DOI: 10.1002/anie.200604774

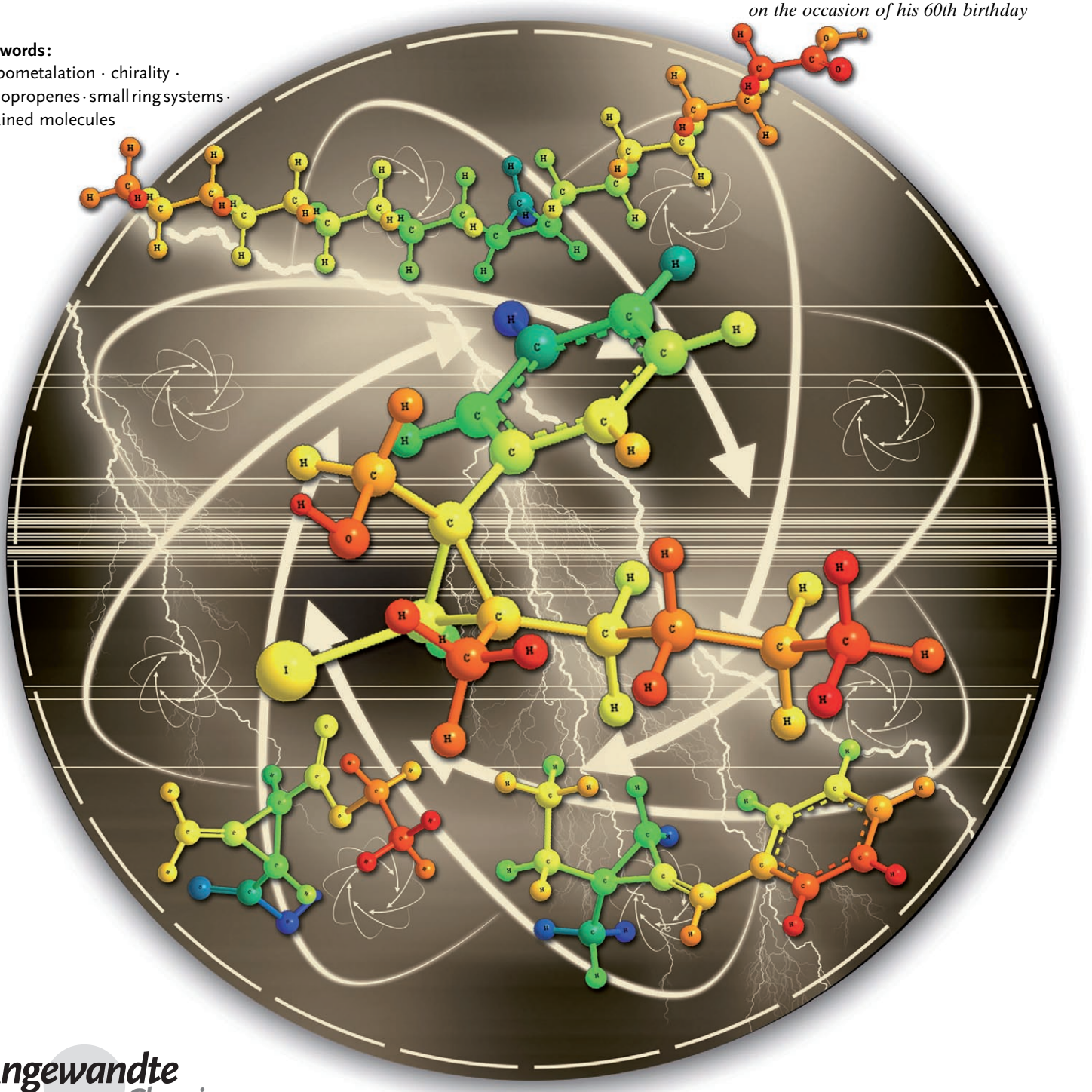
Synthetic Methods

# Enantiomerically Enriched Cyclopropene Derivatives: Versatile Building Blocks in Asymmetric Synthesis

*Ilan Marek,* Samah Simaan, and Ahmad Masarwa*

*Dedicated to Professor David Milstein on the occasion of his 60th birthday*

**Keywords:**
carbometalation · chirality · cyclopropenes · small ring systems · strained molecules



*Enantiomerically enriched cyclopropene derivatives, the smallest possible unsaturated carbocycles, are of great synthetic interest since they serve as versatile reactive building blocks. Their reactivity results from the relief of the ring strain in the small molecule. They can be transformed into a wide variety of complex chiral structures and a special emphasis will be directed towards the preparation of enantiomerically enriched methylene- and alkylidenecyclopropane derivatives. The ready availability of a wide range of these chiral entities now provides an excellent opportunity to discover new and unique transformations that can further enrich mainstream synthetic methodology.*

**From the Contents**



## 1. Introduction

Cyclopropenes are high energy compounds and therefore are extremely reactive molecules with a large spectrum of remarkable activities that extend far beyond the simple reactions typical of olefins.[1] Their chemistry has been the subject of numerous reviews and most of their preparations in racemic form were developed by the mid-1980s.[1] However, in the last few years, using strain as design principle for asymmetric reactions led to a complete renaissance of the field. Indeed, upon breaking the $\pi$ bond, the trigonally coordinated ring carbon atoms can pyramidalize, thus relieving the additional angle strain that results from the presence of carbon atoms that are nominally $sp^2$, rather than $sp^3$, hybridized in the three-membered ring. If such operations could be performed on enantiomerically enriched cyclopropenes, the synthetic value becomes clear as a new route to functionalized chiral compounds. In this Review, we will describe the most recent and significant results for the preparation and reactivity of such enantiomerically enriched cyclopropenes with a special emphasis on their transformation into chiral alkylidenecyclopropane derivatives.

## 2. The Concept of Ring Strain

The strain energy is the difference between the observed heat of formation of a strained molecule and that expected for a strain-free molecule with the same number of atoms. This concept has proven to be valuable to study organic compounds that have unusual geometries or intramolecular interactions. However, the origin of the strain energy has been a point of contention. Initially, Wiberg suggested that the introduction of each trigonal carbon center into a three-membered ring introduces an additional 12–14 kcal mol$^{-1}$.[2] For example, the strain energy of methylenecyclopropane is estimated to be 41 kcal mol$^{-1}$ while the heat of formation of the isomeric 1-methylcyclopropene is 10.2 kcal mol$^{-1}$ higher.[3] The three-membered ring compounds represent the first case in which the exocyclic double bond is found to be more stable than the endocyclic double bond. Johnson and Borden concurred with the explanation that increased angle strain does result from the presence of additional $sp^2$ centers.[4] In a very detailed theoretical study, Bach and Dmitrenko have recently shown that the explanation to the strain-energy problem requires bond-strength analysis of the entire molecule and particularly of the unusually strong C–H bonds.[5] From this study, it would appear that within this three-membered series, cyclopropene exhibits significant angular strain, but it is the weakness of the allylic C–H bond that is partly responsible for the higher energy of 1-methylcyclopropene against methylenecyclopropane. The increased s character of the bonding orbitals of three-membered rings gives rise to stronger C–H bonds.

## 3. Asymmetric Synthesis of Chiral Cyclopropene Derivatives

The first asymmetric synthesis of chiral cyclopropene derivatives was jointly reported by Doyle, Müller, and coworkers in 1992.[6] With a series of diazo esters and propargyl methyl ether, use of a catalytic amount ($\leq$1.0 mol%) of dirhodium(II) tetrakis[methyl 2-oxopyrrolidine-(5*R*)-carboxylate] [$Rh_2$(5*R*-mepy)$_4$][7] results in the formation of enantiomerically enriched cyclopropenes **1** in moderate yields (Scheme 1).

