a Key Step in the Synthesis of Sesquiterpenes

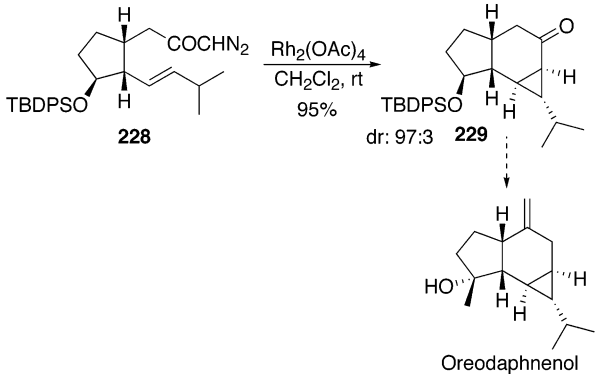


cyclization of diazoketone **225** with copper catalysts led to formation of a 40:60 mixture of diastereoisomers, while $Rh_2(OAc)_4$ improved the selectivity to 20:80 (95%) (eq 61).



However, when the silylated protected alcohol **228** and the rhodium catalyst were used, the diastereoselectivity in the cyclopropanation reaction improved dramatically, thus producing the desired product in 95% yield and with 97:3 diastereoselectivity, favoring **229** (Scheme 11).

Scheme 11. Intramolecular Cyclopropanation of 228 en Route to the Synthesis of Oreodaphnenol



The stereochemical outcome is consistent with the most favorable transition-state model **A**, that minimizes the 1,3-allylic strain (Figure 31). The presence of the bulky TBDPS group increases the diastereomeric ratios.

Systems that are less rigid may afford a mixture of stereoisomers, as shown by Taber in the synthesis of prostaglandin derivatives.[238] Indeed, the intramolecular cyclopropanation of diazoketone **230**, catalyzed by rhodium(II) octanoate dimer, yielded a mixture of diastereoisomers **231** and **232** (eq 62).

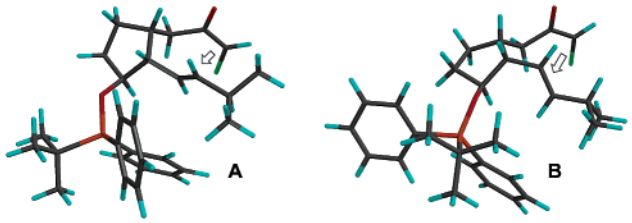
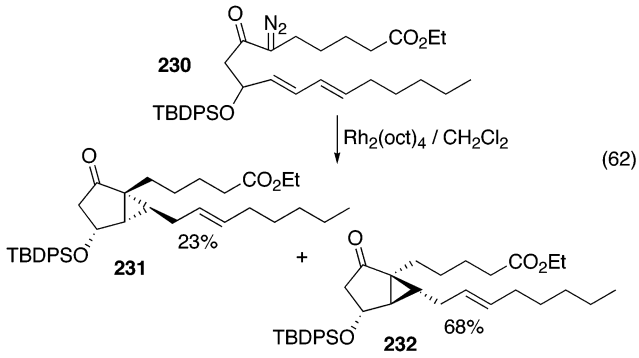
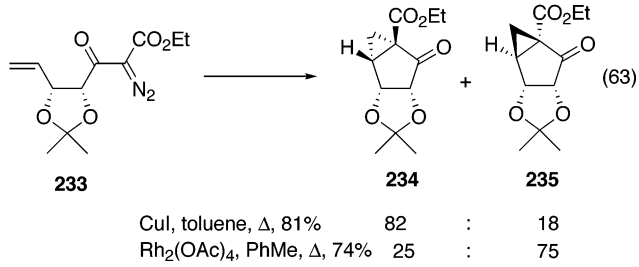


Figure 31. Transition-state models for the intramolecular cyclopropanation of **228**.



Ester-substituted diazoketones have also been extensively used in the intramolecular cyclopropanation.[239] For instance, carbocyclic nucleoside precursors have been prepared this way from ribose derivative **233** (eq 63).[240] The selectivity is catalyst

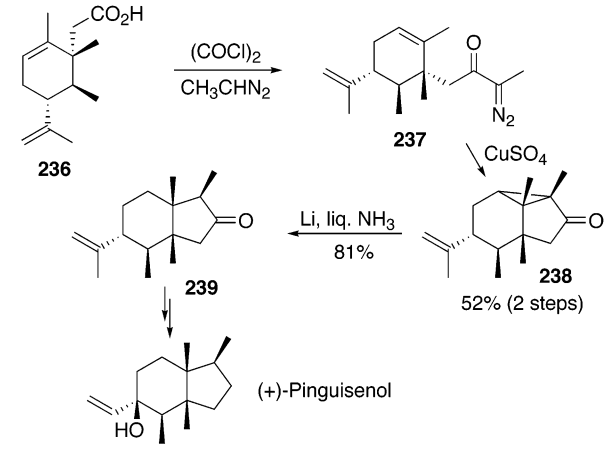


dependent, as the copper catalyst provides an 82:18 mixture of diastereoisomers, favoring **234**. In contrast, $Rh_2(OAc)_4$ produced diastereoisomer **235** with a 75:25 selectivity.

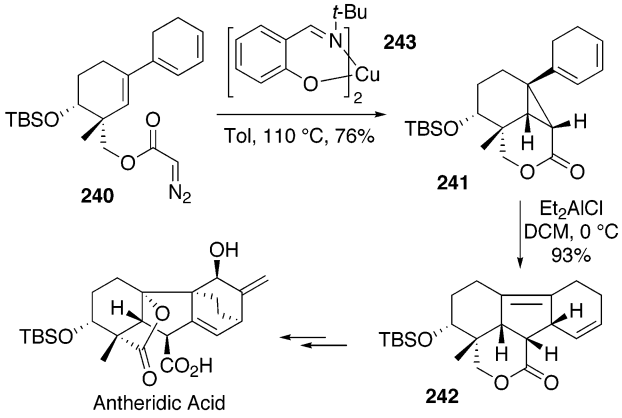
The α-ketocyclopropanes could be further manipulated through carbonyl functionalization or cyclopropane ring opening. Typically, they are more reactive and more versatile than the corresponding cyclopropyllactones, derived from diazoesters. As an example, Srikrishna has recently disclosed the total synthesis of (+)-pinguisenol, a sesquiterpene that contains two vicinal quaternary carbon atoms and four *cis*-oriented methyl groups (Scheme 12).[241,242] The key step to construct the bicyclic system was based on the intramolecular cyclopropanation of diazoketone **237**, followed by regioselective cyclopropane cleavage, resulting in the introduction of the requisite contiguous four *cis*-methyl groups to provide the intermediate **239**.

The combination of the intramolecular cyclopropanation of dienes with the vinylcyclopropane−cyclopentene rearrangement has been employed as a key

Scheme 12. Total Synthesis of Pinguisenol, Featuring an Intramolecular Cyclopropanation Reaction

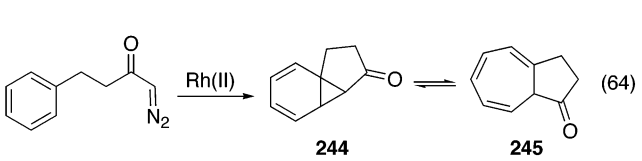


Scheme 13. Corey's Antheridic Acid Synthesis



step in the total synthesis of triquinanes.[5−7] Corey has also used this strategy in the total synthesis of antheridic acid (Scheme 13). The intramolecular cyclopropanation of the diazoacetate **240**, catalyzed by copper(II) bis(salicylaldehyde)*tert*-butylimine catalyst **243**, provided the cyclopropyllactone **241**, which upon treatment with a Lewis acid afforded the key intermediate **242** en route to antheridic acid.

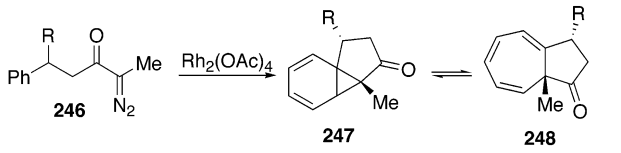
The intramolecular version of the cyclopropanation of aromatic derivatives with diazo reagents, known as the Buchner reaction,[243] has also been reported with copper and rhodium catalysts, the latter being the most efficient. Usually the cyclopropanation product **244** is in dynamic equilibrium with the corresponding cycloheptatriene **245**, which is the more stable tautomer (eq 64).



(64)

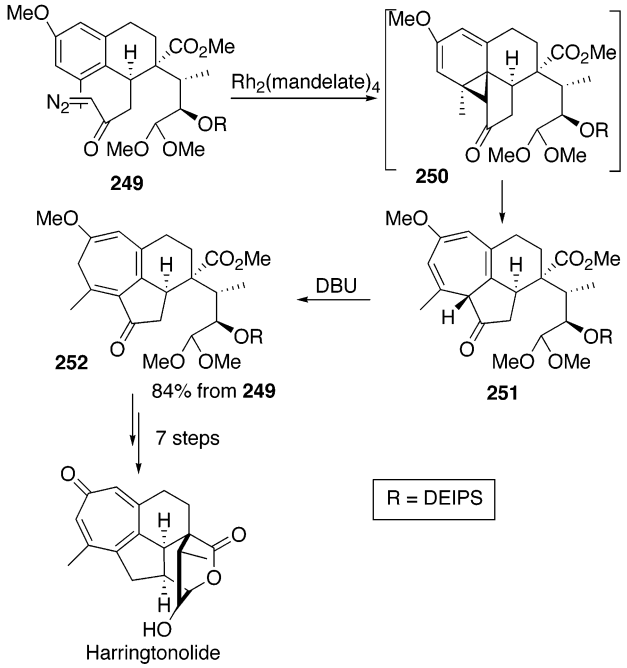
Maguire recently investigated the diastereoselectivity in the intramolecular cyclization of chiral α-diazoketone derivatives of general structure **246**.[244,245] The ratio of diastereoisomers increased as the size of the *β*-substituent increased from Me to

Table 35. Intramolecular Cyclopropanation of Aromatic Derivatives 246



entry	R	yield (%)	ratio
1	Me	87	89:11
2	Et	80	96:4
3	*n*-Pr	74	97:3
4	*n*-Bu	74	98:2
5	*i*-Pr	70	>98:2
6	*t*-Bu	72	>98:2

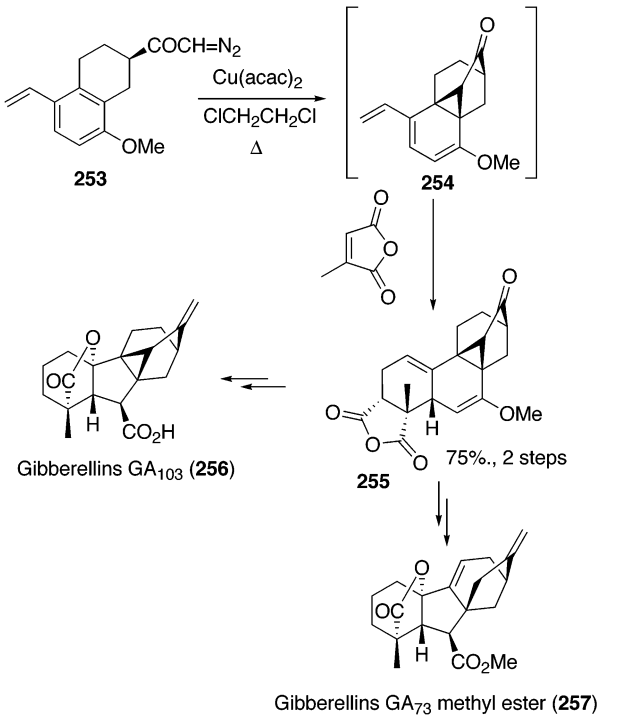
Scheme 14. Buchner Cyclization of Harringtonolide's Precursor 249



Et, Pr, and Bu (Table 35). While an 89:11 mixture was obtained with the methyl group, only a single diastereoisomer could be detected with the isopropyl- and *tert*-butyl-substituted ketones. In all cases, the formation of the *trans* diastereoisomer was favored. The two azulenone products, the norcaradienes (**247**) and the cycloheptatrienes (**248**), are in rapid equilibrium. The cyclopropane derivative can be trapped as a Diels−Alder adduct when reacted with 4-phenyl-1,2,4-triazoline-3,5-dione. Similar trends in the diastereoselectivities were observed with a range of diazoketones bearing methoxy-substituted aryl rings.[246] However, a more complex dynamic equilibrium is observed in the cyclization products via rearrangements of the methoxy-substituted norcaradienes.

The Buchner cyclization has also been exploited in the context of the synthesis of complex polycyclic natural products.[247] For instance, Mander has shown that this strategy was very efficient for the synthesis of 5,7-fused rings of the harringtonolide (Scheme 14).[248] The rhodium-catalyzed cyclopropanation of

Scheme 15. Mander's Gibberellin Derivative Synthesis

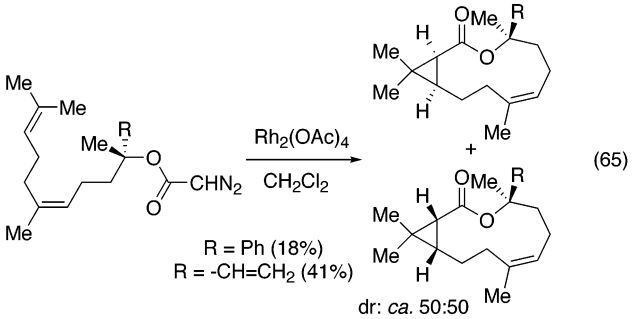


249 led to the formation of the intermediate **250**, which rearranges rapidly to the labile cycloheptatriene **251**, which is then converted to the more stable product **252**.

Furthermore, the same author has described the total synthesis of gibberellin derivatives (**256** and **257**) using a similar strategy (Scheme 15).[249] The cyclopropanation reaction of substrate **253** was best performed in the presence of a copper catalyst that minimizes the formation of byproducts.

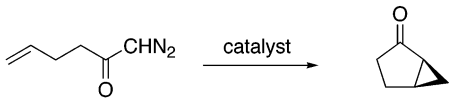
It was observed that rhodium catalysts led to significant amounts of a C−H insertion product. The cyclopropane adduct **254** was not isolated but reacted with citraconic anhydride to furnish the cycloadduct **255** in 75% yield for the two-step process. Subsequent studies led to the synthesis of gibberellins GA_{103} (**256**) and gibberellins GA_{73} methyl ester (**257**) in 8 and 12 steps, respectively, from **255**.

It is also possible to form macrocycles using the transition metal-catalyzed cyclopropanation reaction.[250] The diastereoselectivities are usually quite modest when a chiral precursor is cyclized upon treatment with a catalytic amount of $Rh_2(OAc)_4$ (eq 65).[251]



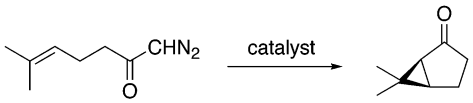
(65)

Table 36. Enantioselective Cyclopropanation of 1-Diazo-5-hexen-2-one



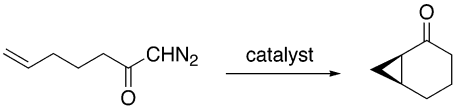
entry	catalyst	solvent	yield (%)	ee (%)
1	**258**	CH_2Cl_2	84	5
2	**194**	CH_2Cl_2	85	23
3	**149**	CH_2Cl_2		25
4	**139**	$ClCH_2CH_2Cl$	50	75
5	(*P*)-**185**	pentane	90	74
6	(*P*)-**185**	CH_2Cl_2	96	65
7	(*P*)-**186**	pentane	96	87
8	(*P*)-**186**	CH_2Cl_2	98	64

Table 37. Enantioselective Cyclopropanation of 1-Diazo-5-methyl-5-hepten-2-one



entry	catalyst	solvent	yield (%)	ee (%)
1	**258**	CH_2Cl_2	91	75
2	**191**	CH_2Cl_2	80	27
3	**149**	CH_2Cl_2	51	63
4	**139**	$ClCH_2CH_2Cl$	58	85
5	(*P*)-**185**	pentane	99	80
6	(*P*)-**185**	CH_2Cl_2	99	52
7	(*P*)-**186**	pentane	99	70
8	(*P*)-**186**	CH_2Cl_2	99	58

Table 38. Enantioselective Cyclopropanation of 1-Diazo-6-hepten-2-one

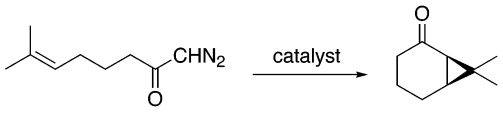


entry	catalyst	solvent	yield (%)	ee (%)
1	**187**	CH_2Cl_2	58	6
2	**139**	$ClCH_2CH_2Cl$	57	95
3	(*P*)-**185**	pentane	96	90
4	(*P*)-**185**	CH_2Cl_2	85	87
5	(*P*)-**186**	pentane	90	95
6	(*P*)-**186**	CH_2Cl_2	92	89

2. Enantioselective Intramolecular Cyclopropanation: Chiral Catalysts

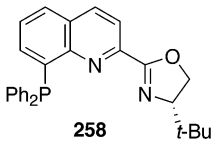
Chiral catalysts have been studied for the enantioselective intramolecular cyclopropanation of unsaturated diazoketones. Until recently, semicorrin copper complex **139**, developed by Pfaltz, was the most efficient catalyst for enantiocontrol.[252] Up to 95% ee was obtained, depending on the substrate, although the yields were always modest (<60%) (Tables 36 and 37, entry 4; Table 38, entry 2; Table 39, entry 3). In comparison, rhodium carboxamide catalysts led to a low level of induction (Tables 36 and 37, entry 2; Tables 38 and 39, entry 1).[253] Neither the chiral biferrocene-based bis(oxazoline) copper complex **149**[254] (Tables 37 and 38, entry 3; Table 39, entry 2) nor the ruthenium complex derived from 8-diphenylphosphino-2-oxazolinylquinoline **258**[255] (Tables 36 and 37, entry 1) provided any significant improvement, the

Table 39. Enantioselective Cyclopropanation of 1-Diazo-7-methyl-6-octen-2-one



entry	catalyst	solvent	yield (%)	ee (%)
1	**187**	CH_2Cl_2	76	17
2	**149**	CH_2Cl_2	12	64
3	**139**	$ClCH_2CH_2Cl$	50	14
4	(*P*)-**185**	pentane	93	80
5	(*P*)-**185**	CH_2Cl_2	67	63
6	(*P*)-**186**	pentane	69	80
7	(*P*)-**186**	CH_2Cl_2	51	63

former suffering from low reactivity and the latter being less selective.



258

$[RuCl_2p\text{-cymene}]_2$

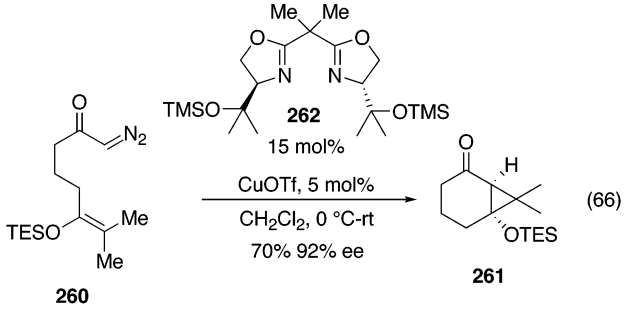
A major breakthrough came recently from the group of Lahuerta, who disclosed that the use of dirhodium(II) complexes **185** and **186**, that contain ortho-metalated aryl phosphine ligands, provide the desired cyclopropane products in very high yield (>90%) and with enantioselectivities that are comparable to those reported by Pfaltz.[256,257] The enantiomeric excesses are significantly dependent on the solvent used, the best being pentane.

[3.1.0] Bicyclic systems were best obtained in 96−99% yield and with 80−87% ee (Tables 36 and 37). In comparison, the formation of [4.1.0] bicyclic products proceeded in 90−96% yield and with 80−95% ee (Tables 38 and 39).

The cyclization of 1-diazo-7-methyl-6-octen-2-one also provided between 7 and 49% of the allylic insertion product, in addition to the cyclopropanation adduct.

The amount of the byproduct can be minimized by using catalyst **185** in pentane. Just like most dirhodium carboxylate complexes that are typically prepared from rhodium acetate and carboxylic acids,[141] dirhodium complexes derived from ortho-metalated arylphosphines **259** are readily obtained as a racemic mixture by the thermal reaction between rhodium acetate dimer and arylphosphines.[258] They were resolved as proline derivatives by column chromatography, and subsequent ligand exchange with trifluoroacetic acid led to the desired catalysts **185** and **186** as pure enantiomers (Scheme 16).

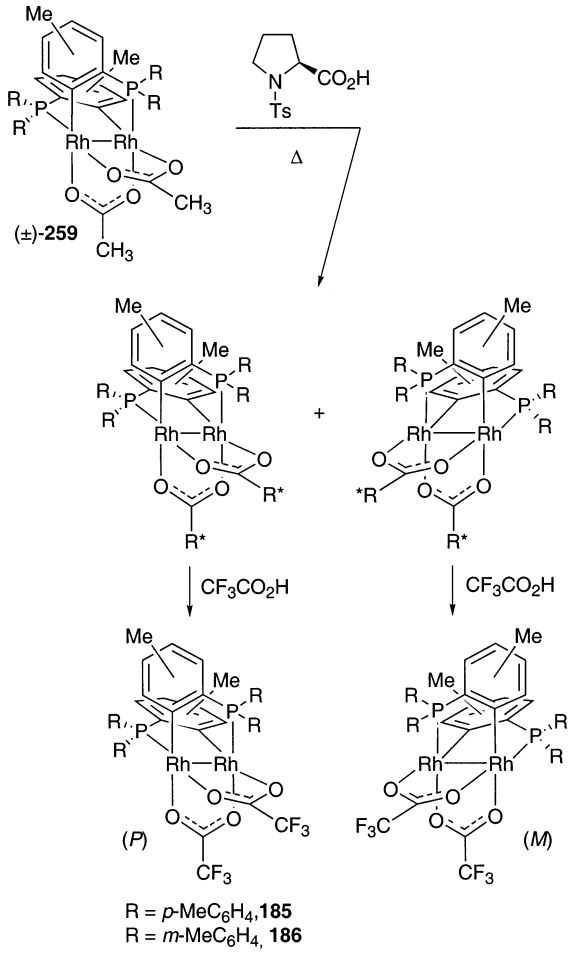
Some specific examples of enantioselective intramolecular cyclopropanation of diazoketones have also been disclosed. Shibasaki has described the synthesis of the phorbol CD-ring skeleton through the asymmetric intramolecular cyclopropanation of silyl enol ether **260**.[259] He found that, after optimization, the desired cyclized product **261** was obtained in 92% ee and 70% yield when 15 mol % of the bis(oxazoline) ligand **262** and 5 mol % of copper triflate were used (eq 66).



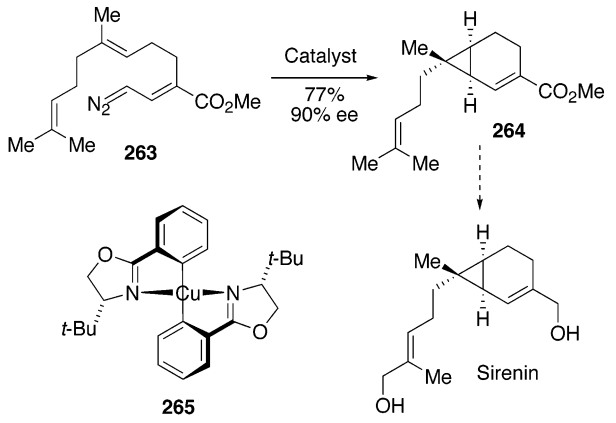
Corey has reported a rare example of an intramolecular cyclopropanation involving a γ-diazocarbonyl derivative.[260] The cyclization of vinyldiazomethane **263** to bicyclic system **264**, a synthetic precursor of sirenin, was studied using various catalysts (Scheme 17). The best-known catalyst produced the desired cyclic compound in 60% ee (copper semicorrin **143)**. To overcome this problem, Corey designed a novel bis(oxazoline) **265** that yielded the desired cyclopropane **264** with 90% ee.

The intramolecular cyclopropanation of diazoacetates bearing an alkene unit is also a very well-known reaction that has found numerous applications in synthesis. The cyclization of unsaturated diazoacetates can be divided into two types: Type A is the most common one and involves the formation

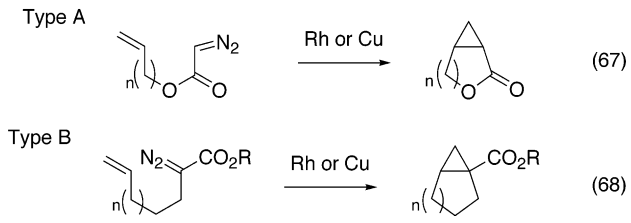
Scheme 16. Preparation of Dirhodium Catalysts 185 and 186



Scheme 17. Corey Sirenin's Synthesis



of a lactone (eq 67). Type B leads to the formation of a cyclopropanecarboxylate (eq 68).

