1

Asymmetric Cyclopropanation

1.1 Introduction

Organic chemists have always been fascinated by the cyclopropane subunit [1]. Its strained structure[1] and interesting bonding characteristics have attracted the attention of the physical organic community [2]. Due to the limited degrees of freedom, these conformationally constrained molecules have very pronounced steric, stereoelectronic, and directing effects, which make them versatile probes for the study of regio-, diastereo-, and enantioselectivity [3].

On the other hand, the cyclopropane subunit is present in many biologically important compounds including terpenes, pheromones, fatty acid metabolites, and unusual amino acids [1j, 4], and it shows a large spectrum of biological properties, including enzyme inhibition and insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumor, and antiviral activities [5]. This fact has inspired chemists to find novel and diverse approaches to their synthesis, and thousands of cyclopropane compounds have been prepared [6]. In particular, naturally occurring cyclopropanes bearing simple or complex functionalities are chiral compounds; thus, the cyclopropane motif has long been established as a valuable platform for the development of new asymmetric technologies [7]. The enantioselective synthesis of cyclopropanes has remained a challenge, since it was demonstrated that members of the pyrethroid class of compounds were effective insecticides [8]. Asymmetric synthesis constitutes the main strategy to gain access to enantioenriched compounds, involving the use of either chiral auxiliaries or catalysts that in turn can be metal-centered, small organic asymmetric molecules or enzymes. New and more efficient methods employing all these methodologies to gain enantiomerically enriched cyclopropanes are still evolving, covering all the main cyclopropanation reactions: those are the well-known Simmons–Smith reaction [9], the transition-metal-catalyzed

[1] 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.

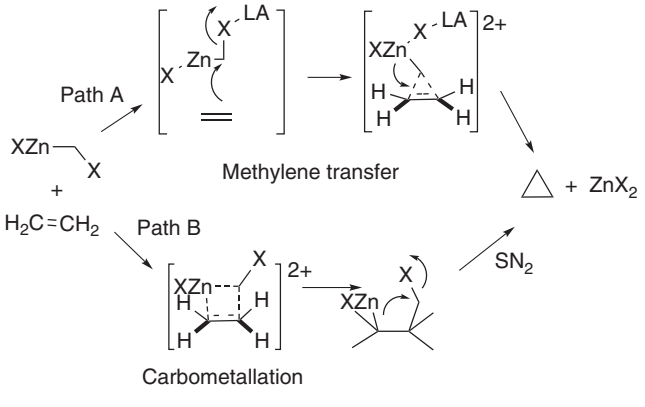
Asymmetric Synthesis of Three-Membered Rings, First Edition.
Hélène Pellissier, Alessandra Lattanzi and Renato Dalpozzo.

decomposition of diazo compounds [10],[2] and the irreversible Michael-initiated ring-closure (MIRC) [11].

1.2 Simmons–Smith Cyclopropanation

In the late 1950s, Simmons and Smith discovered that the reaction of alkenes with diiodomethane in the presence of activated zinc afforded cyclopropanes in high yields [12]. The reactive intermediate is an organozinc species, and the preparation of such species, including $RZnCH_2I$ or $IZnCH_2I$ compounds and samarium derivatives, was developed in the following years [13]. The popularity of the Simmons–Smith reaction arose from the broad substrate generality, the tolerance of a variety of functional groups, the stereospecificity with respect to the alkene geometry, and the *syn*-directing and rate-enhancing effect observed with proximal oxygen atoms [14].

In spite of the practical importance of the asymmetric Simmons–Smith cyclopropanation, the reaction pathway is not completely clear yet [15]. Theoretically, the Simmons–Smith cyclopropanation can proceed via a concerted [2+1] methylene transfer (Scheme 1.1, path A), in which the pseudo-trigonal methylene group of a halomethylzinc halide adds to an alkene π-bond and forms two new carbon—carbon bonds simultaneously, accompanying a 1,2-migration of the halide anion from the carbon to the zinc atom. Alternatively, a [2+2] carbometallation mechanism, in which the halomethyl group and the zinc halide add to both termini of the alkene π-bond followed by intramolecular nucleophilic substitution of the pseudo-carbanion, can be supposed (Scheme 1.1, path B). Experimental studies show that, using a zinc carbenoid, the cyclopropanation very likely proceeds by the [2+1] pathway, primarily because the carbon—zinc bond is covalent and unpolarized. In 2003, Nakamura *et al.* studied the reaction pathways of cyclopropanation using the Simmons–Smith reagent by means of the B3LYP



Scheme 1.1 Possible mechanisms for the Simmons–Smith reaction.

[2] The high reactivity of diazo compounds counterbalances the ring strain generated in the newly formed cyclopropane unit.

hybrid density functional method, confirming that the methylene-transfer pathway was the favored reaction course [15]. It took place through two stages, an S_N2-like displacement of the leaving group by the olefin, followed by a cleavage of the C—Zn bond to give the cyclopropane ring. However, the alternative carbometallation and cyclization pathway was found to be preferred when the carbon—metal bond is more polarized, such as in lithium carbenoids, and this hypothesis has received experimental support [16].

Kinetic studies on the cyclopropanation of dihydropyrroles show an induction period that is consistent with a change in the structure of the carbenoid reagent during the course of the reaction. This mechanistic transition is associated with an underlying Schlenk equilibrium that favors the formation of monoalkylzinc carbenoid $IZnCH_2I$ relative to dialkylzinc carbenoid $Zn(CH_2I)_2$, which is responsible for the initiation of the cyclopropanation. Density functional theory (DFT) computational studies were also conducted to study the factors influencing reaction rates and diastereoselectivities [17].

1.2.1 Chiral Substrates

The simplest method to obtain chiral compounds is to start from enantiopure substrates, and the built-in chirality is then preserved in the remainder of the reaction sequence. However, this requires the availability of enantiopure substances with the right configuration, and the cheapest ones are amino acids and sugars, which are available in nature as single enantiomers. In the present case, only the cyclopropanation of various asymmetric acyclic allylic alcohols has been widely developed instead, using the heteroatom as the directing group, by chelation with the zinc reagent. Most of them are prepared by enantioenriched reduction of unsaturated carbonyl compounds or by cleavage of chiral epoxides. This Simmons–Smith reaction has distinct advantages over the reaction with a simple olefin in relation to the reaction rate and stereocontrol [18]. Moreover, these reactions have been shown to be much faster than those with simple olefins, and the reaction with a cyclic allylic alcohol took place, forming the cyclopropane ring on the same side as the hydroxyl group [13, 19].

1.2.1.1 Chiral Allylic Alcohols

The cyclopropanations of 1-cycloalken-3-ols with five-, six-, and seven-membered rings generally produced very good *syn*:*anti* ratios, while a reversal of selectivity was observed with larger eight- or nine-membered ring [7a]. This can be explained on the basis of simple conformational analysis of the ground state [20]. For instance, in their approach to enantiomerically pure cyclopropyl ketones, Johnson and Barbachyn showed that β-hydroxysulfoximines derived from cyclic enones could produce the cyclopropane *syn* to the hydroxy group [21]. In addition, the synthesis of cyclopropanated sugars is diastereoselective. In particular, the *syn*-isomer was obtained as the major product with halomethylzinc reagents, whereas the *anti*-isomer could be prepared by a multistep sequence [22].

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

coworkers in 1978 [23]. They observed that very high *syn*-selectivity (>200:1) was achieved with (*Z*)-disubstituted olefins, but much lower with (*E*)-disubstituted olefins (<2:1). Charette showed that the nature of the Zn carbenoid used in these reactions is very important for achieving high diastereoselectivities, especially with (*E*)-disubstituted olefins [24]. 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, but other elements have to be taken into account.

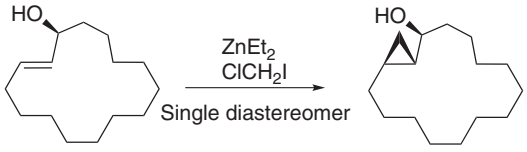
Most of asymmetric cyclopropanations are key steps in the synthesis of natural products of biological interest. For instance, the elegant synthesis of (*R*)-muscone reported by Oppolzer features a diastereoselective cyclopropanation of a chiral macrocyclic (*S*,*E*)-allylic alcohol (Scheme 1.2) [25].

Takemoto and coworkers afforded an asymmetric total synthesis of halicholactone, in which the regio- and stereoselective cyclopropanation is the key step (Scheme 1.3) [26]. It should be noted that the right choice of protecting groups was crucial for the regioselectivity and the occurrence of the reaction.

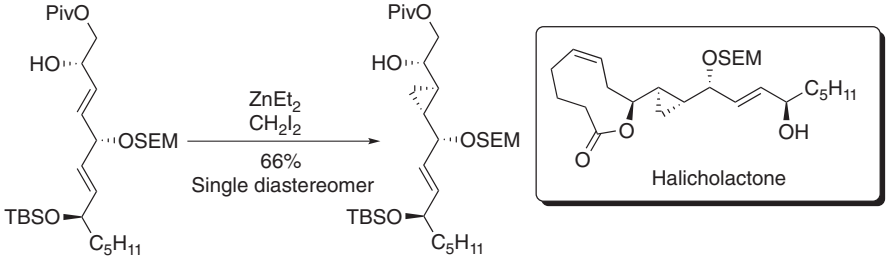
Smith and coworkers afforded the total synthesis of the marine diolide (–)-clavosolide A by direct Simmons–Smith cyclopropanation of an *N*-methoxyamide (Scheme 1.4) [27].

White *et al.* developed a total synthesis of solandelactones E and F (two biologically active oxylipins), having another similar directed Simmons–Smith cyclopropanation as the key step, leading to a single diastereomer, as shown in Scheme 1.5. From this synthesis, authors confirmed that the structures of the two solandelactones were epimeric at C11 [28].

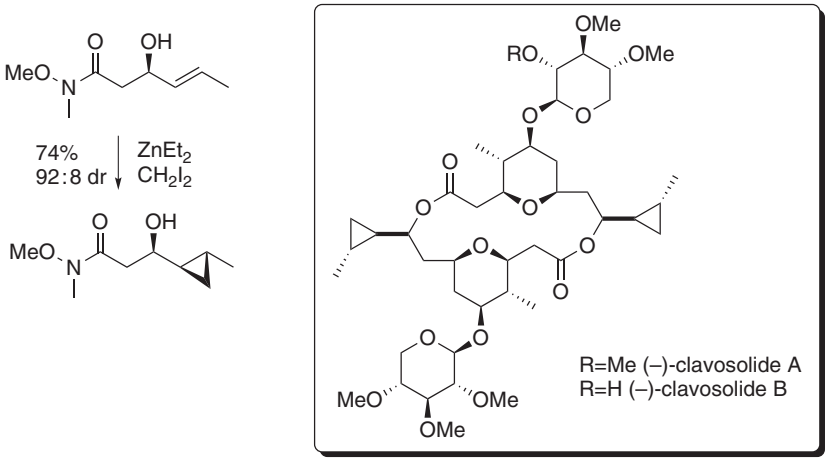
Brevipolides are extracted from the invasive tropical plant of *Hyptis brevipes* and showed interesting drug properties. A diastereoselective synthesis of C1–C12



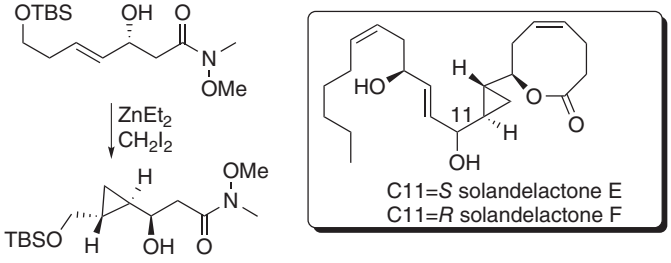
Scheme 1.2 Synthesis of (*R*)-muscone.



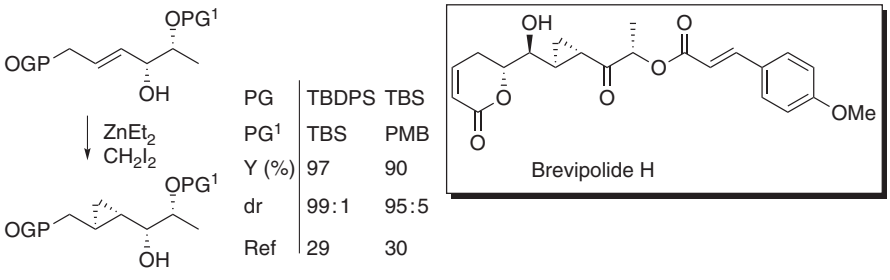
Scheme 1.3 Key step in the asymmetric total synthesis of halicholactone.



Scheme 1.4 Key step in the total synthesis of (–)-clavosolide A.



Scheme 1.5 Key step in the total synthesis of solandelactones E and F.



PG	TBDPS	TBS
PG[1]	TBS	PMB
Y (%)	97	90
dr	99:1	95:5
Ref	29	30

Scheme 1.6 Diastereoselective synthesis of C1–C12 fragment of brevipolide H.

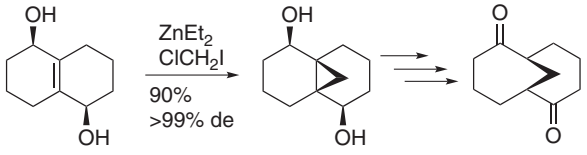
fragment of brevipolide H was synthesized by Mohapatra's group (Scheme 1.6) [29]. More recently, a similar reaction was proposed by Kumaraswamy and coworkers, but with inferior results for the synthesis of 11′-*epi*-brevipolide H [30].

Schmalz's group developed a fully enantioselective synthesis of a C_2-symmetric bicyclo[4.4.1]undecanedione based on a diastereoselective cyclopropanation [31]. It should be noted that the usual Simmons–Smith conditions failed, due to complete decomposition; thus, the desired cyclopropanation was successfully

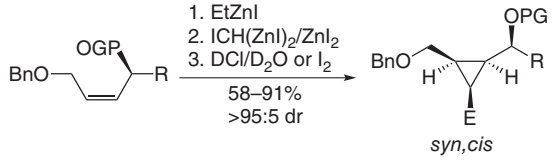
achieved using a $ZnEt_2/ClCH_2I$ reagent, providing the corresponding tricyclic diol as a single diastereomer (Scheme 1.7).

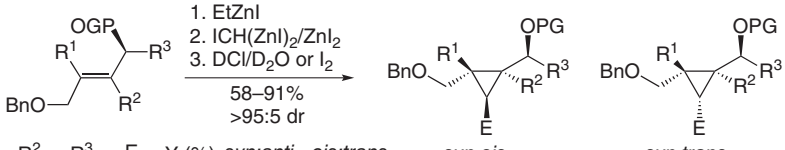
Charette *et al.* reported that the directed cyclopropanation of chiral acyclic allylic alcohols using *gem*-dizinc carbenoids was highly stereoselective, yielding either the *syn* or the *anti*-cyclopropane, depending upon the substitution pattern of the alkenes [32]. Thus, the zinc cyclopropanation of several *cis*-disubstituted allylic alcohols occurred with excellent facial selectivity for the attack of the *gem*-zinc carbenoid, leading to the corresponding *syn*, *cis*-cyclopropyl derivatives in high diastereomeric ratios for a wide range of sterically demanding substituents at the allylic position, even with protected allylic alcohol. The zinc cyclopropanation of the corresponding *trans*-isomer was less stereoselective. However, the introduction of a TMS substituent at either the R^1 or the R^2 position led to the exclusive formation of the *anti*, *cis* or of the *syn*, *trans*-isomer, as shown in Scheme 1.8.

Occhiato's group prepared substituted cyclopropane pipecolic acids as conformationally restricted templates for linear and cyclic peptidomimetics [33]. The synthesis started from commercially available enantiopure γ-hydroxymethyl-γ-butyrolactones, leading to product with complete stereoselectivity even with remote directing group (Scheme 1.9). It should be noted that, sometimes, the reaction conditions deprotected the nitrogen atom, thus avoiding cyclopropanation.

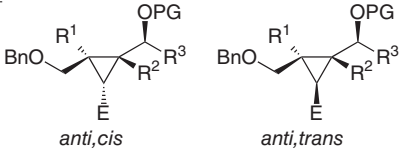


Scheme 1.7 Enantioselective synthesis of a C_2-symmetric bicyclo[4.4.1]undecanedione.

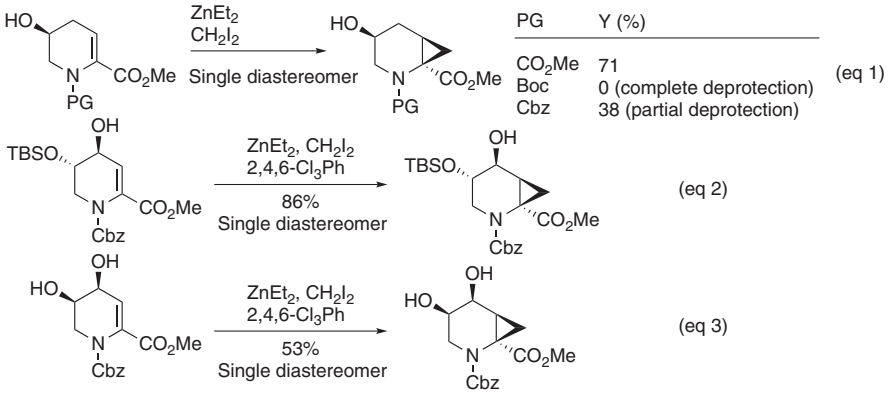




PG	R^1	R^2	R^3	E	Y (%)	*syn:anti*	*cis:trans*
H	H	H	Me	I	85	60:40	28:72
H	H	H	*t*-Bu	D	73	94:6	28:72
TIPS	H	H	*t*-Bu	D	64	>95:5	75:25
H	H	TMS	Me	D	68	<5:95	>95:5
H	H	TMS	*t*-Bu	D	77	<5:95	>95:5
H	TMS	H	*t*-Bu	D	84	>95:5	<5:95
H	TMS	H	*t*-Bu	I	81	>95:5	<5:95



Scheme 1.8 Cyclopropanation of chiral allylic alcohols using *gem*-dizinc carbenoids.



Scheme 1.9 Synthesis of substituted cyclopropane pipecolic acids.

1.2.1.2 Chiral Allylic Amines

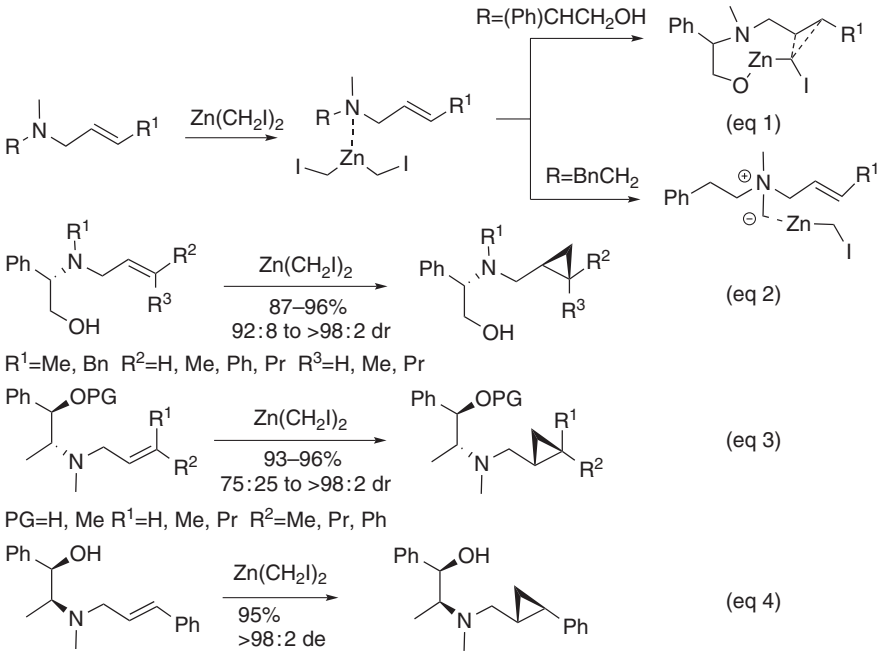
Even though amines have the same potential for binding with the zinc reagent as oxygen functional groups, allylic amines have been much less explored compared to their corresponding alcohols.

Aggarwal and coworkers reported the first highly diastereoselective cyclopropanation of allylic tertiary amines using the Simmons–Smith reagent [34]. They found a divergent behavior of simple allylic amines and those bearing additional chelating groups. In both cases, the reaction was initiated by complexation of the amine with the zinc reagent. However, in the case of a simple allyl-substituted amine (R = $BnCH_2$, Scheme 1.10, eq 1), this species underwent a 1,2-shift to furnish a zinc-complexed ammonium ylide. In the case of an amino alcohol (R = (Ph) $CHCH_2OH$, Scheme 1.10, eq 1), a more stable chelate zinc complex was considered to be formed that did not readily undergo the 1,2-shift. Because of the proximity of the olefin to the tightly held zinc carbenoid, however, cyclopropanation occurred instead. On these bases, they used a range of chiral amino alcohols such as phenylglycinol (Scheme 1.10, eq 2), pseudoephedrine (Scheme 1.10, eq 3), and ephedrine (Scheme 1.10, eq 4), to achieve cyclopropanation with very high diastereoselectivity.

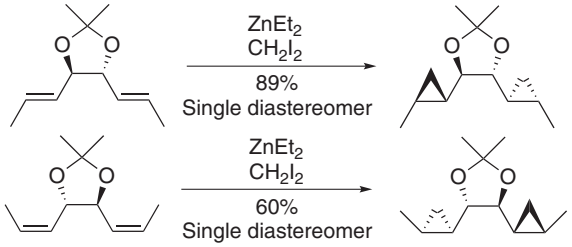
1.2.1.3 Chiral Acetal-Directed Cyclopropanations

Diastereoselective acetal-directed cyclopropanations constitute the key step of some important natural products or drugs containing cyclopropane moieties. The double asymmetric Simmons–Smith cyclopropanation of the (*E*)- and (*Z*)-bis(olefins) could be successfully used to prepare enantioenriched 1,2-bis(2-methylcyclopropyl) ethenes with excellent stereocontrol (Scheme 1.11) [35].

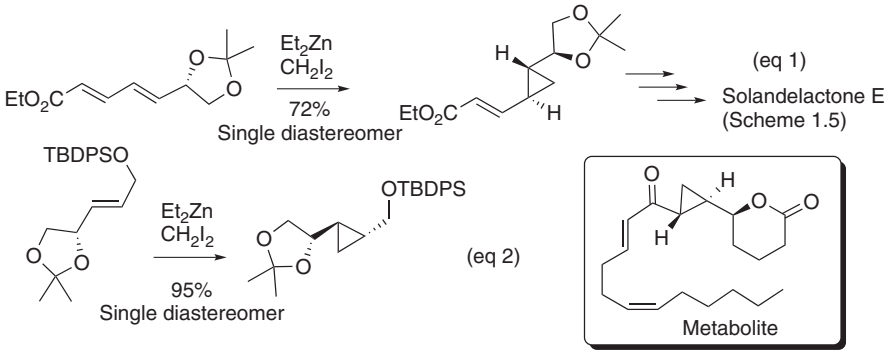
Diastereoselective acetal-directed cyclopropanations also constituted the key step of a total synthesis of solandelactone E (Scheme 1.12, eq 1) [36] and of a total synthesis of a marine fatty acid metabolite having lipoxygenase-inhibiting activity (Scheme 1.12, eq 2) [37], both providing the corresponding cyclopropyl derivative in excellent yield and with high stereoselectivity.



Scheme 1.10 Cyclopropanation of allylic tertiary amines.



Scheme 1.11 Double asymmetric Simmons–Smith cyclopropanation of bis(olefins).



Scheme 1.12 Diastereoselective acetal-directed cyclopropanations.

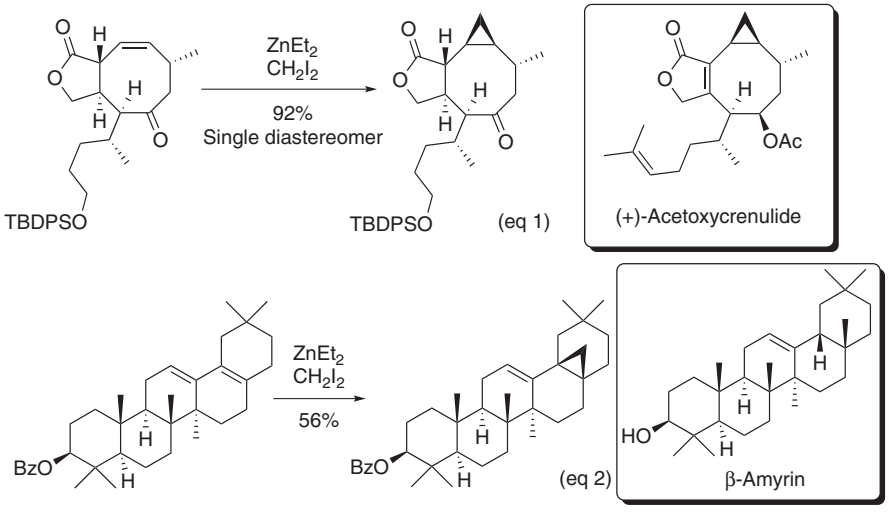
Finally, fluorocyclopropanation of *trans*-styryldioxolane derived from D-glyceraldehyde acetonide afforded the desired cyclopropane in 73% yield, in 94 : 6 dr, and with 99% ee, with the fluorine substituent being oriented *trans* to the dioxolane. The *cis*-isomer led to a 75 : 25 dr, and the major isomer, isolated in 62% yield and with 99% ee, was found to be the all-*cis*-fluorocyclopropane [38].

1.2.1.4 Simple Chiral Alkenes

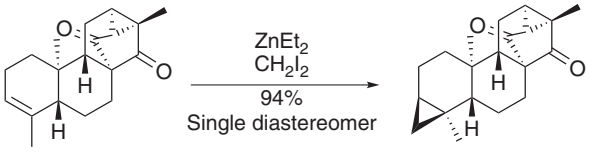
In the absence of a directing group, the cyclopropanation of cyclic olefins is generally subjected to steric effects. The level of stereochemical induction is usually very high, and the sense can be predicted on the basis of the prevailing ground-state conformation of the starting olefin. For instance, a stereoselective cyclopropanation from the more accessible β-face produced a key intermediate in the synthesis of (+)-acetoxycrenulide, as a single isomer (Scheme 1.13, eq 1) [39]. Another stereoselective cyclopropanation was used by Corey and Lee in their β-amyrin total synthesis (Scheme 1.13, eq 2) [40]. The regioselective methylenation of the 17–18 double bond should be also outlined, since the analogous reaction using dibromocarbene added exclusively to the 12–13 double bond.

The stereocontrol in the cyclopropanation of acyclic alkenes, in which the basic group that directed the reagent is not on a stereogenic center, usually was not very high, except when the allylic position bore a bulky dimethylphenylsilyl group. In fact, the cyclopropanation of functionalized (*E*)-crotylsilanes bearing a bis-homoallylic hydroxyl group gave reasonably good diastereoselectivities depending on the nature of the groups on the homoallylic position (the best results are 81% yield and 95 : 5 *anti:syn* ratio). It is worth noting that $AlMe_3$ was the organometallic species generating the carbenoid, because both the zinc- and samarium-derived reagents failed to produce the desired product [41].

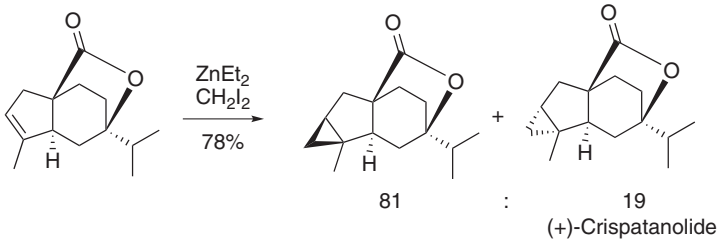
Standard Simmons–Smith conditions were applied by Abad *et al.* to the cyclopropanation of a tetracyclic diterpene [42]. The cyclopropanation took place



Scheme 1.13 Cyclopropanation of simple chiral cyclic olefins.



Scheme 1.14 Cyclopropanation of a tetracyclic diterpene.



Scheme 1.15 Last step of a total synthesis of (+)-crispatanolide.

stereoselectively from the less hindered β-side of the double bond, affording the expected cyclopropane in excellent yield and diastereoselectivity (Scheme 1.14). This tricyclo[3.2.1.0]octane moiety was a key intermediate in the synthesis of trachylobane-, beyerane-, atisane-, and kaurane-type diterpenes.

Based on the same considerations on the steric effects of bulky polycyclic systems, Tori and coworkers applied standard Simmons–Smith conditions in the last step of a total synthesis of (+)-crispatanolide (Scheme 1.15) [43]. Surprisingly, the major product was not the expected (+)-crispatanolide, but a diastereomer, very likely because of the directing effect of the lactone carbonyl group. However, this synthesis allowed similarly assignment of the absolute configuration to the natural (+)-crispatanolide.

Moreover, 2-azabicyclo[3.1.0]hexane-3-carboxylic acids were obtained from chiral 2,3-dihydropyrroles derived from (*R*)-glutamic acid. The asymmetric Simmons–Smith reaction and hydrolysis reaction mainly led to the all-(*R*)-product. In this Simmons-Smith reaction the reaction time was found to influence the *E/Z* ratio and the best ratio was reached after 19.5 h (Scheme 1.16) [44].[3]

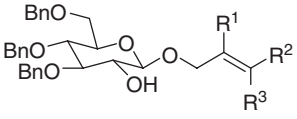
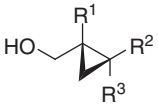
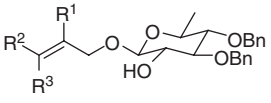
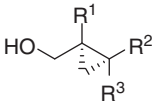
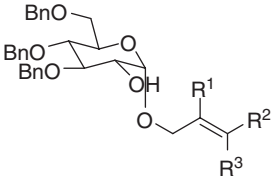
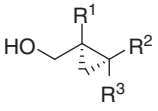
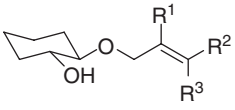
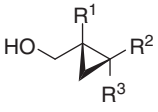
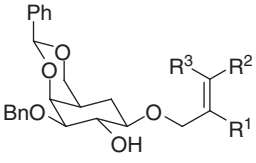
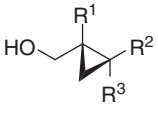
Scheme 1.16 Synthesis of 2-azabicyclo[3.1.0]hexane-3-carboxylic acid.

[3] The paper has only the abstract in English. There the formation of all-(*S*)-product is reported, but schemes report unnatural glutamic acid and it is always numbered R#. Sometimes among Chinese characters some products named S# are reported. Perhaps the reaction was performed from both enantiomers of glutamic acid.

1.2.2 Chiral Auxiliaries

The strategy that uses chiral auxiliaries is based on the transformation into "chiral product equivalents" by binding an enantiomerically pure derivative to the starting material. These compounds are then stereoselectively transformed into new chiral intermediates that contain new stereogenic centers in high diastereomeric excess, with diastereoselectivity being controlled by the presence of the chiral auxiliary fragment. Subsequent cleavage of the chiral auxiliary moiety affords a chiral compound containing a stereogenic center in high enantiomeric excess.[4] Thus, a number of auxiliary-based approaches, which can be encompassed in four general classes, have been reported for the Simmons–Smith cyclopropanation (Table 1.1). Most of these reactions led to cyclopropylmethanols (Scheme 1.17).

Table 1.1 Chiral auxiliaries for Simmons–Smith reaction using $ZnEt_2$, CH_2I_2.

Starting material	Yield (%)	de (%)	Product	References
Allylic ethers				
	≥95	≥98		[45]
	≥95	≥98		[45]
	83–93	92–94		[46]
	90–98[a]	≥93		[47]
	67–95[b]	Up to 100		[48]

(Continued)

[4] The need for additional steps to add and remove the chiral auxiliary reduces the overall yields and leads to wastage of material. However, this strategy was the first used by chemists to obtain enantioenriched products, and only later, the chiral catalysis emerged.

Table 1.1 (Continued)

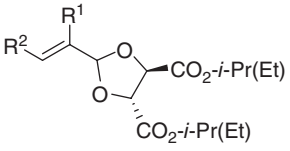
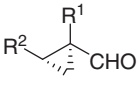
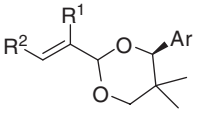
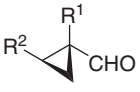
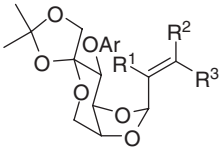
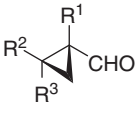
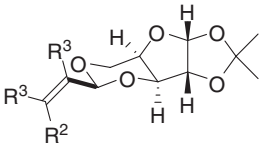
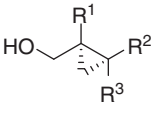
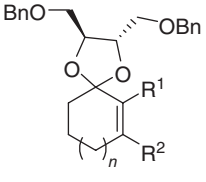
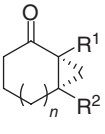
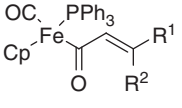
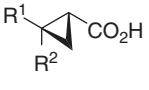
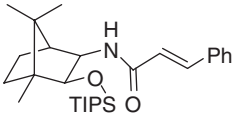
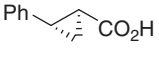
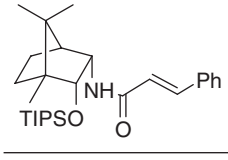
Starting material	Yield (%)	de (%)	Product	References
Acetals				
	50–95	93–97		[49]
	34–67	66–92		[50]
	45–90	21–81		[51]
	69–87[b]	50–100		[52]
	54–99[c]	88–95		[53]
α,β-Unsaturated carbonyl derivatives				
	49–86[d]	94–97		[54]
	62[e]	99		[55]
	56[e]	99		[55]

Table 1.1 (Continued)

Starting material	Yield (%)	de (%)	Product	References
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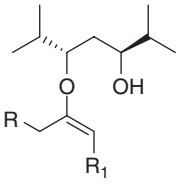
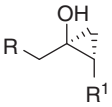
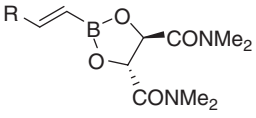
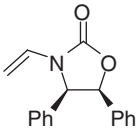
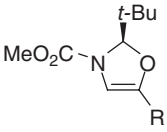
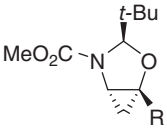
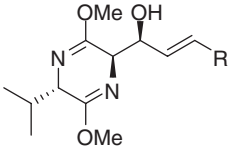
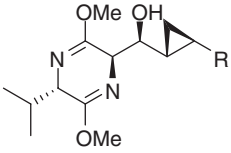
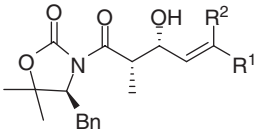
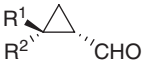
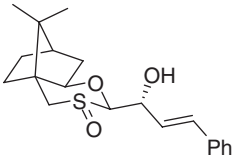
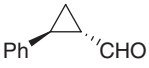
	57–80[f]	99		[56]
	49–67[c]	94–97		[57]
	76[g]	30		[58]
	52–83[c]	>98		[59]
	52–80[h]	36–96		[60]
	89–99[i]	>95		[61]
	95	>98		[62]

a) Carbohydrate-derived chiral auxiliaries acted as bidentate ligands in the complexation of the zinc reagent ($ZnEt_2/ClCH_2I$) with the oxygen atoms at C1 and C2. Therefore, simple chiral 1,2-cyclohexanediol is enough to induce chirality.

b) It should be noted that the reactive face is always the same in both reactions. The obtained opposite enantiomers arose from how the chiral auxiliaries were formed in the two cases. Among acetal-derived auxiliaries, the most efficient auxiliaries were derived from tartaric acid. The configuration of the cyclopropane can be rationalized by coordination of zinc carbenoid to tartrate oxygen atoms.

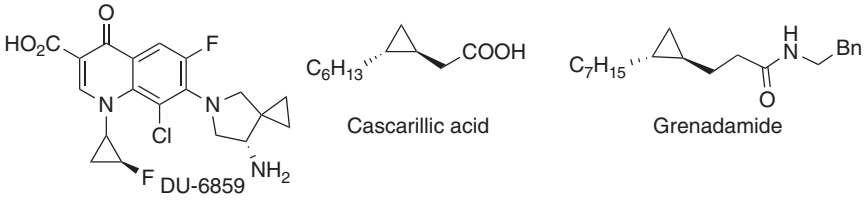
c) Zn/Cu, CH_2I_2.

d) Et_3Al, CH_2I_2.

(Continued)

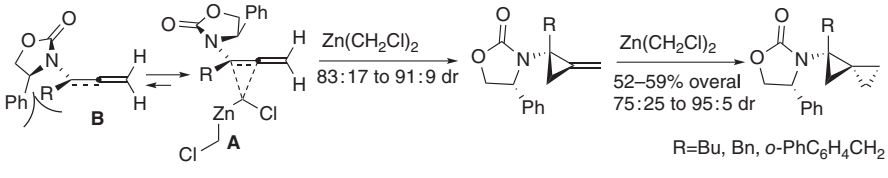
Table 1.1 (Continued)

e) (+)-Diethyltartrate added.
f) This chiral auxiliary can produce one major diastereomer (87 : 13) from more complex diiodoalkane as precursors, in which the R group of the diiodoalkane accommodated in the product *trans* to the hydroxyl moiety.
g) $ZnEt_2$, $CHFI_2$. Chiral 2-fluorocyclopropylamine was also prepared by resolution [63]. It is a key intermediate in the synthesis of DU-6859 (Scheme 1.17), a quinolonecarboxylic acid exhibiting antibacterial activity and little side effects.
h) $ZnEt_2$, R^1CHI_2. Carbenoids of type CHR, from more complex diiodoalkane as precursors, afforded products, in which the R group was on the same side of the OH framework. However, the stereochemistry cannot be completely controlled.
i) The stereo-directing effect was exerted by the hydroxy group, and not by the oxazolidin-2-one group. Enantiomers can be obtained starting from the *N*-acyloxazolidin-2-one of opposite configuration. This methodology was applied to efficient total syntheses of the natural products grenadamide [64], cascarillic acid (Scheme 1.17) [65], and (−)-clavosolide B (Scheme 1.4) [66].



Scheme 1.17 Structures of DU-6859, grenadamide, and cascarillic acid.

The Simmons–Smith cyclopropanation of allenamides was explored in order to develop a direct construction of amidospiro[2.2]pentanes that are interesting potentially biologically active compounds [67]. Hsung and coworkers found that Simmons–Smith cyclopropanation of chiral enamides could be efficiently achieved in very high diastereomeric excesses [68]; thus, they envisaged extending their results to allenamides (Scheme 1.18). Unfortunately, the observed diastereoselectivity was very low, owing to a very little difference in energy between conformations **A** and **B** (from PM3 calculations with the Spartan Model™) much smaller than the corresponding difference between enamide conformations. The enantioselection increased with an increase of the bulkiness of the R substituent, because of enhanced steric crowding in conformation **B** (Scheme 1.18). The first cyclopropanation proceeds by an approach of the zinc carbenoid from the bottom π-face of the more favored conformer **A**. Since both π-faces of amido-methylene cyclopropane are sterically encumbered, the second cyclopropanation reaction occurs much more slowly, and mixtures of mono- and spiro-cyclopropyl derivatives were always obtained with mono/spiro ratio directly correlated with the degree of steric crowding of the π-face of the methylenecyclopropane intermediate.



Scheme 1.18 Simmons–Smith cyclopropanation of chiral allenamides.

1.2.3 Chiral Catalysts

Catalytic methods offer many advantages over "chiral pool" or "chiral auxiliary" methods, namely, achiral starting materials or reduced reaction steps, respectively. Generally, they yield good enantioselectivities, but metal catalysis often requires inert reaction conditions and the use of heavy metals, traces of which could be retained in the products, making them not suitable for pharmaceutical preparation. On the other hand, organocatalysts offer some attractive benefits such as their ready availability and high stability, simple handling and storage, but they require the formation of labile intermediates or tight ion pairs. However, the most ancient papers used stoichiometric amounts of chiral ligands, and only in the past few years, true catalytic methodologies have been published.

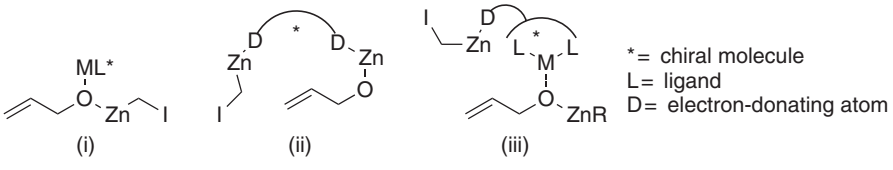
1.2.3.1 Charette's Ligand

The first attempts to control the absolute stereochemistry in the cyclopropanation of substrates by adding external chiral ligands were reported in 1968, when a mixture of (–)-menthol and $IZnCH_2I$ was added to α,β-unsaturated esters or L-leucine was used as a co-additive in the cyclopropanation of vinyl ethers [69]. Also, (1*R*,2*S*)-*N*-methylephedrine-modified halomethylzinc afforded modest enantioselectivities [70]. The addition of diethyl tartrate to a mixture of the allylic alcohol, diethylzinc, and diiodomethane was the first practical stoichiometric system for the enantioselective cyclopropanation of allylic alcohol [71]. Moderate levels of enantioselection (34–92% ee) were observed in the cyclopropanation of silicon-substituted allyl alcohols.

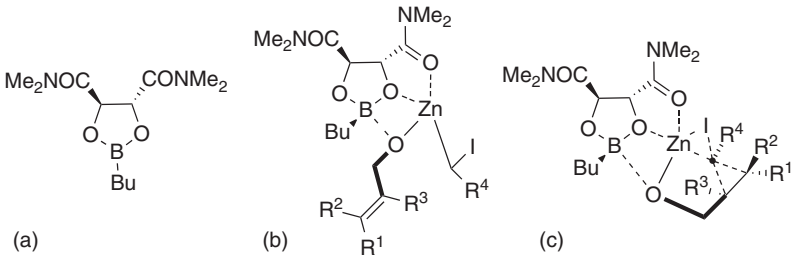
A major breakthrough in this area occurred when a simple bifunctional, nonracemic ligand containing both acidic (different from zinc) and basic sites was found to allow simultaneous chelation of the acidic halomethylzinc reagent and of a basic zinc allylic alkoxide. These aggregates can be of three different types (Scheme 1.19):

i) Capture of an allyloxy(iodomethyl)zinc species by a Lewis acid site of the catalyst
ii) Capture of allyloxyzinc and iodomethylzinc species by a bifunctional chiral catalyst with two identical groups
iii) Capture of the two species by a bifunctional Lewis acid–Lewis base catalyst.

In 1994, Charette and Juteau found that the addition of a stoichiometric amount of a chiral dioxaborolane ligand prepared from the commercially available *N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide and butylboronic acid (Scheme 1.20a) to the classical Simmons–Smith reagents provided asymmetric synthesis of cyclopropanes [72]. By DFT calculations, the Charette chiral dioxaborolane ligand was found to form an



Scheme 1.19 Different types of aggregates among ligands, allylic alcohols, and zinc species.



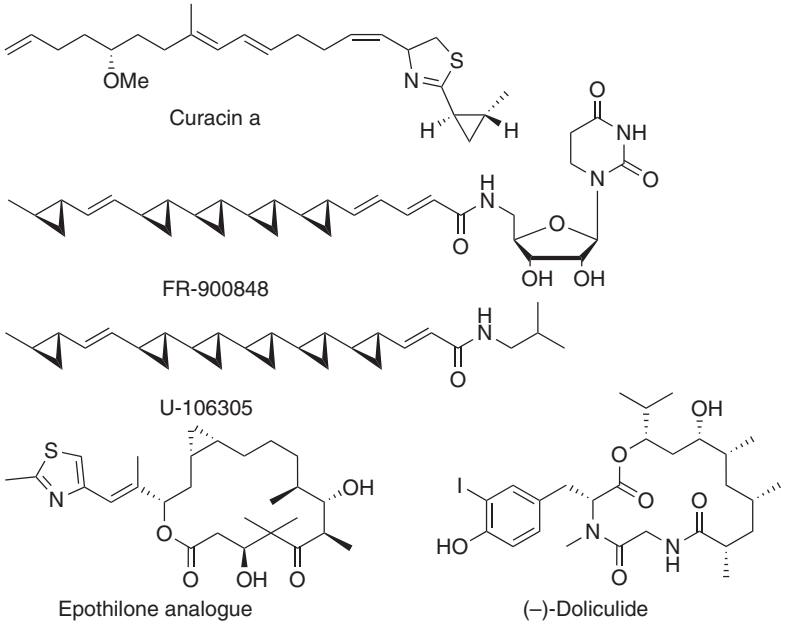
Scheme 1.20 Charette's chiral dioxaborolane ligand (a) and its alcoholate complex (b) and transition state (c).

energetically stable four coordinated chiral zinc–ligand complex, with the zinc bonded to the CH_2I group and coordinated by three oxygen atoms (Scheme 1.20b) [73]. The study of the relative energies of the different transition states allowed the identification of three main factors influencing the enantioselectivity:

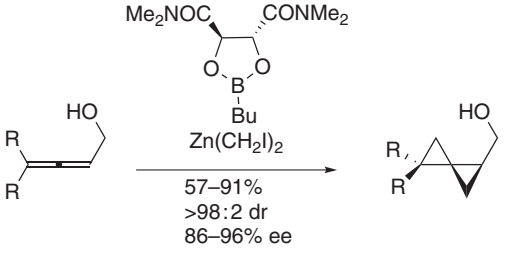
i) the torsional strain along the carbon—carbon bond being formed,
ii) the $A^{1,3}$ strain caused by the chain conformation, and
iii) the ring strain generated in the transition states.

Generally, the effects of these three factors on the enantioselectivity are synergetic, resulting in generation of cyclopropylmethanols with enantiomeric excesses of up to 98% ee with *cis*- and *trans*-disubstituted allylic alcohols as well as with tetra-disubstituted ones. Charette also showed that the reaction could be used in the case of polyenes. Excellent regioselectivity favoring the allylic alcohol was observed, when the substrate contained more than one double bond [74]. This efficient methodology was used in the enantioselective cyclopropanation of important chiral building blocks for natural product synthesis, such as 3-tributylstannyl-2-propen-1-ol [75], 3-iodo-2-propen-1-ol [76], 2-chloro-2-propen-1-ol [77], the chiral cyclopropanes subunits of curacin A [78], FR-900848 [79], U-106305 [80], epothilone analogs [81], and (–)-doliculide (Scheme 1.21) [82]. The same reaction conditions were also applied to the enantio- and diastereoselective cyclopropanation of allenic alcohols, which led to enantiomerically enriched spiropentane derivatives (Scheme 1.22) [83].

The stereoselective synthesis of highly functionalized trisubstituted cyclopropanes is problematic. Even if high diastereoselectivities and enantioselectivities were often recorded with 1,2,3-substituted cyclopropanes, when treated with the reagent formed by mixing 1,1-diiodoalkanes and diethylzinc [84], some other trisubstituted allylic alcohols, such as 1-cyclohexenylmethanol, are converted to the corresponding cyclopropanes in good yield but with low enantiomeric excess. Thus, Charette and coworkers partially modified their *gem*-dizinc carbenoids (EtZnCHIZnEt) into $(IZn)_2CHI{\cdot}4Et_2O$ [85]. The initial deprotonation of the alcohol with diethylzinc was mandatory to prevent *in situ* formation of the classical Simmons–Smith reagent [86]. Under these experimental conditions, *trans*-allyl alcohols were converted into cyclopropylborinates, which, in turn, were subjected to Suzuki–Miyaura reaction conditions with iodoarenes to give products in 26–85% yield, with high diastereomeric ratio (>20 : 1) and 80–97% ee. The



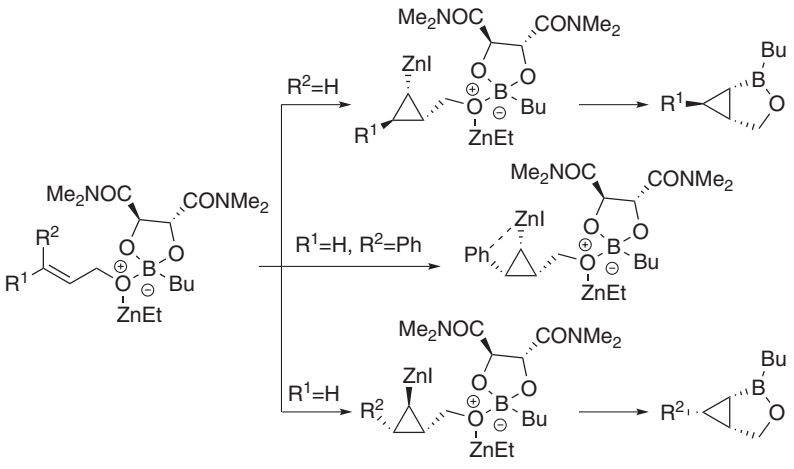
Scheme 1.21 Natural products obtained by enantioselective cyclopropanation with Charette's method.



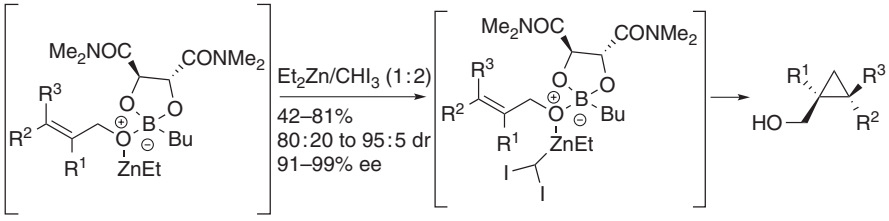
Scheme 1.22 Enantio- and diastereoselective cyclopropanation of allenic alcohols by Charette's method.

reaction of *cis*-allylic alcohols led to a mixture of diastereomeric cyclopropylzinc halides. The all-*cis* gave the expected reaction, while a *trans*-relationship between ZnI and the dioxaborolane moiety disfavored the zinc–boron exchange, which could only occur intramolecularly. The *cis*-cinnamyl alcohol represented an exception, because the favorable π-interaction between the phenyl ring and the zinc atom produced almost exclusively the all-*cis*-isomer, which was then incorporated in the final cyclopropane (Scheme 1.23).

The same research group was also able to adjust the stoichiometric ratio of R_2Zn relative to iodoform in order to increase the proportion of the $RZnCHI_2$ species with respect to the *gem*-dizinc carbenoid, thus allowing iodomethyl-cyclopropanation reactions. In particular, using 1:2 stoichiometric ratio of these reagents, complete conversion into iodocyclopropane was observed (Scheme 1.24) [87].



Scheme 1.23 Stereoselective synthesis of cyclopropanes by partial modification of Charette's method.



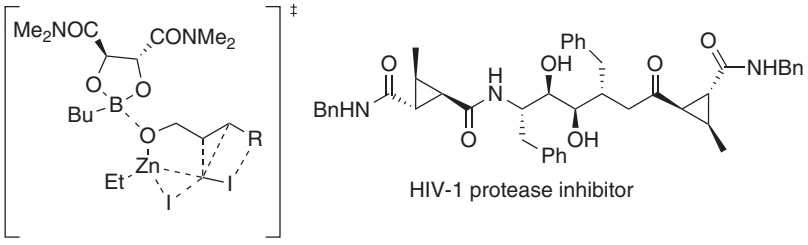
R^1=H, Me R^3=H, Pr

R^2=H, Pr, Ph, 2,4,6-$Me_3C_6H_4$, $Ph(CH_2)_2$, 4-ClC_6H_4, 2-ClC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$NO_2C_6H_4$, PhC=CH, Cy, $TBSO(CH_2)_4$, $I(CH_2)_4$

Scheme 1.24 Stereoselective synthesis of cyclopropanes by adjust the stoichiometric ratio of R_2Zn and iodoform.

The authors proposed a transition-state model for this enantioselective iodocyclopropanation as depicted in Scheme 1.25. The spatial arrangement of substituents was based on the envisaged less sterically congested conformer of the two possible reactive ones. This hypothesis was also corroborated by DFT studies of analogous cyclopropanation reactions [73]. The reaction was scaled up to 10 mmol with comparable yields and selectivity, and, furthermore, an electrophilic trapping of the corresponding cyclopropyllithium occurred with retention of configuration to give access to a variety of enantioenriched 1,2,3-trisubstituted cyclopropanes. In particular, the synthesis of an HIV-1 protease inhibitor (Scheme 1.25) was performed [88].

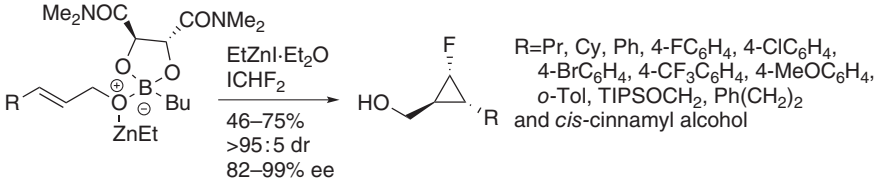
The study of the reaction of chloroiodomethylzinc, diiodomethylzinc, and bromoiodomethylzinc carbenoids demonstrated that bromocyclopropanes were always recovered along with the iodocyclopropanes. In order to explain the different behavior between $BrCHI_2$ and $ClCHI_2$ as the carbenoid precursor, quenching experiments were performed, demonstrating the presence of a halogen scrambling that took place on the zinc carbenoid. Moreover, chloroiodomethylzinc carbenoid was more reactive



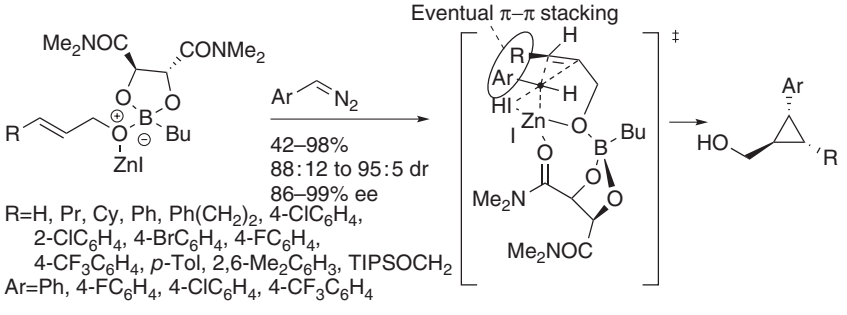
Scheme 1.25 Transition-state model for iodocyclopropanation and protease inhibitor prepared by this method.

than the diiodomethylzinc species, and the latter had reactivity similar to that of bromoiodomethylzinc. The same halogen scrambling was found in the monofluorocyclopropanation reaction [89]. The carbenoid precursor $FCHI_2$ was difficult to be prepared [58], but $ICHF_2$ was readily accessible from inexpensive reagents. The reaction allowed the preparation of monofluorocyclopropanes, where the fluorine atom and the hydroxy group had a *trans*-relationship (Scheme 1.26) [38]. It should be noted that *cis*-relationship could be obtained by an MIRC reaction on α,β-unsaturated amides (see Section 1.4.3). The reaction with secondary allylic alcohols was only performed in diastereoselective manner, that is, without the chiral promoter.

The direct synthesis of cyclopropylmethanols from arylzinc carbenoids was complicated by their instability and by the instability of the parent diiodoarenes. However, Charette's research group overcame this drawback by using diazo reagents as carbenoid precursors, which was a rare application of diazo compounds in a Simmons–Smith cyclopropanation reaction, despite the fact that diazo compounds occupy a vast area of research in cyclopropanation (see Section 1.3) [72f]. The stereo-arrangement of the three substituents on the product (Scheme 1.27),



Scheme 1.26 Preparation of monofluorocyclopropanes.



Scheme 1.27 Aryldiazo reagents as carbenoid precursors in Simmons–Smith reaction.

different from that reported in the analogous reaction depicted in Scheme 1.23, is worth of note. The authors proposed a mechanism for this reaction, in which aryldiazomethane reacted with the adventitious zinc iodide to generate the aryl-substituted carbenoid. The carbenoid species was then delivered selectively to one of the two faces of the dioxaborolane–zinc alcoholate complex, in order to minimize the steric repulsion of the directing group. Moreover, in such an assembly, a favorable π-stacking increased the diastereomeric ratios when R was an aryl rather than an alkyl group. In such a reaction pathway, zinc(II) iodide was regenerated, thus, starting from an enantiomerically pure allyl alcohol, the chiral promoter is unnecessary. Actually, 5 mol% of zinc iodide in dichloromethane and sodium hydride (1.0 equiv., to form the alcoholate) allowed the cyclopropanation reaction of in 95% yield, with 80 : 20 dr and 99% ee [72e].

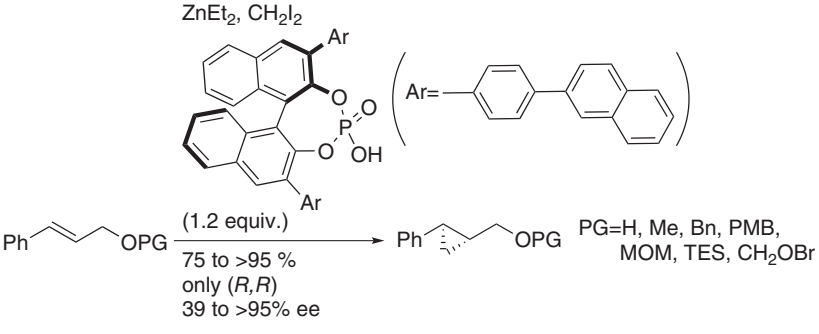
Charette's chiral dioxaborolane ligand was also employed for the gram-scale synthesis of 3-[(1*S*,2*S*)-2-dimethylaminomethylcyclopropyl]-1*H*-indole-5-carbonitrile hydrochloride (38% overall yield after eight steps, 88% ee), a selective serotonin reuptake inhibitor, demonstrating that the reaction was easily scalable without detriment to the stereoselectivity [72d].

Finally, both Charette's (*R*,*R*)- and (*S*,*S*)-dioxaborolanes were employed by Kiyota and coworkers in the synthesis of both enantiomers of cyclopropanated analogs of geraniol (62% and 55% yield, >95% ee always, from (*R*,*R*)- and (*S*,*S*)-ligand, respectively), nerol (74% and 91% yield, >95% ee always), and nor-leaf alcohols (90% and 81% yield and 93% and 95% ee) [90]. It should be noted that cyclopropanation occurred only at the double bond nearest to the alkoxide.

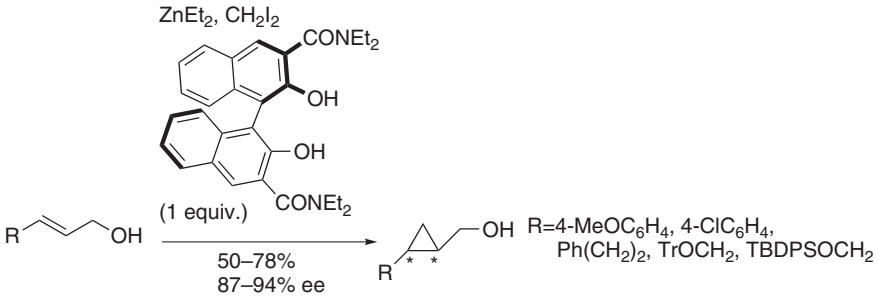
1.2.3.2 Other Stoichiometric Ligands

Charette's group successfully proposed some other chiral promoters. One of these was a chiral 3,3′-disubstituted BINOL-derived phosphoric acid, thus designing a novel chiral zinc phosphate reagent (Scheme 1.28) [91]. The reaction worked well with protected allyl alcohols, while free alcohol gave only 39% ee, albeit in 95% yield. Even when used in catalytic amounts (10 mol%), this chiral phosphoric acid allowed the corresponding chiral cyclopropanes to be obtained in high yield and with up to 95% ee.

Katsuki and coworkers used another binaphthol derivative for the enantioselective cyclopropanation of allylic alcohols (Scheme 1.29) [92]. The scope of the



Scheme 1.28 Chiral zinc phosphate reagent for the enantioselective cyclopropanation.



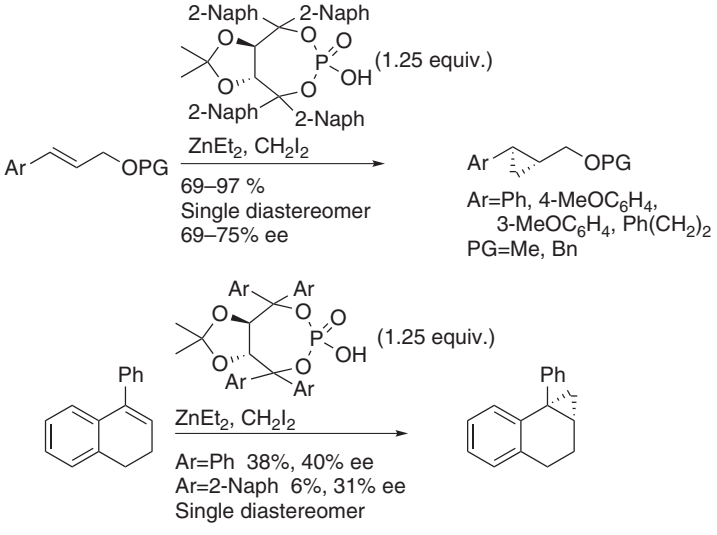
Scheme 1.29 Chiral zinc BINOL reagent for the enantioselective cyclopropanation.

reaction seemed somewhat limited, since only (*E*)-substituted allylic alcohols could be converted into the corresponding cyclopropanes with reasonably good yields and enantioselectivities, while the only example of (*Z*)-substituted allylic alcohols gave cyclopropane in only 34% yield and with 65% ee.

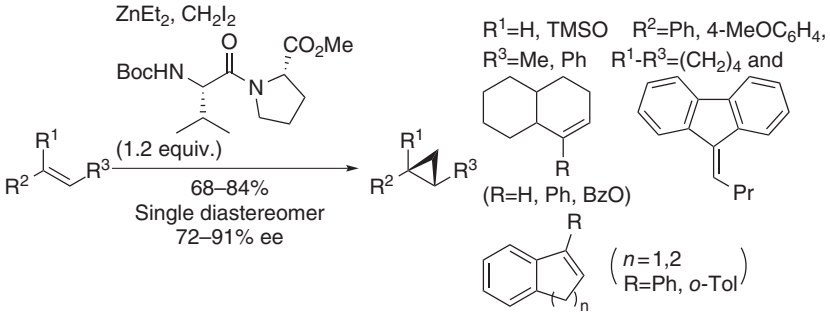
Charette's group also developed a family of chiral phosphates derived from TADDOL [93]. One of the members worked even with unfunctionalized olefins, representing the main advantage over the BINOL phosphate (Scheme 1.30).

Moreover, simple chiral dipeptide, *N*-Boc-L-Val-L-Pro-OMe, combined with $ZnEt_2$ and CH_2I_2, led to an active cyclopropanation system for unfunctionalized olefins with an encouragingly high enantioselectivity (Scheme 1.31) [94]. Then, the same authors found that catalytic amounts were enough for obtaining enantioselectivity (see Section 1.2.3.4).

Since zinc reagents modified by a covalent ligand ($RXZnCH_2I$) are effective for cyclopropanation, a number of chiral alcohols were tested using *trans*-β-methylstyrene as a substrate, in order to induce enantioselectivity in cyclopropanation



Scheme 1.30 Chiral zinc TADDOL reagents for the enantioselective cyclopropanation.