*tert*-Butyl diazoacetate generally reacts with a higher degree of enantiocontrol than methyl or ethyl diazoacetate, but *N*,*N*-dimethyldiazoacetamide elicits the highest level of selectivity among the diazo compounds employed for this

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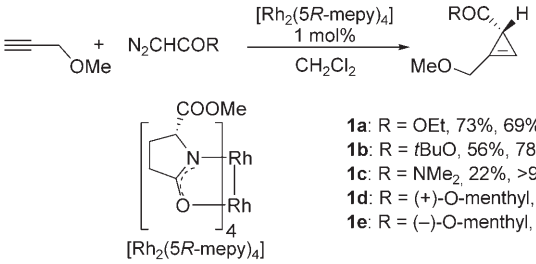
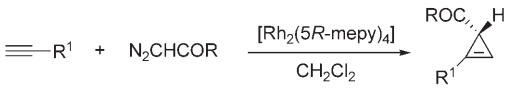



**1a**: R = OEt, 73%, 69% *ee*
**1b**: R = *t*BuO, 56%, 78% *ee*
**1c**: R = $NMe_2$, 22%, >94% *ee*
**1d**: R = (+)-O-menthyl, 43%, 98% *de*
**1e**: R = (−)-O-menthyl, 45%, 43% *de*

***Scheme 1.*** The first asymmetric synthesis of chiral cyclopropene derivatives.



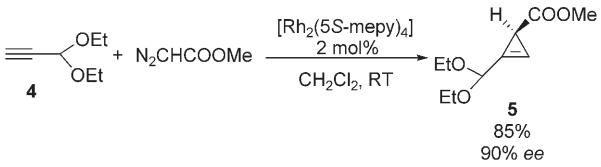

**2a**: R = OEt, $R^1$ = *n*Bu, 70%, 54% *ee*
**3a**: R = OEt, $R^1$ = *t*Bu, 85%, 57% *ee*
**2b**: R = *t*BuO, $R^1$ = *n*Bu, 69%, 53% *ee*
**3b**: R = *t*BuO, $R^1$ = *t*Bu, 57%, 70% *ee*
**2c**: R = $NMe_2$, $R^1$ = *n*Bu, 49%, 78% *ee*
**3c**: R = $NMe_2$, $R^1$ = *t*Bu, 47%, 89% *ee*
**2d**: R = (+)-O-menthyl, $R^1$ = *n*Bu, 46%, 86% *de*
**3d**: R = (+)-O-menthyl, $R^1$ = *t*Bu, 51%, 77% *de*

***Scheme 2.*** Generalization of the method shown in Scheme 1.

investigation. Product yields are generally higher in reactions with ethyl and *tert*-butyl diazoacetate esters than with diazoacetamide.[8] In reactions with menthyl diazoacetate, the intramolecular C–H bond insertion competes with the cyclopropenation reaction and therefore the yields are also lower.[9] The enantioselectivities increase with the steric size of the diazo ester, and the use of $[Rh_2(5R\text{-mepy})_4]$ for reactions with menthyl diazoacetates (MDA) leads to a double stereoselectivity; with (+)-MDA, **1d** is obtained with 98% *de* whereas with (−)-MDA, **1e** is produced with only 43% *de*.[10] The absolute configuration of such cyclopropenes was determined after reduction of the double bond with diimide and correlation with authentic samples.[8] Catalysis with $[Rh_2(5R\text{-mepy})_4]$ predominantly resulted in the production of *R*-configured cyclopropene derivatives.

Similar results were obtained from reactions of MDA with 1-hexyne and 3,3-dimethyl-1-propyne. With $[Rh_2(OAc)_4]$ as a catalyst, reactions of these alkynes with (+)- or (−)-menthyl diazoacetate yielded the corresponding cyclopropene products with *de* values of less than 10%. The diazocarboxylate substituent clearly plays a critical role in the establishment of the more effective carbene orientation within the chiral catalyst environment for addition to the alkyne. The polarity of the alkyne also seems to play a role in the enantioselectivity of the reaction. The fact that the *ee* values of cyclopropenes from reactions with propargyl methyl ether or acetate (Scheme 1) are higher than those from reactions with 1-hexyne and 3,3-dimethyl-1-butyne (Scheme 2) suggests that polar interactions of the alkyne with ligands of the catalyst may be operative.

Following these initial studies, the cyclopropenation of diethoxypropyne **4** with methyl diazoacetate with the *S*-configured catalyst $[Rh_2(5S\text{-mepy})_4]$ was optimized. The procedure for the cyclopropenation involves slow addition (syringe pump, 30 h) of the methyl diazoacetate to **4** (2 equiv) and catalyst (2 mol%) in $CH_2Cl_2$ at room temperature. Under these conditions, cyclopropene **5** was obtained in 85% yield and 90% *ee* (Scheme 3).[11]




***Scheme 3.*** Cyclopropenation of 1,1-diethoxypropyne.

Alternative rhodium(II) carboxamide catalysts derived from (4*R*)-benzyloxazolidinone and (4*S*)-isopropyloxazolidinone or semicorrin[12] copper catalyst provide the corresponding cyclopropene derivatives, but with very low enantiomeric excess values.[13] The use of disubstituted acetylenes gave unsatisfactory results. With 1-phenylpropyne, cyclopropenation with ethyl diazoacetate catalyzed by $[Rh_2(5R\text{-mepy})_4]$ produced the corresponding cyclopropene in 39% yield with only 16% *ee*. Even lower selectivities (<2% *ee*) were found for cyclopropenation of 1-(trimethylsilyl)-1-hexyne.[8] The cyclopropenation of *tert*-butylphenylacetylene by photochemical addition of (−)-menthyl (trimethylsilyl)diazoacetate was also reported, but without any details. The two diastereomers

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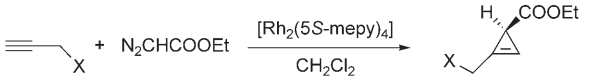
*Samah Simaan, born in 1976 and raised in Nazareth, studied chemistry at the Hebrew University of Jerusalem and received her MSc (Cum Laude) and later on her PhD under the supervision of Silvio Biali on the functionalization of the methylene bridges of calixarenes. She is currently working as a postdoctoral fellow in the group of Ilan Marek on the synthesis and reactivity of enantiomerically pure cyclopropene derivatives.*

were separated by medium pressure liquid chromatography and were optically pure.[14] Diazo decomposition of enynes such as 4-methylpent-3-en-yne catalyzed by $[Rh_2(5R\text{-mepy})_4]$ produced the cycloadduct in 75% yield and with 70% *de*.[8]

Indeed, vinylcyclopropene products derived from these metal carbene reactions are unstable and undergo [2+2] cycloadditions.[15] Cyclopropenation of several propargylamine derivatives such as propargylacetamide, *N*,*N*-bis-(trimethylsilyl)propargylamine, as well as propargyl bromide or chloride with methyl diazoacetate in the presence of $[Rh_2(5S\text{-mepy})_4]$ afforded the corresponding cyclopropene derivatives in low yield and with low enantiomeric excess. Only when the amino group was doubly protected with electron-withdrawing carboxy or sulfonyl groups, were the cyclopropenes obtained with high enantioselectivities (Scheme 4).[16]



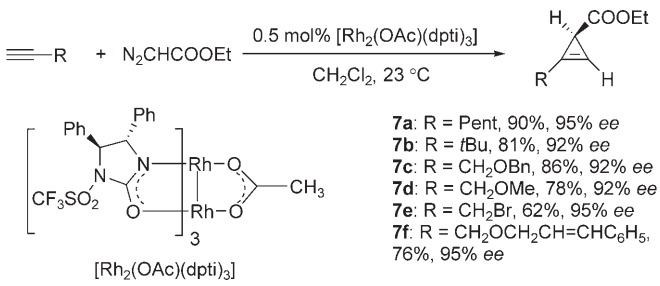

**6a**: X = SuccN, 79%, >95% *ee*
**6b**: X = $(Ns)_2N$, 82%, 80% *ee*
**6c**: X = $(TEOC)_2N$, 85, >97% *ee*

***Scheme 4.*** Cyclopropenation of propargylamine derivatives. SuccN = succinimido, $(Ns)_2N$ = *N*,*N*-di-*para*-nitrophenylsulfonamido, $(TEOC)_2N$ = *N*,*N*-di-(2-trimethylsilylethoxycarbonyl)amino.

Corey and co-workers reported the preparation of a very efficient catalyst, $[Rh_2(OAc)(dpti)_3]$ (dpti = diphenyltriflylimidazolidinone) for the cyclopropenation of terminal alkynes.[17] The results of this study show that ethyl diazoacetate in the presence of 0.5 mol% of this catalyst leads to 2-substituted 2-cyclopropenecarboxylic acid ethyl esters with excellent enantiomeric excesses and yields (Scheme 5).