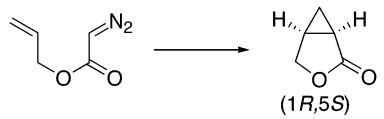


The cyclopropanation reactions of type B are not common, and no chiral catalyst is effective.[261] Conversely, cobalt, copper, rhodium, and ruthenium catalysts have been developed for the intramolecular cyclopropanation of type A. The effectiveness of each catalyst changes with the substitution[262] and the ring size of the fused cyclopropane. In general, dirhodium(II) carboxamidate catalysts are superior for small-ring-fused cyclopropane compounds, whereas the bis(oxazoline)ligated copper(I) catalysts produce higher yields and enantiomeric excesses in the cyclopropanation, leading to medium/large rings. Ruthenium and cobalt catalysts are useful in the synthesis of trisubstituted cyclopropanes, but their use is limited to the intramolecular cyclopropanation involving the formation of small rings (five and six members) (vide infra).

For instance, the best results for the intramolecular cyclopropanation of the simplest case, allyl diazoacetate, were obtained with $Rh_2(5S\text{-MEPY})_4$ (**187**) and $Rh_2(4S\text{-MEOX})_4$ (**191**), that provided the desired 3-oxabicyclo[3.1.0]hexan-2-one with up to 95% yield and 95% ee (Table 40).[263]

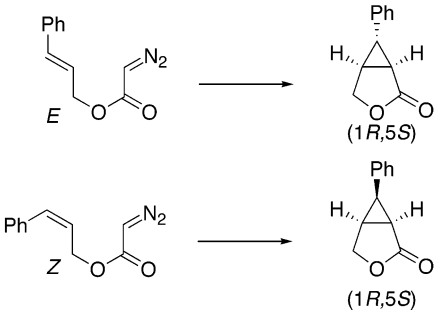
The dirhodium(II) azetidinonecarboxylates were less selective,[208] whereas low stereochemical induction was observed with ruthenium[146a] or copper catalysts. The enantioselectivity is dependent on the double bond substitution, as illustrated in Table 41. Indeed, $Rh_2(5S\text{-MEPY})_4$ (**187**) afforded only 68% ee with the (*E*)-(phenyl)allyl diazoacetate. However, the use of *N*-acylimidazolidinone-ligated catalysts, such as $Rh_2(4S\text{-MPPIM})_4$ (**200**), produced the desired bicyclic systems with greater than 95% ee.[264] In comparison, ruthenium catalysts[265] furnished the product with 82−89% ee, and very low enantioselectivities were observed with copper catalysts.

Table 40. Enantioselective Intramolecular Cyclopropanation of Allyl Diazoacetate



catalyst	yield (%)	ee (%)
$Rh_2(5S\text{-MEPY})_4$ (**187**)	75	95
$Rh_2(4S\text{-MEOX})_4$ (**191**)	95	94
$Rh_2(4S\text{-IBAZ})_4$ (**202**)	92	80
Ru(II) porphyrin (**159**)	45	24
$CuPF_6$/**143**	61	20

Table 41. Enantioselective Intramolecular Cyclopropanation of Phenyl-Substituted Allyl Diazoacetates

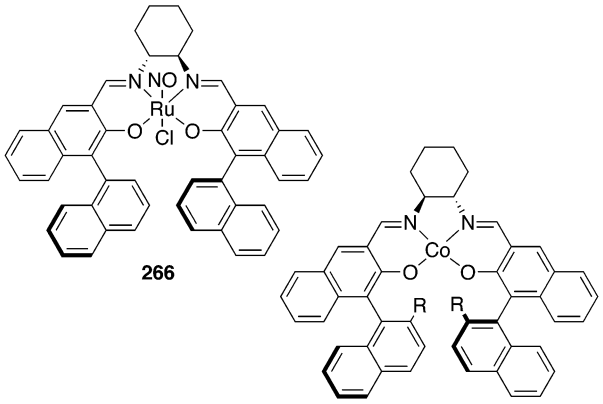


catalyst	*E*/*Z*	yield (%)	ee (%)
$Rh_2(5S\text{-MEPY})_4$ (**187**)	*E*	78	68
$Rh_2(4S\text{-MPPIM})_4$ (**200**)	*E*	61	96
Ru(II) (pybox) (**156**)	*E*	83	86[a]
Ru(II) (pybox) (**157**)	*E*	72	89[a]
Ru(II) porphyrin (**159**)	*E*	60	85
Ru(II) (salen) (**266**)	*E*	54	82
Co(II) (salen) (**267**)	*E*	67	97
Co(II) (salen) (**268**)	*E*	75	95
$CuPF_6$/**143**	*E*	77	4
$Rh_2(5S\text{-MEPY})_4$ (**187**)	*Z*	70	≥94
Ru(II) (pybox) (**156**)	*Z*	79	24
Ru(II) porphyrin (**159**)	*Z*	24	53
Ru(II) (salen) (**266**)	*Z*	24	14
Co(II) (salen) (**267**)	*Z*	16	74
Co(II) (salen) (**268**)	*Z*	24	68

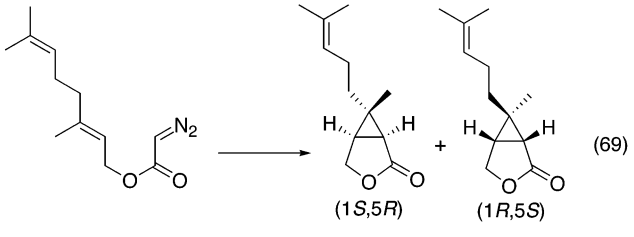
[a] (1*S*,5*R*) Isomer was obtained.

Katsuki developed a series of salen ruthenium and cobalt catalysts that proved to be very efficient for the intramolecular cyclopropanation of (*E*)-alkenyl diazoacetate.[266] For example, the cyclopropanation of (*E*)-(phenyl)allyl diazoacetate proceeded in 97% and 95% ee with catalysts **267** and **268**, respectively.

None of the other reported catalysts were as effective for the intramolecular cyclopropanation of *Z*-substituted allyl acetates, which are obtained consistently with high levels of enantiocontrol. Excellent enantioselectivities were also observed in the intramolecular cyclopropanation of trisubstituted double bonds. In addition, the cyclopropanation of geranyl diazoacetate with $Rh_2(5S\text{-MEPY})_4$ (**187**) revealed that γ-lactone formation was exclusive when other double bonds were present in the substrate.[267] Similar results were recently obtained by Scott, using a ruthenium(II) Schiff base complex (**162**) as catalyst,

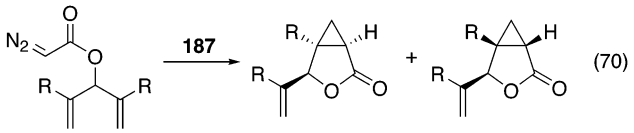


with the exception that slow addition of the substrate was not required (eq 69).[192]



Rh_2(5*S*-MEPY)$_4$ (**187**): 79%, 93% ee (1*S*,5*R*)
Ru(II)schiff base complex **162**: 98%, 85% ee (1*R*,5*S*)

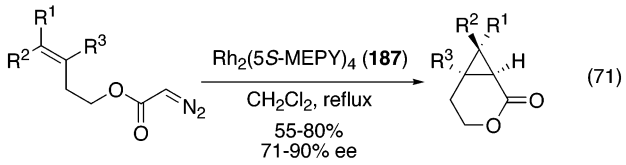
A number of 1,2,3-trisubstituted cyclopropanes were prepared through the enantioselective Rh_2(5*S*-MEPY)$_4$ (**187**)-catalyzed cyclization of allylic diazoacetates with high enantiomeric excesses and have been studied as conformationally restricted peptide isosteres.[268] During the course of this study, Martin has reported that prochiral secondary divinyl diazoacetates undergo cyclopropanation with exceptional enantiocontrol and with moderate to high diastereocontrol (eq 70).[269]



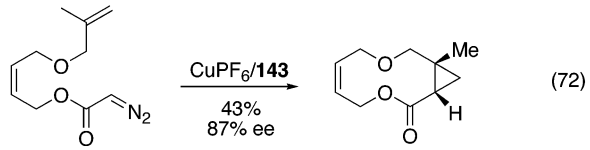
R = H	75%	>95 (≥94% ee)	:	<5
R = Me	73%	45 (92% ee)	:	55 (91% ee)

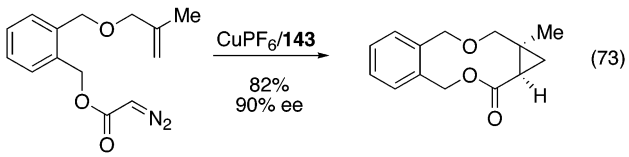
In general, homoallylic diazoacetates afforded the bicyclic products with slightly lower enantiomeric excesses when Rh_2(5*S*-MEPY)$_4$ (**187**) was used, and the enantioselectivity was not highly dependent on the substitution pattern of the double bond (eq 71).[270] Similar levels of enantiocontrol were observed with Rh_2(4*S*-MEOX)$_4$ (**191**), whereas Rh_2(4*S*-MPPIM)$_4$ (**200**) provided lower enantiomeric excesses.

It is interesting to note that copper catalysts, such as the $CuPF_6$/**143** complex, provided a better enantiocontrol for homoallylic diazoacetate (42% ee) than for allylic diazoacetate (20% ee), although the enantioselectivity was far from practical. However, as the

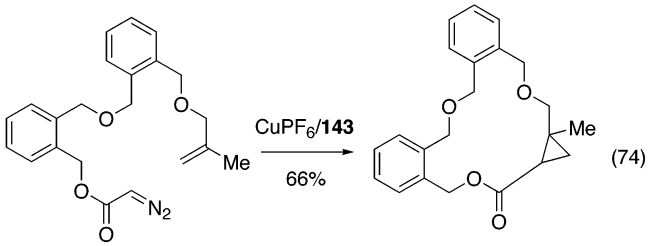


ring size increases, the enantioselectivity increases significantly with the $CuPF_6$/**143** complex, whereas the enantioselectivity decreases with dirhodium(II) carboxamides.[271] Indeed, the formation of 10-membered rings in the presence of the $CuPF_6$/**143** complex proceeded with 87−90% ee (eqs 72 and 73).[272] In addition, the $CuPF_6$/**143** complex has a different chemoselectivity than Rh_2(5*S*-MEPY)$_4$ (**187**), favoring exclusively the macrocyclic product over the allylic cyclopropanation product (eq 72).





Comparable enantiomeric excesses were obtained for the synthesis of 15- and 20-membered ring-fused cyclopropane products, although a mixture of *cis* and *trans* isomers was observed (eq 74).

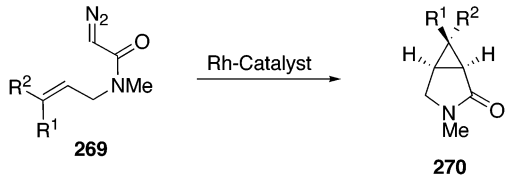


cis:*trans* 69:31
trans: 85% ee

In all macrocyclic cyclizations, the $CuPF_6$/**143** complex was superior to dirhodium(II) carboxamide catalysts. This is not too surprising, since the formation of a macrocycle is similar to intermolecular cyclopropanation, for which copper catalysts usually provide higher enantiomeric excesses. Doyle has also proposed that the selectivity for the catalyst reflects the divergent trajectories of the carbon−carbon double bond to the reacting carbene center.

The enantiocontrol for the intramolecular cyclopropanation of allylic and homoallylic diazoacetamides with dirhodium(II) carboxamide catalysts is similar to that found with allylic and homoallylic diazoacetates.[273,274] The use of a methyl nitrogen substituent favored the desired s-*trans* conformer, in addition to minimizing the amount of the undesired dipolar addition reaction. With substrate **269**, enantiomeric excesses between 93 and 95% could be achieved when Rh_2(5*S*-MEPY)$_4$ (**187**) or Rh_2(4*S*-MPPIM)$_4$ (**200**) was used (Table 42). The homoallylic

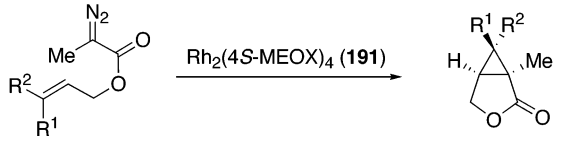
Table 42. Enantioselective Intramolecular Cyclopropanation of Allylic Diazoacetamides 269



269 270

R^1	R^2	catalyst	yield (%)	ee (%)
H	H	Rh_2(5*S*-MEPY)$_4$ (**187**)	62	93
H	H	Rh_2(4*S*-MPPIM)$_4$ (**200**)	20	75
Me	Me	Rh_2(4*S*-MPPIM)$_4$ (**200**)	88	94
n-Pr	H	Rh_2(4*S*-MPPIM)$_4$ (**200**)	88	95
H	*n*-Pr	Rh_2(4*S*-MPPIM)$_4$ (**200**)	93	92
Me	$Me_2C{=}CH(CH_2)_2{-}$	Rh_2(4*S*-MPPIM)$_4$ (**200**)	95	93

Table 43. Intramolecular Cyclopropanation of α-Substituted Diazoacetates



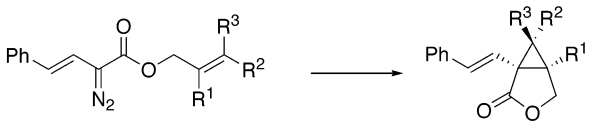
R^1	R^2	yield (%)	ee (%)
Me	Me	81	71
n-Pr	H	62	85
Ph	H	65	78
H	*n*-Pr	46	52
H	Ph	70	43

diazoacetamide provided the bicyclic product, with slightly lower enantiomeric excesses.

A few unsaturated α-substituted diazoacetates have been tested in intramolecular cyclopropanation reactions. Depending on the electronic nature of the substituents, rhodium or copper catalysts were used. When the substituent is an alkyl such as methyl, dirhodium(II) carboxamidate systems are still effective at catalyzing the cyclopropanation reaction. Doyle has shown that Rh_2(4*S*-MEOX)$_4$ (**191**) provided the best enantiocontrol, leading to the desired cyclopropanes with 71−85% ee for the *trans* isomers and 43−52% ee for the *cis* isomers (Table 43).[275]

The diazo decomposition of vinyl- and aryl-substituted diazoacetates requires a more reactive catalyst. Davies and Doan made a breakthrough in this area by disclosing that dirhodium tetracarboxylates [such as Rh_2(*R*-DOSP)$_4$ (**175**)] are effective for the decomposition of these diazoacetate reagents to carbenoid intermediates (Table 44).[276] More recently, Doyle has reported that dirhodium(II) azetidinonecarboxylate catalysts [such as Rh_2(4*S*-IBAZ)$_4$ (**202**) and Rh_2(4*S*-MEAZ)$_4$ (**204**)] enhance the reactivity toward diazo decomposition and are also effective for the intramolecular cyclopropanation of unsaturated vinyl- and aryl-substituted diazoacetates.[277] For instance, the cyclization of allyl-α-styryl-α-diazoacetate proceeded in 81% yield and with 28% ee when Rh_2(*R*-DOSP)$_4$ (**175**) was used, whereas 58 and 59% ee's were observed when Rh_2(4*S*-IBAZ)$_4$ (**202**) and Rh_2(4*S*-MEAZ)$_4$ (**204**) were used, respectively. The latter catalysts have not been tested with more substituted

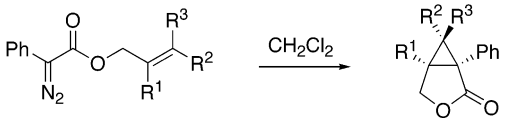
Table 44. Enantioselective Intramolecular Cyclopropanation of α-Styryl-α-diazoacetates



R^1	R^2	R^3	catalyst	yield (%)	ee (%)
H	H	H	Rh_2(*R*-DOSP)$_4$ (**175**)	81	28
H	H	H	Rh_2(4*S*-IBAZ)$_4$ (**202**)	59	58[a]
H	H	H	Rh_2(4*S*-MEAZ)$_4$ (**204**)	56	59[a]
H	Me	H	Rh_2(*S*-DOSP)$_4$ (**175**)	54	25
H	H	Me	Rh_2(*S*-DOSP)$_4$ (**175**)	72	72
H	H	Et	Rh_2(*S*-DOSP)$_4$ (**175**)	56	69
H	Me	Me	Rh_2(*S*-DOSP)$_4$ (**175**)	62	74
Me	H	H	Rh_2(*S*-DOSP)$_4$ (**175**)	53	87
Me	Me	H	Rh_2(*S*-DOSP)$_4$ (**175**)	68	45
Me	Me	Me	Rh_2(*S*-DOSP)$_4$ (**175**)	46	60

[a] (1*R*,5*S*) Isomer was obtained.

Table 45. Enantioselective Intramolecular Cyclopropanation of (Phenyl)diazoacetates



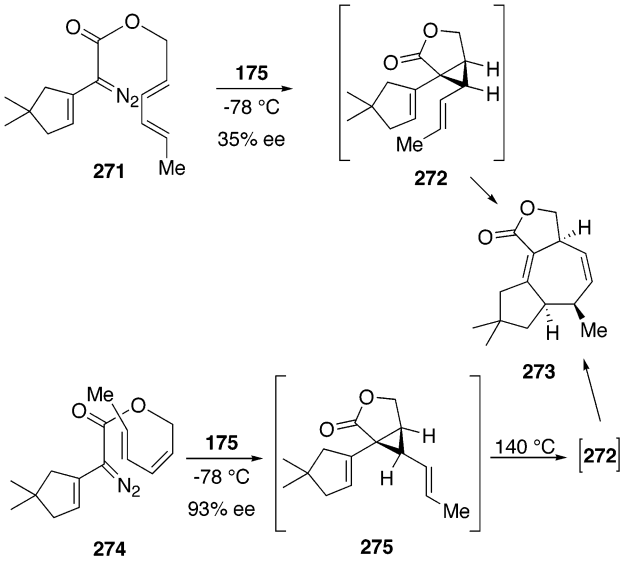
R^1	R^2	R^3	catalyst	yield (%)	ee (%)
H	H	H	Rh_2(*S*-DOSP)$_4$ (**175**)	92	28
H	H	H	Rh_2(*S*-DOSP)$_4$ (**175**)[a]	93	36
H	H	H	Rh_2(4*S*-IBAZ)$_4$ (**202**)	83	64
H	H	H	Rh_2(4*S*-MEAZ)$_4$ (**204**)	80	68
Me	H	H	Rh_2(*S*-DOSP)$_4$ (**175**)	90	29
Me	H	H	Rh_2(*S*-DOSP)$_4$ (**175**)[a]	77	51
Me	H	H	Rh_2(4*S*-IBAZ)$_4$ (**202**)	80	68
Me	H	H	Rh_2(4*S*-MEAZ)$_4$ (**204**)	82	84
H	Me	Me	Rh_2(*S*-DOSP)$_4$ (**175**)	76	29
H	Me	Me	Rh_2(*S*-DOSP)$_4$ (**175**)[a]	85	44
H	Me	Me	Rh_2(4*S*-IBAZ)$_4$ (**202**)	92	19
H	Me	Me	Rh_2(4*S*-MEAZ)$_4$ (**204**)	93	45

[a] Pentane as solvent.

double bonds. In the case of dirhodium tetracarboxylate catalysts, a wide range of substitutions patterns have been examined. Although the *E* isomer afforded low enantioselectivities (≤25% ee), the *Z* isomer as well as the 1,1-disubstituted alkene provided a good level of enantiocontrol (69−84% ee) with Rh_2(*S*-DOSP)$_4$ (**175**).

The dirhodium(II) azetidinonecarboxylate catalysts [such as Rh_2(4*S*-IBAZ)$_4$ (**202**) and Rh_2(4*S*-MEAZ)$_4$ (**204**)] proved to be equally or more effective for the enantioselective cyclization of α-phenyl-α-diazoacetates (Table 45). With an unsubstituted allyl group, the desired bicyclic system was isolated with 68% ee, whereas the 1,1-disubstituted alkene derivatives afforded the product in 84% ee. In the case of trisubstituted olefins, both catalysts, Rh_2(*S*-DOSP)$_4$ (**175**) and Rh_2(4*S*-MEAZ)$_4$ (**204**), were equally effective, leading to the cyclopropane fused-lactone in 44−45% ee. Davies has also shown that the intramolecular cyclopropanation of vinyldiazoacetates and dienes, followed by a Cope rearrangement of the resulting divinylcyclopropane intermediate, afforded fused cycloheptadienes with good to excellent levels of enantioselectivity.

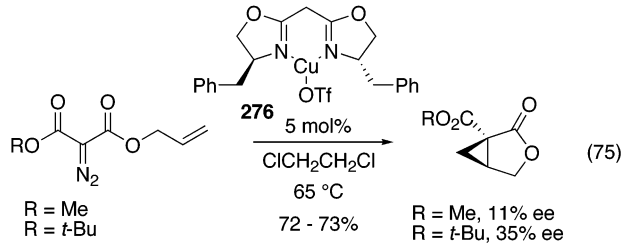
Scheme 18. Intramolecular Cyclopropanations of Diazo 271



Using this strategy, Davies has reported a short asymmetric synthesis of the tremulane skeleton (Scheme 18).[278] The initial attempts in the intramolecular cyclopropanation of *E*,*E*-diene **271** with Rh_2(*S*-DOSP)$_4$ (**175**) proceeded with low enantiocontrol, as is usually the case for systems with *trans* alkenes. However, the enantioselectivity could be enhanced to 93% ee by using the *Z*,*E*-diene **274** at −78 °C, thus affording the *trans*-divinylcyclopropane **275**.

Cyclopropane **275** is stable at room temperature, but it rearranges on heating, presumably through initial equilibration to the *cis*-divinylcyclopropane **272**, via a diradical intermediate. The desired fused seven-membered ring **273** was isolated in 85% yield with high enantiomeric excess.

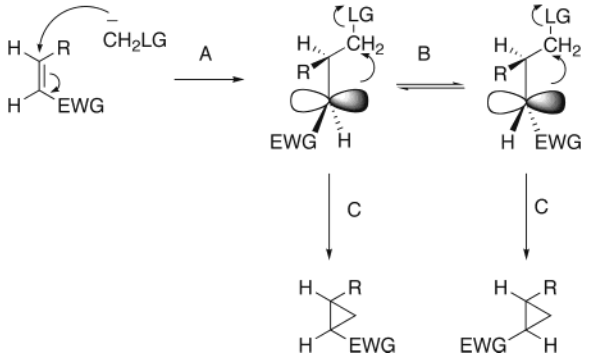
Few examples of enantioselective intramolecular cyclopropanation of the very unreactive diazomalonates have been reported so far.[279] Only copper catalysts are effective for this purpose, but low enantiomeric excesses were observed.[280] For example, Koskinen has reported that the cyclization of Me and *t*-Bu allyl diazomalonates in the presence of copper bioxazoline complex **276** afforded the desired cyclopropylactones in 72−73% yield and with 11% and 35% ee, respectively (eq 75).[281]



(75)

In conclusion, intramolecular cyclopropanation reactions prove to be a very useful transformation for the construction of complex cyclopropane-fused systems. Generally, high levels of diastereo- and enantiocontrol can be achieved with the appropriate catalysts. However, there is still room for improvement with some substituted diazo substrates.

Scheme 19. Michael-Initiated Ring Closure Cyclopropanation Reaction



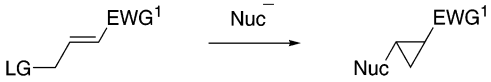
IV. Michael-Initiated Ring Closure

A. Introduction

Cyclopropanation reactions which involves a conjugate addition to an electrophilic alkene to produce an enolate, which then subsequently undergoes an intramolecular ring closure, are defined as Michael-initiated ring closure (MIRC) reactions.[282] Although there are exceptions, cyclopropanations via the MIRC reaction of acyclic olefins are usually nonstereospecific, and both (*E*)- and (*Z*)-olefins give the *trans*-cyclopropanes.

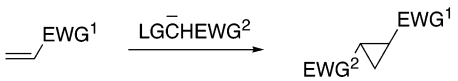
Stereospecific cyclopropanation reactions using the MIRC reaction are observed only when the ring-closure process (Scheme 19, step C) is faster than the rotation around the single bond in the first intermediate formed (Scheme 19, step B). Conversely, the formation of a configurationally stable tetrahedral intermediate after the first addition may also lead to a stereospecific process.

Two types of substrates/reactants can give rise to MIRC reactions. The first type involves the formation of cyclopropanes by nucleophilic addition to electrophilic substrates containing a leaving group (eq 76). A variety of nucleophiles can be used, such as alkoxides, thiolates, cyanides, enolates, Grignard reagents, hydrides, phosphites, and phosphonates.[283]



(76)

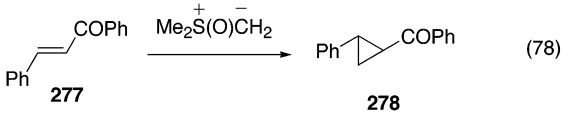
Cyclopropane-forming reactions, in which the leaving group is present on the nucleophile, constitute the other class of the MIRC reactions (eq 77).