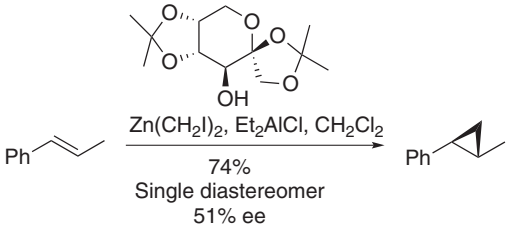
Scheme 1.31 Chiral zinc dipeptide reagent for the enantioselective cyclopropanation.

reactions [95]. Generally, the cyclopropanations were very sluggish, but they were accelerated by the addition of a catalytic amount of Et_2AlCl. The best enantioselectivity (51% ee) was achieved for the cyclopropane product using fructose-derived alcohol (Scheme 1.32).

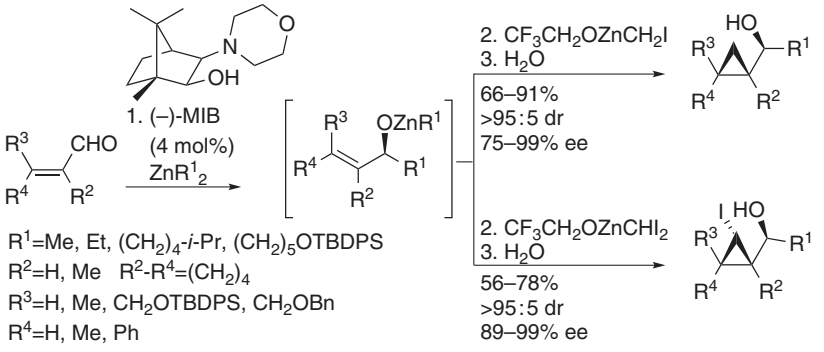
1.2.3.3 Walsh' Procedure

In 2005, Walsh and coworkers proposed a highly enantio- and diastereoselective generation of cyclopropyl alcohols [96]. This methodology consisted of an initial enantioselective C—C bond formation generating a key allylic zinc alkoxide intermediate by asymmetric alkyl addition to α,β-unsaturated aldehydes in the presence of a catalytic amount of (−)-MIB. Then a diastereoselective cyclopropanation affords the corresponding cyclopropyl alcohols having up to four stereogenic centers with very high ee and de (Scheme 1.33). Actually, this methodology is not a strictly asymmetric Simmons–Smith cyclopropanation reaction. In fact, it adopts an asymmetric organocatalyzed synthesis of allyl alcohol, and the Simmons–Smith reaction works on an enantioenriched substrate. This addition/cyclopropanation sequence gives similar stereoselectivities to the cyclopropanation of isolated chiral allylic alcohols, but it is more efficient. As well as Charette's dioxaborolane, the scope of Walsh' methodology was extended to the synthesis of chiral halocyclopropyl alcohols by using, for instance, iodoform in place of diiodomethane as the carbenoid precursor [96]. Then the asymmetric bromo- and chlorocyclopropanation furnished halocyclopropyl alcohols with 89–99% ee and >95 : 5 dr but only in 56–80% yield [97].

A second tandem addition/cyclopropanation sequence based on hydroboration/transmetallation method was developed by the same group, generating a



Scheme 1.32 Sugar zinc reagent for the enantioselective cyclopropanation.

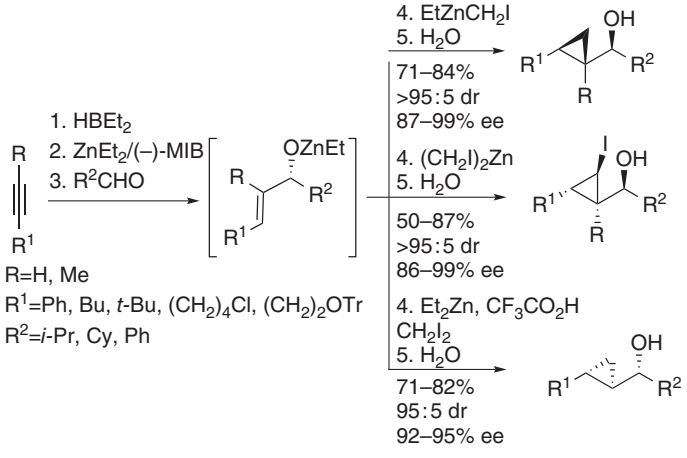


Scheme 1.33 Walsh' procedure.

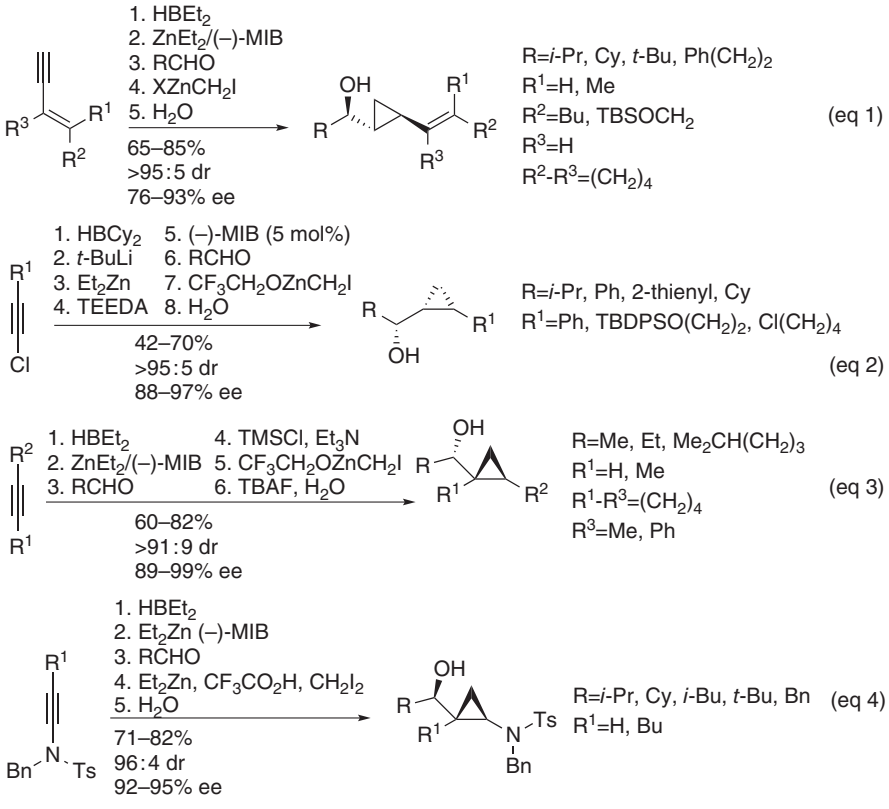
vinyl zinc reagent. In the presence of (–)-MIB, vinylation of an aldehyde proceeded to furnish the allylic alkoxide intermediate necessary for the cyclopropanation (Scheme 1.34) [96]. However, these substrates gave generally low conversions and variable diastereoselectivities, but later, Kim and Walsh were able to overcome this drawback and accelerate the cyclopropanation reaction rate by adding trifluoroacetic acid, minimizing the potential zinc(II)–π interactions [98]. This alternative procedure produced iodocyclopropyl alcohols in 50–87% yields with 86–99% ee and >95:5 dr [97]. The different configuration between iodocyclopropanes obtained from the two alternative ways is worth of note, although the *syn*-relationship between OH group and cyclopropyl ring is maintained.

Walsh' procedures were then applied to the synthesis of the following:

i) *syn*-Vinylcyclopropylalkanols, in which the carbenoid only reacted at the double bond nearest to the alkoxide (Scheme 1.35, eq 1) [99]
ii) *syn-cis*-Disubstituted cyclopropylalkanols in an eight-step *in situ* procedure from chloroalkynes (Scheme 1.35, eq 2) [99]
iii) *anti*-Cyclopropylmethanols from silyl ethers, in order to prevent *syn*-cyclopropanation typical of free alcohols (Scheme 1.35, eq 3) [99]



Scheme 1.34 Tandem addition/cyclopropanation sequence by Walsh' procedure.



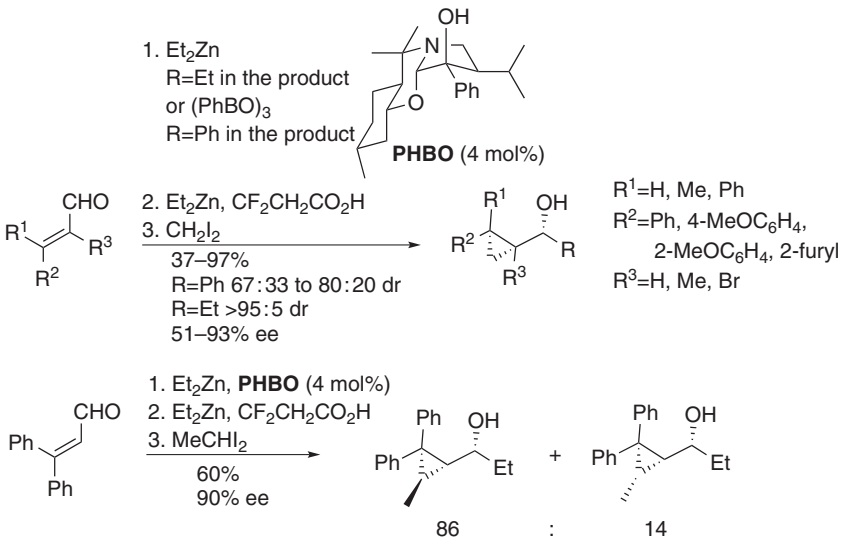
Scheme 1.35 Other applications of Walsh' procedure.

iv) Aminocyclopropylmethanols with three contiguous stereocenters in a five-step one-pot procedure from ynamides (Scheme 1.35, eq 4) [100]
v) Fluorocyclopropane by Charette's group [38]. They found that with increasing bulkiness of the zinc reagent, the yield declined, but diastereoselectivity increased and enantioselectivity did not show a clear trend.

In 2013, a chiral perhydrobenzoxazine was proposed for the enantio- and diastereoselective one-pot ethylation/or arylation/cyclopropanation reaction of α,β-unsaturated aldehydes instead of (–)-MIB (Scheme 1.36) [101]. The catalytic system tolerated a wide range of di- and trisubstituted enals, affording the corresponding *syn*-hydroxycyclopropanes. The presence of substituents at the α-position of the enal bulkier than methyl constituted a limitation to the substrate scope. The use of 1,1-diiodoethane afforded the corresponding cyclopropanes, with good enantiocontrol, although moderate diastereoselectivity.

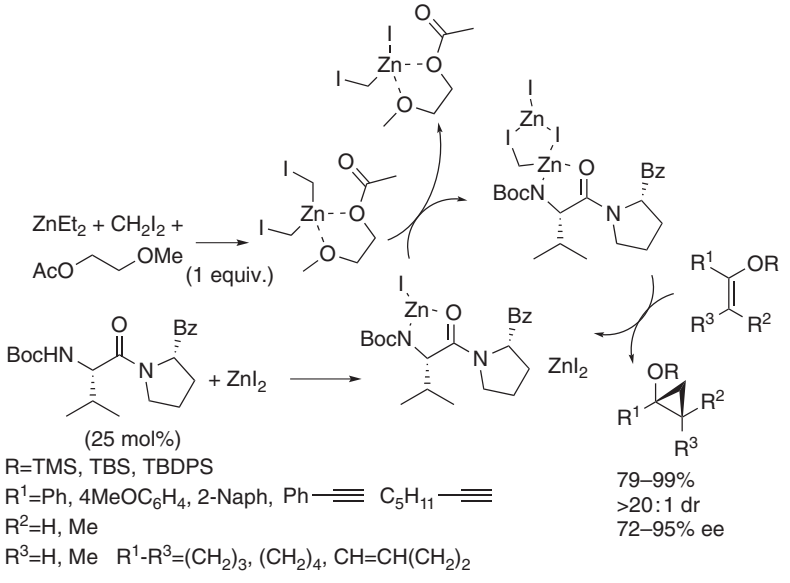
1.2.3.4 True Catalytic Procedures

Only in the past decade, organocatalysis has been developed in Simmons–Smith reaction. For instance, as shown in Scheme 1.31, the cyclopropanation promoted by chiral dipeptide, *N*-Boc-L-Val-L-Pro-OMe, combined with $ZnEt_2$ and CH_2I_2,



Scheme 1.36 Chiral perhydrobenzoxazine for the enantioselective cyclopropanation.

is described. In the presence of catalytic amounts (25 mol%), the enantioselectivity was decreased, due to an enhanced background reaction from $Zn(CH_2I)_2$. However, an achiral additive (ethyl methoxyacetate) that is able to coordinate $Zn(CH_2I)_2$ could reduce the background reaction, and the corresponding chiral cyclopropanes were obtained with comparable ee values to those obtained by the original stoichiometric procedure [102]. In 2006, the same group reported the use of another chiral dipeptide as ligand to promote the asymmetric Simmons–



Scheme 1.37 Chiral zinc dipeptide catalyst for the enantioselective cyclopropanation.

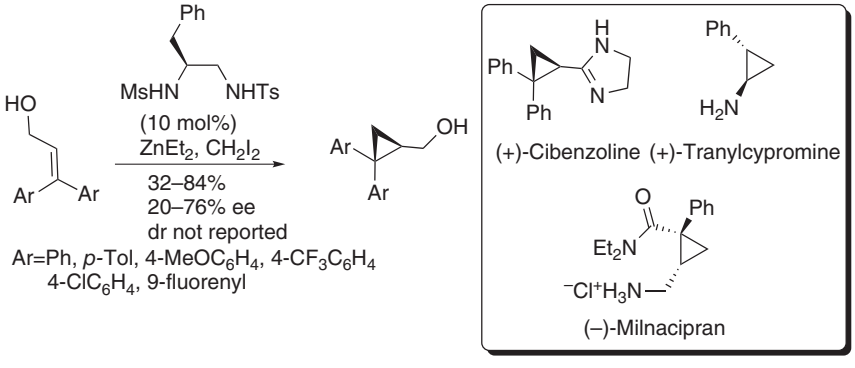
Smith cyclopropanation of silyl enol ethers in the presence of ethyl methoxyacetate as additive (Scheme 1.37) [103].

In 2009, the same authors investigated the mechanism of the reaction in order to interpret the factors influencing the experimentally observed enantioselectivity [104]. They found that asymmetric cyclopropanation was achieved only if the organozinc compound deprotonated the N–H of the dipeptide ligand and that zinc(II) iodide played an important role in promoting the cyclopropanation. From these features, they envisaged the catalytic cycle as depicted in Scheme 1.37. Then, Zheng and Zhang, using B3LYP hybrid density functional methods, further supported the experimental evidence reported by Shi [105]. In fact, theoretical calculations allowed an interpretation of the enantioselectivity according to the "three-point contact model" involving ring formation and two steric repulsions.

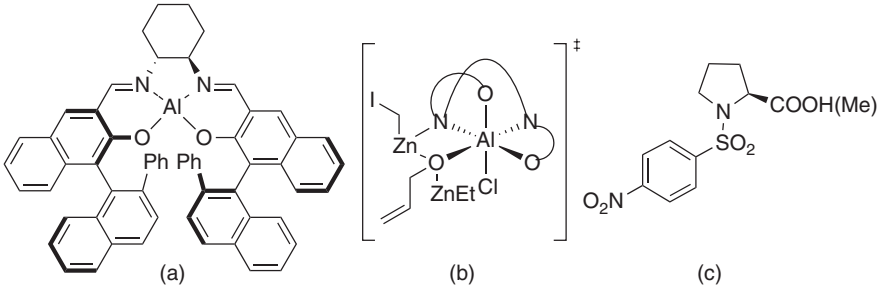
A catalytic amount of (*S*)-phenylalanine-derived disulfonamides was successfully employed in the cyclopropanation reaction of a range of 3,3-diaryl-2-propen-1-ols in the presence of Et_2Zn and CH_2I_2, providing the corresponding cyclopropylmethanols with moderate-to-good enantioselectivity (Scheme 1.38) [106]. The chiral cyclopropane derived from the appropriate allyl alcohol was further converted into (+)-cibenzoline, an antiarrhythmic agent [107], (+)-tranylcypromine, a strong monoamineoxidase inhibitor, and (–)-milnacipran, a serotonin–noradrenaline reuptake inhibitor [108].

Shitama and Katsuki reported a Simmons–Smith cyclopropanation by asymmetric catalysis with an aluminum complex (10 mol%, Scheme 1.39a), in which the aluminum atom and a nitrogen atom from the ligand acted as the Lewis acid and the Lewis base site, respectively (Scheme 1.39b) [109]. Unfortunately, good substrates were limited to *trans*-disubstituted allylic alcohols [92–99% isolated yield with 63–94% ee of the (*S*,*S*)-cyclopropylmethanol], while the enantioselectivity of the reaction of (*Z*)-cinnamyl alcohol was moderate (58% ee of the *R*,*S*-isomer). Another enantioselective cyclopropanation of cinnamyl alcohol (93% yield, 53% ee of the *R*,*R*-isomer) has been accomplished in the presence of chiral sulfonamides derived from L-proline and L-proline methyl ester (Scheme 1.39c) [110].

Finally, the asymmetric Simmons–Smith cyclopropanation of allylic alcohols was also performed in the presence of an enantiomerically pure tridentate catalysts,



Scheme 1.38 (*S*)-Phenylalanine-derived disulfonamides as the organocatalysts in cyclopropanation reactions.

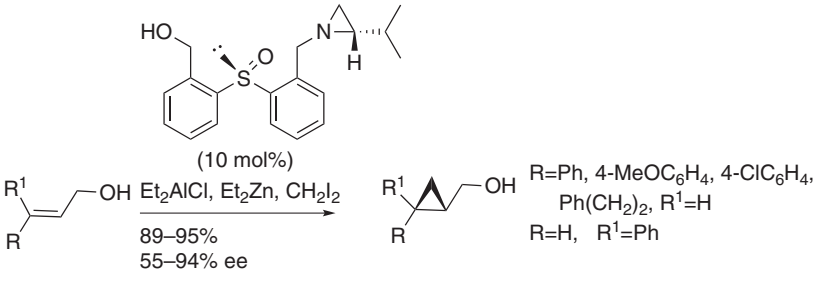


Scheme 1.39 Aluminum complexes and chiral sulfonamides derived from L-proline for catalytic Simmons–Smith cyclopropanation.

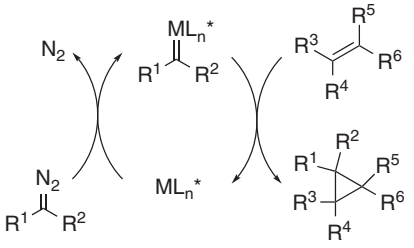
bearing hydroxy, stereogenic sulfinyl, and chiral aziridine moieties. It was found that both stereo-defined groups synergically exerted asymmetric induction on the product, but that only inversion of the aziridine configuration afforded the enantiomeric cyclopropane (Scheme 1.40) [111].

1.3 Transition-Metal-Catalyzed Decomposition of Diazoalkanes

Since the pioneering work of Nozaki *et al*. in 1966 [112], the transition-metal-catalyzed cyclopropanation of alkenes with diazo compounds has emerged as one of the most highly effective and stereocontrolled routes to functionalized cyclopropanes. The diasterocontrol in the cyclopropanation is often governed by the particular substituents on both the alkene and the diazo compounds, and thus, the catalyst must be cleverly designed in order to enhance selective formation of *cis* versus *trans* or *syn* versus *anti*-cyclopropanes. As already seen in the previous section, the most ancient attempts to achieve enantioenriched cyclopropanes used chiral auxiliaries. Since the 1990s, many chiral ligands surrounding the metal center of the catalyst have been introduced for obtaining the enantiocontrol. The accepted catalytic cycle of the carbenoid cyclopropanation reaction involves interaction of the catalyst with the diazo precursor to afford a metallo-carbene complex followed by transfer of the carbene species to the alkene (Scheme 1.41).



Scheme 1.40 Tridentate catalyst bearing hydroxy, sulfinyl, and aziridine moieties.



Scheme 1.41 Accepted catalytic cycle for the carbenoid cyclopropanation reaction.

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 is divided into inter- and intramolecular cyclopropanation reactions, and in each subsection, chiral auxiliaries are described before and then chiral ligands are listed according to the involved metal ion.

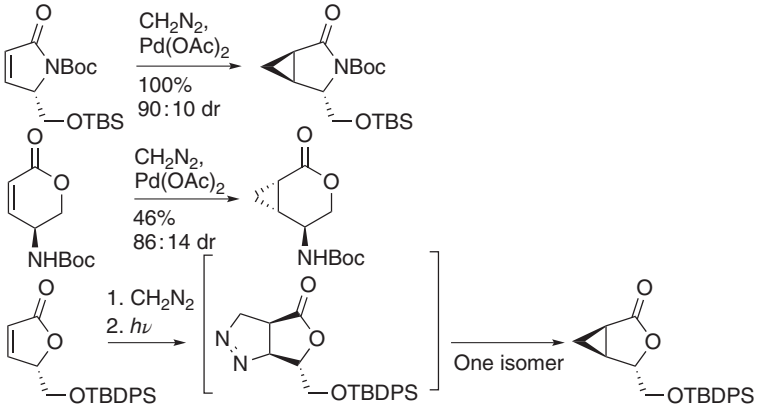
1.3.1 Intermolecular Cyclopropanation

1.3.1.1 Chiral Auxiliaries

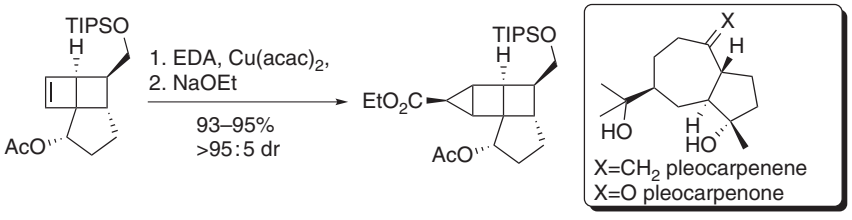
Chiral cyclic alkenes with sterically demanding groups near the olefin undergo cyclopropanation with good diasterocontrol under Pd catalysis or by 1,3-dipolar cycloaddition with diazomethane and nitrogen extrusion (Scheme 1.42) [113].

Moreover, in the asymmetric cyclopropanation of α′-acetoxy-α,β-unsaturated cyclopentanone and cyclohexanone, the five-membered-ring enone afforded only the *anti* diastereomer in 98% yield, whereas the six-membered enone afforded both the *syn*- and *anti*-diastereomers (*syn:anti* = 63 : 34) [114].

In the course of developing total asymmetric syntheses of pleocarpenene and pleocarpenone, Snapper's group observed a considerable stereochemical control in the cyclopropanation/deacetylation reaction of a chiral cyclobutene with ethyl diazoacetate (EDA), using $Cu(acac)_2$ as the catalyst (Scheme 1.43) [115].



Scheme 1.42 Cyclopropanation under Pd-catalysis and 1,3-dipolar cycloaddition with diazomethane.

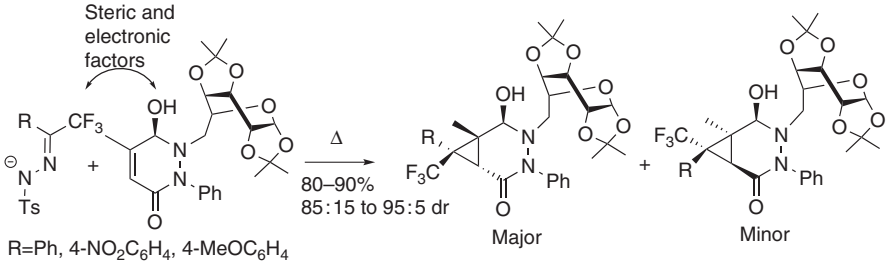


Scheme 1.43 EDA cyclopropanation/deacetylation reaction of chiral cyclobutene.

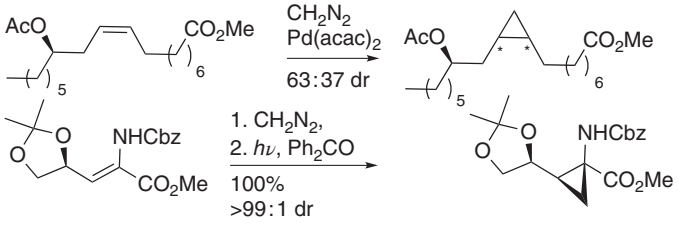
Finally, trifluoromethylcyclopropanes substituted with carbohydrate analogs were prepared by the addition of diazo compounds to 5-(*R*)-hydroxypyridazin-3-one derivative of D-(+)-galactose in high *syn*-selectivity. The observed π-facial selectivity was explained by taking into account the steric interaction and electronic factors of C5-OH atom with the CF_3 group of the diazo compound (Scheme 1.44) [116].

On the other hand, if the cyclopropanations of chiral acyclic alkenes with scarcely demanding chiral auxiliaries usually did not proceed with a high level of stereocontrol [117], the 1,3-dipolar cycloaddition of diazomethane to chiral acyclic alkenes led to cyclopropanes often as a single diastereomer (Scheme 1.45) [118].

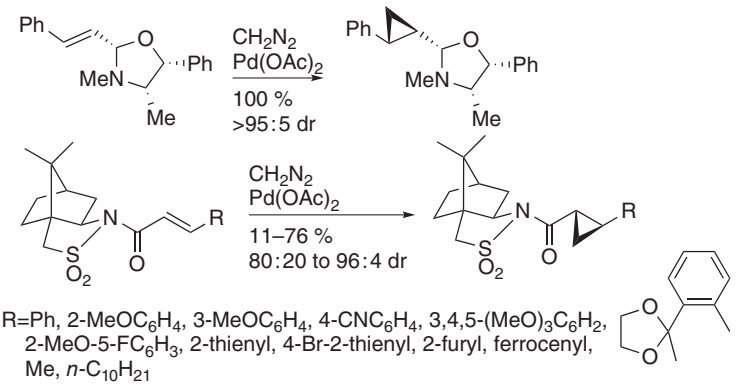
A number of chiral auxiliaries were developed for the cyclopropanation of acyclic alkenes. For example, cinnamaldehyde, upon treatment with ephedrine, produced single oxazolidine diastereomer, then cyclopropanation also gave a single diastereomer; finally, the auxiliary was cleaved by treatment with silica gel [119]. Unfortunately, this auxiliary was tested only with cinnamaldehyde. Oppolzer's chiral sultam was also employed instead of ephedrine (Scheme 1.46) [120]. Although the diastereomeric excesses were quite modest, the diastereomeric products could be recrystallized to remove the minor isomer (from 98:2 dr to almost exclusively



Scheme 1.44 Addition of diazo compounds with high *syn*-selectivity.



Scheme 1.45 1,3-Dipolar cycloaddition of diazomethane to chiral acyclic alkenes.

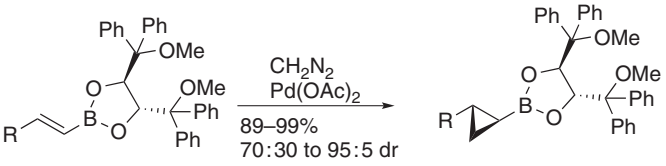


Scheme 1.46 Oppolzer's chiral sultam in cyclopropanation reaction.

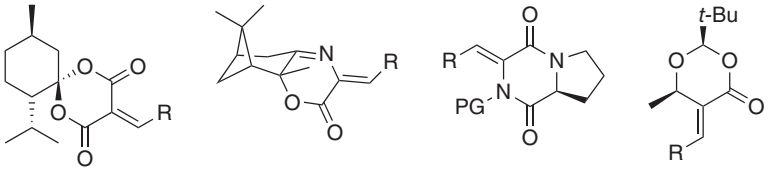
one diastereomer). This synthesis was then applied to an important intermediate of novel melatonergic agents [121].

Pietruszka and coworkers prepared chiral cyclopropylboronic acid by a lithium–aluminum–hydride reduction, followed by hydrolysis of the resulting borohydride. This step limits the tolerance of substituents on the substrate. However, several derivatives were cyclopropanated with good diastereoselectivities, and diastereomeric products were easily separated by chromatography (Scheme 1.47) [122]. The cyclopropanations of the corresponding *cis*-isomer were tested, but the diastereoselectivities were significantly lower (65:35 to 87:13) [122g]. More recently, Florent and coworkers revisited the reaction of a (*Z*)-alkenylboron compound and, although the diastereomeric ratio between the two cyclopropane derivatives was not reported, more than 96% optical purity was achieved after removal of the chiral auxiliary [123].

Other chiral auxiliaries that allow control of the facial selectivity of the 1,3-dipolar cycloaddition of diazomethane have also been developed for specific substrates with dr always >95:5 (Scheme 1.48) [124]. However, these procedures often suffered from the stereoselective preparation of the alkene precursor or the photoinduced nitrogen extrusion.



Scheme 1.47 Synthesis of cyclopropanes through a chiral boronic acid derivative.



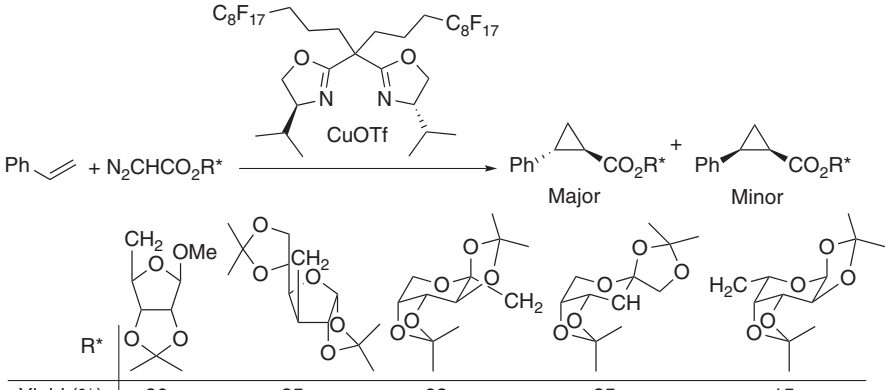
Scheme 1.48 Different chiral auxiliaries for the 1,3-dipolar cycloaddition of diazomethane.

In addition, carbohydrate derivatives have been employed as chiral auxiliaries in asymmetric cyclopropanation. However, the relatively few examples as chiral ligands in the Cu-catalyzed reactions of olefins with diazoacetates showed generally low *E/Z* ratios and enantioselectivities (see Section 1.3.1.3) [125]. Interestingly, Ferreira and coworkers reported the simultaneous use of an α-diazoacetate with a carbohydrate-derived chiral auxiliary and a chiral Cu(I) catalyst to induce chirality in the cyclopropanation reaction (Scheme 1.49) [126]. These authors studied the role of both the chiral auxiliary and the ligand, showing the remarkable importance of the carbohydrate-based chiral auxiliary on the enantioselectivities and the unexpected effect of the ligand on the *E/Z* ratios.

Finally, stable optically pure phosphino(silyl)carbenes, derived from photolysis of the corresponding diazo compounds, were cyclopropanated with methyl acrylate with high stereoselectivity [127]. A total *syn*-diastereoselectivity (with respect to the phosphino group) was observed (Scheme 1.50).

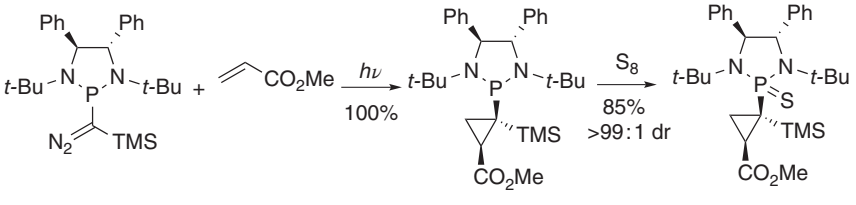
The cyclopropanation of TBS-protected D-glucal as well as other protected glycals in the presence of $Rh_2(OAc)_4$ as the catalyst was among the most ancient methods using chiral auxiliaries and rhodium catalysts (Scheme 1.51) [128].

Rhodium complexes were also found to be the best catalysts for the decomposition of aryl and vinyldiazoesters in the presence of alkenes, leading to the

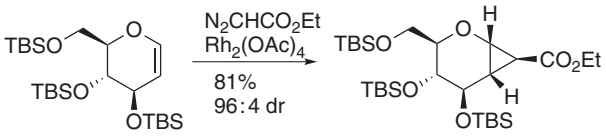


Yield (%)	30	25	62	35	15
de (%)	90	60	50	92	79
ee_{trans} (%)	60	19	<10	34	2
ee_{cis} (%)	53	26	<10	2	92

Scheme 1.49 Cyclopropanation reaction by the use of α-diazoacetate with a carbohydrate-derived chiral auxiliary and a chiral Cu(I) catalyst.



Scheme 1.50 Cyclopropanation with phosphino(silyl)carbenes from photolysis of the corresponding diazo compounds.

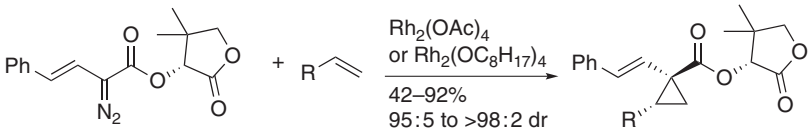


Scheme 1.51 Glucal as chiral auxiliary for Rh-catalyzed cyclopropanation.

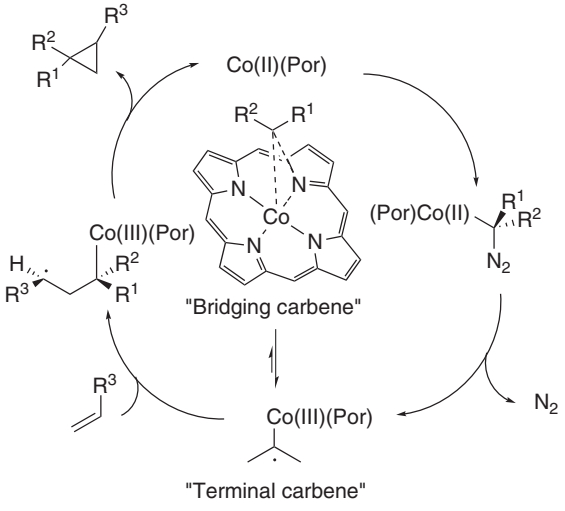
corresponding cyclopropanes with a high level of diasterocontrol, and the introduction of a simple chiral auxiliary on the ester moiety generates an enantiomerically enriched product (Scheme 1.52) [129], except for the intermolecular cyclopropanation of styrene [130].

1.3.1.2 Chiral Catalysts: Cobalt

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. In 2009, Doyle published a highlight article collecting what was known on this topic [131]. The mechanism of this reaction was examined by EPR and electrospray ionization–mass spectrometry (ESI-MS) techniques, especially when cobalt–porphyrin catalysts were used, and evidence for a two-step mechanism was uncovered (Scheme 1.53) [132].



Scheme 1.52 Chiral auxiliary in the cyclopropanation of rhodium-catalyzed vinyldiazoester decomposition.



Scheme 1.53 Mechanism of cobalt–porphyrin catalysis.

The first step is an adduct formation that could exist as two isomers: the "terminal carbene" and the "bridging carbene." In the former, the "carbene" behaves as a redox noninnocent ligand having a d^6 cobalt center and the unpaired electron resides on the "carbene" carbon atom. In the latter, the "carbene" is bound to the metal and one of the pyrrolic nitrogen atoms of the porphyrin. DFT calculations suggested that the formation of the carbene is the rate-limiting step and that the cyclopropane ring formation proceeds by way of a stepwise radical process. Conclusive evidence for the existence of cobalt(III) carbene radicals has been obtained [133]. In fact, in the absence of the alkene substrate, the "terminal carbene" arising from diazoacetate dimerizes to afford binuclear cobalt(III)–porphyrin complex, characterized by X-ray structural analysis. DFT calculations prove the inability of the "terminal carbene" to abstract hydrogen atoms from the solvent, and the radical arising from allylic resonance can be trapped by TEMPO [133, 134]. Other calculations confirmed that the "terminal carbene" complex has a single bond from the metal to the carbon atom and radical character with localized spin density on the carbon. In addition, the carbon is nucleophilic in character and "tunable" through the introduction of different R substituents in order to achieve the desired reactivity. Based on these findings, rational design strategies to enhance catalytic activity can be proposed [135], highly increasing the low level of diastereo- and enantiocontrol of the early work in this area [136]. Applications of cobalt porphyrins in diastereo-and enantioselective cyclopropanation reactions are listed in Table 1.2.

Since 2003 [145], Zhang's research group used a series of novel *meso*-chiral cobalt–porphyrin complexes to catalyze the cyclopropanation of styrene with EDA, affording the desired cyclopropane ester as a *trans*-dominant form in excellent yields [146]. However, only low enantioselectivities were observed (≤12% ee), because of the orientation and flexibility of the chiral appendages. In addition, these authors found that similar reactions could be efficiently catalyzed by vitamin B_{12} derivatives such as aquocobalamin [147].

Sometimes, the use of DMAP as an additive allowed the *trans*- and enantioselectivities to be increased, suggesting a significant *trans* influence of potential coordinating ligands on the metal center [148]. Moreover, the high stereochemical outcome was explained through the potential hydrogen bonding interactions between the chiral amide N–H donor and acceptor units on the "terminal carbene" intermediate. The enantioselectivity was also improved by the use of bulkier ligands, for instance, bearing a *meso*-2,6-dimethoxyphenyl group and by further tightening the structure by intramolecular O···H—N hydrogen-bonding interactions. All of these interactions rigidified the intermediate toward its subsequent reaction with the alkene and thus led to a more selective catalytic process.

It should be noted that addition of α-nitrodiazoacetates to alkenes was reported to afford cyclopropanes as atypical dominant *Z*-isomers [140]. Conversely, rhodium-based chiral catalysts provided predominantly the *E*-isomers (see Section 1.3.1.4) [149].

Cobalt-salens and analogs are other potential efficient catalysts for asymmetric cyclopropanations (Table 1.3), since Yamada showed that 3-oxobutylidenea minatocobalt(II) complexes were quite effective in a *trans*-selective reaction [150]. The addition of a catalytic amount of *N*-methylimidazole (NMI) often

Table 1.2 Cobalt porphyrins in enantioselective cyclopropanation reactions.

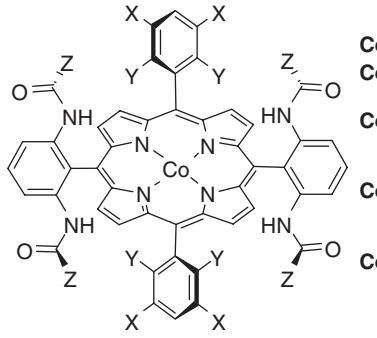
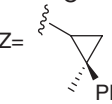
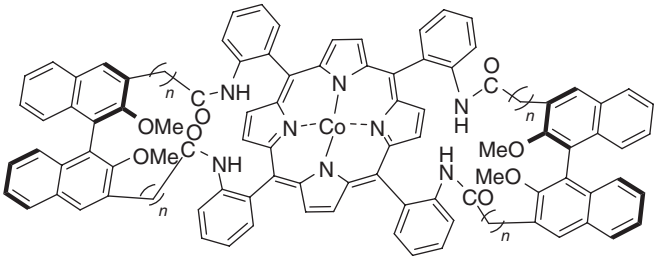
Cobalt porphyrin	Reactants	Yield (%)	dr	ee (%)	References
	**CoP1:** X=*t*-Bu; Y=H Z= 3,5-(*t*-Bu)$_2$C$_6$H$_3$ **CoP2:** X=*t*-Bu; Y=H Z=  **CoP3:** X=H; Y=OMe Z=  **CoP4:** X=H; Y=OMe Z=  **CoP5:** X=*t*-Bu; Y=H *ent*-Z=				
CoP1 (1 mol%) DMAP (100 mol%)	X=C; R=Et, *t*-Bu; R^1=R^3=H; R^2=Ph	86–88	97:3 to >99:1 (*E*/*Z*)	78–95 (*E*)	[137]
CoP2 DMAP	X=C; R=Et, *t*-Bu; R^1=H; R^2=Ph, C_6F_5, 4-MeOC_6H_4, *p*-Tol, *m*-Tol, *o*-Tol, 4-*t*-BuC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$CF_3C_6H_4$, 4-AcOC_6H_4, 2-Naph; R^3=H, Me, Ph	60–95	93:7 to >99:1 (*E*/*Z*)	68–98 (*E*)	[138]
CoP2 DMAP	X=C; R=Et, *t*-Bu; R^1=H; R^2=Me, Et, *n*-C_5H_{11}, CN, CO_2Et, CO_2*t*-Bu, $CONH_2$, $CONMe_2$, CONH*i*-Pr; R^3=H, CO_2Me, COMe, CN	40–94	62–38 to 99:1 (*E*/*Z*)	61–97 (*E*)	[139]
CoP2 (1 mol%)	X=C; R=Et, *t*-Bu; R^1=NO_2; R^2=Ph, *p*-Tol, *m*-Tol, *o*-Tol, 4-*t*-BuC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$CF_3C_6H_4$, 3-$NO_2C_6H_4$, C_6F_5, Bu, Ph$(CH_2)_2$, CO_2Me, CO_2Et; R^3=H	42–97	10:1 to 99:1 (*Z*/*E*)	75–95 (*Z*)	[140]
CoP2 (5 mol%) DMAP (50 mol%)	X=C; R=Su; R^1=H; R^2=Ph, *p*-Tol, 4-*t*-BuC_6H_4, 4-MeOC_6H_4, 4-ClC_6H_4, 4-AcOC_6H_4, 4-$CF_3C_6H_4$, 3-$NO_2C_6H_4$, 2-Naph, CO_2Et, $CONMe_2$, Ac; R^3=H	33–90[a]	49:1 to >99:1 (*E*/*Z*)	89–98 (*E*)	[141]
CoP4 (1 mol%)	X=S; R=Me, *p*-Tol, 4-$NO_2C_6H_4$; R^1=H; R^2 =Ph, 4-*t*-BuC_6H_4, 4-MeOC_6H_4, 4-$CF_3C_6H_4$, 3-$NO_2C_6H_4$, 2-Naph, CO_2Me, CO_2Et, CN, Ac; R^3=H	64–99	99:1 (*E*/*Z*)[b]	89–97 (*E*)[b]	[142]

Table 1.2 (Continued)

Cobalt porphyrin	Reactants	Yield (%)	dr	ee (%)	References
CoP2 (1 mol%)	X=C; R=*t*-Bu; R^1=CN; R^2=Ph, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 3-$NO_2C_6H_4$, C_6F_5, CO_2Me, CO_2Et, $CONMe_2$, $CONH_2$, Ac, CN, Bu, *n*-Hex, $Ph(CH_2)_2$, AcO, *t*-$BuCO_2$; R^3=H	72–99	>99:1 (*E*/*Z*)[c]	71–99 (*E*)	[143]
CoP2 (5 mol%)	X=C; R=*t*-Bu; R^1=Ac; R^2=Ph, *p*-Tol, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-BrC_6H_4, 3-$NO_2C_6H_4$, C_6F_5, 3-$CHOC_6H_4$, *N*-Boc-Indol-3-yl, PhCH=CH, EtO_2CCH=CH, CO_2Me, CN, C_6H_{13} R^3=H, Me	46–94	95:5 to >99:1 (*E*/*Z*)	60–99 (*E*)	[144]
 **CoP6:** *n*=1 **CoP7:** *n*=2					
CoP6 (0.5 mol%)	X=C; R=Et; R^1=H; R^2=Ph, *p*-Tol, 4-ClC_6H_4, CH_2=C(Me); R^3=H, Me, Ph[d]	85–99	2:1 to 5.25:1 (*E*/*Z*)	8–90 (*Z*) 12–71 (*E*)	[134]
CoP7 (0.5 mol%)	X=C; R=Et; R^1=H; R^2=Ph, *p*-Tol, 4-ClC_6H_4, CH_2=C(Me); R^3=H, Me, Ph[d]	85–98	2:1 to 8:1 (*E*/*Z*)	5–80 (*Z*) 8–75 (*E*)	[134]

a) The best enantiomeric excess value was attained with **CoP2**, but the use of **CoP1** afforded the best yield.

b) Except for acrylonitrile, where dr = 79:21 and ee = 61%. **CoP4** led to the 1*R*,2*S*-isomer as the main product (where C-1 is the carbon carrying the sulfonic moiety). With catalysts **CoP1** and **CoP2**, the 1*S*,2*R*-enantiomer was recovered, albeit in low enantiomeric excess.

c) Except for acrylonitrile, where dr = 74:26. Cyclopropanes could be chemoselectively reduced with full retention of configuration to the corresponding primary alcohols or primary amine without affecting the nitrile or the ester functionality, respectively.

d) Stereoselection was not predictable. In fact, (1*R*,2*S*)-*cis* and (1*R*,2*R*)-*trans*-isomers predominated with styrenes, but (1*S*,2*R*)-*cis* and (1*S*,2*S*)-*trans*-isomers predominated with α-methylstyrenes.

increased the rate of the reaction as well as the enantioselectivity, by occupying one additional coordination site on the catalyst. In 2010, mechanistic studies conducted in gas phase, and supported by DFT calculations, showed that the "bridging carbene" is energetically favored conversely from porphyrins, where it

Table 1.3 Cobalt-salen complexes in enantioselective cyclopropanation reactions.

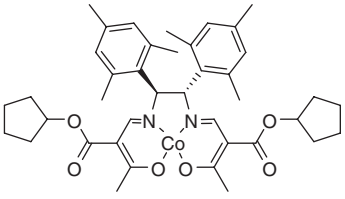
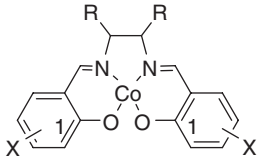
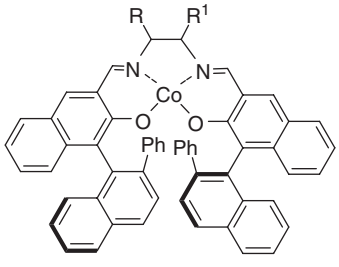
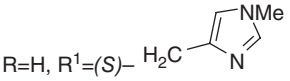
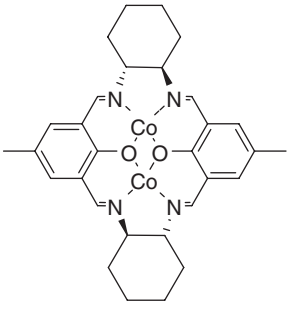
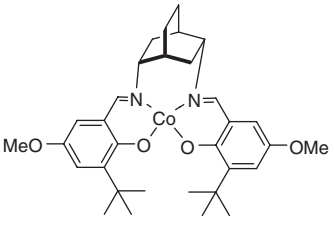
Cobalt-salen	Reactants	Yield (%)	dr	ee (%)	References
 (5 mol%) NMI	R=*t*-Bu; R^1=R^3=H; R^2=Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-Naph	85–99	82:18 to 91:9 (*E*/*Z*)[a]	92–96 (*E*)	[150]
 R=(*R*)-Ph, X=4-MeO (1 mol%)	R=*t*-Bu; R^1=R^3=H; R^2=Ph	91	96:4 (*E*/*Z*)	93 (*E*)	[151]
R=(*S*,*S*)-$(CH_2)_4$, X=3,4-Cl_2-6-*i*-BuO[b] (10 mol%)	R^2=H; R^3=Ph, 4-ClC_6H_4, *p*-Tol, 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$, 4-BrC_6H_4, *m*-Tol, 2,4-$Me_2C_6H_3$, 3-$NO_2C_6H_4$, 3-ClC_6H_4, *o*-Tol[c]	49–95	2:1 to 180:1 (*E*/*Z*)	84–97 (*R*,*R*)	[152]
 R=R^1=(*R*,*R*)-$(CH_2)_4$ (5 mol%) NMI (10 mol%)	R=*t*-Bu; R^1=H; R^2=Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-Naph; R^3=H, Me	39–94	83:17 to 98:2 (*Z*/*E*)	95–99 (*Z*)	[153]

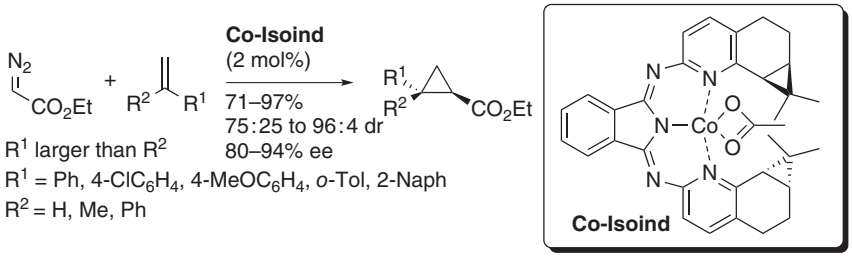
Table 1.3 (Continued)

Cobalt-salen	Reactants	Yield (%)	dr	ee (%)	References
 R=H, R^1=(*S*)–	R=*t*-Bu; R^1=H; R^2=Ph, *p*-Tol,4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-ClC_6H_4; R^3=H	93–100	89:11 to 99:1 (*Z*/*E*)[d]	93–96 (*Z*)	[154]
	R=Et; R^1=R^3=H; R^2=Ph	92	74:26 (*E*/*Z*)	88 (*E*) 94 (*Z*)	[155]
 (5 mol%)	R=Et; R^1=H; R^2=Ph, 2-$MeOC_6H_4$, 2-$MeO_2CC_6H_4$, *p*-Tol, 4$CF_3C_6H_4$, 4-$MeOC_6H_4$, SPh, 3,4-$(MeO)_2C_6H_3$, 2-furyl, 3-CO_2Et-5-Ph-2-furyl, 2-thienyl. 1-Naph, CH_2-1-Naph R^3=Me, Et, Pr, Bu, CH_2CO_2Et, $(CH_2)_2CO_2Me$, cyclopropyl	87–97	16:1 to 50:1 (*E*/*Z*)	83–98 (*E*)[e]	[156]

a) The diastereoselectivity in the cyclopropanation of styrene decreases to 83:17 if methyl diazoacetate is used. The reaction with α-methylstyrene led only to 47% yield and 47:53 (*E*/*Z*) ratio.
b) Triphenylarsine in sulfuric acid–sodium acetate buffer was used as axial auxiliary ligand.
c) The diazo derivative is obtained *in situ* from 2,2,2-trifluoroethanamine.
d) The reaction with α-methylstyrene led only to 45% yield and 55:45 (*Z*/*E*) ratio.
e) KSAc was used as axial auxiliary ligand. The isolated product is enantiomeric with respect to that depicted in the figure above the table.

is excluded (Scheme 1.53). Moreover, the same studies established that the rate-determining step was the addition [157].

Other cobalt ligands have been introduced for the asymmetric cyclopropanation of diazo compounds such as a complex based on bis(2-pyridylimino)isoindoles (Scheme 1.54) [158].



Scheme 1.54 Bis(2-pyridylimino)isoindoles complex for asymmetric cyclopropanations.

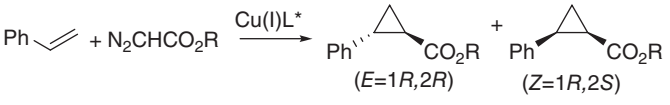
1.3.1.3 Chiral Catalysts: Copper

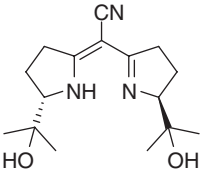
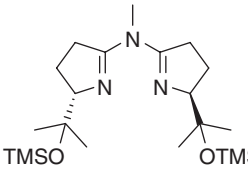
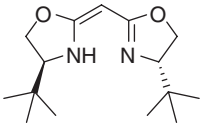
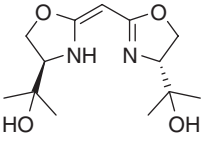
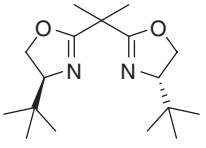
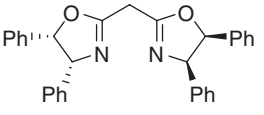
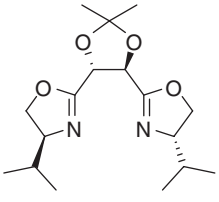
Chiral copper-based catalysts are the most effective catalysts for the preparation of the *trans*-isomer of cyclopropanes with the widest reaction scope. Among them, nonracemic C_2-symmetric bidentate bisoxazoline (box) ligands have been used in cyclopropanation reactions with copper for more than 30 years [159]. Many investigations have shown that the ligand structure has a strong influence on the stereoselectivity of the cyclopropanation. Even very small structural changes often have drastic and sometimes unpredictable effects on the enantioselectivity, and the phenomenon comprehension is complicated by very low enthalpic barrier for the transition states leading to the *R*- and *S*-products. However, since 2001, using DFT calculations, Salvatella and coworkers rationalized the stereochemical prediction of the cyclopropanation. The calculated relative energies are in good agreement with the experimental enantiomeric excesses as well as with the *Z/E* ratio [160]. In 2004, Mend *et al.* studied again this reaction by means of DFT, showing that it was exothermic and that the turnover-limiting step was the formation of metal catalyst–cyclopropyl carboxylate complexes [161]. Then, Maseras and coworkers found a barrier, which arises from the entropic term, in the Gibbs free-energy surface compatible with the experimentally observed enantioselectivity [162]. The enantioselectivity of asymmetric catalysis was predicted based on quantitative quadrant-diagram representations of the catalysts and quantitative structure–selectivity relationship (QSSR) modeling [163]. The data set included 30 chiral ligands belonging to four different oxazoline-based ligand families. In a simpler approach, the derived stereochemical model indicated that an enantioselective catalyst could be obtained by placing very large groups at two diagonal quadrants and leaving free the two other quadrants. A higher-order approach revealed that bulky substituents in diagonal quadrants operate synergistically.

Chiral ligands for the copper-catalyzed cyclopropanation are listed in Table 1.4. Only the diastereo- and enantioselectivities achieved for the cyclopropanation of styrene are shown in order to compare efficiency, but most of them presented a wide spectrum of activity with many other alkenes (see Table 1.4 footnotes). In the table, bisoxazoline ligands derived from camphoric acid are not reported owing to the poor ee values obtained; somewhat better result was obtained for 1,1-diphenylethylene (81% ee) [201].

The use of ionic liquids offered the possibility of combining the positive aspects of both homogeneous and heterogeneous catalysis. The reaction took place in a

Table 1.4 Copper(I)-box catalysts employed in enantioselective cyclopropanation reactions.



Ligand	R	*E*/*Z*	ee (%)	References
 **box1**	D-Menthyl	82:18[a]	97 (*E*) 95 (*Z*)	[159]
 **box2**	D-Menthyl	84:16	98 (*E*) 95 (*Z*)	[164]
 **box3**	D-Menthyl	86:14	98 (*E*) 96 (*Z*)	[165, 166]
 **box4**	D-Menthyl	83:17	90 (*E*) 90 (*Z*)	[166]
 **box5**	BHT	94:6[b,c]	99 (*E*)	[167]
	Et[d]	77:23	99 (*E*)	[168]
	Et[d]	72:28	98 (*E*)	[169]
 **box6**	$CHCy_2$	94:6	36 (*E*) 20 (*Z*)[e]	[170]
 **box7**	L-Menthyl	85:15	89 (*E*) 89 (*Z*)	[171]

(Continued)

Table 1.4 (Continued)

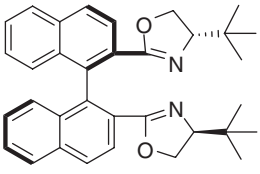
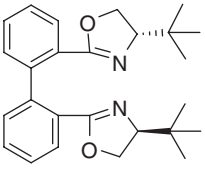
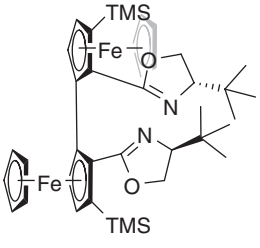
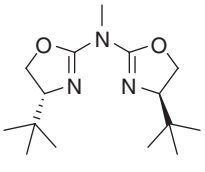
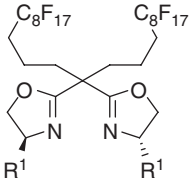
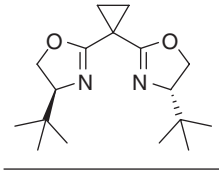
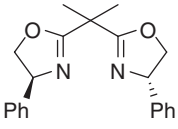
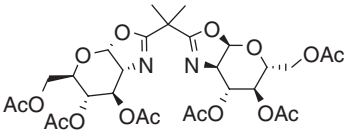
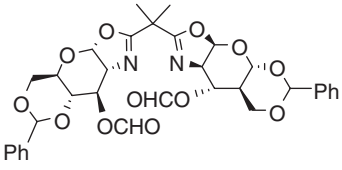
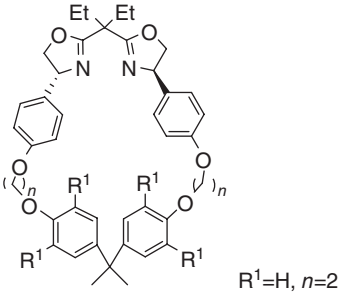
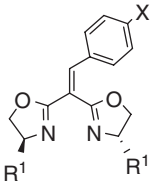
Ligand	R	*E*/*Z*	ee (%)	References
 **box8**	L-Menthyl	68:32	95 (*E*) 97 (*Z*)	[172]
 **box9**	L-Menthyl	81:19	84 (*E*) 92 (*Z*)	[173]
 **box10**	L-Menthyl	77:23	94 (*E*) 79 (*Z*)	[174]
 **box11**	Et	73:27	92 (*E*) 84 (*Z*)[f]	[175]
 R^1= *i*-Pr (**box12**)	Et	62:38	63 (*E*) 63 (*Z*)	[176]
R^1=*t*-Bu (**box13**)	Et	62:38	84 (*E*) 81 (*Z*)	[176]
R^1=Ph (**box14**)	Et	69:31	64 (*E*) 56 (*Z*)	[176]
 **box15**	Et	84:16	100 (*E*) 100 (*Z*)	[177]

Table 1.4 (Continued)

Ligand	R	*E*/*Z*	ee (%)	References
 **box16**	Et	70:30	66 (*E*) 54 (*Z*)[g]	[178]
 **box17**	Et	80:20 (*S*,*S*)	82(*E*) 82 (*Z*)[h]	[179]
 **box18**	Et	73:27 (*S*,*S*)	95 (*E*) 94 (*Z*)[i]	[180]
 **(box19)**	Et	93:7	65 (*E*) 59 (*Z*)	[181]
R^1=Me, *n*=3 (**box20**)	Et	94:6	75 (*E*) 31 (*Z*)	[181]
 R^1=Ph, X=H **(box21)**[j]	Et	65:35	57 (*E*) 45 (*Z*)	[182]
R^1=*t*-Bu, X=H (**box22**)	Et	62:38	84 (*E*) 77 (*Z*)	[182]
R^1=*t*-Bu, X=Cl (**box23**)	Et	65:35	87 (*E*) 78 (*Z*)	[182]
R^1=*t*-Bu, X=OMe (**box24**)	Et	62:38	83 (*E*) 75 (*Z*)	[182]

(Continued)

Table 1.4 (Continued)

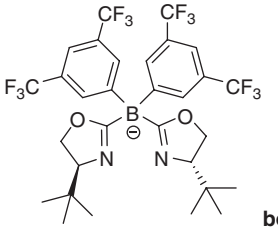
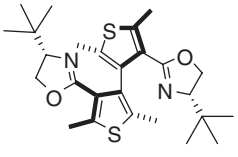
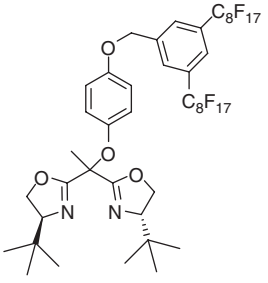
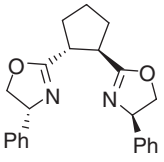
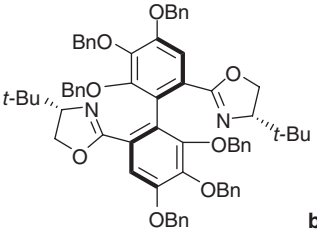
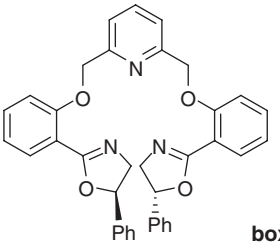
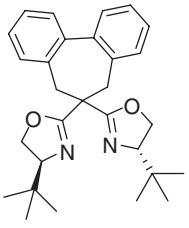
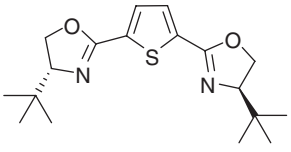
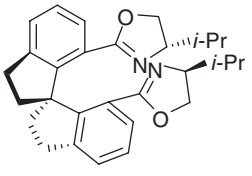
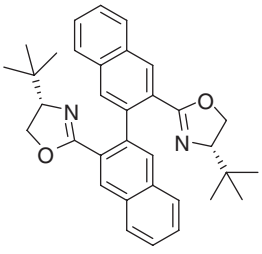
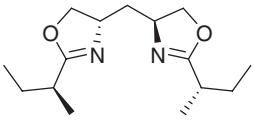
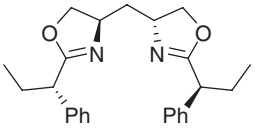
Ligand	R	*E*/*Z*	ee (%)	References
 **box25**	BHT	99:1	98(*E*)[k]	[183]
 **box26**	Et	67:33	67 (*E*)	[184]
 **box27**	Et	65:35	78 (*E*)	[185]
 **box28**	Et	72:28	36 (*E*) 26 (*Z*)	[186]
 **box29**	Et	59:41	82 (*E*) 81 (*Z*)	[187]
 **box30**	Et	76:24	68 (*E*) 61 (*Z*)	[188]

Table 1.4 (Continued)

Ligand	R	*E/Z*	ee (%)	References
 **box31**	Et	61:39	63 (*E*) 54 (*Z*)	[189]
 **box32**	Et	89:11	88 (*E*) 84 (*Z*)[l]	[190]
 **box33**	D-Menthyl	89:11 (*S,S*)	70 (*E*) 62 (*Z*)[m]	[191]
 **box34**	D-Menthyl	83:17 (*S,S*)	89 (*E*) 96 (*Z*)	[192]
 **box35**	Et	40:60 (*S,S*)	69 (*E*) 70 (*Z*)	[193]
 **box36**	Et	37:63 (*S,S*)	61 (*E*) 64 (*Z*)	[193]

a) The relative low Lewis acidity causes low yields with inactivated alkenes. The main discriminating stereo-chemical element is the steric interaction between the ester group and the semicorrin substituent upon pyramidalization of the carbene center.

b) ***ent*-box5** is used, this catalyst is effective also in the cyclopropanation of some mono- (93:7 to 94:6 dr, ee >99% (*E*)) and 1,1-disubstituted alkenes (ee >99%)[167], 1,1-disubstituted-acyclic (1:1 dr, 95% ee (*Z*), 74–90% ee (*E*)) and cyclic silyl enol ethers (1:3 *E/Z* ratio, 92% ee (*Z*), 87% ee (*E*)) [194].

c) **box5** is effective also in the cyclopropanation of furans (91% ee) [195], protected allylic alcohols (8:2 to 91:9 *E/Z* ratio, 92–95% ee (*E*)) [196], with EDA, and α-fluorostyrene with *t*-butyl diazoacetate (81:19 *E/Z* ratio, 93% ee (*E*), 89% ee (*Z*)) [197].