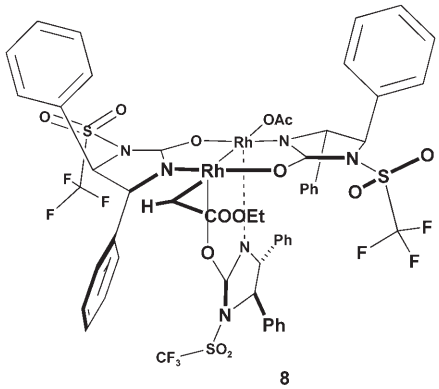
Even when a double bond is present in the carbon skeleton, the cycloaddition of ethyl diazoacetate to the ene–yne substrate proceeds selectively at the acetylenic linkage (formation of **7f**, Scheme 5). The excellent results obtained with this new catalyst were rationalized by formation of a triply bridged structure **8** of the Rh–carbenoid intermediate, and reaction with the terminal alkyne by a pathway via assembly **9**, in which the more labile acetate bridge to the rhodium that bears the carbenoid fragment has been broken (Scheme 6). The product-forming step therefore involves a

*Ahmad Masarwa, born in Taibe in 1981, graduated (Cum Laude)in 2005 in chemistry at the Technion, Haifa, where Ahmad received three times the Technion award for outstanding student. He is now working for his MSc under the supervision of Ilan Marek on the synthesis of enantiomerically pure alkylidenecyclopropane derivatives.*

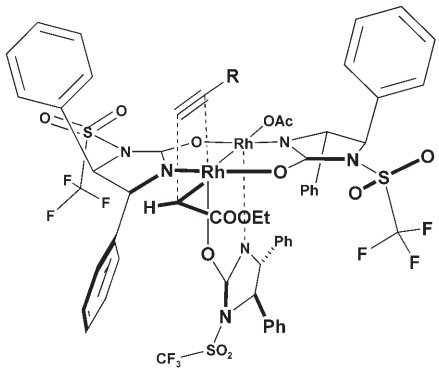



**7a**: R = Pent, 90%, 95% *ee*
**7b**: R = *t*Bu, 81%, 92% *ee*
**7c**: R = $CH_2OBn$, 86%, 92% *ee*
**7d**: R = $CH_2OMe$, 78%, 92% *ee*
**7e**: R = $CH_2Br$, 62%, 95% *ee*
**7f**: R = $CH_2OCH_2CH{=}CHC_6H_5$, 76%, 95% *ee*

***Scheme 5.*** Catalytic asymmetric synthesis of chiral cyclopropene derivatives.




**8**




**9**

***Scheme 6.*** Proposed mechanism for the asymmetric synthesis of cyclopropene derivatives.

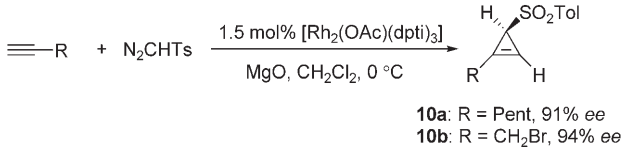
rather unusual [2+2] cycloaddition of the alkyne to **8** followed by a reductive elimination to form the (1*S*)-cyclopropenecarboxylate. This mechanistic model is completely different from the more classical system for which the assumption was that the carbenoid complex retains the symmetrically bridged framework of the catalyst $[Rh_2L_4]$. In this [2+2] cycloaddition, the energetically more-stable arrangement of the carbenoid fragment HCCOOEt, with the bulky COOEt group *cis* to the Rh–O bond and opposite to the bulkier NCHPh group, is involved. It is believed that the attack by ethyl acetate occurs at the (foremost) rhodium center of catalyst **8** that has one nitrogen and two oxygen substituents (Scheme 6).

However, some recent studies that combined experimental kinetic isotope effects and theoretical calculations are more in favor of the tetrabridged intermediate rather than the

tribridged rhodium carbenoid and an end-on approach.[18] To further probe his initial hypothesis, Corey and co-workers performed a complete and detailed investigation of the synthesis and catalytic properties of a series of thirteen complexes of the type $[Rh_2(OAc)_n(dpti)_{4-n}]$. The complexes were prepared, their structures independently characterized,[19] and then applied as catalysts to determine their effectiveness in the synthesis of chiral ethyl 2-pentyl-2-cyclopropenecarboxylate from 1-heptyne and ethyl diazoacetate. This study provides a basis for more rational planning of the stereocontrolled synthesis of complexes of the series $[Rh_2(OAc)_n(ligand)_{4-n}]$[20]

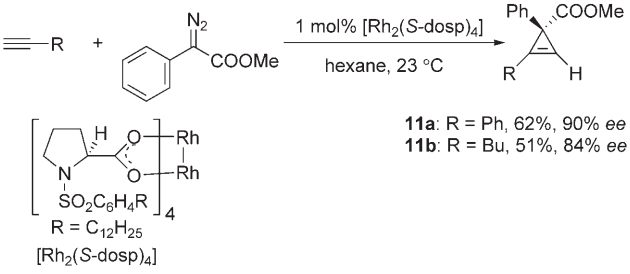
When 4-toluenesulfonyldiazomethane was added to several alkynes such as 1-heptyne or propargyl bromide with the same catalyst $[Rh_2(OAc)(dpti)_3]$, the corresponding cyclopropenes were obtained in excellent enantiomeric purities (91 and 94% *ee*, respectively, Scheme 7).[21] However, when **10a** was purified on silica gel or stirred for 30 minutes at 30°C, only the racemic cyclopropenylsulfone **10a** was obtained. The explanation for this facile thermal racemization reaction was reported to be a reversible [2,3] sulfone–sulfinate allylic rearrangement.[22]




***Scheme 7.*** Asymmetric synthesis of cyclopropenylsulfone derivatives. Tol = tolyl.

To further expand the range of readily accessible chiral cyclopropenes to those that contain a quaternary stereocenter, aryldiazoacetates were tested with a dirhodium(II) tetraprolinate $[Rh_2(S\text{-dosp})_4]$ catalyst (1 mol%). Under these conditions, the reaction with phenylacetylene generated the cyclopropene **11a** in 62% yield and with 90% *ee*. Similar reactions and *ee* values were obtained with various aryl-substituted acetylenes. The cyclopropenation could also be conducted on alkyl-substituted alkynes but with slightly diminished yield and enantioselectivity (Scheme 8).[23] The cyclopropenation can be extended to a range of aryldiazoacetates and in most cases yields were in the 50–65% range and enantioselectivities between 86–90%.[23]

Overall, these methods are excellent for the preparation of enantioenriched 1-substituted cyclopropenes **12**, although there is still no direct method for the preparation of enantiomerically enriched 1,2-disubstituted cyclopropenes **13** by asymmetric cyclopropenation reactions (Figure 1). In this case an additional chemical step is necessary: either the direct palladium-catalyzed arylation of chiral terminal cyclopropenes **12**[24] or the trapping of nucleophilic chiral cyclopropenyl metal species with various electrophiles (Scheme 9).[21,25] Both approaches have been successfully developed. The arylation reaction leads to the 1,2-disubstituted cyclopropene **13a** in excellent yields and with complete preservation of stereochemistry (path A, Scheme 9). As the alkenyl hydrogen atoms of cyclopropenes are more acidic than those of unstrained alkenes, the deprotonation reaction led to an interesting source of carbanions. However, attempts to directly metalate the ester-substituted cyclopropene **12** usually resulted in rapid ring opening to the rearrangement product **14**, (path B, Scheme 9)[26] The solution of this problem was proposed by Fox and co-workers[25a] and is based on the formation of dianions of carboxylic acids. The ring opening was suppressed because of Coulombic repulsion (path C, Scheme 9).