(77)

These nucleophiles include the α-halo carbanions,[284,285] but the most effective reagents for methylene transfer to electron-deficient olefins are probably the heteroatom-derived ylides. Sulfur, phosphorus, arsenium, and telluronium ylides have all been used as cyclopropane precursors. Cyclopropanation reactions involving sulfonium salts were first

reported in 1950.[286] Nevertheless, the understanding and the synthetic potential of this reaction were appreciated only in the 1960s, when Corey reported that the addition of methylenedimethylsulfoxonium to chalcone (**277**) gave *trans*-1-benzoyl-2-phenylcyclopropane (**278**) (eq 78).[287,288]



(78)

These studies were quickly followed by the development of several new sulfur ylide reagents that have unique properties as cyclopropanating reagents. Since the chemistry of these reagents has been previously reviewed, it will be only briefly presented in this review (representative examples of the four types of sulfur ylides are shown in Figure 32).[289,290] The

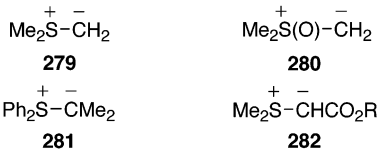
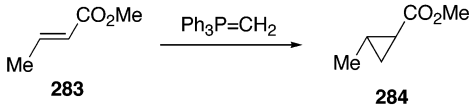


Figure 32. Selected examples of sulfur ylides.

reactions involving methylenesulfonium **279** are restricted to esters and amides derived from α,*β*-unsaturated carboxylic and sulfonic acids. Unsaturated aldehydes and ketones react with **279** to give oxirans. In contrast, the reaction of conjugated ketones with the methylenesulfoxonium **280** usually produces cyclopropanes (aldehydes also form oxirans). Substituted methylene reagents have also been developed. Thus, the addition of isopropylidenediphenylsulfurane **281** to conjugated carbonyl compounds (ketones, esters, and amides) leads to *gem*-dimethylcyclopropane derivatives.

In contrast to that of other sulfur ylides (vide supra), the stereochemistry of the alkene is usually maintained with **281** (*Z*-olefins give *cis*-cyclopropanes, and *E*-olefins give *trans*-cyclopropanes). Finally, the ester-substituted ylide **282** reacts readily with α,*β*-unsaturated ketones, nitriles, esters, and aldehydes to provide ester-substituted cyclopropanes. The reaction of sulfur ylides with α,*β*-unsaturated thioamides has also been recently published.[291]

The phosphorus ylides were also reported to be effective cyclopropanating reagents. In 1962, Bestmann and Seng observed that the reaction of methylenetriphenylphosphorane with crotonate ester **283** gave the corresponding cyclopropane **284** (eq 79).[292]



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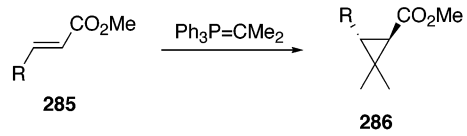
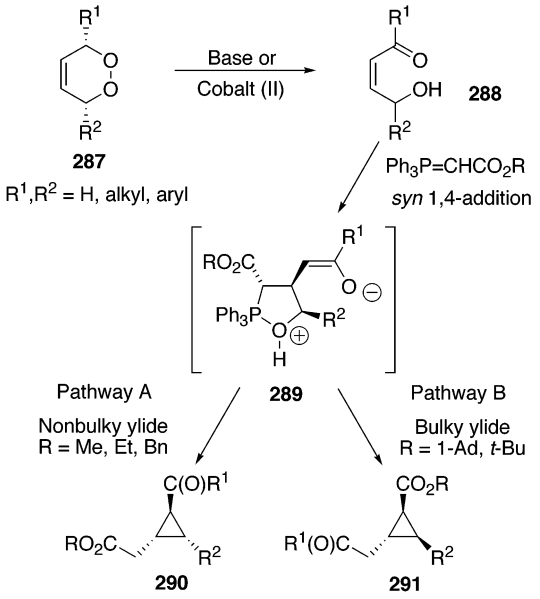


(80)

Ten years later, Grieco proposed a convenient synthesis of *trans*-2,2-dimethylcyclopropanecarboxylic esters **286** based on the 1,4-addition of isopropylidenetriphenylphosphorane to *trans*-α,*β*-unsaturated esters (eq 80).[293,294] This reagent also reacts with conjugated ketones to afford the corresponding cyclopropyl derivatives. Until recently, this approach was limited to *unstabilized* phosphorus ylides, as *stabilized* phosphorus ylides do not produce cyclopropanes upon addition to α,*β*-unsaturated carbonyl compounds.

Scheme 20. Cyclopropanation of 1,2-Dioxines 287 with Phosphorus Ylides

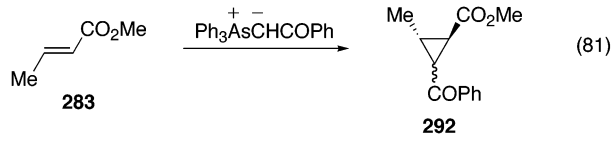


Recently, Taylor and co-workers have shown that the reaction of stabilized phosphorus ylides with 1,2-dioxines leads to the formation of diastereomerically pure trisubstituted cyclopropanes (Scheme 20).[295] The reaction has been shown to proceed through the *cis*-*γ*-hydroxy enone **288** intermediate, which can arise from 1,2-dioxine **287** by base-induced rearrangement or cobalt-assisted radical rearrangement. Subsequent *syn* 1,4-Michael addition of stabilized ylides to the enone then leads, via the oxaphospholane intermediate **289**, to either cyclopropane isomer **290** or **291**, depending on the steric nature of the ylide.

The same research group also established that stabilized phosphonates could be used and represent a viable alternative to ylides in the cyclopropanation reaction involving 1,2-dioxine **287**.[296] They showed that, if *cis*-*γ*-hydroxy enone **288** is enantiopure, then the resultant cyclopropane, formed on addition of ylide, is also enantiopure.[297] Conversely, they performed the first catalytic asymmetric ring opening of *meso*-1,2-dioxines, which relies on the use of chiral cobalt *β*-ketoiminato or cobalt salen complexes; subsequent capture by an ylide afforded enantioenriched cyclopropanes.[298] However, in this case, the enantioselectivity ranged from 30 to 78%.

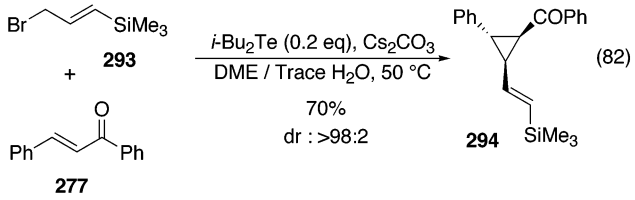
Stabilized arsonium ylides, such as carbomethoxy- and benzoylmethylenetriphenylarsorane, are also known to react with conjugated esters and ketones and to lead to cyclopropanes (eq 81).[299]

As an alternative to sulfur and phosphorus ylides, silylated telluronium ylides, which are prepared from bromide **293**, have been developed for cyclopropana-



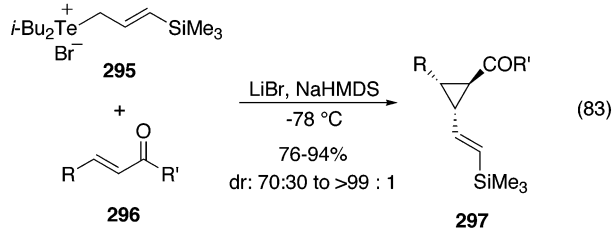
(81)

tion of α,β-unsaturated ketones, amides, esters, and diesters.[300] In the case of chalcone (**277**), high yields and diastereoselectivities were obtained.[301] A catalytic version of this reaction that minimized the amount of tellurium was also developed (eq 82).[302]



(82)

The stereochemical outcome has been demonstrated to be highly dependent on lithium salts for the cyclopropanation of conjugated ketones, esters, and amides.[303] The allylic telluronium ylides **295**, in the presence of lithium salts, reacts with α,β-unsaturated amides or esters to afford *trans*-2-vinyl-*trans*-3-substituted cyclopropyl carboxamides or carboxylates **297**, respectively, with high selectivity and generally with excellent yields (eq 83). In the absence



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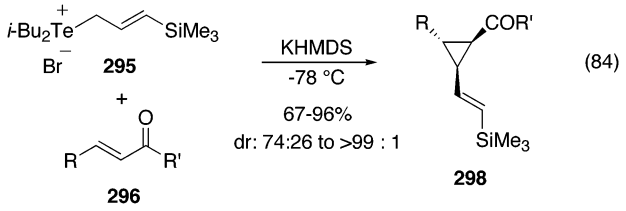


(84)

of lithium salts, the stereoselectivity of these reactions changes to give *cis*-2-vinyl-*trans*-3-substituted cyclopropyl carboxylates or carboxamides **298** (eq 84). The ratio of the two isomers varies from 99:1 to 1:99, depending of the reaction conditions. It was also shown that the *cis*,*trans* isomer can be mainly produced in the presence of lithium salts when more than 2 equiv of HMPA was added.[304]

The authors postulated that, in the presence of lithium ion, a chelating six-membered-ring transition state is involved, whereas an open transition state is operative in the presence of a less coordinated species, such as potassium (Figure 33). However, the same reaction with alkylidene malonic esters was found to be independent of the reaction conditions, and the *trans*,*trans* isomers were always obtained.[305]

Conversely, allylindium reagents have been also added to α,β-unsaturated ketones to yield vinyl-

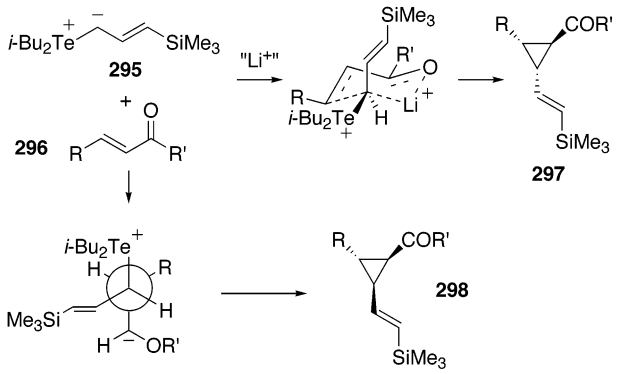


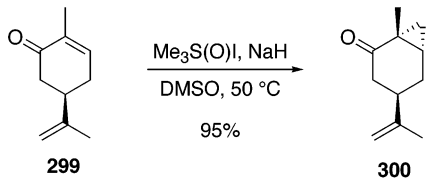
Figure 33. Transition-state models for the diastereoselective cyclopropanation with telluronium ylides.

cyclopropanes.[306] Recently, the use of electrochemical techniques for the activation of various precursors suitable for MIRC reactions and leading to cyclopropanes was described.[307] The absolute stereocontrol for this reaction has not yet been introduced.

Few asymmetric versions of the Michael-initiated ring closure reactions have been reported, and the main stereocontrolling elements were mostly based on steric and stereoelectronic effects.[308] The following sections summarize the recent advances in stereoselective cyclopropanation reactions by the nucleophilic addition−ring closure sequence.

B. Relative Diastereoselection (Addition to Chiral Substrates)

The reactions involving sulfur ylides and substituted cyclohexenones are well known to proceed with very high diastereoselectivities under steric control, although in some cases, stereoelectronic arguments could also be invoked.[289a] For example, the cyclopropanation of (*R*)-(−)-carvone (**299**) with methylenedimethylsulfoxonium provides the desired cyclopropylcarvone **300** in 95% yield, as a single diastereoisomer, which results from the attack of the ylide on the less hindered face (eq 85).[309,310]

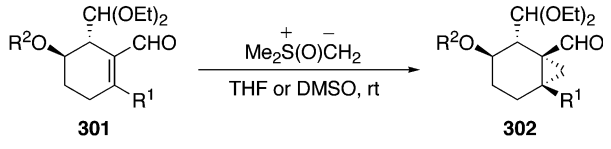


(85)

Sterner used a similar reaction with cyclohexenecarboxaldehyde **301** and demonstrated that cyclopropanation of tri- and tetrasubstituted unsaturated aldehydes with methylenedimethylsulfoxonium could be achieved, leading to **302** with excellent diastereoselectivities, but in low to moderate yields (Table 46).[311]

The authors have postulated that the addition to cyclohexenal derivatives **301** (which predominantly exist as the diaxial conformer) favors the formation of an axial carbon−carbon bond in the initial nucleophilic attack. The preference for the axial attack may be attributed to stereoelectronic control. In the transition state, an axial attack generates the half-chair cyclohexane conformer directly, whereas an

Table 46. Stereoselective Cyclopropanation of 5,6-Disubstituted 1-Cyclohexenecarboxaldehyde



R^1	R^2	yield (%)
H	Ac	24
CH_3	Ac	65
CH_3	TBS	52
$(CH2)_6CH_3$	TBS	29

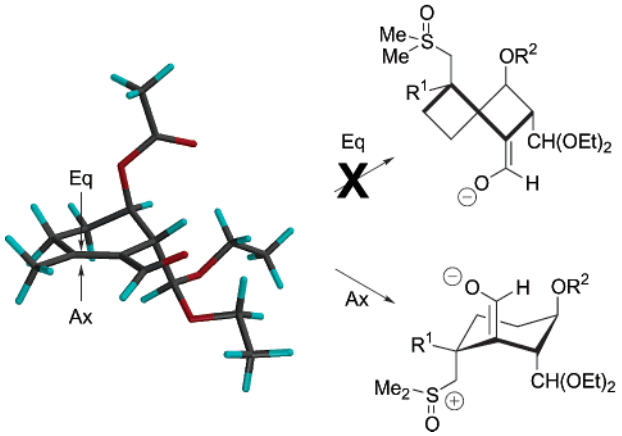
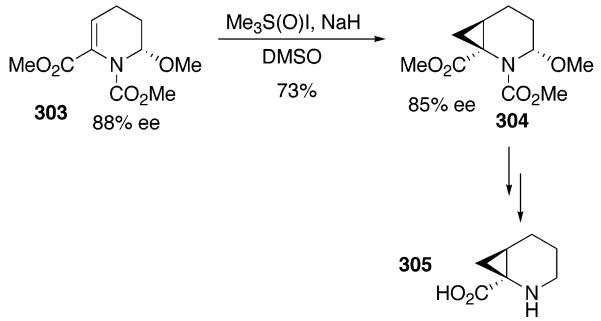


Figure 34. Intermediates formed in the diastereoselective cyclopropanation of cyclohexenal **301**.

Scheme 21. Diastereoselective Cyclopropanation of 2,3-Didehydropipecolate 303

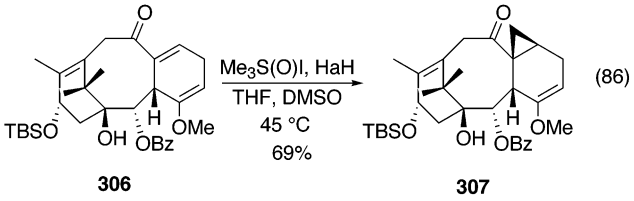


equatorial attack generates the less stable twist−boat conformer (Figure 34).[312]

Enantioenriched 2,3-methanopipecolic acid **305** was prepared from 2,3-methano-6-methoxypipecolate **304**, which arose from the reaction between 2,3-didehydropipecolate **303** and methylenedimethylsulfoxonium (Scheme 21).[313]

The cyclopropanation proceeded with an excellent diastereomeric ratio (>98%); however, the starting material could not be prepared in an enantiomerically pure form.

7,8-Cyclopropyltaxol analogues **307** have been shown to be almost as potent as taxol in a number of biological assays.[314] Wender has disclosed the preparation of such derivatives from enone **306** using sulfur ylide chemistry.[315] Only one diastereoisomer was obtained in 69% yield when methylenedimethylsulfoxonium was used (eq 86).



Steric arguments can be invoked to explain the selectivity, as the bottom face of the enone is blocked by the A ring (Figure 35).

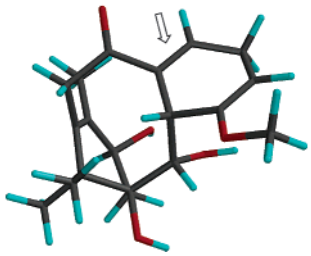
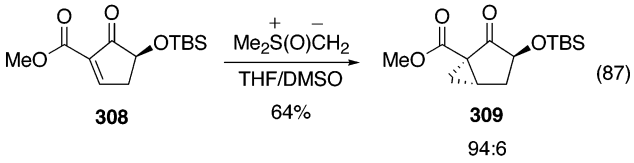


Figure 35. Cyclopropanation of taxol derivative **306**.

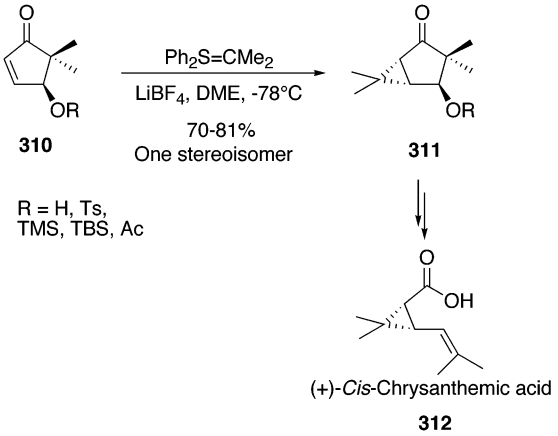
During the course of his work on the synthesis of 1α,25-dihydrovitamin D_3 and its analogues as potential bioactive compounds, Dauben developed methods for the enantioselective synthesis of bicyclo[3.1.0]-hexanes.[316] The first method involved the stereoselective cyclopropanation of a chiral γ-alkoxy-α-diazo-β-keto ester, but a low diastereoselectivity was obtained.[317] To circumvent that problem, he elaborated a diastereoselective intermolecular cyclopropanation reaction involving the addition of methylenedimethylsulfoxonium ylide to chiral cyclopentenone **308** (eq 87).[318] The bicyclo[3.1.0]hexane **309** was obtained in a diastereomeric ratio of 94:6. The stereochemical outcome of the reaction is easily explained by assuming that the sulfur ylide attacks the more accessible face of the olefin.



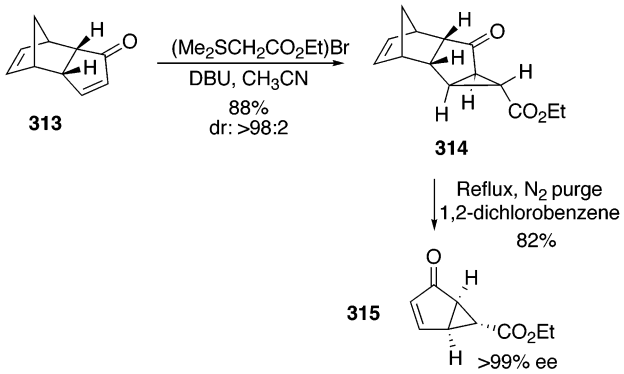
Krief described a novel and highly convergent synthesis of (±)-*cis*- and (+)-*cis*-chrysanthemic acid (**312**) from bicyclo[3.1.0]hexane derivatives **311**, involving the cyclopropanation of suitably 4-functionalized 5,5-dimethyl-2-cyclopentenones **310** with isopropylidenediphenylsulfonium (Scheme 22).[319] Only one stereoisomer was obtained in good yield for the cyclopropanation of several derivatives of **310**. This approach was extended to ethylidenediphenylsulfonium, but stereoselectivities were much lower when the reaction was carried out under the same conditions.

Excellent diastereoselectivities are usually obtained when using a bicyclic template, as shown by Moher.[320] The cyclopropanation of (+)-dicyclopentadienone **313**, readily available by enzymatic resolution,[321] proceeded with high selectivity, affording **314** as a single diastereoisomer; the desired bicyclo[3.1.0]-hexane derivative **315** could be revealed by a retro-

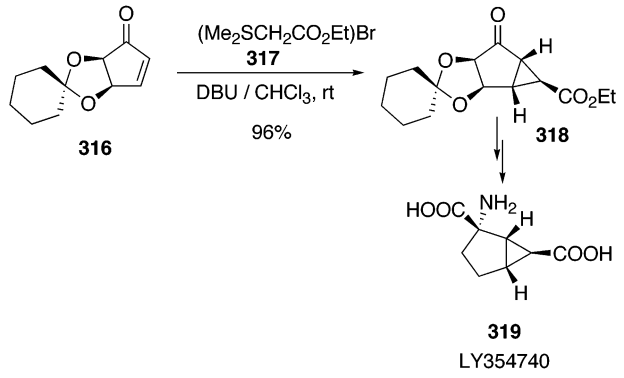
Scheme 22. Diastereoselective Cyclopropanation of Cyclopentenone 310



Scheme 23. Diastereoselective Cyclopropanation of (+)-Dicyclopentadienone 313



Scheme 24. Total Synthesis of (+)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (LY354740)



Diels−Alder reaction (Scheme 23). The delivery of the methylene group arises from the convex face of the bicyclic system.

The asymmetric synthesis of (+)-2-aminobicyclo-[3.1.0]hexane-2,6-dicarboxylic acid (**319**, LY354740), a potent and selective agonist for a glutamate receptor involved in the mammalian central nervous system, was achieved by Domínguez and co-workers.[322] The cyclopropanation of the protected dihydroxycyclopentenone **316** with sulfonium bromide **317** and DBU afforded the *exo* product **318** exclusively, in almost quantitative yield (Scheme 24).[323]

Crich used the sulfur ylide chemistry to prepare the enantiomerically pure cyclopropatryptophane

Scheme 25. Synthesis of Cyclopropatryptophane Derivative 322

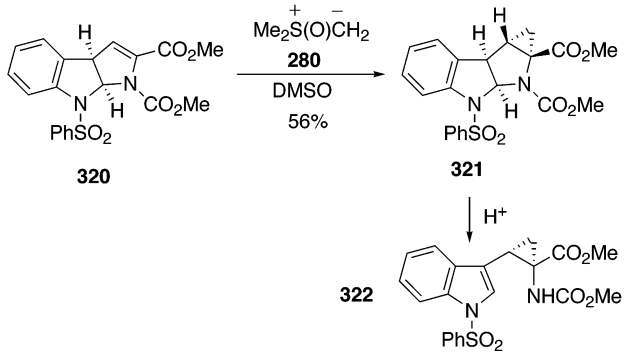
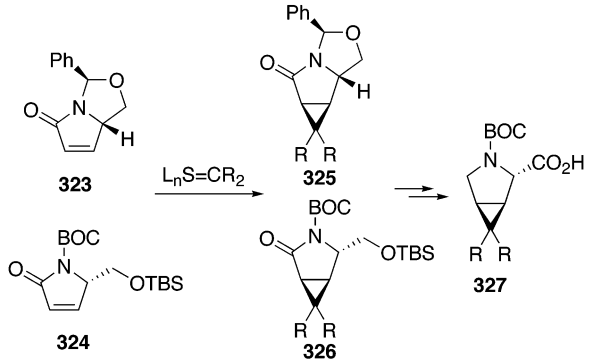


Table 47. Cyclopropanation of *O,N*-Acetal 323 and *N*-BOC-Pyrrolinone 324 with Various Sulfur Ylides

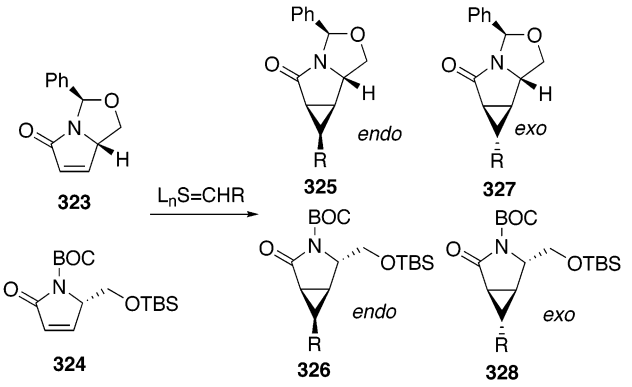


entry	substrate	$L_nS{=}CR_2$	yield (%)
1	**323**	$Ph_2S{=}CMe_2$	89
2	**323**	$Me_2S(O){=}CH_2$	78
3	**323**	$Ph(NMe_2)S(O){=}CH_2$	60
4	**324**	$Ph_2S{=}CMe_2$	79
5	**324**	$Me_2S(O){=}CH_2$	trace
6	**324**	$Ph(NMe_2)S(O){=}CH_2$	19

derivative **322** (Scheme 25).[324] Only one isomer was obtained, resulting from the ylide addition to the convex face of the tricyclic system **320**.