Table 1.4 (Continued)

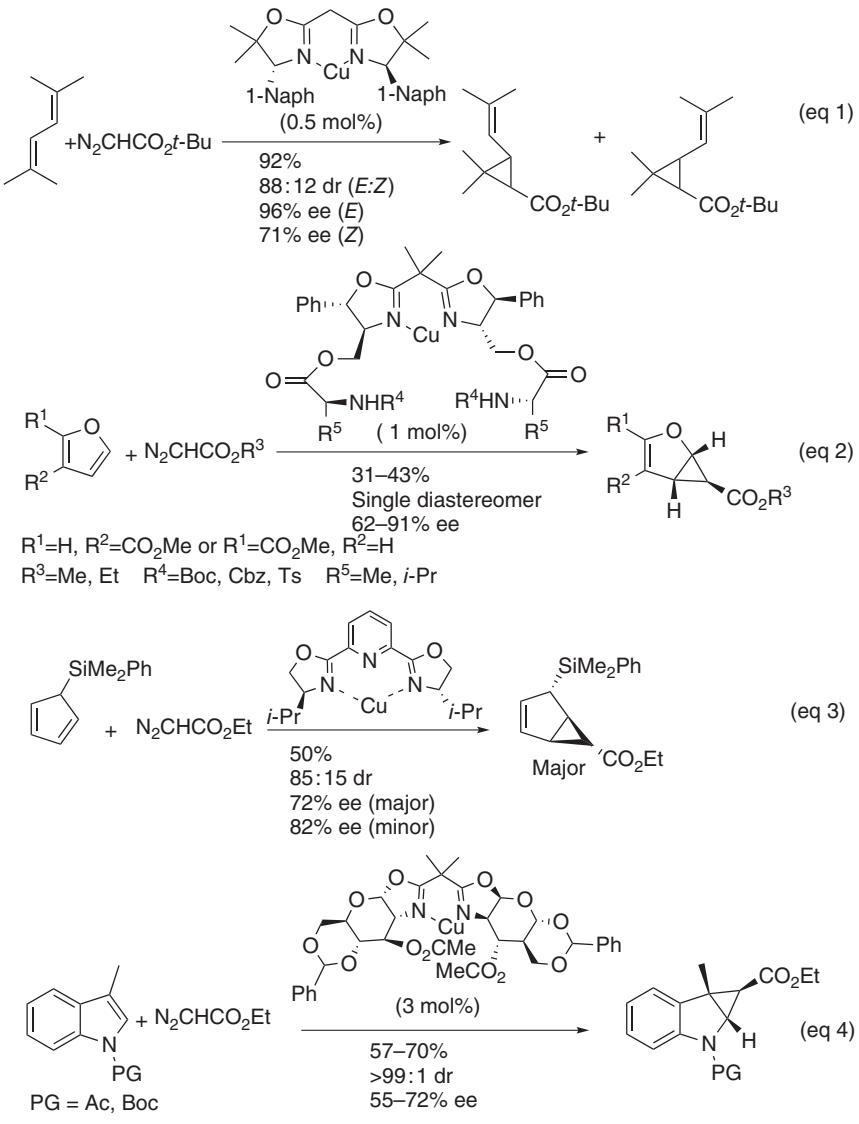
d) In ionic liquid [BMIM][BF_4].
e) **box6** is much more efficient in the cyclopropanation of trisubstituted and asymmetrically 1,2-disubstituted alkenes (86 : 14 to 99 : 1 dr, 82–95% ee).
f) In ionic liquid [EMIM] [OTf], the stability of the copper complex is increased and the reusability of the catalyst solution improved, with 83–98% ee [198].
g) In ionic liquid [BMIM] [BF_4], enantioselectivities rose up to 92% ee [199].
h) **box17** is also effective in the cyclopropanation of 4-MeO-styrene (65 : 35 dr, ee 77% (*E*), 80% (*Z*) and 1,1-phenylethene (ee 75% (*E*))). A similar pyridylbisthiazoline ligand affords only ee ≤ 28% [200].
i) **box18** is also effective in the cyclopropanation of non-1-ene or oct-1-ene: 73 : 27 dr, ee 77% (*E*), 80% (*Z*) in both cases.
j) α-Methylstyrene gives 56 : 44 *E/Z* ratio, and 86% ee.
k) **box25** is also effective in the cyclopropanation of 4-MeO-styrene (96 : 4 dr, 97% ee), 3-phenylpropene (92 : 8 dr, 97% ee) and 1-octene (99 : 1 dr, 95% ee).
l) **box32** is also effective in the cyclopropanation of 4-MeO-styrene (91 : 9 dr, ee 90% (*E*), 87% (*Z*)) and 4-Cl-styrene (88 : 12 dr, ee 85% (*E*), 82% (*Z*)). The substitution of the *t*-Bu with Et group in this catalyst allowed the cyclopropanation of 1,1,-diphenylethene in 91% ee.
m) **box33** is also effective in the cyclopropanation of substituted styrenes (82 : 18 to 86 : 14 dr, 52–82% ee (*E*)).

homogeneous phase with high activity and selectivity, and it is possible to easily separate the products after the reaction and reuse the catalyst, as in the case of heterogeneous catalysis [202].

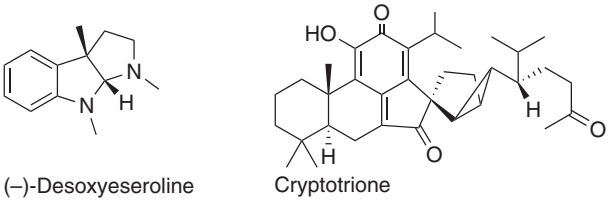
Alkenes that were more complex were also involved in copper–bisoxazoline-catalyzed cyclopropanation with diazoalkanes. The cyclopropanation of 2,5-dimethyl-2,4-hexadiene with *t*-butyl diazoacetate (Scheme 1.55, eq 1) [203] and that of furans in the presence of protected α-amino-acid-containing bisoxazoline ligands (Scheme 1.55, eq 2) [204] are examples. In addition, cyclopentadienylsilane was also desymmetrized by Cu-catalyzed cyclopropanation (Scheme 1.55, eq 3) [205], and a carbohydrate-based bisoxazoline ligand allowed for the copper-catalyzed cyclopropanation of *N*-acyl indoles (Scheme 1.55, eq 4) [206].

Some of these copper(I)-box catalyzed reaction were then employed in multistep synthesis of natural products [207]. For instance, cyclopropanation of furans was applied to the total syntheses of some key intermediates of natural products and drugs [208]. More recently, the ligand **box18** was used in the reaction of non-1-ene and EDA for the total synthesis of unnatural (+)-grenadamide (Scheme 1.17, for the structure of the natural product) [180]. Moreover, the cyclopropanation of *N*-Boc-3-methylindole yielded a key building block for the synthesis of the indole alkaloid (–)-desoxyeseroline in 59% overall yield with 96% ee (Scheme 1.56) [206]. Moreover, ligand **box37** (Scheme 1.57) performed the stereoselective preparation of the tetracyclic core, and key intermediate, of cryptotrione (Scheme 1.56) in 93% yield with >91 : 9 dr. The enantiomeric excess was not reported, but a negative α_D was given [209]. The use of a copper(II) salt instead of the classical copper(I) salt should be noted in this reaction.

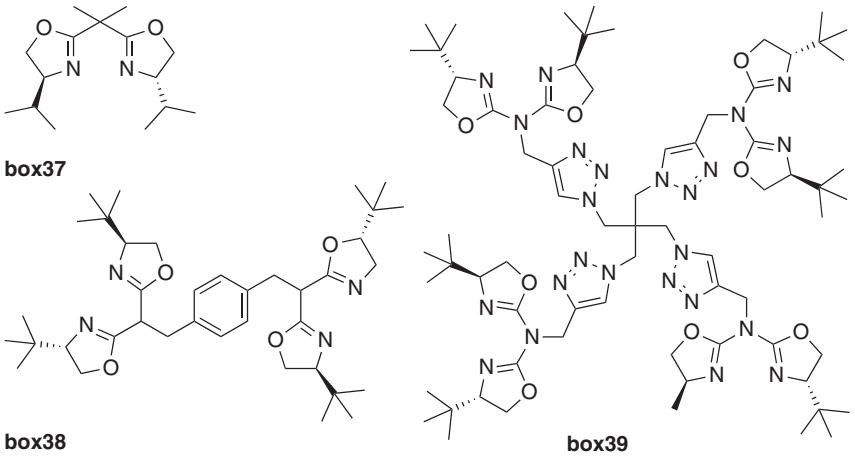
The synthesis of new bicyclo[4.1.0] compounds was attempted with little success under copper-**box6** catalysis. In fact, good enantioselectivities were achieved only starting from enantiopure cyclic enamides [210]. Finally, the copper complexes of polytopic chiral ligands based on bis(oxazoline) units (Scheme 1.57) were tested in



Scheme 1.55 Copper–bisoxazoline-catalyzed cyclopropanation of complex alkenes.



Scheme 1.56 Some natural products prepared by copper-box-catalyzed cyclopropanation.

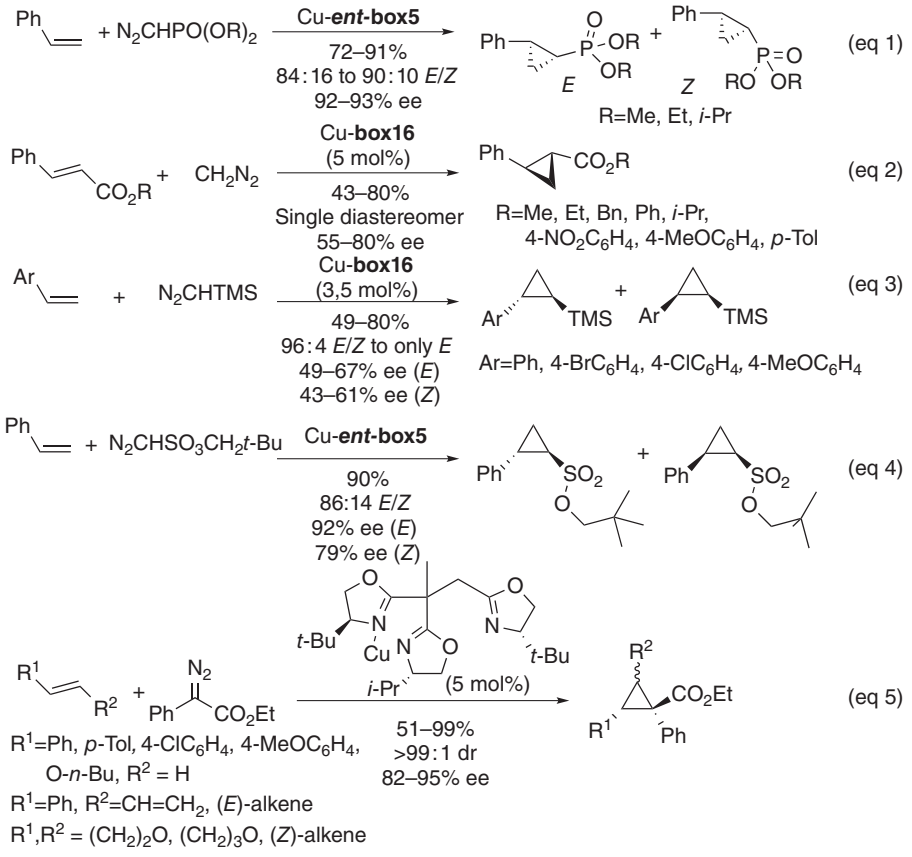


Scheme 1.57 Other box ligands proposed for copper-box-catalyzed cyclopropanation.

the cyclopropanation reaction of styrene with EDA, using a release–capture strategy based on the formation of coordination polymers at the end of the reaction to recover and recycle catalysts [211]. Two points should be outlined: using the Cu-**box38**, the *cis*-cyclopropane constituted the predominant product, conversely from the corresponding Cu-**box5** (see Table 1.4) [212]; the tetratopic **box39** could be recovered and reused in up to 20 reaction cycles always with very good yields and enantioselectivities.

Diazoalkanes other than alkyl diazoacetates have also been employed in copper–bisoxazoline-catalyzed cyclopropanations. For instance, α-diazophosphonate diazomethane was used to obtain cyclopropylphosphonate derivatives under ***ent*-box5** catalysis (Scheme 1.58, eq 1). However, Nishiyama's ruthenium catalyst (see Section 1.3.1.5) gave better results and can be used with a wider range of substrates (88 : 12 to >98 : 2 *E/Z* ratio, 90–96% ee also with substituted styrenes, α-methylstyrene, and 1-phenylbuta-1,3-diene) [213]. Other examples are the reaction of diazomethane with *trans*-cinnamate esters (Scheme 1.58, eq 2) [149, 214], the reaction of (TMS) diazomethane with olefins (Scheme 1.58, eq 3) [215], the cyclopropanation of styrene with diazosulfonate esters (Scheme 1.58, eq 4) [216], and the cyclopropanation of alkenes with ethyl phenyldiazoacetate (Scheme 1.58, eq 5) [217].

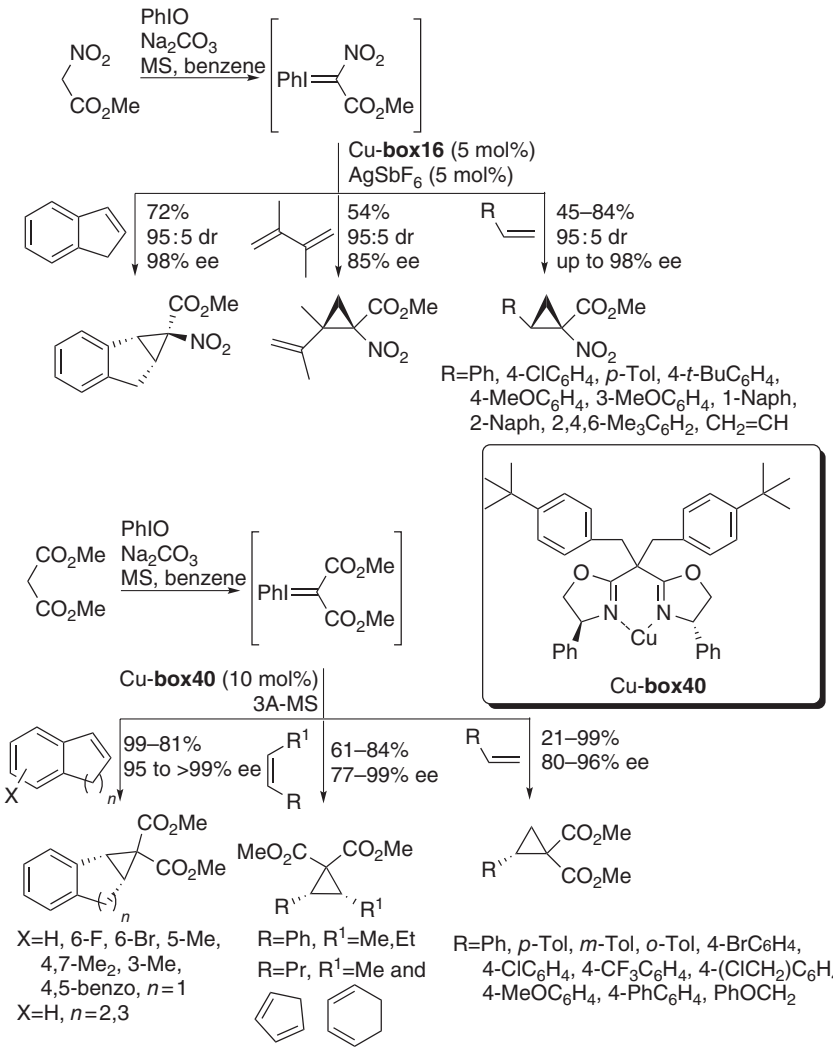
Asymmetric carbene transfer involving diazo decomposition is almost exclusively restricted to the research laboratory owing to the often unjustified prejudice regarding diazo compounds and the reagents used to prepare them, which are believed to be toxic, carcinogenic, and potentially explosive. Therefore, the development of reactions avoiding diazo precursors is of considerable interest. For example, phenyliodonium ylides are potential substituted of diazo compounds. In fact, they are generally superior carbene precursors, but they are often unstable. Thus, their use is advantageous only if the carbene transfer can be carried out in a one-pot procedure, in which the phenyliodonium ylide is generated and decomposed *in situ*, as in the copper(I)-catalyzed asymmetric cyclopropanations depicted in Scheme 1.59 [218].



Scheme 1.58 Copper–bisoxazoline-catalyzed cyclopropanation of some diazoalkanes.

Many copper-box ligands were synthesized on polymer supports, but the most ancient attempts afforded enantioselectivities usually lower than those observed in solution [219]. Later, polystyrene or commercial Merrifield resin supported copper(II)–bisoxazoline catalysts were developed by Salvadori and coworkers, affording up to 71:29 dr and >90% ee or 71–93% ee, respectively, in the heterogeneous cyclopropanation of alkenes with EDA [220].

Mayoral group studied bisoxazoline ligands immobilized on laponite by electrostatic interactions, demonstrating a previously unknown role of the catalyst surface, although the enantioselectivity was low (≤55% ee) [221]. The same group also studied the use of homopolymers of bisoxazoline ligands [222]. The use of suitable dendrimers as cross-linkers in the polymerization process allowed high productivity of chiral cyclopropanes per molecule of chiral ligand and enantioselectivities of up to 78% ee were obtained. Box ligands onto silicaceous mesocellular foams (MCFs) afforded high enantioselectivity (up to 87% ee) and reactivity, but only 64:36 dr [223]. A partial modification of the surface of these MCFs with TMS groups prior to the use of the bisoxazolines enhanced enantioselectivities (up to 95% ee), but slowly increased dr (67:33) [224]. Due to their higher binding affinity toward copper,



Scheme 1.59 Copper–bisoxazoline-catalyzed cyclopropanation with phenyliodonium ylides.

immobilized azabisoxazolines onto various polymeric supports are far superior, compared to their corresponding bisoxazolines. For instance, up to 99% ee was obtained for the reaction of styrene with EDA [225]. The use of polyisobutylene oligomers (in particular, PIB_{2300}) as soluble supports for the immobilization of bisoxazoline prepared from phenylglycine provides cyclopropane in 48% yield, 81:19 *E/Z* ratio, 92% (*E*), and 68% (*Z*) ee [226]. The catalyst could be reused five to six times. Moreover, a chiral ferrocenyl–bisoxazoline derivative with a biphenyl unit can be used as a ligand of the Cu-catalyzed cyclopropanation of styrene with EDA, providing a 55% yield of a mixture of *trans*- and *cis*-cycloadducts in a 65:35 ratio and 20% and 23% ee, respectively [227].

Burke's research group grafted a box ligand on a Wang resin. The copper(I) catalyst gave superior results than copper(II) and its selectivity remained constant

over four cycles (5–61% yield, *E/Z* ratios of about 67 : 33, and 13–71% ee) [228]. The same catalyst was also immobilized in a noncovalent manner on an ion-exchange resin with comparable results, but leaching of the catalyst was an important factor after a few cycles [228]. Chiral copper(II)-box catalysts were also anchored onto mesoporous silica or encapsulated onto copper(II)-exchanged zeolites. Enantioselectivities of the cyclopropanation of styrene with diazoacetate were consistently lower than those obtained in homogeneous phase in all cases, although in zeolites, they appeared to increase with a decreasing pore size [229].

A polymersome nanoreactor was found to be able to catalyze asymmetric cyclopropanation reactions of some 4-substituted styrenes in water with 68 : 32 to 75 : 25 *E/Z* ratios and 53–84% ee (*E*-isomer). The hydrophobic environment around the catalyst was demonstrated to be substrate selective, because only hydrophobic substrates were readily converted into the corresponding cyclopropane products, while hydrophilic substrates (i.e., 4-COOH and 4-NH_2-styrenes) did not undergo any reaction [230].

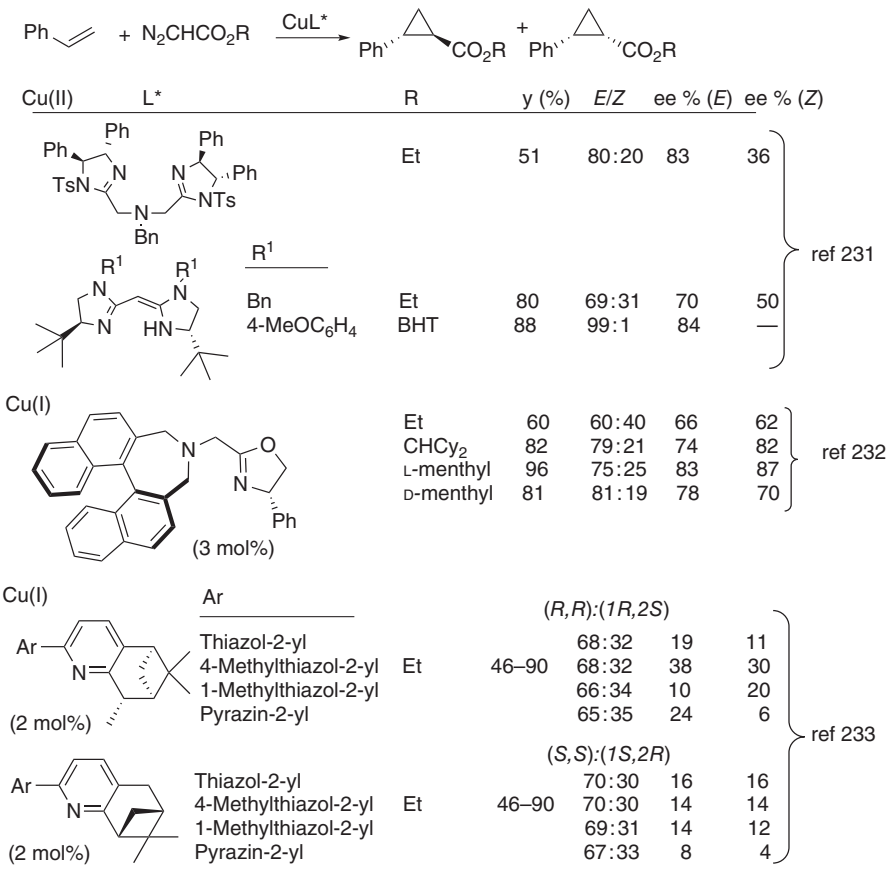
Thus, in summary, the covalently immobilized catalysts could be superior in terms of activity, selectivity, and recycling compared to their noncovalently immobilized counterparts, but much work has yet to be carried out in terms of increasing the usability and efficiency of heterogeneous over homogeneous catalysts.

Regulating the electron density of the oxazoline ring has remained an unsolved problem. On the other hand, the two *N*-substituents of an imidazoline may serve as handles to tune the electronic and conformational properties of the ligand. For instance, the Cu-catalyzed cyclopropanation of styrene with EDA, performed in the presence of bis-imidazoline ligands, provided the corresponding cyclopropanes in high yield with good ee (Scheme 1.60) [231]. In addition, chiral dihydrodinaphthazepinyloxazolines were demonstrated to be effective ligands in the Cu-catalyzed cyclopropanation of styrene and its derivatives (Scheme 1.60) [232]. Finally, Kwong *et al.* have designed a series of chiral C_1-symmetric bidentate ligands, possessing two different nitrogen heterocycles (Scheme 1.60) [233].

Chiral thienyl pyridines as *N,S*-ligands [234] or 2-(2-phenylthiophenyl)-5,6,7,8-tetrahydroquinolines [235] provided effective copper catalysts in the cyclopropanation of styrene with EDA, but offering a low enantioselectivity (≤10% and ≤5% ee, respectively). Bis-azaferrocene ligand was also tested in the reaction of N_2CHCO_2BHT with monosubstituted alkenes, leading to good diastereo- and enantioselectivities (for instance, in the reaction with styrene: 96 : 4 *E/Z* ratio and 94% (*E*) and 79% (*Z*) ee) [236].

Several types of nitrogen-containing ligands, other than bisoxazolines and their derivatives, have been investigated for the asymmetric cyclopropanation of alkenes (Table 1.5). In addition, Baldwin and coworkers allowed L-menthyl diazoacetate to react with isotopically labeled styrenes, providing the corresponding four isotopically labeled L-menthyl-(1*S*,2*S*)-2-phenylcyclopropanecarboxylates with >99% ee, in the presence of a very simple diamine ligand derived from (1*S*,2*S*)-1,2-diphenylethylenediamine [253].

An iminodiazaphospholidine (Scheme 1.61) was used as the copper ligand in the asymmetric cyclopropanation of styrene with EDA leading to 99 : 1 (*E/Z* ratio) and 94% ee (*E*) [254]. Asymmetric pyridine derivatives, in particular pyridine-based

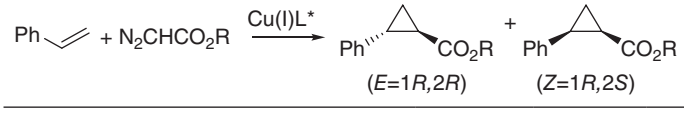


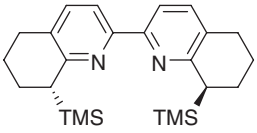
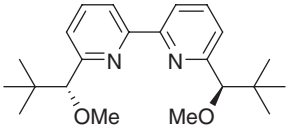
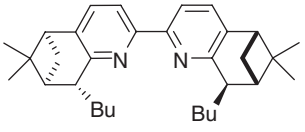
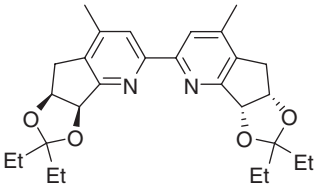
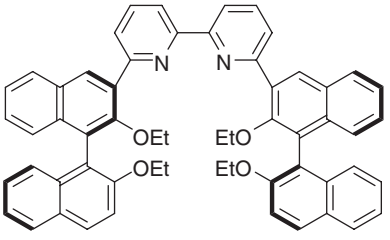
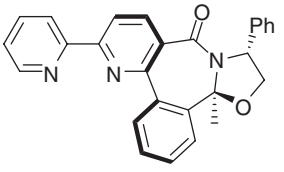
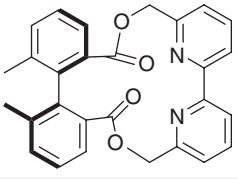
Scheme 1.60 Other bidentate ligands for copper catalyzed cyclopropanation.

12-membered tetraaza-macrocycles (Scheme 1.61), are other used ligands. Catalytic reactions were run, and cyclopropanes were obtained in 45–83% yield with poor diastereomeric ratio (50:50 to 67:33) and enantiomeric excess (33–50% (*Z*) and 15–65% (*E*)). The absence of α-substituents on the styrene as well as the bulkier *tert*-butyl diazoacetate led to worse results in terms of both yield and stereoselectivity. The reaction was also applied to 2,5-dimethylhexa-2,4-diene, but the results were modest. The (*R*)-catalyst gave *cis*-(1*R*,2*S*)-2-methyl-2-phenylcyclopropanecarboxylate and *cis*-(1*S*,2*R*)-2-phenylcyclopropanecarboxylate, whereas the *trans*-(1*R*,2*R*)-isomers were obtained with the (*S*)-isomer. Similar results were obtained for other similar catalysts with different substituents and stereoselectivities at the 4, 8, and 13 positions, all leading to *trans*-(1*R*,2*R*)-isomers as the major products [255].

Planar chiral terpyridine–copper(II) complexes (Scheme 1.61) exhibited moderate diastereomeric excesses with good enantioselectivities of *cis*-cyclopropanes from reactions of various styrene derivatives with ethyl diazoacetate (4–68% yields, 23:77 to 68:32 *E/Z* ratio, 18–82% ee (1*S*,2*S*), 65–91% ee (1*S*,2*R*)). Only 4-(trifluoromethyl) styrene gave racemic mixture of *trans*-isomer and only 5% ee for the *cis*-isomer [256].

Table 1.5 Other nitrogen-containing ligands for copper catalysts employed in enantioselective cyclopropanation reactions.



Ligand	R	*E/Z*	ee (%)	References
Bipyridine				
	*t*-Bu	86:14	92 (*E*) 98 (*Z*)	[237]
	Et	80:20	91 (*E*) 82 (*Z*)	[238]
	Et	80:20[a]	90 (*E*) 82 (*Z*)	[239]
	Et	67:33	74 (*E*) 78 (*Z*)	[240]
	BHT	99:1	70 (*E*)	[240]
	Et[b]	80:20	82 (*E*)	[241]
	Et	64:36 (*S,S*)	75 (*E*)	[242]
	Et[c]	60:40	57 (*E*) 46 (*Z*)	[243]
	Et[d]	76:24	56 (*E*) <20 (*Z*)	[244]

(Continued)

Table 1.5 (Continued)

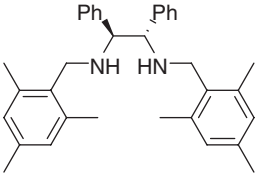
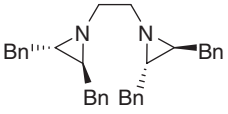
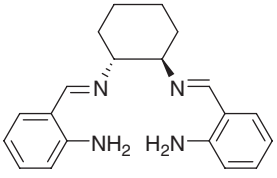
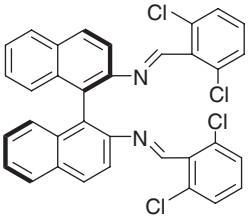
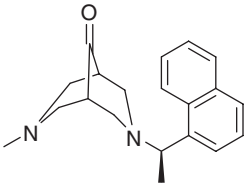
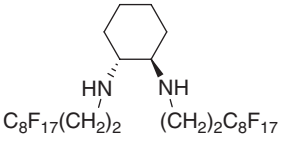
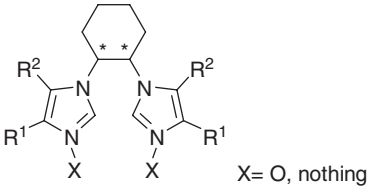
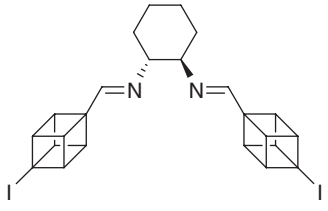
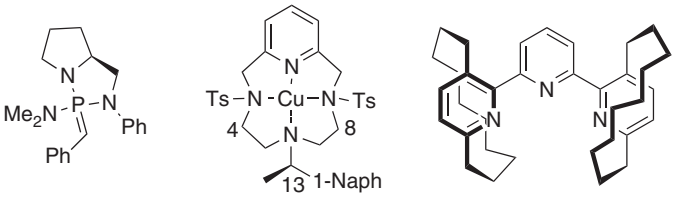
Ligand	R	*E/Z*	ee (%)	References
Chiral diamines and diimines				
	L-Menthyl	93:7	96 (*E*) 66 (*Z*)	[245]
	Et	75:25	90 (*E*)	[246]
	L-Menthyl	70:30	2 (*E*) 8 (*Z*)	[247]
	L-Menthyl	90:10[e]	68 (*E*) 81 (*Z*)	[248]
	Me	75:25	79 (E) 98 (Z)	[249]
	Et[f]	67:33	47 (*E*) 47 (*Z*)	[250]
 X= O, nothing **=(*S,S*),(*R,R*) R^1=Me, Ph R^2=Me, Ph	Et	67:33 to 81:19	1–20 (*E*) up to 94 (*Z*)	[251]

Table 1.5 (Continued)

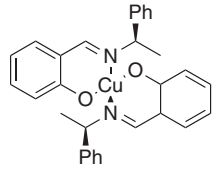
Ligand	R	*E/Z*	ee (%)	References
	Et	58:42	6 (*E*) 8 (*Z*)[g]	[252]

a) The enantiomer of this catalyst gives the enantiomeric cyclopropane in comparable selectivity [239].
b) This catalyst was also employed in the reaction of *t*-butyl diazoacetate with 4-F-styrene (92:8 *E/Z* ratio, 99% ee) and 4-Br-styrene (95:5 *E/Z* ratio, 83% ee). The high stereoselectivities were attributed to a structural rigidification provided by the chiral acetal moieties.
c) *t*-Butyl diazoacetate gave better *E/Z* ratios but lower enantioselectivities. Other styrenes were tested, but enantiomers of the corresponding *trans*-cyclopropanes could not be determined. A pyridylmonooxazoline ligand was also tested but gave somewhat lower ee values (up to 53%).
d) Phenanthroline-containing macrocycles gave somewhat better results (78:22 *E/Z* ratio, ee: 67% (*E*), <20% (*Z*)) and with phenantroline a simple structural modification of the chiral cavity allowed the successful control of the *trans*- or *cis*-diastereoselectivity of the reaction (up to 9:91 *E/Z* ratio) [244].
e) Effective also in the cyclopropanation of 2-vinylnaphthalene (90:10 *E/Z* ratio, ee 76% (*E*), 62% (*Z*)), α-methylstyrene (72:28 *E/Z* ratio, ee 61% (*E*), 78% (*Z*)), 1,1-diphenylethene (98% ee).
f) These ligands showed similar activities, but lower enantioselectivities than those achieved using more synthetically demanding fluorous ligands such as fluorous bisoxazolines (see Table 1.4). Moreover, C_2-symmetric diimines derived provided better enantioselectivities (up to 67% ee) but low diastereoselectivities (≤14% de).
g) The poor stereoselectivity was explained by the lack of steric hindrance on either face of the copper complex in the pseudo six-membered ring conformation calculated as the most stable by both M06L and B3LYP calculations.

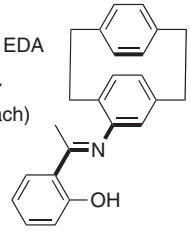


Scheme 1.61 Other nitrogen ligands for copper catalyzed cyclopropanation.

The copper–salicylaldimino complexes were also tested, but the decomposition of EDA in the presence of styrene gave scarce results (Scheme 1.62) [257]. Better results were obtained with a copper(II) planar (*R*)-paracyclophanylimine, and the enantiomeric induction was attributed to the restricted rotation around the cyclophane nitrogen [258]. Other Cu-salen catalysts are efficient especially in the synthesis of chrysantemate esters (Scheme 1.62, eq 1 [259], and eq 2 [260]). In eq 2, the best result was obtained by combining the copper Schiff base complex with a Lewis acid, such as $Al(OEt)_3$, which enhanced the catalytic efficiency. The reaction pathway of the asymmetric induction in the

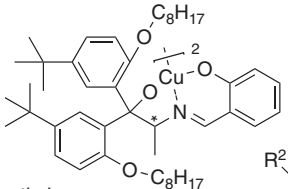


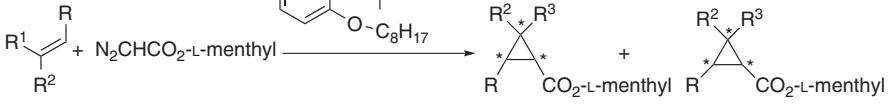
Styrene + EDA
72%
70:30 *E*/*Z*
6% ee (each)
(ref. 257)



Olefin	DA	*E*/*Z*	ee_Z (%)	ee_E (%)
Styrene	Et	67:34	61	76
	t-Bu	82:18	78	88

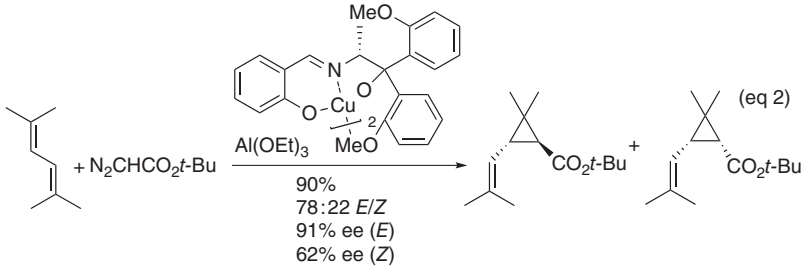
α-Methylstyrene up to 95% ee
(ref. 258)





Olefin	Catalyst Config	*Z*/*E*	ee_Z (%)	ee_E (%)
Styrene	*R*	14/86	54 (1*S*,2*R*)	69 (1*S*,2*S*)
	S	18/82	78 (1*R*,2*S*)	81 (1*R*,2*R*)
Oct-1-ene	*R*	17/83	46 (1*S*,2*R*)	76 (1*S*,2*S*)
	S	22/78	64 (1*R*,2*S*)	84 (1*R*,2*R*)
(*E*)-Oct-4-ene	*R*	—	—	82 (+)
	S	—	—	84 (–)
trans-Anethole	*R*	9/91	44 (+)	81 (+)
	S	12/88	60 (–)	89 (–)
1,1-Diphenylethene	*R*	—	—	75 (+)
	S	—	—	64 (–)
α-Methylstyrene	*R*	40/60	86 (nd)	68 (nd)
	S	36/64	68 (nd)	58 (nd)
2-Methyl-2-butene	*R*	79/21	—	—
	S	77/23	—	—
2-Methyl-5,5,5-trichloropent-2-ene	*S*	85/15	91 (1*R*,2*S*)	(with EDA)
2,5-dimethylhexa-2,4-diene	*R*	7/93	46 (1*R*,2*S*)	94 (1*R*,2*R*)

(eq 1)

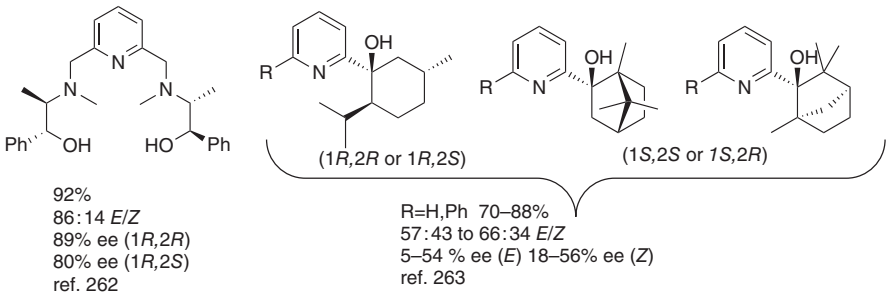


90%
78:22 *E*/*Z*
91% ee (*E*)
62% ee (*Z*)

(eq 2)

Scheme 1.62 Cu-salen catalysts for asymmetric cyclopropanation.

synthesis of (1*R*,3*R*)-chrysanthemic acid ester in the presence of Cu(I)-salen complexes was elucidated with the aid of hybrid DFT calculations [261]. The key features were that the alkoxycarbonyl carbene complex intermediate was intrinsically chiral and that the intramolecular hydrogen bonding in the carbene complex transmitted the chirality information from the side chain to the carbene complex.

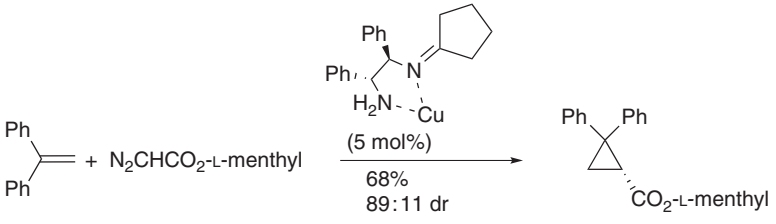


Scheme 1.63 Chiral aminoalcohols as ligands for asymmetric cyclopropanation.

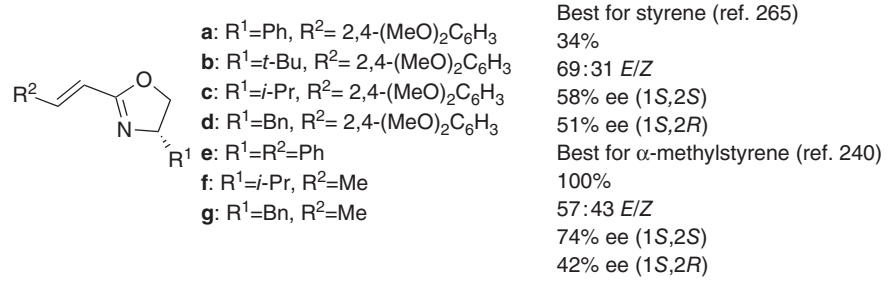
Chiral amino alcohols, for example, ligands derived from (1*R*,2*S*)-ephedrine [262] or various chiral *N*,*O*-pyridine alcohols [263] provided the expected cyclopropane from the reaction of styrene with EDA (Scheme 1.63).

Monodentate chiral ligands were only rarely employed in catalytic asymmetric synthesis for the main reason that they fail to form the compact catalytic manifolds that are pivotal for high asymmetric induction. On the other hand, monodentate ligands are in general less structurally complex, and thus, the synthesis, in principle, is less demanding. Among these examples, the Cu-catalyzed cyclopropanation of 1,1-diphenylethylene with menthyl diazoacetate was performed in the presence of a chiral imidazolidine ligand (Scheme 1.64) [264].

Chiral monodentate oxazoline ligands (Scheme 1.65) were proposed for the cyclopropanation reaction of styrene and α-methylstyrene and EDA with only



Scheme 1.64 Chiral imidazolidine ligand for asymmetric copper-catalyzed cyclopropanation.



Scheme 1.65 Chiral oxazoline ligands for asymmetric copper-catalyzed cyclopropanation.

moderate success [239, 265]. Computational calculations indicated that the active catalyst most likely incorporates two ligands per copper atom in an assembly similar to box ligands [239]. As a consequence, monodentate ligands were tested in both homo- and hetero-complexes with Cu $(MeCN)_4PF_6$, and homo-combinations were found to be superior to hetero-combinations.

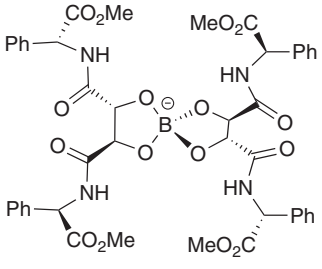
Arndtsen and coworkers reported the preparation of a library of α-amino-acid-bound borate anions. Ion pairing of these anions to a copper cation could be used to induce enantioselectivity in the cyclopropanation of styrene with EDA (Scheme 1.66) [266].

Furusho's group showed that complementary double-helical molecules showing optical activity owing to their helicity could be enantioselectively synthesized and could catalyze the asymmetric cyclopropanation of styrene with EDA in the presence of a copper catalyst (Scheme 1.66) [267]. The results showed an almost linear relationship between the helix-sense excesses and the ee values of *trans*-cyclopropane. Moreover, the results suggested that the chiral space generated by the rigid double-helical structure was effective and indispensable for the high enantioselectivity.

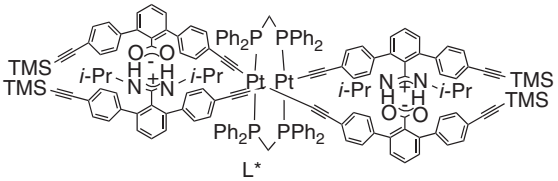
1.3.1.4 Chiral Catalysts: Rhodium

Although many transition metal chiral complexes have been developed, dirhodium(II) complexes are among the most attractive catalysts, because of their activity and efficiency. Dirhodium(II) catalysts with very high turnover numbers have been reported, and consequently, the cost and toxicity of rhodium can be greatly overshadowed by the ability to use tiny amounts of the catalyst to generate large quantities of value-added products. The use of dirhodium(II) catalysts in inter- and intramolecular asymmetric cyclopropanation has been recently reviewed [268], and readers are invited to read this review for other information.

Rhodium-based chiral complexes were synthesized and tested in both inter- and intramolecular cyclopropanations. In particular, the development of dirhodium(II) carboxylate and carboxamidate catalysts (Scheme 1.67) has resulted in many highly chemo-, regio-, and stereoselective reactions of α-diazocarbonyl compounds [269].



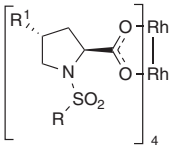
34% ee (*trans*)
19% ee (*cis*)



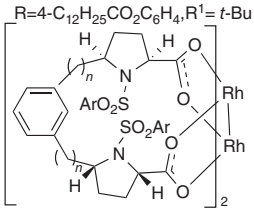
L*

Helix-sense excess of L* (10 mol%):
41%, 62:38 *E*/*Z*, 23% ee (*E*)
Helix-sense excess of L* (10 mol%):
38%, 63:37 *E*/*Z*, 44% ee (*E*)
Helix-sense excess of L* (10 mol%):
39%, 63:37 *E*/*Z*, 80% ee (*E*)
Helix-sense excess of L* (50 mol%):
95%, 62:38 *E*/*Z*, 85% ee (*E*)

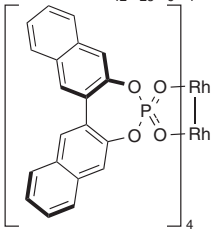
Scheme 1.66 α-Amino-acid-bound borate anions and double-helical molecules for asymmetric cyclopropanation.



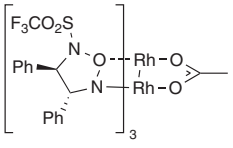
Rh_2(*S*-BSP)$_4$: R=Ph, R^1=H
Rh2(*S*-TBSP)$_4$: R=4-*t*-BuC_6H_4, R^1=H
Rh_2(S-DOSP)$_4$: R=4-$C_{12}H_{25}C_6H_4$, R^1=H
(a): R= C_6F_{17}, R^1=H
Rh_2(*trans*-HYP)$_4$:
R=4-$C_{12}H_{25}CO_2C_6H_4$,R^1= *t*-Bu



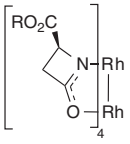
n=0, Ar=4-*t*-BuC_6H_4
n=0, Ar=2,4,6-(*i*-Pr)$_3C_6H_2$ **Rh_2(*S*-biTISP)$_2$**
n=1, Ar=4-*t*-BuC_6H_4
n=1, Ar=2,4,6-(*i*-Pr)$_3C_6H_2$
n=1, Ar=4-$C_{12}H_{25}C_6H_4$



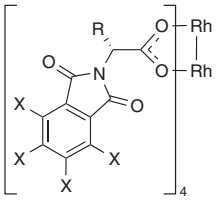
Rh_2(*R*-BNP)$_4$



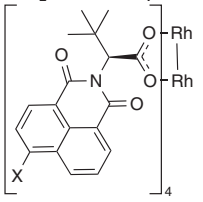
Rh_2(OAc)(DPTI)$_3$



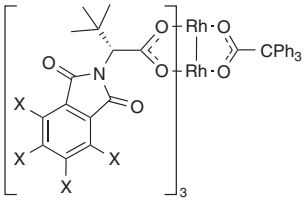
Rh_2(*S*-IBAZ)$_4$: R=*i*-Bu
Rh_2(*S*-BNAZ)$_4$: R=Bn
Rh_2(*S*-MEAZ)$_4$: R=Me
Rh_2(*S*-TBAZ)$_4$: R=CH_2-*t*-Bu
Rh_2(S-CHAZ)$_4$: R=Cy
Rh_2(4*S*-*R*-MenthAZ)$_4$: R=L-Menthyl



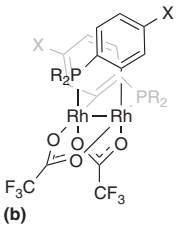
Rh_2(R-PTAD)$_4$:
X= H, R=1-adamantyl
Rh_2(*R*-PTTL)$_4$: X= H, R=*t*-Bu
Rh_2(*R*-TCPTTL)$_4$: X=Cl, R=*t*-Bu
Rh_2(*R*-TBPTTL)$_4$: X=Br, R=*t*-Bu



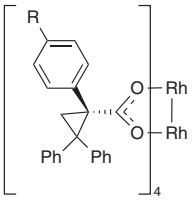
Rh_2(S-NTTL)$_4$: X=H
Rh_2(*S*-4-Br-NTTL)$_4$: X=Br



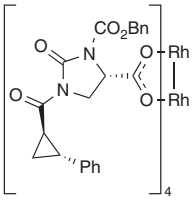
Rh_2(*R*-PTTL)$_3$TPA



(b)
1 R=4-BrC_6H_4, X=Br
2 R=4-*t*-BuC_6H_4, X=4-*t*-Bu
3 R=4-TMSC_6H_4, X=TMS



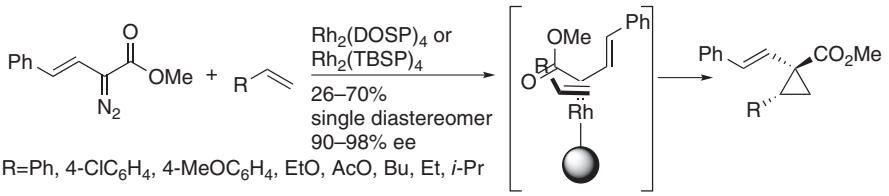
Rh_2(*R*-TPCP)$_4$: R=H
Rh_2(*R*-BTPCP)$_4$: R=Br
Rh_2(*R*-BPCP)$_4$: R=Ph



Rh_2(4*S*,2′*R*,3′*R*-HMCPIM)$_4$

Scheme 1.67 Chiral dirhodium catalysts for asymmetric cyclopropanations.

As a general guideline, the level of diasterocontrol with rhodium carbenes does not match that observed with copper, ruthenium, or cobalt carbenes, even when sterically hindered α-diazoesters are used. This drawback has minimized the use of rhodium catalysts in intermolecular processes involving simple α-diazoesters in the most ancient period of asymmetric synthesis. Then, better results were obtained when *ab initio* studies clarified the reaction mechanism.

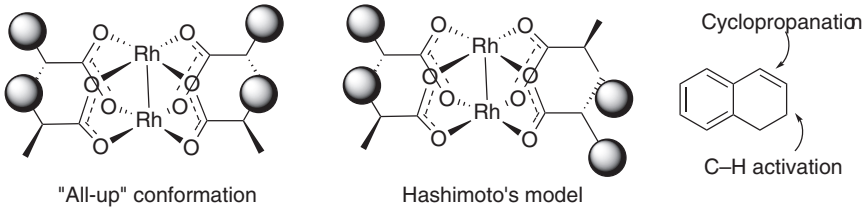


Scheme 1.68 First model proposed for diastereoselective rhodium-catalyzed cyclopropanation.

The first model proposed to explain the diastereo- and enantiofacial selectivity using these rhodium catalysts is reported in Scheme 1.68 [270]. The presence of an electron-withdrawing substituent and an electron-donating substituent seemed crucial for high diastereoselectivity, because, when this combination of donor/acceptor functionality was lacking, much lower diastereoselectivities were observed.

Then, the approach of the alkene occurred on the side of the electron-withdrawing group, because the developing positive charge on the most substituted carbon could be stabilized by the oxygen lone pairs of the carboxyl group. This mechanism suggested that the reactive catalyst conformer had to possess D_2 symmetry, because the approach of the alkene to this conformer from the most accessible trajectory correctly predicted the sense of induction in these reactions. Thus, new rhodium(II) dicarboxylates with the prerequisite D_2 symmetry were prepared and tested (Rh_2(*S*-biTISP)$_4$ and analogs), but three of them led to lower enantiomeric excesses than those observed with Rh_2(DOSP)$_4$ and only the triisopropylphenyl substituted catalyst with $n = 1$ was as effective as Rh_2(DOSP)$_4$. In 2003, Che *et al.* reported the use of a rhodium D_4-porphyrin to catalyze the cyclopropanation of various alkenes with EDA, providing TON>1000, but moderate enantioselectivities (up to 68% ee) and low *E/Z* ratios [271].

Then theoretical and kinetic isotope studies pointed out that the cyclopropanation occurs in a concerted nonsynchronous manner. The greater bulk of the electron-withdrawing group of the diazo compound results in high diastereoselectivity, because it avoids destabilization of the electrophilic carbenoid by aligning out of the plane of the rhodium–carbon π-bond. Based on X-ray structure and DFT calculations, Fox's research group proposed a structure ("all-up" conformation), in which a C_2-symmetric chiral cavity explained the enantioselectivity of typical carboxylate dirhodium complexes (Scheme 1.69) [272].



Scheme 1.69 Representation of the C_2-symmetric "all-up" chiral cavity and Hashimoto's model and cyclopropanation versus C–H activation reaction sites.

DFT calculations also demonstrated that the presence of chlorine or bromine atoms on the phthaloyl ring, such as in catalysts Rh_2(*S*-TCPTTL)$_4$ and Rh_2(*S*-TBPTTL)$_4$, significantly rigidifies the conformation in solution, through intramolecular halogen bonds between adjacent ligands and that the carbene leaves its *Si*-face accessible for reaction with the alkene. When the alkyl substituent is small, there is competing reactivity on the *Re*-face through a conformation, in which the carbene is aligned with the narrow dimension of the chiral cavity. In other cases, the stereochemistry was well predicted by Hashimoto's model [273], in which the chiral dirhodium complex adopts a C_2-symmetrical arrangement, with two adjacent groups positioned on the top face and the next two on the bottom face of the complex.

The TONs of these reactions were studied by tracking the disappearance of the C=N$_2$ stretch frequencies in the infrared spectra. In this way, in the reactions of styrene with diazoacetate, phenyl diazoacetate, and diazomalonate, the TONs were determined to be higher for the more stabilized donor/acceptor carbenoids [274]. Moreover, the highest TONs were achieved under solvent-free conditions with very active trapping agents, such as styrene and cyclopentadiene, in which the catalyst:substrate ratios were as low as 0.6 ppm, resulting in TONs of up to 1.8 million. However, since the reaction is exothermic, solvent-free reactions are difficult to perform on large scale.

Davies provided guidelines for choosing the optimal chiral dirhodium(II) catalyst for cyclopropanation of aryldiazoacetates. Depending on the aryl substituent, Rh_2(*R*-DOSP)$_4$, Rh_2(*S*-PTAD)$_4$, or Rh_2(*R*-BNP)$_4$ can be utilized to obtain the desired cyclopropane with a high level of enantioinduction. The substitution on the alkene has instead only moderate influence on the level of asymmetric induction in cyclopropanation reactions [275].

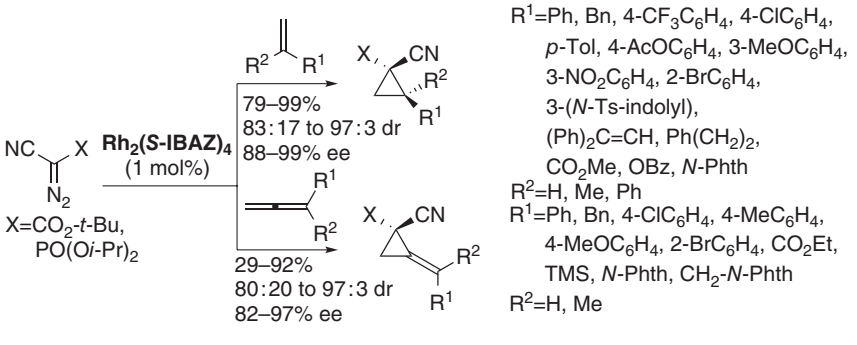
Substrates with an allylic moiety have a potentially competing pathway to cyclopropanation: allylic C–H insertion (Scheme 1.69). The latter reaction will not be discussed here, but the factors influencing the two pathways should be mentioned. Davies and coworkers used *p*-bromophenyldiazoacetate as the carbenoid species, different electron-rich alkenes, and various dirhodium catalysts including Rh_2(*S*-biTISP)$_4$, Rh_2(*S*-DOSP)$_4$, and Rh_2(*S*-PTAD)$_4$ [276]. C–H insertion more easily occurred in the reactions of *cis*-1,2-disubstituted alkenes or more highly substituted alkenes. In general, methyl allylic sites were much harder to functionalize than methylene allylic sites. Catalyst Rh_2(*S*-DOSP)$_4$ gave predominantly the cyclopropanes in 70–88% yield, with >97 : 3 de and 89–95% ee. The other two catalysts were less selective toward the cyclopropanation, and Rh_2(*S*-biTISP)$_4$ mainly favored C–H insertion. Finally, the Rh_2(*S*-DOSP)$_4$ catalyst afforded opposite enantioinduction with respect to Rh_2(*S*-PTAD)$_4$. Moreover, dihydronaphthalene, another good candidate for studies on cyclopropanation versus C–H activation, showed that the combination of methyl 2-diazopent-3-enoate and Rh_2(*S*-PTAD)$_4$ strongly favored the cyclopropanation. On the other hand, the catalyst Rh_2(*S*-DOSP)$_4$ and encumbered diazo compounds, such as methyl 3-(*tert*-butyldimethylsilyloxy)-2-diazopent-3-enoate, favored the C–H activation [277]. Interestingly in this reaction, C–H activation product was well predicted by Hashimoto's model [273].

Historically, the most ancient reports showed a low diasterocontrol, although the level of enantioselection was sometimes excellent [278]. Only Rh_2(*4S-R-*

MenthAZ)$_4$ led to good *cis*-selectivity (82:18 and 92:8 dr) and excellent enantiocontrol (97% ee, *cis*) in the cyclopropanation of substituted styrenes with *tert*-butyl diazoacetate, but with low yield relative to the alkene (44% and 21%) [279]. This catalyst also allowed the cyclopropanation of 3-diazo-3,6-dihydro-2*H*-pyran-2-one with various alkenes [74–86 yields, 83:17 to >95:5 dr, 73–86% ee (*S*,*S*)] [280]. Then the efficiency of a series of chiral azetidinone–dirhodium(II) catalysts was tested in the cyclopropanation of various olefins with diazomalonates. These reactions gave access to the corresponding cyclopropanes with enantioselectivities of up to 50% ee [278, 281]. Moreover, Rh$_2$(*S*-MEAZ)$_4$ afforded cyclopropanes from styrene and α-nitroesters in up to 76% yield, but with only 33% ee [149]. Charette's research group found Rh$_2$(*S*-IBAZ)$_4$ as an efficient catalyst for cyclopropanation of α-cyanodiazophosphonate and α-cyanodiazoacetate (Scheme 1.70) [282]. The particular electrophilicity of cyanocarbene intermediates permitted the use of allenes as substrates, affording the first catalytic asymmetric alkylidene cyclopropanation reaction using diazo compounds. In fact, α-cyanocarbenes are forced to stay in-plane, conversely from other electron-withdrawing groups, which adopt an out-of-plane conformation (see below). The in-plane conformation is highly energetic, thus leading to a more electron-deficient reactive carbene, allowing less nucleophilic π-systems such as allenes to react.

Charette *et al.* screened a variety of structurally diverse chiral dirhodium catalysts for enantioselectivity of styrene with α-nitro-α-diazo carbonyl compounds and observed modest-to-high yields in a wide range of solvents, but with only modest enantioselectivities (≤41% ee) [149]. A family of bisoxazoline complexes of coordinatively unsaturated monomeric rhodium(II) have been described by Tilley *et al.* and subsequently employed as catalysts for the cyclopropanation of olefins with EDA, giving excellent yields (66–94%) and enantioselectivities of up to 84% ee [283].

However, Rh$_2$(DOSP)$_4$ and Rh$_2$(TBSP)$_4$ were revealed as the most active catalysts [284]. For instance, Rh$_2$(DOSP)$_4$ provided the highest enantiocontrol for many alkenes, but *trans*-disubstituted alkenes did not react under these conditions. This Rh-catalyzed cyclopropanation was also applied to the synthesis of cyclopropane α-amino acids [285], from reaction of alkynyldiazoacetates (61–91% yields, 92:8 to 99:1 dr, 56–95% ee) [286], aryldiazoesters (82–90% yields, 60:40 to 98:2 dr, 80–97%



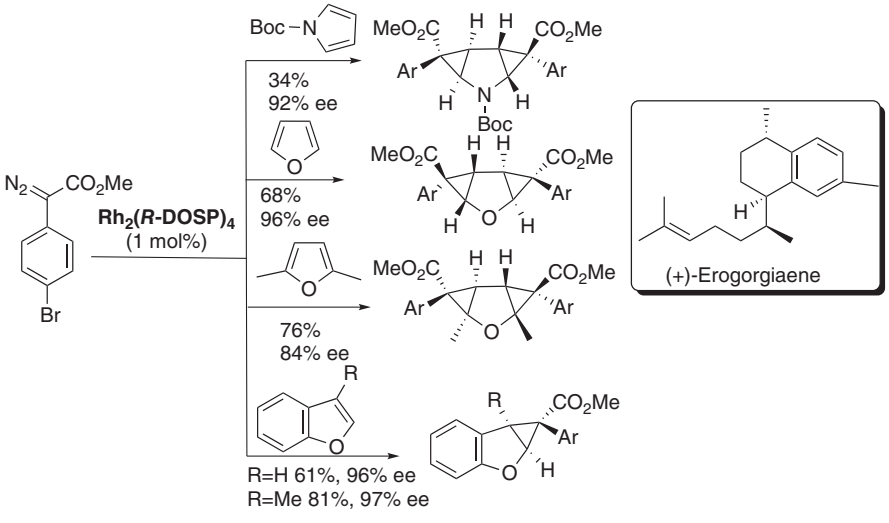
Scheme 1.70 Asymmetric cyclopropanation of α-cyanodiazophosphonate and α-cyanodiazoacetate.

ee) [287], and heteroaryldiazoacetates (92:8 to 99:1 dr, 23–89% ee) with olefins [288]. The reaction of ethyl 3,3,3-trifluoro-2-diazopropionate with various olefins catalyzed by Rh_2(*R*-DOSP)$_4$ was also explored [289]. The reaction between this diazo compound and 1,1-diphenylethylene gave 72% yield and 40% ee, whereas the cyclopropanation of monosubstituted olefins led to *Z/E* mixtures of the corresponding cyclopropanes with a maximum of 75% ee for 4-methoxystyrene.

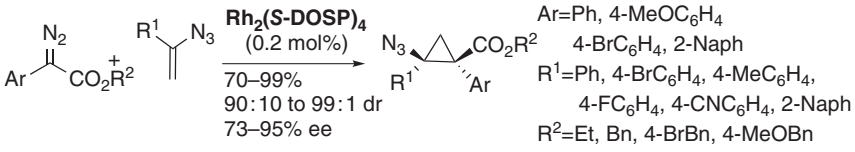
On the other hand, Rh_2(*R*-DOSP)$_4$ was also used to induce the decomposition of aryldiazoacetates in the presence of pyrroles or furans, resulting in the formation of mono- or bis-cyclopropanes of the heterocycle (Scheme 1.71) [290]. It should be noted that the enantioinduction was markedly influenced by the structure of the heterocyclic substrate and depended upon which bond of the heterocycle initially interacted with the carbenoid, thus either face of the heterocycle can be attacked under the influence of the same chiral catalyst. The control was governed by a delicate interplay of steric and electronic influences. This methodology was applied to the total synthesis of a natural product, (+)-erogorgiaene, by the cyclopropanation of a dihydronaphthalene [291].

Moreover, this reaction was extended to a solid-phase cyclopropanation between phenyldiazoacetate and a resin-bound alkene by pyridine linker. The stereoselectivities were almost identical to those observed in solution [292]. However, this immobilization strategy showed high level of rhodium leaching upon recycling after the first reaction.

Therefore, a single ligand of Rh_2(*S*-DOSP)$_4$ was exchanged with a ligand that could undergo a grafting reaction to a solid support. As this substitution could break the high symmetry that is characteristic of these complexes, the attachment was carefully designed to limit negative influence on the enantioselectivity. In fact, the chiral pocket would be still maintained in the catalyst structures when one or more of the chiral carboxylate ligands of the rhodium complex were replaced (see the following discussion). The cyclopropanation catalyzed by this



Scheme 1.71 Asymmetric cyclopropanation of pyrroles or furans catalyzed by Rh_2[(*R*)-DOSP]$_4$.



Scheme 1.72 Enantioselective preparation of *cis*-β-azidocyclopropane esters.

grafted catalyst was repeated over five consecutive reactions and always provided similar levels of both yield and enantioinduction [293]. Other chiral dirhodium catalysts could be immobilized on a polymer, providing yields and selectivities for cyclopropanations comparable to those with the homogeneous catalyst (up to 84% ee and 87% yield) [294]. In particular, Davies and Walji developed a very effective strategy for the heterogenization of chiral dirhodium catalysts, exhibiting all the reactivity features of the homogeneous catalysts, with the advantage of excellent recyclability [295].