***Scheme 8.*** Chiral cyclopropenes with quaternary stereocenters.

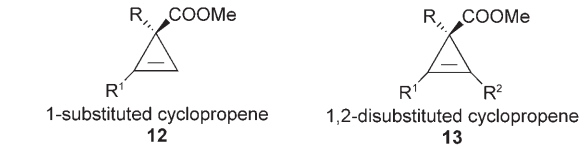
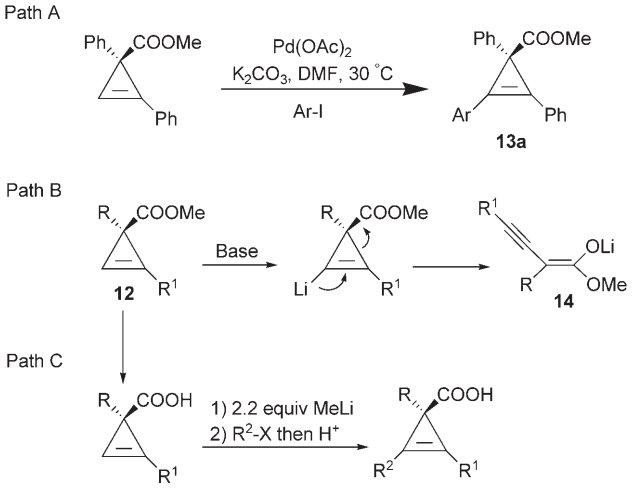



***Figure 1.*** 1- and 1,2-substituted cyclopropenes.



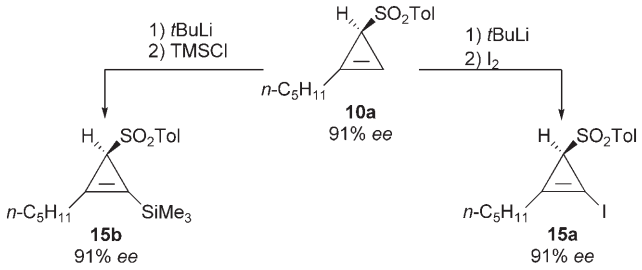

***Scheme 9.*** Palladium-catalyzed arylation reaction (path A) compared with metalation reaction (path C) of cyclopropene derivatives for the synthesis of enantiomerically enriched 1,2-disubstituted cyclopropenes.

Cyclopropenecarboxylate dianions can also serve as nucleophiles in $Pd^0$-catalyzed cross-coupling reactions. A transmetalation with $ZnCl_2$, followed by the addition of catalytic $[Pd(PPh_3)_4]$, leads to carbon–arene bond formation. The action of the strong base *t*BuLi on the cyclopropenylsulfone **10a** (91% *ee*) in THF at −78°C results in the deprotonation of the vinylic hydrogen (no deprotonation α to the

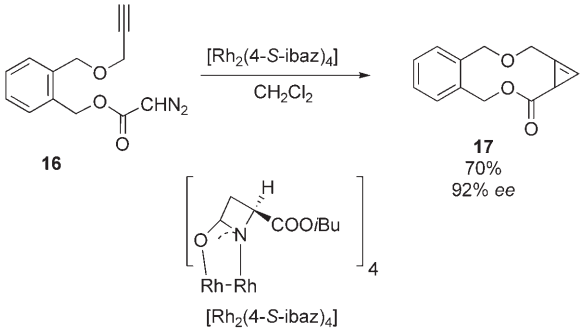
$TolSO_2$ group since it would form a high energy anti-aromatic ($4\pi$-type) carbanion intermediate, Scheme 10).

Intramolecular cyclopropenation has been also investigated,[27] but in those cases in which ring strain is further




***Scheme 10.*** Reactivity of cyclopropenyllithium derivatives.

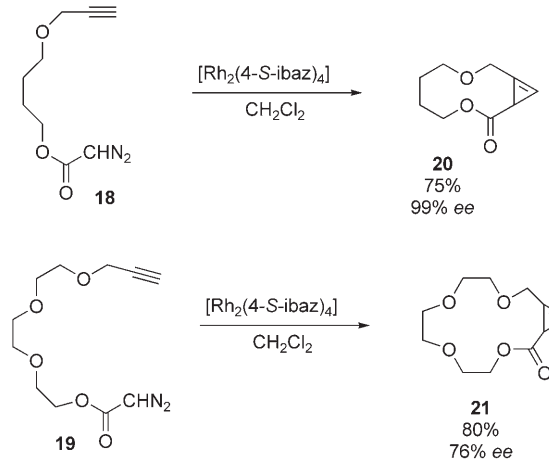
increased, the cyclopropene, in the presence of transition-metal catalysts employed for their formation, rapidly decompose to vinylcarbenes. In some cases, catalytic decomposition of diazoester such as **16** resulted in the formation of bicyclic cyclopropene as the sole product in yields ranging from 62 to 92%, depending on the chiral catalysts used. Of all the catalysts employed, $[Rh_2(4\text{-}(S)\text{-ibaz})_4]$ exhibited the highest enantiocontrol at 92% ee (Scheme 11).[28]



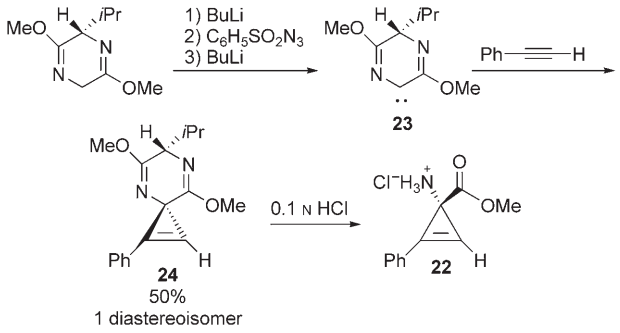

***Scheme 11.*** Intramolecular cyclopropanation of aromatic derivatives.

The absolute configuration of **17** induced by this *S*-configured dirhodium(II) catalyst was established by hydrogenation catalyzed by 5% $Pd(OH)_2/C$ and comparison with an authentic sample of the product.[29] That macrocyclic cyclopropenation of **16** to **17** is not merely a function of the geometry of the reactants, is evident in results obtained with the propargyl diazoacetates **18** and **19** having diol linkers (Scheme 12).[30,31]

A structural variant of $\beta,\gamma$-unsaturated amino acid hydrochloride, 1-Amino-2-aryl-cyclopropene-1-carboxylic ester **22**, has been prepared enantioselectively by reaction of the carbene **23** derived from the corresponding bislactim ether with arylethyne. Only one diastereoisomer was formed. Hydrolysis of the carbene adduct **24** to **22** and formation of the hydrochloride of the amino acid ester was easily achieved (Scheme 13).[32]




***Scheme 12.*** Intramolecular cyclopropanation of non-aromatic species.




***Scheme 13.*** Asymmetric preparation of the hydrochloride of the 1-amino-2-aryl-cyclopropene-1-carboxylic ester.

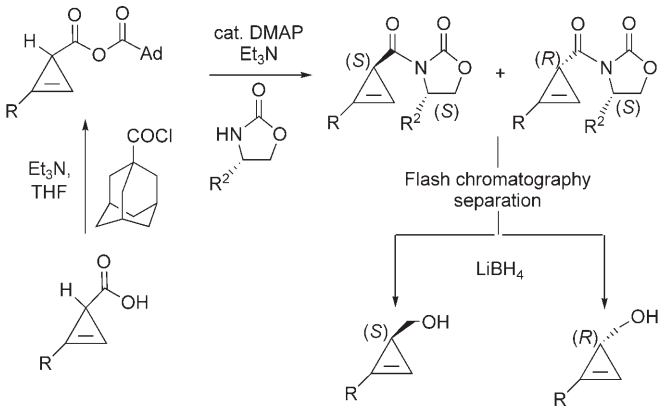
## 4. Optical Resolution of Cyclopropene Derivatives

The first resolution of 1-methyl-2-phenylcyclopropene-3-carboxylic acid was carried out by formation of the diastereomeric salts with (−)-ephedrine.[33] The same principle was applied to the preparation of enantiomerically pure 1-bromo-2,3-(*R*)-dimethylcyclopropene.[34] A more efficient and general method for resolving cyclopropenecarboxylic acids was recently disclosed by Fox and co-workers,[35] and is based on the formation of diastereomeric *N*-acyloxazolidines prepared from enantiomerically pure oxazolidinones (Scheme 14). This method is general and can be used to resolve significant quantities of cyclopropene derivatives.

Several commercially available oxazolidinones were used and the best auxiliaries in terms of resolving ability were those from (*S*)-phenylalaninol, (*S*)-phenylglycinol and (1*R*,2*S*)-1-amino-2-indanol. Separation was carried out using simple flash chromatography to provide diastereomerically pure materials. The separation for most of the *N*-acyloxazolidinones tested was excellent ($\Delta R_f > 15\%$). A simple reduction with $LiBH_4$ leads to the corresponding enantiomerically pure alcohols (Scheme 14). Several cyclopropenylcarbinols with quaternary stereocenters were prepared accordingly.