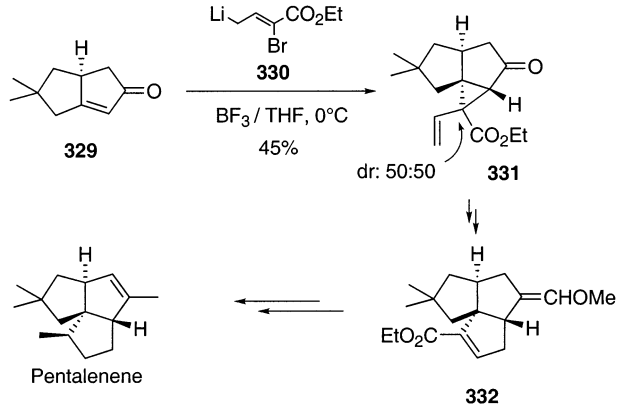
Madalengoitia prepared new 3-aza-bicyclo[3.1.0]-hexane ring systems that are designed as proline-templated amino acids.[325] The cyclopropanation of *O,N*-acetal **323** and *N*-BOC-pyrrolinone **324** with isopropylidenediphenylsulfonium smoothly afforded the desired products in 89% and 79% yields, respectively (Table 47, entry 1 and 4). Both products arise from the cyclopropanation of the less hindered *exo* face. The unsubstituted cyclopropane derived from **323** was successfully prepared from methylenedimethylsulfoxonium and $Ph(NMe)_2S(O){=}CH_2$ in 76% and 60% yields, respectively (entry 2 and 3). However, reaction of **324** with $Me_2S(O){=}CH_2$ afforded mainly a dimerization product, with only trace amounts of the desired product (entry 5). The reaction was attempted with the less basic ylide, $Ph(NMe_2)S(O){=}CH_2$, but this also resulted in a low yield of cyclopropane (entry 6). Interestingly, the acidity of the methine proton was not a problem in the reaction of **324** with other sulfur ylides (Table 48). Indeed, the cyclopropane derivatives can be prepared in good yields from **323** and **324** by using a variety of unsymmetrical substituted sulfur ylides. The *endo*:

Table 48. Cyclopropanation of *O,N*-Acetal 323 and *N*-BOC-Pyrrolinone 324 with Various Unsymmetrical Substituted Sulfur Ylides



entry	substrate	L$_n$S=CHR	yield (%)	ratio *endo*:*exo*
1	**323**	Ph_2S=CHMe	84	1:2.5
2	**323**	Ph_2S=CHCH=CH_2	60	5:1
3	**323**	Ph_2S=CHEt	82	1:1.3
4	**323**	Me_2S=$CHCO_2Me$	78	1:1
5	**324**	Ph_2S=CHMe	54	1:4
6	**324**	Ph_2S=CHCH=CH_2	68	1:1
7	**324**	Ph_2S=CHEt	62	1:3
8	**324**	Me_2S=$CHCO_2Me$	82	1:1

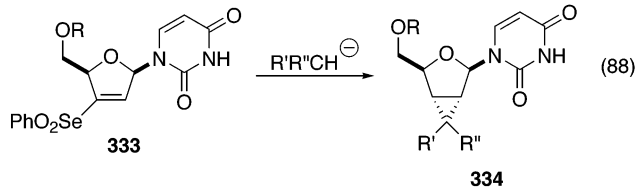
Scheme 26. MIRC Reaction of Enone 329



exo ratio varies with the substituent on the ylide and the substrate.

The vinylcyclopropane **331** can be prepared by the addition of the lithium dienolate anion **330**, derived from ethyl 2-bromocrotonate, to the conjugated system **328** (Scheme 26).[326] The reagent was added to β,β-disubstituted enone **329**, and the cyclopropanation was directed to the more accessible face. Although the facial selectivity was excellent, the diastereomeric ratio at the ester center could not be controlled.[327] Pyrolysis of vinylcyclopropane **331** gave triquinane **332**, which is a precursor for pentalenene, a biological intermediate involved in the biogenesis of the antibiotic pentalenolactone.

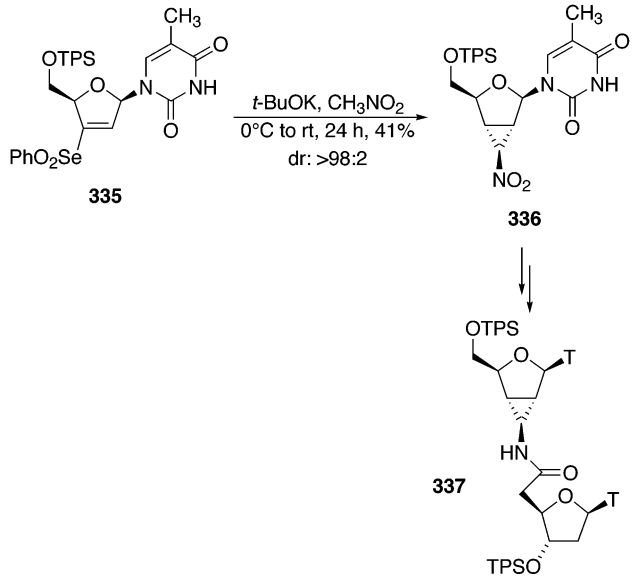
As a part of his program related to the discovery of new types of dideoxynucleosides as specific inhibitors of the HIV reverse transcriptase, Chattopadhyaya has developed a new stereospecific synthesis of [3.1.0] bicyclic cyclopropane analogues of 2′,3′-dideoxyuridine.[328] The 5′-protected α,β-ene-3′-phenylselenone **333** is a synthetic equivalent of a dication, $CH_2^+-CH_2^+$. It reacted with carbon dinucleophiles such as sodium malonate, and conjugate bases of nitromethane, acetophenone, isobutylcyanoacetate, and both methylene bisdiethyl phosphate and bisphenyl sulfone, to give access to 2′,3′-deoxy-2′,3′-α-methylene[3.1.0]nucleosides derivatives (**334**) in 18−67% yields (eq 88). In all cases, only one isomer was obtained, resulting from the delivery of the methylene group on the more accessible face of the dideoxynucleoside.



(88)

Recently, Sanghvi used the Chattopadhyaya's strategy for the preparation of a new conformationally constrained dimeric building block **337** containing a cyclopropylamide functionality (Scheme 27).[329,330]

Scheme 27. Synthesis of Cyclopropyl Nucleoside Derivative 335

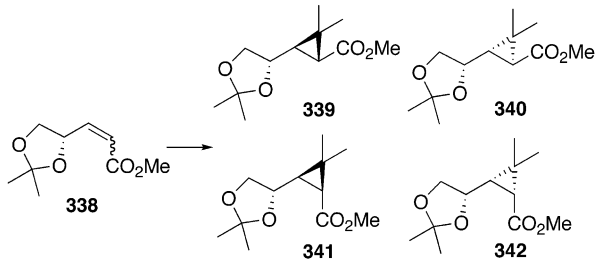


Only one isomer was observed for the MIRC reaction of **335**.

As illustrated above, highly diastereoselective MIRC reactions have been reported for a number of cyclic systems, in which the stereochemical induction is based on steric arguments. Conversely, the highest selectivities with acyclic systems are observed with conformationally constrained alkenes. One well-studied system involves the use of 1,2-*O*-isopropylidene-D-glyceraldehyde-derived esters. Mulzer demonstrated that the addition of isopropylidenetriphenylphosphorane to γ-alkoxy-α,β-unsaturated esters derived from D-glyceraldehyde proceeded with good diastereoselectivity and yield.[331]

Krief exploited this transformation in the course of a study directed toward the synthesis of chrysanthemic acids. A systematic investigation of cyclopropanation of various γ-alkoxy-α,β-unsatured carbonyls, derived from D-glyceraldehyde using several ylides, was reported (Table 49).[332]

Table 49. Cyclopropanation of (*E*)- and (*Z*)-α,β-Unsaturated Esters Derived from D-Glyceraldehyde with Various Reagents



	reagent	yield (%)	dr **339:340:341:342**
E-**338**	$Ph_3P{=}CMe_2$	55	90:10:0:0
	$Me_2CS(O)(NTs)CLiMe_2$	70	93:7:0:0
	$Ph_2S{=}CMe_2$	92	2:98:0:0
Z-**338**	$Ph_3P{=}CMe_2$	61	6:94:0:0
	$Me_2CS(O)(NTs)CLiMe_2$	48	39:61:0:0
	$Ph_2S{=}CMe_2$	84	0:0:2:98

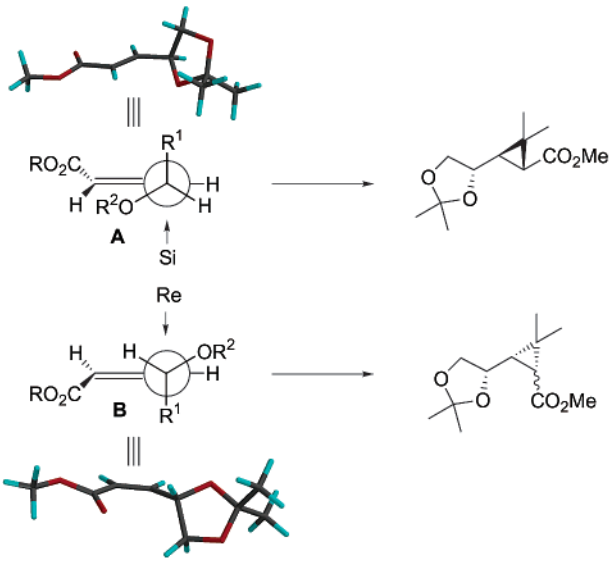


Figure 36. Reactive conformers for the diastereoselective cyclopropanation of (*E*)-**338** and (*Z*)-**338**.

It was found that the reactivity and selectivity observed with 2-lithio-2-propyl-*N*-tosylisopropylsulfoximide are closely related to those obtained with isopropylidenetriphenylphosphorane. However, the behavior of isopropylidenediphenylsulfurane is dramatically different. With (*E*)-**338**, both phosphorus and lithium reagents delivered the isopropylidene moiety to the *si* face, while the sulfur ylide attacked the *re* face of the alkene. The initial geometry of the double bond has some effect on the sense of induction. With (*Z*)-**338**, the attack of all three reagents occurred on the *re* face. However, the reaction of the sulfur ylide was highly stereoselective, leading to the formation of the *cis*-cyclopropane **342**. Conversely, both the phosphorus and lithium reagents led to the isomerized *trans*-cyclopropanes **339** and **340**.

Krief proposed two models based on Stork's work to rationalize these results.[333] He suggested that the conformation shown in model **A** (Figure 36), which results from a favorable interaction between the π orbital of the double bond and the electron pair of the γ oxygen, is operative in the (*E*)-series of compounds with the phosphorus and lithium reagents. This model is not favored, due to 1,3-allylic strain between the ester group and the γ-substituent in the (*Z*)-series (with all reagents), which now adopt the conformation shown in the model **B**. Nevertheless, no transition-state model has been proposed to account for the stereochemical outcome of the reaction between the closely related sulfur ylide and (*E*)-**338**.

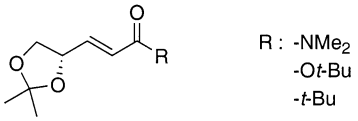
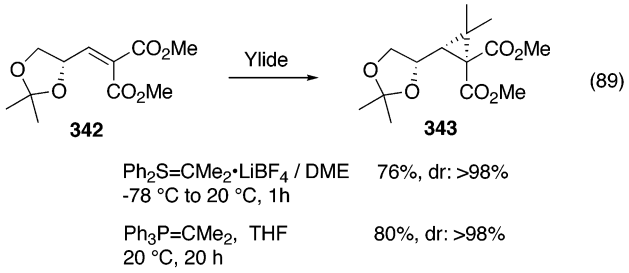


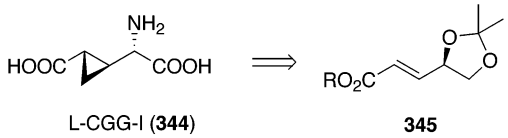
Figure 37. Other conjugated systems derived from D-glyceraldehyde.

Similarly, Krief reported that the related tertiary amide, the *tert*-butyl ester, and the *tert*-butyl ketone, derived from D-glyceraldehyde, gave results similar to those shown above (Figure 37).[334] He also showed that the cyclopropanation of dimethyl alkylidene malonate **342** with either sulfur or phosphorus ylides afforded dimethyl cyclopropane-1,1-dicarboxylate **343** with good yields and very high diastereoselectivities (eq 89).[335]



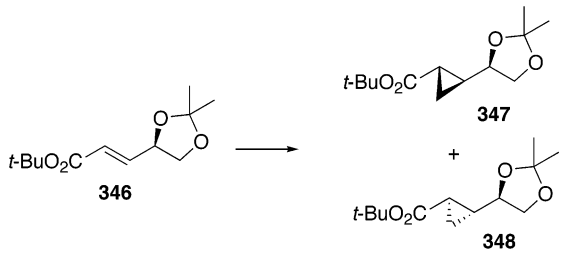
(89)

Ma used a similar strategy in the synthesis of (2*S*,1′*S*,2′*S*)-(carboxycyclopropyl)glycine (**344**, L-CCG-I), an isotype-selective agonist of metabotropic glutamate receptors (eq 90).[336]



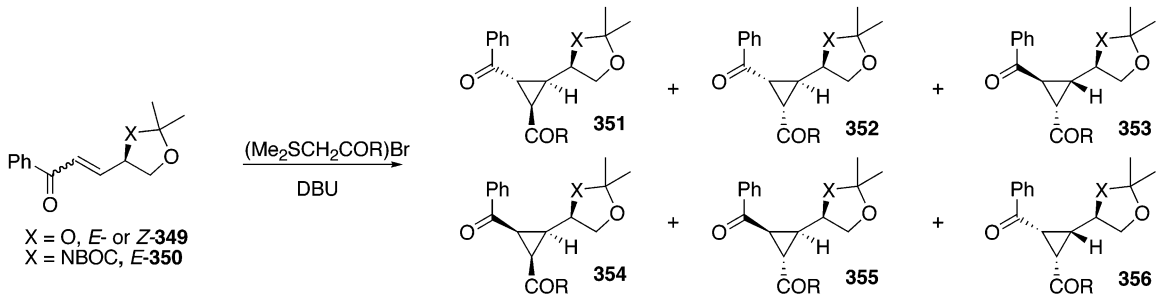
(90)

Table 50. Cyclopropanation of 1,2-*O*-Isopropylidene-D-Glyceraldehyde Ester 346



entry	reagent	conditions	yield (%)[a]	ratio **347**:**348**
1	Ph_3PCH_3I, *n*-BuLi	20 °C, 0.5 h	66	57:43
2	Ph_3PCH_3I, *n*-BuLi	0 °C, 5 h	0	
3	$Me_3S(O)I$, NaH	55 °C, 1 h	82	67:33
4	$Me_3S(O)I$, NaH	20 °C, 5 h	82	67:33
5	$Me_3S(O)I$, NaH	0 °C, 5 h	80	80:20
6	$Me_3S(O)I$, NaH	−30 °C, 5 h	73	95:5

Table 51. Synthesis of 1,2,3-Trisubstituted Cyclopropanes from (*S*)-Glyceraldehyde Acetonide- and Garner's Aldehyde-Derived Enones



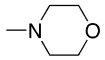
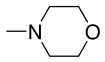
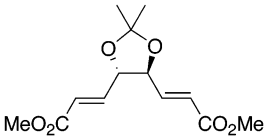
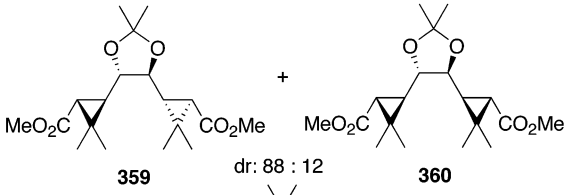
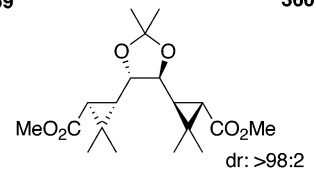
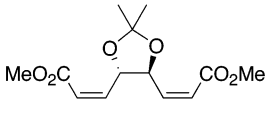
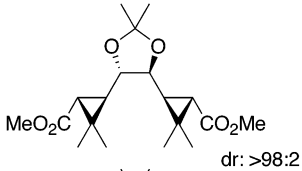
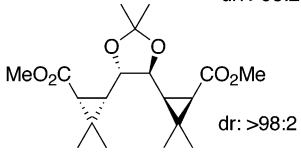
Entry	Substrate	R	Conditions	Yield	Ratio
	E-**349**				**351 : 352 : 353**
1		OEt	Toluene, -20 °C, 6h	74% (**351**+**353**)	80 : 12 : 8
2		O*t*-Bu	Toluene, 0 °C, 10 h	52% (**351**)	87 : 13 : 0
3			Toluene, 0 °C, 10 h	53% (**351**)	86 : 14 : 0
4			Toluene, 0 °C, 10 h	34% (**351**) 25% (**352**)	58 : 42 : 0
	Z-**349**				**354 : 355 : 356**
5		OEt	Toluene, -40 °C, 6h	96% (**354**+**356**)	90: 1 : 9
	E-**350**				**351 : 352 : 353**
6		OEt	Toluene, 0 °C, 7h	72% (**351**)	86 : 14
7		O*t*-Bu	Toluene, 0 °C, 24 h	72% (**351**)	88 : 12
8		Me	Toluene, 0 °C, 24 h	68% (**351**)	75 : 25
9		Ph	Toluene, 0 °C, 24 h	30% (**351**)	75 : 25
10			MeCN, 0 °C, 10 h	24% (**351**)	64 : 36

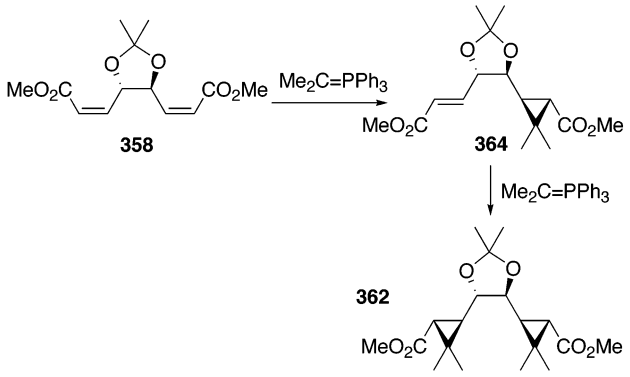
Table 52. Diastereoselective Cyclopropanation of Bis(Unsaturated Ester) Derived from Tartaric Acid

Substrate	Reagent	Products	Yield
 **357**	$Me_2C{=}PPh_3$	 **359** dr: 88 : 12 + **360**	75%
	$Me_2C{=}SPh_2$	 **361** dr: >98:2	82%
 **358**	$Me_2C{=}PPh_3$	 **362** dr: >98:2	65%
	$Me_2C{=}SPh_2$	 **363** dr: >98:2	70%

The key stereoselective cyclopropanation involved the ylide reaction of the 1,2-*O*-isopropylidene-D-glyceraldehyde-derived ester **346**. While the phosphorus ylide was poorly reactive and diastereoselective, the desired cyclopropane **347** was prepared from methylenedimethylsulfoxonium at low temperature, with good yield and diastereoselectivity (Table 50).

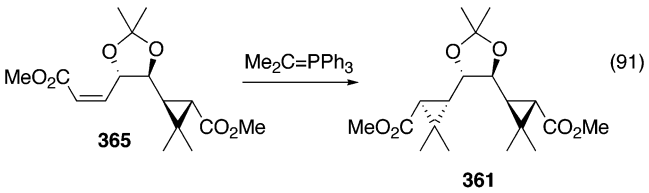
Ma also prepared a series of 1,2,3-trisubstituted cyclopropanes from (*S*)-glyceraldehyde acetonide- and Garner's aldehyde-derived enones (Table 51).[337]

Scheme 28. Diastereoselective Cyclopropanation of (*Z*)-Bis(conjugated ester) 358



Good yields and diastereoselectivities could usually be obtained with ester-substituted ylides, leading mainly to products **351** and **354** from *E* isomers and *Z* isomers, respectively (entries 2, 5, and 7). The *cis*-enone gave better geometry selectivity than the *trans*-enone. Although the reaction proceeded with amide-substituted ylides, the yields and the selectivities were mediocre.

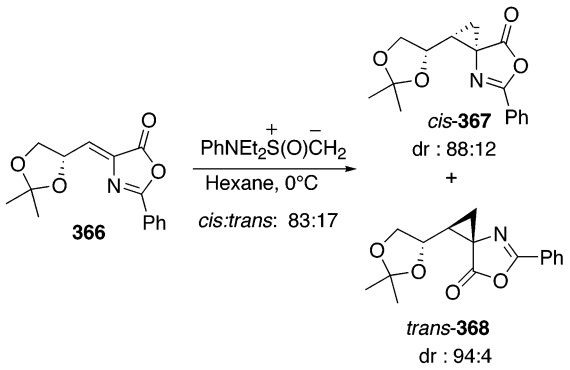
Krief extended this approach to C_2-symmetric bis-(unsaturated esters) **357** and **358** (Table 52).[338] These bis(unsaturated esters) are easily prepared from tartaric acid and generate two hemicaronaldehyde units per molecule of bis(adduct), after cyclopropanation and oxidative cleavage. These hemicaronaldehydes can be easily transformed into *trans*-chrysanthemic acid or its analogues. Both phosphorus and sulfur ylides were used with the bis(unsaturated esters) **357** and **358**, and the results correlated well with those of the simpler system. Surprising results were obtained in the reaction between the (*Z*)-bis-(conjugated ester) **358** and the phosphorus reagent, which led to **362** (Scheme 28). Conversely, the reaction between **358** and only 1 equiv of phosphorus ylide gave a 1:1:1 mixture of **358**:**362**:**364**. When the (*Z*)-monoadduct **365** was resubmitted to the same reaction conditions, **361** (and not **362**!) was formed in the process (eq 91). These observations led the authors to assume that a *Z*-to-*E* isomerization took place via an unknown mechanism on the betaine resulting from the first addition of the ylide.



(91)

The overall stereochemical outcome of the reaction must then be consistent with the following events: (a) the addition of the ylide across one of the (*Z*)-carbon−carbon double bonds, leading to a betaine; (b) the stereoselective isomerization (*Z* to *E*) of the remaining olefinic linkage; (c) cyclization of the betaine; and (d) cyclopropanation of the second carbon−carbon double bond.

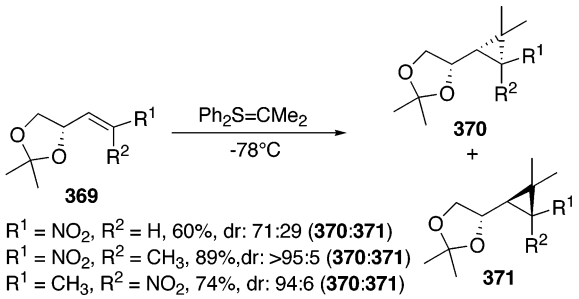
The cyclopropanation of chiral (*Z*)-oxazolone derived from 1,2-*O*-isopropylidene-D-glyceraldehyde **366** has also been reported (eq 92).[339] Both methylene-



(92)

dimethylsulfoxonium and -(diethylamino)phenylsulfoxonium produced the desired cyclopropanes **367** and **368**, but the latter is superior. A 83:17 *cis*:*trans* ratio was obtained when the reaction was run in hexane. The model presented in Figure 36 accounts for the observed sense of induction.

Pätzel has used the isopropylidenediphenylsulfonium ylide for the cyclopropanation reactions of various nitroalkenes **369** (derived from (*R*)-2,3-isopropylideneglyceraldehyde) to produce the corresponding dimethyl-substituted nitrocyclopropanes **370** in good yields and diastereomeric ratios (eq 93).[340] The sense of induction can be predicted by

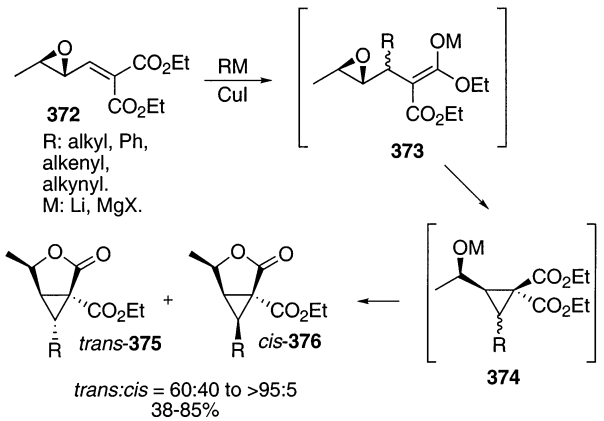


(93)

minimization of the 1,3-allylic strain. However, when methylenediphenylsulfonium was used, both the yield and the diastereoselectivities were poor, and the corresponding isoxazaline *N*-oxide became an important byproduct.

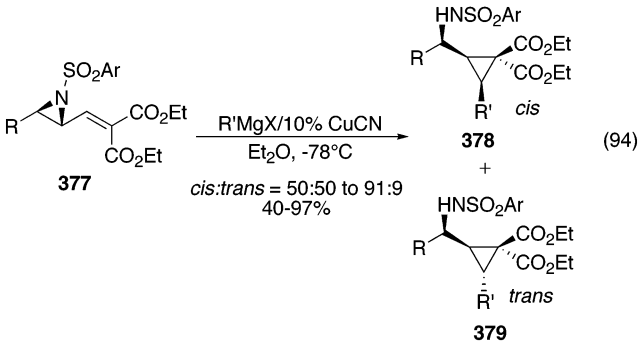
Kasatkin reported the synthesis of cyclopropane dicarboxylates using MIRC reactions with diethyl (2,3-epoxybutylidene)malonate **372** (Scheme 29).[341]

Scheme 29. MIRC Reaction with Diethyl (2,3-Epoxybutylidene)malonate 372



Treatment of the epoxide **372** with either a Grignard or an organolithium reagent in ether in the presence of 5 mol % CuI led to cyclopropane-bearing lactones **375** in 38−85% yield and with 60:40 to >95:5 *trans*:*cis* selectivities via intermediates **373** and **374**.