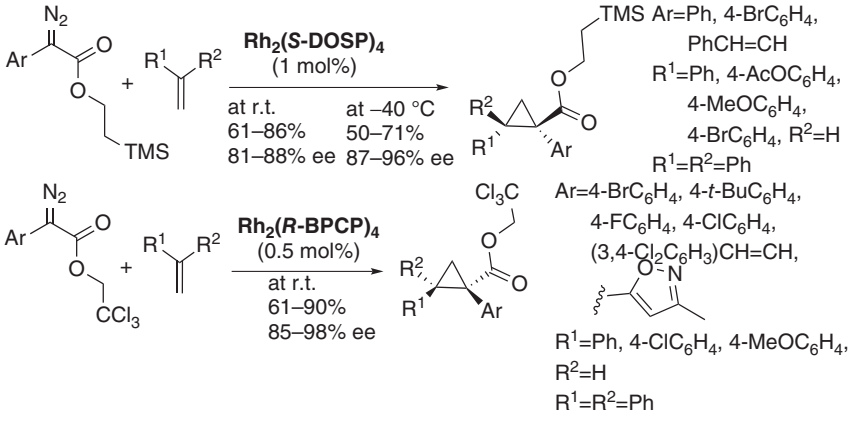
Moreover, Rh_2(*S*-DOSP)$_4$ provided mixtures of cyclopropanes and C–H insertion products in a 2:1 ratio in the reaction of diazoacetate and *N*-Boc ethyl alkenylamines. The (1*S*,2*R*)-cyclopropanes were recovered in 55–64% yield with 95:5 dr and 92–96% ee. Other rhodium catalysts were tested, but product distribution was not significantly affected [296].

β-Aminocyclopropane carboxylic acids are widely used in peptide syntheses, but they cannot be efficiently prepared from asymmetric cyclopropanation of *N*-protected enamines [297]. However, azidoalkenes could be regarded as alternative precursors of *cis*-β-aminocyclopropane carboxylic acids, and Rh_2(*S*-DOSP)$_4$ was found to be an efficient catalyst for the preparation of (1*R*,2*S*)-isomers (Scheme 1.72) [298]. The reaction can be carried out on gram scale with the same yield but with slightly lower enantioselectivity and longer reaction time.

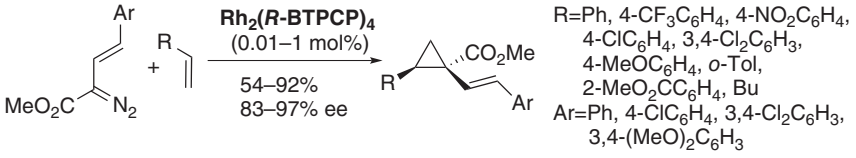
Finally, intermolecular asymmetric cyclopropanations of aryldiazoacetates with labile protecting groups on the ester and styrene derivatives can be catalyzed by chiral dirhodium(II) complexes Rh_2(*S*-DOSP)$_4$ and Rh_2(*R*-BPCP)$_4$. In particular, the trimethylsilylethyl aryldiazoacetates gave the best results with Rh_2(*S*-DOSP)$_4$, while trichloroethyl aryldiazoacetates with Rh_2(*R*-BPCP)$_4$ (Scheme 1.73) [299].

Similar dirhodium complex Rh_2(*R*-BTPCP)$_4$ was found to be an effective chiral catalyst for the enantioselective cyclopropanation of styryldiazoacetates (Scheme 1.74) [300]. DFT computational studies at the B3LYP and UFF levels suggested that when the carbenoid binds to the catalyst, two of the 4-bromophenyl groups rotate outward to make room for the carbenoid. Then, the ester group aligns perpendicular to the carbene plane and blocks attack on its side. Thus, the substrate approaches over the donor group, but it finds the *Re*-face blocked by the aryl ring of the ligand and only the *Si*-face open for the attack, in agreement with the observed absolute configuration of the product.

Hansen's research group introduced catalysts Rh_2(*trans*-HYP)$_4$ and Rh_2(*cis*-HYP)$_4$ and compared them with Rh_2(*S*-DOSP)$_4$ in the reaction of styrene and phenyldiazoacetate, finding very similar yields and enantiomeric excess values [301]. As expected, Rh_2(*trans*-HYP)$_4$ and Rh_2(*cis*-HYP)$_4$ displayed opposite enantioselectivity to each other, because the enantioselectivity of proline-derived



Scheme 1.73 Enantioselective synthesis of cyclopropanecarboxylates with labile protecting groups on the ester.

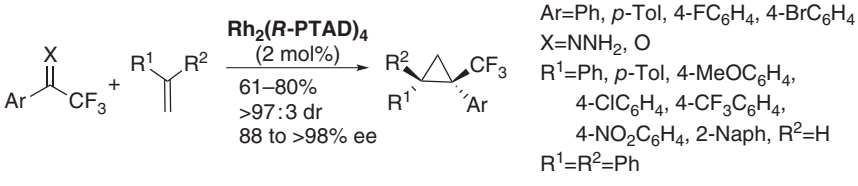


Scheme 1.74 Cyclopropanation of styryldiazoacetates.

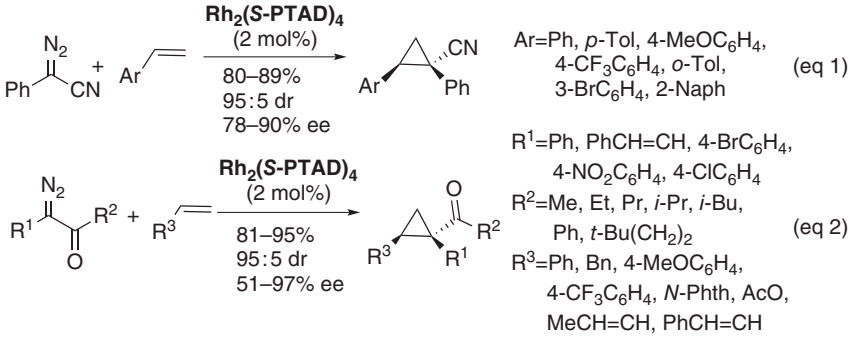
catalysts is governed by the stereochemistry at the C2 of proline. These results are in agreement with an active "all-up" C_4-symmetric conformation.

Dirhodium complex, Rh_2(*R*-PTAD)$_4$ was found efficient in the reaction of 1-aryl-2,2,2-trifluorodiazoethanes with alkenes, generating the corresponding trifluoromethyl-substituted cyclopropanes, an example of the important class of fluorinated cyclopropanes [302], with very high diastereo- and enantioselectivities (Scheme 1.75) [303].

The enantiomer Rh_2(*S*-PTAD)$_4$ catalyzed the stereocontrolled synthesis of nitrile-substituted cyclopropanes from 2-diazo-2-phenylacetonitrile and aryl alkenes (Scheme 1.76, eq 1) [304]. It is worth noting that the small cyano acceptor group would be unable to influence the selectivity. In fact, as reported earlier, studies on the mechanism asserted that the bulkiness of the electron-withdrawing group drives the selectivity. This is true for alkylethenes (formed as 61 : 39 to



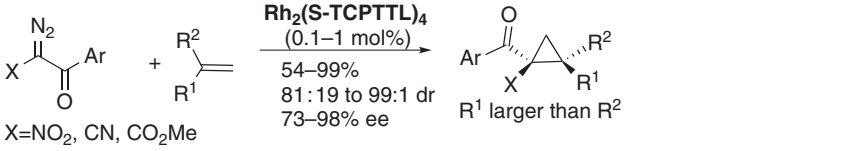
Scheme 1.75 Asymmetric synthesis of fluorinated cyclopropanes.



Scheme 1.76 Asymmetric synthesis of some cyclopropanes catalyzed by Rh_2(S-PTAD)$_4$.

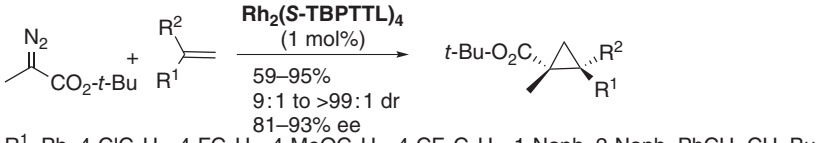
46:54 mixtures of diastereomers), but high diastereoselectivity was observed with styrenes. Therefore, the authors claimed an attractive π-stacking interaction between the aryl rings of styrene and phthalimide during the cyclopropanation that is absent in alkyl-substituted alkenes. Catalyst Rh_2(*S*-PTAD)$_4$ also catalyzed the reaction of aryl-α-diazo ketones with activated alkenes (Scheme 1.76, eq 2) [305]. The enantioselectivity dropped when either the aryl group in R^1 was substituted with a styryl group or bulky groups were close to the carbonyl and increased when the alkyl chain of the ketone group was lengthened, but C–H insertion became a competing reaction for lengths beyond propyl. Vinyl acetate, dihydrofuran, and dienes were less enantioselective, while vinyl ether and inactivated alkenes were not effective substrates.

Similar results were obtained in the cyclopropanation of alkenes with diazoacetophenones under Rh_2(*S*-TCPTTL)$_4$ catalysis (Scheme 1.77) [306]. The reaction could be carried out on a multigram scale. Different substituted diazoacetophenones showed similar efficiency, except for the 4-dimethylamino derivative that achieved only 38% yield. Unfortunately, alkyl-substituted alkenes did not provide the corresponding cyclopropanes in useful yields, and dienes afforded only Cope-rearranged achiral products. The enantioselectivity outcome is in good agreement with an "all-up" conformation of the catalyst and once more with π-stacking interactions between the aryl ketone moiety and phthalimide, while the electron-withdrawing group (X) did not play a crucial role in the stereocontrol of the reaction. Thus, nitro, nitrile, or a methyl ester in the starting diazo derivative leads to high stereocontrol.

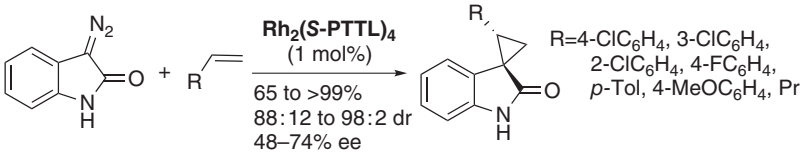


X=NO_2, CN, CO_2Me
Ar=4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 3-$MeOC_6H_4$
R^1=Ph, *p*-Tol, 4-*t*-BuC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 4-$CF_3C_6H_4$,
2-ClC_6H_4, 2-FC_6H_4, 3-$MeOC_6H_4$, 3-$NO_2C_6H_4$, 3-$CF_3C_6H_4$, *m*-Tol, 1-Naph, OBz
R^2=H, Me

Scheme 1.77 Enantioselective synthesis of *cis*-cyclopropane α-amino acid precursors.



Scheme 1.78 Enantioselective cyclopropanation with α-diazopropionate.

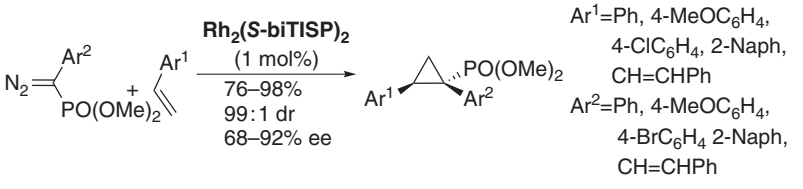


Scheme 1.79 Enantioselective synthesis of spirocyclopropyloxindoles.

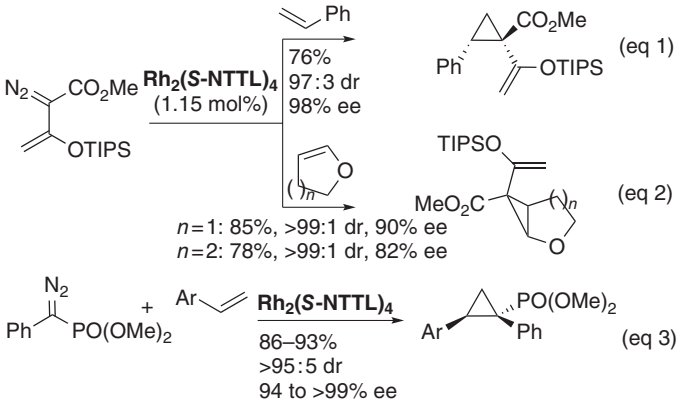
Hashimoto described that the reaction of 1-aryl-substituted and related conjugated alkenes with *tert*-butyl α-diazopropionate by catalysis with Rh_2(*S*-TBPTTL)$_4$ led to the corresponding (1*R*,2*S*)-cyclopropanes containing a quaternary stereogenic center (Scheme 1.78) [307].

Awata and Arai achieved the asymmetric cyclopropanation of diazooxindoles with Rh_2(*S*-PTTL)$_4$ as the catalyst. Spirocyclopropyloxindoles, which constitute biologically important compounds, were obtained in good yield and diastereoselectivity (Scheme 1.79) [308]. Then the mechanism of this reaction was detailed by DFT calculations, which demonstrated that the origin of the *trans*-diastereoselectivity lies in the π–π interactions between the *syn*-indole ring in carbenoid ligand and the phenyl group in styrene. The enantioselectivity could be ascribed both to steric interaction between the phenyl ring in styrene and the phthalimide ligand and to stabilization of π–π and CH–π interactions in the transition states [309].

Rh_2(*S*-biTISP)$_2$ was able to catalyze the cyclopropanation of styrene with methyl phenyldiazoacetate with high turnover number (92 000) and turnover frequency (4000 h^{-1}) [310]. This is one of the rare examples of a large-scale reaction with rhodium catalysts; in fact, with a substrate/catalyst ratio of 100 000, 92% yield and 85% ee were obtained on a crude of 46 g. In addition, this catalyst, immobilized on highly cross-linked polystyrene resins with a pyridine attachment, provided up to 88% ee for this reaction [311]. Finally, the same catalyst was applied to the stereoselective synthesis of cyclopropylphosphonates containing quaternary stereocenters by the reaction of dimethyl aryldiazomethylphosphonates (Scheme 1.80) [312].



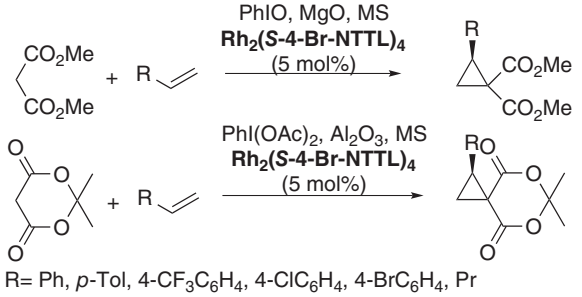
Scheme 1.80 Asymmetric synthesis of cyclopropylphosphonates catalyzed by Rh_2(*S*-biTISP)$_2$.



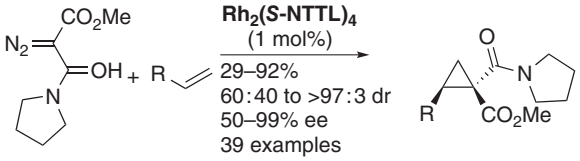
Scheme 1.81 Asymmetric cyclopropanations with Rh_2(*S*-NTTL)$_4$.

The Rh_2(NTTL)$_4$ catalyst allowed an exceptional diastereo- and enantioselective cyclopropanation of styrene (Scheme 1.81, eq 1), dihydrofuran, and dihydropyran (Scheme 1.81, eq 2) with (silanyloxyvinyl)diazoacetates [313]. This methodology, applied to alkyl diazo(trialkylsilyl)acetates, furnished the corresponding cyclopropanes in good yield, but with low enantioselectivity (<54% ee) [314]. Hence, the use of ethyl diazo(triethylsilyl)acetate led to 69% yield, with 82 : 18 dr and 54% ee. The same catalyst was also the best-performing catalyst in the synthesis of cyclopropylphosphonate derivatives (compare Schemes 1.80 and 1.81, eq 3) [315]. The selectivity is independent of the size of the phosphonate group and can be predicted by Hashimoto's model. The use of Meldrum's acid, methyl diazostyrylacetate, and methyl diazophenylacetate instead of the phosphonate ester group dramatically deteriorated the asymmetric induction.

Then, studies on the shape of the complex Rh_2(*S*-NTTL)$_4$ demonstrated that the 4-substituent lies at the cavity rim, thus exerting a strong influence on the enantiofacial discrimination of the incoming alkene during carbene transfer [316]. Therefore, larger 4-substituents should improve the outcome, and bromine was found to be the best choice. Actually, the complex Rh_2(*S*-4-Br-NTTL)$_4$ catalyzed the one-pot asymmetric cyclopropanation of alkenes with ylides from dimethyl malonate or Meldrum's acid producing the *S*- and *R*-isomers for aromatic and aliphatic alkenes, respectively (Scheme 1.82).



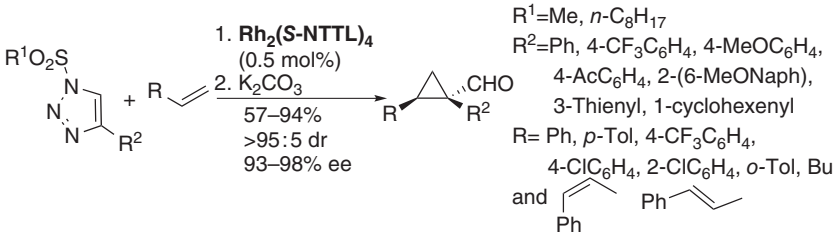
Scheme 1.82 Asymmetric cyclopropanation of alkenes by using *in situ* generated ylides.



Scheme 1.83 Asymmetric cyclopropanation of alkenes with diazo reagents having "*trans*-directing ability" of the amide.

As suggested by Marcoux and Charette, the so-called *trans*-directing ability of the amide group present in the diazo derivative could increase Rh_2(*S*-NTTL)$_4$ selectivity (Scheme 1.83) [317]. The in–out conformation was preferred in the transition state, and the larger amide group was the out-of-plane group. Then the alkene attacked the electrophilic carbene by orienting its largest substituent on the side of the in-plane ester group and the chiral ligands discriminate between the two transition-state faces. Aliphatic alkenes afforded only trace amounts of the corresponding cyclopropane, but the problem was overcome by selective cyclopropanation of the less-hindered double bond of a diene, followed by hydrogenation. The synthetic versatility of these cyclopropanes was demonstrated by their transformation into different derivatives with preservation of the enantiomeric purity. The addition of a sulfonic amide for decomposing the diazo derivative did not affect enantioselectivity and yield; thus, various achiral additives were checked. If the diazo derivative possessed two acceptor groups (such as NO_2, CN, RCO, CO_2R), the presence of trifluoromethanesulfonamide and DMAP enhanced the stereoselectivity, thus suggesting a correlation between the additive and the corresponding symmetry of the catalyst, but how additives increase the enantiomeric excess and diastereomeric ratio remains unclear. Donor–acceptor rhodium(II) carbenes instead were negatively influenced by the additives.

N-Sulfonyl-1,2,3-triazoles are stable synthetic equivalents of unstable azavinyl carbenes and allow the synthesis of cyclopropanecarboxaldehydes from either aromatic or aliphatic alkenes (Scheme 1.84) [318]. It is surprising that *trans*-1-phenylpropene produced the corresponding cyclopropanecarboxaldehyde with excellent 98% enantioselectivity, while the *cis* analog delivered almost racemic product. Starting triazoles can be easily prepared either by cycloaddition of sulfonylazides and nitriles or more simply by *in situ* generation of *N*-triflyl azavinyl carbenes from *NH*-1,2,3-triazoles treated with triflic anhydride in the presence of Rh_2(*S*-NTTL)$_4$.



Scheme 1.84 Asymmetric cyclopropanation with *N*-sulfonyl-1,2,3-triazoles.

Complex Rh_2(4*S*,2′*R*,3′*R*-HMCPIM)$_4$ allowed the cyclopropanation of styrene with EDA in 68% ee and 59% yield, but with almost no diastereoselectivity [319]. Tetrakis-dirhodium(II)-(*S*)-*N*-(*n*-perfluorooctylsulfonyl)prolinate (named (**a**) in Scheme 1.67) has been used in a homogeneous or fluorous biphasic manner, displaying the best chemo- and enantioselectivities in the cyclopropanation of styrene with ethyl phenyldiazoacetate, (81% yield, 74% ee), when using perfluoro(methylcyclohexane) as the solvent [320].

Sambasivan and Ball described the preparation of rhodium–peptide catalysts for use in cyclopropanation reactions [321]. Over 200 sequences were prepared, and the so-called normal provided *Re*-face addition products and were characterized by bulk amino acids (i.e., leucine, isoleucine, phenylalanine) at the second and sixth positions. In contrast, polar carboxamide side chains (glutamine and asparagine) at the same positions characterized the "enantiomeric" sequences, providing *Si*-face addition. Both sequences carried two aspartate moieties in the third and seventh positions, which favored the formation of cyclopropanes. The reaction of aryldiazoacetates and monosubstituted alkenes with these catalysts (0.25 mol%) afforded (1*R*,2*S*)- or (1*S*,2*R*)-cyclopropanecarboxylates in 42–99% yields and with 38–97% ee.

The chiral pocket of dirhodium complexes is still maintained in the catalyst structures when one or more of the chiral carboxylate ligands of the rhodium complex are replaced by an achiral ligand (heteroleptic complexes). This chance has already been mentioned for the immobilization of Rh_2(DOSP)$_4$, but it was also applied in homogeneous catalysis. For instance, dirhodium complexes bearing bulky *ortho*-metallated arylphosphines (Scheme 1.67, group **b**) produced high *cis*-diastereo- and (1*R*,2*S*)-enantioselectivities in the cyclopropanation of styrene with EDA [322]. The substituents largely influenced the diastereoselectivity of the reaction, since increasing the size of the substituents, Br < *t*-Bu < TMS, *Z/E* ratios went from 53 : 47 to 90 : 10, but yields decreased from 80% to 39%. Enantiomeric excesses of the *cis*-isomer ranged from 81% to 91% ee without correspondence with substituent bulkiness. Interestingly, similar reaction could be performed in water as the solvent. Moreover, the immobilization of these catalysts on a cross-linked polystyrene resin gave higher yields, compared to those obtained with the standard homogeneous trifluoroacetate derivatives, whereas the diastereo- and enantioselectivities were generally lower in the cyclopropanation of styrene with EDA [323]. Corey and coworkers reported the reaction of styrene with EDA in the presence of another dirhodium catalyst, Rh_2(OAc)(DPTI)$_3$, affording the corresponding product in 84% yield with 67 : 33 *Z/E* ratio, 99% ee (*cis*), and 94% ee (*trans*) [324]. It is noteworthy that the major diastereomer was the *cis*-cyclopropane. Later, Charette's and Fox's research groups independently hypothesized that a large aromatic surface area in the achiral ligand was necessary for maintaining the selectivity [325]. In particular, Fox used Rh_2(*S*-PTTL)$_3$-TPA in the cyclopropanation reactions of α-alkyl-α-diazo esters with aliphatic and aromatic alkenes, obtaining 53–99% yields, with 71 : 29 to 99 : 1 dr and 65–97% ee, values comparable or superior to those achieved with Rh_2(*S*-PTTL)$_4$ as the catalyst [325b].[5] Charette's research group prepared various

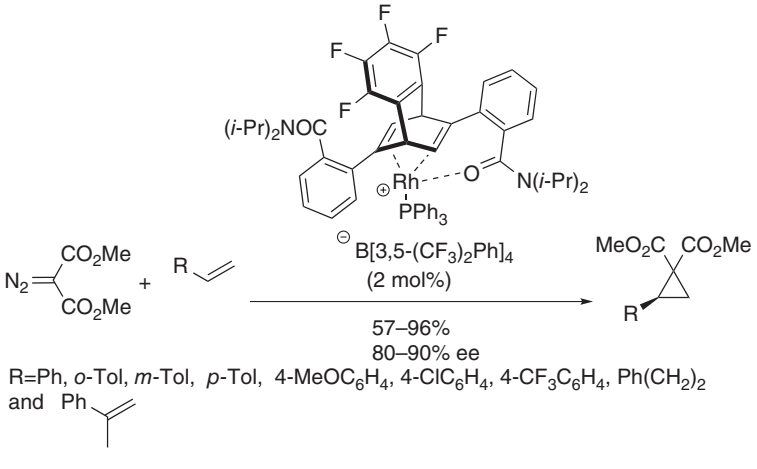
[5] It should be noted that α-alkyl-α-diazo esters are known to undergo β-hydride elimination to form alkenes, but sterically demanding carboxylate ligands drastically decrease this side reaction.

heteroleptic complexes and tested them in the cyclopropanation reaction of styrene with α-nitrodiazoacetophenones [325a]. Thus, the replacement of one tetrachlorophthalimide ligand from Rh_2(*S*-TCPTTL)$_4$ with phthalimide, succinimide, or 1,8-naphthalimide ligands did not significantly affect the asymmetric induction, whereas 2-naphthylacetate as the fourth ligand furnished a racemic product. The absence of enantioinduction was ascribed to a lack of rigidifying halogen bonds in the 2-naphthylacetate complex and to the absence of the *N*-imido moiety evidently necessary in all ligands to achieve a high asymmetric induction, independently of whether or not the fourth carboxylate is chiral. Charette also found that the asymmetric induction increased, replacing one of the four chiral ligands with a ligand that has a *gem*-dimethyl group instead of the chiral center, because of a conformational change in the catalyst owing to the presence of the two methyl groups in the fourth ligand.

Finally, just one rhodium(I) chiral catalyst was reported for the cyclopropanation of alkenes with dimethyl diazomalonate (Scheme 1.85) [326]. By using the (*R*,*R*)-configured tetrafluorobenzobarrelene complex, the *S*-configured cyclopropanes have been recovered. The reaction of α-methylstyrene gave only 57% ee, and in the reaction of 4-phenylbut-1-ene, as the representative of aliphatic alkenes, the enantioselectivity and yield were both low. Experimental evidence supported a transition state wherein the carbonyl oxygen on the ligand was coordinated to the rhodium(I) center. An active single coordination site on the rhodium cation was essential for the catalytic activity. In fact, the more bonded chloride ion, instead of the tetraborate, was not catalytically active.

1.3.1.5 Chiral Catalysts: Ruthenium

The success of the rhodium complexes in catalyzing carbene-transfer reactions is tempered by the high price of this metal. Therefore, ruthenium, a direct neighbor of rhodium in the periodic table, has been more recently introduced in the field of catalytic cyclopropanation, because it costs roughly one-tenth the price of rhodium. Another reason for focusing attention on ruthenium catalysts is the



Scheme 1.85 Asymmetric cyclopropanation catalyzed by a rhodium(I) complex.

greater diversity of complexes to be evaluated, due to the richer coordination chemistry, as compared to rhodium [327].

Thus, many highly active and selective homogeneous catalysts have been introduced for the asymmetric cyclopropanation of alkenes (Scheme 1.86) [328]. Indeed, in a short time, ruthenium has emerged as the third important catalyst metal for the carbenoid chemistry of diazo compounds, besides copper and rhodium. However, a significant drawback of Ru catalysts is the rather low electrophilic character of the presumed ruthenium–carbene intermediates, which often restricts the application to terminal activated alkenes and double bonds with a higher degree of alkyl substitution. Another limitation of some ruthenium complexes is the ability to catalyze other alkene reactions as well as cyclopropanation leading to many by-products. However, if ruthenium catalysts work successfully, they often rival rhodium catalysts in terms of effectiveness and relative, as well as absolute, stereochemistry.

Some methods of heterogenization of ruthenium catalysts, for instance, supporting them on polymer or porous silica supports, have been investigated. Their activity, selectivity, and recyclability have all been compared to those of the analogous homogeneous catalysts.

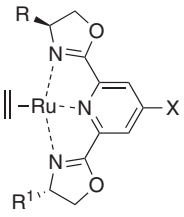
By commenting on the Scheme 1.58, eq 1, Nishiyama's catalyst [329] has already been mentioned as better catalyst compared to Cu-***ent*-box5** catalyst in the synthesis of cyclopropylphosphonate derivatives [213]. In the reactions with pybox ligands, the geometry of the recovered products is consistent with a model, in which the phenyl group of styrene approaches the carbenoid species away from the ester and isopropyl groups. Two interesting observations have been made.

i) A remote stereoelectronic effect exerted by the substituent in the 4-position of the pyridine ring has been reported [330]. Electron-donating substituents decrease (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). The *E/Z* ratios were instead not affected by the substituents.
ii) Non-C_2-symmetric ligands are also quite effective in this reaction. For example, Ru-**Pybox4** afforded the cyclopropane not only with high enantioselectivity but also with an improved diastereoselectivity, very likely because the removal of one of the oxazoline substituents created more space for the ester group in the chiral pocket [331].

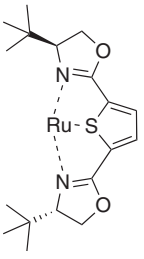
Garcia and coworkers reported an extensive comparison of the two enantioselective catalytic systems Ru-**Pybox** and Cu-**box** complexes by *ab initio* calculations in the cyclopropanation of alkenes with methyl diazoacetate [332]. The geometries of the key reaction intermediates and transition structures calculated at the QM/MM level were generally in satisfactory agreement with the full-QM calculated geometries. Furthermore, the QM/MM energies were often in better agreement with the stereoselectivity experimentally observed compared to full-QM calculations.

Later, Deshpande *et al.* used Nishiyama's catalyst to catalyze the cyclopropanation of styrene with EDA, providing the corresponding *trans*-cyclopropane in 98% yield, with 96 : 4 dr, and 86% ee (*trans*) [333].

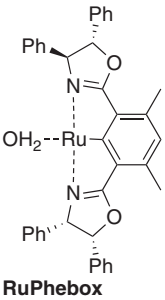
Moreover, 1-tosyl-3-vinylindoles were excellently cyclopropanated by Nishiyama's catalyst with ethyl and *t*-butyl diazoacetate (Scheme 1.87) [334]. It



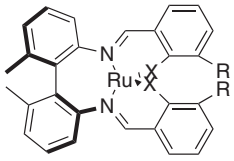
RuPybox
1: R=R^1=*i*-Pr, X=H
Nishiyama's catalyst
2: R=H, R^1=*t*-Bu, X=H
3: R=R^1=*i*-Pr, X=CO_2Me
4: R=R^1=CH_2OH, X=H



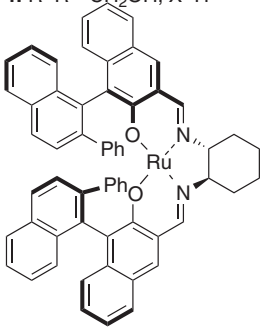
RuThibox



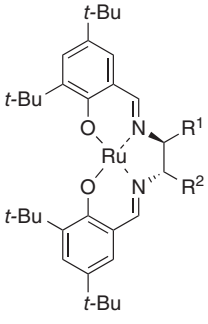
RuPhebox

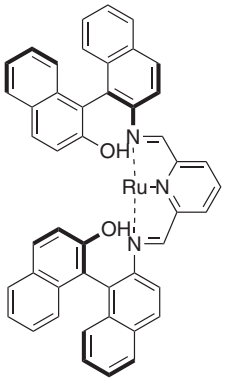


Ru–salen
1: X=O, R=*i*-Pr
2: X=PPh_2 R=H

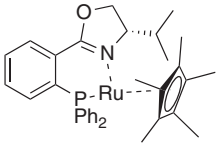


Ru–salen3

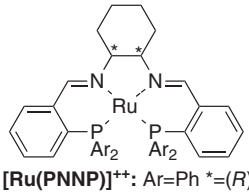




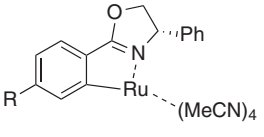
Ru–salen
4: R^1-R^2=$(CH_2)_4$
5: R^1=H, R^2=Me
6: R^1=R^2=Ph
7: R^1=R^2=H



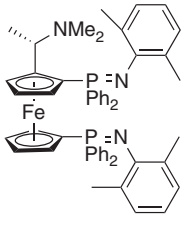
RuPN

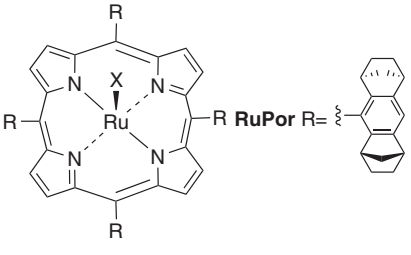


[Ru(PNNP)]$^{++}$: Ar=Ph *=(*R*)
[Ru(CF_3PNNP)]$^{++}$: Ar=4-$CF_3C_6H_4$ *=(*S*)

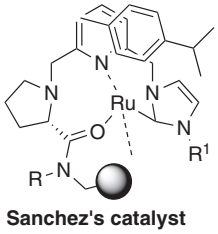


RuPheox
1: R=H
2: R=CH_2OH



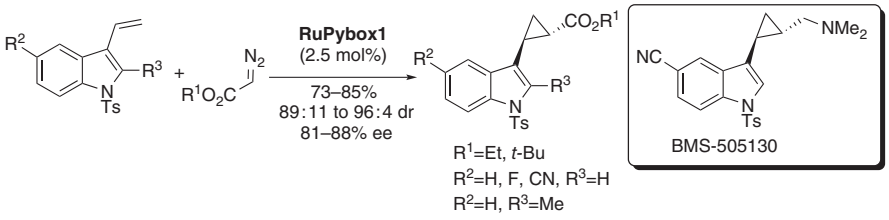


RuPor R=



Sanchez's catalyst

Scheme 1.86 Chiral ruthenium catalysts for asymmetric cyclopropanations.



Scheme 1.87 Asymmetric cyclopropanation of 1-tosyl-3-vinylindoles.

should be noted that the *E/Z* diastereoselectivity was notably improved when using *t*-butyl diazoacetate. Moreover, the utility of this method was demonstrated by the conversion of one of the resulting chiral cycloadducts into BMS-505130, a selective serotonin reuptake inhibitor.

Nishiyama also developed the water-soluble hydroxymethyl derivative (Ru-**Pybox4**). The reaction of styrene with different diazoacetates in aqueous media provided the corresponding cyclopropanes in 24–75% yields, with 92 : 8 to 97 : 3 *E/Z* ratio, 57–94% ee (1*S*,2*S*), and 26–76% ee (1*R*,2*S*) [335].

Simmoneaux *et al.* examined chiral 2,6-bis(thiazolinyl)pyridines as ligands for the Ru-catalyzed cyclopropanation of olefins. The comparison of the enantiocontrol for the cyclopropanation of styrene with chiral ruthenium bisoxazoline and bisthiazoline allowed the evaluation of the different situation with regard to the diastereoselectivity and enantioselectivity when an oxygen atom was substituted by sulfur. They found many similarities with, in some cases, good enantiomeric excesses (up to 84% ee for *trans*-cyclopropylphosphonate were observed) [336].

Nishiyama's catalyst was immobilized in different manners:

i) By grafting on a Merrifield-type resin and on supports prepared by the polymerization of 4-vinyl-substituted ligands, providing yields of over 60% with up to 91% ee in four successive reactions. The enantioselectivity and the recyclability were strongly dependent upon the catalyst preparation method and the total exclusion of oxygen and moisture in the filtration process [337].
ii) By preparing Ru-**Pybox** monolithic miniflow reactors on styrene–divinylbenzene polymeric backbones having different compositions and pybox chiral moieties. Under conventional conditions and in supercritical carbon dioxide, the continuous flow cyclopropanation reaction between styrene and EDA led to good enantioselectivity (up to 83% ee) demonstrating these highly efficient and robust heterogeneous chiral catalyst and allowing the development of environmentally friendly reaction conditions [338].
iii) By microencapsulation into linear polystyrene (60–68% yields, 75–85% ee in up to four successive reactions were achieved in the benchmark cyclopropanation reaction between styrene and EDA) [339].
iv) On modified starch, providing the cyclopropanation of styrene with EDA in 67% yield, 89 : 11 dr and 77% ee for the *trans*-isomer [340].

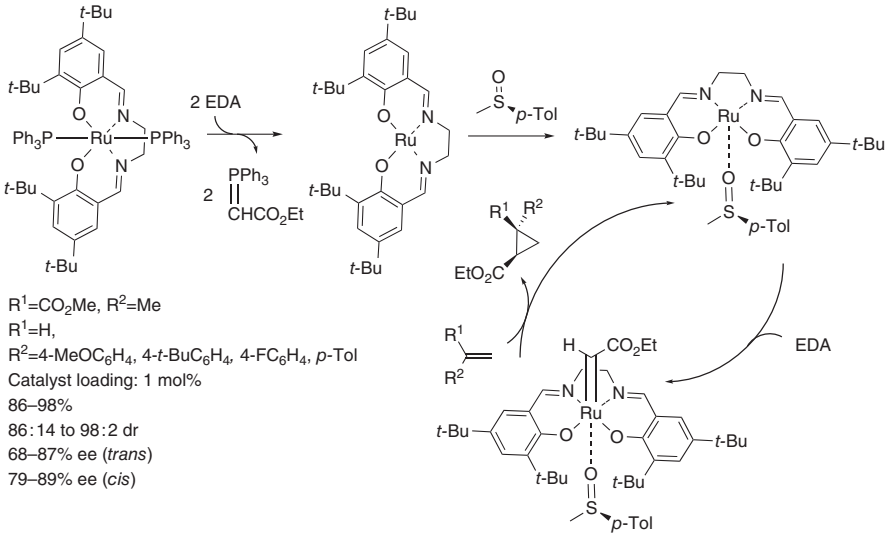
Zingaro and coworkers tested a modified Nishiyama's catalyst (Ru-**Thibox**) and obtained 70–82% yields with 79 : 21 to 82 : 18 *E/Z* ratio and 87% to >99% ee

(1*R*,2*R*), 82% to >99%ee (1*S*,2*R*) for the cyclopropanation of styrenes and 1,1-diphenylethene with EDA [341].

Bis(oxazolinyl)phenyl ruthenium complex (Ru-**Phebox**) was efficient for the cyclopropanation reactions of various styrene derivatives with *tert*-butyl diazoacetate (85–92% yields with 82 : 18 to 96 : 4 *E/Z* ratio and 98–99% ee (1*R*,2*R*)) [342]. Only α-methylstyrene afforded the *cis*-isomer (80% overall yield, 67 : 33 dr, 98% ee (*cis*), and 93% ee (*trans*)). The cyclopropanation of aliphatic alkenes proceeded in lower yield but with good diastereo- and enantioselectivities, whereas cyclopropanation of 1,2-disubstituted alkenes, such as 1-phenylpropene or indene, did not occur. The ruthenium carbene intermediate should be obtained by replacement of the equatorial H_2O ligand with the diazoacetate group, and then the alkene approached the *Re*-face to minimize the steric repulsion between the *tert*-butyl group of the diazo compounds and the R group of the alkene.

Ru-**salen1–3** systems displayed *cis*-selectivity in the cyclopropanation reaction (83 : 17 to 93 : 7 *Z/E* ratios, >97% ee) [343]. In particular, catalyst Ru-**salen2** was effective for the cyclopropanation of 2,5-dimethyl-2,4-hexadiene, producing the *cis*-isomer in 75% ee (94 : 6 dr) but only in 18% recovered yield [343a–c]. Ru-**salen4–6**, with the two free coordinating sites occupied by pyridine ligands, gave excellent enantiomeric excesses in the cyclopropanation of mono or 1,1-disubstituted alkenes (30–97% yields, 66 : 34 to >99 : 1 *E/Z* ratios, 69–99% ee (*trans*)) [344]. The cyclopropanation of styrene with EDA in the presence of Ru-***ent*-salen4** catalysts (99% yield, 92 : 8 *E/Z* ratio, 99% ee (1*R*,2*R*) and 96% ee (1*S*,2*R*)) constituted the key step of the synthesis of chiral *trans*-cyclopropyl β-amino acid derivatives [345]. Jones and coworkers modified Ru-**salen4-(Py)$_2$** complex by substituting one of the *para-tert*-butyl groups with a linker for grafting onto polymer or mesoporous silica [346]. The heterogeneous catalysts generated the desired cyclopropanes, by reaction with EDA and styrenes, in good *trans*-selectivity but with moderate enantioselectivities. Aliphatic alkenes also reacted but in very low yields. The highest selectivities and yield were obtained with longer linker between the Ru-**salen** active site and the polymer support, probably for a lessened steric hindrance around the catalytic site. The silica support resulted in important background reactions on the silica surface, thus lowering enantioselectivity. The addition of pyridine during the washing steps between catalytic cycles stabilized the complex, preventing both leaching of this ligand and losses in activity and selectivities upon recycling. Better results were obtained with a pair of interpenetrated and noninterpenetrated chiral metal organic frameworks constructed by incorporation of Ru-**salen4** into the zinc–carboxylate cubic unit [347]. Both catalysts, differing by the open channel sizes, gave products with good diastereoselectivities (up to 91 : 9) and very high enantioselectivities (up to >99%), albeit in low yields (11–55%), in the reaction of terminal alkenes and diazoacetate. The noninterpenetrated catalyst gave higher isolated yields of cyclopropanation products, presumably because of the larger open channels.

A different approach in the Ru-salen catalyzed cyclopropanations was proposed by Nguyen and coworkers, who achieved successful induction of asymmetry by introducing (*R*)-methyl-*p*-tolylsulfoxide as axial ligand on achiral Ru-**salen7** catalyst (Scheme 1.88) [348]. The proposed mechanism to explain the asymmetric induction involved the axial coordination of the chiral sulfoxide to the ruthenium



Scheme 1.88 Asymmetric cyclopropanation in the presence of a chiral sulfoxide additive.

center as the key induction step. The chiral additive bound preferentially to one of the two chiral conformers of the achiral (salen)ruthenium complex, thus effectively forcing the larger achiral salen ligand to adopt a preferred chiral conformation. The asymmetry of the additive was transmitted and amplified to the opposite axial position, where the other axial triphenylphosphine ligand was replaced by EDA, thus forming the ruthenium carbene. Finally, the carbene stereoselectively interacted with the olefin to complete the cyclopropanation cycle.

Several chiral diphosphines salen-like complexes, such as the chiral $[RuCl(PNNP)]^+SbF_6^-$, were used as ruthenium catalysts [349]. This catalyst was able to cyclopropanate various alkenes with EDA with *cis*-diastereoselectivity [33–69% yields, 85:15 to 99:1 *Z/E* ratio, 96–99% ee (1*R*,2*S*), 58–98% ee (1*S*,2*S*)]. Later, the same research group compared this catalyst with chiral $[Ru(OH_2)_2(PNNP)]^{2+}$ and the chloride-free catalysts formed from $[RuCl_2(PNNP)]$ and $AgSbF_6$ and found both to be less effective than $[RuCl(PNNP)]^+SbF_6^-$ [350].

Mezzetti's group also investigated the possibility of controlling the absolute configuration at the metal center by means of both monodentate chiral phosphoramidite [351] and chiral phosphine [352] ligands (Scheme 1.86 for the structures). After activation with $TlPF_6$, $AgSbF_6$, or $(Et_3O)PF_6$ as halide scavenger, these complexes were used to catalyze the cyclopropanation of styrene and α-methylstyrene with EDA, but the results were always unsatisfactory.

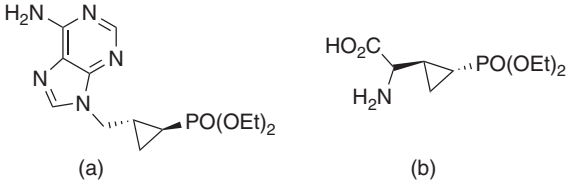
Another chiral phosphine bidentate ligand (Ru**PN**) was tried out for the *cis*-selective cyclopropanation of styrene with EDA with 36% yield 75:25 *Z/E* ratio, and 74% ee [353]. Better results were obtained by ruthenium complexes of chiral (iminophosphoranyl)ferrocenes (Scheme 1.86 for the structure); in fact, *cis*-cyclopropanecarboxylates from a range of olefins with EDA were recovered in up to 79% yield, with up to 95:5 dr and up to 99% ee [354]. Indeed, this new type of ligands were shown

to be comparable to, or better than, the well-known ligands, such as bisoxazolines or semicorrin, in terms of asymmetric induction.

Recently, Ru-**pheox1** was found to be an efficient catalyst for the cyclopropanation reaction of monosubstituted alkenes with succinimidyldiazoacetate [355]. The desired cyclopropanes were obtained in 94–98% yield with >99 : 1 *E/Z* ratio. The enantiomeric excess was calculated after reduction without epimerization of succinimidyl cyclopropanecarboxylates to cyclopropylmethanols and found in the range of 91–99% (1*R*,2*R*). The preferred face for the attack of the ruthenium carbene by the terminal alkene was determined by the steric crowding around the seven-membered ring resulting after the coordination between the succinimidyl carbonyl group and the ruthenium metal center. Then, the same research group applied the Ru-**Pheox1** catalyzed cyclopropanation:

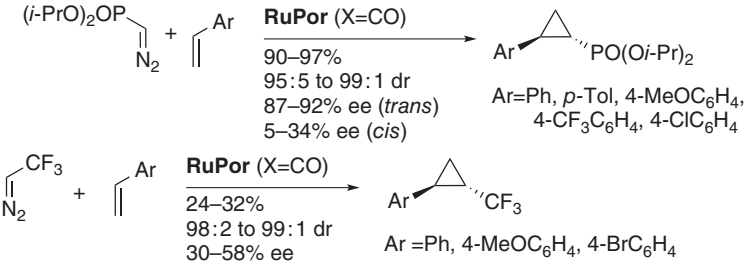
1) To vinylcarbamates with diazoesters (77–99% yields, up to 96 : 4, with *N*,*N*-disubstituted vinylcarbamates and up to 99% ee). However, the reaction of carbobenzyloxyvinylamine and *tert*-butyldiazoacetate or succinimidyl diazoacetate led to about equimolecular amounts of *cis*- and *trans*-isomers, the latter with low enantiomeric excess [356].
2) To diazomethylphosphonate with alkenes (72–93% yields, 62 : 38 to 99 : 1 *E/Z* ratio, 94–99% ee (*R*,*R*)) and α,β-unsaturated carbonyl compounds (33–87% yields, 98 : 2 to 99 : 1 *E/Z* ratio, 78–98% ee (*R*,*R*)). These compounds were used as key intermediates in the synthesis of the analogs of nucleotide and L-Glu (Scheme 1.89) [357].
3) To allenes with succinimidyl diazoacetate (60–92% yields, 90 : 10 to 99 : 1 *E/Z* ratio, 84–99% ee (*R*,*R*)). It should be noted that only the less sterically hindered double bond was attacked and that the reduction of the exocyclic double bond was performed with high stereoselectivity, affording enantioenriched *cis*-cyclopropanes [358].

On the other hand, the cyclopropanation of styrene with diazoacetate catalyzed by Ru-**Pheox2** was attempted, but despite the high *trans*-enantioselectivity (97% ee), the cyclopropanation product was isolated in only 30% yield [359]. Better results are obtained with Ru-**Pheox2** supported on a macroporous polymer; in fact, the corresponding (*R*,*R*)-cyclopropanecarboxylates were obtained in 80–99% yield and with 91–99% ee [360]. The most relevant features of this catalyst were the best results achieved among the heterogeneous catalysts and its reusability, because it was recycled more than 10 times, even after 3 months of storage of the used catalyst, without any loss in its catalytic activity or selectivity.



Scheme 1.89 Analogues of nucleotide (a) and L-Glu (b) from Ru-**Pheox1**-catalyzed cyclopropanation of diazomethylphosphonate with α,β-unsaturated esters.

X (in **RuPor**)	R	Y (%)	dr	ee % (*trans*)	ee % (*cis*)
CO	Me	79	66:34	90	43
CO	H	80	96:4	87	34
PF_3	OTMS	98	70:30	83	38
PF_3	Ph	45	83:17	96%	14

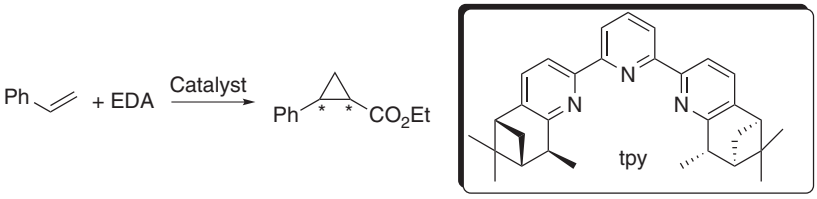


Scheme 1.90 Asymmetric cyclopropanation catalyzed by ruthenium porphyrin.

Cobalt porphyrins have provided robust catalysts for asymmetric cyclopropanations as described in Table 1.2, but ruthenium–porphyrin catalysts were also often employed in this reaction. In 2003, a comparison between rhodium and ruthenium–porphyrin complexes for similar reactions showed that better *E/Z* ratios and higher ee values for the *trans*-isomer were obtained with ruthenium complexes than with the corresponding rhodium complexes [271]. Moreover, Ru-**Por** (Scheme 1.86 for the structure) afforded cyclopropanation of alkenes with EDA [361] and of substituted styrenes with diisopropyl diazomethylphosphonate [362] or with 2,2,2-trifluorodiazoethane [363] (Scheme 1.90). The reactions of EDA [364] and 2,2,2-trifluorodiazoethane [363] were also investigated, giving similar results, under heterogeneous conditions with the corresponding metalloporphyrin polymers, obtained from a chiral ruthenium–porphyrin complex, functionalized with four vinyl groups and copolymerized with divinylbenzene.

Another partially unsuccessful attempt to apply heterogeneous ruthenium catalysts in the cyclopropanation reaction was reported by Sanchez and coworkers [365]. They prepared neutral unsymmetrical pyridine pincer-type ligands with a lateral (*S*)-prolinamide donor functionality and an *N*-heterocyclic carbene moiety incorporated onto mesoporous silica gel. The complex obtained from the ruthenium chloride salt was inactive in the reaction of diazoacetates with styrene or α-methylstyrene, while the hexafluorophosphate salt afforded cyclopropanes (as *Z/E* mixtures) from various aryldiazoacetates and diazoacetates, except for *tert*-butyldiazoacetate, in 75–100% yield but with only 5% ee. Moreover, this supported catalysts required longer reaction times than the corresponding homogeneous catalyst to reach high yields, and the activity of such immobilized catalysts decreased somewhat after recycling.

Finally, to complete these last three sections, the copper(II), rhodium(III), and ruthenium(II) complexes, of formula $[Cu(tpy)Cl_2]$, $[Rh(tpy)Cl_3]$, and $[Ru(tpy)(CO)Cl_2]$, respectively, should be mentioned (Scheme 1.91) [366]. It should be



Catalyst	Y (%)	*trans*/*cis* Ratio	ee % (*trans*)	ee % (*cis*)
$Cu(tpy)Cl_2$ (10 mol%)	84	66:34	72 (1*R*,2*R*)	82 (1*R*,2*S*)
$Rh(tpy)Cl_3$ (2 mol%)	54	30:70	65 (1*S*,2*S*)	71 (1*S*,2*R*)
$Ru(tpy)(CO)Cl_2$ (2 mol%)	98	84:16	60 (1*S*,2*S*)	67 (1*S*,2*R*)

Scheme 1.91 Copper(II), rhodium(III), and ruthenium(II) salts complexed with chiral terpyridine ligands.

noted that the copper complex afforded the enantiomers opposite to those obtained with rhodium and ruthenium complexes, while the *cis*-isomer, unusually, prevailed with the rhodium complex.

1.3.1.6 Chiral Catalyst: Other Metals

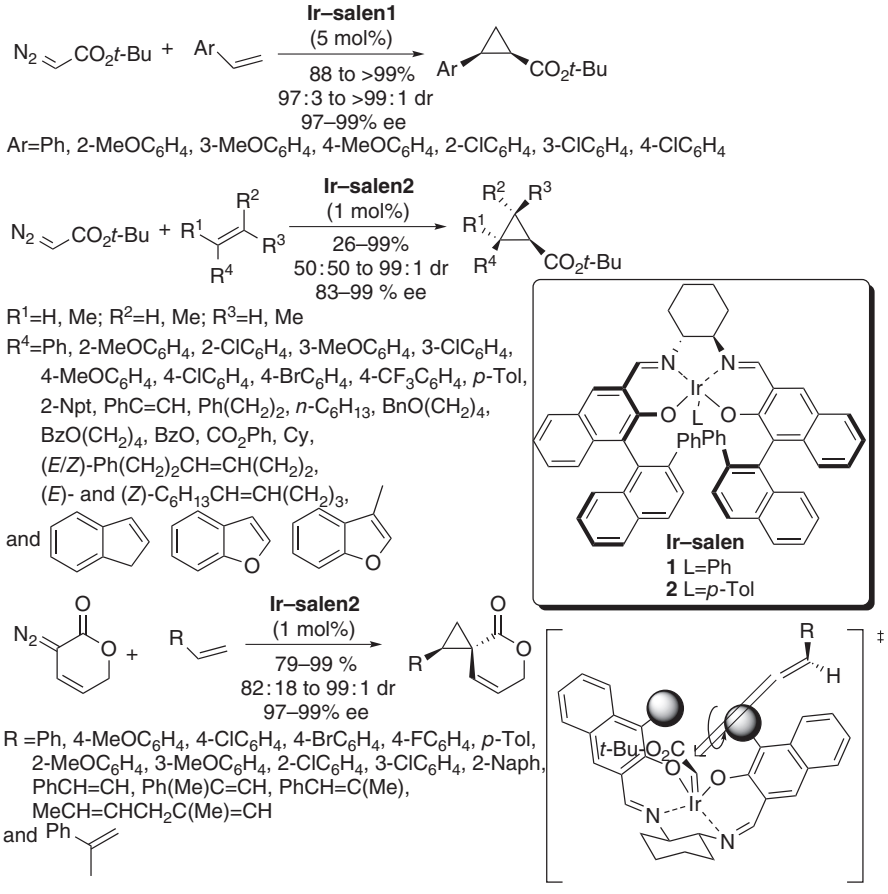
Cobalt, copper, rhodium, and ruthenium are the most frequently metal ions used to prepare asymmetric complexes for cyclopropanation reactions, but some examples of other metal ion complexes have been reported as well.

Denmark and coworkers firstly introduced chiral ligands on the palladium complexes for the diazomethane-mediated cyclopropanation of alkenes. However, although a large number of chiral complexes have been tested, no enantioselection was observed, very likely because either partial or complete decomplexation of the ligand occurred during the course of the reaction [367].

On the other hand, the cheap, nontoxic, and environmentally benign iron was employed to catalyze cyclopropanations in the presence of chiral porphyrins. As an example, the same porphyrin depicted in Scheme 1.86, but complexed with iron chloride, induced the cyclopropanation of alkenes with EDA [368] and with 2,2,2-trifluorodiazoethane [363], providing the corresponding *trans*-cycloadducts in 56–70% yields with 92:8 to 96:4 and 74–86% ee and in 60–96% yields with 90:10 to 95:5 and 71–75% ee, respectively. Comparing these data with those reported in Scheme 1.90, it should be noted that iron porphyrin is a more efficient catalyst in the synthesis of chiral trifluoromethylphenylcyclopropanes. Thus, the scope of this methodology was extended to the use of the corresponding macroporous iron–porphyrin polymer, but yields and ee values were unsatisfactory [363].

Chiral iridium-salen complexes were developed for the *cis*-cyclopropanations of a wide range of alkenes with *tert*-butyl diazoacetate (Scheme 1.92) [369].

A large excess of alkene (up to 10 equiv.) was necessary to obtain high yields, and in contrast to most of the reactions reported earlier, (1*R*,2*S*)-cyclopropanecarboxylates were recovered as the major products. It should be noted that the reactions with *trans*-1-phenylpropene were sluggish, *cis*-1-phenylpropene gave only a modest yield, and reactions of both conjugated and nonconjugated enynes and dienes proceeded exclusively at the terminal alkene. The authors suggested a mechanism



Scheme 1.92 Asymmetric cyclopropanations catalyzed by iridium-salen catalysts.

supported with *ab initio* calculations, in which the classical carbene species occupies the apical position in the iridium complex. The incoming alkene directed its larger substituent away from the carbenoid ester group, in a perpendicular approach. Then, a counterclockwise rotation led to the major product, while the clockwise rotation was less favorable due to steric repulsion between the substituent and the basal salen ligand.

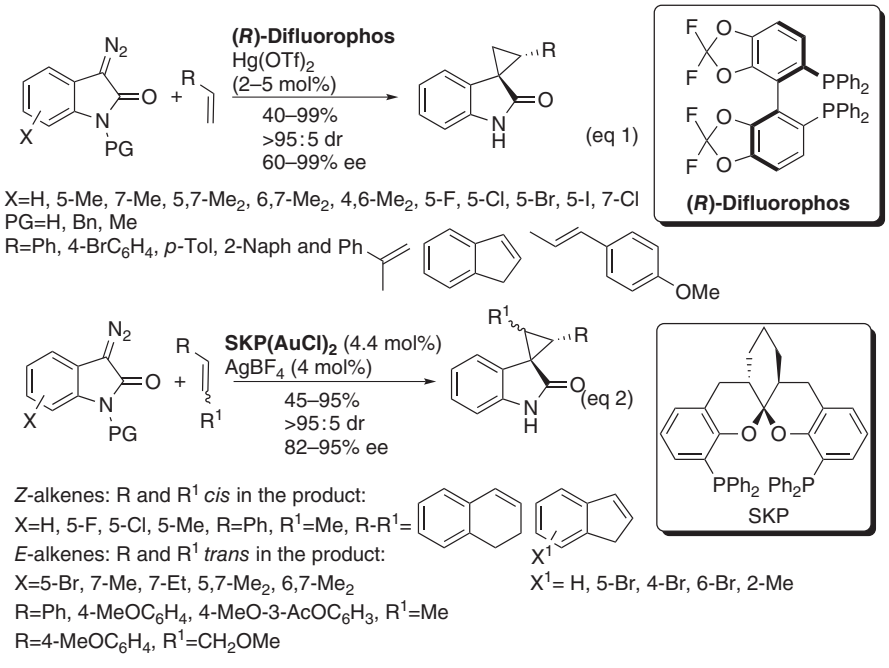
The iridium-salen complex also allowed the synthesis of 5-oxaspiro[2.5]oct-7-en-4-ones, by reaction of a six-membered diazolactone with monosubstituted alkenes and dienes [370]. The most interesting features were the high *trans*-selectivity, in contrast with diazoacetate and the essential addition of molecular sieves to reduce the amount of alkene from ten- to twofold, by suppressing the competitive insertion of adventitious water on the lactone. Finally, it is worth noting that, in all Ir-salen catalyzed reactions depicted in Scheme 1.92, the less-hindered double bond was always attacked.

The cyclopropanation of substituted styrenes with EDA was also performed in the presence of chiral osmium complexes bearing sterically bulky Schiff-base

ligands such as bis(3,5-di-*tert*-butylsalicylidene)-1,2-(*R*,*R*)-cyclohexane-diamine [up to 83 : 17 dr and up to 79% ee (*S*,*S*)] [371]. In the presence of chiral Mo_3CuS_4 clusters, both diastereo- and enantioselectivities were only moderate for both inter- and intramolecular processes [372].

Moreover, (*R*)-Difluorophos/$Hg(OTf)_2$-catalyzed cyclopropanation of diazooxindoles and alkenes has been reported (Scheme 1.93, eq 1) [373]. Unfortunately, the stereoselectivity for highly substituted cyclopropanes was not given. It should be noted that the obtained spiroxindoles were diastereomeric with respect to those obtained with rhodium catalysis (see Scheme 1.79). The stereochemistry was in agreement with an alkene approach to the carbenoid intermediate over the lactam group, with the substituent of the alkene away from the bulky metal, thus leading to the formation of the *trans*-isomer as the major product. A spiroketal bisphosphine derived chiral digold complex also allowed the cyclopropanation of diazooxindoles with *cis*- and *trans*-1,2-disubstituted alkenes (Scheme 1.93, eq 2) [374].

Finally, a particular metal-catalyzed decomposition of diazoalkanes is represented by the cyclopropanation of a variety of acrylamides and acrylates with ethyl diazoacetate catalyzed by a variant of cytochrome P450 from *Bacillus megaterium* five mutations away from wild type. (1*S*,2*R*)-Diethyl 1-(4-methylphenyl)cyclopropane-1,2-dicarboxylate and 13 different (1*R*,2*S*)-alkyl 2-(*N*,*N*-dialkylcarbamoyl)-2-arylcyclopropanecarboxylates were obtained in 50–99% yields with 89 : 11 to 99 : 1 dr and 57–98% ee [375].



Scheme 1.93 Enantioselective mercury(II)-catalyzed cyclopropanation of diazooxindoles.

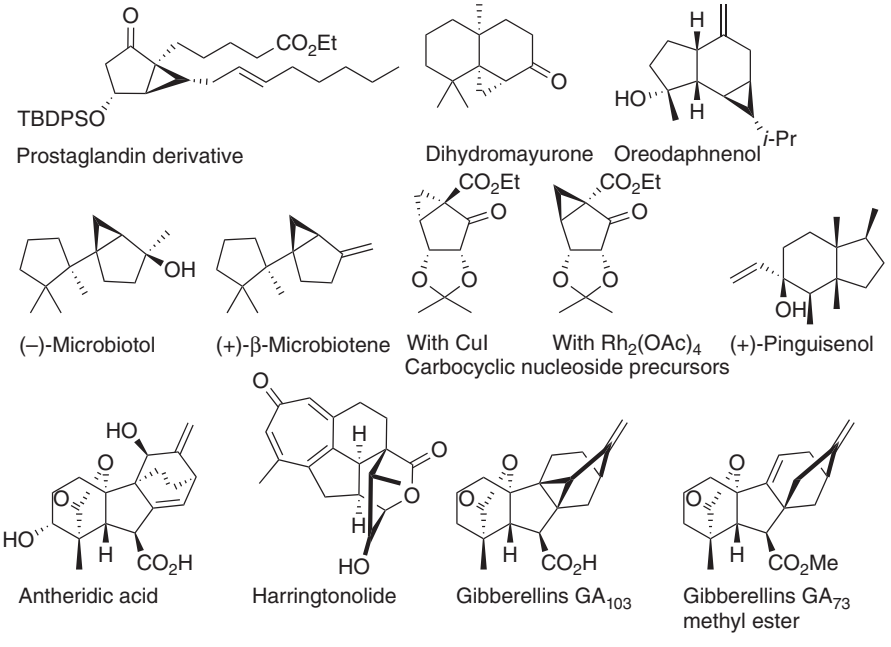
1.3.2 Intramolecular Cyclopropanation

When both functionalities, the diazo unit and the alkenes are in the same molecule, an intramolecular cyclopropanation is possible in the presence of the appropriate catalyst, thus generating synthetically versatile [*n*.1.0]bicycloalkanes. In contrast to the intermolecular reaction, only one diastereomer is obtained when forming five- or six-membered rings, thus the most successful systems involve cyclization of either γ,δ- or *δ,ε*-unsaturated diazocarbonyl systems. It is also possible to form macrocycles using the intramolecular cyclopropanation reaction, but the diastereoselectivity is no longer sure [376]. Finally, it is important to consider the chemoselectivity, as, in some cases, the C–H insertion may become the major pathway.

1.3.2.1 Chiral Auxiliaries and Chiral Compounds

Initially, intramolecular cyclopropanation reactions were carried out with an appropriate chiral substrate, and generally proceeded with complete stereocontrol, leading to the exclusive formation of one stereoisomeric bicyclic product. Homogeneous and heterogeneous copper and rhodium catalysts were more popular for this reaction. Systems that are less rigid, such as prostaglandin derivatives (Scheme 1.94), afforded a mixture of stereoisomers (91% yield, 69 : 31 dr) under rhodium catalysis [377].