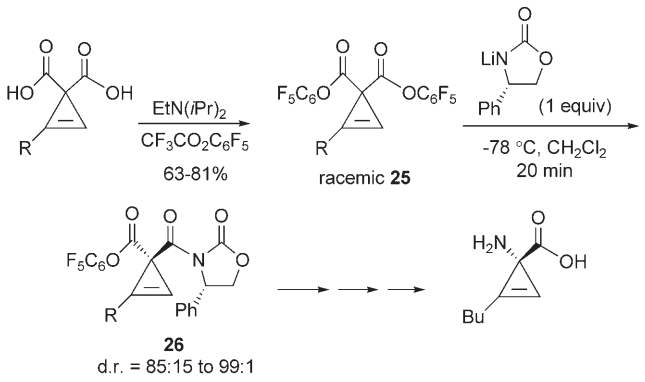
Interestingly, if DMAP is excluded from the reaction, a kinetic resolution is observed. To further increase the efficiency of this resolution, a parallel kinetic resolution of

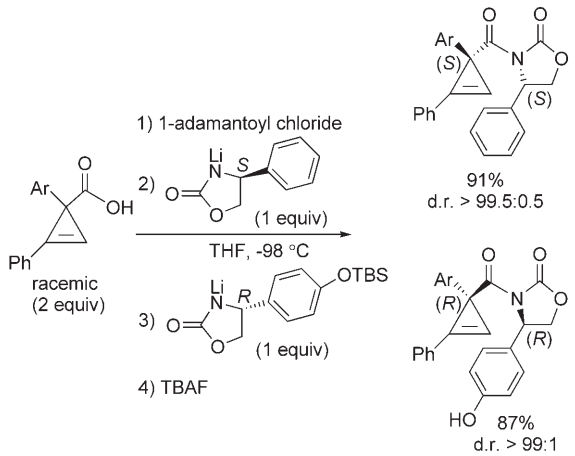



***Scheme 14.*** Optical resolution of cyclopropenyl carbinol. DMAP = dimethylaminopyridine.

cyclopropenes was also developed by Fox and co-workers.[36] The principle of this process is that quasi-enantiomers that have very similar reactivities give products in which the chromatographic properties diverge upon the addition of fluoride ion (Scheme 15). The specific application of this parallel kinetic resolution is the preparation of a large variety of cyclopropenecarboxylic acids with all quaternary stereocenters. A theoretical model for such kinetic resolutions was developed.[36] The desymmetrization of malonate-derived cyclopropene 3,3-dicarboxylic acids as a new route to cyclopropene α-amino acids was also reported. Activation of both acid functions by the formation of bis(pentafluorophenylesters) **25** followed by the reaction with the lithium salt of 4-phenyloxazolidinone led to cyclopropenes **26** with excellent diastereoselectivities (Scheme 16).[37]

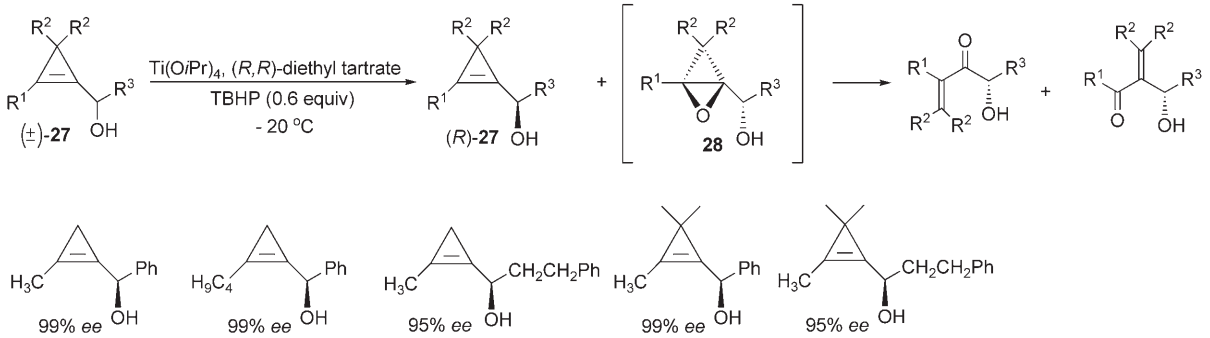



***Scheme 16.*** Desymmetrization of malonate-derived cyclopropene 3,3-dicarboxylic acids.




***Scheme 15.*** Parallel kinetic resolution of cyclopropenes. TBAF = *tert*-butylammoniumfluoride, TBS = *tert*-butyldimethylsilyl.

Recently, our research group has described the preparation of enantiomerically pure cyclopropenyl carbinols by kinetic resolution upon Sharpless epoxidation (Scheme 17).[38] When the racemic alcohol **27** was subjected to the epoxidation conditions using (*R*,*R*)-(+)-diethyl tartrate as a chiral ligand,[39] despite the highly reactive nature of the strained double bond, a very efficient kinetic resolution was observed at −20 °C. Only one enantiomer is epoxidized to lead to the putative unstable chiral 2-oxabicyclo[1.1.0]butane **28**.[40] Two enantiomerically pure α,β-unsaturated hydroxyketones are formed in equal amounts (each isolated in 22–25 % yields) as a result of the isomerization of the oxabicyclobutane by cleavage of either one of the two peripheral σ bonds. Oxabicyclobutanes have been postulated several times to be intermediates in various thermal[41] and photochemical reactions,[42] but were not detected in these cases. Although we were also not able to isolate such intermediates, this type of kinetic resolution implies that the expected oxabicyclobutane is indeed formed as a reactive intermediate. The remaining non-oxidized products, namely the cyclopropenylcarbinols **27**, were obtained with very high enantiomeric excesses and




***Scheme 17.*** Enantiomerically pure cyclopropenyl carbinols by kinetic resolution upon Sharpless epoxidation. TBHP = *tert*-butylhydroperoxide.

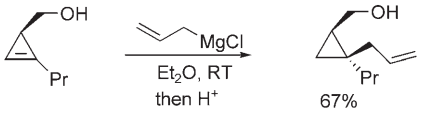
  

yields (95–99% *ee* and 40–47% yield of isolated products). The scope of the kinetic resolution is broad as several different alkyl groups can be present either on the double bond of the cyclopropenyl unit ($R^1 = CH_3$ and $C_4H_9$) or on the cyclopropene ring itself ($R^2 = H$ or $CH_3$, Scheme 17). Aryl and alkyl groups can be interchangeably used as secondary substituents at the allylic position $R^3$, although the enantiomeric excess obtained is slightly higher when $R^3$ is an aryl group (99% *ee*) rather than an alkyl group (≈95% *ee*, Scheme 17).[43]

## 5. Reactivity of Enantiomerically Enriched Cyclopropene Derivatives

The chemistry of cyclopropene derivatives is extremely diverse and has been summarized in excellent reviews.[1] However, the transformation of enantiomerically enriched cyclopropene derivatives is a relatively new field of research and below the most prominent results are summarized, in particular for the preparation of chiral methylene- and alkylidenecyclopropane derivatives.