Zwanenburg has developed an analogous method for the nucleophilic addition/ring-closing tandem process of activated aziridinylmethylenemalonates **377** (eq 94).[342]



A variety of *cis*-substituted cyclopropane dicarboxylic ester derivatives **278** could be prepared with a moderate level of diastereoselection (*cis*:*trans* ratios ranged from 50:50 to 91:9). The Grignard reactions catalyzed by CuCN provide the highest diastereoselectivities. The preferred formation of the *cis*-cyclopropane derivative is opposite to that observed by Kasatkin during the MIRC reaction of the epoxide analogue (vide supra). Transition-state models have been proposed on the basis of the work of Yamamoto on the conjugate addition of organocuprate reagents to γ-alkoxy α,β-unsaturated diester derivatives.[343,344] For cuprate reagents, it is presumed that the steric factors are more important than the stereoelectronic factors; thus, the conformer in which the carbon−carbon bond of the epoxide is perpendicular to the alkene is favored. In contrast, the steric hindrance of the arylsulfonyl group on the aziridine nitrogen atom influences the preferred conformation of the substrate in the transition state. In the favored conformation, one face of the Michael acceptor is effectively shielded by the *N*-arylsulfonyl group, implying a selective approach of the nucleophilic reagent to the other face of the double bond moiety (Figure 38).

Very few diastereoselective MIRC reactions of acyclic precursors, in which the chiral center does not contain a C-heteroatom bond, have been reported so far. Zercher has reported one of these examples with the ylide-mediated bis(cyclopropane) formation.[345] Low diastereoselectivities were observed, the best case being the (*E*)-*cis*-cyclopropanecarboxylate **380**, which led to a 75:25 ratio of the bis(cyclopropane) products **381** and **382** (eq 95).

Arene metal−π complexes and related systems constitute another category of substrates that are suitable for MIRC reactions. In some cases, good diastereoselectivities were obtained by using a sulfur ylide. For instance, the cyclopropanation of arene chromiumtricarbonyl complex **383** with trimethyl-

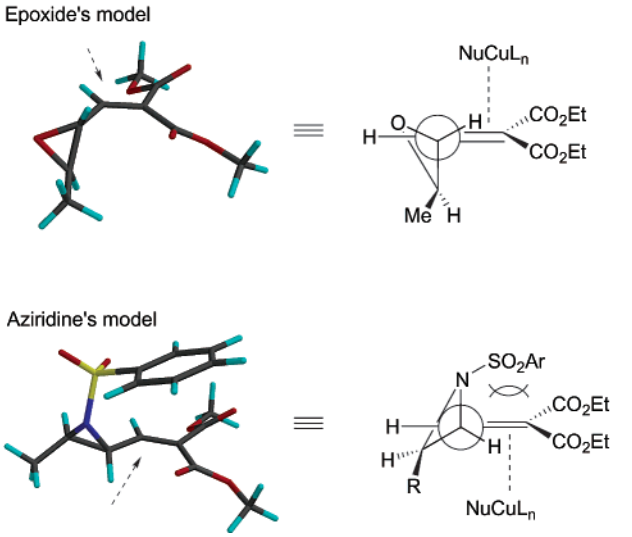
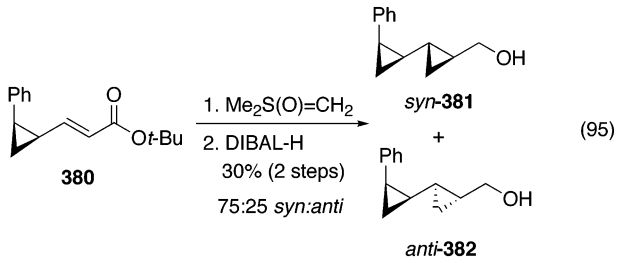
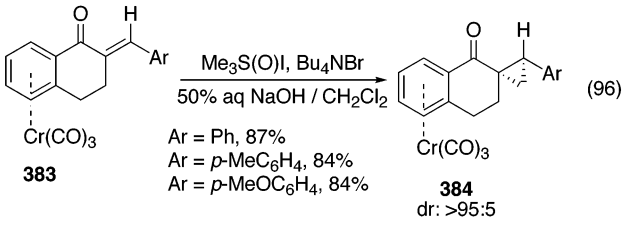


Figure 38. Reactive conformers for the cyclopropanation of 2,3-epoxybutylidene- and *trans*-aziridinylmethylenemalonate.



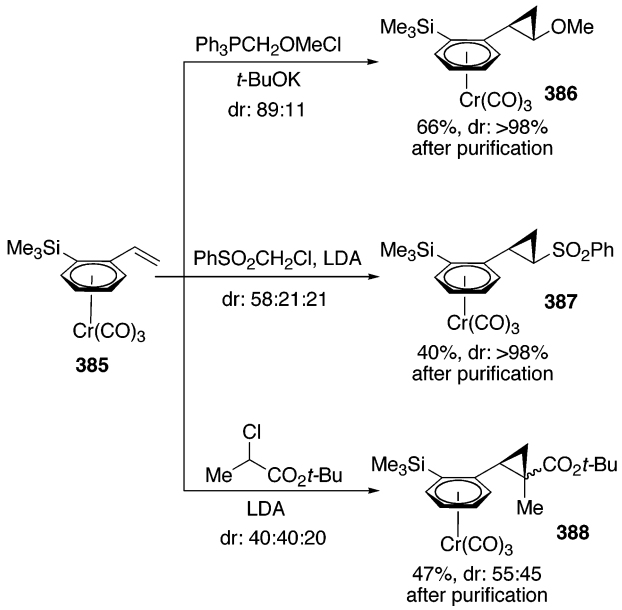
sulfoxonium iodide under phase-transfer catalysis conditions yielded the corresponding cyclopropane **384** as a single diastereoisomer (eq 96).[346]



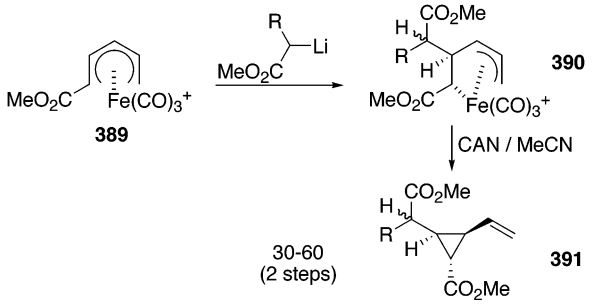
In contrast to other nucleophilic additions to arene chromium complexes, the product resulting from an *endo* addition (*syn* to the chromium) is formed. This *syn*-directing effect may be the result of an initial ylide coordination to the $Cr(CO)_3$ group.[347]

The double bond in tricarbonyl(styrene)chromium(0) complexes is polarized such that nucleophilic attack occurred at the β-carbon of the alkene; the α-carbanions generated upon nucleophilic attack may be quenched with electrophiles.[348] Accordingly, these substrates are suitable for MIRC reactions, as shown by Gibson and co-workers.[349] The cyclopropanation of tricarbonyl(styrene)chromium(0) complexes with sulfur and phosphorus ylides proceeded in good yields. When the enantiomerically pure 2-(trimethylsilyl)styrene complex **385** was submitted to (methoxymethyl)triphenylphosphonium chloride and potassium *tert*-butoxide, an 89:11 mixture of two

Scheme 30. Diastereoselective Cyclopropanation of Tricarbonyl(styrene)chromium(0) Complexe 385



Scheme 31. Synthesis of Chiral Cyclopropanes from Chiral (Pentenediyl)iron Complexes



diastereoisomers (out of a possibility of four) was obtained (Scheme 30). The major diastereoisomer **386** was purified and isolated in 66% yield and with a diastereomeric ratio greater than 98%. The nucleophilic attacks of α-chloro carbanions were less selective, leading to a mixture of three diastereoisomers. The cyclopropyl sulfone **387** was purified and isolated as a single diastereoisomer, whereas the trisubstituted cyclopropane **388** could be obtained only as a mixture of two unseparable diastereoisomers.

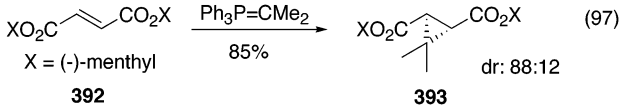
The authors have postulated that an equilibration process, which leads to the thermodynamically more stable diastereoisomer, could explain the stereochemical outcome. However, a metal-mediated delivery process, such as the one described above, can be also envisioned to account for the observed stereoselectivity.

Finally, chiral (pentadienyl)iron complexes **389** have also been converted to chiral cyclopropanes under oxidative conditions by using ceric ammonium nitrate (Scheme 31).[350,351] The oxidatively induced reductive elimination of **390** proceeds with retention of configuration at the two centers undergoing C−C bond formation. Such a strategy has been used for the synthesis of cyclopropylglycine derivatives.[352] The chiral enantioenriched starting material **389** was prepared from the racemic mixture by resolution.

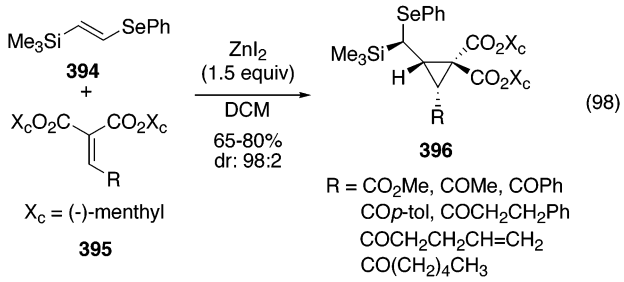
C. Removable Chiral Auxiliaries

1. Chiral Michael Acceptors

α,β-Unsaturated chiral esters constitute the first class of chiral auxiliaries used as Michael acceptors in these reactions. This approach was explored very early, but generally low diastereoselectivities were observed.[353] Krief reported that the cyclopropanation of bis-(−)-menthyl fumarates **392** with isopropylidenetriphenylphosphorane afforded an 88:12 mixture of stereoisomers (eq 97).[354]

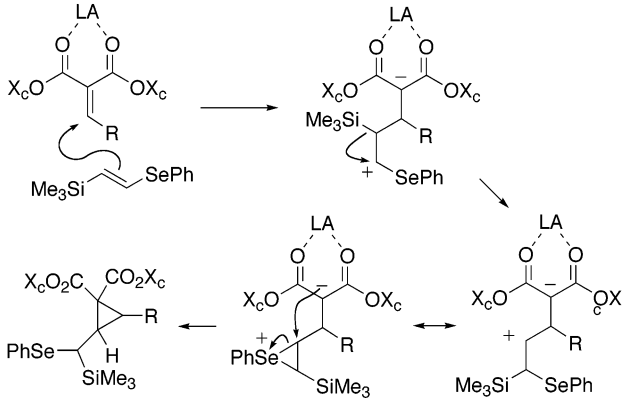


Yamazaki also reported the use of menthyl esters as chiral auxiliaries for the diastereoselective cyclopropanation of 1-seleno-2-silylethene **394** with di-(−)-menthyl ethene-1,1-dicarboxylates **395** in the presence of zinc halides (eq 98).[355]



Scheme 32 outlines a possible reaction course for the cyclopropanation with 1-seleno-2-silylethene **394**. The nucleophilic addition of the vinyl selenide **394** to the unsaturated ester, activated by the Lewis acid, generates the first zwitterionic species. A synclinal addition involving Se−C═O secondary orbital interactions (not shown) has been postulated. The 1,2-migration of the silicon atom yields the second zwitterionic species, which is stabilized by the selenium atom. The ring closure then produces the desired cyclopropane.

Scheme 32. Proposed Reaction Course for the Cyclopropanation with 1-Seleno-2-silylethene



The transition-state model shown in Figure 39 illustrates the stereochemical outcome of the reaction. Both menthyl groups were fixed by the chelation

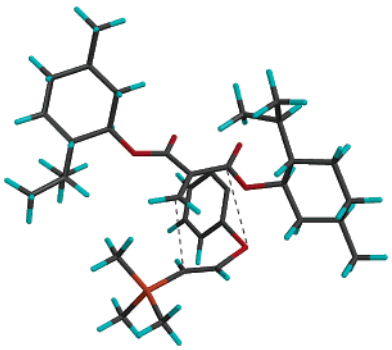
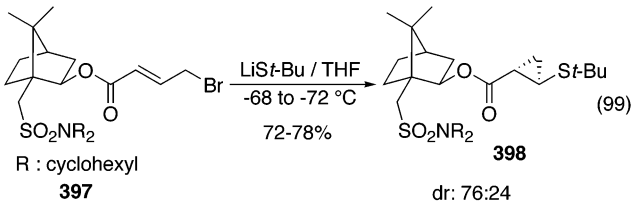


Figure 39. Synclinal approach of the vinylselenide **394** from the *si* face of the di-(−)-menthyl ethene-1,1-dicarboxylate **395** (R group was omitted for clarity).

with zinc iodide (not shown). The synclinal addition of vinyl selenide **394** occurred from the *si* face of di-(−)-menthylethene-1,1-dicarboxylate **395**. Approach from the *re* face would have resulted in steric repulsion between the selenium and the isopropyl moiety of the menthyl group.

The effectiveness of (−)-menthol, (−)-8-phenylmenthol, 10-dicyclohexylsulfanoyl-D-isoborneol, and Oppolzer's sultam-derived auxiliary has been tested by Little.[356] After considerable optimization, cyclopropyl derivative **398** was obtained in ca. 75% yield with very low diastereoselectivity (eq 99). No improvement in the diastereoselectivity was observed when Oppolzer's sultam was used. The use of (−)-menthol and (−)-8-phenylmenthol-derived auxiliary could not produce any stereochemical induction.



The attack of the nucleophile is speculated to occur preferentially from the backside at the β-carbon, in accord with Oppolzer's original model (Figure 40). The modest diastereoselectivity is imputed to a rapid equilibration between s-*cis* and s-*trans* conformers of the substrate in solution, each leading to two opposite enolates, **399** and **400**.

The use of (−)-8-phenylmenthyl-derived 3-aryl-2-phosphonoacrylates **403** also afforded a mixture of diastereoisomers upon treatment with methylenedimethylsulfoxonium (eq 100).[357] The reaction of *E* isomers afforded preferentially the *trans* isomers **407** (*trans*:*cis* = 67−75:25−33). The diastereoselectivity was better for the *trans* isomers (**407**/**405** = 85−93%) than for the *cis* isomers (**406**/**404** = 70−75%). The cyclopropanation of the *Z* isomers gave a nearly equimolar mixture of *cis*- and *trans*-cyclopropanes, with poor diastereoselectivities for both isomers.

One could explain the formation of the minor diastereoisomer with the *E* isomer here again by a rapid equilibration between s-*cis* and s-*trans* conformers. The same argument could also be used to account for the lack of selectivity with the *Z* isomer. However, the authors have postulated the contribution of a low-lying conformer, in which the acrylate moiety is twisted out of conjugation and both faces of the double bond are equally opened (Figure 41).

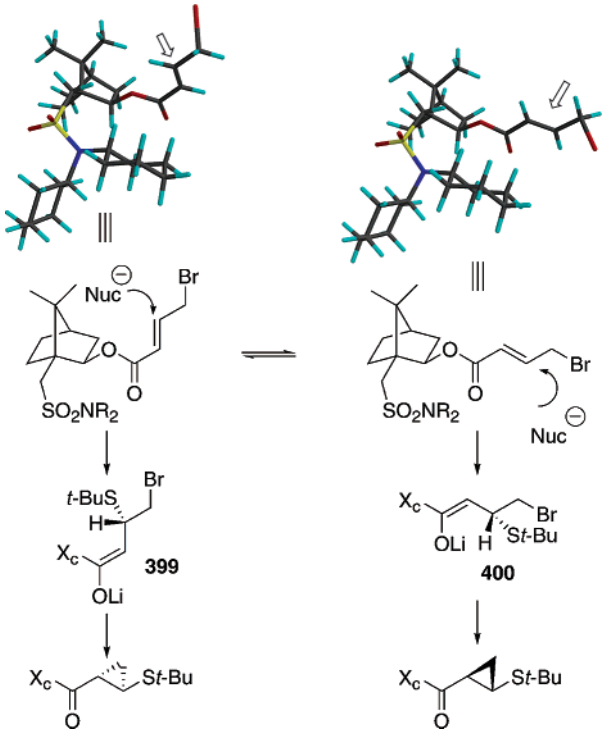
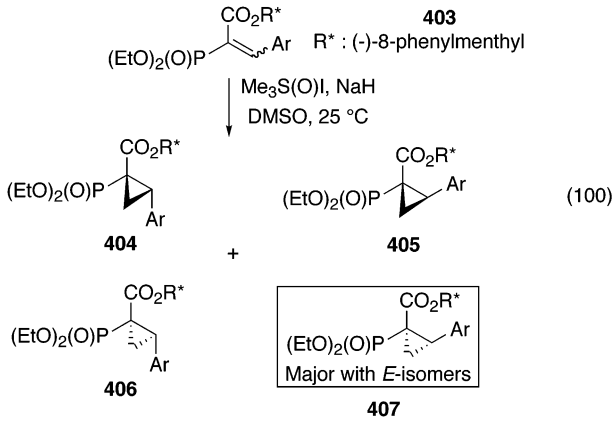


Figure 40. Stereochemical course for the cyclopropanation using 10-dicyclohexylsulfanoyl-D-isoborneol-derived auxiliary.



Tang and co-workers have reported that a variety of (−)-8-phenylmenthyl α,β-unsaturated esters could react with silylated allylic telluronium ylide **295** to provide silylvinylcyclopropane derivatives **408** with good diastereoselectivities and yields (Table 53).[358]

The phenyl group was proposed to block the *si* face of the alkene by a π-stacking effect between the phenyl and the dienyl groups of the (−)-8-phenylmenthyl α,β-unsaturated ester (Figure 42). The telluronium ylide attacked at C-3 on the *re* face; thus, compound **408** was sterically preferred and formed as the major product.

Scolastico described one example of a chiral auxiliary involving a chiral γ-substituted conjugated ester.[359] Isopropylidenetriphenylphosphorane reacted with oxazolidine **410** with excellent π-face selectivity (eq 101). Removal of the chiral auxiliary (1. $BF_3{\cdot}Et_2O$, $HSCH_2CH_2SH$; 2. MeI, H_2O, $CaCO_3$) afforded the

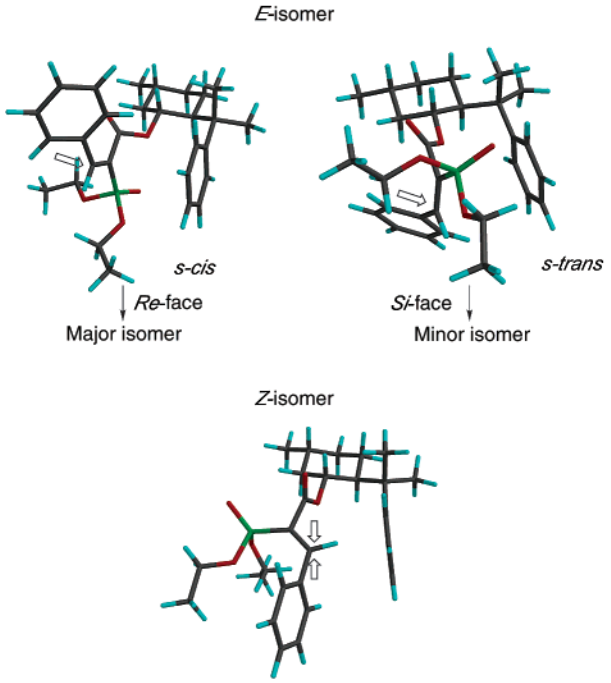
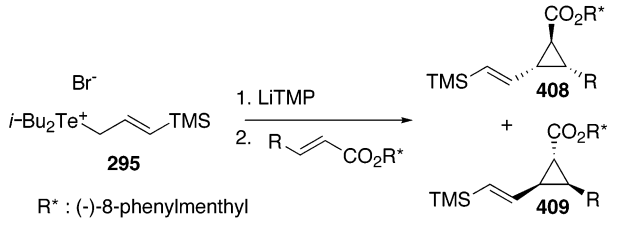
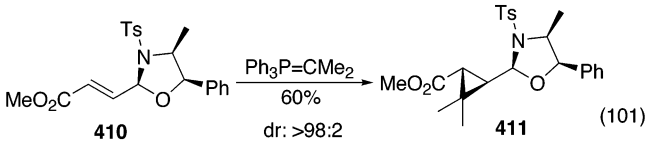


Figure 41. Speculated angle of attack in the cyclopropanation of (*E*)- and (*Z*)-(−)-8-phenylmenthyl-derived 3-aryl-2-phosphonoacrylates.

Table 53. Diastereoselective Cyclopropanation of (−)-8-Phenylmenthyl α,β-Unsaturated Esters with Silylated Allylic Telluronium Ylides



entry	R	yield (%)	ratio **408:409**
1	Ph	83	92:8
2	H	72	86:14
3	*p*-ClC_6H_4	94	88:12
4	*p*-FC_6H_4	100	90:10
5	*p*-MeC_6H_4	89	89:11
6	*p*-$CF_3C_6H_4$	94	88:12
7	*p*-$MeOC_6H_4$	90	86:14



(101)

corresponding hemicaronic aldehyde, which is a key intermediate for most syntheses of pyrethroids, such as chrysanthemic acid.[360]

The proposed transition state involves the conformer **412**, in which the A(1,3) strain is minimized and the most electronegative substituent (oxygen) is perpendicular to the π orbital of the alkene (Figure 43).[361]

Madalengoitia showed that the cyclopropanation of chiral *N*-enoyl oxazolidinones **413** with isopropylidenediphenylsulfonium in the presence of Lewis acids proceeded with a good level of diastereocontrol

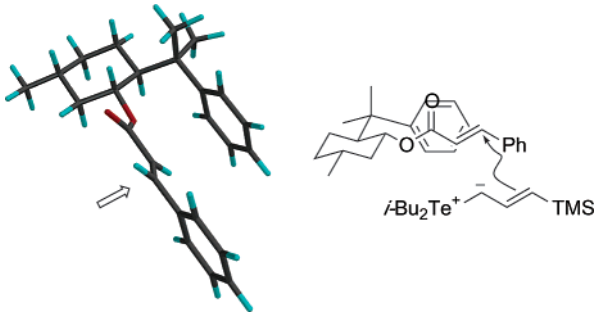


Figure 42. Postulated reactive conformer for the cyclopropanation of (−)-8-phenylmenthyl α,β-unsaturated esters and silylated telluronium ylides.

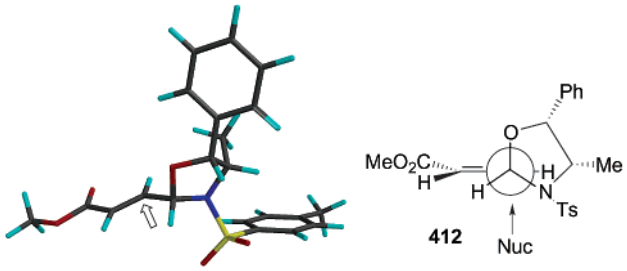
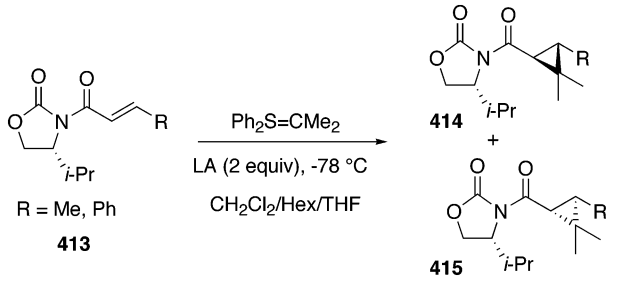


Figure 43. Preferred conformer for the diastereoselective cyclopropanation using oxazolidine auxiliary.

Table 54. Stereoselectivity in Lewis Acid-Mediated Cyclopropanation of *N*-Enoyl Oxazolidinones



entry	R	Lewis acid	yield (%)	ratio **414:415**
1	Me	none	79	33:67
2	Me	$Yb(OTf)_3$	84	91:9
3	Me	$Y(OTf)_3$	87	89:11
4	Ph	none	75	30:70
5	Ph	$Yb(OTf)_3$	75	93:7
6	Ph	$Y(OTf)_3$	71	70:30

to generate **414** (Table 54).[362] In the absence of Lewis acids, the diastereoselectivities were low, favoring **415** (entries 1 and 4).

However, when 2 equiv of $Yb(OTf)_3$ or $Y(OTf)_3$ was used, the stereoselectivity of the reaction was reversed, affording respectively a 10:1 and an 8:1 **414**:**415** ratio (entries 2 and 3). The same trend was observed with cinnamoyl oxazolidinone, albeit with a lower selectivity (entries 5 and 6). It was suggested that the Lewis acids chelates both carbonyl groups of the substrate, affording a dominant reactive rotamer in which one face of the β-carbon is shielded from attack (Scheme 33).