Both copper and rhodium catalysts were used to synthesize terpenes such as dihydromayurone (36% and 57% yield of only one stereoisomer) [378], while



Scheme 1.94 Some molecules prepared by intramolecular cyclopropanation of chiral diazo compounds.

rhodium-catalyzed intramolecular cyclopropanation was employed in the synthesis of the tricarbocyclic framework (95% yield and with 97 : 3 dr) of oreodaphnenol (Scheme 1.94) [379]. A Cu-catalyzed intramolecular cyclopropanation (75% yield) allowed the synthesis of (–)-microbiotol and (+)-β-microbiotene from a chiral diazo ketone derived from the readily available cyclogeraniol [380].

Carbocyclic nucleoside precursors were prepared from ribose derivative (81% and 74% yield from copper and rhodium catalysis, respectively). It is worth noting that copper and rhodium catalysts gave rise to different stereoisomers (82 : 18 dr and 25 : 75 dr, respectively) [381].

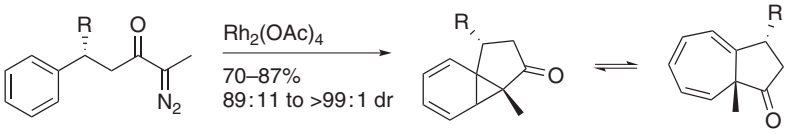
The key step in the construction of the bicyclic system of (+)-pinguisenol was based on the intramolecular cyclopropanation of a chiral diazoketone (52% yield with $CuSO_4$), followed by regioselective cyclopropane cleavage [382]. The combination of the intramolecular cyclopropanation of dienes with the vinylcyclopropane-cyclopentene rearrangement was employed as a key step in the total synthesis of antheridic acid [383].

The Buchner cyclization was investigated under rhodium catalysis by Maguire with chiral α-diazoketone derivatives (Scheme 1.95) [384] and exploited in the synthesis of the natural product harringtonolide [385]. On the other hand, gibberellin derivatives were obtained in the presence of a copper catalyst that minimized the formation of the significant amounts of a C–H insertion product observed with rhodium catalysts [386].

The substituents were found to play an important role in the double diastereotopic differentiation strategy of α-diazophosphonate templates with the (*R*)-pantolactone auxiliary using $Rh_2(OAc)_4$-catalyzed intramolecular cyclopropanation. Furthermore, the double diastereoselective intramolecular cyclopropanation of a pseudo-C_2-symmetric phosphonate was performed with excellent diastereoselectivity (Scheme 1.96) [387].

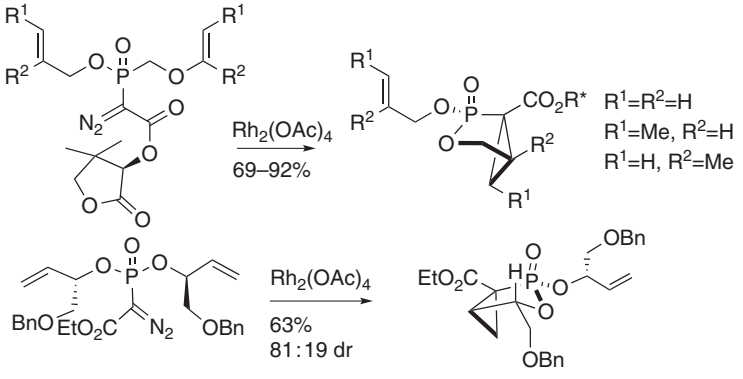
The intramolecular cyclopropanation of diazoacetates prepared from butane-2,3-diacetals of L-threitol in the presence of $Rh_2(OAc)_4$ afforded two cyclopropane diastereomers in a ratio of 70 : 30. Up to 91 : 9 dr was instead obtained in the presence of a chiral catalyst such as Rh_2(*S*-MEPY)$_4$, thus demonstrating that the trajectory of the double bond onto the metal carbene was dependent upon both the configurations of the catalyst and the reacting substrate (Scheme 1.97) [388].

Finally, a Mn(III)-mediated cyclopropanation of a chiral allyl acetoacetate led to the corresponding 3-oxabicyclo[3.1.0]hexan-2-one (Scheme 1.98) [389], then applied to the syntheses of several furofuranones and furofuran lignans. It should be noted that, in this case, the carbene was not obtained from diazoacetate decomposition.

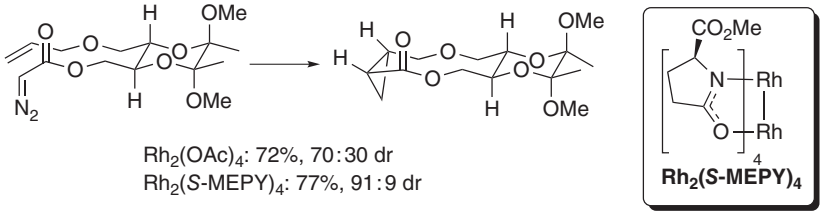


R=Me, Et, Pr, Bu, *i*-Pr, *t*-Bu

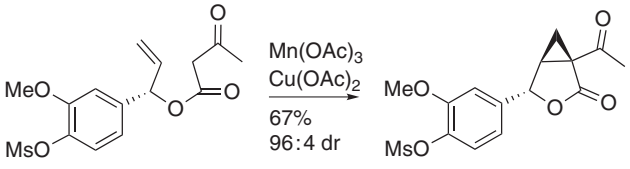
Scheme 1.95 Buchner cyclization.



Scheme 1.96 Asymmetric cyclopropanation of chiral diazophosphonates.



Scheme 1.97 Asymmetric cyclopropanation of butane-2,3-diacetal of L-threitol.



Scheme 1.98 Asymmetric cyclopropanation of chiral allyl acetoacetate.

1.3.2.2 Chiral Catalysts

Larger diffusion in the chemical community had found chiral catalysts for the enantioselective intramolecular cyclopropanation of unsaturated diazoketones. Cobalt, copper, rhodium, and ruthenium catalysts described in Sections 1.3.1.2–1.3.1.6 as well as new specific metal catalysts have been applied to the intramolecular cyclopropanation. The effectiveness of each catalyst changes with the substitution and the ring size of the fused cyclopropane [390].

In general, dirhodium(II) carboxamidate catalysts are superior for small-ring fused cyclopropane compounds, whereas the copper(I) bis(oxazoline) catalysts for medium/large-ring fused cyclopropane compounds. Ruthenium and cobalt catalysts are useful in the synthesis of trisubstituted cyclopropanes, especially when involving the formation of five- and six-membered rings. On the other

hand, diazocarbonyl compounds in intramolecular processes can be divided into three major categories:

i) diazoketones
ii) diazoesters
iii) diazoacetamide derivatives.

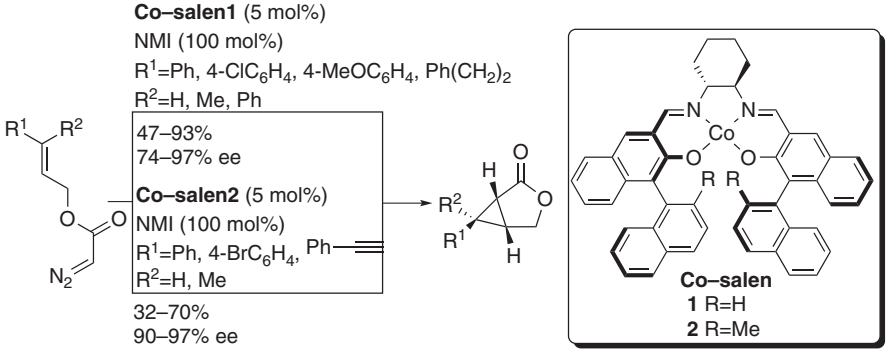
Semicorrin copper complex **box1** was the most efficient and frequently used catalyst to ensure enantiocontrol for a long period of time [391]. Up to 95% ee was obtained, depending on the substrate, but the yields were always modest (<60%) In comparison, other catalysts led to a low level of induction [392]. Only *ortho*-metallated aryl phosphine dirhodium(II) complexes (Scheme 1.67, group **b**) provided the desired cyclopropane products in very high yield (>90%) and with enantioselectivities comparable to those achieved with Cu-**box1** [393].

The most efficient enantioselective intramolecular reaction is summarized here following the same order used earlier for intermolecular reactions.

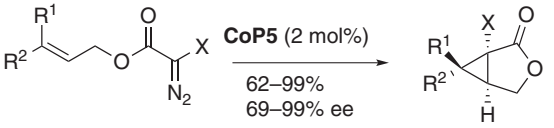
Among chiral cobalt catalysts, salen complexes were found to be very efficient (Scheme 1.99). These catalysts were found to be superior to the corresponding Ru(II) salen complexes (see the following discussion) [394].

Cobalt(II) porphyrin (**CoP5**, Table 1.2) [395] and bis(2-pyridylimino)isoindoles complexes (Co-**Isoind**, Scheme 1.54) [158] were also employed to synthesize [*n*.1.0]bicyclic ring systems directly from linear unsaturated diazo precursors (Scheme 1.100). It should be noted that the two catalysts afforded enantiomeric products 1*R*,5*S*,6*S* and 1*S*,5*R*,6*R*, respectively. In particular, with the former complex, the absolute configuration was in agreement with the absolute (*R*,*R*)-configuration of the Z-substituent in **CoP5**.

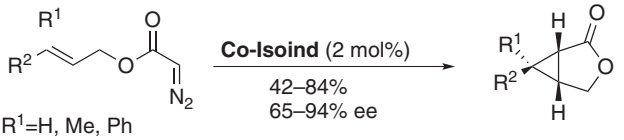
Moreover, the corresponding 3-oxabicyclo[3.1.0]hexan-2-one was generated as a single diastereomer, except for compounds with R^2=PhCH=CH, R^1=H and R^2=H, R^1=Et. These results were consistent with the stepwise radical mechanism described in Scheme 1.53, also demonstrating that the last ring-closure step is a low-barrier or a barrierless process. The γ-butyrolactone unit was selectively opened to produce examples of cyclopropane derivatives difficult to be prepared directly by asymmetric intermolecular cyclopropanation, and the cyclopropane unit was successfully



Scheme 1.99 Asymmetric intramolecular cyclopropanation catalyzed by Co-salen complexes.

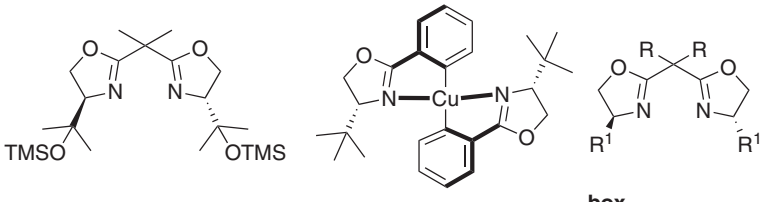


X=CN, NO_2, COR, CO_2R, H, Me R_1=H, Me, Et
R^2=H, Ph, 4-*t*-BuPh, *p*-Tol, *o*-Tol, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 2-furyl, 3-*N*-Boc-indolyl, PhCH=CH



R^1=H, Me, Ph
R^2=H, Ph, *p*-Tol, 4-BrC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$

Scheme 1.100 Other cobalt(II) complexes in intramolecular cyclopropanation.



box41

Cu-box42

box
43: R=Bn, R^1=*i*-Pr
44: R=R^1=Me
45: R=H, R^1=Bn

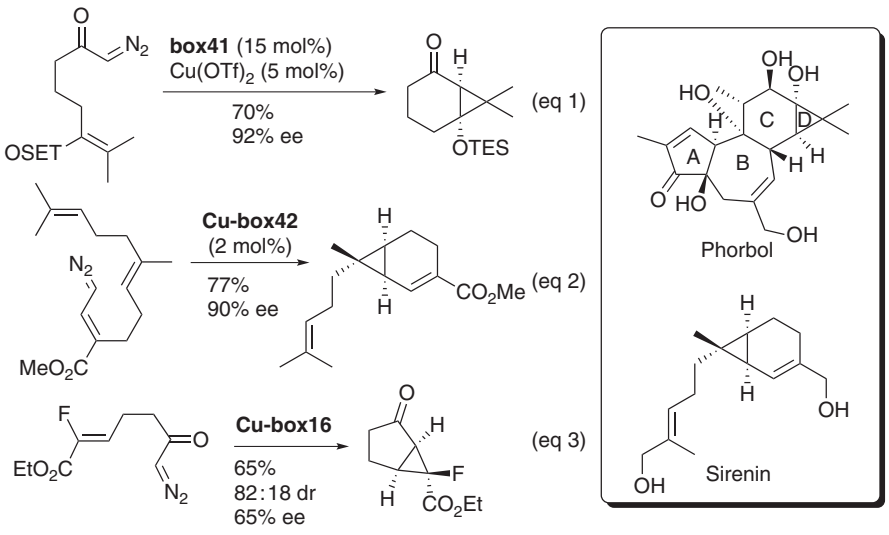
Scheme 1.101 Other box ligands proposed for intramolecular copper-box-catalyzed cyclopropanation.

enlarged through 1,3-dipolar cycloaddition with dipolarophiles. Both reactions proceeded to form a single diastereomer without loss of optical purity.

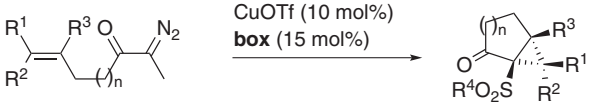
Regarding copper catalysts, in addition to the aforementioned copper–semicorrin Cu-**box1**, other catalysts have been employed in asymmetric intramolecular cyclopropanations (Scheme 1.101). For instance, the synthesis of the phorbol CD-ring skeleton was achieved through the asymmetric intramolecular cyclopropanation of a silyl enol ether with the catalyst obtained mixing 15 mol% of the **box41** ligand and 5 mol% of $Cu(OTf)_2$ (Scheme 1.102, eq 1) [396]. Corey reported the synthesis of a synthetic precursor of sirenin by cyclization of a γ-diazocarbonyl derivative (Scheme 1.102, eq 2) [397]. The classical Cu-box catalysts were scarcely efficient; thus, Corey designed a novel Cu-box catalyst (Cu-**box42**).

Cu-**box16** (Table 1.4) was an efficient catalyst for the preparation of an enantiopure fluorobicycloketone (Scheme 1.102, eq 3) [398].

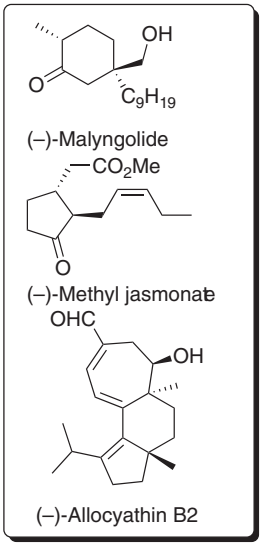
For a decade, Nakada's group was interested in the enantioselective Cu-**box**-catalyzed intramolecular cyclopropanations of a range of α-diazo-β-keto sulfones (Scheme 1.103) [399]. The cyclopropanes present a (1*R*,5*R*) stereochemistry, which is interestingly diastereomeric with respect to most of the other described



Scheme 1.102 Some copper-catalyzed asymmetric intramolecular cyclopropanations.



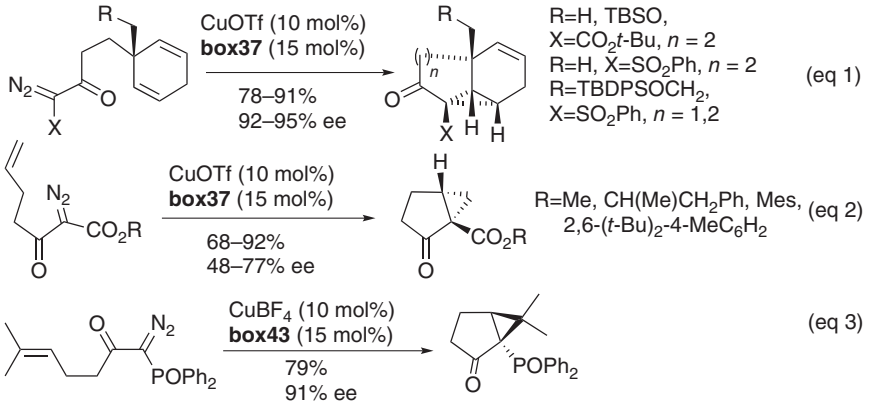
R^1	R^2	R^3	R^4	*n*	box	Y (%)	ee (%)
H	H	H	Ph	1	**43**	61	73
H	H	H	Mes	1	**43**	87	93
H	H	Me	Mes	1	**37**	96	81
H	H	Br	Mes	1	**37**	68	92
Me	Me	H	Mes	1	**37**	74	74
H	H	CH_2OTr	Mes	1	**44**	91	78
H	H	H	Ph	2	**37**	58	92
H	H	Me	Ph	2	**43**	62	93
H	H	H	Mes	2	**43**	31	98
H	H	Me	Mes	2	**43**	43	98
H	H	Ph	Mes	1	**43**	95	96
H	H	3,4-$(BzO)_2C_6H_3$	Mes	1	**43**	96	93
H	H	3,4-$(TBSO)_2C_6H_3$	Mes	1	**43**	77	55
H	H	3,4-$(OCH_2O)C_6H_3$	Mes	1	**43**	86	55
H	H	3,4-$(MeO)_2C_6H_3$	Mes	1	**43**	55	0



Scheme 1.103 Asymmetric intramolecular cyclopropanation of α-diazo-β-keto sulfones.

reactions. Studies on structure–enantioselectivity relationships were performed with the following results:

i) In compounds with R^3= 3,4-R_2Ph, no selectivity was observed when R = MeO, moderate enantioselectivity when R—R=OCH_2O or R=TBSO, and high enantioselectivity without substituents or when R=BnO [400].



Scheme 1.104 Preparation of tricyclo[4.4.0.0^7]dec-2-ene and cyclopropanation of α-diazo-β-keto esters.

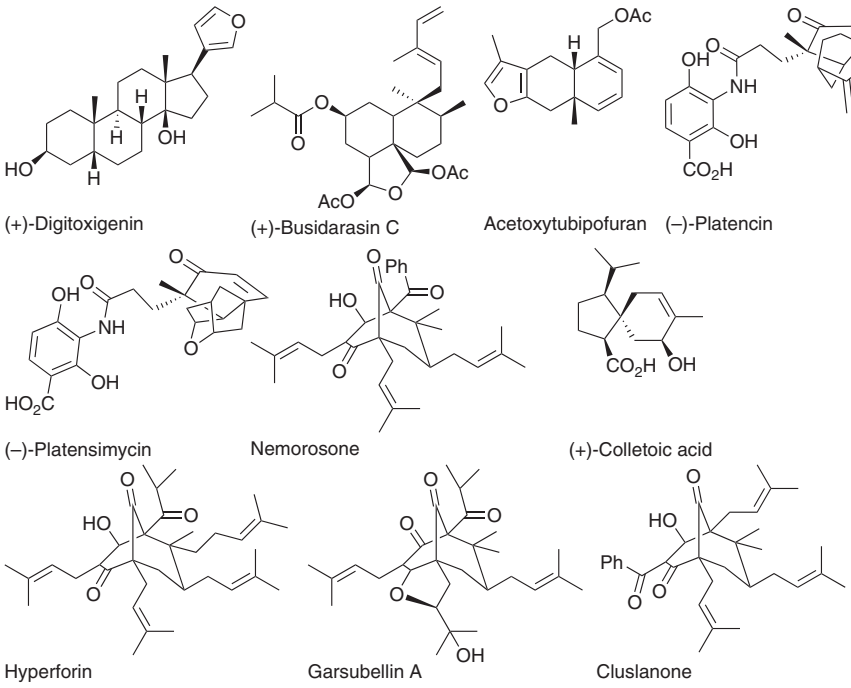
ii) High enantioselectivity was attained in particular when the methyl substitution on the phenyl ring of the sulfone moiety is in the 2-position [401].
iii) Regarding the R^1 group on the catalyst, the benzyl group was found to give the best enantiomeric excess, but the yield was only 67%, thus $R^2 = i$-Pr was preferred. The bulkiness of R group on the catalyst increased enantiomeric excess, but reaction yields decreased [402].

The success of this methodology prompted its application to the total syntheses of several biologically active products, such as (–)-allocyathin B_2 [403], (–)-malyngolide [404], and (–)-methyl jasmonate [405].

Nakada's group also developed the enantioselective preparation of tricyclo[4.4.0.0]dec-2-ene derivatives (Scheme 1.104, eq 1) [406] and tricyclo[4.3.0.0] nonenone in either catalytic (10 mol%) or stoichiometric amounts in 48% (66% conversion and 79% ee) and 69% yield (84% conversion and 80% ee), respectively [407]. The resulting chiral cyclopropanes were utilized for enantioselective syntheses of natural products (+)-busidarasin C, acetoxytubipofuran [406], (+)-digitoxigenin [408], (–)-platensimycin, (–)-platencin, nemorosone [407], garsubellin A, clusianone, and hyperforin (Scheme 1.105) [409].

The same methodology was also applied to the intramolecular cyclopropanation of various 2-diazo-3-oxo-6-heptenoic acid esters [the best enantioselectivities were achieved in the case of substrates bearing a bulky ester group (Scheme 1.104, eq 2)] [410] and to the reaction of α-diazo-β-oxo-5-hexenyl phosphonate in the presence of Cu-**box43** ligand (Scheme 1.104, eq 3) [411]. The obtained (1*R*,5*S*)-bicyclo[3.1.0]hexane was the key intermediate in the enantioselective total synthesis of (+)-colletoic acid (Scheme 1.105) [411].

A better enantiocontrol was observed with Cu-**box5** complex, increasing the ring size. Thus, allylic diazoacetate gave only 20% ee, whereas the formation of 10-membered rings proceeded with 87–90% ee. Moreover, Cu-**box5** complex exclusively favored the macrocyclic product over the allylic cyclopropanation product [412]. Comparable enantiomeric excesses (85% ee) were obtained for the

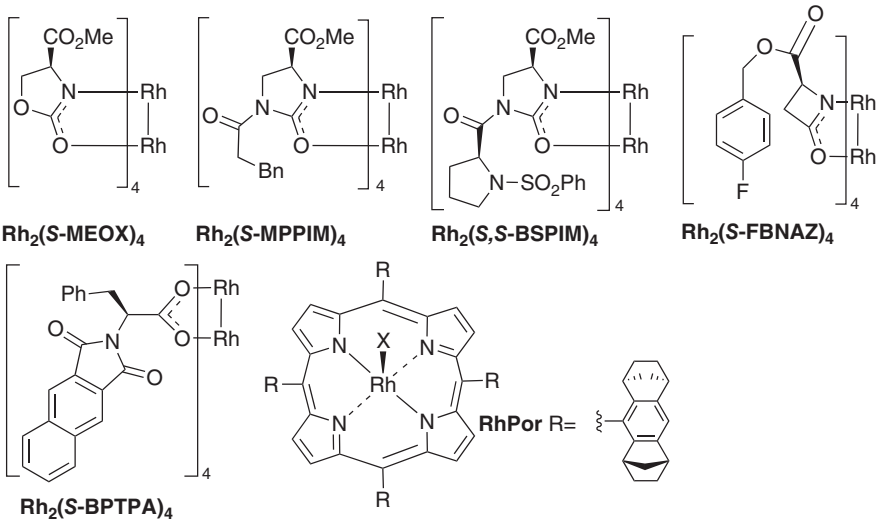


Scheme 1.105 Some natural products prepared from α-diazo-β-keto sulfones, esters, and phosphonates.

synthesis of 15- and 20-membered ring-fused cyclopropane products, although as a mixture of *cis*- and *trans*-isomers (69 : 31 dr).

The very unreactive diazomalonates were reported to react under Cu-**box45** catalysis in 72–73% yield with 11–35% ee [413].

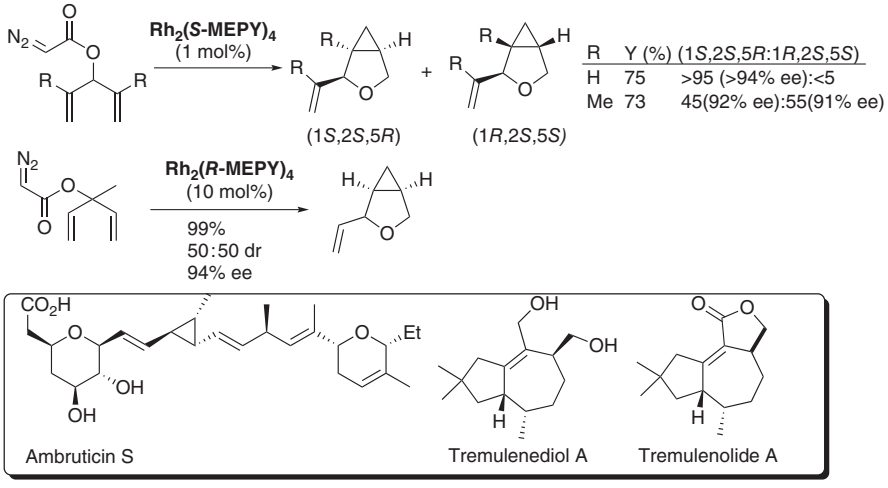
Chiral carboxylate and carboxamidate ligands were mainly developed in the preparation of dirhodium catalysts. In most cases, C_1-symmetric ligands from simple amino acids are coordinated around the dirhodium core to give the chiral rhodium catalysts. Catalysts already used in intermolecular reactions and new specific rhodium catalyst were employed. Generally, these catalysts, such as $Rh_2(MEPY)_4$, are more electron-rich compared to the tetracarboxylates and have a different reactivity profile [414]. For instance, in Scheme 1.96, $Rh_2(S\text{-}MEPY)_4$ has already been mentioned in the reaction of a chiral substrate. Moreover, this catalyst and $Rh_2(S\text{-}MEOX)_4$ (Scheme 1.106) provided 3-oxabicyclo[3.1.0]hexan-2-one from intramolecular cyclopropanation of allyl diazoacetate in 95% ee (75% and 95% yield, respectively) [415], whereas lower stereochemical induction was observed with ruthenium, copper, or other dirhodium catalysts. The enantioselectivity depends on the double-bond substitution. Indeed, (*E*)- and (*Z*)-(phenyl)allyl diazoacetate afforded the corresponding product in 78% and 70% yield with 68% and >94% ee, respectively. On the other hand, the catalyst $Rh_2(S\text{-}MPPIM)_4$ produced the desired bicyclic system from the (*E*)-isomer with >95% ee (61% yield) [416]. In addition, the cyclopropanation of farnesyl diazoacetate with $Rh_2(S\text{-}MEPY)_4$ exclusively formed the γ-lactone



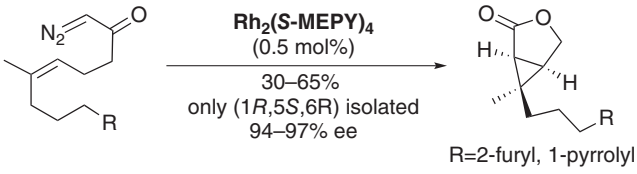
Scheme 1.106 Some dirhodium catalysts for intramolecular cyclopropanation.

[417]. It should be noted the different chemoselectivity with respect to Cu-**box5** complex, which always preferred the farthest double bond (see the previous discussion) [412].

Rh_2(*S*-MEPY)$_4$-catalyzed cyclization of allylic diazoacetates also led to 1,2,3-trisubstituted cyclopropanes, as rigid replacements of dipeptide arrays in several biological systems, with high enantiomeric excesses [418]. Moreover, Martin reported that secondary divinyldiazoacetates underwent cyclopropanation with exceptional enantiocontrol (Scheme 1.107) [419]. The presence of a methyl group in the diene system drastically decreased diastereoselectivity [420].



Scheme 1.107 Cyclopropanation of divinyldiazoacetates.



Scheme 1.108 Asymmetric intramolecular cyclopropanation of allyldiazoacetates.

This reaction was applied to the synthesis of ambruticin S [421], tremulenediol A, and tremulenolide A [422] and to the synthesis of various cyclopropane-derived peptidomimetics [423].

Homoallylic diazoacetates afforded the bicyclic products under Rh_2(*S*-MEPY)$_4$ catalysis in 55–80% yields with 71–90% ee [424], and it was found that the enantioselectivity was not highly dependent on the substitution pattern of the double bond. Rh_2(*S*-MEOX)$_4$ provided similar levels of enantiocontrol, whereas Rh_2(*S*-MPPIM)$_4$ was less enantioselective. It is also worth noting, but not too surprising, that the enantioselectivity decreased, increasing the ring size conversely from copper complexes (see the previous discussion) [412]. In fact, the formation of a macrocycle is more similar to intermolecular cyclopropanation, for which copper catalysts usually provided higher enantiomeric excesses. Finally, another application of Rh_2(*R*-MEPY)$_4$ is depicted in Scheme 1.108 [425].

Both Rh_2(*S*-MEPY)$_4$ and Rh_2(*S*-MEAZ)$_4$ were immobilized on an ArgoPore resin and tested in the enantioselective intramolecular cyclopropanation of allyl diazoacetates [295]. Up to 95% ee along with about 80% product yield was obtained.

Diazoacetamides (20–95% yields, 75–93% ee) underwent intramolecular cyclopropanation under Rh_2(*S*-MPPIM)$_4$ catalysis with an enantiocontrol similar to that found with diazoacetates (65–75% yields, 89–95% ee), especially with a methyl nitrogen substituent, which favors the desired *S-trans*-conformer, minimizing the amount of the undesired dipolar addition reaction [426]. The homoallylic diazoacetamide provided the bicyclic product, with slightly lower enantiomeric excesses. Moreover, one of the resulting cyclopropanated products from diazoacetate was converted into a highly potent group 2 and group 3 glutamate receptor agonist [319].

Doyle showed that Rh_2(*S*-MEOX)$_4$ provided the best enantiocontrol in the intramolecular cyclopropanation of substituted allyl diazoacetates, leading to the desired cyclopropanes with 71–85% ee and 43–52% ee for the *trans* and the *cis* starting materials, respectively, with yields ranging from 46% to 81% [427].

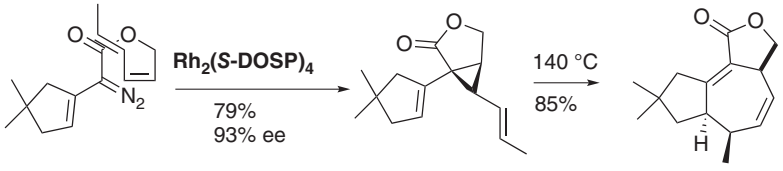
The diazo decomposition of vinyl- and aryl-substituted diazoacetates required a more reactive catalyst [428]. For instance, the cyclization of allyl α-styryl-α-diazoacetate proceeded in 81%, 59%, and 56% yields with 28%, 58%, and 59% ee with Rh_2(*R*-DOSP)$_4$, Rh_2(*S*-IBAZ)$_4$, or Rh_2(*S*-MEAZ)$_4$, respectively. Rh_2(*R*-DOSP)$_4$ catalyst was also examined with a wide range of substituted allyl α-styryl-α-diazoacetates, affording the expected products in 46–72% yields with 25–87% ee. The reactions of *cis*-alkenes resulted in much higher asymmetric induction compared to *trans*-alkenes, while the highest enantioselectivity was achieved with a disubstituted terminal alkene. On the other hand, Rh_2(*S*-MEAZ)$_4$ proved to be equally effective or more effective than Rh_2(*R*-DOSP)$_4$ for the enantioselective

cyclization of allyl α-phenyl-α-diazoacetates. With an unsubstituted allyl group, the desired bicyclic system was isolated with 68% ee, instead of 36% ee, but the yield was 80% instead of 93%, whereas with a 1,1-disubstituted alkene, the enantiomeric excess was 45%, and the product was recovered in 85% yield. It should be noted that the bicyclic lactones have opposite configuration in the reaction of allyl α-styryl-α-diazoacetates and allyl α-phenyl-α-diazoacetates, although the catalysts have the same configuration. The reaction catalyzed with azetidinone-carboxylate (AZ) ligands was then improved and a series of substituted allyl α-phenyl-α-diazoacetates were cyclized in 74–93% yields with 45–84% ee [429].

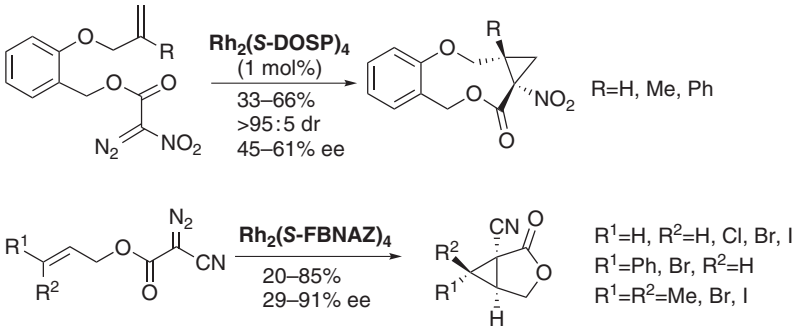
The intramolecular cyclopropanation of vinyldiazoacetates and dienes, followed by a Cope rearrangement of the resulting divinylcyclopropane intermediate, afforded fused cycloheptadienes, which are intermediates in the asymmetric synthesis of the *epi*-tremulane skeleton (Scheme 1.109) [430].

Charette *et al.* reported an intramolecular cyclopropanation involving α-nitro- [149] and α-cyano- [431] α-diazo carbonyl compounds. The former reaction, catalyzed by Rh_2(*R*-DOSP)$_4$, led to the formation of nine-membered nitrocyclopropyllactones (Scheme 1.110), while the latter used Rh_2(*S*-FBNAZ)$_4$ as the chiral catalyst.

Furthermore, the asymmetric intramolecular cyclopropanation of allyl diazoacetates was performed in the presence of Rh**Por** in 31–65% yields with 31–49% ee [271]. In the presence of *ortho*-metallated arylphosphines dirhodium complex **b1** (Scheme 1.67 for the structure), allyl diazoacetate cyclized in 93% yield and with 56% ee [322c, 432]. Other chiral dirhodium(II) catalysts (**b2** and **b3**, Scheme 1.67) were employed in the enantioselective intramolecular cyclopropanation of 1-diazo-



Scheme 1.109 Synthesis of the *epi*-tremulane skeleton.



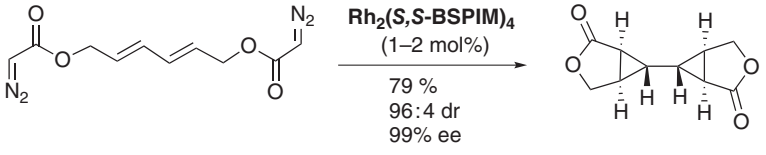
Scheme 1.110 Asymmetric intramolecular cyclopropanation of α-nitro- and α-cyano-α-diazo carbonyl compounds.

6-methyl-3-(2-propenyl)-5-hepten-2-one (up to 90% ee) [433] and in a total synthesis of sabina lactone [434].

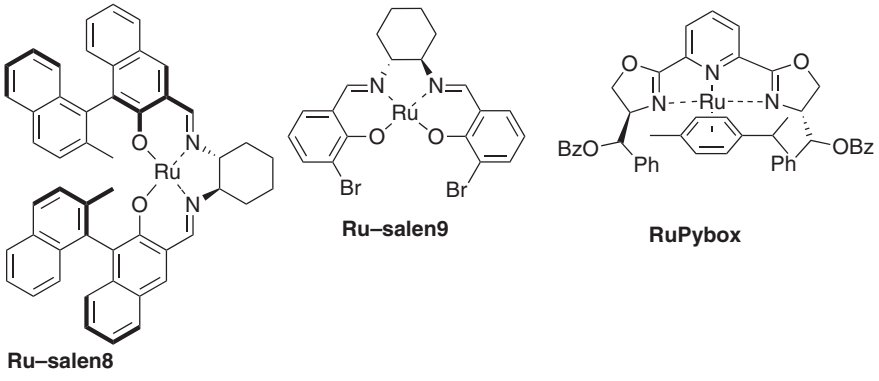
An interesting and original sequence of two successive intramolecular cyclopropanations involved a bis-diazoacetate under Rh_2(*S*,*S*-BSPIM)$_4$ catalysis (Scheme 1.111) [435].

Moreover, (triethylsilyl)-substituted allyl diazoacetate was decomposed with Rh_2(*S*-NTTL)$_4$ or Rh_2(*S*-BPTPA)$_4$ and the latter was more efficient (82% vs 76% yield and 56% vs 38% ee) [314]. The scope of this methodology was extended to allyl 2-diazo-3-silanyloxybut-3-enoates under Rh_2(*S*-PTTL)$_4$ catalysis and provided the corresponding lactones in 57–93% yields with 78–67% ee (1*R*,5*S*-isomer) [313c, 436].

Finally, several chiral ruthenium complexes have been used, in recent years, to catalyze the intramolecular cyclopropanation of allyl diazoacetates. As an example, Ru**Por** led to the corresponding (1*S*,5*S*)-lactones in 65–85% yields with 30–85% ee [271]. Ru-**salen3** (Scheme 1.86) and Ru-**salen8** (Scheme 1.112) were efficient catalysts to induce chirality for the intramolecular cyclopropanation of various alkenyl α-diazoacetates (33–82% yields with 33–89% ee) [343g, 394]. The cyclization was strongly affected by the substitution pattern of the alkenyl group of the substrate and the length of the carbon chain connecting the alkenyl and diazomethyl moieties. Ru-**salen4** was found to be a general catalyst for the asymmetric intramolecular cyclopropanation of *trans*-allylic diazoacetates leading to (1*S*,5*R*,6*R*)-3-oxabicyclo[3.1.0]hexan-2-ones (75–91% yields and 58–98% ee), while a *cis*-allylic diazoacetate gave lower enantiomeric excess value (51%) and



Scheme 1.111 Double intramolecular cyclopropanation of bis-diazoacetate.



Scheme 1.112 Chiral ruthenium catalysts for asymmetric intramolecular cyclopropanations.

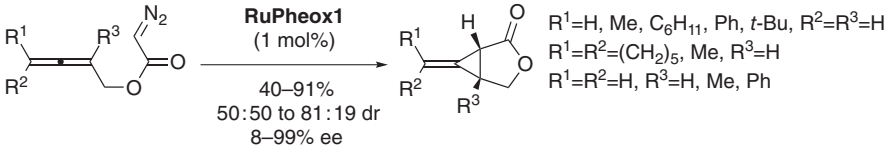
yield (48%), and the disubstitution gave similar yield (77%) but low enantiomeric excess value (58%) [437].

On the other hand, Ru-**salen9**, containing PPh_3 ligands, was effective in the intramolecular cyclopropanation of *cis*-substituted allylic diazoacetate (46–71% yields, 44–90% ee (1*S*,5*R*,6*S*-isomer)) [438]. The yields and stereochemical outcomes were consistent with those reported in Scheme 1.99 for the same reaction catalyzed by **CoP5**. DFT calculations at the 6-31G level suggested a reaction pathway involving a carbene, which replaced the apical ligand, thus the irradiation with light became essential, because the apical CO ligand is difficult to remove. In contrast, Ru**Phebox** allowed the intramolecular reaction of *trans*-cinnamyl diazoacetate in 96% yield and with 99% ee with a opposite (1*R*,5*S*,6*S*)-stereochemistry, with respect to **CoP5** or Rh-**salen** [342]. Ru**Pybox** catalyst allowed the same reaction in up to 86% yield and with up to 77% ee depending on the solvent used [335].

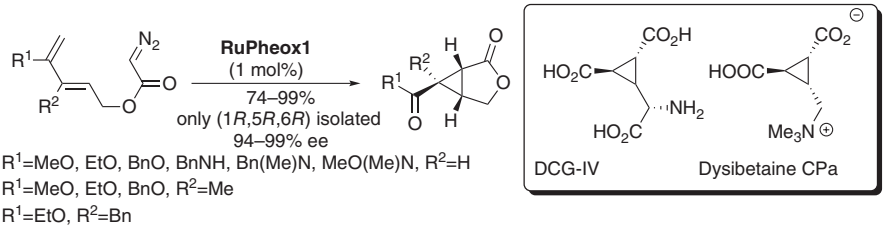
Ru**Pheox2** is completely water soluble and insoluble in diethyl ether; thus, Iwasa's research group reported an interesting intramolecular cyclopropanation in water as reaction medium. The easy separation of the ether phase, containing the cyclopropane product, from the catalyst in the water phase allowed for a very simple reuse of the catalyst at least five times without significant decrease in reactivity or enantioselectivity [359]. The reaction of *trans*-allylic diazoacetates afforded (1*S*,5*R*,6*R*)-3-oxabicyclo[3.1.0]hexan-2-ones in 89–99% yield with 83–98% ee, disubstituted allylic diazoacetates gave lower enantioselection (76–95% yield, 36–97% ee), while *cis*-allylic diazoacetates were not tested. It should be noted that Ru**Pheox2** supported on a macroporous polymer was more effective than the unsupported catalyst. In fact, *trans*-allylic diazoacetates reacted in less than a minute to give products in comparable yields and ee values.

Ru**Pheox1** successfully carried out the intramolecular cyclopropanation of various symmetric and racemic allenic diazoacetates to afford the corresponding bicyclic alkylidenecyclopropane fused γ-lactones (Scheme 1.113) [358]. In particular, racemic allenic diazoacetates with increasing R^1 substituent size improved diastereoselectivity (up to *E/Z* = 81 : 19), but the enantioselectivity of the *E*-isomer fell up to 48% ee. Moreover, lower yield (up to 40%) and enantioselectivity (up to 8%) were obtained increasing R^3 substituent size.

Finally, the enantioselective intramolecular cyclopropanation of electron-deficient allylic diazoacetates, in the presence of **RuPheox1,** was reported (Scheme 1.114). One of the corresponding cyclopropane-fused γ-lactones was the key intermediate in the synthesis of DCG-IV and dysibetaine CPa [439].



Scheme 1.113 Asymmetric intramolecular cyclopropanation of various allenic diazoacetates.



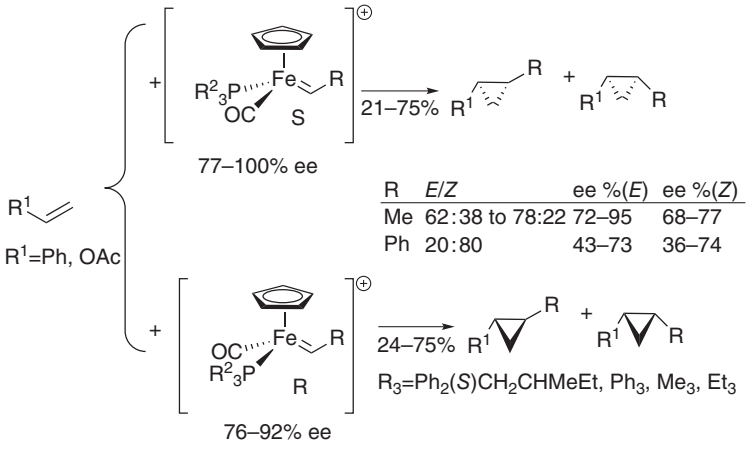
Scheme 1.114 Asymmetric intramolecular cyclopropanation of various electron-deficient allylic diazoacetates.

1.3.3 Chiral Stoichiometric Carbenes

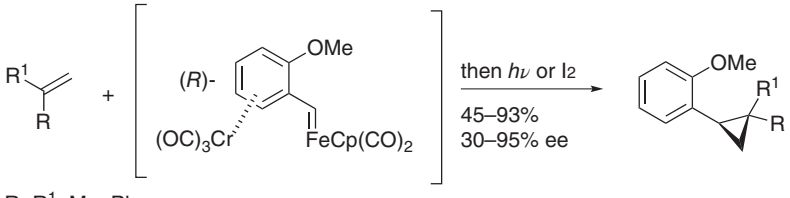
In the previous sections, transition-metal-catalyzed cyclopropanation of olefins with diazo reagents have been presented. In addition, some chiral stoichiometric metal carbene systems as cyclopropanating reagents have been reported in the literature, although they have not been used extensively.

Since 1974, chiral iron complexes have been used in the stereoselective synthesis of cyclopropanes, but only 40% ee was observed for the methylene transfer [440]. Much higher enantioselectivities could be achieved when the carbene carbon was prochiral (Scheme 1.115) [441]. Typically, *trans*-methyl *cis*-phenylcyclopropanes were preferentially obtained.

Hossain reported the cyclopropanation reactions of optically pure (+) or (–) iron carbene complexes, prepared from iron and chromium complexes and aldehydes (Scheme 1.116) [442]. The reaction was also applied to the synthesis of a precursor for cilastatin. The origin of diastereoselectivity resided in the stability of the carbene and in a late transition state, which accounted for the *trans*-selectivity observed with nonaromatic alkenes, while the *cis*-isomer with aromatic alkenes was explained by the formation of a strong π-stacking effect.



Scheme 1.115 Alkylidene asymmetric transfer from chiral cationic iron–carbene complexes.



R=R^1=Me, Ph
R=H, R^1=Ph, *p*-Tol, 4-ClC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$ *cis: trans* 75:25 to 91:9
R=H, R^1=Me, vinyl *cis: trans* 25:75 to 12:88

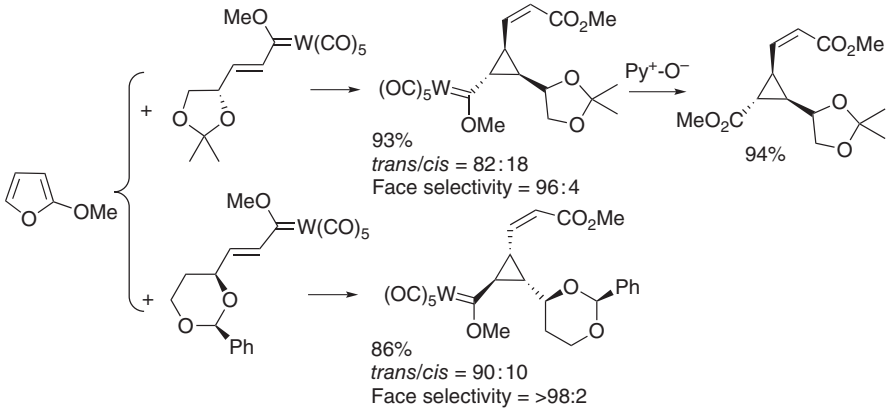
Scheme 1.116 Carbene transfer from chiral cationic iron–chromium complexes.

Chiral oxazolines were used as chiral auxiliaries for the cyclopropanation with chromium complex with 55:45 to 94:6 dr and 70–99% ee, but, unfortunately, the chiral auxiliary could not be removed without destroying the cyclopropyl moiety [443].

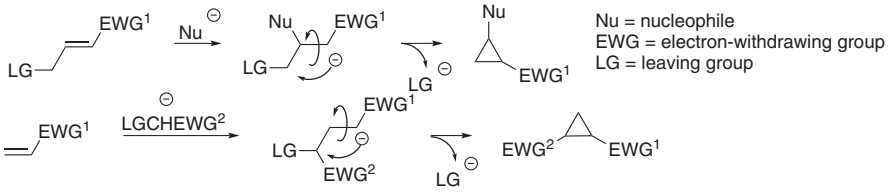
Chiral Fischer carbene complexes derived from tungsten allowed the cyclopropanation of 2-methoxyfuran. The reaction involved the conjugate nucleophilic addition of 2-methoxyfuran to the carbene complex, followed by ring closure of the resulting zwitterionic intermediate species. Finally, oxidation of the resulting carbene gave rise to the corresponding enantiopure 1,2,3-trisubstituted cyclopropane (Scheme 1.117) [444].

1.4 Michael-Initiated and Other Ring Closures

Michael-initiated ring-closure (MIRC) reactions are a very successful method for obtaining cyclopropanes. These reactions involve a conjugate addition to an electrophilic alkene generally to produce an enolate, which then undergoes an



Scheme 1.117 Asymmetric cyclopropanations with Fischer tungsten-derived carbene complexes.



Scheme 1.118 Michael-initiated ring-closure cyclopropanation reaction.

intramolecular ring closure. Stereospecific cyclopropanation reactions using the MIRC reaction are observed only when the ring-closure process is faster than the rotation around the single bond in the first intermediate formed (Scheme 1.118), or when the first intermediate is configurationally stable, for example, by intramolecular hydrogen or coordination bonds. Two types of substrates/reactants can give rise to MIRC reactions:

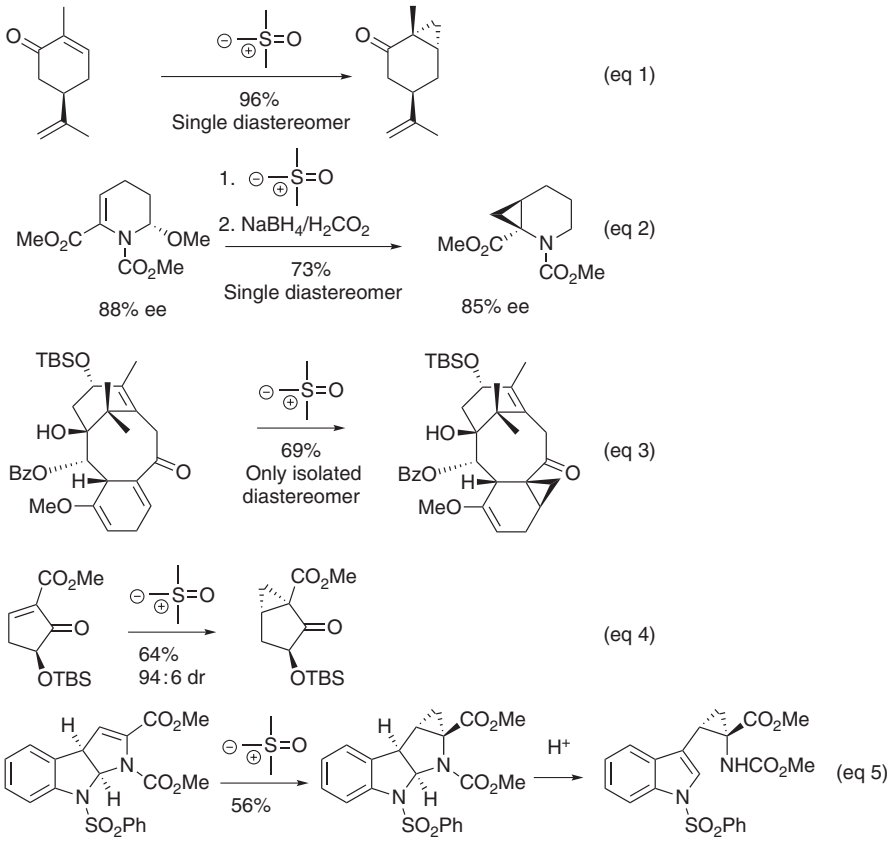
i) Nucleophiles, such as alkoxides, thiolates, cyanides, enolates, Grignard reagents, hydrides, phosphites, and phosphonites, which add to electrophilic substrates containing a leaving group
ii) Nucleophiles containing the leaving group, such as α-halo carbanions or sulfur, phosphorus, arsenium, and telluronium ylides, which add to electron-deficient olefins.

Although chiral auxiliaries linked to the electrophilic moiety have been the choice for ensuring asymmetric induction in the past, more recently, the growing popularity of organocatalysis has prompted organic chemists to meet the challenge and to carry out MIRC reaction using this approach.

1.4.1 Chiral Substrates

The reactions involving sulfur ylides and enantiomerically pure cyclohexanone derivatives are well known to proceed with very high diastereoselectivities under steric control.

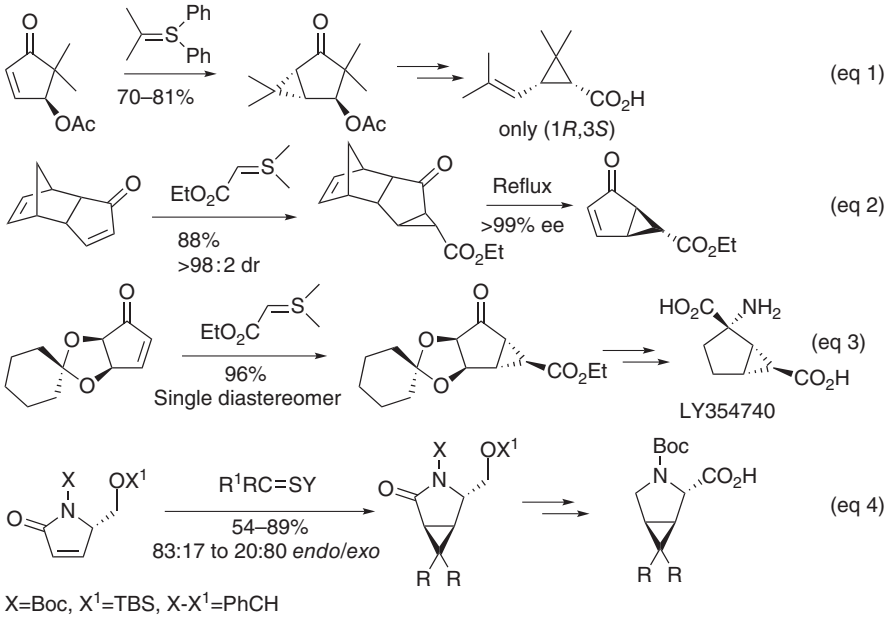
For example, the cyclopropanation of (*R*)-carvone with methylenedimethylsulfoxonium provided the desired cyclopropylcarvone, as the single diastereoisomer resulting from the attack of the ylide on the less-hindered face (Scheme 1.119, eq 1) [445]. Enantioenriched 2,3-methanopipecolic acid was prepared under similar conditions (Scheme 1.119, eq 2) [446]. Only one diastereoisomer of 7,8-cyclopropyltaxol (a potent taxol analogue) was successfully obtained when methylenedimethylsulfoxonium was used. The selectivity could be easily explained by steric arguments, as the bottom face of the enone is blocked by the A ring (Scheme 1.119, eq 3) [447]. A diastereoselective intermolecular cyclopropanation involving the addition of methylenedimethylsulfoxonium ylide to a chiral cyclopentanone derivative allowed the formation of bicyclo[3.1.0]hexane (Scheme 1.119, eq 4) [448]. Another example of sulfur ylide chemistry was the synthesis of an enantiomerically pure cyclopropatryptophan derivative (Scheme 1.119, eq 5) [449]. In the last two reactions, the observed stereochemical outcome is originated by the sulfur ylide attack from the more accessible convex face of the starting compound.



Scheme 1.119 Reactions involving methylenedimethylsulfoxonium ylide.

Isopropylidenediphenylsulfonium ylide reacted with suitably 4-functionalized 5,5-dimethyl-2-cyclopentenones to give only one stereoisomer of bicyclo[3.1.0]hexane derivatives, which was converted into (+)-*cis*-chrysanthemic acid (Scheme 1.120, eq 1) [450]. The cyclopropanation of (+)-dicyclopentadienone, readily available by enzymatic resolution, exclusively occurred from the convex face of the bicyclic system and afforded a single diastereoisomer (Scheme 1.120, eq 2) [451].

The asymmetric synthesis of LY354740, a potent and selective agonist for a glutamate receptor involved in the mammalian central nervous system, was achieved by the cyclopropanation of a protected dihydroxycyclopentenone, which exclusively afforded the *exo*-product (Scheme 1.120, eq 3) [452]. Analogously, the total syntheses of 4-acylamino analogs of LY354740 were achieved by the cyclopropanation of (*S*)-*tert*-butyl 4-oxocyclopent-2-enylcarbamate with $Me_2S{=}CHCO_2Et$, which worked in 73% yield producing a single diastereomer [453]. 3-Aza-bicyclo[3.1.0] hexane ring systems (a proline template amino acid) were obtained from *O*,*N*-acetal and *N*-Boc-pyrrolinone with sulfur ylides by the cyclopropanation of the less-hindered *exo*-face [454]. Only the unsubstituted cyclopropane derived from Boc-pyrrolinone was recovered in trace from $Me_2S(O){=}CH_2$ and in 19% yield from



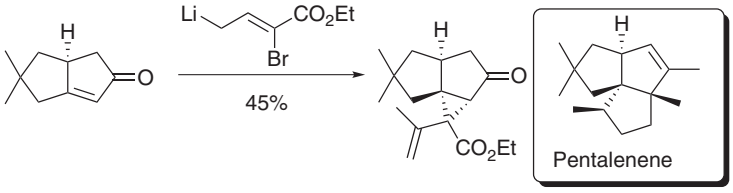
Scheme 1.120 Reactions involving other sulfur ylides.

$Ph(NMe)_2S(O){=}CH_2$ (Scheme 1.120, eq 4). The *endo*:*exo* ratio varied with the substituent on the ylide and the substrate. It is worth noting that, in all the reactions described in eqs 2–4, the acidity of the methine proton was not a problem.

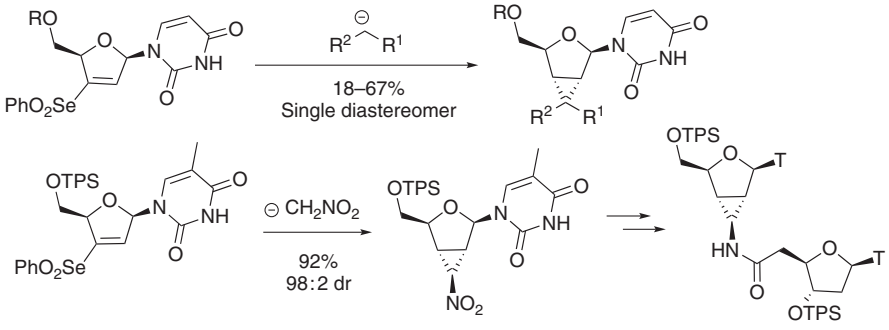
Lithium dienolate anion from ethyl 2-bromocrotonate was another reagent for cyclopropanation reactions as depicted in Scheme 1.121 [455]. The resulting cyclopropane ring was built at the more accessible face, but the diastereomeric ratio at the ester center could not be controlled. This compound is a key intermediate in the synthesis of pentalenene, involved in the biogenesis of the antibiotic pentalenolactone.

Chattopadhyaya used a 5′-protected α,β-ene-3′-phenylselenone as a synthetic equivalent of a $(CH_2)_2^{2+}$ ion in the reaction with carbon dinucleophiles such as sodium malonate, and conjugate bases of nitromethane, acetophenone, isobutylcyanoacetate, and both methylene bis-diethylphosphate and bis-phenylsulfone, to give bicyclo[3.1.0]cyclopropane analogues of 2′,3′-dideoxyuridine (Scheme 1.122) [456]. In all cases, the isomer resulting from the delivery of the methylene group on the more accessible face of the dideoxynucleoside was exclusively formed. The same procedure was then applied to the preparation of a conformationally constrained dimeric building block containing cyclopropylamide functionality [457].

In acyclic systems, the highest selectivities were generally observed with conformationally constrained alkenes. For example, (*S*,*E*)-methyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate reacted with 2-lithio-2-propyl-*N*-tosylisopropylsulfoximide and isopropylidenetriphenylphosphorane mainly leading to the corresponding (1*S*,3*S*)-2,2-dimethylcyclopropanecarboxylate from attack at the *Si*-face (93:7 and



Scheme 1.121 MIRC Reaction of an enone.

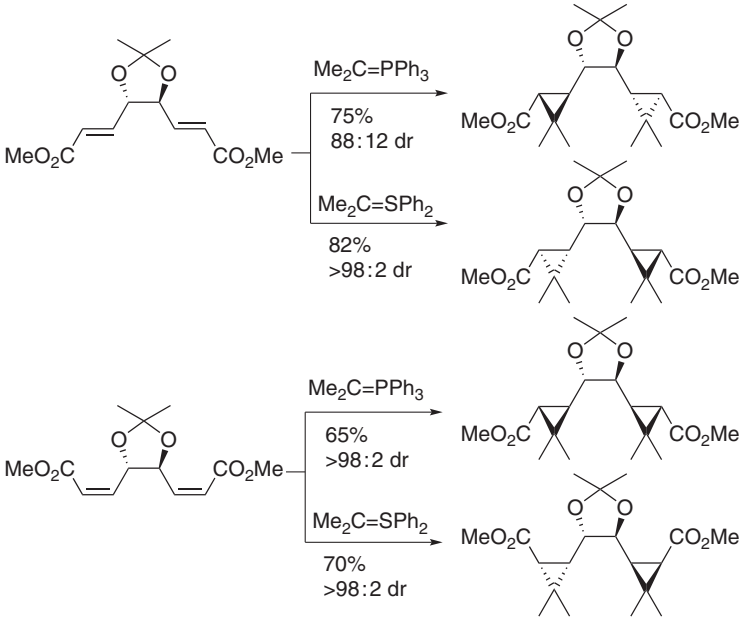


Scheme 1.122 Synthesis of cyclopropyl nucleoside derivatives.

90:10 dr, respectively) [458]. On the other hand, isopropylidenediphenylsulfurane attacked the *Re*-face of the alkene (98:2 dr in favor of the (1*R*,3*R*)-isomer).

With the (*S*,*Z*)-acrylate, the attack of all three reagents occurred on the *Re* face. However, the reaction of the sulfur ylide led to the formation of the *cis*-cyclopropane (98:2 dr in favor of the (1*S*,3*R*)-isomer), while both the phosphorus and lithium reagents led to the isomerized *trans*-cyclopropanes (94:6 and 61:39 dr in favor of the (1*R*,3*R*)-isomer, respectively). The authors proposed models to rationalize these results only with phosphorus and lithium reagents, but not with sulfur ylide. Other acrylates from D-glyceraldehyde gave similar results [459], as well as the cyclopropanation of dimethyl alkylidene malonate with either sulfur or phosphorus ylides occurred in >98:2 dr (2*S*) and 76% and 80% yields, respectively [460]. The methodology was also applied to the synthesis of (2*S*,1′*S*,2′*S*)-(carboxycyclopropyl) glycine, and best results were obtained with methylenedimethylsulfoxonium ylide at low temperature (73% yield, 95:5 dr) [461]. A series of 1,2,3-trisubstituted cyclopropanes were also prepared from enones derived from (*S*)-glyceraldehyde acetonide and Garner's aldehyde [(*S*)-3-Boc-2,2-dimethyloxazolidine-4-carboxaldehyde] and sulfur ylides in 24–96% yields [462]. Good diastereoselectivities were achieved with ester-substituted ylides, leading mainly to *all-R* products and (1*R*,2*S*,3*R*,ω*R*)-isomer[6] from *E* and *Z* isomers, respectively, whereas with amide-substituted ylides, the yields and the selectivities were unsatisfactory. This approach was extended to C_2-symmetric bis-(unsaturated esters) from tartaric acid, which afforded products easily transformable into *trans*-chrysanthemic acid or its analogs (Scheme 1.123)

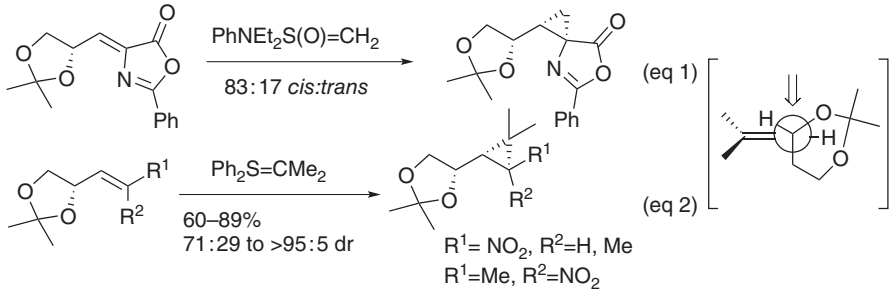
[6] Pay attention that the new substituents also make (*R*) the stereocenter of the glyceraldehyde moiety, although it is not changed.