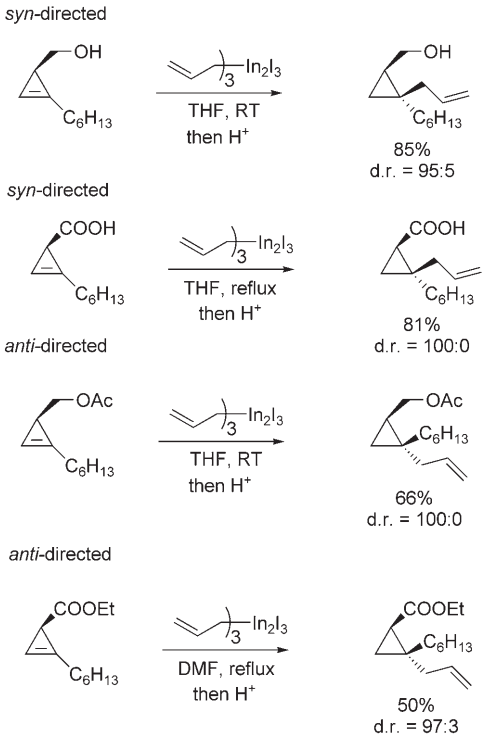
It has originally been shown that the allylmagnesation reaction of cyclopropenylcarbinol is regioselective and generates the all-carbon quaternary center as shown in Scheme 18.[44] Such carbomagnesation reactions proceed




***Scheme 18.*** Regioselective allylmagnesation reaction of cyclopropenylcarbinol.

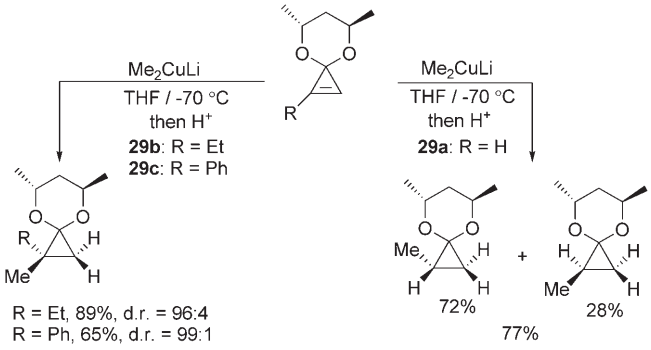
only with allylmagnesium halides and not with other types of Grignard reagents. Similarly, the allylindation of cyclopropenes that possess hydroxymethyl and carboxylic acid functions is controlled to give the *syn* adducts,[45] whereas the analogous addition reactions of their acetates and esters occurred on the opposite face to yield the *anti* product (Scheme 19).[46]

The *cis* stereoselectivity in the allylindation of the carboxy- and hydroxymethyl-bearing cyclopropenes can be explained by an intramolecular coordination of the hydroxy group to the indium atom. The regio- and stereoselectivity can be regulated both by the location of the hydroxy group in the molecules and the solvents used.[47] In particular, the allylindation in water shows marked differences from that in organic solvents: the regio- and stereoselectivity were totally reversed. Halogenation of the resulting cyclopropylindium leads to the expected halocyclopropanes.[44] Allylgallation of cyclopropenes with allylgallium sesquibromide leads to similar results.[48] Although the allylmetalation reactions proceed well, the addition of other organometal derivatives is still challenging.[49] An elegant solution came with the carbocupration reaction of the parent chiral cyclopropene acetal (CPA) **29a**. Organocuprate smoothly reacts with CPA, although with modest stereoselectivity (Scheme 20).[50] On




***Scheme 19.*** Allylindation of cyclopropenes with hydroxymethyl and carboxylic acid functions and derivatives.

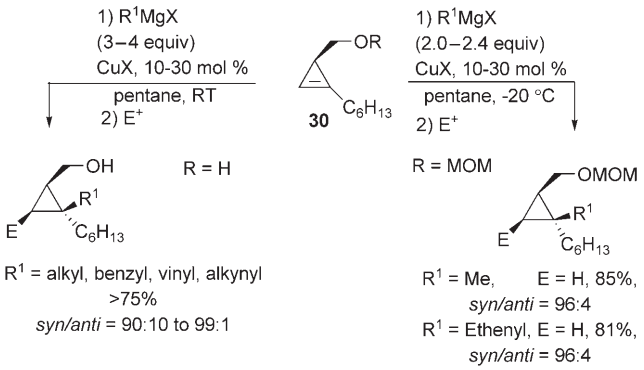
the other hand, the reaction of substituted CPAs **29b,c** (R = alkyl and phenyl, respectively) not only strongly favors the formation of the 2,2-dialkyl adduct, but also is much more selective than on the parent chiral CPA **29a** (R = H) and with an opposite sense of addition (Scheme 20).[50]



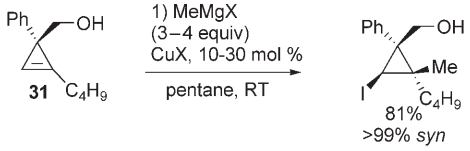

***Scheme 20.*** Carbocupration reaction of chiral cyclopropene acetal.

Following this pioneering study, the copper-mediated addition of various alkyl, alkenyl, and alkynyl magnesium reagents to 3-hydroxymethyl cyclopropenes **30** was successfully carried out to directly form defined quaternary stereocenters (Scheme 21).[51] The resulting cyclopropylmetal species can be captured with a variety of electrophiles to yield useful functionalized cyclopropanes in enantiopure form.[51] The Cu-catalyzed carbomagnesation reaction of **31** is also very effective for the preparation of cyclopropyl derivatives that possess two quaternary stereocenters (Scheme 22).[52]



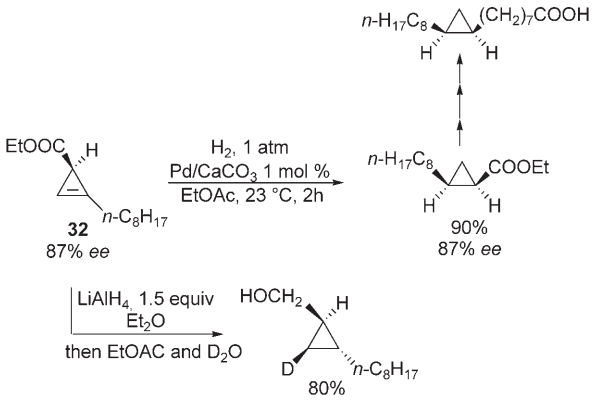

***Scheme 21.*** Copper-mediated addition of magnesium reagents to 3-hydroxymethyl cyclopropenes. MOM = methoxymethyl.




***Scheme 22.*** Copper-catalyzed carbomagnesation reaction.

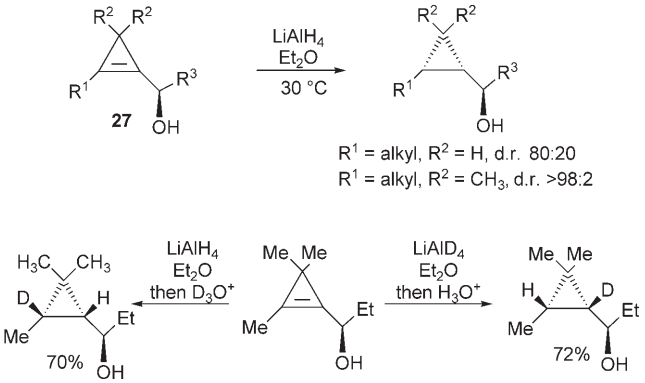
As cyclopropanes may undergo ring-opening reactions when treated with hydrogen and Pd/C,[53] the facial selectivity in catalytic hydrogenations of cyclopropenes has to be carried out in the presence of $Pd/CaCO_3$.[11,54] Corey and co-workers illustrated this approach by the completely diastereoselective $Pd/CaCO_3$-catalyzed hydrogenation of nonracemic cyclopropene **32** in the synthesis of the naturally occurring (9*R*,10*S*)-dihydrosterculic acid, a common cyclopropyl fatty acid in microorganisms and subtropical plants (Scheme 23).[17] It is noteworthy that the reductive transformations presented in Scheme 23 afford access to the *cis*- or *trans*-disubstituted cyclopropane derivatives that would result from cyclopropanation of terminal alkenes with diazoesters, but without problems of *cis*/*trans* stereoselectivity.

Hydrometalation reactions of cyclopropenes[55] were studied by deuterium labeling and were found to be both regio- and diastereoselective.[56] Recently, our group has shown that the diastereoselectivity of the $LiAlH_4$ reduction



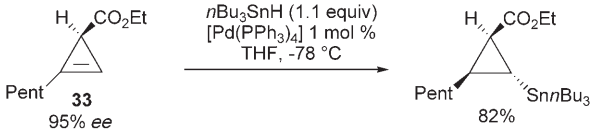

***Scheme 23.*** Diastereoselective $Pd/CaCO_3$-catalyzed hydrogenation of nonracemic cyclopropene.

of cyclopropenylcarbinols can be controlled by the presence of the secondary allyl alcohol moieties (for the preparation of enantiomerically pure **27**, see Scheme 17).[57] The regioselectivity of the hydrometalation reaction was established on the basis of deuterium labeling studies (Scheme 24).