Meyers developed a very useful chiral auxiliary based on chiral bicyclic lactams prepared from l-valinol or l-*tert*-leucinol.[363] Cyclopropanations of the unsaturated lactams **416** were performed first, using

Scheme 33. Lewis Acid-Mediated Cyclopropanation of *N*-Enoyl Oxazolidinones

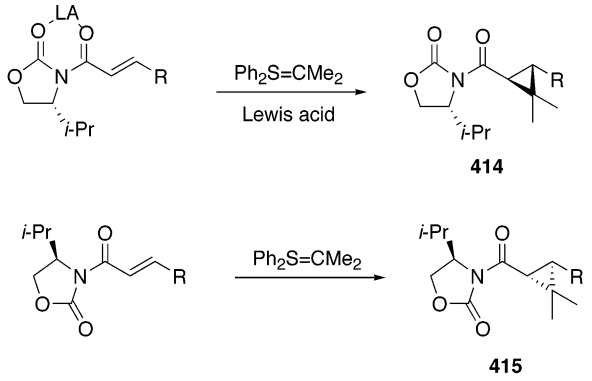
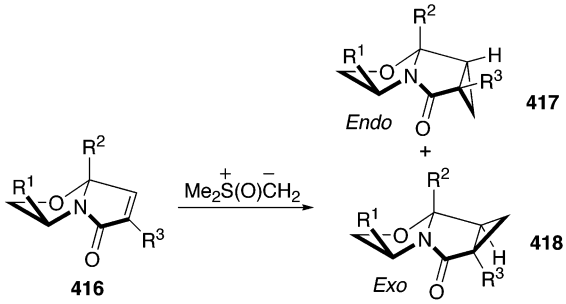


Table 55. Cyclopropanation of Chiral Unsaturated Lactams with Methylenedimethylsulfoxonium



entry	R^1	R^2	R^3	yield (%)	ratio **417**:**418**
1	*i*-Pr	CH_3	H	64	98:2
2	*i*-Pr	CH_3	CO_2CH_3	65	>99:1
3	*i*-Pr	CH_3	Ph	60	>98:2
4	*i*-Pr	CH_3	$SOCH_3$	90	>95:5
5	*i*-Pr	CH_3	SO_2CH_3	70	>95:5
6	*t*-Bu	CH_3	H	81	95:5
7	*i*-Pr	H	$SOCH_3$	50	<5:95<
8	*i*-Pr	H	CO_2CH_3	50	<3:97
9	*t*-Bu	H	H	40	<5:95<

methylenedimethylsulfoxonium ylide, and furnished the desired cyclopropane adduct **417** in good to excellent yields (Table 55).[364]

In all the cases, the cyclopropanation proceeded with a high degree of *exo*:*endo* (**416**:**417**) diastereoselectivity. However, the mode of addition was found to be highly dependent on the angular substituent of the unsaturated lactam, and a simple change from methyl to hydrogen leads to a complete reversal in *endo*:*exo* selectivity (Table 55, entries 1−6 vs 7−9). This method has been used recently for the preparation of a key precursor to (−)-indolizomycin.[365]

Substituted sulfonium ylides were also employed for the cyclopropanation of the unsaturated lactams and led to very high *endo*:*exo* selectivities. For example, treatment of **419** with isopropylidenediphenylsulfonium afforded the *gem*-dimethyl cyclopropyl adduct **420** in 94% yield and >99:1 dr (eq 102).[366]

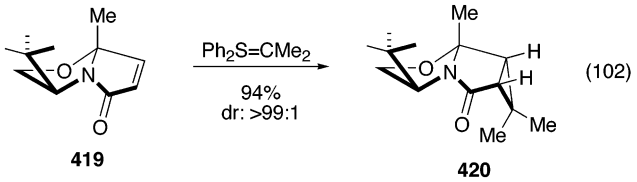
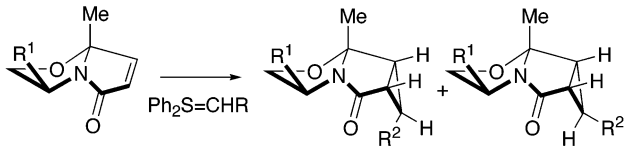
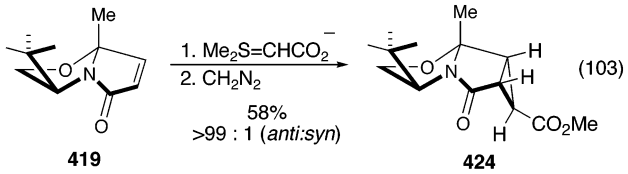


Table 56. Cyclopropanation of Chiral Unsaturated Lactams with Substituted Sulfur Ylides



entry	R^1	R^2	yield (%)	ratio **422**:**423**
1	*t*-Bu	Me	95	83:17
2	*t*-Bu	vinyl	59	97:3
3	*t*-Bu	Ph	41	88:12
4	*i*-Pr	Ph	47	>99:1

Unsymmetrical substituted sulfonium ylides produced very high *endo*:*exo* ratios and modest to excellent *anti*:*syn* selectivities. Methyl-, phenyl-, and vinylmethylenediphenylsulfonium gave 3:1 to >50:1 *syn*:*anti* ratios (Table 56), while the carboxymethylene sulfonium derivative led to the exclusive formation of the *anti* isomer **424** (eq 103),[367] probably as



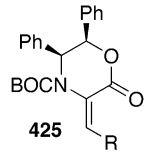
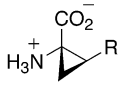
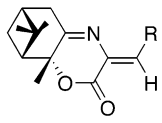
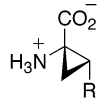
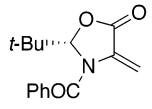
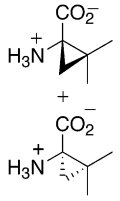
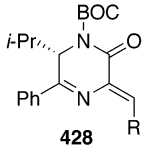
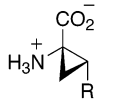
the result of thermodynamic equilibration of the initially formed *endo*-*syn*-carboxycyclopropyl adduct.

Removal of the chiral auxiliary from the cyclopropyl bicyclic lactam adducts was carried out using two procedures. In one procedure, acid hydrolysis led to the corresponding cyclopropylcarboxylate, but epimerization occurred in some cases prior to completion of the cleavage. An alternative way involved reduction of the lactam, followed by mild acid hydrolysis, to give the keto aldehyde.

Although the Cieplak effect was proposed as a possible explanation for the high facial selectivity observed during cyclopropanations, no directing effect was observed during cyclopropanation of the unsaturated lactam substituted in the angular position by a pentafluoroethyl group. Conversely, the steric environment in these systems is such that the nucleophiles (sulfur ylides) approach from the most sterically hindered *endo* face, thus eliminating simple steric arguments. Actually, the predominant mode of cyclopropanation can be predicted simply on the basis of the size of the angular substituent present in the bicyclic lactam. Nevertheless, whether another stereo or stereoelectronic effect is also operating is still an open question.[368]

A number of chiral auxiliaries have been elaborated for the preparation of enantiomerically pure cyclopropyl α-amino acids.[369] All these cyclic chiral auxiliaries, presented in Table 57, are based on a stereoselective cyclopropanation of an exocyclic double bond via an addition/elimination sequence. [(Diethylamino)phenyl]methylenesulfoxonium reacts with the diphenyltetrahydrooxazinone **425**, developed by Wil-

Table 57. Chiral Auxiliaries for Preparation of Cyclopropyl Amino Acids

Entry	Chiral Auxiliary	Conditions Yield (%) (dr (%))	Product of cleavage (**429**)
1	 **425**	$Ph(NEt_2)\overset{+}{S}(O)\overset{-}{C}H_2$ 79-96 (83-98)	
2	 **426**	$Me_2\overset{+}{S}(O)\overset{-}{C}H_2$ 45-95 (>99)	
3	 **427**	$Ph_3P{=}CMe_2$ *ca* 60 (0 or >98 after purification)	
4	 **428**	$Me_2\overset{+}{S}(O)\overset{-}{C}H_2$ 70-79 (83-92)	

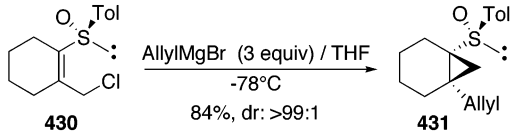
liams, to give cyclopropyl derivatives with excellent diastereoselectivities (Table 57, entry 1).[370]

π-Stacking between the phenyl group of the ylide and the aryl substituents was proposed to explain the fact that reactions occur on the same face as the diphenyl substituent of the oxazinone. Moreover, with a nonaromatic sulfoxonium ylide such as methylenedimethylsulfoxonium, lower diastereoratios were obtained (from 67:33 to 75:25). Reductive or oxidative cleavage of the chiral auxiliary liberated the cyclopropyl α-amino acid. Only the *trans* isomers were demonstrated to be accessible using this approach; the corresponding *cis* isomers have not been prepared by an analogous method.

A pinanone-derived chiral auxiliary **426** was described by Calmes. Methylenedimethylsulfoxonium addition afforded only one cyclopropyl derivative in 45−95% yield (Table 56, entry 2).[371] Nucleophilic attack occurred from the less hindered face opposite to the *gem*-dimethyl group, and elimination occurred prior to bond rotation. The same reaction, when applied to the *E* isomers, led to a mixture of two inseparable diastereoisomers (55:45). Alkylcyclopropane can be liberated from the chiral auxiliary by acid hydrolysis. However, cleavage of the chiral auxiliary from aryl cyclopropyl derivatives led to the opening of the cyclopropane.

Nájera and co-workers used Seebach's oxazolidine auxiliary **427** in the cyclopropanation reaction with phosphorus ylide (Table 56, entry 3).[372] Unfortunately, a 50:50 mixture of diastereoisomers was obtained. Nevertheless, they were separated by flash chromatography and recrystallization, and both enantiomers were obtained in enantiomerically pure form after acidic cleavage. The same authors also reported a six-membered-ring version, the chiral (*Z*)-α,β-didehydroamino acid derivatives **428**, as an equivalent of amino acid olefins (entry 4).[373] The cyclopropanation with Corey's dimethylsulfoxonium methylide furnished the corresponding spiro compounds as 92:8 (R = Me) and 96:4 (R = Et) mixtures of diastereoisomers. The major stereoisomers were isolated in 70% (R = Me) and 79% (R = Et) yields. Many attempts to hydrolyze the chiral auxiliary afforded decomposed products; only a 24% yield of *allo*-norcoronamic acid in high enantiomerical purity (>98% ee) was isolated after treatment with 3 M hydrochloric acid at 100 °C for 4 days. Only the *cis* isomers were reported.

Chiral vinyl sulfoxides have been used as Michael acceptors with a variety of nucleophiles, and the 1,4-addition proceeds generally with high asymmetric induction.[374] For example, the optically active vinylic sulfoxide **430** was stereoselectively transformed into the chiral cyclopropane **431** by means of a Michael addition reaction with an allyl Grignard reagent (eq 104).[375]



430 **431** (104)

One diastereoisomer was obtained, but the major product was contaminated with the coupling byproduct to the extent of about 10%. The yield of the desired cyclopropane decreases in favor of the coupling byproduct when cuprate reagents are used as the nucleophile or mesylate groups as the leaving group. Conversely, only the coupling product was observed with either methyl Grignard or methyl cuprate reagents. The transition-state model depicted in Figure 44 can rationalize the stereoselectivity. The

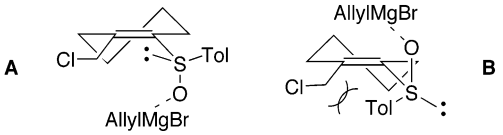
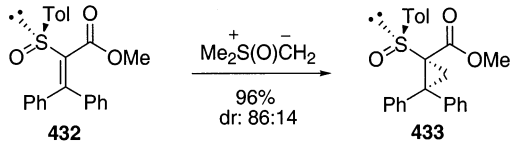


Figure 44. Models for the stereoselective addition of Grignard reagents to chiral sulfoxide **430**.

coordination of the Grignard reagent to the oxygen atom of the sulfinyl group was involved, followed by the preferential delivery from the bottom face through the energetically more favorable conformer **A**.

Acyclic chiral vinyl sulfoxides have also been converted into cyclopropanes. Michael addition of methylenedimethylsulfoxonium to optically pure methyl α-(*p*-tolylsulfinyl) acrylate **432** provided cyclopropylcarboxylic ester **433** in high yield and moderate stereoselectivity (eq 105).[376]



432 **433** (105)

The proposed transition state involves a nonchelate model in which the dipoles of the *p*-tolylsulfinyl and the carbonyl group are opposed (Figure 45). The 1,3-

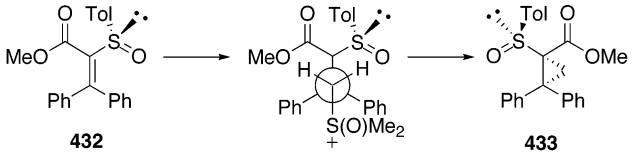
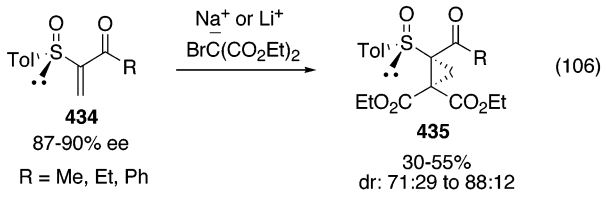


Figure 45. Model for the diastereoselective cyclopropanation of acyclic chiral vinyl sulfoxide **432**.

elimination occurred preferentially from the lone pair side of the *p*-toluenesulfinyl, leading to the formation of the major diastereoisomer.

Hiroy extended this strategy to the addition of the bromomalonate carbanion to chiral α-ketovinylic sulfoxide **434**. An acylcyclopropane derivative **435** was prepared in moderate yields and diastereoselectivities (eq 106).[377] The polarity and complexing ability of the solvent, as well as the nature of the base and the counterion, were shown to influence both the yield and the selectivity.



(106)

The diastereofacial selectivity in the enolate addition is opposite to that obtained with sulfur ylide (vide supra), since chelate formation between the carbonyl and sulfoxide oxygen is possible due to the presence of a complexing metal. The addition of bromomalonate enolate occurred from the sterically less crowded lone-pair side of the chiral sulfinyl substituent (Figure 46).

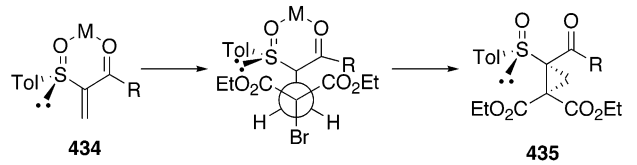
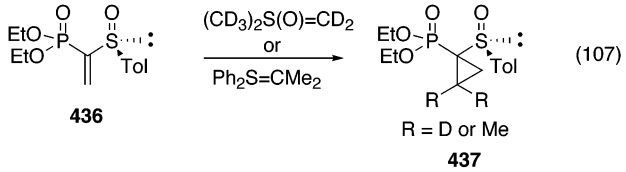


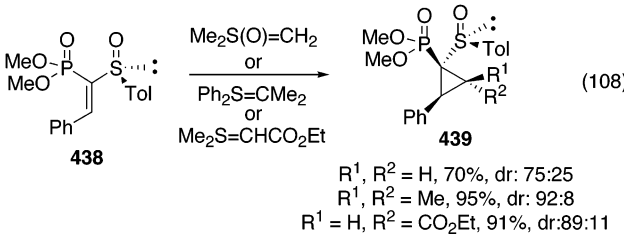
Figure 46. Model for the diastereoselective cyclopropanation of acyclic chiral vinyl sulfoxide **434**.

The (*S*)-(+)-α-(diethoxyphosphoryl)vinyl *p*-tolyl sulfoxide **436** reacted with deuterated methylenedimethylsulfoxonium and isopropylidenediphenylsulfonium, to form the corresponding cyclopropane **437** as a single diastereoisomer in good yield (eq 107).[378] However, the relative stereochemistry has not been established.



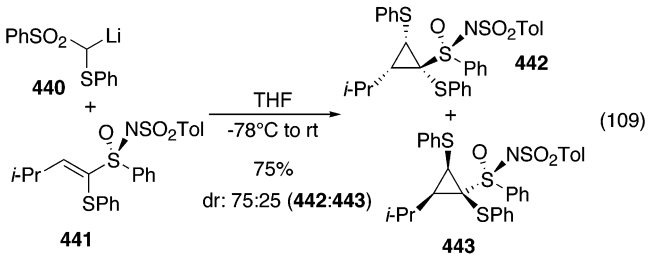
(107)

The same research group also reported the synthesis of 2-amino-3-phenyl-1-cyclopropanephosphonic acid, a constrained analogue of phaclofen, using a similar strategy.[379] Indeed, the cyclopropanation of chiral (*E*)-(*S*)-(1-dimethoxyphosphoryl-2-phenyl)vinyl *p*-tolyl sulfoxide **438** with various sulfur ylides afforded the desired cyclopropane derivatives with diastereomeric ratios ranging from 75:25 to 92:8 (eq 108).



(108)

Chiral sulfoximide can also be used as a chiral Michael acceptor.[380] Reaction between lithiated phenyl phenylthiomethyl sulfone **440** and 1-(phenylthio)-vinylsulfoximide **441** produced a mixture of two stereoisomeric cyclopropanes (**442** and **443**) in a 75:25 ratio (eq 109).[381]



(109)

2. Chiral Nucleophiles

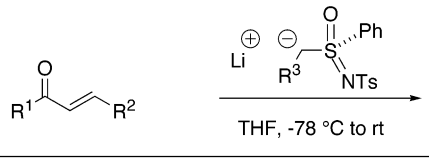
A variety of stoichiometric chiral nucleophiles have been developed in recent years to perform enantio- and diastereoselective cyclopropanation of alkenes. Indeed, chiral sulfur, phosphorus, and arsenic ylide derivatives as well as chiral enolates have been added to α,β-unsaturated carbonyl derivatives.

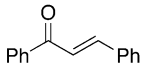
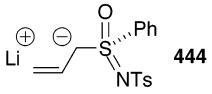
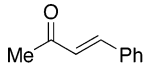
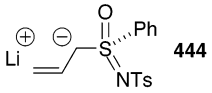
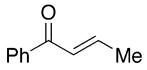
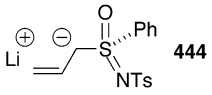
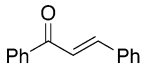
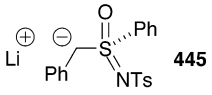
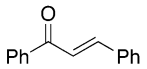
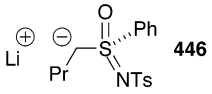
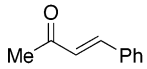
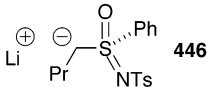
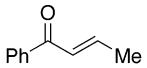
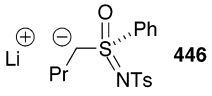
The asymmetric cyclopropanation using chiral sulfur ylides was reported as early as the 1960s, albeit with low enantioselectivities. Johnson was a pioneer in this area, developing a series of chiral aminosulfoxoniums which produce the optically active disubstituted cyclopropanes with up to 49% ee.[382]

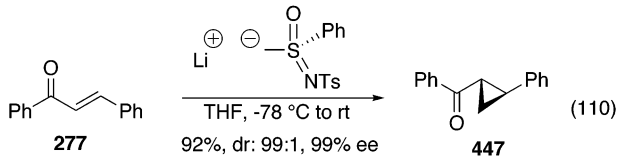
More recently, Pyne found that highly enantioenriched cyclopropanes were produced from lithiated *S*-allyl- (**444**), *S*-benzyl- (**445**), and *S*-alkyl-*N*-tosylsulfoximines (**446**) and enones (Table 58).[383] The stabilized lithiated sulfoximides undergo highly diastereoselective Michael reactions with the enones at −78 °C. The initially formed anionic Michael adducts ring-close upon warming to room temperature by an intramolecular displacement of the sulfonimidoyl group with inversion of configuration, to yield cyclopropanes.

Although moderate diastereoselectivities were obtained with the *S*-allyl derivative (**444**), the *S*-benzyl- (**445**) and *S*-alkyl-*N*-tosylsulfoximines (**446**) provided the corresponding cyclopropane with diastereomeric ratios greater than 96:4. The unsubstituted sulfoximine yielded the 1,2-disubstituted cyclopropanes **447** with a diastereomeric ratio of 99:1 and in 99% ee in the presence of chalcone (**277**) (eq 110). Lower yields and diastereomeric ratios were obtained with cyclohexenone derivatives.

Table 58. Asymmetric Cyclopropanation of Enones with Chiral Lithiated Sulfoximines



Entry	Enone	Sulfoximine	Cyclopropane Yield (%)	dr	ee, % (Major)
1		 **444** Rac	83	79:21	---
2		 **444** Rac 94% ee	91 91	91:9 91:9	--- 95
3		 **444** Rac	84	84:16	---
4		 **445** Rac	96	98:2	---
5		 **446** 99% ee	90	99:1	nd
6		 **446** 99% ee	58	99:1	nd
7		 **446** 99% ee	68	96:4	>98

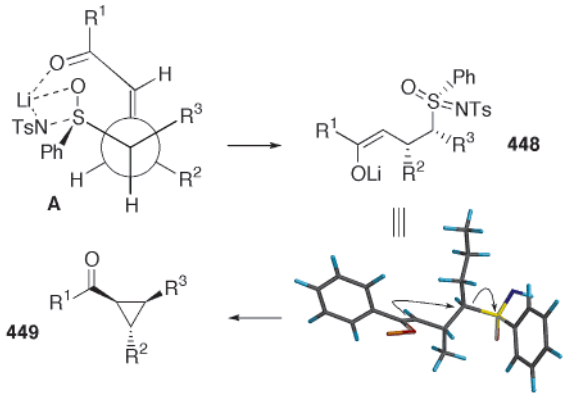


277 447 (110)

The stereochemical outcome of the reaction has been rationalized by the transition state **A**, in which the largest groups of the sulfoximide (the sulfonimidoyl moiety) and the enone (R^2) are *anti* in order to minimize steric interactions (Scheme 34). When the reaction was quenched with acetic acid at −78 °C, the 1,4-adduct derived from enolate **448** was isolated. In contrast, this enolate underwent an intramolecular displacement of the sulfonimidoyl moiety upon warming to room temperature, with inversion of configuration.

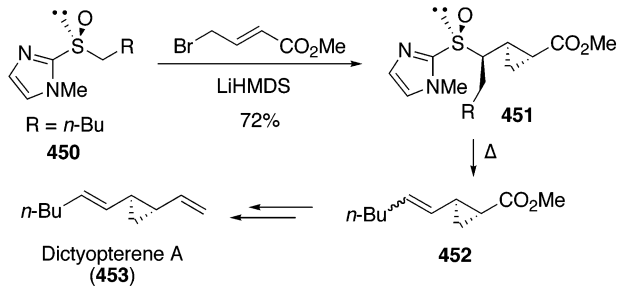
Other types of sulfur reagents were recently tested. Indeed, Walker found that the addition of chiral imidazolyl sulfoxide **450** to methyl 4-bromocrotonate

Scheme 34. Transition-State Model for the Enantioselective Cyclopropanation of Enones with Chiral Lithiated Sulfoximines

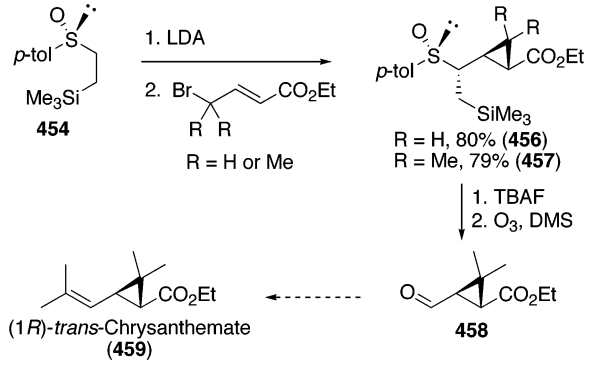


produced the cyclopropane **451** as a single diastereoisomer in good yield (Scheme 35).[384] Thermolysis of the cyclopropyl sulfoxide gave the vinyl cyclopropane

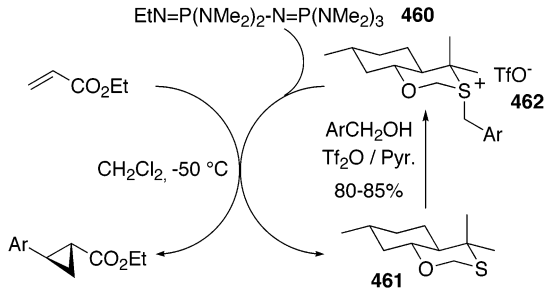
Scheme 35. Cyclopropanation Reaction with Chiral Sulfoxide 450



Scheme 36. Cyclopropanation Reaction with Chiral Sulfoxide 454



Scheme 37. MIRC Reaction with Chiral Oxathiane 461

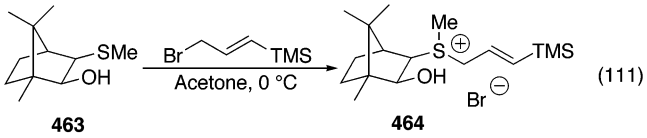


452 as a mixture of isomers. Standard transformations afforded dictyopterene A (**453**) in 50% overall yield.