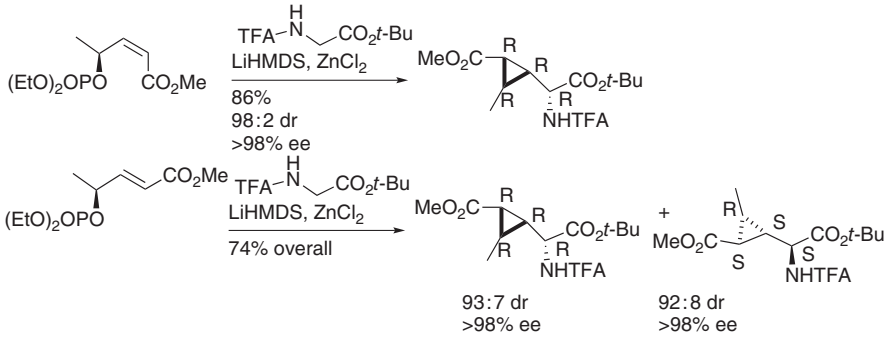
Scheme 1.123 Diastereoselective cyclopropanation of bis(unsaturated esters).

[463]. In this case, the *Z*-to-*E* isomerization of the *Z*,*Z* isomer with phosphorus ylide is worth noting. A further evidence was the reaction with only 1 equiv. of phosphorus ylide, in which a 1:1:1 mixture of starting material, (*E*)-monoadduct, and product was recovered. Conversely, the (*Z*)-monoadduct resubmitted to the same reaction conditions affords the (1*S*,1′*S*,3*S*,3′*S*)-isomer and not the expected (1*R*,1′*S*,3*R*,3′*S*)-isomer.

The cyclopropanation of other derivatives of chiral 1,2-*O*-isopropylideneglyceraldehyde, namely (*Z*)-oxazolone and nitroalkenes derivatives, was performed with methylene(diethylamino)phenylsulfoxonium ylide (Scheme 1.124, eq 1) [464] and with isopropylidenediphenylsulfonium ylide, respectively (Scheme 1.124, eq 2) [465]. The sense of induction was predicted by the conformation depicted in Scheme 1.124.



Scheme 1.124 Cyclopropanation of chiral (*Z*)-oxazolone and nitroalkenes.



Scheme 1.125 Syntheses of chiral cyclopropyl amino acids.

The Zn-chelate-glycine ester enolates were highly efficient nucleophiles in MIRC reaction on methyl 4-(diethoxyphosphoryloxy)pent-2-enoate (Scheme 1.125) [466]. In particular, the reaction of the *Z*-isomer gave only one stereoisomer with up to four stereogenic centers created in one step.

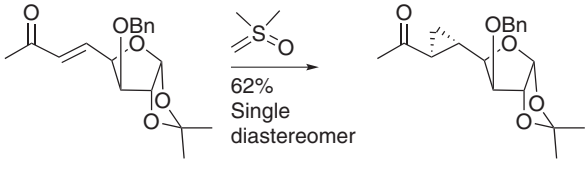
The asymmetric cyclopropanation of a chiral olefin derived from D-glucose with trimethylsulfoxonium ylide afforded the corresponding cyclopropane as a single product, which was the key intermediate in a carbohydrate-based approach for the enantioselective synthesis of the polyketide acid unit present in nagahamide A (Scheme 1.126) [467].

1.4.2 Chiral Auxiliaries

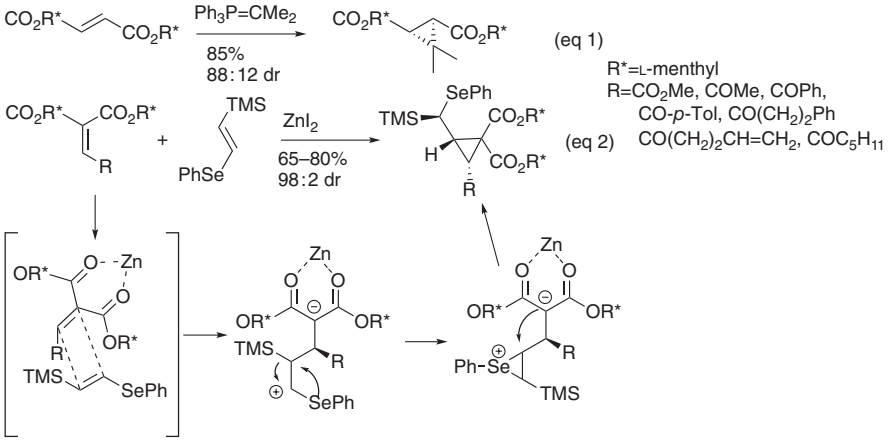
1.4.2.1 Chiral Michael Acceptors

The first class of chiral auxiliaries, used as Michael acceptors, were α,β-unsaturated chiral esters, but low diastereoselectivities were generally observed in the most ancient papers [468]. Later, menthyl esters as chiral auxiliaries were employed (Scheme 1.127, eq 1) [469]. The surmised reaction course for the cyclopropanation with 1-seleno-2-silylethene (Scheme 1.127, eq 2) contemplated the nucleophilic addition of the vinylselenide to the unsaturated ester, activated by the Lewis acid. Steric repulsion between the selenium and the isopropyl moiety of the menthyl group favored the approach from the less-hindered *Re*-face.

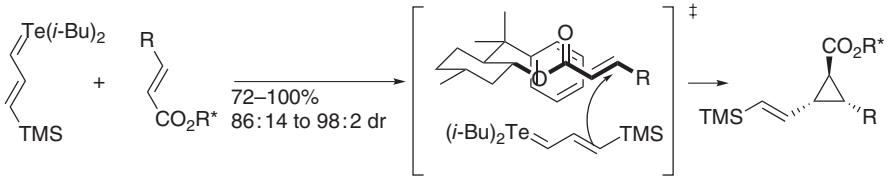
(–)-8-Phenylmenthyl α,β-unsaturated esters were able to react with silylated allylic telluronium ylide. The aryl group very likely blocked the *Si*-face of the alkene by a π-stacking effect between the phenyl and the dienyl groups of the α,β-unsaturated ester, thus the telluronium ylide attacked at C-3 on the *Re*-face (Scheme 1.128) [470].



Scheme 1.126 Asymmetric cyclopropanation of D-glucose-derived enone.



Scheme 1.127 Menthyl esters as chiral auxiliaries.



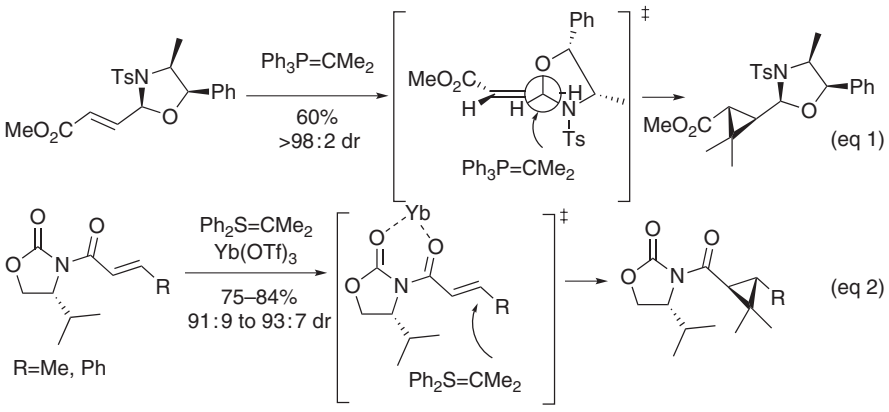
R*=(–)-8-phenylmenthyl, R=H, Ph, 4-ClC_6H_4, 4-FC_6H_4, *p*-Tol, 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$

Scheme 1.128 Telluronium ylide addition to chiral α,β-unsaturated esters.

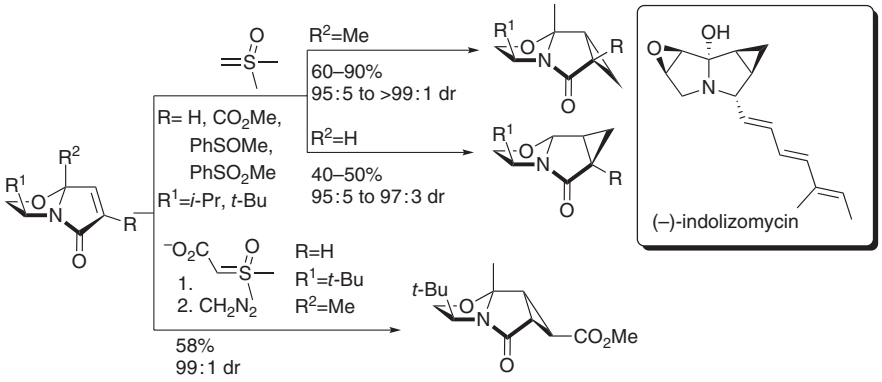
Scolastico described one example involving the reaction of a chiral γ-oxazolidine-substituted conjugated ester with isopropylidenetriphenylphosphorane with excellent π-face selectivity. The proposed transition state involved the conformer with minimum $A^{1,3}$-strain and with the most electronegative substituent (oxygen) perpendicular to the π orbital of the alkene (Scheme 1.129, eq 1) [471]. The cyclopropanation of chiral *N*-enoyloxazolidinones (Scheme 1.129, eq 2) with isopropylidenediphenylsulfonium ylide in the presence of Lewis acids proceeded with a good level of diasterocontrol, but cinnamoyloxazolidinone gave the lowest selectivity [472]. The Lewis acid, chelating both carbonyl groups, afforded a dominant reactive rotamer, in which one face of the β-carbon was shielded from attack. On the other hand, in the absence of the Lewis acid, free rotation around the C—N bond afforded low diastereoselectivity, and the rotamer with the isopropyl group far from the incoming ylide was favored, leading to slight predominance of the diastereomer with the cyclopropane and isopropyl moieties in *syn*-relationship.

Chiral bicyclic lactams prepared from L-valinol or L-*tert*-leucinol reacted with methylenedimethylsulfoxonium ylide with a high degree of *exo*:*endo*-diastereoselectivity, which, however, depends on the angular substituent of the unsaturated lactam (Scheme 1.130) [473]. Substituted sulfonium ylides were also employed:

i) Isopropylidenediphenylsulfonium ylide afforded the *gem*-dimethyl cyclopropyl adduct in 94% yield and >99:1 dr.



Scheme 1.129 Reaction of unsaturated chiral γ-oxazolidine derivatives.



Scheme 1.130 Cyclopropanation of chiral unsaturated lactams.

ii) Unsimmetrically substituted sulfonium ylides produced cyclopropanes in 41–95% yields with almost exclusive formation of the *endo*-isomer and 83:17 to >99:1 *syn:anti* ratios under kinetic control.
iii) Carboxymethylenesulfonium ylide led to the exclusive formation of the *anti*-isomer probably as a result of thermodynamic equilibration.

This method was also used for the preparation of a key precursor to (–)-indolizomycin [474].

Chiral auxiliaries were elaborated in order to enable a stereoselective cyclopropanation of an exocyclic double bond for the preparation of enantiomerically pure cyclopropyl α-amino acids [475].

An optically active vinyl sulfoxide was used as Michael acceptor with an allyl Grignard reagent leading to one diastereoisomer (Scheme 1.131, eq 1) [476].

The coordination of the Grignard reagent to the oxygen atom of the sulfinyl group was envisaged to explain the selectivity, the energetically more favorable

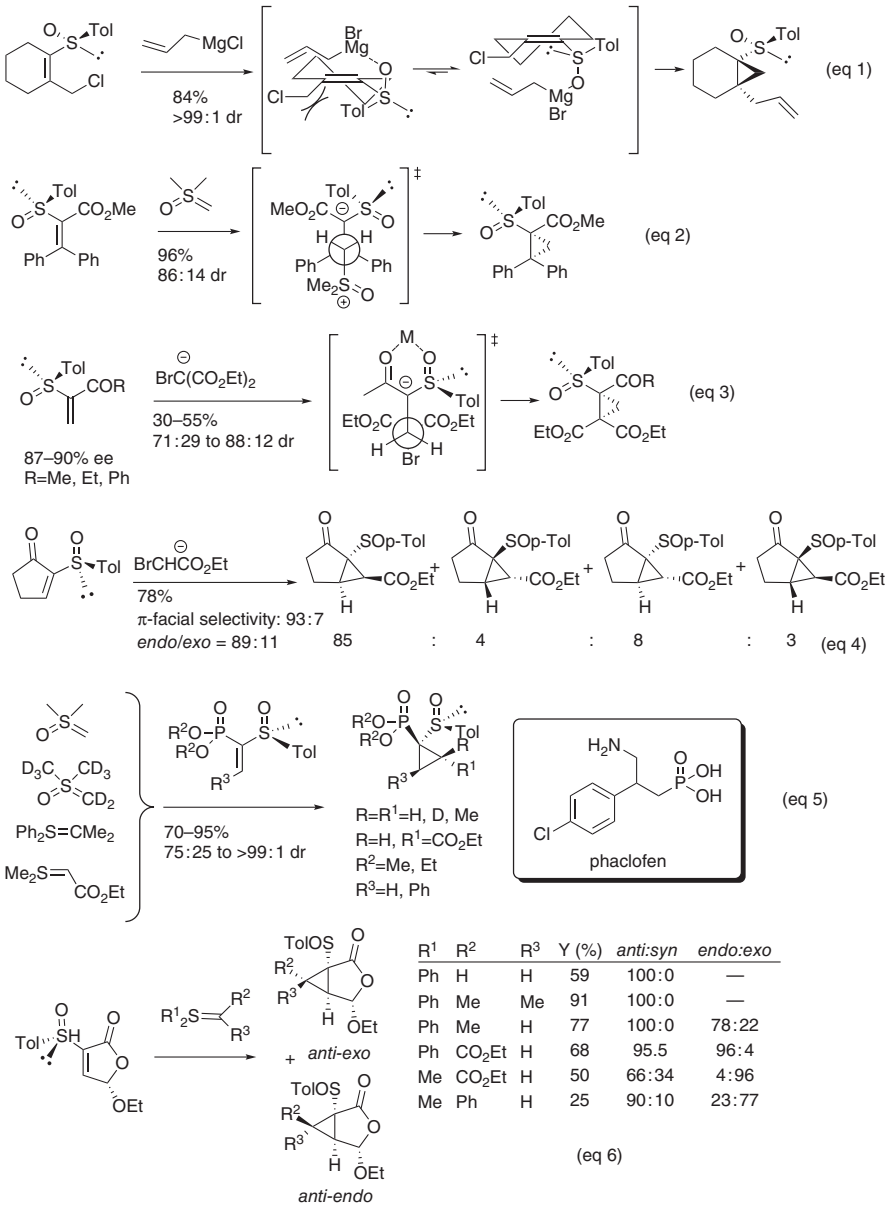
conformer then allowed the preferential delivery from the bottom face. Acyclic chiral vinyl sulfoxides have also been converted into cyclopropanes (Scheme 1.131, eq 2) [477].

The proposed transition state involved a nonchelate model in which 1,3-elimination occurred preferentially from the lone pair side of the *p*-toluenesulfinyl group. This strategy was extended to the addition of the bromomalonate carbanion to a chiral α-ketovinylsulfoxide (Scheme 1.131, eq 3) [478]. The nature of the solvent, the base, and the counterion influenced both the yield and the selectivity. It should be noted that, with respect to the previous reaction, the formation of a chelate between the carbonyl and sulfoxide oxygen, which led to an opposite diasterofacial selectivity, by the addition of bromomalonate enolate from the sterically less crowded lone-pair side of the chiral sulfinyl substituent. In addition, chiral sulfinylcyclopentenones efficiently reacted with the α-bromoacetate carbanion (Scheme 1.131, eq 4) [479].

The cyclopropanation of chiral (*E*,*S*)-(1-dimethoxyphosphoryl-2-phenyl)vinyl *p*-tolyl sulfoxide with various sulfur ylides allowed the synthesis of 2-amino-3-phenyl-1-cyclopropanephosphonic esters, constrained analogs of phaclofen (Scheme 1.131, eq 5) [480]. Moreover, the reaction between lithiated phenyl phenylthiomethylsulfone and 1-(phenylthio)vinylsulfoximide produced a mixture of two stereoisomeric cyclopropanes in 75% yield and 75:25 ratio [481]. Chiral sulfinylfuranones reacted with sulfonium ylides via the addition of the sulfur nucleophile to the double bond from the opposite face to that occupied by the OEt group, with nonstabilized ylides [482]. The formation of the *endo*- or *exo*-adducts was completely dependent upon the steric hindrance of the substituents at sulfur. Consequently, dimethylsulfonium derivatives yielded mainly the *exo*-products, while, with the diphenylsulfonium ylides, the *endo*-products predominated (Scheme 1.131, eq 6).

In 2008, Marek and coworkers exploited an MIRC reaction on chiral alkylidene bis(*p*-tolylsulfoxides) with the trimethylsulfoxonium ylide (Scheme 1.132) [483]. The corresponding chiral bis(*p*-tolylsulfinyl) cyclopropanes were then used to prepare enantiomerically enriched polyalkylated cyclopropane derivatives. They found, in fact, that a *syn*-selective sulfoxide–lithium exchange with retention of configuration at the carbon center occurred at the more hindered position, because strain was released. Then, a second sulfoxide–lithium exchange can be carried with the same features, leading to enantiomerically pure products. Permutation of the electrophiles introduced after each of the two sulfoxide–lithium exchange reactions allowed for the formation of two products, having opposite configurations at the quaternary center. This methodology was used for the preparation of (9*R*,10*S*)-dihydrosterculic acid [484].

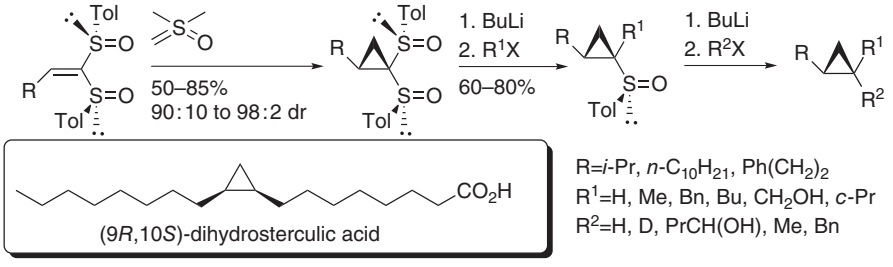
The reaction of (*S*)-(1-diethoxyphosphoryl)vinyl *p*-tolylsulfoxide and (*E*,*S*)-(1-dimethoxyphosphoryl-2-phenyl)vinyl *p*-tolyl sulfoxide with (dimethylsulfuranylidene)acetate mainly allowed for the preparation of (1*S*,2*S*)-(1-diethoxyphosphoryl-2-ethoxycarbonyl)cyclopropyl *p*-tolylsulfoxides (Scheme 1.133). However, the two diastereomers were easily separable, and they could be converted into enantiomerically enriched 2-(2′-phosphonocyclopropyl)glycines, which are among the most important sources of active analogs for the glutamic acid receptors [485]. The same substrate was allowed to react with a sulfonium



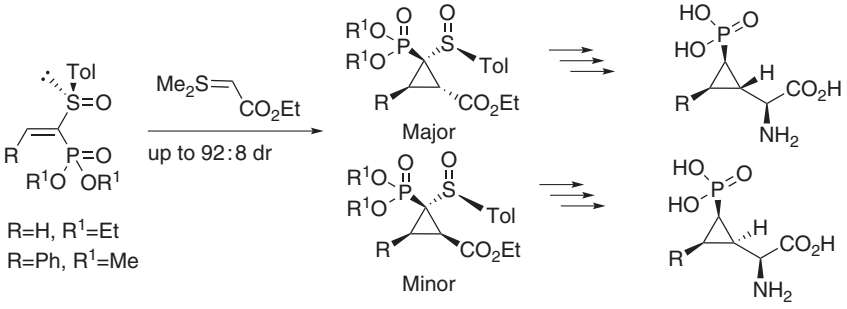
R^1	R^2	R^3	Y (%)	*anti:syn*	*endo:exo*
Ph	H	H	59	100:0	—
Ph	Me	Me	91	100:0	—
Ph	Me	H	77	100:0	78:22
Ph	CO_2Et	H	68	95.5	96:4
Me	CO_2Et	H	50	66:34	4:96
Me	Ph	H	25	90:10	23:77

Scheme 1.131 Asymmetric cyclopropanation of sulfinyl compounds.

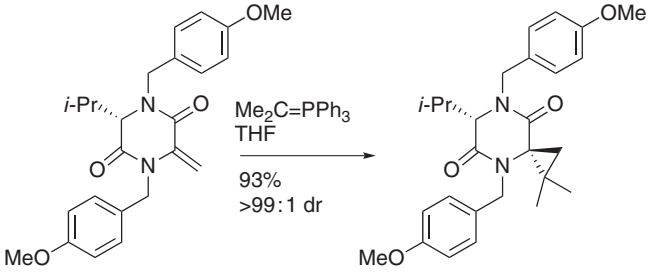
ylide containing a ketone moiety bonded to the ylide carbon atom, instead of CO_2Et group. The cyclopropane was recovered in 86% yield, the major diastereomer (5:1 dr) having the ketone in *cis*-relationship with phosphonate, differently from that depicted in Scheme 1.133. Unfortunately, the chiral auxiliary sulfinyl group could not be removed from the product [486].



Scheme 1.132 Preparation of enantiomerically pure polyalkylated cyclopropane derivatives.



Scheme 1.133 Stereocontrolled synthesis of 2-(2′-phosphonocyclopropyl)glycines.

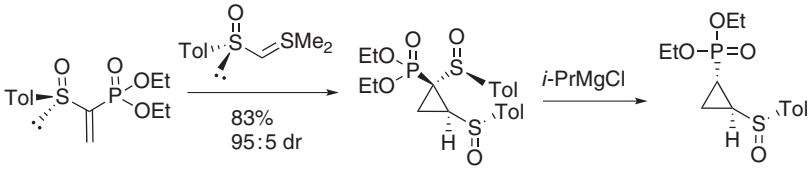


Scheme 1.134 Asymmetric cyclopropanation of dehydroalanine acceptor.

The conjugate addition of an *in situ* generated phosphonium-derived ylide to a chiral dehydroalanine acceptor allowed the preparation of the corresponding cyclopropane-substituted diketopiperazine (Scheme 1.134) [487].

After cross metathesis with ethyl vinyl ketone, the readily available (3*R*,4*R*)-1,5-hexadiene-3,4-diol provided the chiral substrate for cyclopropanation with dimethylsulfoxonium ylide, leading to the disubstituted *trans*-cyclopropane in 79% yield and >20 : 1 dr, the key intermediate in the total synthesis of brevipolides (see Scheme 1.6 for the structure) [488].

Finally, the asymmetric cyclopropanation using two sulfinyl auxiliaries, one on the Michael acceptor and the other on the nucleophile, can usefully close this



Scheme 1.135 Asymmetric cyclopropanation using two sulfinyl auxiliaries.

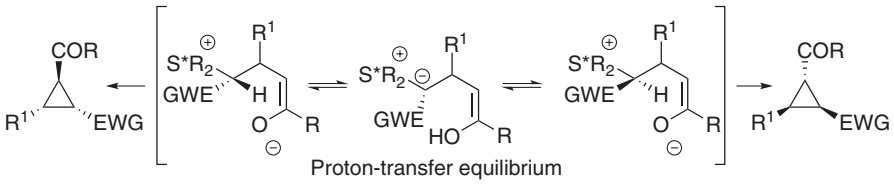
chapter and introduce the next one. The product was obtained with full diastereoselectivity and very high facial selectivity. The crowding of the phosphonate moiety is usually considered as a *trans*-directing driving force, but also dipole–dipole interaction between both sulfinyl substituents has to be considered, and leads to the same isomer. The reaction of with isopropylmagnesium chloride allowed the removal of only one sulfinyl group selectively (Scheme 1.135) [489]. A possible explanation of the observed stereochemistry of the final product could be the attack of the Grignard reagent on sulfinyl sulfur atom α to phosphoryl group with subsequent epimerization of carbanionic center before quenching.

In addition, the key step of the synthesis of (–)-*trans*-2-aminomethylcyclopropanecarboxylic acid, a partial agonist for GABAc receptor, was the asymmetric cyclopropanation of L-menthyl acrylate with ammonium ylides derived from *tert*-butyl bromoacetate and quinidine or quinine [490]. *Trans*-substituted cyclopropanes were exclusively obtained. Unfortunately, the reaction did not go to completion; however, 89% and 63% yields (based on recovered starting material) were obtained for 75:25 and 7:93 (*R*,*R*):(*S*,*S*) mixtures with quinidine or quinine ylides, respectively. From these observations, L-menthyl acrylate and quinidine or quinine derivative could be considered stereochemically mismatched or matched, respectively.

1.4.2.2 Chiral Nucleophiles

A variety of stoichiometric chiral nucleophiles can perform enantioselective cyclopropanation of alkenes. Chiral sulfur, selenium, nitrogen, phosphorus, and arsenic ylides as well as chiral enolates have been added to α,β-unsaturated carbonyl derivatives. The asymmetric cyclopropanation using chiral sulfur ylides has been carried out since the 1960s, albeit with low enantioselectivities [491].

It is worth of the first mention that, owing to the analogy with the reaction sequence reported in Scheme 1.135, the reaction of deuterated achiral 2-phosphonateacrylates using (*S*)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide, allowed the preparation of (1*R*)-ethyl-1-diethylphosphono-2,2-dideuteriocyclopropanecarboxylate, in 67% overall yield and 80% ee [492]. It should be noted that, when the phosphoryl and sulfinyl substituents were on the same side of the cyclopropane ring, during sulfoxide–metal exchange, 1,2-migration of a phosphoryl group could take place, leading to desulfinylated cyclopropane of an entirely different structure. Then, the asymmetric cyclopropanation of vinylphosphonates using other optically active sulfonium and selenonium ylides derived from terpenes led to ethyl 1-(diethoxyphosphoryl)-2-phenylcyclopropanecarboxylate, diethyl 1-(diethoxyphosphoryl)cyclopropane-1,2-dicarboxylate, diethyl 1-[(phenylsulfonyl)-2-phenylcyclopropane]-phosphonate,



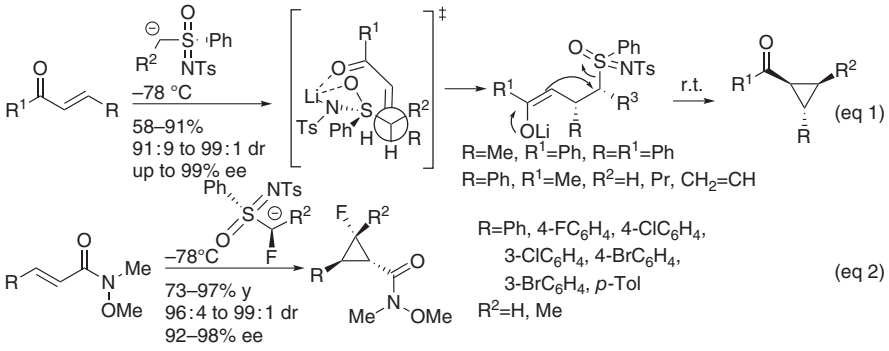
Scheme 1.136 Mechanism accounting for enantioselectivity in the asymmetric ylide-promoted MIRC reaction.

and diethyl-[(phenylsulfonyl)-2-carboethoxycyclopropane]-phosphonate in 53–94% yields with 56:44 to 81:19 *trans:cis* ratio and up to 98% ee. With regard to the *trans*-isomer, menthol-derived selenonium ylide mainly gave (*S*,*R*)-cyclopropane, whereas an isothiocineole-derived ylide led to an (*R*,*S*)-isomer. The stereochemical outcome of these reactions is easily rationalized by the mechanism of the reaction described in Scheme 1.136 [493]. Finally, the asymmetric synthesis of (1*S*,2*R*)-1-amino-2-methylcyclopropanephosphonic acid, a phosphonic analog of (–)-norcoronamic acid, was set up, starting from 1-cyanovinylphosphonic acid and (*S*)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide. It is worth noting that the nitrile group changed the stereoselectivity of the reaction with respect to the CO_2R framework, thus avoiding 1,2-migration of the phosphoryl group on the cyclopropane ring [494].

Aggarwal's research group studied the mechanism of the cyclopropanation of acyclic enones with chiral sulfur ylides [495]. However, this model could also be applied to nitrogen and phosphorus ylides and was able to rationalize the outcome of a variety of substituents on the ylides in terms of chemo- and enantioselectivity. In particular, a clear correlation between ylide stability (ketone > ester > amide) and enantiomeric excess (25%, 46%, and 89% ee, respectively) was observed. The enantioselectivity was governed by an unusual proton-transfer step prior to ring closure: the more stable the ylide is, the slower the ring closure and higher the enantioselectivity (Scheme 1.136). The proposed mechanism is strongly supported by experiments with deuterium-labeled ylides, in which higher enantioselectivities were observed in agreement with the slower deuteron transfer.

Chiral lithiated *N*-tosylsulfoximines were efficiently used, because they overcome the additional step needed to remove the chiral auxiliary, being spontaneously removable in the elimination step (Scheme 1.137).

In fact, the lithiated sulfoximines afforded diastereoselective Michael reactions at low temperature, arranging a transition state in which the large sulfonimidoyl moiety and the substituent (R) in the Michael acceptor were *anti* in order to minimize steric interactions. Then ring closure occurred upon warming to room temperature by an intramolecular displacement of the sulfonimidoyl group with inversion of the configuration. They were found to produce enantioenriched cyclopropanes when reacted with enones (Scheme 1.137, eq 1) [496] or cinnamyl hydroxamic acid derivatives (Scheme 1.137, eq 2) [497]. In addition to the examples reported in Scheme 1.137, eq 2, alkyl-substituted hydroxamic acid derivatives were tested and led to products in 62% yield with 94% ee for the major diastereoisomer, but three diastereoisomers were detected, in a ratio of 75:19:6.



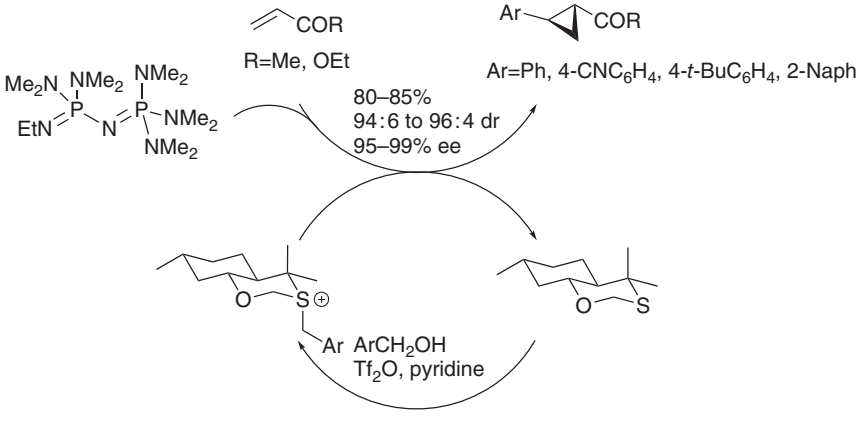
Scheme 1.137 Cyclopropanation of enones with chiral lithiated sulfoximines.

Moreover, two examples of cyclopropanes with a quaternary fluorinated center (R^2=Me) were reported in 70–75% yield, 7:1 dr, and 76–87% ee.

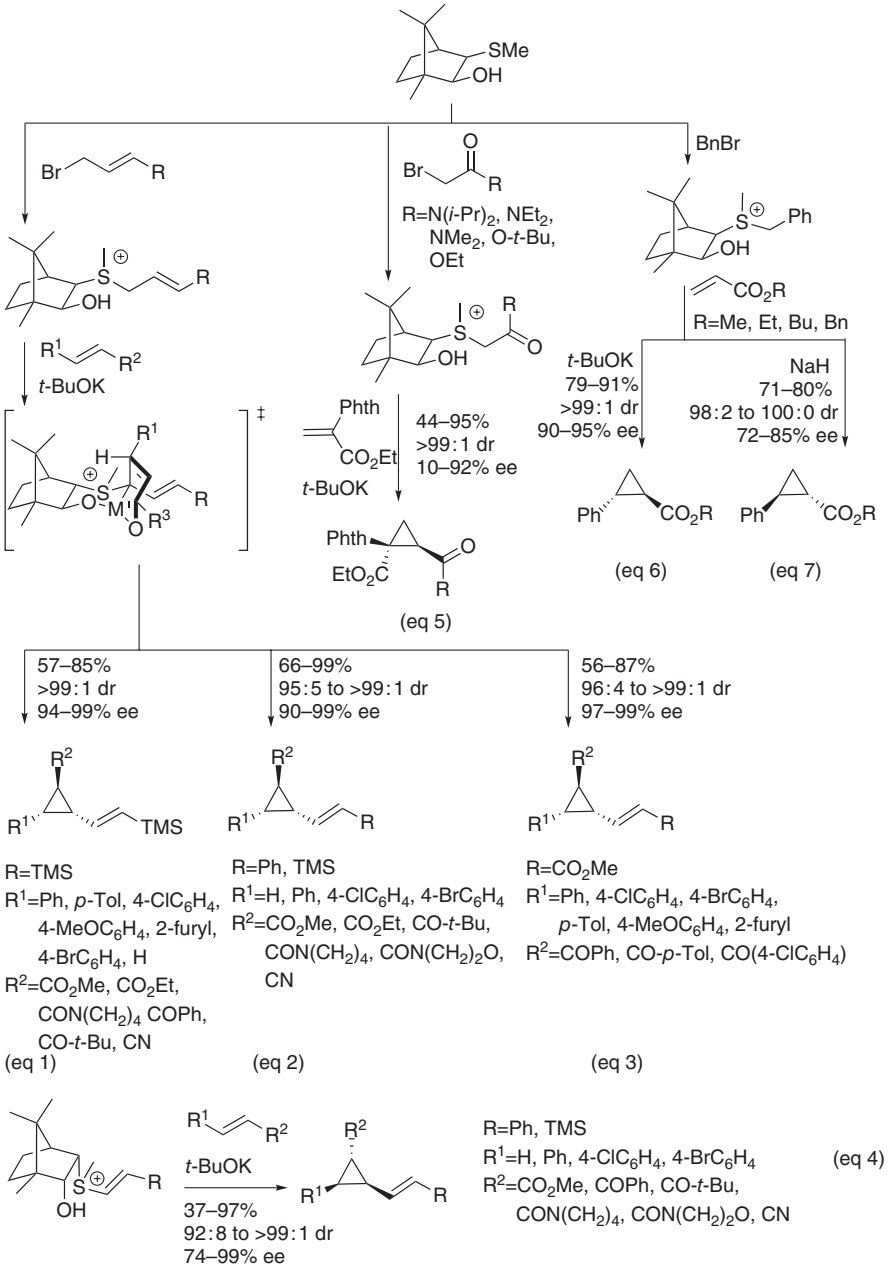
A single diastereoisomer (about 80% yield) was observed in the synthesis of β-(trimethylsilyl)ethyl cyclopropanecarboxylate derivatives (chrysantemate precursors) from chiral *p*-tolyl β-(trimethylsilyl)ethyl sulfoxide [498].

The reaction of chiral oxathiane with arylmethyl alcohols in the presence of triflic anhydride produced a series of (arylmethyl)sulfonium salts, which can be converted *in situ* into chiral sulfonium ylides, before reacting with ethyl acrylate or methyl vinyl ketone (Scheme 1.138) [499]. It should be noted that acrolein led mainly to the corresponding epoxides.

A large literature produced by Tang and coworkers explained the reaction of the chiral sulfonium salt prepared from D-camphor. The first example reported the preparation of (1*S*,2*S*,3*R*)-1,2-disubstituted 3-(trimethylsilylvinyl)cyclopropanes with high enantioselectivities (Scheme 1.139, eq 1) [500]. Low yields were observed with aliphatic or *Z*-configured alkenes.



Scheme 1.138 MIRC reaction with chiral oxathiane.



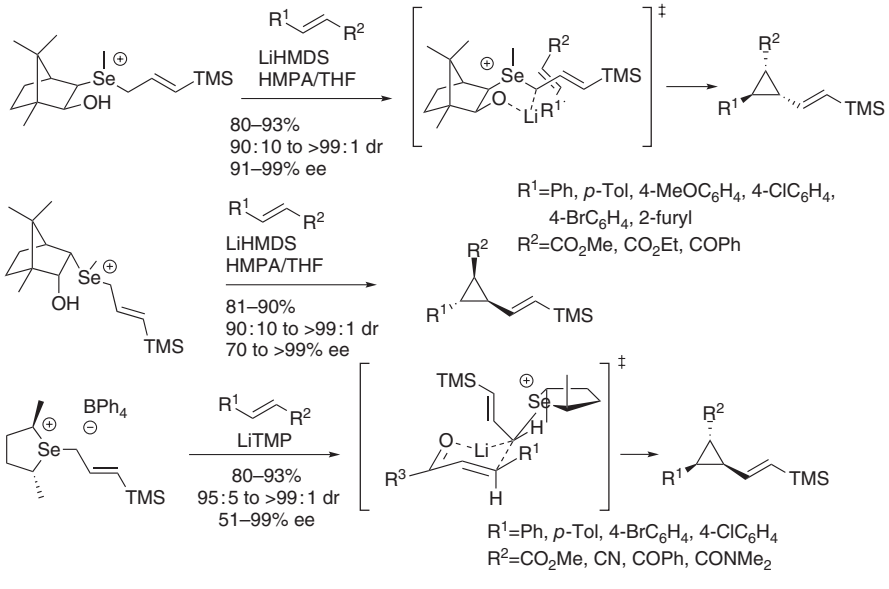
Scheme 1.139 Asymmetric cyclopropanations via camphor-derived sulfonium ylides.

The transition-state model, accounting for the observed stereochemical outcome, contemplated the carbonyl group of the substrate coordinated to the metal of the ylide via a six-membered ring. Then, the substrate reacts at the *Re*-face of the ylide to avoid the steric interaction between the R group and the methyl substituent

of the sulfur. Later, the same group prepared other 1,2-disubstituted-3-vinylcyclopropanes (Scheme 1.139, eq 2 [501], and 3 [502]). It should be noted that the use of *endo*-type sulfonium ylides allowed the isolation of the products with opposite absolute configuration (Scheme 1.139, eq 4) [501]. Moreover, dehydroaminoacid derivatives allowed the preparation of 1-aminocyclopropanecarboxylic acids (Scheme 1.139, eq 5) [503]. The steric hindrance of the amide sulfonium salts significantly influenced the cyclopropanation process. In fact, with increasing crowding yield, enantiomeric excess decreased. The phthaloyl group could be easily removed at room temperature to provide the amino acid in moderate overall yield.

In a similar manner, Huang and Huang developed an enantioselective synthesis of 2-phenyl-1-cyclopropane-carboxylates [504]. Two features are worth noting: the starting chiral sulfide could be recovered almost quantitatively and reused conveniently, and the enantioselectivity could be tuned by changing the base. Indeed, when potassium *tert*-butoxide or sodium hydride was used, (1*R*,2*R*) or (1*S*,2*S*)-2-phenyl-1-cyclopropane carboxylates were obtained, respectively (Scheme 1.139, eqs 6 and 7, respectively). Acrylonitrile as electrophile can also be used, providing the corresponding cyclopropane in 75% yield, as a single diastereomer with 91% ee. In the light of Aggarwal's mechanism, which is more recent, the different bases have to influence the proton transfer step.

Interestingly, the reaction of camphor selenonium ylide afforded 1,2,3-trisubstituted cyclopropanes, with a different stereochemistry, notwithstanding the close similarity of sulfonium and selenonium ylides. In fact, the *exo*-isomer led to (1*R*,2*R*,3*R*)-1,2,3-trisubstituted cyclopropanes and the *endo*-isomer to (1*S*,2*S*,3*S*)-cyclopropanes (Scheme 1.140) [505].

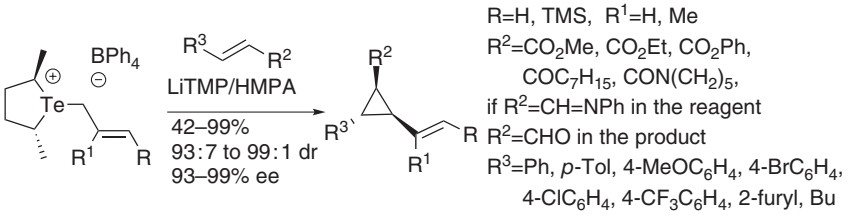


Scheme 1.140 Asymmetric synthesis of cyclopropanes via chiral selenonium ylides.

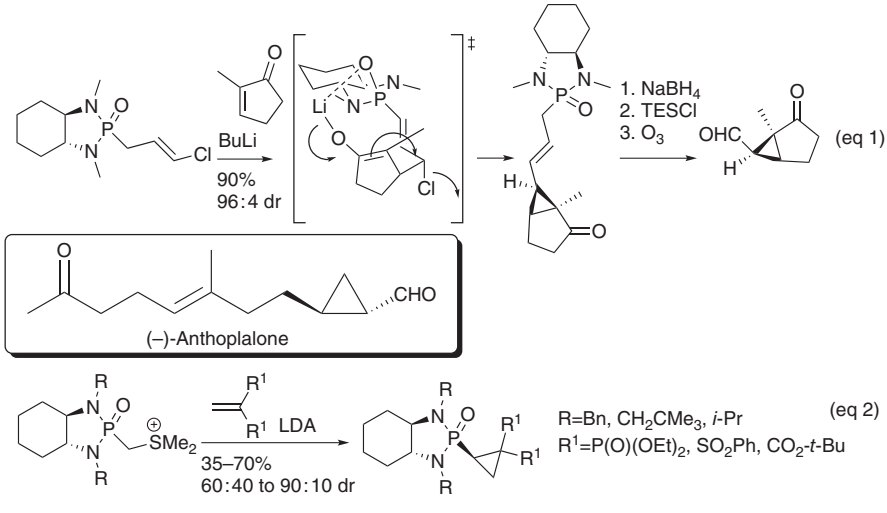
The enantioselectivity was higher with free OH group with respect to the methoxy derivative, suggesting that a negatively charged oxygen atom might play an important role in assembling the transition state. Although not mentioned in the paper, a role of the base in directing the selectivity cannot be excluded, because the base strength of LiHMDS/HMPA is quite different from *tert*-butoxide, as Huang and Huang demonstrated [504]. Moreover, in the same paper, ylides derived from (2*R*,5*R*)-dimethyltetrahydroselenophene reacted with various α,β-unsaturated compounds, affording the corresponding (1*R*,2*R*,3*S*)-cyclopropanes. In all reactions, selenium by-products could be easily recovered and reused to prepare the starting ylides.

In the literature, also, chiral allylic ylides derived from (2*R*,5*R*)-dimethyltetrahydrotellurophene were reported to be able to react with α,β-unsaturated esters, amides, imines, and ketones, providing the corresponding 1,3-disubstituted 2-vinylcyclopropanes (Scheme 1.141) [506].

An instance of phosphorus ylide, that is, a chiral phosphonamide derived auxiliary, was reported to be added to cyclic enones, leading to the formation of the corresponding *endo,endo*-cyclopropane after ring closure (Scheme 1.142, eq 1) [507].



Scheme 1.141 Asymmetric allylic telluronium-ylide-mediated cyclopropanations.



Scheme 1.142 An example of the diastereoselective cyclopropanation using chiral phosphonamide.

The chiral auxiliary was removed by ozonolysis to generate the cyclopropanecarboxaldehyde. The *exo*,*endo*-isomer could be obtained both by epimerization of the *endo*,*endo*-cyclopropanecarboxaldehyde or from reaction with the *cis*-chloroallylphosphonamide. This method was extended to α,β-unsaturated γ-lactones, δ-lactones, γ-lactams, and acyclic esters. In all reactions, the *endo*,*endo*-isomers were recovered in 51–88% yields with 95 : 8 to >98 : 2 dr. The phosphonamide derivatives could be manipulated to generate functionally diverse cyclopropanes without affecting the stereochemistry, for example, in the total synthesis of the cytotoxic agent (–)-anthoplalone [508]. The suggested mechanism claimed an attack of the γ-chloroallylic anion on the *Re*-face of the cyclic enone, leading to a Li-chelated enolate intermediate, with the enolate and chloride in *anti* relationship, thus favoring the leaving atom expulsion.

In addition, a sulfur–phosphorus ylide reacted with olefins to give a mixture of two cyclopropane diastereomers (Scheme 1.142, eq 2) [509]. It should be noted that the presence of two electron-withdrawing groups in ethylene was essential for the reaction occurrence. In fact, only one activating group did not lead to the corresponding cyclopropanes.

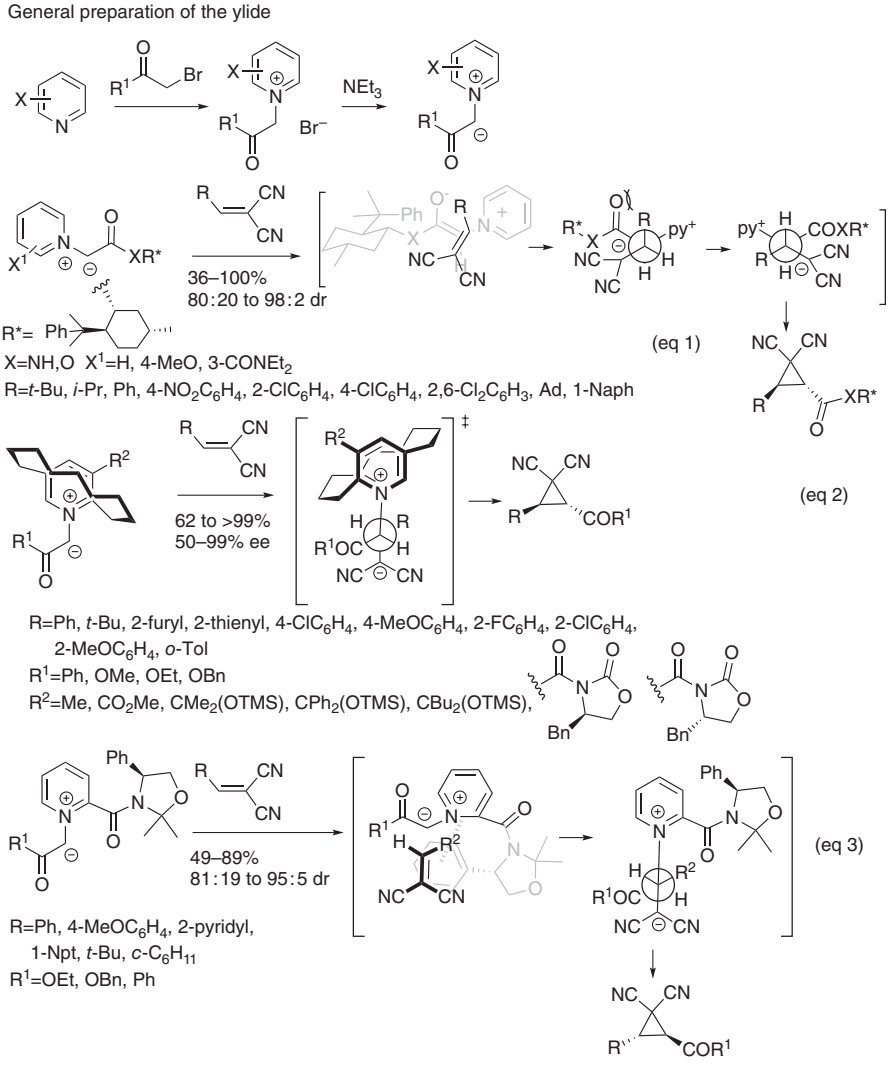
Chiral pyridinium ylides, generally prepared *in situ* from the corresponding pyridinium salts and triethylamine, were also applicable for cyclopropanation, especially with β-substituted methylidenemalonitriles, giving rise to the corresponding *trans*-cyclopropanes. In particular, α-pyridinium acetate or acetamide bearing an 8-phenylmenthyl group as the chiral auxiliary (Scheme 1.143, eq 1) [510] and *para*-pyridinophane ylides (Scheme 1.143, eq 2) [511] led to the (1*R*,3*S*)-isomers, while chiral pyridinium ylides, the conformation of which was fixed through a cation–π interaction, afforded the (1*S*,3*R*)-isomers (Scheme 1.143, eq 3) [512].

The stereochemical outcome of the first reaction was explained by surmising that the enolate, in which the large pyridyl and 8-phenylmenthyloxy groups were in a *trans*-relationship, was expected to be predominant upon deprotonation. The reaction with the Michael acceptor occurred at the less sterically encumbered face of the enolate.

However, the zwitterionic intermediate had severe steric hindrance; thus, under the basic reaction conditions, it epimerized before cyclization. In the second reaction, the steric bulk of the R^1 substituent in the ylide drove the enantioselectivity, but also a moderate "remote stereocontrol" effect was exerted by the R^2 substituents. DFT (B2LYP/6-31G**) calculations were in good agreement with the experimental results. Finally, in the third reaction, the electron-deficient olefin would approach the ylide from the less-hindered side, with the R group far from COR^1 group in order to avoid steric repulsion.

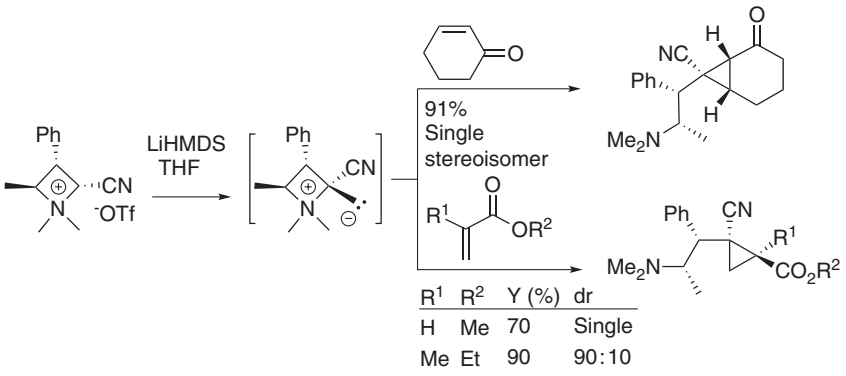
In addition, ephedrine-derived azetidinium ylides showed a remarkable ability to perform the cyclopropanation of Michael acceptors, allowing the formation of tri- or tetrasubstituted products, bearing one or two quaternary carbon centers along with one or two tertiary centers (Scheme 1.144) [513].

Enolates bearing chiral auxiliaries were also used in MIRC reactions. For example, the enolate derived from Evans's chiral auxiliary and (*E*)-ethyl-3-(trifluoromethyl) acrylate afforded cyclopropanes as a mixture of two out of eight possible stereoisomers (Scheme 1.145, eq 1) [514]. The stereochemical outcome was explained on the basis of the formation of the *anti*-isomer after 1,4-addition

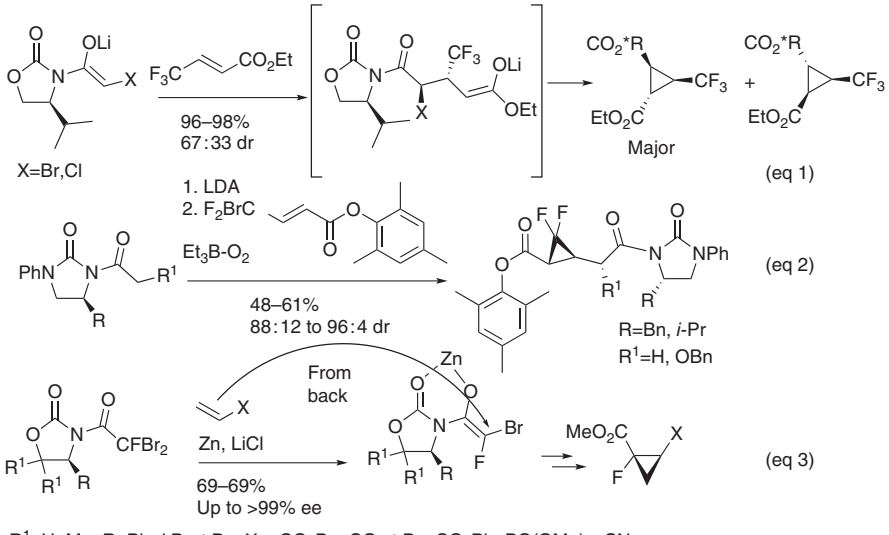


Scheme 1.143 Asymmetric pyridinium-ylide-mediated cyclopropanation.

in agreement with other oxazolidinones. Elimination provided two possible cyclopropyl derivatives, and a subsequent epimerization at the ester moiety accounted for the erosion of the diastereoselectivities. Moreover, the addition of lithium enolate of chiral *N*-acylimidazolidinone to 2,4,6-trimethylphenyl 4-bromo-4,4-difluorocrotonate allowed the synthesis of difluorocyclopropanecarboxylates (Scheme 1.145, eq 2) [515]. Finally, a borderline reaction between an MIRC and a Simmons–Smith reaction should be mentioned [516]. Since the authors proposed the formation of a chelated zinc enolate in the *Z*-configuration favored by the steric effect of the voluminous bromine atom instead of a carbenoid species, it is included here. The enolate underwent a highly selective 1,4-conjugate addition,



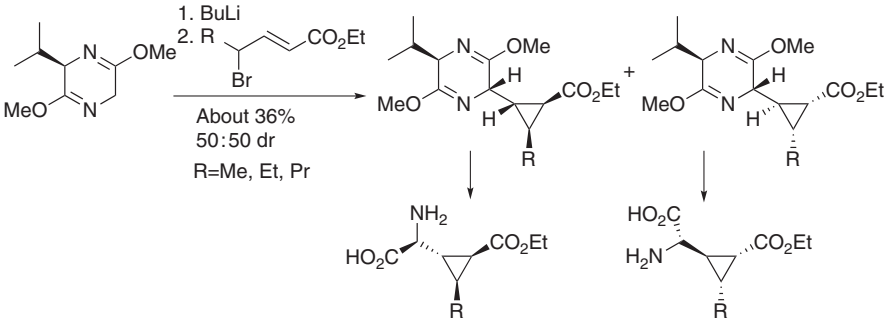
Scheme 1.144 Asymmetric azetidinium-ylide-mediated cyclopropanation.



Scheme 1.145 Asymmetric cyclopropanation with Evans's chiral auxiliary.

followed by a less selective cyclization, where the steric effect and the chelating power of the X group played a fundamental role in the formation of the *trans*- or the *cis*-configured cyclopropane (Scheme 1.145, eq 3). Cleavage of the chiral auxiliary proceeded smoothly with no epimerization of the cyclopropanes and with very good recovery of the chiral auxiliary.

The last instance is the alkylation of a lithiated chiral bislactim ether with 4-alkyl-4-bromobut-2-enoates, which led to only 50:50 mixture of the corresponding diastereoisomers, but fortunately, they could be separated by flash



Scheme 1.146 Enantiomerically pure α-cyclopropyl-α-amino acids from chiral bislactim ether.

chromatography and thus hydrolyzed to enantiomerically pure α-cyclopropyl-α-amino acids (Scheme 1.146) [517].

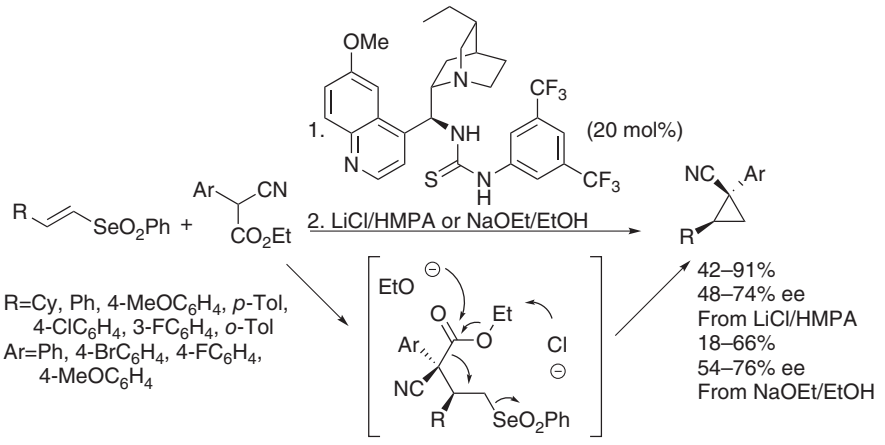
The preparation of stereochemically defined cyclopropanes could also be achieved from vinyl sulfones derived from sugars equipped with a leaving group at the 4-position [518]. The advantage of the large available variety of both nucleophiles and sugars, which allow for the preparation of a myriad of cyclopropanes with all three cyclic carbons stereodefined, was counteracted by the tedious preparation of starting materials.

1.4.3 Organocatalysis

More recently, a strong emphasis has been placed on the development of catalytic methods to generate chiral cyclopropanes via MIRC reactions. Classical iminium–enamine, carbene, and noncovalent organocatalysis approaches have been proposed as elegant asymmetric methods for the cyclopropanation of electron-poor alkenes, such as enals, enones, α,β-unsaturated esters, amides, and nitriles. The aim of the catalyst is the shielding of one of the double bond faces and then the prevention of the rotation around the newly formed single bond before ring closure. One of the first examples was the synthesis of 1,2,3-trisubstituted cyclopropanes from halocycloalkenones and stabilized carbanions by phase-transfer organocatalysts, but only 49–83% ee values were obtained [519].

More recently, Russo and Lattanzi studied the addition of 1,3-dicarbonyl compounds on enone γ-diphenylphosphinates (leaving group = $OPOPh_2$), under basic conditions. Among the reported examples, they employed some cinchona alkaloids derivatives in stoichiometric amounts as the bases and observed promising levels of enantiocontrol, but the reaction was restricted to only one example with different promoters [520].

The addition of an α-substituted cyanoacetate to a vinylselenone, catalyzed by a bifunctional urea catalyst provided adducts, which cyclized smoothly by elimination of benzeneseleninate in a one-pot sequence (Scheme 1.147) [521]. It should be noted that, ethylate-promoted cyclization always gave lower yields but higher enantiomeric excesses compared to chloride-promoted ones, with the same substrate. It is also noteworthy that this procedure complemented the rho-



Scheme 1.147 Cyclopropanes from organocatalytic MIRC of vinyl selenones.

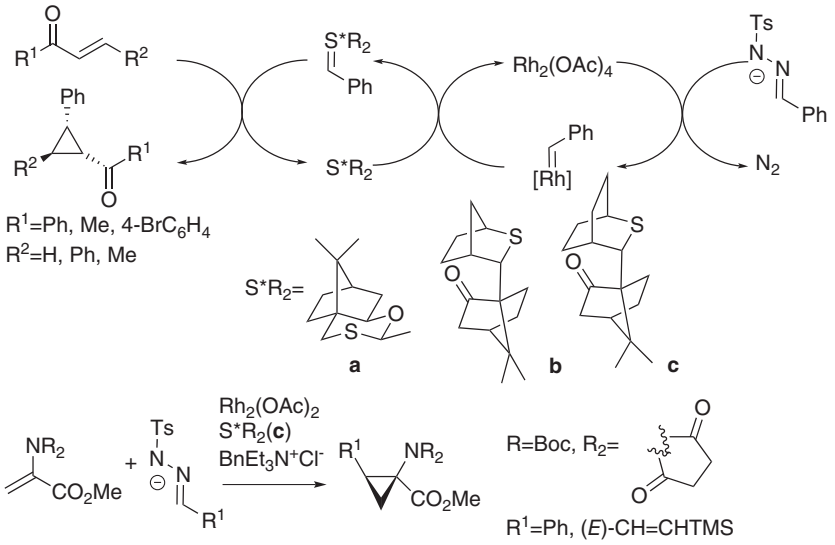
dium-catalyzed cyclopropanation of alkenes by 2-diazo-2-phenylacetonitrile, in which an *E* relationship between the nitrile and the R group was obtained (Scheme 1.76, eq 1) [304].

However, ylides, bromonitromethane, and halocarbonyl compounds have been the most used substrates in MIRC reactions, and the following sections are dedicated to them.

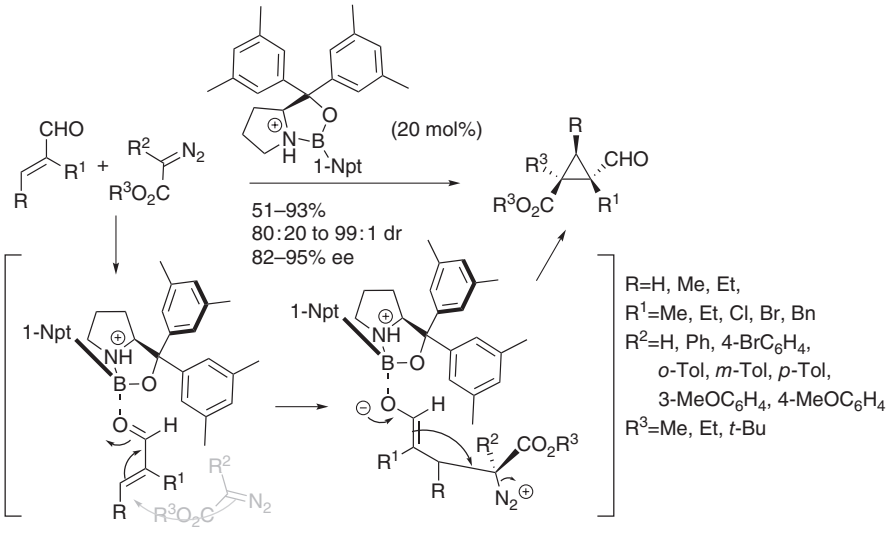
1.4.3.1 Ylides

In the previous sections, ylides were often the reagent of choice for MIRC reactions. They carried asymmetric moieties or reacted on chiral substrates. However, under organocatalysis, both partners can be asymmetric and the catalyst provides the chiral environment. The reaction set up by Aggarwal's group, who mixed carbene and sulfur ylide chemistry in the synthesis of enantioenriched cyclopropanes, represents a borderline between MIRC reactions carried out under stoichiometric or catalytic conditions and under organo or metal catalysis (Scheme 1.148) [522]. In fact, the chiral sulfur ylide was generated both stoichiometrically and catalytically from a metal carbene intermediate, which derived from the reaction of rhodium acetate and a diazo reagent (see Section 1.3). Under the best conditions [phase-transfer catalyst and S^*R_2(**c**)], the yield were anyway low (10–73%) and the diastereoselectivity about 80 : 20 and 80–92% ee. Later, a further application, by using $Cu(acac)_2$ instead of rhodium acetate and S^*R_2(**b**), allowed access to a precursor to the pharmacologically important compound (+)-LY354740 (see Scheme 1.120, eq 3 for the structure) [523]. The reaction conditions employed had influence on both the diastereo- and enantioselectivities: under catalytic conditions, a good enantioselectivity with a low diastereoselectivity was observed, while under stoichiometric conditions, a low enantioselectivity with a high diastereoselectivity was observed.

However, diazo compounds could themselves react as ylides under the appropriate reactions conditions. Actually, diazoacetates and acroleins underwent cyclo-



Scheme 1.148 Rhodium-catalyzed asymmetric cyclopropanation with chiral sulfides.



Scheme 1.149 Oxazaborolidinium ion-catalyzed cyclopropanation of acroleins with diazoacetates.

propanation with chiral oxazaborolidinium ions as the catalyst (Scheme 1.149) [524]. Unfortunately, 4-methoxyphenyldiazoacetate yielded an unsatisfactory *trans*/*cis* ratio (55:45), although enantiocontrol was still high (95% ee for *trans*, 94% ee for *cis*). Moreover, every reaction needed different temperatures and times, which had to be optimized whenever required. The mechanism envisaged by the

authors and depicted in Scheme 1.149 successfully predicted the experimentally determined absolute configuration.