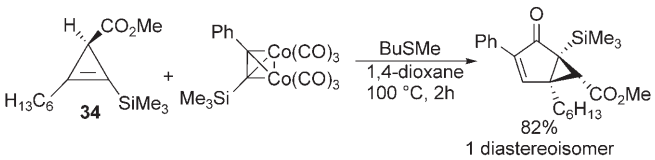

***Scheme 24.*** Regioselective hydrometalation reaction of cyclopropenylcarbinols.

The palladium-catalyzed *cis*-selective hydrostannylation of cyclopropenes **33** proceeds extremely rapidly and stereoselectively (Scheme 25).[17,58]




***Scheme 25.*** Palladium-catalyzed *cis*-selective hydrostannylation of cyclopropenes.

The ethyl ester of cyclopropene derivative **34** was reported to react with exceptional efficiency with dicobalthexacarbonyl complexes (Pauson–Khand reactions) in the presence of sulfide or *N*-oxide promoters.[59] A single cyclopentenone was isolated with an exclusive *exo* diastereoselectivity (Scheme 26).[60] Chiral cyclopropene derivatives are also valuable building blocks for several cycloaddition reactions.[17]



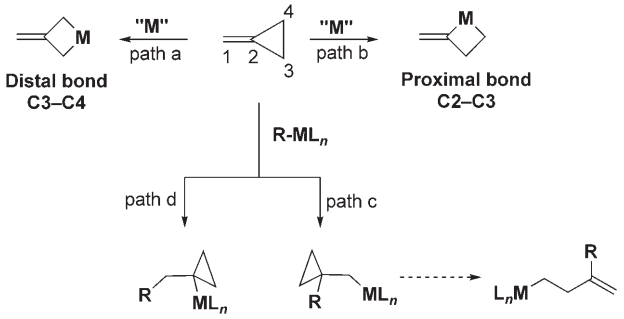

***Scheme 26.*** Pauson–Khand reaction of cyclopropenes.

## 6. Enantioselective Synthesis of Chiral Methylene- and Alkylidenecyclopropane Derivatives

Although both cyclopropene and methylenecyclopropane are strained compounds, the latter has a strain energy

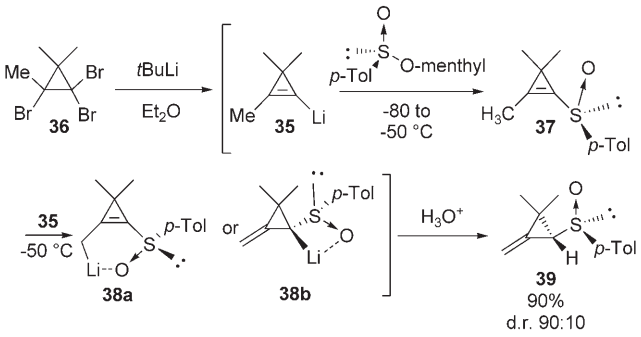
10.3 kcal mol$^{-1}$ lower than the former.[2–5] Nevertheless, since the 1970s, the chemistry of racemic methylenecyclopropanes[61] in the presence of transition-metal catalysts has been extensively explored.[62] The reaction course of methylene- and alkylidenecyclopropanes in the presence of transition-metal catalysts M can be summarized into the following patterns: a) insertion of M into the distal C3–C4 bond; b) insertion of M into the proximal C2–C3 bond; c) anti-Markovnikov addition of a organometallic derivative RM across the exomethylene double bond eventually followed by further ring opening of the cyclopropyl unit; d) Markovnikov addition of the same RM across the double bond (Scheme 27).




***Scheme 27.*** Possible reactions of methylene- and alkylidenecyclopropanes in the presence of transition-metal catalysts.

In the catalytic [3+2] cycloaddition of methylenecyclopropanes, the cleavage of the cyclopropane ring takes place at either the proximal or the distal bond. The reaction involving distal-bond cleavage proceeds through the formation of a metallacyclobutane species followed by insertion of an X=Y multiple bond to give five-membered carbo- or heterocycles.[62a] On the other hand, in the proximal-bond cleavage, either direct attack of a catalyst to a proximal bond[63] or formation of a metallacyclopentane followed by β-carbon–metal elimination takes place to give alternative five-membered rings.[64] Usually, the mode of ring opening mainly depends on the choice of catalysts; for example, cycloadditions catalyzed by nickel(0) catalysts preferentially lead to proximal-bond cleavage.[65] Thus the presence of a carbon stereocenter on the cyclopropane should lead to a transfer of chirality into the final product. Particularly interesting would be the presence of quaternary stereocenters in the alkylidenecyclopropane since insertion into the distal bond may be totally avoided. Unfortunately, because of the inherent difficulties of their preparation, few enantiomerically enriched methylene- and alkylidenecyclopropanes have been reported and the transformation of chiral cyclopropenes into methylene- and alkylidenecyclopropanes that are known are discussed below.[66]

Chiral methylenecyclopropane derivatives can be prepared by a three-component reaction from 1,1,2-trihalocyclopropanes, chiral sulfinyl ester, and electrophiles. Cyclopropenyllithium **35** is obtained from 1,1,2-tribromocyclopropane **36** (prepared by reaction of 2-bromo-3-methyl-2-butene derivative with bromoform in the presence of cetrimide as a phase-transfer catalyst)[67] by a successive 1,2-dehalogenation reaction followed by a halogen–lithium exchange as described in Scheme 28. Then, after addition of (−)-menthyl (*S*)-*p*-toluenesulfinate,[68] the corresponding cyclopropenyl sulfoxide is formed as an intermediate. The optimal conditions for




***Scheme 28.*** Reactivity of cyclopropenylsulfoxide.

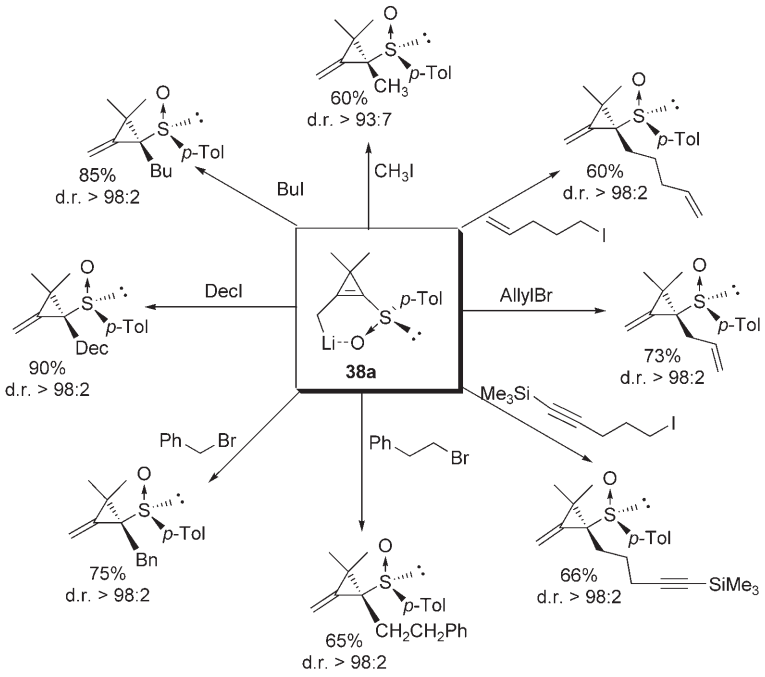
the in situ formation of the allyl species **38a,b** was determined to be by deprotonation of the cyclopropenyl sulfoxide **37** with cyclopropenyllithium **35** itself, with concomitant formation of the volatile 1,2,2-trimethylcyclopropene derivative. Therefore, two equivalents of **35** are necessary for the completion of the reaction (Scheme 28). After the addition of water, the corresponding chiral methylenecyclopropane **39** is obtained in excellent yield with a diastereomeric ratio of 90:10.[69] In the conformation **38a**, the *p*-tolyl residue at the sulfur atom shields one face of the allyllithium and therefore the electrophile $H^+$ approaches from the opposite face according to an $S_E2'$ mechanism. Alternatively, the lithiated methylenecyclopropane **38b** could also be envisaged as a reactive intermediate, in which a four-membered-ring chelation would be operative. It has been shown that the two possible structures for lithiated allyl sulfoxides were slightly different in energy; the α-lithioallyl sulfoxide being favored over the γ-lithioallyl sulfoxide by only 2.2 kcal mol$^{-1}$.[70] On the other hand, methylenecyclopropane is 10.3 kcal mol$^{-1}$ more stable than its cyclopropenyl congener.