A single diastereoisomer was also observed in the synthesis of β-(trimethylsilyl)ethyl cyclopropanecarboxylate derivatives from chiral *p*-tolyl β-(trimethylsilyl)ethyl sulfoxide **454** (Scheme 36).[385] The cyclopropanecarboxylate **457** was converted into cyclopropanecarboxaldehyde **458**, a chrysanthemate precursor.[386]

Chiral sulfonium ylides have been also reported for the asymmetric cyclopropanation of electrophilic alkenes. The reaction of chiral oxathiane **461** with arylmethyl alcohols in the presence of triflic anhydride produced a series of (arylmethyl)sulfonium salts **462** in 80−85% yield (Scheme 37).[387] The corresponding chiral sulfonium ylides were generated in situ upon treatment with a strong base, such as phosphazene bases [EtN═P(NMe$_2$)$_2$−N═P(NMe$_2$)$_3$] (**460**), and reacted with ethyl acrylate, leading to the corresponding cyclopropanes with good diastereoselectivities, favoring the *trans* isomers in high diastereomeric ratios and very high enantioselectivities (95−99% ee). Methylvinyl ketone is compatible with the reaction conditions, while acrolein led mainly to the corresponding epoxide. The chiral oxathiane **461** could be recovered from the reaction mixture with 80−89% yield.

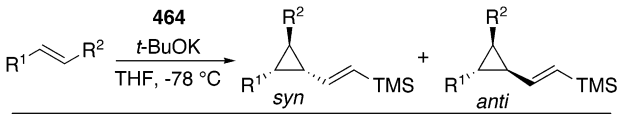
Using a similar strategy, Tang and co-workers prepared 1,2,3-trisubstituted vinylcyclopropanes with high enantioselectivities.[388] The chiral sulfonium salt **464** is readily available from the corresponding sulfide **463**, which is easily prepared from D-camphor (eq 111).



(111)

Excellent diastereo- and enantioselectivities were obtained with (*E*)-aryl-α,β-unsaturated carbonyl derivatives (Table 59), whereas low yields were observed with aliphatic alkenes as well as with *Z* isomers.

Table 59. Asymmetric Cyclopropanation of Michael Acceptors with 464



Entry	Alkene	Ratio (*syn* : *anti*)	Yield (%)	ee (%)
1	Ph, CO_2Me	>99 : 1	85	97
2	*p*-MeC_6H_4, CO_2Me	>99 : 1	80	97
3	*p*-$MeOC_6H_4$, CO_2Me	>99 : 1	59	96
4	2-furyl, CO_2Et	>99 : 1	57	97
5	Ph, $N(CH_2)_4$	>99 : 1	70	97
6	Ph, COPh	90 : 10	81	94
7	*p*-ClC_6H_4, CO*t*-Bu	92 : 8	64	95
8	Ph, CN	>99 : 1	61	94
9	*p*-BrC_6H_4, CN	>99 : 1	79	99
10	CO_2Me	>99 : 1	83	95

To account for the observed stereochemical outcome, the authors have proposed the transition-state model shown in Figure 47, in which the carbonyl group of the substrate is coordinated to the metal via a six-membered ring. The substrate reacts with the ylide from the *re* face to avoid the steric interaction between the R^1 group and the methyl substituent of the bicyclic system.

Aggarwal has developed a new and very elegant process for the in situ preparation of sulfur ylides and

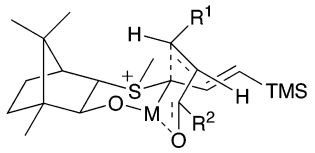
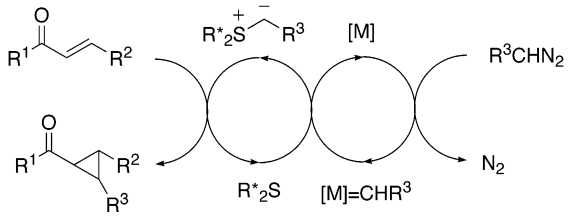


Figure 47. Proposed transition state for the cyclopropanation using **464**.

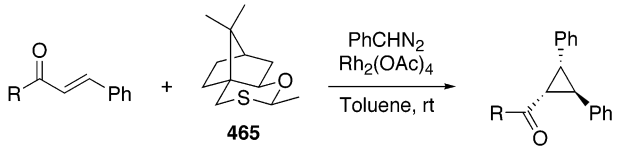
Scheme 38. Catalytic Cycle for the Formation of Sulfur Ylides from Diazo Reagents



has used this technology for asymmetric cyclopropanation reactions.[389] The chiral sulfur ylide is generated catalytically from a metal carbene intermediate which derived from the reaction of a metal complex and a diazo reagent (Scheme 38).

In the presence of a stoichiometric amount of chiral sulfide **465** and phenyldiazomethane, and a catalytic amount of rhodium acetate, cinnamate derivatives were transformed to the corresponding cyclopropane products with high enantiomeric excesses and moderate yields and diastereomer excesses (Table 60).[390]

Table 60. Rhodium-Catalyzed Asymmetric Cyclopropanation of Enones with Phenyldiazomethane and Chiral Sulfide 465

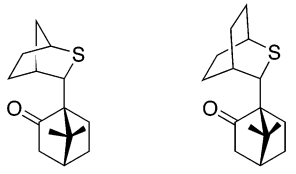


465

entry	R	sulfide (equiv)	yield (%)	dr	ee (%)
1	Ph	1.0	60	80:20	97
2	Ph	0.2	38	80:20	97
3	Me	1.0	55	80:20	>98
4	Me	0.2	14	80:20	>98
5	*p*-BrC_6H_4	1.0	35	80:20	>98

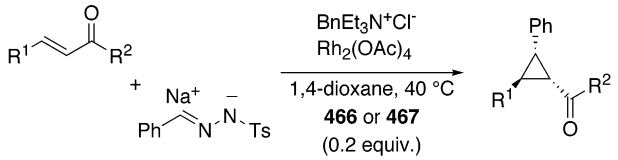
The major diastereoisomer is chiral, while the meso isomer was obtained in about 20%. In theory, the chiral sulfur ylide could be recycled and used in a substoichiometric amount. However, reduced yields were obtained when substoichiometric amounts of sulfide **465** were used.

A second generation of chiral sulfides, **466** and **467**, were developed and were shown to be more efficient for the catalytic version of the reaction.[391]



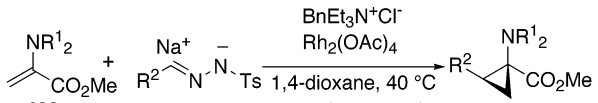
466 **467**

Table 61. Rhodium-Catalyzed Asymmetric Cyclopropanation of Enones with Chiral Sulfides 466 and 467

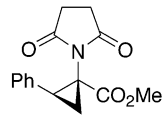
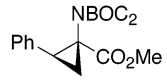
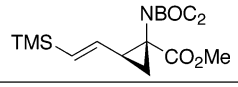


Entry	Alkene	Sulfide	Yield (%)	dr	ee (%)
1	Ph, COPh	**466**	30	84:16	89
2	Ph, COPh	**467**	73	80:20	91
3	Me, COPh	**467**	50	80:20	90
4	Ph, COMe	**467**	5	---	---
5	CO_2Me	**467**	10	88:12	---

Table 62. Synthesis of Cyclopropyl Amino Acids



469 **468** **467**, (0.2 equiv.) **470**

Entry	Cyclopropane	Yield (%)	dr	ee (%)
1		55	88:12	91
2		72	83:17	92
3		65	83:17	75

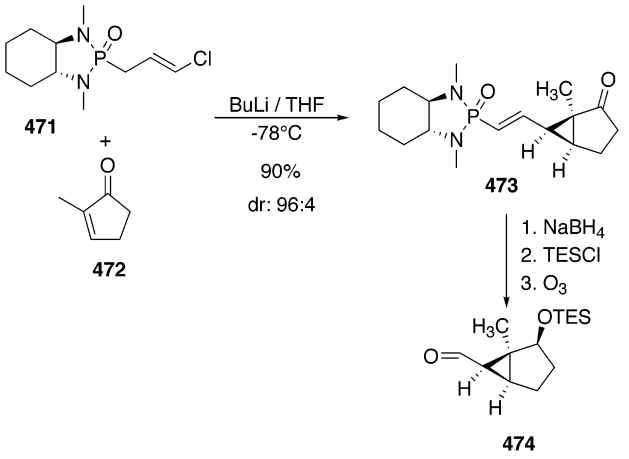
Indeed, the cyclopropane derived from chalcone was produced in 73% yield and 91% ee using 0.2 equiv of chiral sulfide **467**, albeit with a moderate diastereoselectivity of 60% (Table 61).

The in situ generation of the diazo reagent from the corresponding tosyl hydrazone derivatives **468**, using a phase-transfer catalyst, constitutes another improvement in this process. Cyclopropyl amino acids **470** can also be prepared from amino acrylate derivatives **469** with greater than 90% ee by using this strategy (Table 62).

Although phosphorus ylides are not as commonly used as sulfur ylides, several applications have been reported. Hanessian described an efficient and versatile protocol, involving a chiral phosphonamide-derived auxiliary, for the stereoselective synthesis of substituted cyclopropane derivatives.[392] The method consists of the highly stereocontrolled conjugate 1,4-addition of the anion derived from *trans*-chloroallyl phosphonamide **471** to conjugated compounds (such as **472**) (Scheme 39). A subsequent ring closure leads to the formation of the corresponding *endo,endo*-cyclopropane with excellent yields and diastereoselectivities. The chiral auxiliary was removed by ozonolysis to generate the cyclopropyl aldehyde **474**, which can be epimerized to the *exo,endo* isomer. Alternatively, the use of the *cis*-chloroallyl phosphonamide reagent under the same conditions led to the *exo,endo* product.

This method was extended to a variety of Michael acceptors, such as α,*β*-unsaturated *γ*-lactones, *δ*-lac-

Scheme 39. Hanessian's Chiral Auxiliary for the MIRC Reaction



tones, γ-lactams, and acyclic esters. Again, the preponderant or exclusive products were the *endo,endo* isomers (95:8 to >98:2 diastereoselectivity), in 51−88% yield. The phosphonamide derivatives could be further manipulated by chemoselective reactions to generate functionally diverse cyclopropanes.[393,394] Such a strategy was used for the enantioselective and total synthesis of the cytotoxic agent (−)-anthoplalone.[395,396]

It was suggested than the approach of the carbonyl substrate most probably occurs from the more accessible "left cleft" of the reagent, as shown in Figure 48. Attack of the γ-chloroallylic anion occurs on the

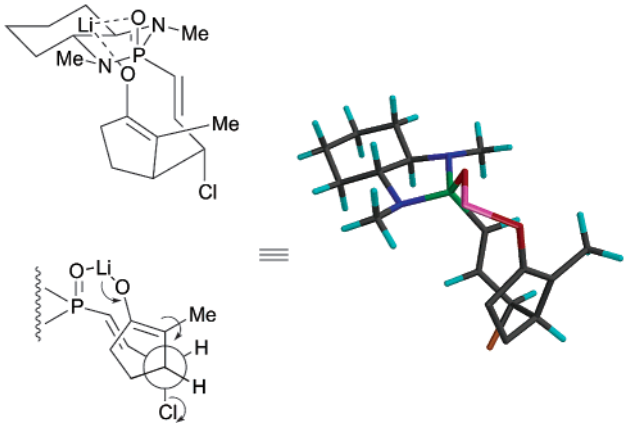


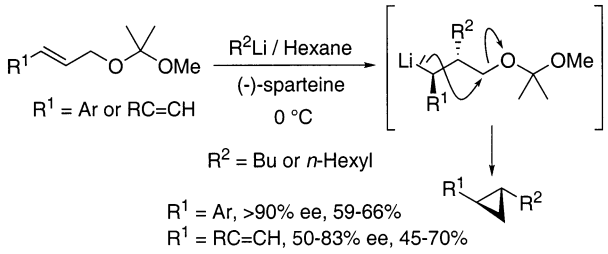
Figure 48. Transition-state model for the diastereoselective cyclopropanation using chiral phosphonamide **471**.

re face of the cyclic enone, leading to a Li-chelated enolate intermediate, which expels chloride to give the observed product.

Other chiral ylides, such as pyridinium and arsonium ylides, have been reported, but low enantioselectivities were typically observed.[397,398] The use of lithium anions and enolates as chiral reagents for MIRC reactions have also been described, as outlined below.

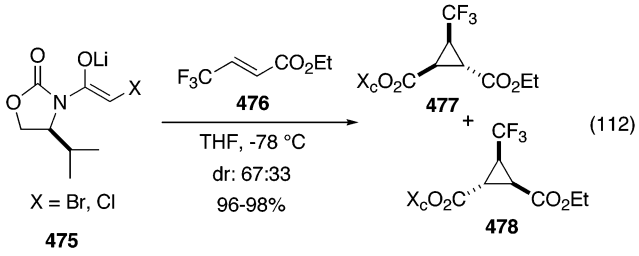
Chiral cyclopropane subunits were also prepared from alkenes via the (−)-sparteine-catalyzed carbolithiation reaction, as reported by Marek and coworkers.[399] High enantioselectivities (>90% ee) were obtained when cinnamate derivatives were used

Scheme 40. Enantioselective Carbolithiation of Alkenes Leading to Chiral Cyclopropanes



(when R^1 = Ph), while vinylcyclopropanes (R^1 = RCH=CH) were produced in 50−83% ee (Scheme 40).[400]

In the course of studies directed toward the synthesis of trifluoromethylated compounds, Yamazaki and Kitazume explored the use of the enolate derived from Evans's chiral auxiliary as a chiral nucleophile in the cyclopropanation reaction.[401] Reaction between (*E*)-ethyl-3-(trifluoromethyl) acrylate (**476**) and α-haloacyloxazolidinone enolate **475** afforded chiral cyclopropanes **477** and **478** as a 67:33 mixture of two out of eight possible stereoisomers (eq 112).



(112)

On the basis of the results of 1,4-addition of the other oxazolidinones to the (*E*)-ethyl-3-(trifluoromethyl)acrylate (**476**), Yamazaki and Kitazume proposed the formation of the *anti* isomer **479** (Figure 49). Elimination provided two possible cyclopropyl

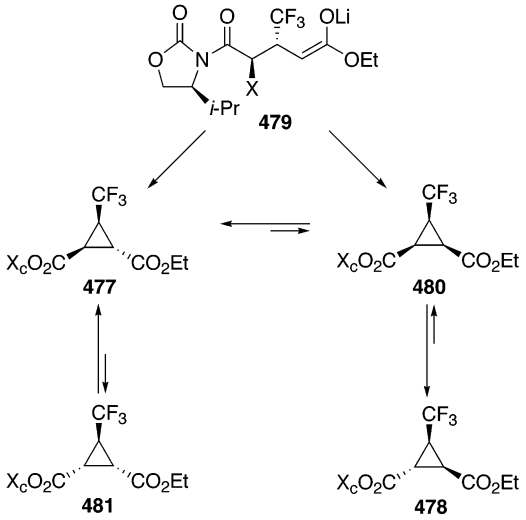
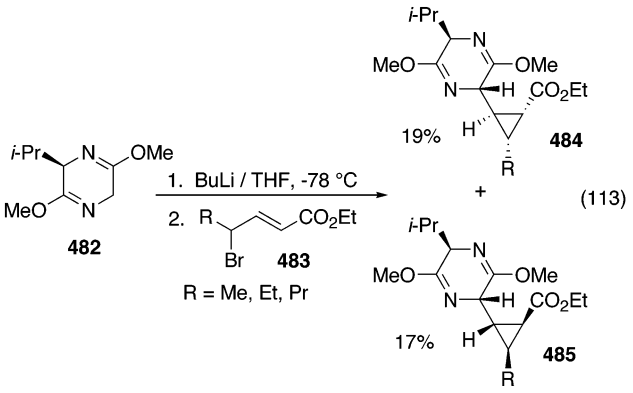


Figure 49. Proposed mechanism for the stereoselective cyclopropanation.

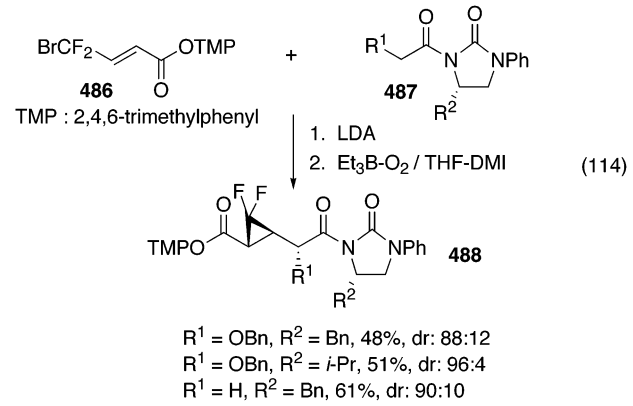
derivatives, **477** and **480**, and a subsequent epimerization at the ester center accounted for the erosion of the diastereoselectivities.

Stoichiometric chiral nucleophiles that are added to electrophilic substrates containing a leaving group have been also developed, as illustrated by the two examples below. The alkylation of lithiated bislactim ethers **482** with racemic 4-alkyl-4-bromobut-2-enoates **483** led to a 50:50 mixture of the corresponding diastereoisomers, which could be separated by flash chromatography (eq 113).[402] The hydrolysis of the adducts afforded the enantiomerically pure α-cyclopropyl-α-amino acids.



(113)

The synthesis of *trans-gem*-difluorocyclopropanecarboxylates **488** was achieved with good diastereoselectivities via the Michael addition of the lithium enolate of homochiral *N*-acylimidazolidinone **487** to 2,4,6-trimethylphenyl 4-bromo-4,4-difluorocrotonate (**486**), followed by a triethylborane-mediated intramolecular substitution reaction (eq 114).[403]



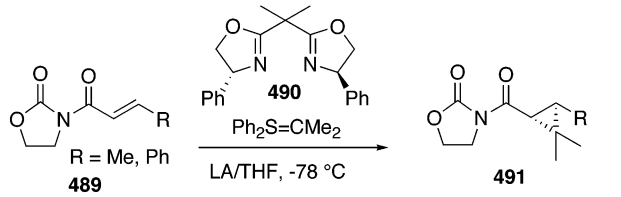
(114)

The examples above have illustrated that research toward the development of efficient chiral auxiliaries for MIRC reactions has been very active. Although chiral acceptors were first introduced, highly versatile chiral nucleophile systems are now available.

D. Stoichiometric and Catalytic Promoters

Until now, few promoters have been reported for enantioselective MIRC reactions. Madalengoitia reported the first examples of chiral Lewis acid-mediated asymmetric cyclopropanations of a Michael acceptor with a sulfur ylide.[362] The cyclopropanation of *N*-enoyloxazolidinones **489** with isopropylidenediphenylsulfonium, mediated by Lewis acids complexed to chiral bis(oxazoline) **490** (1 equiv), proceeded with high enantioselectivities, as shown in Table 63.

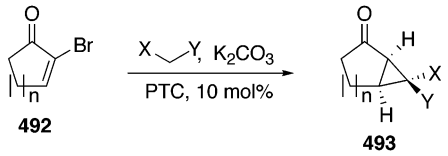
Table 63. Chiral Lewis Acid-Mediated Enantioselective Cyclopropanation of *N*-Enoyloxazolidinones



entry	R	Lewis acid	yield (%)	ee (%)
1	Me	$Zn(OTf)_2$ (1 equiv)	63	95
2	Me	$Mg(OTf)_2$ (1 equiv)	57	92
3	Me	$ZnBr_2$ (1 equiv)	60	93
4	Me	$ZnCl_2$ (1 equiv)	53	92
5	Me	$Zn(OTf)_2$ (0.75 equiv)	65	82
6	Me	$Zn(OTf)_2$ (0.5 equiv)	63	55
7	Ph	$Zn(OTf)_2$ (1 equiv)	69	36
8	Ph	MgI_2 (1 equiv)	70	14

It is apparent that a number of Lewis acids afforded the desired cyclopropane in good yields and excellent levels of enantioselection (entries 1−4). Interestingly, the asymmetric reaction of the cinnamate derivatives proceeded in low enantiomeric excess (entries 7 and 8) and appears to parallel the trends observed with the chiral auxiliary (see Table 54). Unfortunately, the course of the reaction is dependent on Lewis acid stoichiometry; thus, a loss of stereoselectivity was observed with less than 1 equiv of Lewis acid (entries 5 and 6).

Shioiri reported the use of phase-transfer catalysts (PTCs) for the synthesis of 1,2,3-trisubstituted cyclopropanes **493** from α-halocycloalkenones **492** and stabilized carbanions (eq 115).[404]



(115)

Good yields and moderate to high diastereoselectivities were observed. However, modest enantioselectivities (49−83% ee) were typically obtained with chiral PTCs.[405]

Finally, chiral Lewis acids have been tested in the cycloaddition reactions of 1-seleno-2-silylethene, but low yields (33−41%) and enantioselectivities (43−47%) have been observed.[406]

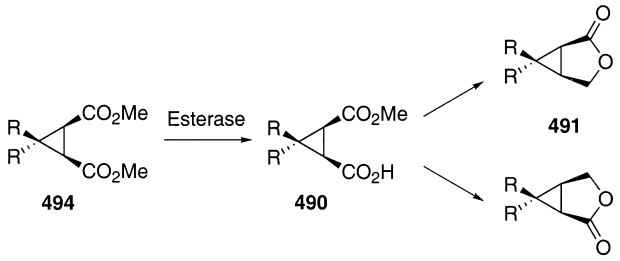
In conclusion, a practical level of enantioselectivity has yet to be achieved in catalytic MIRC reactions. The use of chiral auxiliaries or stoichiometric promoters is still the best choice to produce enantioenriched cyclopropanes with ylide chemistry. A number of efficient chiral nucleophiles have recently been developed and are particularly useful for the synthesis of enantioenriched 1,2,3-trisubstituted cyclopropanes.

V. Other Methods

A. Enzymatic Methods

Other methods have been developed over the years to access chiral enantioenriched cyclopropanes. This

Scheme 41. Enzymatic Desymmetrization of Meso Diesters

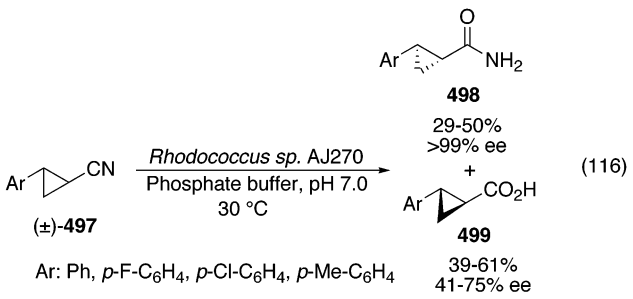


section will briefly outline some of these methods by focusing on the most recent examples.

Enzymes and microorganisms have been extensively used for the resolution of racemates and the desymmetrization of meso compounds, thus producing enantioenriched building blocks.[407] Among them, the hydrolases, such as lipases and esterases, have been frequently used in the synthesis of chiral cyclopropanes. Many processes were reported in the 1980s and early 1990s for the desymmetrization of diester cyclopropanes such as **494**. The enantiomeric excess ranges from 20 to 100%, depending on the substituents and the esterase source (Scheme 41).[408]

Lipases[409] are the other category of hydrolases that have been extensively studied. Indeed, the hydrolysis of *cis*-diacetoxy-1,2-cyclopropylcarbinols produces enantioenriched cyclopropylmethanol units with up to 99% ee, by enantiotopic group differentiation.[410] Such a strategy was used for the preparation of chiral fluorocyclopropanes with greater than 90% ee.[411] Seebach has reported the use Ti-taddolates as an alternative to hydrolytic enzymes for the ring opening of cyclic *meso*-anhydrides, including cyclopropane derivatives.[412]

In general, the kinetic resolution of cyclopropanes using hydrolases provides modest selectivities compared to those observed in the desymmetrization of meso compounds. Selectivity factors (*e*) greater than 40 are rarely observed.[413] Sometimes, better selectivities are observed with substituted substrates or substrates containing chiral centers other than the cyclopropane moiety.[414] The kinetic resolution of racemic substituted cyclopropanyl carboxylic acids, anchored on a solid support with lipase, has been also described, providing a simple technique for the separation of the starting material and the product.[415] Recently, the hydrolytic kinetic resolution of *trans*-2-arylcyclopropanecarbonitriles **497** using a microbial cell, *Rhodococcus sp* AJ270, was described (eq 116).[416]



(116)

The corresponding amides **498** were recovered with good to excellent enantioselectivities for a variety of aryl substrates bearing *para* substituents, such as methyl, chloro, and fluoro. In contrast, the reaction with 2-(4-methoxyphenyl)cyclopropanecarbonitrile proceeded with a poor selectivity.