In Table 1.6, the most important reactions involving asymmetric cyclopropanation by the use of sulfur ylides are summarized.

Studer envisaged the mechanism depicted in Scheme 1.150 to explain the stereochemical outcome of the reaction with *N*-heterocyclic carbene [528]. The oxidant allowed for the formation of an acyl derivative from the alcohol obtained by the addition of the catalyst to the enal. Then, ylide addition should occur at the less-hindered face, and substituents should accommodate in order to minimize steric interactions. Finally, since all three stereocenters were set before the final esterification, the different selectivities observed with different alcohols were attributed to a competitive alcoholysis reaction of the acyl derivative, before cyclopropanation reaction. In fact, these α,β-unsaturated esters obviously led to a racemic product.

Chen, Xiao, and coworkers supposed two intermediates to be involved in the mechanism of their reaction [529] in agreement with NMR studies and DFT calculations (Scheme 1.151). The hydrogen bonds directed the reactants into the proper positions and induced the observed facial selectivities.

Liu, Feng, and coworkers surmised an iminium ion intermediate, in which its *Re*-face of the ketone was less hindered, and the sulfonium ylide was addressed to this face by hydrogen bonding with the secondary amine moiety (Scheme 1.152) [530].

1.4.3.2 Nitrocyclopropanation

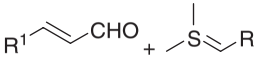
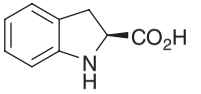
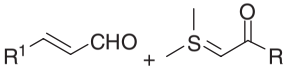
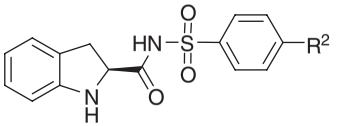
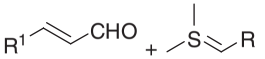
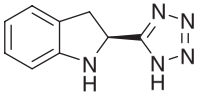
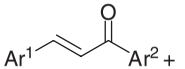
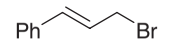
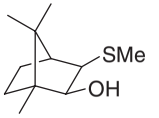
Nitrocyclopropanes are versatile intermediates, since they are substructures in a variety of biologically active natural and unnatural compounds, and the nitro group is the way to other synthetically useful groups. Thus, the organocatalyzed MIRC addition of bromonitromethane to electron-deficient alkenes under basic conditions has attracted great attention from organic chemists. Many examples have appeared in the literature, and they are listed in Table 1.7.

Interestingly, under their reaction conditions, Wang and coworkers kinetically resolved racemic 4-substituted cyclohex-2-en-1-ones. In fact, only the 4*S*-isomer reacted with 0.6 equiv. of bromonitromethane, leading to the corresponding cyclopropane and, thus, enriching the mixture with the unreactive 4*R*-isomer [535].

The asymmetric synthesis of (1*S*,2*R*,5*R*,6*S*)-3-thiabicyclo[3.1.0]hexanes has also been achieved by a one-pot, domino sulfa-Michael/aldol condensation/MIRC sequence of α,β-unsaturated aldehydes with 1,4-dithiane-2,5-diol catalyzed by **JHC** (Scheme 1.153) [539]. Very likely, organocatalyst generated an iminium ion, which was attacked by *in situ* generated mercaptoacetaldehyde from the less-hindered *Re*-face. Then, an intramolecular aldol condensation reaction occurred to form (*R*)-2-aryl-2,5-dihydrothiophene-3-carbaldehyde iminium ion. Finally, MIRC reaction proceeded on this iminium ion, and the initial carbon—carbon bond formation had to occur at its less-hindered *Si*-face.

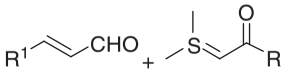
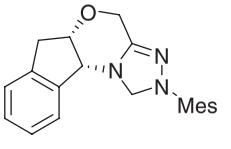
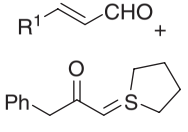
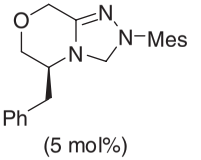
The reaction of alkylidene oxindoles [540], tetralones, indanones, chroman-4-ones [541], and 1,3-indandiones [542] was also explored (Scheme 1.154). In particular, the reaction with oxindoles also worked with 1-bromonitroethane in 65–91% yield with 60:40 to 83:17 dr and 92% to >99% ee (1*R*,2*R*,3*S*-isomer C1 = spiro,

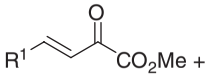
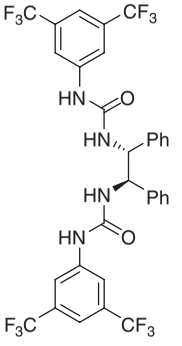
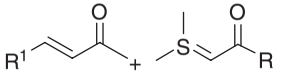
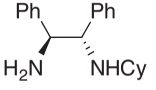
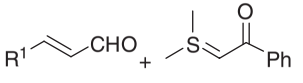
Table 1.6 Organocatalytic asymmetric MIRC reaction with sulfur ylides.

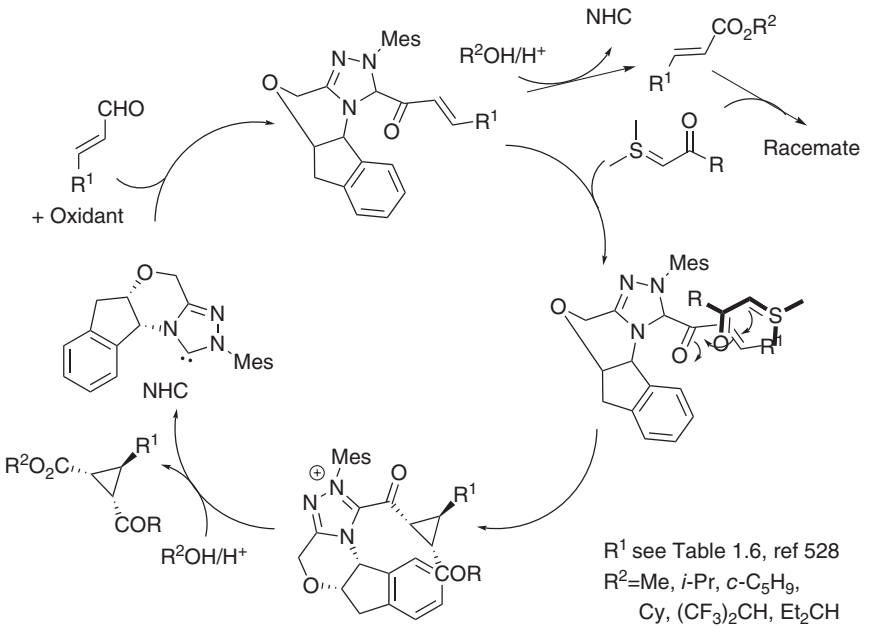
Reactants	Catalyst	Yield (%)	dr	ee (%)	References
 R^1=Me, *n*-Pr, *i*-Pr, Ph, $CH_2OCH_2CH{=}CH_2$, $CH_2{=}CH(CH_2)_4$ R=Bz, 4-BrC_6H_4, *p*-Tol, CO-t-Bu	 (20 mol%)	85–63	86:14 to 99:1	89–96 (1*R*,2*S*,3*R*)	[525]
 R^1=Me, *n*-Pr, Ph, *n*-$PrOCH_2$ R=Ph, 4-BrC_6H_4	 R^2=NO_2,MeO (20 mol%)	21–60	>97:3	88–99 (1*R*,2*S*,3*R*)	[526]
 R^1=Me, *n*-Pr, Ph, $CH_2{=}CHOCH_2$, *c*-C_5H_9 R=Ph, 4-BrC_6H_4	 (20 mol%)	74–91	98:2 to 99:1	99 (1*R*,2*S*,3*R*)	[527]
  Ar^1=Ph, 4-ClC_6H_4, 4-BrC_6H_4, *p*-Tol, 4-$MeOC_6H_4$ Ar^2=Ph, *p*-Tol	 (20 mol%)/$CsCO_3$	66–92	75:25 to 87:13	78–82 (1*S*,2*S*,3*R*)	[502]

(Continued)

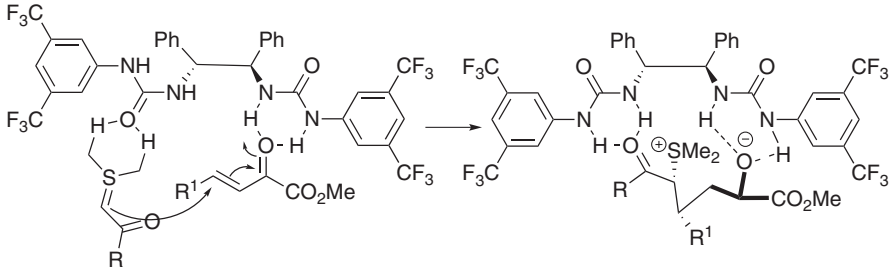
Table 1.6 (Continued)

Reactants	Catalyst	Yield (%)	dr	ee (%)	References
 R^1=Ph, 4-$MeOC_6H_4$, *p*-Tol, 4-$NO_2C_6H_4$, 4-$MeO_2CC_6H_4$, 4-AcC_6H_4, 4-ClC_6H_4, 2-$NO_2C_6H_4$, 2-Naph, 2-furyl R=Ph, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4	 (5 mol%) 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone	24–74	67 : 34 to 95 : 5	62–99 (1*R*,2*S*,3*S*)	[528]
 R^1=*p*-Tol, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$	 (5 mol%) 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone DABCO	30–43	91 : 9 to 95 : 5	76–87 (1*S*,5*R*,6*R*,*Z*)	[528]

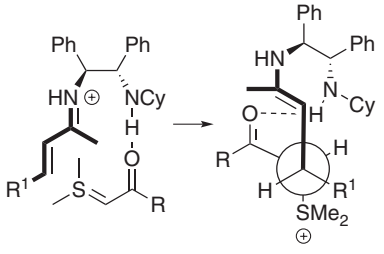
 R^1=Ph, 4-$MeOC_6H_4$, *p*-Tol, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 2-$MeOC_6H_4$, 2-thienyl, PhCH=CH, $Ph(CH_2)_2$ R=Ph, 4-$MeOC_6H_4$, *p*-Tol, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 2-FC_6H_4, 2-ClC_6H_4, PhCH=CH	 (10 mol%)	35–86	67:33 to 94:6	42–80 (1*S*,2*R*,3*R*)	[529]
 R^1=Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-$CF_3C_6H_4$, 4-PhC_6H_4, 3-$MeOC_6H_4$, 2-Naph, 2-furyl, Pr, *i*-Pr, R=Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, *p*-Tol, 2-Naph	 (20 mol%) PhCOOH (20 mol%)	50–68	>95:5	67–93 (1*S*,2*R*,3*S*)	[530]
 R^1=Ph, 4-ClC_6H_4, 4-BrC_6H_4, 3-$CF_3C_6H_4$, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 2-Naph, 2-thienyl	Supported peptide (20 mol%)	82–88	93:4:3 to 97:1:2	98–99 (1*R*,2*S*,3*R*)	[531]



Scheme 1.150 Mechanism of the enantioselective cyclopropanation of unsaturated aldehydes by oxidative NHC catalysis.

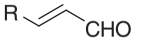
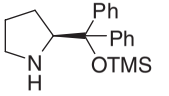
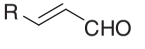
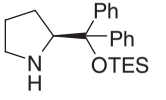
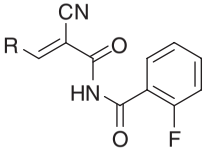
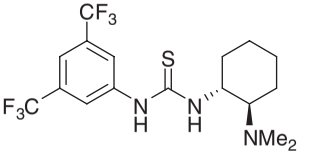


Scheme 1.151 Envisaged intermediates in the asymmetric cyclopropanation of sulfur ylides with β,γ-unsaturated-α-keto esters.



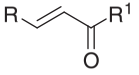
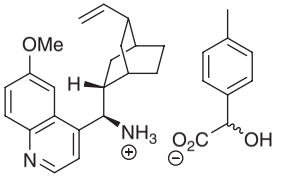
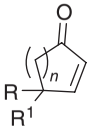
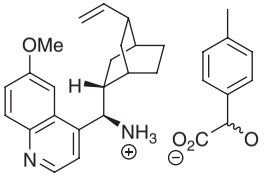
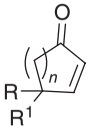
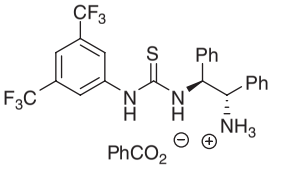
Scheme 1.152 Envisaged intermediates in the asymmetric organocatalytic cyclopropanation with a simple diamine.

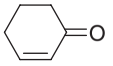
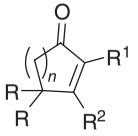
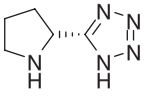
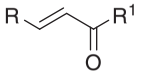
Table 1.7 Asymmetric cyclopropanation of electron-deficient alkenes with bromonitromethane.

Alkene	Catalyst, base	Yield (%)	dr	ee (%)	References
 R=Ph, Pr, 4-BrC_6H_4, 4-ClC_6H_4, 2-Naph	 **JHC** (20 mol%), Et3N (1 equiv)	42–95[a]	50:50 to 75:25[b]	91–99	[532]
 R=Ph, 4-ClC_6H_4, *p*-Tol, 3-ClC_6H_4, 2-ClC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-furyl, 3-pyridyl[c]	 (10 mol%), NaOAc (1 equiv)	46–68	50:50 to 70:30[b]	86–96	[533]
 R=Ph, *p*-Tol, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 4-BrC_6H_4, 1-Naph	 (10 mol%), Et_3N (1.5 equiv)	75–81	50:50 to 73:17[d]	98–99	[534]

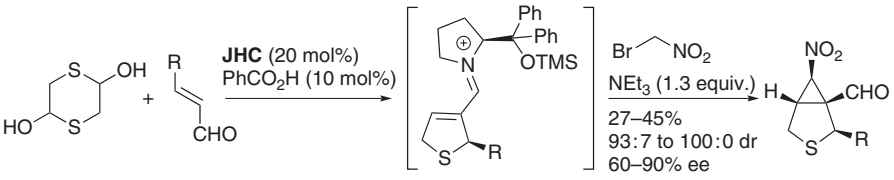
(Continued)

Table 1.7 (Continued)

Alkene	Catalyst, base	Yield (%)	dr	ee (%)	References
 R=Ph, 4-ClC_6H_4, 3-PhC_6H_4, *p*-Tol, 4-$NO_2C_6H_4$, 3-furyl, R^1=Ph, 4-ClC_6H_4, 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$, 2-Naph	 (20 mol%), then *trans*-dimethylpiperazine (1.2 equiv)	60–85	69:31 to 99:1[e]	71–99	[535]
 n = 1–3, R=R^1=H; n = 2, R=R^1=Me, R=H, R^1=CMe_2Et[f]	 (20 mol%), 4-methylmorpholine (1 equiv)	83–99	—[g]	83–99	[535]
 n = 1–3, R=H; n = 2, R=Me	 (20 mol%), 4 -methylmorpholine (1 equiv)	31–98	—[g]	88–99	[536]

		80	—[g]	77	[537]
 $n = 1–3$, R=R^1=R^2=H, $n = 1$, R^1=Me, R=R^2=H; $n = 1–2$, R^2=Me, R=R^1=H; $n = 2$, R=Ph, R^1=R^2=H[h]	 (30 mol%), morpholine (3 equiv)	8–100	—[g]	14–90	[538]
 R=Me, Pr, *i*-Pr, *n*-C_5H_{11} R^1=Me, Et, Ph[i]		42–84	61:39 to 75:14:11[j]	29–76	[538]

a) In the case of R=Pr, large amounts of unreacted starting material were recovered.
b) Major isomer: R and CHO have a *cis*-relationship and the nitro group is *trans* to these two groups. Minor isomer: R and CHO have a *trans*-relationship and the nitro group is *cis* to CHO.
c) The reaction was also applied to 1-bromonitroethane, 1-bromonitropropane, and 1-bromo-1-phenylnitromethane (28–68% yield, 95–99% ee), with prevalence of the isomer with R and CHO in a *trans*-relationship and the nitro group *cis* to CHO. Under similar reaction conditions, acyclic α,β-unsaturated ketones were unreactive [536].
d) Major isomer: R and CN have a *cis*-relationship and the nitro group is *trans* to these two groups. Minor isomer: R, CN, and the nitro group have a *cis*-relationship.
e) Major isomer: R and COR^1 have a *trans*-relationship and the nitro group is *cis* to COR^1. Minor isomer: R and COR^1 have a *cis*-relationship and the nitro group is *trans* to these two groups. Note the obtained different diastereomers with respect to those obtained in entries 1 and 2.
f) 1-Bromonitroethane reacted in 54% yield and 97% ee, but phenylbromonitromethane was unreactive.
g) Major isomer: the nitro group is *trans* to the cycle.
h) 3-Methoxycyclohexanone was unreactive, owing to the electron-donating power of this substituent.
i) A twofold excess of bromonitropropane was used. β-Substituted alkenes and vinyl ethers gave no reaction. Only 1*S*,2*S*,3*R* and 1*S*,2*S*,3*S* isomers were recovered. The third diastereomer was not formed very likely for unfavorable interaction with the nitro group.
j) (1*S*,2*S*,3*R*):(1*S*,2*S*,3*S*):(1*R*,2*S*,3*R*) ratio, with C1 is the carbon carrying COR^1 and C2 that carrying NO_2.



R=Ph, *o*-Tol, 2-MeOC$_6$H$_4$, 2-BrC$_6$H$_4$, 2-NO$_2$C$_6$H$_4$, 2-CF$_3$C$_6$H$_4$, *m*-Tol, 3-MeOC$_6$H$_4$, 3-CF$_3$C$_6$H$_4$, 3-BrC$_6$H$_4$, *p*-Tol, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-Me-5-NO$_2$C$_6$H$_3$, 2-furyl

Scheme 1.153 Asymmetric synthesis of 3-thiabicyclo[3.1.0]hexanes.

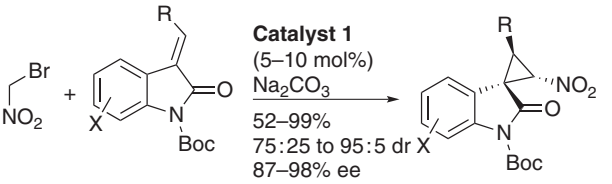
C2 = C-NO$_2$). Moreover, the pseudo-enantiomeric thiourea catalyst led to the enantiomer in comparable yields and ee values [540]. In addition to the examples reported in Scheme 1.154, eq 2, squaramide was also tested with *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate leading to 3-spirocyclopropane-2-oxindole skeleton in 98% yield with 94:6 dr and 96% ee [541]. Finally, an alternative MIRC reaction employs β-bromo-β-nitroalkenes as the 2C synthon. For example, the enantiomer of the spiro derivative depicted in Scheme 1.154 eq 3 was obtained from bromonitrostyrene and 1,3-indandione, although in moderate yield and enantioselectivity [542].

However, the most important instances of this reaction were reported by Dou and Lu [543] and Alèman's group [544], who described the synthesis of spiroxindoles and simple cyclopropanes, respectively (Scheme 1.155). In the former reaction, it should be noted that, in the absence of DABCO, spirocyclopropyloxindoles were obtained without diastereoselectivity. In the presence of DABCO, the cyclopropane opened the ring and the following ring closure led mainly to the most stable isomer, which had the spiro stereocenter inverted with respect to the products obtained by Bencivenni's group (compare eq 1 in both Schemes 1.154 and 1.155) [543].

O-Alkylation to produce furoindoles was never observed, and the reaction was scalable to a 0.5 mmol scale. Alèman proposed a mechanism based on DFT calculations, in which, in the first step, aldehydes and bromo nitroalkenes reacted following the accepted reaction course for Jørgensen–Hayashi catalyst, and in the second step, the intramolecular bromo substitution was catalyzed by DABCO.

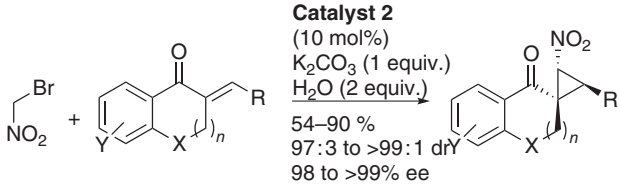
The stereochemistry was based on the inversion of the anion formed with DABCO. With alkyl substituents, π-stacking could occur only with C═O moiety, favoring the eclipsed conformation, which formed **A**. With R^1=Ph, the favorable π-stacking occurred between the two aryl groups, leading to the eclipsed conformation, which formed **B** [544]. Actually, the reaction of (*E*)-1-bromo-1-nitrohex-1-ene, in which π-stacking cannot be formed, did not give cyclopropanation.

Finally, the synthesis of nitrocyclopropanes was achieved from reaction of nitroalkenes and malonate derivatives under oxidative conditions (Scheme 1.156) [545]. It is interesting to compare this reaction and that depicted in Scheme 1.112 [316h]. In fact, both reactions used a malonate and a phenyliodoacetate to form cyclopropanes, but here phenyliodoacetate was used as an oxidant of a Michael adduct, while in Ghanem's reaction, phenyliodoacetate was used to give a phe-



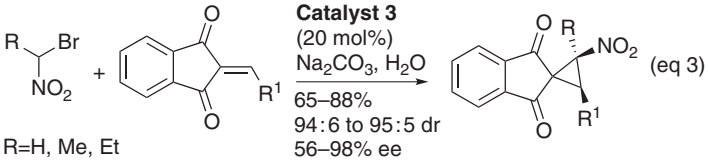
(eq 1)

X=H, 5-Br, 5-Cl, 6-Cl, 5-Me R=CO_2Et, COPh, Bu, Ph, *o*-Tol



(eq 2)

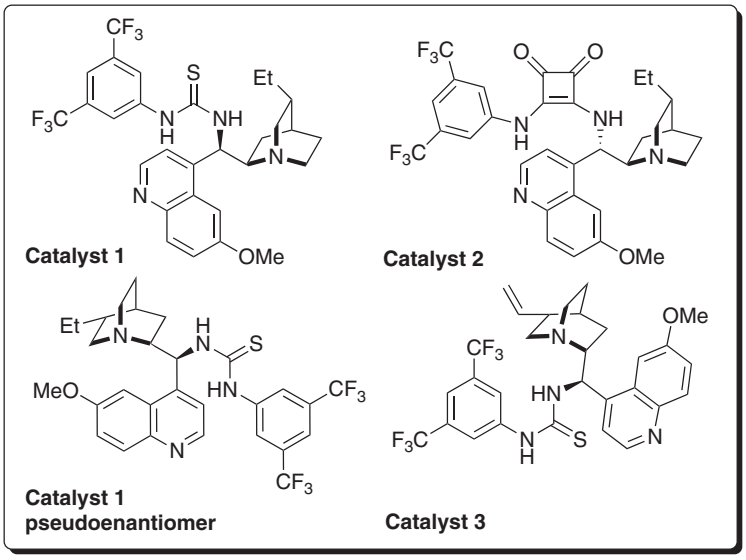
n=1, X=O, CH_2, Y=H, 6-F, 6-Cl, 6-Me
R=Ph, *p*-Tol, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-CNC_6H_4,
o-Tol, 2-BrC_6H_4, 2-$NO_2C_6H_4$, 2,4-$Cl_2C_6H_3$, 1-Naph, 2-thienyl, 3-pyridinyl
n=0, X=CH_2, Y=H, 5-Cl, 5-Br, R=Ph, *p*-Tol



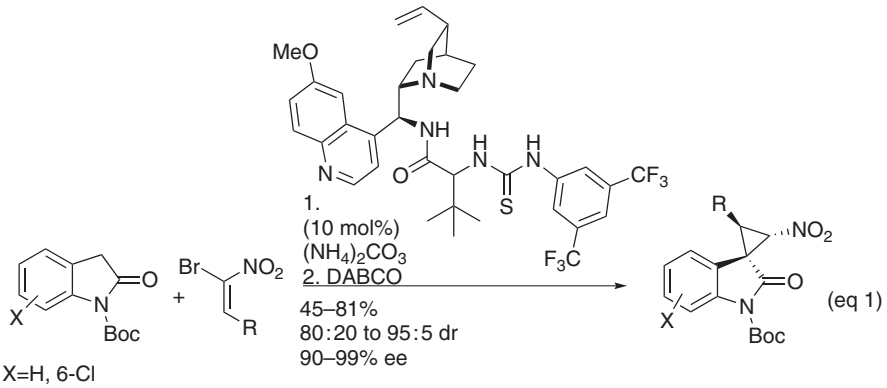
(eq 3)

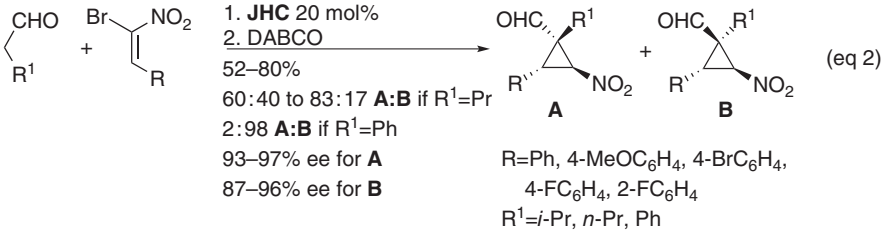
R=H, Me, Et

R^1=Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-CNC_6H_4, 4-*t*-BuC_6H_4, *p*-Tol
o-Tol, 2-BrC_6H_4, 3-FC_6H_4

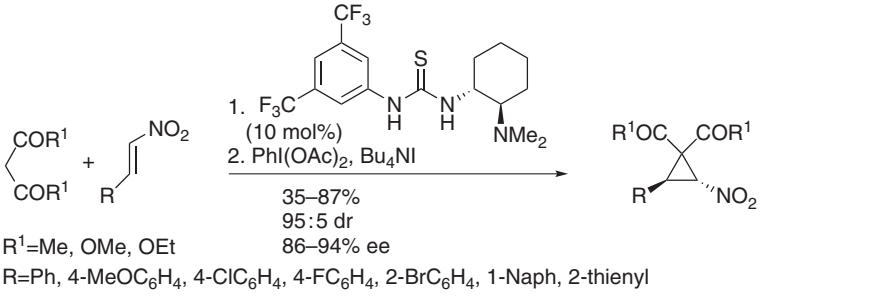


Scheme 1.154 Enantioselective nitrocyclopropanation of alkylidene oxindoles, tetralones, indanones, and chroman-4-ones.





Scheme 1.155 Enantioselective cyclopropanation with β-bromo-β-nitroalkenes.



Scheme 1.156 Synthesis of nitrocyclopropanes by oxidative cyclization.

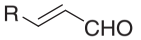
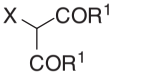
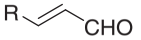
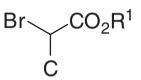
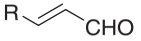
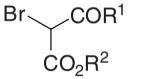
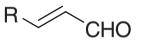
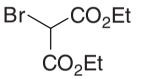
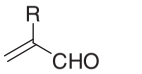
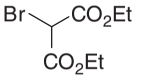
nyliodonium ylide with malonate. However, the introduction of bromomalonates in this reaction avoided the oxidation step (see next section and Table 1.8).

1.4.3.3 Halocarbonyl Compounds

As mentioned at the end of the previous section, bromomalonate and analogs provide a straightforward tool for MIRC reactions. Many examples are reported in the literature with different electron-poor alkene and organocatalysts, and they are listed in Table 1.8.

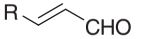
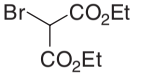
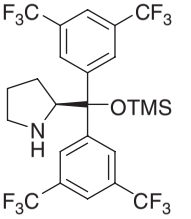
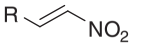
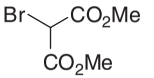
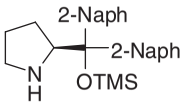
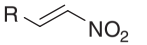
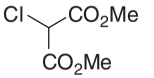
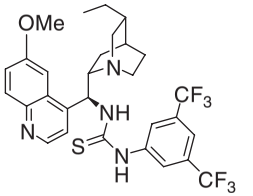
Generally, Jørgensen–Hayashi catalyst and analogs worked via classical iminium or enamine catalysis. On the other hand, with thiourea catalysts from cinchona

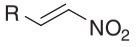
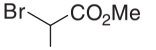
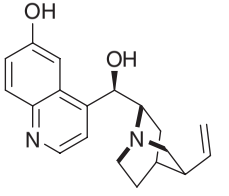
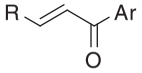
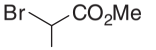
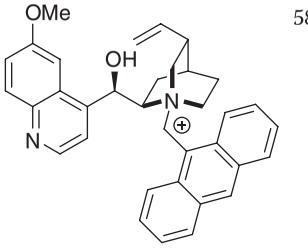
Table 1.8 Asymmetric cyclopropanation of electron-deficient alkenes with bromodicarbonyl compounds.

Alkene	Dicarbonyl compound	Catalyst, base	Yield (%)	dr	ee (%)	References
 R=Ph(CH_2)$_2$, Pr, Me, MeCH=CH, CO_2Et, Ph, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 3-ClC_6H_4, 2-Naph	 R^1=OEt, OBn, Me X=Cl, Br	**JHC** (10–20 mol%), NEt_3 (1 equiv.)	50–88[a]	90:10 to 96:4	90–99 (2*R*,3*S*)	[546]
 R=Ph, 4-$NO_2C_6H_4$, 4-FC_6H_4, 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 2-ClC_6H_4, 2-$MeOC_6H_4$, 2-furyl, Et, *n*-C_5H_{11}	 R^1=Me, Et, Bn, *i*-Pr	**JHC** (10 mol%), 2,6-lutidine (1 equiv.)	42–94	>97:3	90–98 (2*R*,3*S*)	[547]
 R=Ph, 4-$NO_2C_6H_4$, 4-CNC_6H_4, 4-BrC_6H_4, Et, Bu	 R^1=Me, *t*-Bu R^2=Et, Me, *t*-Bu	**JHC** (20 mol%), NEt_3 (1.2 equiv.)	68–95	70:30 to 96.4:1[b]	63–99 (1*S*,2*R*,3*S*)	[548]
 R=Ph, 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 2-BrC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, *p*-Tol, 4-$CF_3C_6H_4$		**JHC** (20 mol%), NEt_3 (0.7 equiv.)	66–88	—[b]	93–98 (2*R*,3*S*)	[549]
 R=H, Bn, Me, Et, Bu, $MeO_2C(CH_2)_2$, *i*-Pr		**JHC** (20 mol%), lutidine (3 equiv.) or NMI (5 equiv.)	35–81	—	79–97 (*R*)	[550]

(Continued)

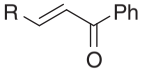
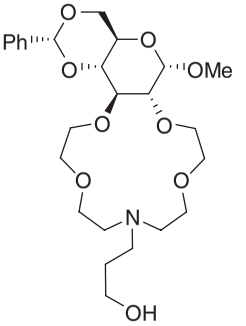
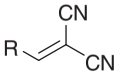
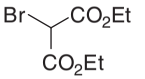
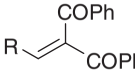
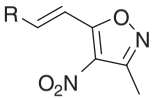
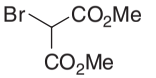
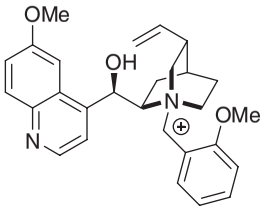
Table 1.8 (Continued)

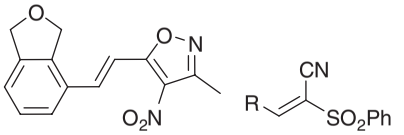
Alkene	Dicarbonyl compound	Catalyst, base	Yield (%)	dr	ee (%)	References
 R=Ph, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 2-furyl		 (20 mol%), H_2O [d]	56–84	91:9	92–99 (2*R*,3*S*)	[551]
 R=Ph, *p*-Tol, 4-$CF_3C_6H_4$, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4, 1-Naph, 2-thienyl, 2-furyl[e]		 (30 mol%), DABCO (1 equiv)	45–69	—	17–49 (2*S*,3*R*)	[552]
 R=Ph, 4-BrC_6H_4, 2-Naph, 2-thienyl		 (2 mol%) DBU	65–73	>99:1	25–47 (2*S*,3*R*)	[553]

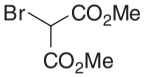
 R=Ph, 4-ClC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-BrC_6H_4, *p*-Tol, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 1-Naph, 2-thienyl, 2-furyl[e,f]		 (5 mol%), DABCO (1 equiv)	47–78	—	75–99 (2*S*,3*R*)	[554]
 Ar=Ph, 4-ClC_6H_4, 4-FC_6H_4, *p*-Tol, R=Ph, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$		 (10 mol%), K_2CO_3 (0.5 equiv)	58–98	—	68–82[g]	[555]

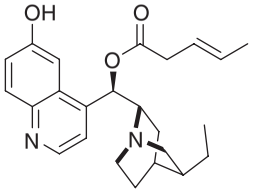
(Continued)

Table 1.8 (Continued)

Alkene	Dicarbonyl compound	Catalyst, base	Yield (%)	dr	ee (%)	References
			28–52	—	42–88[h]	[556]
R=Ph, 4-ClC_6H_4, 4-$NO_2C_6H_4$						
			41–84	—	17–92[g]	[556]
R=Ph, 4-ClC_6H_4, 4-$NO_2C_6H_4$, *p*-Tol, 3-ClC_6H_4, 3-$NO_2C_6H_4$, *m*-Tol, 2-ClC_6H_4, 2-$NO_2C_6H_4$, *o*-Tol						
		(15 mol%)	31–52	—	5–60[h]	[556]
R=Ph, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$		Na_2CO_3 (2 equiv.)				
			91–99	—	84–96 (2*S*,3*S*)[i]	[557]
R=Ph, 4-$MeOC_6H_4$, 2,3-$Cl_2C_6H_3$, 2-ClC_6H_4, 4-FC_6H_4, 2-$MeOC_6H_4$, 2-BrC_6H_4, 2,4-$(MeO)_2C_6H_3$, 2-furyl, 2-thienyl, *n*-C_7H_{15}		(5 mol%), K_3PO_4/H_2O (5 equiv, 1:1)				







(10 mol%),
K_2CO_3 (1 equiv)

73–99	—	58–82 (2*S*,3*R*)	[558]

a) In the reaction of hexa-2,4-dienal, only the double bond in the 2-position reacted. Increasing steric bulk of the ester fragment, the enantioselectivity rose, but yields decreased. The reaction was also applied to ethyl 2-bromo-3-oxobutanoate (84% yield, 94% ee and 75:25 dr) in favor of diastereomer with CO_2Et and CHO in a *cis*-relationship.

b) Aldehydes were prepared *in situ* by oxidation of the corresponding alcohol with MnO_2, thus yields were calculated based on the allylic alcohol.

c) NMI as the base greatly accelerated the reaction rate (3 h vs 144 h), but the yields were generally lowered.

d) An *O*-(trimethylsilyldiaryl)prolinol catalyst incorporating a hydrophobic alkyl side chain in the 4-position was also tested with poor results.

e) Unsuccessful with β-alkylnitroalkenes.

f) The reaction suffered from steric hindrance of the aryl substituent on the nitroalkene.

g) Major isomer: (–); absolute configuration not given.

h) Major isomer: (+); absolute configuration not given.

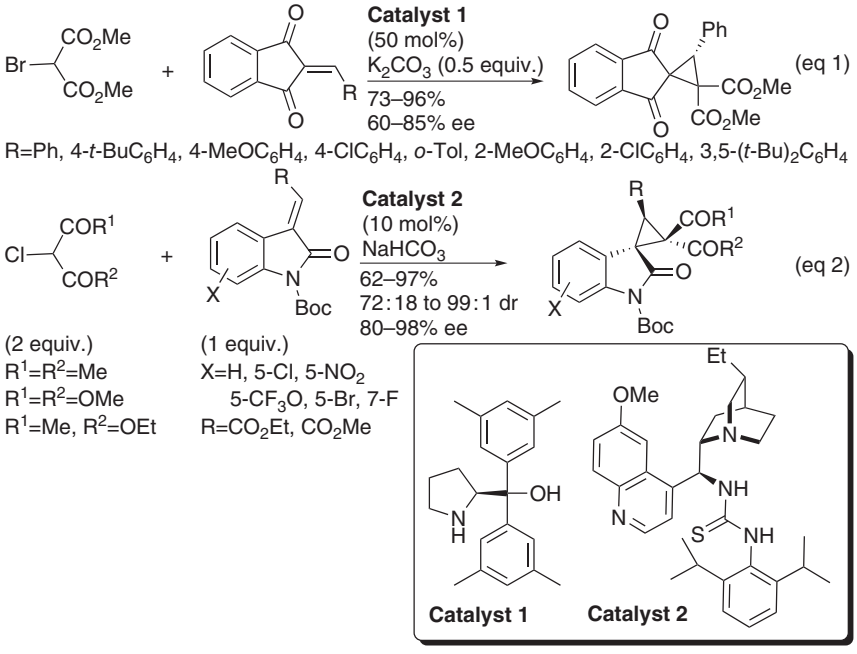
i) A multigram scale-up of the reaction was possible, without loss of yield or enantioselectivity. The use of a pseudo-enantiomeric catalyst gave the opposite enantiomers in similar yield but lower enantiomeric excess.

alkaloids, hydrogen bonds linked the thiourea motif to the carbonyl derivative and the quinuclidine moiety to the β-dicarbonyl nucleophile. The final cyclization geometry was forced by this first stereoselective carbon—carbon bond formation.

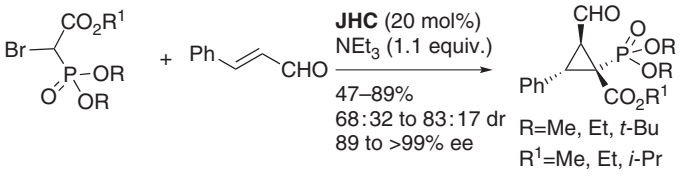
The Wang reaction conditions [547] were applied in the key step of a total synthesis of podophyllic aldehydes [559]. Both (+)- and (–)-podophyllic aldehydes are obtained by switching the organocatalyst in the asymmetric cyclopropanation, which was achieved with **JHC** and ***ent*-JHC** in 91% and 88% yield, respectively, and with always 95% ee.

Jørgensen–Hayashi catalyst (20 mol%) was also applied in the synthesis of chiral cyclopropane-fused tetrahydroquinolines. (1*S*,3*R*)-3-Formylcyclopropanes were obtained from MIRC reaction of dimethyl bromomalonate with *ortho*-N-protected aminophenyl α,β-unsaturated aldehydes in 61–94% yields and 92–97% ee, using $(ClCH_2)_2$ as the solvent with NEt_3 (1.5 equiv.) as the base. These products were then submitted to aza-cyclization under basic conditions for the formation of the tetrahydroquinolines. The two steps could be carried out in a one-pot procedure without affecting stereoselectivity [560].

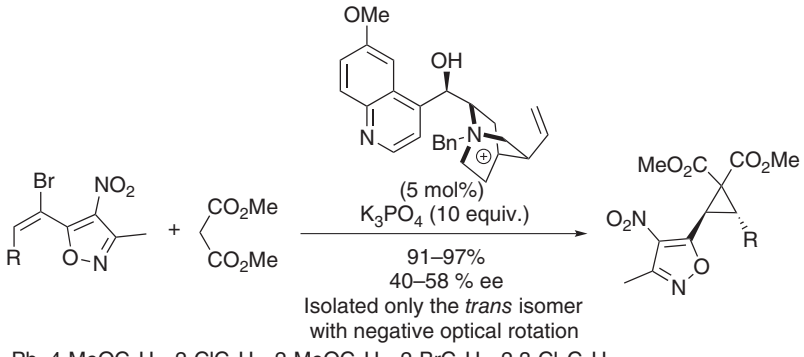
In addition to alkylidenes 1,3-indandiones and oxindoles being useful substrates for MIRC reaction with bromonitroalkanes, they were used for 2-bromo-1,3-dicarbonyl compounds. In fact, (*S*)-cyclopropanes-1,3-indandiones were recovered from the reaction of 1,3-indandiones under modified Jørgensen–Hayashi catalyst (Scheme 1.157, eq 1) [561]. The reaction was also performed with chlorodicarbonyls and oxindoles (Scheme 1.157, eq 2) [562].



Scheme 1.157 Spirocyclopropanation with halodicarbonyl compounds.



Scheme 1.158 Organocatalytic synthesis of α-cyclopropylphosphonates.



Scheme 1.159 MIRC reaction of 4-nitro-5-bromostyrylisoxazoles with dimethyl malonate.

Although α-bromophosphonoacetate synthesis is not simple, Phillips and Barros were able to find a valuable route to these compounds and then to study their reactivity in MIRC reactions (Scheme 1.158) [563]. The (1*R*,2*S*,3*S*)-product stereochemistry was easily predicted by a classical iminium ion mechanism followed by an S_N2 ring-closure step.

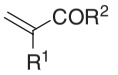
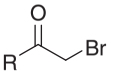
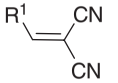
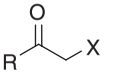
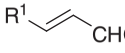
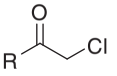
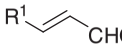
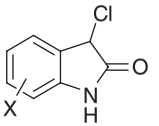
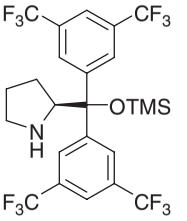
As well as in nitrocyclopropanation reaction, β-bromo-β-nitroalkenes as the 2C synthon can be employed in MIRC reactions. An instance was the reaction of 4-nitro-5-bromostyrylisoxazoles with malonate esters under the catalysis of a cinchona-derived phase-transfer catalyst (Scheme 1.159) [564], providing an alternative route to the reaction proposed by the same research group [557]. It should be noted that malonates with bulkier substituents compared to methyl provided products with lower enantioselectivity, with diphenyl malonate giving only a racemic mixture.

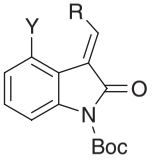
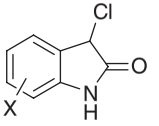
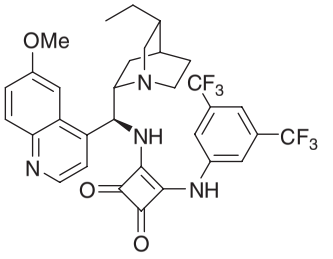
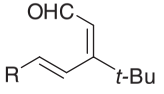
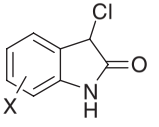
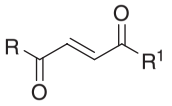
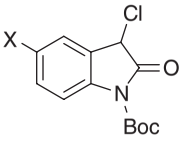
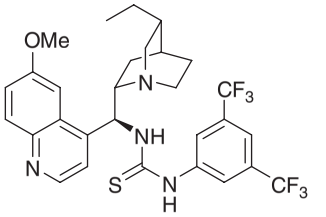
The authors compared these results with those previously obtained and justified the lower enantioselectivity observed with 4-nitro-5-bromostyrylisoxazoles (compare the results reported in Scheme 1.159 with those reported in Table 1.8 [557]) because of a shield of bromine on the NO_2, thus limiting its fundamental interaction with the catalyst.

Finally, the cyclopropanation reaction also proceeds with simple halocarbonyl derivatives (Table 1.9).

Gaunt and coworkers extended their reaction conditions [565] to the intramolecular version, allowing (1*S*,6*R*,7*S*)-[4.1.0]bicycloheptanes to be formed in

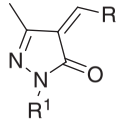
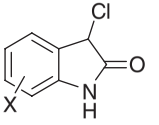
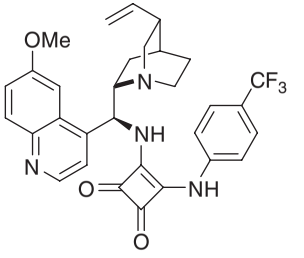
Table 1.9 Asymmetric cyclopropanation of electron-deficient alkenes with α-halocarbonyls.

Alkene	Carbonyl compound	Catalyst, base	Yield (%)	dr	ee (%)	References
 R^1=H, Me, NHBoc, R^2=Ph, 4-$(NEt_2)C_6H_4$, 4-BrC_6H_4, OBn, OMe	 R=O-*t*-Bu, NEt_2	Methoxyquinine (20 mol%) Cs_2CO_3 (1.2 equiv.)	63–96	—	80–97 (1*S*,2*S*)[a]	[565]
 R^1=Ph, 2-ClC_6H_4, *t*-Bu	 X=Cl, Br R^1=Ph, 2-ClC_6H_4	Cinchonidine (1 mol%) Na_2CO_3 (2 equiv.)	27–81	—	20–82 (2*S*,3*R*)	[566]
 R^1=Ph, *m*-Tol, 2-FC_6H_4, *p*-Tol, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4	 R=Ph, *p*-Tol, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-FC_6H_4, 2-ClC_6H_4, 3-BrC_6H_4, 2-furyl, *N*-Boc-3-indolyl	*ent*-JHC (20 mol%) NEt_3 (1 equiv.)	62–85	—	90–99 (1*S*,2*S*,3*S*)[b]	[567]
 R^1=Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 2-thienyl, 2-furyl	 X=H, 4-Br, 5-Br	 (20 mol%) $NaHCO_3$	44–76	83 : 17 to 95 : 5[c]	96 to >99 (1*S*,2*R*,3*S*)	[562b, 568]

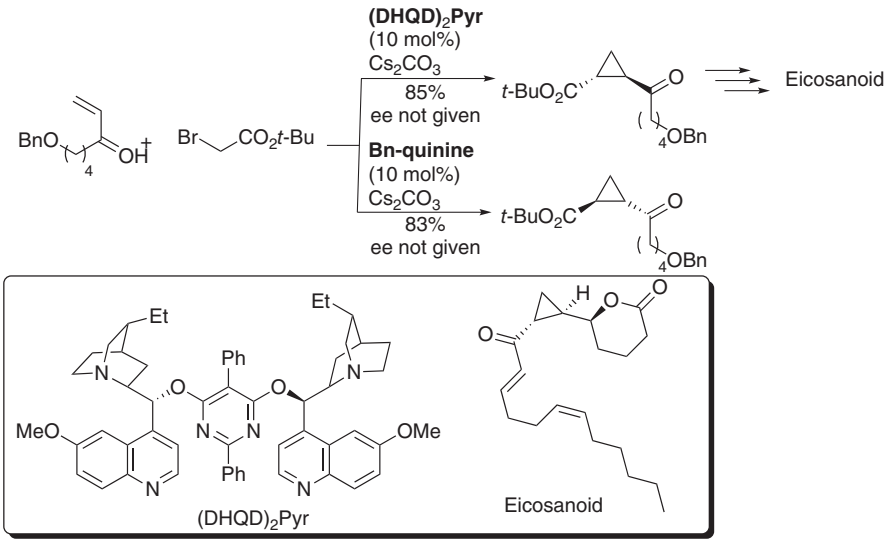
 Y=H, Cl, Br, Me, R=CO_2Me, CO_2Et, CN, 4-$NO_2C_6H_4$	 X=H, 5-NO_2, 5-Br, 7-F	 (20 mol%) $NaHCO_3$	71–99	91 : 9 to 95 : 5	83–99 (1*S*,2*S*,3*S*)	[562b, 568]
 R=Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 3-ClC_6H_4, *o*-Tol, 2-thienyl	 X=H, 5-Br, 5-Cl, 5-Me, 6-F	JHC (5 mol%) Na_2CO_3 (1 equiv.)	56–91	86 : 14 to 94 : 6	92–99 (*E*, 1*R*,2*S*,3*S*)[d]	[569]
 R=R^1=Ph, 4-BrC_6H_4, *p*-Tol, 4-ClC_6H_4, 4-$NO_2C_6H_4$ R=Me, R^1=Ph, 4-$NO_2C_6H_4$	 X=H, Br	 (10 mol%) $NaHCO_3$ (2 equiv.)	53–81[e]	90 : 10 to 95 : 5	68–87 (2*S*,3*S*)	[570]

(Continued)

Table 1.9 (Continued)

Alkene	Carbonyl compound	Catalyst, base	Yield (%)	dr	ee (%)	References
 R=Ph, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 2-BrC_6H_4, R^1=Ph, 4-ClC_6H_4	 X=H, 4-Cl, 4-Br, 6-Cl	 (5 mol%) K_2CO_3 (1 equiv.)	91–99	70 : 30 to 87 : 13	40–74[f]	[571]

a) The other enantiomer could be obtained by using methoxyquinidine.
b) The absolute configuration of the catalyst affected the stereochemistry of C-2, by directing the approach of the chloroketone to the iminium intermediate.
c) Crotonaldehyde and 3-methylbut-2-enal gave moderate diastereoselectivity: 67 (75% ee):33 (87% ee) and 80 (36% ee):20 (89% ee), respectively.
d) The exclusive δ-site selectivity should be noted.
e) Unsaturated keto esters gave noncyclized compound as the main product.
f) Major isomer: (+); absolute configuration not given.



Scheme 1.160 Organocatalytic synthesis of the cyclopropyl moiety of eicosanoid.

27–84% yields, as single diastereomers, and with 95–99% ee [572]. Kumaraswamy, instead, applied this reaction [565] to prepare the cyclopropyl moiety of eicosanoid, one example of the oxylipin class of natural products (Scheme 1.160) [573]. Both enantiomers could be obtained with $(DHQD)_2Pyr$ and the benzyl ether of quinine, but the two enantiomeric excesses were not reported. However, at the end of the multistep synthesis, the stereochemistry of eicosanoid from the product obtained with $(DHQD)_2Pyr$ was found to be superimposable with the natural compound, thus confirming the stereochemistry. The same research group then reported some changes in the reaction procedure: *tert*-butyldiphenylsilyl protection of the starting hydroxy ketone led to the cyclopropane in low yields; the use of 2-bromo-*N*,*O*-dimethylacetamide in place of *tert*-butylbromoacetate yielded the two enantiomeric cyclopropanes in 88% and 85% isolated yield, respectively, but the ee values were not reported again [574].

1.4.4 Metal Catalysis

Only a few instances of such methods are reported. The first example of chiral bis(oxazoline) complexed to Lewis acid that mediated asymmetric cyclopropanations of a Michael acceptor with a sulfur ylide was the cyclopropanation of *N*-enoyloxazolidinones with isopropylidenediphenylsulfonium [472]. Stoichiometric amounts of zinc salts complexed with (4*R*,4′*R*)-2,2′-(propane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole) gave the best results (53–63% yield and 92–95% ee) with (*E*)-3-but-2-enoyloxazolidin-2-one, but the asymmetric reaction of the cinnamate derivatives proceeded in much lower enantiomeric excess, in analogy with that observed with the chiral auxiliary (see Scheme 1.129, eq 2). Moreover, a loss of stereoselectivity was observed with catalytic amounts of Lewis acid.

Chiral Lewis acids complexed with BINOL derivatives were tested in the cycloaddition reactions of 1-seleno-2-silylethene, but low yields (33–41%) and enantioselectivities (43–47%) were observed [575].

Then, bicyclo[3.1.0]hexanes were obtained in 54–99% yields >99 : 1 dr, 74–96% ee by an enantioselective intramolecular cyclopropanation of sulfur ylide allylic esters through a synergistic effect of a bimetallic gold catalyst from dimeric TADDOL–phosphoramidite ligand and $AgNTf_2$ [576]. It should be noted that both the *E* and *Z* isomers and even regioisomer of the allylic moiety (i.e., (*E*)- and (*Z*)-2-buten-1-yl and 1-methyl-2-propen-1-yl frameworks) gave the cyclopropane with the same configuration. Thus, it is possible to use starting materials with low regio and geometric purity to produce diastereomerically pure, enantioenriched (1*S*,4*S*,5*R*)-bicyclo[3.1.0]hexanes. Very likely, after the formation of the allylic–gold complex, the substrate isomers could interconvert before ring-closure reaction. This reaction was also employed for the asymmetric synthesis of butenolide natural products, such as *trans*-(−)-cognac lactone.

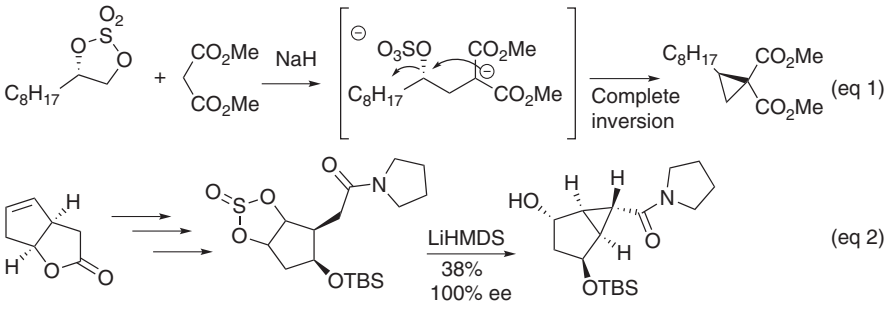
The reaction of dibenzylideneacetone with allyl iodide in the presence of (*S*)-methyl mandelate (1 equiv.) and indium led to the cleavage of the C═O bond and addition of two allyl fragments from the reagent, providing the cyclopropane in 71% yield and 60% ee (*S*-isomer) [577]. This cyclopropane was further submitted to a Ru-catalyzed ring-closing metathesis to generate a norcarene unit ((1*S*,6*S*)-1-(*E*)-2′-(phenylethenyl)-bicyclo[4.1.0]hept-2-ene) without loss of enantiopurity.

The conjugate addition of Grignard reagents to 4-chloro-α,β-unsaturated esters, thioesters, and ketones, catalyzed by CuI-(*R*)-TolBINAP (1.5 mol%), allowed the formation of (*R*,*R*)-1-alkyl-2-substituted cyclopropanes in 50–92% yield and 26–98% ee [578]. The precise control of the amount of Grignard reagent (the best amount was 1.2 equiv.) was essential for obtaining good yields of the cyclopropanes, because a deficiency of the Grignard reagent led to a significant amount of acyclic product, whereas with large excesses, a subsequent addition of the Grignard reagent to the carbonyl moiety of the corresponding cyclopropane occurred. Moreover, the lowest yield and enantioselectivity were observed with phenylmagnesium bromide. The reaction was applied to the syntheses of cascarillic acid and grenadamide (Scheme 1.17 for the structures).

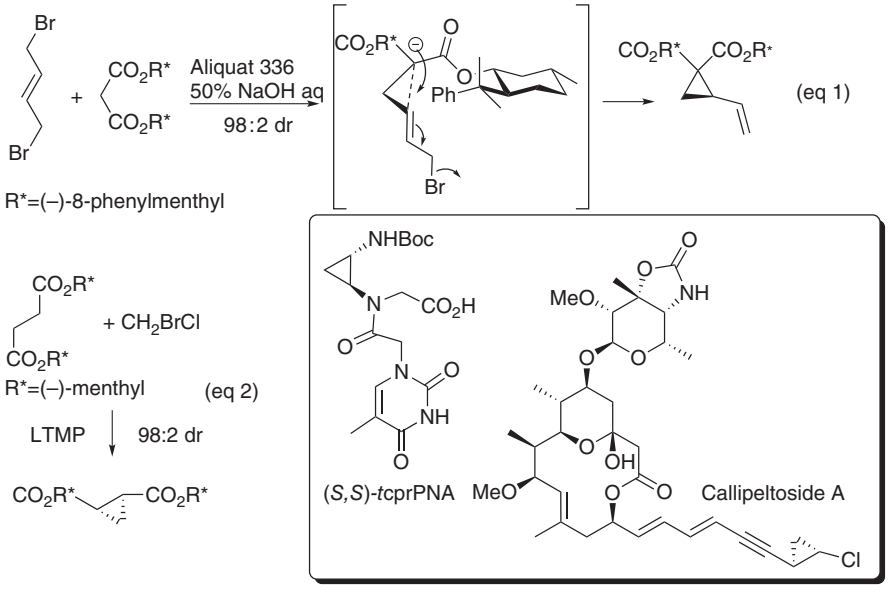
Finally, the enantioselective synthesis of (2*S*,3*R*)-configured nitrocyclopropanes (70–99% yield, >99 de, and 85–99% ee) was achieved by reaction of bromomalonates and nitroalkenes promoted by a chiral nickel complex (5 mol%) in the presence of DBU [579]. The authors proposed that the 1,2-cyclohexanediamine nickel catalyst activated the bromomalonate anion in a bidentate fashion, forcing the attack at the *Si*-face of the double bond of the nitroalkene.

1.4.5 Other Ring Closures

Various other ring-closure reactions forming chiral cyclopropanes have been reported, generally involving the intramolecular displacement of a leaving group, such as halides or sulfonates, with an enolate. One of the fist examples was reported by Sharpless, who allowed reaction of cyclic sulfates of vicinal diols with malonate anions, leading to cyclopropanes with complete inversion of the



Scheme 1.161 Cyclopropanes from vicinal diol cyclic sulfur derivatives.



Scheme 1.162 Cyclopropanes from chiral dicarboxylates.

configuration (Scheme 1.161, eq 1) [580]. Then, these compounds were used for the synthesis of other enantioenriched methylenecyclopropanes [581].

On the other hand, the synthesis of bicyclo[3.1.0]hexane carboxylic acid derivatives was performed by intramolecular cyclopropanation of chiral cyclic sulfites as the key step (Scheme 1.161, eq 2) [582]. It should be noted with respect to the previous reaction that the chiral centers did not involve the sulfite moiety.

Enantioenriched vinylcyclopropane derivative was also obtained by using bis-(–)-8-phenylmenthyl malonates in reaction with 1,4-dibromo-2-butene, because the chiral auxiliary allowed a stable conformation in which the allyl bromide moiety is opposite to the bulky phenylmenthyl substituent (Scheme 1.162, eq 1) [583].

Alternatively, the dianion of (–)-dimenthylsuccinate could be added to bromochloromethane (Scheme 1.162, eq 2) [584]. This method was used in the total

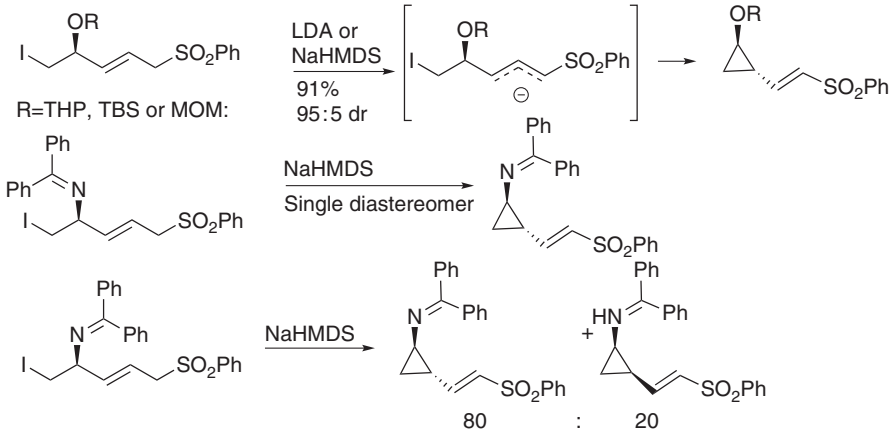
synthesis of ambruticin (Scheme 1.107 for the structure) [585], callipeltoside A [586], and peptide nucleic acids (PNA) with a cyclopropane in the backbone, such as (*S*,*S*)-*t*cprPNA [587].

The diastereoselective iodocarbocyclization of bis-(–)-8-phenylmenthyl allylmalonate produced cyclopropylmethyl iodide in 89% yield and with 93% ee when titanium tetra(*tert*-butoxide) and pyridine were used to trap the HI generated during the reaction [588]. It should be noted that attempts to induce the enantioselectivity using a chiral titanium complex instead of the chiral auxiliary failed [589].

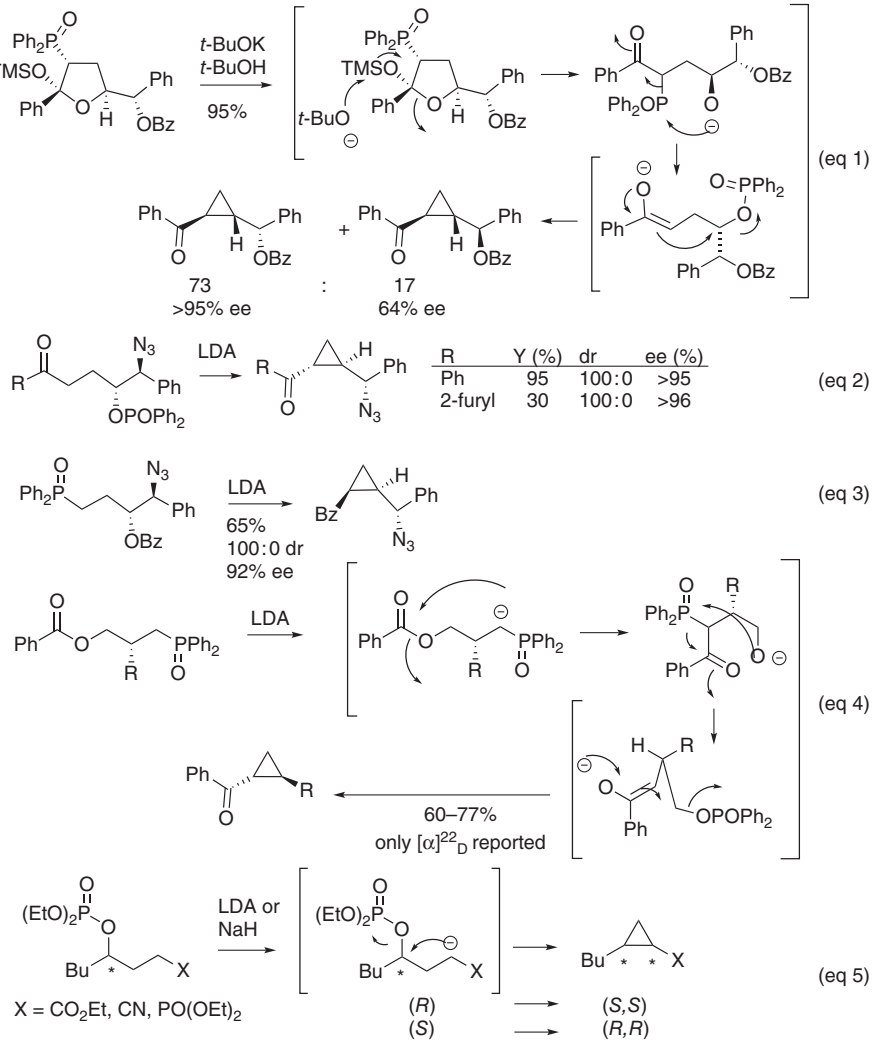
The intramolecular rearrangement of both isomers of (allyloxy)dimesitylsilyllithium reagent bearing a phenyl group on the olefin part exclusively led to dimesityl-[(1*R*,2*S*,3*S*)-2-methyl-3-phenylcyclopropyl]silanol (68–79% yield, 98% ee) [590]. The substituent effect was revealed by *ab initio* calculations in terms of the regioselectivity in the reaction of silyllithiums with an olefin. Tandem lithium-ene cyclization, followed by thiophenoxide expulsion, produced only one vinylcyclopropane diastereoisomer, when starting from a chiral allylic alcohol [591].