It is actually relatively difficult to propose a preference between species **38a** and **38b**. For the sake of rationalization, we will consider the intermediate **38a** as the reactive species herein, which makes the stereochemical results easier to explain. When the electrophile is an alkyl halide, the diastereoselectivity improves from 90:10 to greater than 98:2 in all cases, as shown in Scheme 29.[69]

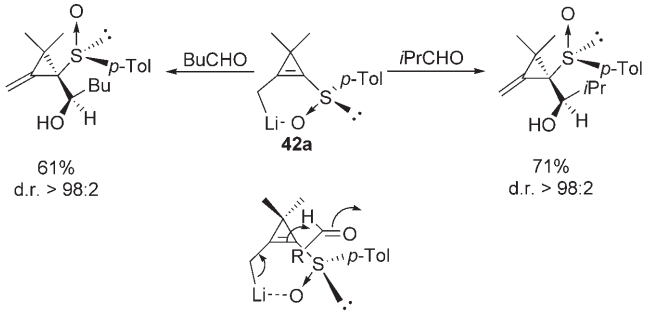
Interestingly, carbonyl derivatives can also be used as the electrophiles, and the expected methylenecyclopropylcarbinols are obtained as unique diastereoisomers (Scheme 30).[69]

The relief of ring strain as a driving force for the isomerization of cyclopropenes into methylenecyclopropanes was also investigated for 2-bromomethyl-2-cyclopropenyl 4-tolyl sulfone (**40**). When chiral **40** (91% *ee*) was treated with 1 equiv of $Na_2CO_3$ in MeOH at 23 °C, the corresponding methylenecyclopropane **41** was obtained with 89% *ee* (Scheme 31, top).[21] This isomerization has been used for a




***Scheme 29.*** Various reactions with cyclopropenylsulfoxide. Bn = benzyl, Dec = decyl.

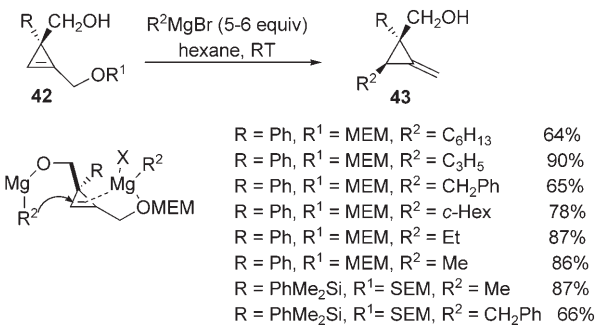



***Scheme 30.*** Stereoselective preparation of methylenecyclopropylcarbinols.

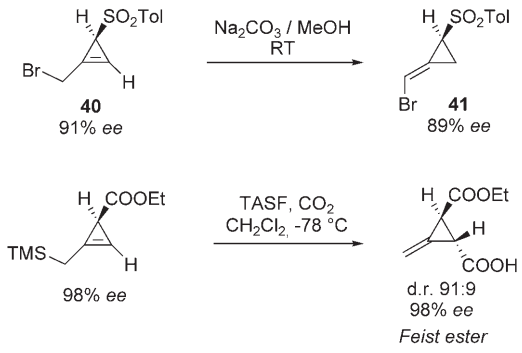
direct and straightforward enantioselective preparation of the Feist ester (Scheme 31).

The regio- and diastereoselective synthesis of methylenecyclopropanes **43** from cyclopropenes **42** by a $S_N2'$-type process by using an excess of Grignard reagents (RMgBr) was also recently investigated (Scheme 32).[71] All reactions gave a single diastereoisomer (d.r. > 95%). Methyl-, alkyl- (1° or 2°), allyl-, and benzylmagnesium bromide are suitable nucleophiles and methoxyethoxymethyl or 2-(trimethylsilyl)ethoxymethyl ethers were found to be the best leaving groups for such reactions in terms of regio- and diastereoselectivity. Although the exact mechanism is still unclear at this point, a large excess of the respective Grignard reagent is needed (5–6 equiv) to avoid the formation of dienes as side products.[71]

To reach products with quaternary stereocenters, the copper-catalyzed formal $S_N2'$ reaction was performed on enantiomerically pure cyclopropenylcarbinols, which were prepared as described in Scheme 17. Secondary allyl alcohol derivatives led to alkylidenecyclopropanes in good to excellent yields with a complete transfer of chirality, regardless of the nature of the alkylmagnesium halide. Moreover, in all these experiments, the unique or major isomer detected had *E* configuration. Without the addition of the copper salt, the reaction did not proceed (Scheme 33).[38] The absolute configurations of the starting cyclopropenylcarbinols **27** and the final alkylidenecyclopropanes **47** imply an overall *syn* $S_N2'$ displacement of the alcohol moiety.



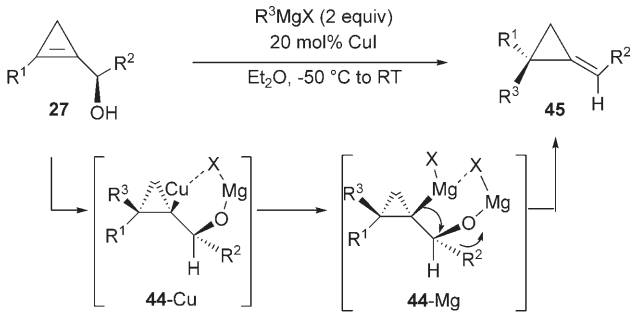

***Scheme 32.*** $S_N2'$-addition of Grignard reagents to functionalized cyclopropenes. MEM = Methoxyethoxymethyl, SEM = 2-(trimethylsilyl)-ethoxymethyl.




***Scheme 31.*** Isomerization of cyclopropenes into methylenecyclopropanes; application to the enantioselective preparation of the Feist ester. TASF = Tris(dimethylamino)sulfoniumdifluorotrimethylsilicate.

Under the stated conditions, the addition products—cyclopropylmetal complexes **44**-Cu or **44**-Mg—were isolated in moderate yield and finally eliminate to give the alkylidenecyclopropane **45**. Clearly, the reaction proceeds by way of a copper-catalyzed carbomagnesation reaction (addition of an organocopper reagent across the strained double bond) followed by a transmetalation reaction to give an organomagnesium species and subsequent β elimination.[72] As the deprotonation of the alcohol precedes the addition, the most stable conformer of the cyclopropenylcarbinolate is given is Scheme 33, and has the smallest substituent (the hydrogen atom) "inside" and the aryl group "outside", away from the allylic methyl substituent (minimum 1,3-strain). Thus, this catalytic reaction proceeds through a *syn* addition/*syn* elimination mechanism (Scheme 33) rather than a *syn* $S_N2'$ process.




$R^1$ = Me, $R^2$ = Ph, $R^3$ = Ph, 66%, *E*/*Z* = 85:15, 97% *ee*
$R^1$ = Me, $R^2$ = Ph, $R^3$ = Bu, 70%, *E*/*Z* = 97:3, 97% *ee*
$R^1$ = Me, $R^2$ = Ph, $R^3$ = Et, 72%, *E*/*Z* = 96:4, 95% *ee*
$R^1$ = Me, $R^2$ = *p*-$BrC_6H_4$, $R^3$ = Et, 88%, *E*/*Z* = 97:3, 99% *ee*

***Scheme 33.*** Copper-catalyzed addition/elimination reactions on enantiomerically pure cyclopropenylcarbinols.

## Conclusion

Enantiomerically enriched cyclopropene derivatives, the smallest-possible unsaturated carbocycles, are versatile reactive building blocks for organic synthesis, and can be elaborated to a wide variety of more complex chiral structures. In the last few years, there has been a renaissance of the field, and in this Review, we have highlighted the most prominent examples. The direction from these new insights and the ready availability of a wide range of these chiral entities now provide an excellent opportunity to discover new and unique aspects of this chemistry that can then further enrich mainstream synthetic methodology.

*This research was supported by the German–Israeli Project Cooperation (DIP-F.6.2) and the Fund for the Promotion of Research at the Technion. I.M. is holder of the Sir Michael and Lady Sobell Academic Chair.*

Received: November 24, 2006
Published online: July 31, 2007

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