Scheme 42. Lipase-Catalyzed Kinetic Resolution of Cyclopropyl Acetals

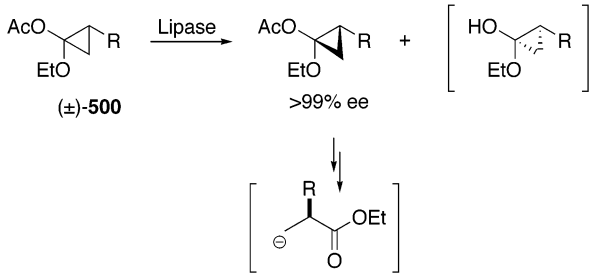
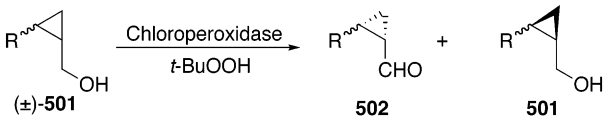


Table 64. Chloroperoxidase-Catalyzed Kinetic Resolution of Cyclopropylmethanol



		aldehyde		alcohol		
entry	R	yield (%)	ee (%)	yield (%)	ee (%)	*e*
		E Isomer				
1	Ph	34	3	60	15	1.2
2	$ArOCH_2$	39		31	20	1.6
3	$BrCH_2CH_2$	48	18	31	21	1.7
4	$Br(CH_2)_3$	33	31	46	22	2.3
		Z Isomer				
5	Ph	7	65	>90	18	6.0
6	$C_6H_4CH_3$	32	66	45	95	35
7	CH_3	37	90	60	37	27
8	CH_3CH_2	30	89	57	57	30
9	*n*-Pr	44	82	42	93	34
10	$ArOCH_2$	40	92	57	57	44
11	$BrCH_2CH_2$	35	91	50	83	60

The lipase-catalyzed kinetic resolution of cyclopropyl acetals **500** was recently disclosed (Scheme 42).[417]

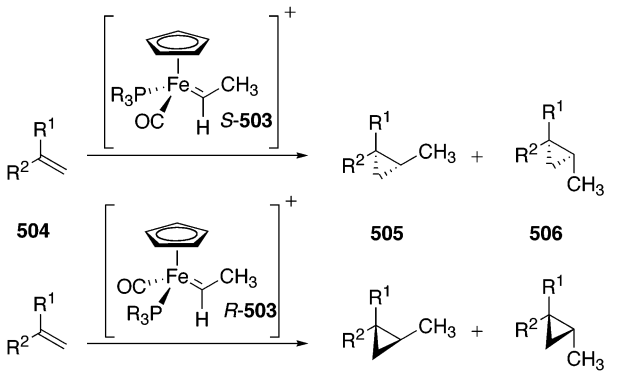
After the reaction, the starting material could be recovered with greater than 99% ee when *Candida antarctica* was used. A different enzyme, *Pseudomonas cepacia*, was used to isolate the other enantiomer of the starting material with 96−98% ee. Subsequent opening of the cyclopropyl acetals with $ZnCl_2$ leads to chiral, nonracemic α-substituted zinc homoenolate.

Jones showed that enzymes that catalyze oxidation reactions could be successfully used for the desymmetrization of meso diols, leading to enantiomerically pure γ-lactones in a convenient one-step route.[418] Very recently, Dordick disclosed the use of chloroperoxidase as a catalyst for the oxidation of cyclopropylmethanols, using *tert*-butyl hydroperoxide as the terminal oxidant.[419] Although the selectivity of the enzyme with the *trans* isomer of the cyclopropylmethanols was very low, a practical level of selectivity was observed with the *cis* isomer, leading to the desired aldehyde with 82−92% ee, when the substituent was aliphatic (Table 64).

B. Chiral Stoichiometric Carbenes

Previously in this review, we discussed the transition metal-catalyzed cyclopropanation of olefins with

Table 65. Ethylidene Transfer from Chiral Cationic Iron−Carbene Complexes 503 to Alkenes



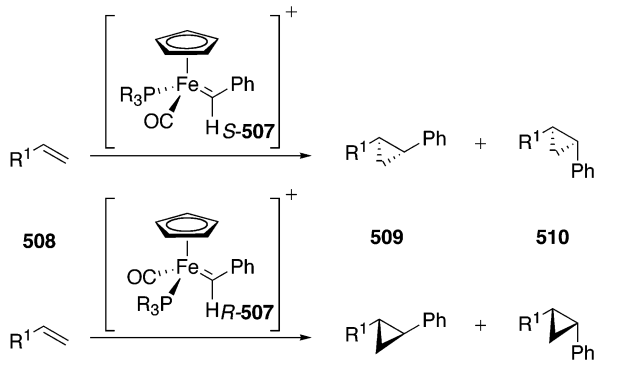
	carbene complex			alkene		cyclopropane		
entry	R^3	chirality at Fe	ee (%)	R^1	R^2	yield (%)	ratio *E*:*Z*	ee (%) product *E*/*Z*
1	Ph_2R^a	*S*	98	H	Ph	75	3.5:1	88/84
2	Ph_2R^a	*R*	92	H	Ph	75	4.0:1	83/77
3	Ph_2R^a	*S*	96	H	OAc	33	1.9:1	72/64
4	Ph_2R^a	*S*	98	OAc	Me	40	1:1.3	92/86
5	Ph_3	*S*	100	H	OAc	30	2.3:1	95/83
6	Me_3	*R*	77	H	OAc	50	1.6:1	70/70
7	Et_3	*R*	76	H	OAc	35	1.8:1	71/68
8	Me_3	*S*	87	H	OAc	59	1.6:1	76/76
9	Et_3	*S*	77	H	OAc	27	1.8:1	75/73

[a] R = (*S*)-$CH_2CH(CH_3)CH_2CH_3$.

diazo reagents, thought to involve the intermediacy of metal carbene complexes. In parallel to these processes, the development of chiral stoichiometric metal carbene systems as cyclopropanating reagents has also been disclosed in the literature.[420] Although they have not been used extensively, success has been achieved with iron-[421] and chromium-derived carbene systems.[422] The introduction of chiral iron complexes in the stereoselective synthesis of cyclopropanes appeared as early as 1974;[423] however, low enantiomeric excesses (40% ee) were observed for the methylene transfer.[424] Brookhart demonstrated later that much higher enantioselectivities could be achived when the carbene carbon was prochiral. Indeed, the cyclopropanation reaction of styrene, vinyl, and isopropenyl acetate with enantiomerically pure or enriched cationic iron carbene complexes **503** yielded the corresponding methylcyclopropanes with moderate to good enantioselectivities (Table 65).[425] However, the *trans*:*cis* ratio was typically below 4:1, favoring the *trans* isomer. Brookhart also described the benzylidene transfer from iron complexes **507** (Table 66).[426] In this case, the formation of the *cis* isomer was predominant with vinyl acetate.

Hossain reported a simple, efficient method to generate electrophilic iron carbenes from diversely substituted aldehydes.[427] For instance, he could easily prepare chiral iron carbenes from chiral aldehydes. Indeed, the reaction of the [$CpFe(CO)_2$] anion **511** with chiral (+) or (−)-*o*-anisaldehyde(tricarbonyl)-chromium **512** in the presence of chlorotrimethylsilane produced the optically pure (+) or (−) bimetallic complex **513** (Scheme 43). Subsequent treatment with trimethylsilyltriflate produced the chiral carbene **514**.

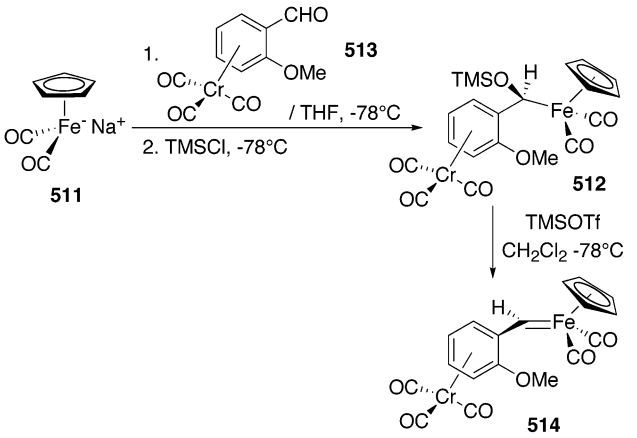
Table 66. Benzylidene Transfer from Chiral Cationic Iron−Carbene Complexes 507 to Alkenes



	carbene complex			olefin	cyclopropane		
entry	R^3	chirality at Fe	ee (%)	R^1	yield (%)	ratio *E*:*Z*	ee (%) product *E*/*Z*
1	Ph_2R^a	*S*	96	CH_3	nd[b]	1.5:1	73/51
2	Ph_2R^a	*R*	90	CH_3	nd	1.5:1	64/41
3	Ph_2R^a	*S*	96	OAc	30	1:4.0	83/69
4	Ph_2R^a	*R*	90	OAc	30	1:4.0	92/74
5	Et_3	*R*	nd	OAc	24	1:4.0	43/36
6	Et_3	*S*	nd	OAc	21	1:4.0	47/35

[a] R = (*S*)-$CH_2CH(CH_3)CH_2CH_3$. [b] nd, not determined.

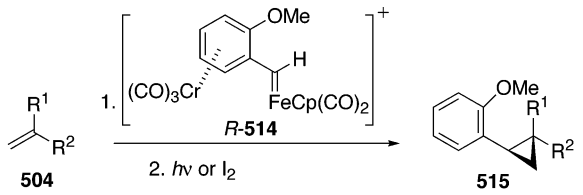
Scheme 43. Preparation of Chiral Carbene 511



The reactions of these chiral iron carbene complexes with olefins, followed by the decomplexation reaction with iodine or photolysis, provided the corresponding cyclopropanes in high yield (Table 67).[428]

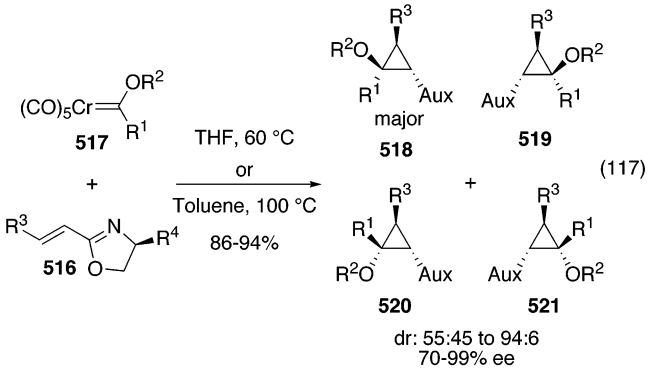
Upon reaction with *gem*-disubstituted olefins, carbene **514** produced the desired cyclopropanes with excellent enantioselectivity. In the presence of styrene derivatives, mainly the *cis* isomer was obtained, but with moderate to low enantioselectivities. It was also reported that alkyl-substituted alkenes gave predominantly the *trans* isomers, although no enantiomeric excesses were disclosed. Hossain has investigated the origin of diastereoselectivitity and found that the carbene **514** is quite stable and less reactive, resulting in a late transition state, which accounts for the *trans* selectivity observed with nonaromatic alkenes.[429] The formation of the *cis* isomer with aromatic alkenes may be explained by a strong π-stacking effect.

Table 67. Enantioselective Carbene Transfer Reactions from 514 to Alkenes



entry	R^1	R^2	yield (%)	ratio *Z*:*E*	ee (%) *Z*/*E*
1	Me	Me	90		>95
2	Ph	Ph	85		92
3	Ph	H	93	10:1	60/−
4	*p*-MeC_6H_4	H	90	7:1	55/−
5	*p*-ClC_6H_4	H	60	6:1	46/53
6	*p*-$CF_3C_6H_4$	H	45	3:1	30/72

A variety of substituted cyclopropanes have been synthesized from chromium carbenes and alkenes.[430] This approach has been particularly useful for the synthesis of alkoxy-substituted cyclopropanes. Although the diastereoselectivity of this reaction has been investigated considerably, an enantioselective version, with chiral metal complexes, has yet to be described.[431] Recently, Barluenga reported that chiral oxazolines **516** could be used as chiral auxiliaries for the cyclopropanation with chromium complex **517** (eq 117).[432]



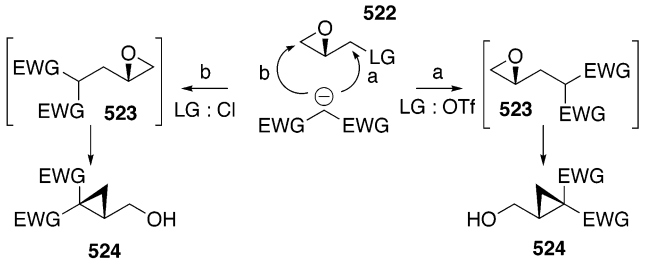
The reaction proceeded with good diastereocontrol and high enantiomeric excesses (70−99% ee). However, the chiral auxiliary cannot be removed without destroying the cyclopropyl moiety.

C. Other Ring-Closing Reactions of Chiral Precursors

Chiral cyclopropanes have been also elaborated from chiral building blocks, mainly chiral 1,2-electrophiles. Among them, epichloro- or epibromohydrins, glycidol derivatives, and cyclic 1,2-sulfates[433] are very popular, as they are readily available. A variety of nucleophiles, including malonate-, β-phosphonate-, ketone-, sulfone-, and nitrile-derived carbanions, were studied.[434−436] Two pathways are possible for the double displacement of epichloro- or epibromohydrins and the glycidol derivatives, which are dependent on the nature of the leaving group (Scheme 44).[437]

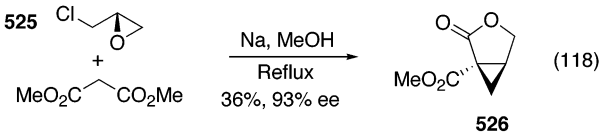
In path a, the direct displacement of the leaving group is followed by the ring opening of the epoxide,

Scheme 44. Synthesis of Chiral Cyclopropanes from Chiral Epoxides

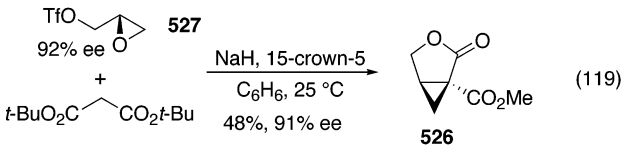


whereas the ring opening of the epoxide is the first step in path b, followed by the Payne rearrangement to generate a new epoxide, and then cyclization. The importance of controlling the two pathways is instrumental; each of them gives access to the opposite enantiomer.

Pirrung first observed that the reaction with sodium dimethylmalonate and optically pure epichlorohydrin (**525**) proceeded through path b and the corresponding bicyclic lactone **526** was isolated in 36% yield and 93.4% ee (eq 118).[438]



Conversely, Burgess disclosed that the reaction of glycidyl triflate **527** (92% ee) and sodium di-*tert*-butylmalonate led to the formation of the lactone **526** with the opposite configuration in 48% yield and 91% ee (eq 119).[439]



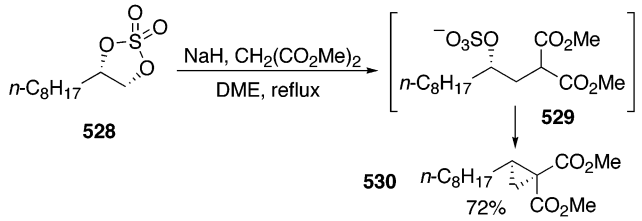
Otera and Furukawa showed that the yield could be slightly improved by using glycidyl 3-nitrobenzenesulfonate (nosylate) and cesium fluoride.[440] More recently, Shuto and co-workers reported the synthesis of substituted chiral cyclopropane lactones from phenyl- or phenylsulfonylacetonitrile and epichlorohydrin in 67% and 82% yield and with 96% and 98% ee, respectively.[441,442]

Sharpless demonstrated that cyclic sulfates of vicinal diols such as **528** could serve as 1,2-electrophile for double displacement with malonate anions, thus producing cyclopropane derivatives in good yields and with complete inversion of configuration (Scheme 45).[443]

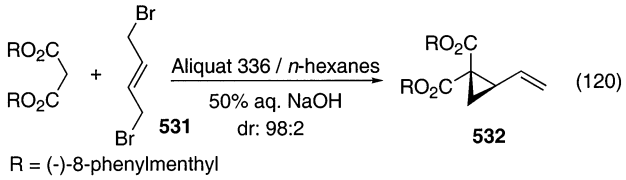
In general, better yields are obtained with cyclic sulfates compared to epoxide derivatives.[444,445] Such a strategy was used for the synthesis of enantioenriched methylenecyclopropanes.[446] In addition, the use of chiral 1,2-electrophiles has found many applications in the synthesis of aminocyclopropanecarboxylic acids from masked glycine nucleophiles.[447,448]

Bis-(−)-8-phenylmenthyl malonates were also used to prepare enantioenriched cyclopropanes by a double alkylation procedure using 1,4-dibromo-2-butene (**531**)

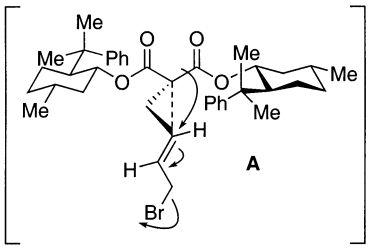
Scheme 45. Formation of Cyclopropanes from Vicinal Diol Cyclic Sulfates



as electrophile.[449] The desired vinylcyclopropane **532** was obtained in 96% de, and the stereochemical outcome results from transition state **A**, in which the allyl bromide moiety is opposite to the bulky substitutent of the chiral auxiliary (eq 120).

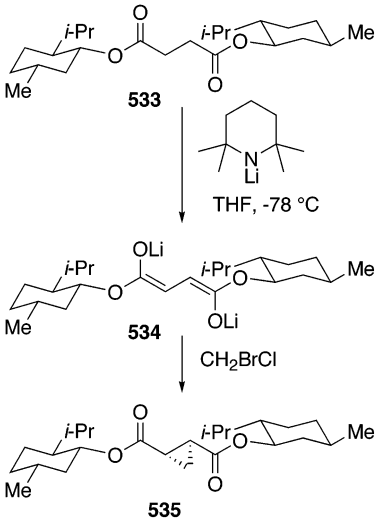


(120)



Yamamoto showed that the dianion of (−)-dimenthyl succinate (**533**), a chiral 1,2-nucleophile, could be added to bromochloromethane, thus producing the desired (*E*)-dimenthyl cyclopropanedicarboxylate **535** with very high diastereoselectivity (Scheme 46).[450]

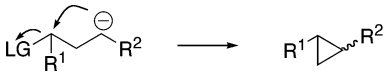
Scheme 46. Cyclopropanation Reaction with the Dianion of (−)-Dimenthyl Succinate



The best results were obtained with lithium 2,2,6,6-tetramethylpiperidide as a base in tetrahydrofuran.

This method was used in the total synthesis of ambruticin by Kende[451] and, more recently, by Trost[452] for the total synthesis of Callipeltoside A.[453]

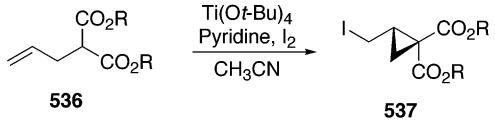
Many examples of intramolecular ring closure reactions, forming cyclopropanes, were reported.[454] This 1,3-elimination leads to chiral cyclopropanes if the leaving group or the anion is a stereocenter, and complete chirality transfer is generally observed (eq 121).



(121)

Traditionally, the reaction involves the intramolecular displacement of a leaving group, such as halides or sulfonates, with an enolate.[455] The intramolecular opening of epoxides was also reported.[456] Furthermore, the use of unstabilized carbanions, although more limited, was studied.[457] More recently, it was shown that the treatment of γ-hydroxystannanes with a Lewis acid yielded cyclopropane derivatives in good yields.[458]

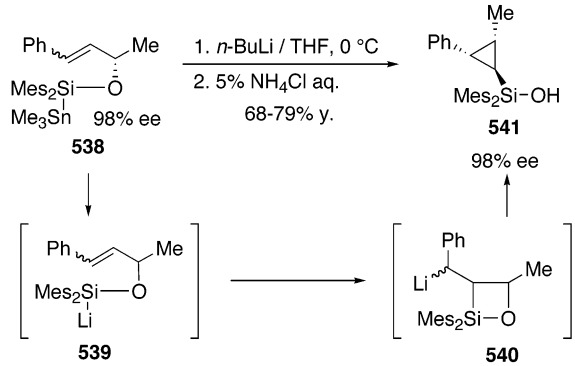
Taguchi disclosed the diastereoselective iodocarbocyclization of 8-phenylmenthyl allylmalonate.[459,460] The corresponding cyclopropylmethyl iodide **537** was isolated in 89% yield and with 93% ee when titanium tetra(*tert*-butoxide) and pyridine were used to efficiently trap the HI generated during the reaction (eq 122). All attempts to induce the enantioselectivity using a chiral titanium complex failed, leading to the racemic product.[461]



(122)

Other anionic cyclizations with alkenes producing cyclopropanes were reported.[462] The intramolecular rearrangement of (allyloxy)dimesitylsilyllithium led to cyclopropylsilanes as a single diastereoisomer.[463] Both isomers of the olefin provided the same diastereoisomeric cyclopropane **541** (Scheme 47). It is

Scheme 47. Intramolecular Rearrangement of (Allyloxy)dimesitylsilyl Lithium

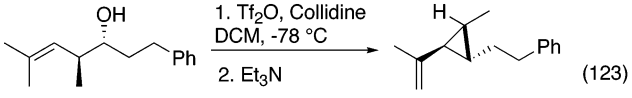


believed that one of the enantiomers of the benzylic anion **540** cyclizes with retention of configuration and the other with inversion, leading to the same product.

Cheng also reported a tandem lithium-ene cyclization, followed by a thiophenoxide expulsion, that produces fused vinylcyclopropanes with excellent

yields.[464,465] Only one diastereosiomer was observed when starting from a chiral allylic alcohol.

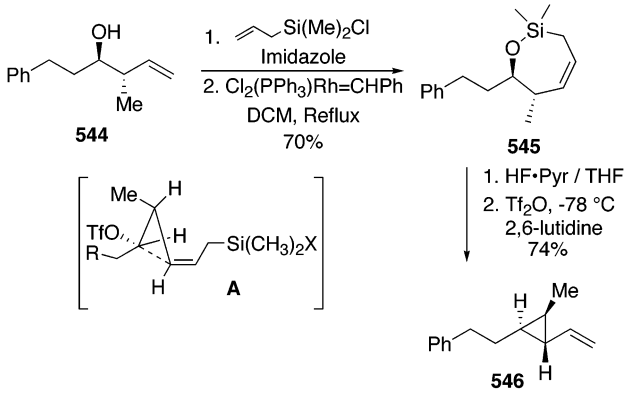
Cationic cyclizations that lead to cyclopropanes are scarce, due to the difficulty in controlling the behavior of the C_4H_9 cation.[466] Suzuki showed in 1995 that the installation of two methyl groups altered the situation, with the *tert*-cyclopropylmethyl cation being favored, and led to the formation of the desired cyclopropane.[467] A variety of nucleophiles were used with homoallylic alcohols, leading to the corresponding cyclopropanes with 61−93% yield. The chirality can be transferred in this process, as the trisubstituted cyclopropanes **543** was obtained with greater than 99% ee when starting from the enantiopure homoallylic alcohol **542** (eq 123). In this case, the addition of a base allowed the elimination reaction, leading to a vinylcyclopropane.



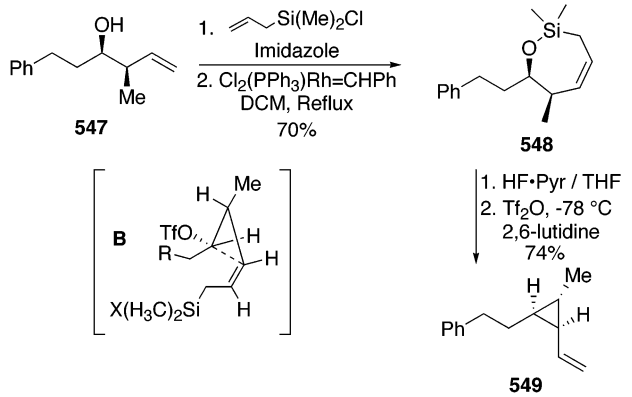
542 62%, dr: >99:1, >99% ee **543** (123)

A similar approach was disclosed by Taylor and coworkers.[468] In this case, the use of a β-silyl group to stabilize the cation allowed the formation of the cyclopropane derivatives. The allyl silane was prepared in two steps from the corresponding homoallylic alcohol, via the formation of silyloxycycloheptene by ring-closing metathesis, followed by nucleophilic opening. This strategy was applied for the synthesis of 1,2,3-trisubstituted cyclopropanes (Schemes 48 and 49). The *anti*-propionate subunit **544** provided the

Scheme 48. Cyclization of Homoallylic Alcohol 544



Scheme 49. Cyclization of Homoallylic Alcohol 547



trans-cyclopropane **546**, whereas the *cis*-cyclopropane **549** was produced when starting from the diastereomeric *syn* homoallylic alcohol **547**.

The reverse in the stereochemical outcome between the two diastereoisomers could be explained through the two transition-state models, **A** and **B**, in which the 1,3-allylic strain is minimized for the $-CH_2$-$SiMe_2X$ substituent.

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