The allylic sulfones are also acidic enough to easily generate anions, which can cyclize if a leaving group is present in an appropriate position. Thus, Diez *et al.* developed a highly diastereoselective synthesis of chiral cyclopropanols [592] and of chiral *N*-diphenylmethylene-2-vinyl-substituted cyclopropylamines (Scheme 1.163) [593]. It is worth noting the exclusive three-membered instead of the five-membered ring closure and, in the case of imines, the influence of the *E*,*Z*-isomerism on the diastereoselection of the reaction. This methodology was then applied to the synthesis of a large variety of cyclopropanol amino acids due to its simplicity, high yield, and high diastereocontrol [594].

Ring-closing reactions involving phosphorus transfer, to generate both nucleophile and leaving group, yielded cyclopropanes. In fact, under basic conditions, chiral silyloxytetrahydrofuranes led to a mixture of two *trans*-cyclopropanes with a poor diastereoselectivity via phosphine oxide-mediated cascade reactions (Scheme 1.164, eq 1) [595]. Similarly, γ-azido ketones yielded *trans*-cyclopropanes (Scheme 1.164, eqs 2 and 3) [596].



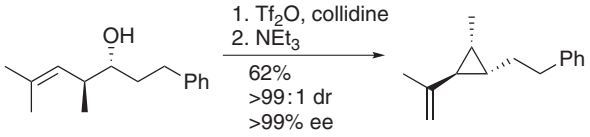
Scheme 1.163 Asymmetric cyclopropanations of allyl sulfones.



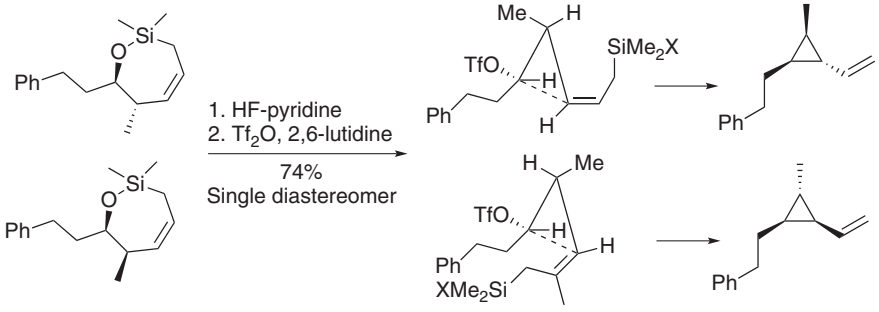
Scheme 1.164 Phosphorus-mediated asymmetric cyclopropanations.

More recently, a three-step cascade reaction was reported to produce cyclopropanes from phosphine oxides (Scheme 1.164, eq 4) [597]. Unfortunately, starting materials had to be prepared via a long, moderate yielding and tedious reaction procedure, in which a chiral oxazolidinone was the chiral auxiliary. Krawczyk and coworkers were able to easily prepare enantioenriched phosphates, and the cyclization of (*S*)-phosphates was found to lead to (1*R*,2*R*)-cyclopropanes (Scheme 1.164, eq 5) [598]. Interestingly, the enantiomeric excess of the products remained very close to that of the starting materials in both reactions.

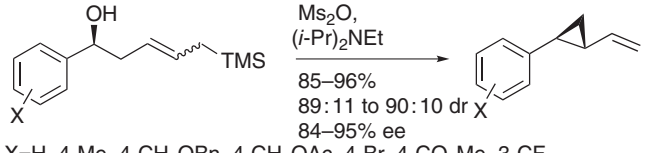
Cationic cyclizations that lead to cyclopropanes are scarce, because the behavior of the C_4H_9 cation cannot be efficiently controlled, except when two methyl groups (*tert*-cyclopropylmethyl) [599] or a silicon substituent gives more stable cations. In



Scheme 1.165 Cyclopropane from cyclization of chiral homoallylic alcohols.



Scheme 1.166 Cyclopropane from chiral silyloxycycloheptene.



X=H, 4-Me, 4-CH_2OBn, 4-CH_2OAc, 4-Br, 4-CO_2Me, 3-CF_3

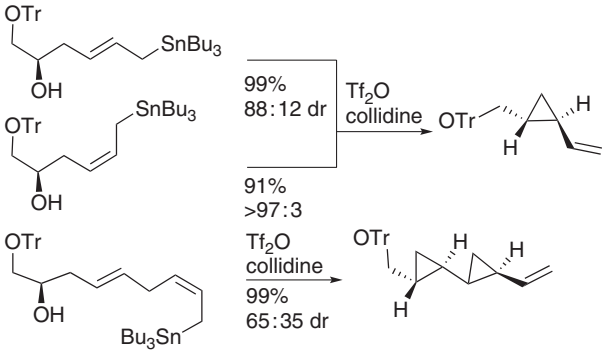
Scheme 1.167 Asymmetric cyclopropanation of allylsilane homoallylic alcohols.

the first case, cyclopropanes were obtained in 61–93% yields, and the chirality was efficiently transferred, as starting from the enantiopure homoallylic alcohol, the corresponding product was obtained with greater than 99% ee (Scheme 1.165 for an example).

In the second case, silyloxycycloheptene was opened by a nucleophile. The two diastereoisomers of the silyloxycycloheptene led to *trans*- or *cis*-cyclopropane, owing to two different transition states in which the $A^{1,3}$ strain was minimized for the -CH_2SiMe_2X substituent (Scheme 1.166) [600].

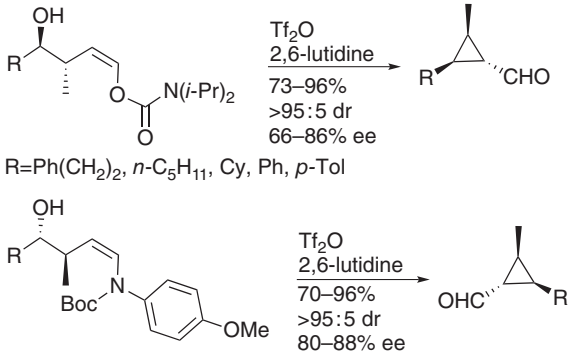
Moreover, allylsilane homoallylic alcohols were a source of vinylcyclopropanes through an intermediate β-silylcyclopropylcarbinyl cation (Scheme 1.167) [601]. It should be noted that electron-withdrawing substituted phenyl rings showed higher enantiospecificity for the cyclization, whereas an appreciable loss of enantiomeric purity was observed with electron-rich ones.

In addition, White and coworkers studied the corresponding reaction with a tributylstannyl substituent instead of TMS [602]. Both (*E*)- and (*Z*)-olefins were submitted to the same methodology, affording the same products with a higher diastereoselectivity from the (*Z*)-olefin (Scheme 1.168). Moreover, a nonconju-

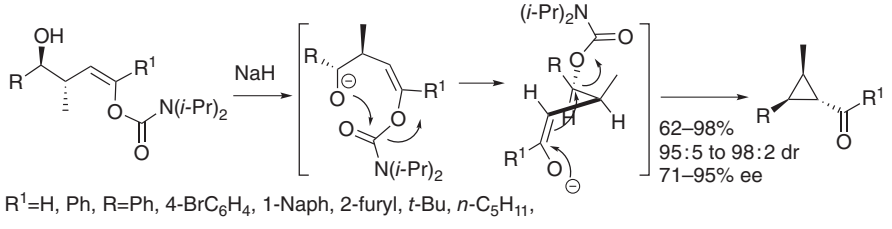


Scheme 1.168 Asymmetric cyclopropanations of tributylstannane homoallylic alcohols.

gated diene led to the quantitative formation of three enantiomerically pure, stereoisomeric bicyclopropanes in which the *trans,syn,trans*-isomer was predominant. This bicyclopropane could be converted into an intermediate employable in the synthesis of FR-900848 (Scheme 1.21 for the structure) [602] and into the key cyclopropane intermediate for the synthesis of solandelactones (Scheme 1.5 for the structure) [603].



Scheme 1.169 Asymmetric cyclopropanations of *O*- and *N*-enecarbamates.

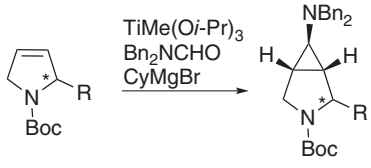


Scheme 1.170 Asymmetric cyclopropanation of homoallylic alcohols.

Then the reaction was extended to *O*- and *N*-enecarbamates, thus providing both enantiomers of the cyclopropanecarboxaldehydes (Scheme 1.169) [604]. The ring closure took place with inversion of configuration at the alcohol center in a stereospecific manner.

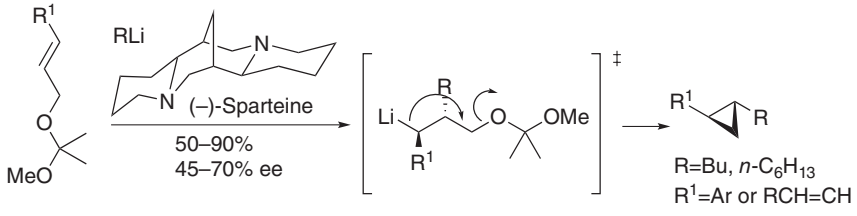
However, the simple treatment of chiral homoallylic alcohols with NaH furnished the corresponding cyclopropanes with excellent diastereoselectivity, complete chirality transfer, and high efficiency (Scheme 1.170) [605]. Very likely, the *N*,*N*-diisopropylcarbamoyl group migrated to the O-4 atom, forming a (*Z*)-enolate, which underwent cycloalkylation by nucleophilic substitution of the carbamate group with stereoinversion. In this step, the enolate moiety had to occupy an *anti*-position to avoid steric repulsion with the methyl and R groups.

The Ti-mediated reductive cyclopropanation reactions of chiral 3,4-dehydroprolinol derivatives in the presence of dibenzylformamide should also be mentioned (Scheme 1.171) [606]. Application of similar conditions to L-*N*-allyl-(*N*,*N*-dibenzyl) prolineamide allowed the synthesis of tricyclic cyclopropylamine [607].

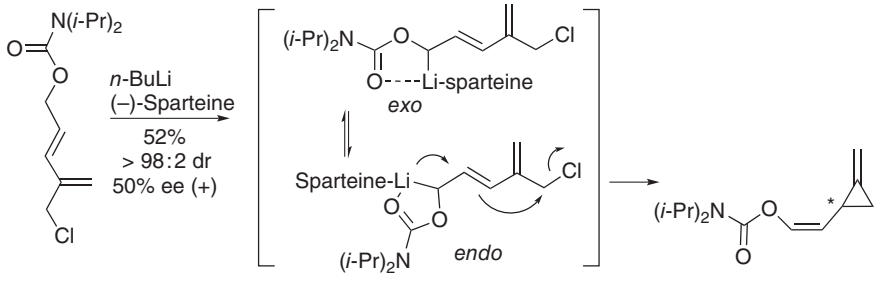


R	Y (%)	dr	ee (%)
(*S*)-CO_2-*t*-Bu	50	100:0	95
(*R*)-CH_2OH	69	100:0	100

Scheme 1.171 Ti-catalyzed reductive asymmetric cyclopropanation reactions.



Scheme 1.172 Enantioselective carbolithiation of alkenes.



Scheme 1.173 Asymmetric synthesis of via (–)-sparteine-induced intramolecular S'_E-cycloalkylation reaction.

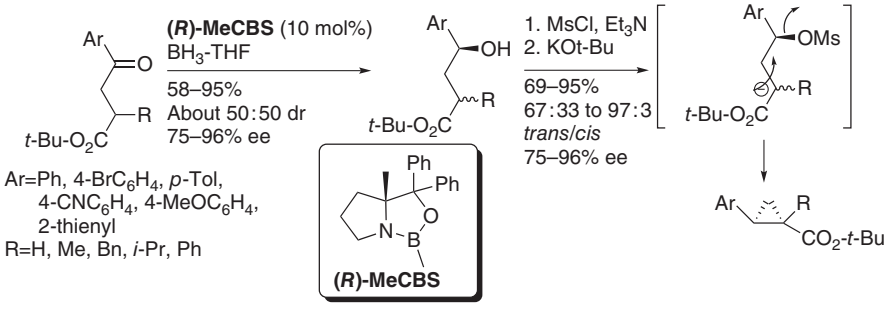
The methods reported until now start from chiral substrates, but some ring-closing reactions are also reported under chiral catalysis. As an example, chiral cyclopropane subunits were prepared from alkenes via (–)-sparteine-catalyzed carbolithiation reaction (Scheme 1.172) [608].

In other reactions, the alkyllithium reagent can act as a base, analogously with reaction depicted in Scheme 1.163. In such a manner, an asymmetric synthesis of (*Z*)-1-methylene-2-vinylcyclopropanes by intramolecular S'_E-cycloalkylation reaction was reported (Scheme 1.173) [609]. The stereoselectivity of the reaction was explained by the fact that the α-lithiated intermediate reacted from the (2*E*)-*endo* rather than (2*E*)-*exo* conformation. However, the stereochemistry of the chiral center was not attributed, and only a positive optical rotation was reported.

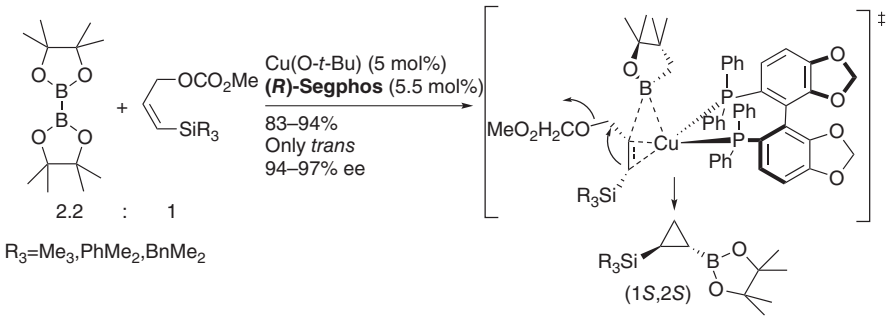
Later, further studies on the mechanism were conducted, starting from (*E*)-5-chloro(bromo)-4,4-dimethylpent-2-enyl diisopropylcarbamate [610]. Chloro derivative gave better yields (90% vs 79%) and selectivity (57% vs 38% ee), and the product was recognized as a (*Z*)-configured enantioenriched (*S*)-vinylcyclopropane. The deprotonation was demonstrated to give mainly (*S*)-lithium derivative. However, the product was demonstrated to arise through an *anti*-S'_E pathway, thus, the reaction should proceed via a dynamic kinetic resolution in which the rates of epimerization and cycloalkylation were of similar magnitude.

The preparation of (1*R*,2*S*)-1-amino-2-vinylcyclopropane-carboxylic-acid-derived sulfonamide and ethyl ester was attempted by a cinchona phase-transfer organocatalysis, starting from (*E*)-*N*-alkylideneglycine ethyl ester and 1,4-dibromo(chloro)-2-butenes. Unfortunately, only the reaction of (*E*)-*N*-benzylideneglycine ethyl ester and *trans*-1,4-dibromo-2-butene led to satisfactory yields (88%), diastereo- (95:5), and enantioselectivity (80%) [611]. However, these compounds are common building blocks in the preparations of potent HCV NS3 protease inhibitors.

A quite different manner of using chiral catalysis was represented by the synthesis of an enantioenriched compound, which subsequently underwent stereoselective ring closure. For instance, 4-aryl-4-oxobutanonic esters, readily available by Friedel–Crafts acylation reaction, were asymmetrically and chemoselectively reduced to an alcohol, the alcohol activated, and the ring closed through the ester enolate. The cyclization step afforded the (*S*,*S*)-configured cyclopropanes without affecting the enantiomeric excess of the starting alcohol (Scheme 1.174) [612].



Scheme 1.174 Intramolecular ring closure of activated chiral benzyl alcohols.



Scheme 1.175 Synthesis of optically active boron–silicon bifunctional cyclopropanes.

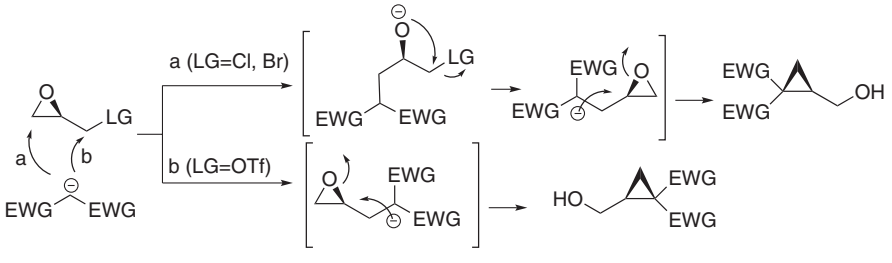
Finally, allylcarbonates with a γ-silicon substituent with bis(pinacolato)diboron afforded (*S*,*S*)-cyclopropylboronates using copper(I)-(*R*)-segphos catalyst [613]. The reaction rate greatly depended on the configuration of the substrates, and *Z*-isomers gave the best results. The stereochemical outcome was explained surmising a transition state free from steric repulsion between the substituents of the (*Z*)-allylcarbonate and the phenyl groups of the ligand (Scheme 1.175). Then, the boron functionality was stereoselectively modified by Suzuki–Miyaura coupling and converted to cyclopropylamines [613, 614].

1.5 Miscellaneous Reactions

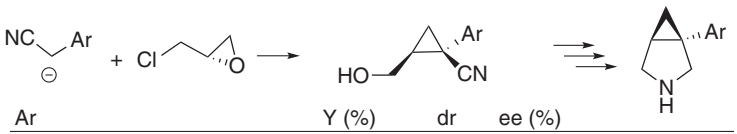
Various other reactions forming chiral cyclopropanes with different mechanisms with respect to those reported in the previous sections have been reported, and they are listed in this section.

1.5.1 Rearrangement of Chiral Oxiranes

Epichloro- or epibromohydrins and glycidol derivatives have been commonly used to form cyclopropanes, as they are readily available. Two pathways are possible depending on the nature of the leaving group: the displacement of the leaving group after (path a) or before the ring opening (path b) of the epoxide (Scheme 1.176) [615]. It should be noted that, depending on what mechanism is



Scheme 1.176 Mechanisms for the formation of chiral cyclopropanes from chiral epoxides.



Ar	Y (%)	dr	ee (%)	
3,4-$Cl_2C_6H_3$	95	85:15	96	DOV21947
p-Tol	95	85:15	>97	Bicifadine

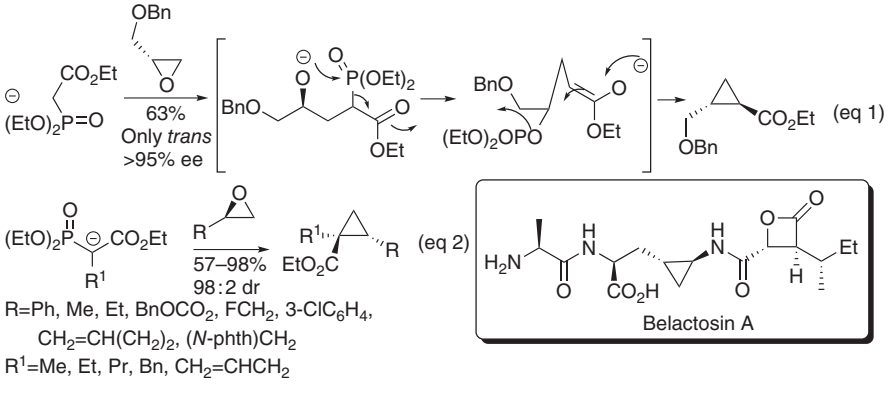
Scheme 1.177 Asymmetric epoxy nitrile coupling.

operative, the opposite enantiomers are formed. Nucleophiles include carbanions derived from malonates, β-phosphonates, ketones, sulfones, and nitriles.

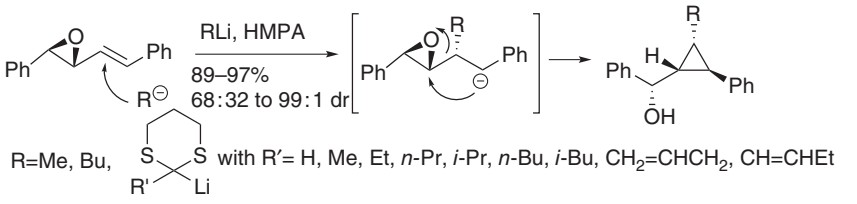
For instance, the reaction between sodium dimethylmalonate and optically pure epichlorohydrin proceeded through "path a" and the corresponding product was isolated as bicyclic lactone by transesterification reaction between the carboxylate and hydroxy moieties in *cis*-relationship (36% yield and 93.4% ee) [616]. Phenyl- or phenylsulfonylacetonitrile and epichlorohydrin led to substituted chiral cyclopropane lactones in 67% and 82% yield and with 96% and 98% ee, respectively [617]. Other arylacetonitriles afforded the corresponding hydroxyl nitriles in high ee values, when the aggregation state of the nitrile anion was properly manipulated [618]. This methodology was successfully applied to the total syntheses of two neurotransporters, bicifadine and DOV21947, in a single-stage process without the isolation of any intermediates (Scheme 1.177).

Conversely, glycidyl triflate (92% ee) and sodium di-*t*-butyl malonate led to the formation of the lactone with the opposite configuration (therefore by "path b") in 48% yield and 91% ee [619]. The use of glycidyl 3-nitrobenzenesulfonate and cesium fluoride improved the yields [620]. Robinson and Aggarwal applied this strategy in the total synthesis of solandelactone E (Scheme 1.5 for the structure) [621]. The leaving group was a sulfonate from (2*R*,3*R*)-2-hydroxymethyl-3-allyloxirane, the nucleophile lithiated acetonitrile, and the (1*R*,2*R*)-2-((*R*)-1-hydroxybut-3-enyl)cyclopropanecarbonitrile was recovered in 77% yield (*trans*/*cis* = 85:15).

In Scheme 1.164, phosphorus derivatives mediated asymmetric cyclopropanations. Optically pure epoxides were used to transfer the enantiomeric excess to



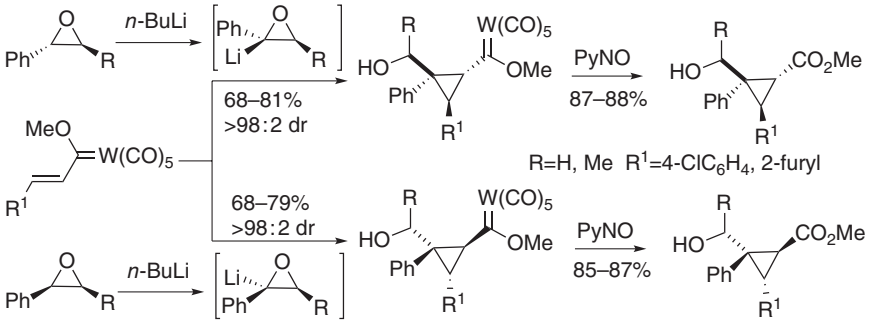
Scheme 1.178 Wadsworth–Emmons cyclopropanation of chiral epoxides.



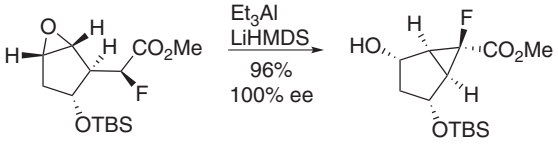
Scheme 1.179 Asymmetric cyclopropanation of phenyl vinyl epoxide with lithiated carbanions.

cyclopropane by the Wadsworth–Emmons cyclopropanation. For example, (*S*)-glycidol benzyl ether led to the corresponding enantiopure cyclopropane. The proposed mechanism involved an epoxide opening, followed by a migration of the phosphonate group from carbon to oxygen and a subsequent S_N2 ring closure (Scheme 1.178, eq 1) [622]. This reaction was also applied to a total synthesis of a potent antitumor agent, belactosin A. Later, Bray and Minicone extended the reaction scope of this reaction (Scheme 1.178, eq 2) [623]. They did not report enantiomeric excesses, but they affirmed that the chiral center of the epoxides retained the configuration in the final product. Wadsworth–Emmons cyclopropanations are known to be easily scalable, and therefore, the potential utility of these procedures could be greater if they are scalable, in turn.

Chiral phenyl vinyl epoxide reacted with lithiated 2-alkyl-1,3-dithiane or alkyllithium in the presence of HMPA (Scheme 1.179) [624]. The reaction was considered a tandem conjugated addition–epoxide opening sequence.



Scheme 1.180 Asymmetric cyclopropanations of α,β-unsaturated Fischer carbene complexes with lithiated oxiranes.



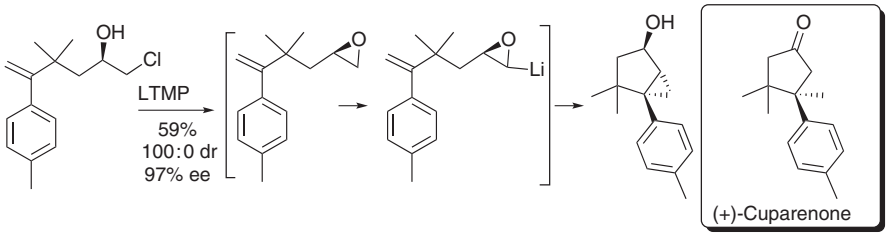
Scheme 1.181 Asymmetric Et_3Al-mediated intramolecular opening of epoxide.

Lithiated chiral oxiranes were also condensed onto α,β-unsaturated Fischer tungsten-derived carbene complexes in a diastereo- and enantiospecific manner, providing the corresponding tetrasubstituted cyclopropane carbenes, then converted into the corresponding cyclopropanecarboxylates (Scheme 1.180) [625].

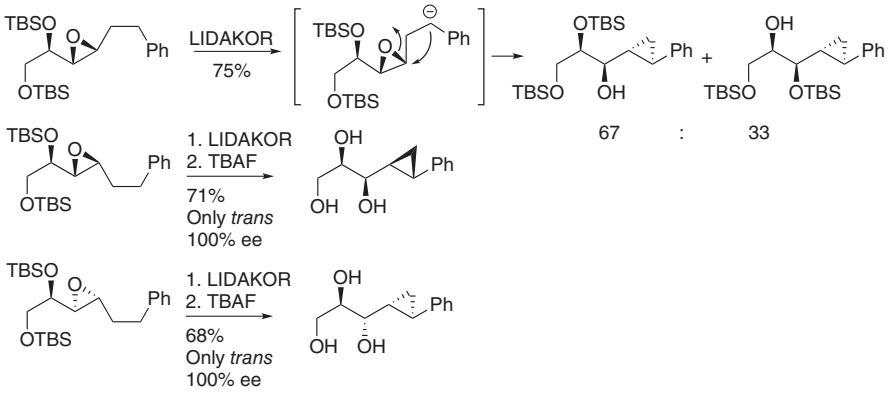
In addition, several examples of intramolecular opening of chiral epoxides have been reported. The Et_3Al-mediated synthesis of bicyclo[3.1.0]hexane system was an example (Scheme 1.181) [626]. Interestingly, this transformation provided perfect F-*endo* selectivity. It was also applied to the total syntheses of metabotropic glutamate receptor agonists (mGluR2/3 agonists).

LTMP-induced intramolecular cyclopropanation of unsaturated terminal epoxides provided an efficient and completely stereoselective entry to bicyclo[3.1.0]hexan-2-ols and bicyclo[4.1.0]heptan-2-ols. This synthesis was applied in a total synthesis of (+)-cuparenone, starting from a chiral chlorohydrin converted into the corresponding bicyclohexanol (Scheme 1.182) [627].

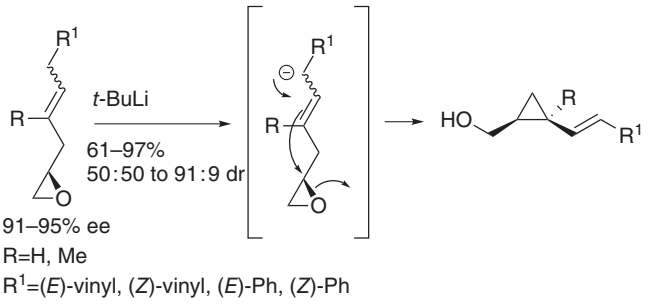
Superbasic mixtures, such as LIDAKOR, allowed the 3-*exo*-cyclization of suitably substituted oxiranes lacking strong electron-withdrawing substituents to be achieved [628]. The reaction was highly stereoselective, leading to the corresponding *trans*-cyclopropanes. Moreover, the outcome of the rearrangement process did not depend on the configuration of the starting chiral oxirane ring or in the relative stereochemistry of the silyloxy substituent. The reaction mixture always contained two isomers, owing to a *tert*-butyldimethylsilyl



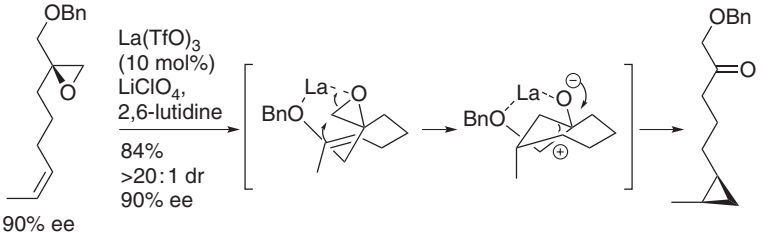
Scheme 1.182 Asymmetric LTMP-mediated intramolecular cyclopropanation of chlorohydrin.



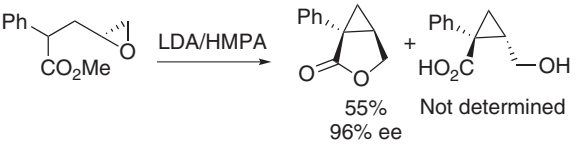
Scheme 1.183 LIDAKOR-promoted rearrangements of oxiranes to cyclopropanes.



Scheme 1.184 Synthesis of cyclopropane from terminal enantioenriched epoxides.



Scheme 1.185 Methylene-transfer from enantioenriched epoxides.



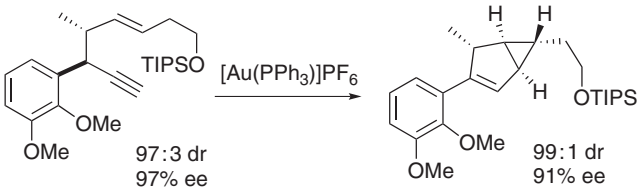
Scheme 1.186 An enantioselective synthesis of levomilnacipran.

group migration to the neighboring oxygen during the isomerization process. However, fluoride deprotection of silyl groups overcame this drawback (Scheme 1.183).

Terminal enantioenriched epoxides were prepared in 53–98%, with 91–95% ee via organocatalytic asymmetric enamine chlorination with the MacMillan catalyst. If a *Z*-double bond was present in the 2-position of the side chain of the epoxides, these compounds were stereoselectively rearranged into cyclopropanes (Scheme 1.184) [629].

Just one example of a methylene-transfer reaction from enantioenriched epoxides obtained from Sharpless asymmetric epoxidation to furnish the enantioenriched cyclopropane was reported (Scheme 1.185) [630].

Starting from a bicyclolactone prepared by a stereoselective rearrangement of the corresponding enantioenriched epoxide, an enantioselective synthesis of

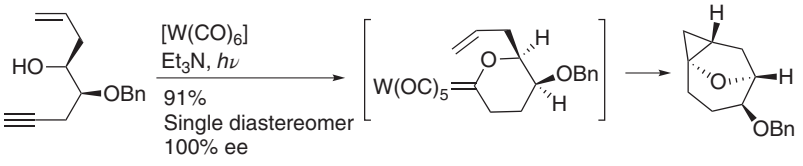


Scheme 1.187 Au-catalyzed asymmetric cyclopropanation of 1,5-enynes.

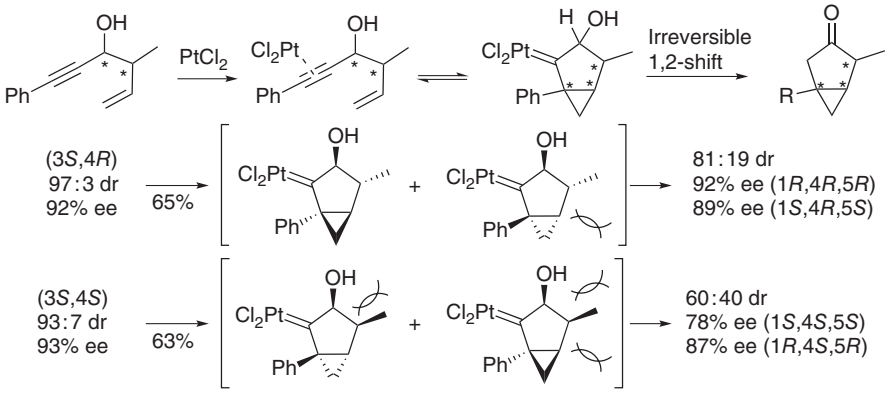
(–)-milnacipran was set up (Schemes 1.186 and 1.38 for the structure of (–)-milnacipran) [631].

1.5.2 Cycloisomerization of 1,*n*-Enynes

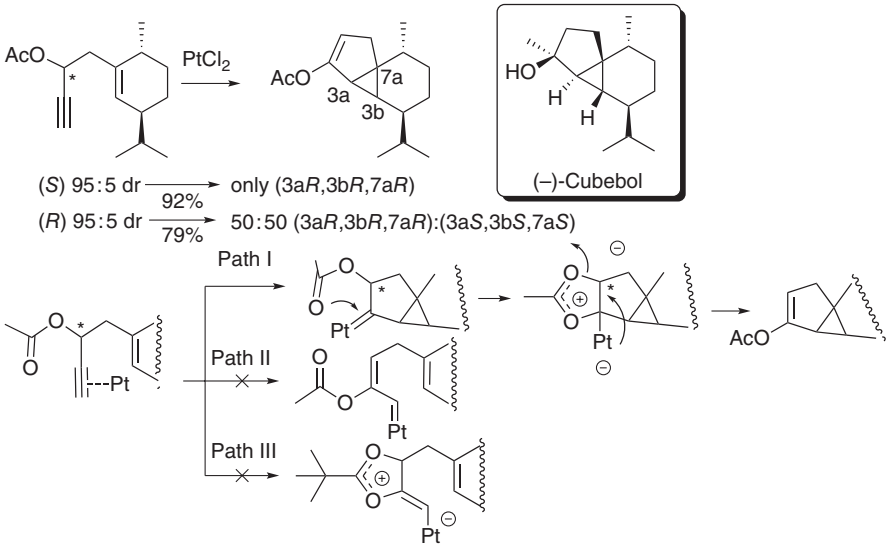
The transition-metal-catalyzed cycloisomerization reaction of 1,*n*-enynes has emerged as an atom-economical process for the preparation of diverse cyclic compounds over the last 90 years [632]. Obviously, in the recent years, some enantioselective versions of this reaction have been set up. For instance, in the presence of a gold catalyst, enantioenriched 1,5-enynes underwent cycloisomerization into bicyclo[3.1.0]hexane derivatives (Scheme 1.187 depicts an example) [633]. In another example, trichloro(pyridine)gold(III) stereospecifically rearranged the enantioenriched enyne derivatives into the corresponding bicyclo[3.1.0]ketones with over 19:1 dr [634].



Scheme 1.188 W-catalyzed asymmetric cyclopropanation of hydroxylated enynes.



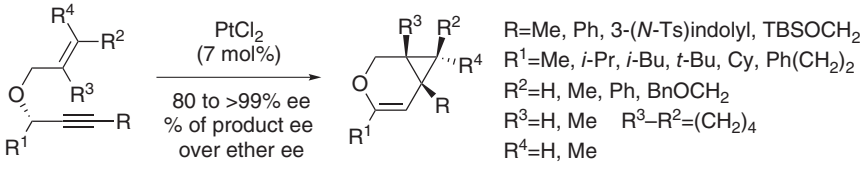
Scheme 1.189 Pt-catalyzed asymmetric cyclopropanations of hydroxylated enynes.



Scheme 1.190 Pt-catalyzed asymmetric cyclopropanations of propargyl esters.

Irradiation of a chiral hydroxylated enyne in the presence of $W(CO)_6$ provided the corresponding tricyclic product as a single stereoisomer (Scheme 1.188) [635]. In addition, a platinum catalyst can catalyze this reaction if a hydroxyl group at the propargylic position is present on the chiral enyne (Scheme 1.189) [636]. An irreversible 1,2-hydrogen shift from the bicyclo[3.1.0]hexane carbene skeleton moved the equilibrium platinum complex–platinum carbene toward products. Steric hindrance in the bicyclo[3.1.0]hexane skeleton was invoked to explain the significantly higher de in the *syn* series.

Platinum also catalyzed cycloisomerization of a chiral propargyl ester (Scheme 1.190) [637]. It should be noted that in the case of acetates, (*S*)-propargyl ester afforded the corresponding tricyclic product with high selectivity, paving an efficient route to (–)-cubebol, while with (*R*)-configured isomer, the reaction was not stereoselective. This feature persuaded the authors that the configuration of the stereogenic center carrying the acetate unit translated into the stereochemistry of the product (Scheme 1.190, path I). Consequently, a vinylcarbene intermediate cannot be formed prior to cyclization (Scheme 1.190, path II), because it implied that both isomers led to the same product distribution. Almost at the same time, another research group published the same strategy, starting from pivaloates instead of acetates and providing similar results (70–74% yields, (*R*)-pivaloate gave 80:20 dr,



Scheme 1.191 Cycloisomerization of enantioenriched allyl propargyl ethers.

whereas (*S*)-pivaloate gave 60:40 dr) [638]. In order to justify their results, these authors postulated a concerted *C*—C bond-formation/*C*—O bond-breaking pathway, (Scheme 1.190, path III). Soriano and Marco-Contelles settled the issue by computational methods performing a detailed relaxed potential energy surface scan [639]. The result of these calculations allowed for retaining the mechanism depicted in Scheme 1.190, and path I is the most plausible to justify the stereochemical outcome of the reactions.

Finally, enantioenriched allyl propargyl ethers were reported to give an enantiospecific cycloisomerization to oxabicycloheptanes (Scheme 1.191) [640]. The stereochemistry depicted in Scheme 1.191 was confirmed by X-ray structural analysis.

However, the use of chiral catalysts represents an improvement also in this procedure. Actually, catalytic methodologies have gradually replaced those starting from chiral reagents more recently.

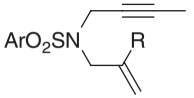
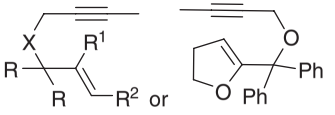
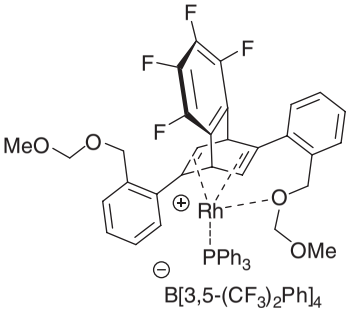
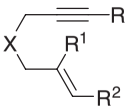
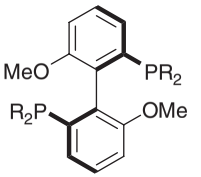
For instance, the enantioselective cycloisomerization of nitrogen-bridged 1,6-enynes, affording azabicyclo[4.1.0]hept-4-enes, was widely studied (Table 1.10). The reaction mechanism depicted in Scheme 1.192 is generally accepted for these reactions. The relative steric bulk of both the nitrogen and the catalyst substituents assembled the more stable conformation, which directed the subsequent 6-*endo*-dig cyclization, responsible for the final stereochemistry.

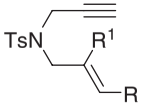
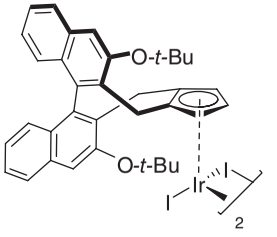
A quite different approach to the cyclization of 1,6-enynes was performed using a cyclopentadienylruthenium catalyst containing a tethered chiral sulfoxide (Scheme 1.193) [645]. In fact, 1,6-enynes containing a racemic propargyl alcohol moiety assembled [3.1.0] instead of [4.1.0] bicycles with (*R*,*R*)-stereochemistry. Besides sterically hindered sulfonamide, diphenylphosphoramidate and malonate derivatives worked well in this reaction and a [4.1.0]bicyclic piperidine was prepared from a 1,7-enyne (56% yield, 70% ee). Interestingly, when the reaction was carried out with enantioenriched propargyl alcohols, 84% and 36% ee were obtained with the (*R*)- and the (*S*)-propargyl alcohol and the 60% ee obtained from the racemic compound was almost the average value.

The preparation of enantioenriched cyclopropanes was also performed by combining the power of asymmetric synthesis of enynes with gold-catalyzed cycloisomerization chemistry. Some of these compounds are key intermediates for the synthesis of terpenoid compounds. For instance, chiral phosphine–gold(I) catalyzed the cycloisomerization of propargyl derivatives to cycloheptenes or cyclooctenes (Scheme 1.194) [646]. It is worth noting that yields and enantiomeric excesses are slightly better than those reported in Table 1.10 for azabicyclic compounds [643]. However, the best catalyst was found to vary for different examples, and the reaction was highly substrate-dependent, thus difficult to reproduce. About the mechanism, a gold-stabilized vinyl carbenoid was surmised after gold-mediated 1,2-shift of the OR^1 group. The two isomers of this carbenoid could equilibrate, and the less abundant but required (*E*)-TS had to be subtracted from the equilibrium. On the other hand, an external and more reactive alkene such as 1,1-diphenylethylene led to the products arising from the most stable (*Z*)-TS [647].

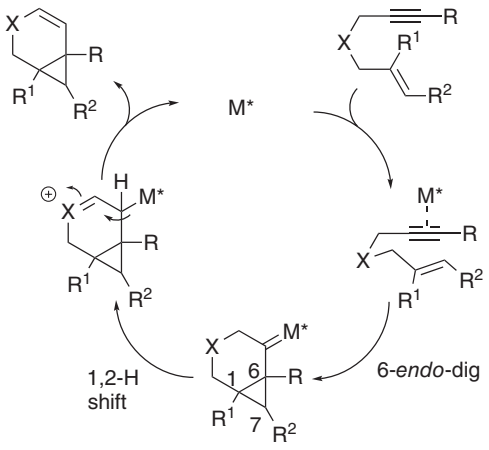
A P,N-bidentate ligand with a C_2-symmetric *N*-heterocycle enabled reactive α-oxo gold carbene intermediates generated *in situ* to undergo asymmetric intramolecular

Table 1.10 Organocatalytic cycloisomerization of 1,6-enynes.

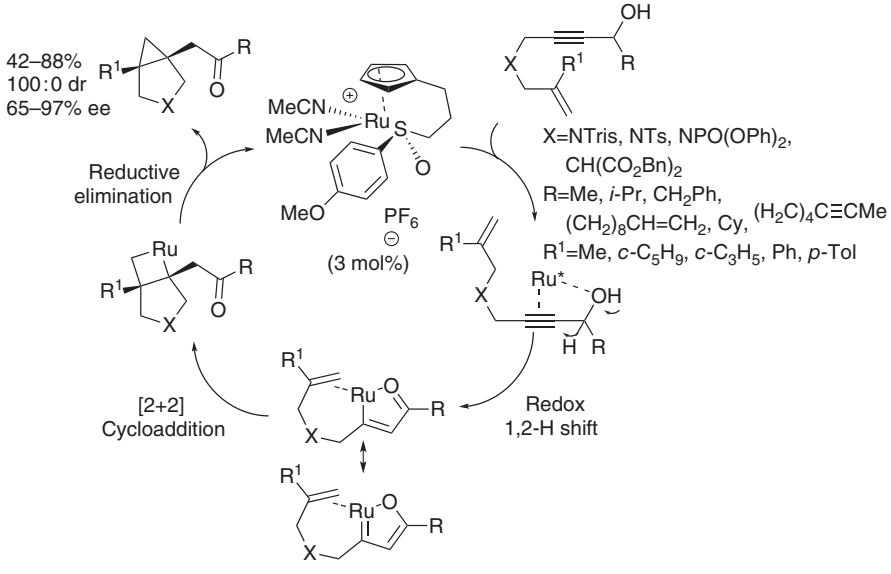
Reactant	Catalyst	Yield (%)	ee (%)	References
 Ar=Me, *o*-Tol, R=Ph, 4-ClC_6H_4, *p*-Tol, 2-Naph	$[IrCl(Cod)]_2$ (10 mol%), *p*-TolBINAP (20 mol%) AgOTf (24 mol%) CO (1 atm)	57–71	64–71 (—)[a]	[641]
 X=NTs, NTf, O R=H, Ph R^1=H, Me, R^2=H, Ph, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 2,6-$Me_2C_6H_3$, 4-ClC_6H_4	 $B[3,5\text{-}(CF_3)_2Ph]_4$ (5 mol%)	71–94	68–99 (1*S*,6*R*,7*R*)	[642]
 X=NTs, O, R^1=H, Me, R^2=H, Ph, 4-$MeOC_6H_4$, R=H, Ph, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 3,5-$Me_2C_6H_3$, 4-$MeO_2CC_6H_4$, 3-BrC_6H_4	 R=3,5-(*t*-Bu)$_2$-4-$MeOC_6H_2$ (3 mol%) AgOTf (6 mol%)	8–64	13–99[b]	[643]

 R=H, Ph, 4-$MeOC_6H_4$, 4-$CF_3OC_6H_4$, *p*-Tol, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 3-ClC_6H_4, 3,5-$Me_2C_6H_3$, 2-Naph, 2-thienyl, 3-furyl, 2-benzothienyl, 2-benzofuryl, 5-benzo[*d*][1,3]dioxolyl, CH_2OBn, R^1=H, Me, Ph, 5-benzo[*d*][1,3]dioxolyl	 (5 mol%)	47–87[c]	63–94 (1*S*,6*S*,7*S*)	[644]

a) Only negative optical rotation was reported.
b) Only optical rotation (mainly negative) was reported. In schemes, the same configuration as under rhodium catalysis was depicted where the optical rotation values were positive. However, these are enantiomeric with respect to those reported in Scheme 1.191 [640]. Although, the two papers do not have compounds with the same substituents, the opposite optical rotations reported indirectly confirmed this analytically unsupported stereochemistry.
c) Olefin with *cis*-relationship between R and CH_2NTs groups was not reactive.

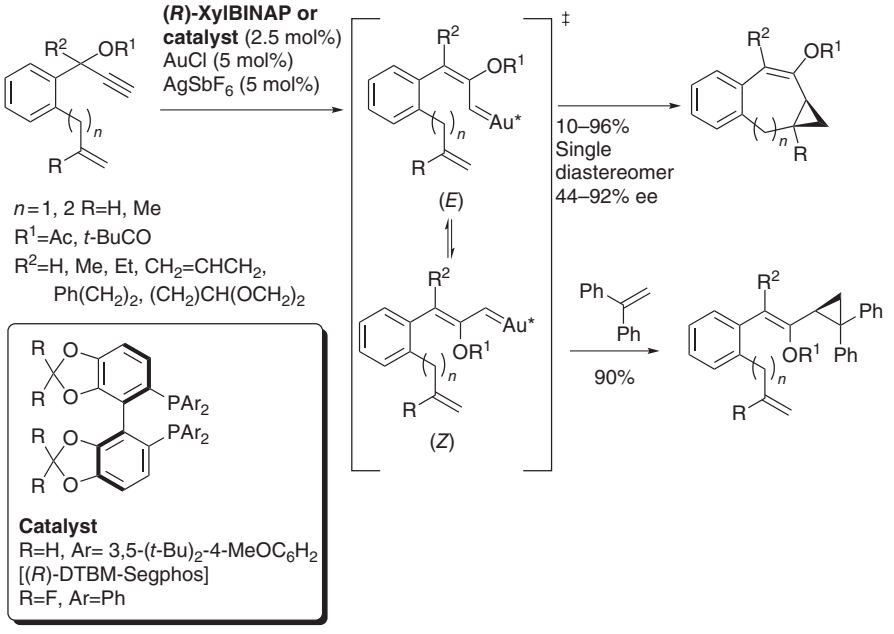


Scheme 1.192 Proposed catalytic cycle for the cyclization of 1,6-enynes.

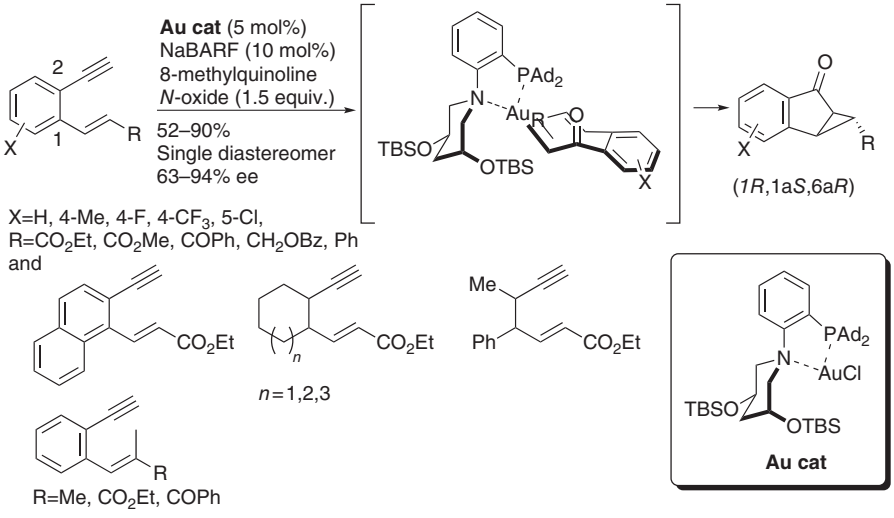


Scheme 1.193 Ru-catalyzed asymmetric redox bicycloisomerization reaction.

cyclopropanation (Scheme 1.195) [648]. This reaction was applied to the synthesis of LY354740 (Scheme 1.120, eq 3 for the structure). The reaction of (*E*)-ethyl 3-(2-ethynylphenyl)but-2-enoate proceeded in 78% yield but only with 11% ee. Moreover, ethyl 3-(2-ethynylphenyl)-2-methylacrylate (prepared as an inseparable 5:1 mixture of (*E/Z*)-isomers) was converted into the corresponding cyclopropane diastereomers in an almost identical ratio (91% combined yield), thus indicating that the cyclopropanation was concerted and stereospecific. The stereochemical outcome was



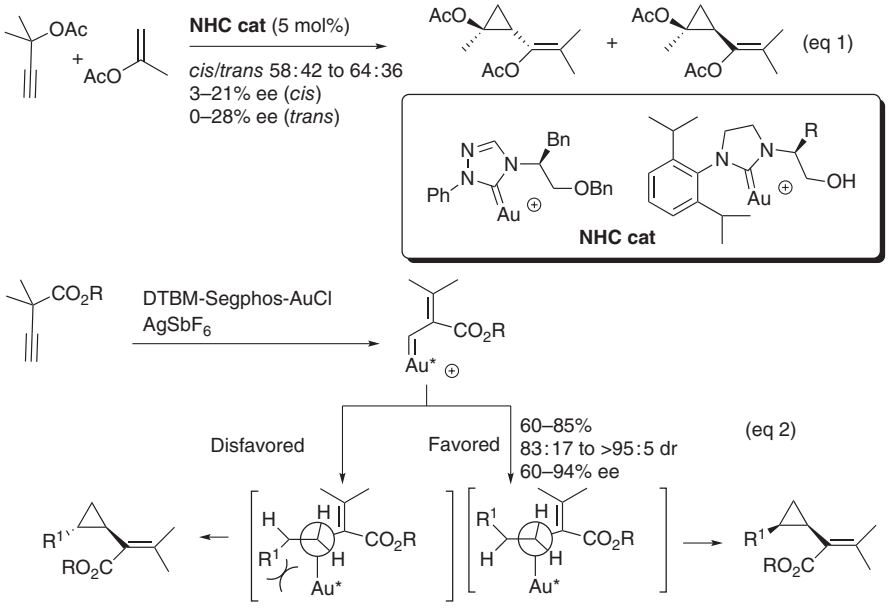
Scheme 1.194 Intramolecular gold(I)-catalyzed cyclopropanations.



Scheme 1.195 Enantioselective oxidative intramolecular cyclopropanation.

envisaged arising from a transition state in which the axial TBSO group of the piperidine ring shielded the *Re*-face of the carbene center from alkene attack.

The intermolecular version of this reaction was also developed. For instance, propargyl esters were used for the preparation of vinylcyclopropanes. Chiral imidazolium- and triazolium-based gold(I)–NHC catalysts were tested with poor



Scheme 1.196 Au-catalyzed cyclopropanation of olefins with propargyl esters.

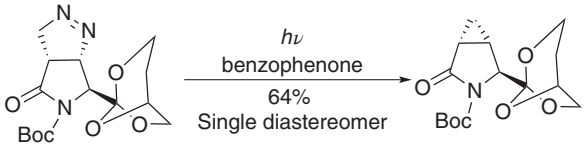
results (Scheme 1.196, eq 1) [649], while DTBM-Segphos gave high *cis*-selectivity and enantioselectivity (Scheme 1.196, eq 2) [650].

Finally, these reactions were also attempted in heterogeneous catalysis. In particular, asymmetric catalyst was prepared by encapsulating metallic nanoclusters in chiral self-assembled monolayers immobilized on mesoporous SiO_2 support and activated through metal oxidation by $PhICl_2$. Under these conditions, Au–diproline/MCF-17 catalyzed intermolecular and intramolecular cyclopropanation reactions with up to 51% and 30% enantiomeric excess, respectively [651].

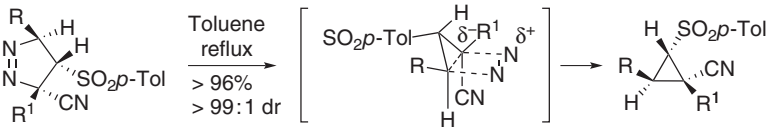
To close this section, a related reaction should be mentioned, since it anyway involves double and triple carbon—carbon bonds, that is, the cotrimerization of alkenes and diethyl acetylenedicarboxylate, leading to functionalized (*R*,*R*)-furylcyclopropanes in 34–62% yield with 97–99% ee and >19:1 dr [652].

1.5.3 Denitrogenation of Chiral Pyrazolines

The decomposition of pyrazolines has proved to be an excellent method for the preparation of cyclopropanes. The reaction works under photo, thermal, acid, and microwave decomposition.



Scheme 1.197 Photolysis of pyrazoline.

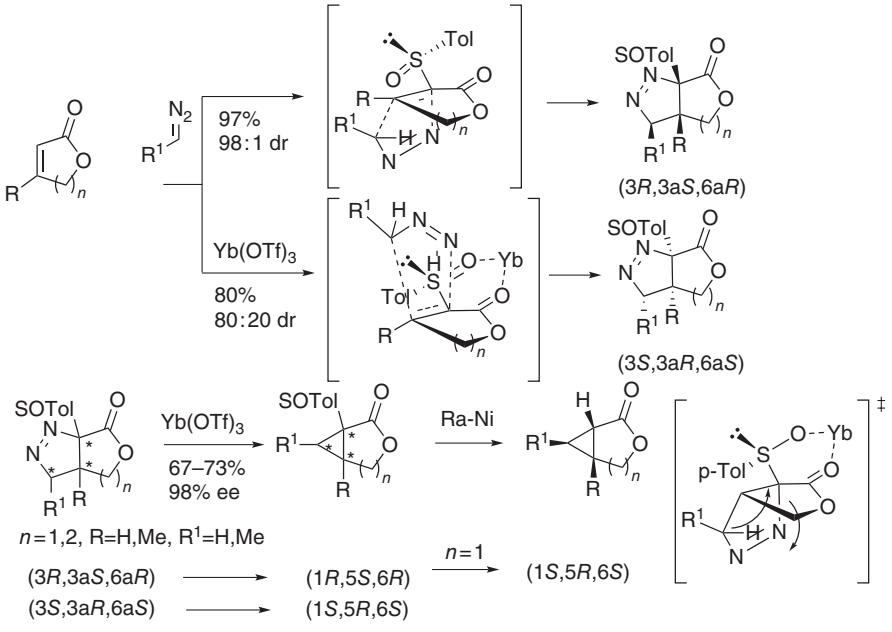


Scheme 1.198 Thermolysis of sulfonylpyrazolines.

As an example of photolysis, in the presence of benzophenone as a photosensitizer, chiral pyrazolines afforded the corresponding cyclopropanes as unique isomers (Scheme 1.197) [653]. This process very likely involved the formation of diradicals. This reaction was applied to the syntheses of pharmacologically important cyclopropane proline amino acids.

The thermal extrusion of nitrogen from pyrazolines mainly gave olefins, and, when yielding cyclopropanes as the main products, they usually gave low stereoselectivity. However, Garcia Ruano's research group developed a successful thermolysis of chiral sulfonylpyrazolines (Scheme 1.198) [654]. This extrusion took place with complete retention of configuration of all the chiral centers. A polar transition state was consistent with this concerted thermal decomposition [655].

Garcia Ruano also described the addition of diazomethane or diazoethane to enantiopure (*S*)-3-[(4-methylphenyl)sulfinyl]lactones with almost complete π-facial selectivity. The configurations of pyrazolines could be rationalized by the approach of the diazoalkane from the less-hindered bottom face (far from the tolyl group) of



Scheme 1.199 $Yb(OTf)_3$-catalyzed synthesis and denitrogenation of sulfinylpyrazolines.

the conformation, in which the electrostatic repulsion between the sulfinyl and carbonyl oxygen atoms was minimized. In the presence of $Yb(OTf)_3$, the formation of a chelated species was preferred, and the change in the spatial arrangement of the tolyl group caused the inversion of the facial selectivity. Then, the isolated pseudoenantiomers were submitted to the denitrogenation in the presence of a substoichiometric amount of $Yb(OTf)_3$ (Scheme 1.199) [656].

The reaction evolved with complete retention of configuration at both carbons flanking the nitrogen atoms and the subsequent desulfinylation by treatment with Ni Raney resulted in the formation of enantiomerically pure cyclopropanecarboxylic acid derivatives. Regarding the mechanism, the metal could form a chelated species with the sulfinyl and carbonyl oxygens; thus, the enhanced electronic deficiency of this carbon provoked the concerted migration of C3 with extrusion of nitrogen. The reaction of γ-lactones was more efficient, and 87–97% and 68–98% yields were obtained from (3*R*,3a*S*,6a*R*) and (3*S*,3a*R*,6a*S*) isomers, respectively [656]. It should be noted that decomposition of the pyrazolines did not occur at −78 °C, thus allowing the synthesis and purification of the (3*S*,3*aR*,6*aS*)-lactones in the first step of this synthesis.

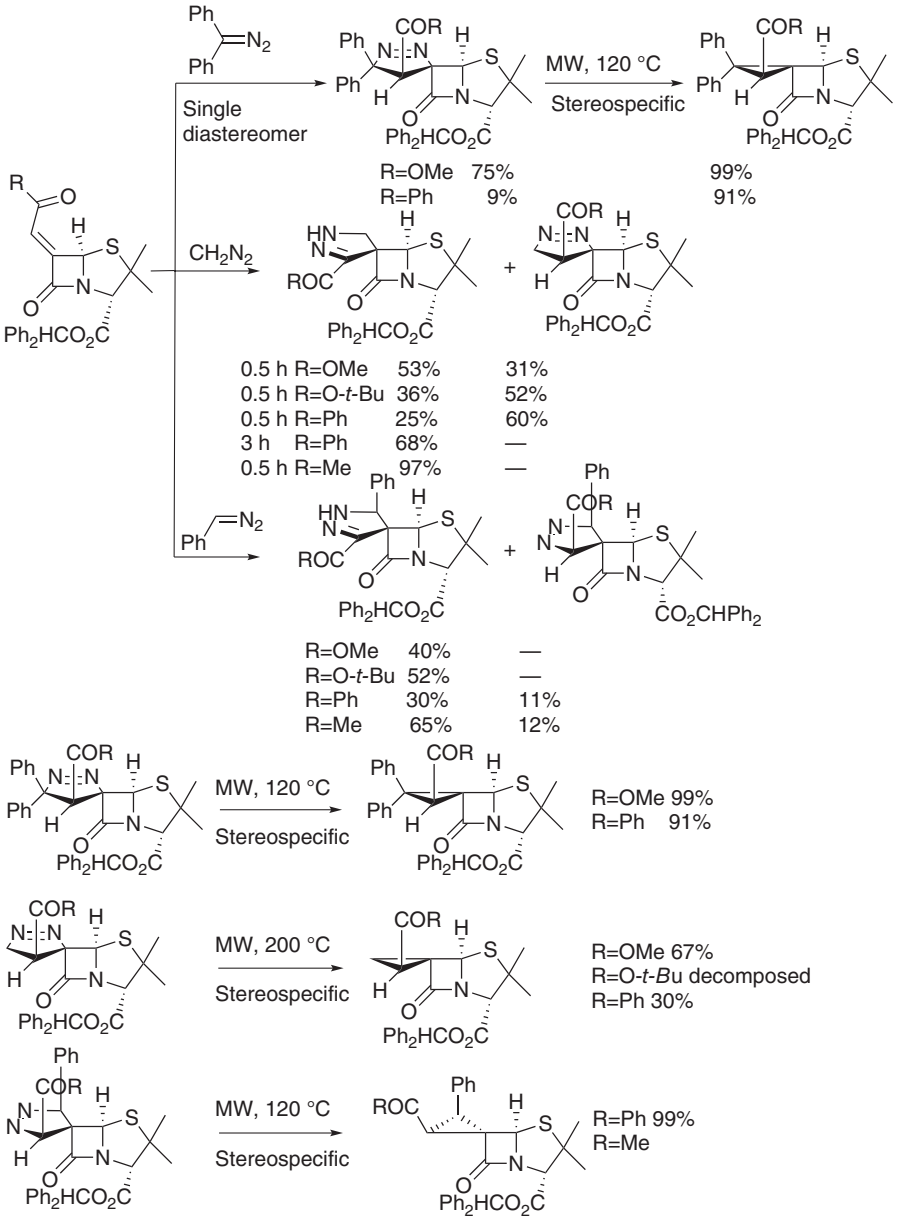
Finally, chiral spiropyrazolinepenicillanates, obtained from 1,3-dipolar cycloaddition reactions of 6-alkylidenepenicillanates with diphenyldiazomethane, phenyldiazomethane, and diazomethane, were submitted to stereospecific microwave-induced ring contraction to chiral spirocyclopropylpenicillanates (Scheme 1.200) [657]. However, the preparation of starting material was closely dependent on the diazoalkanes. Thus, phenyldiazomethane reacted regio- and stereoselectively with all tested 6-alkylidenepenicillanates, whereas diphenyldiazomethane only with 6-(*Z*)-(1-methoxycarbonylmethylene)- and 6-(*Z*)-(1-benzoylmethylene)penicillanates, albeit to give a different regioisomer. Both diphenyldiazomethane and diazomethane with 6-(*Z*)-(1-*tert*-butoxycarbonylmethylene)penicillanate and diazomethane with 6-(*Z*)-(1-methoxycarbonylmethylene)penicillanates led to two regioisomers. Finally, the 1,3-dipolar cycloaddition reactions of diazomethane with the acetyl and benzoyl derivatives were regiospecific.

1.5.4 C–H Insertion

Satoh and coworkers set up a series of syntheses of enantioenriched bicyclo[*n*.1.0]alkanes by employing a magnesium carbenoid C–H insertion reaction (Scheme 1.201) [658]. The starting materials were prepared from various carbonyl derivatives and (*R*)-chloromethyl-*p*-tolylsulfoxide, then a highly stereoselective reaction with the lithium enolate of a carboxylic acid *tert*-butyl ester occurred, exclusively leading to compounds in which the absolute configuration of the chlorine bearing carbon atom was *S*.

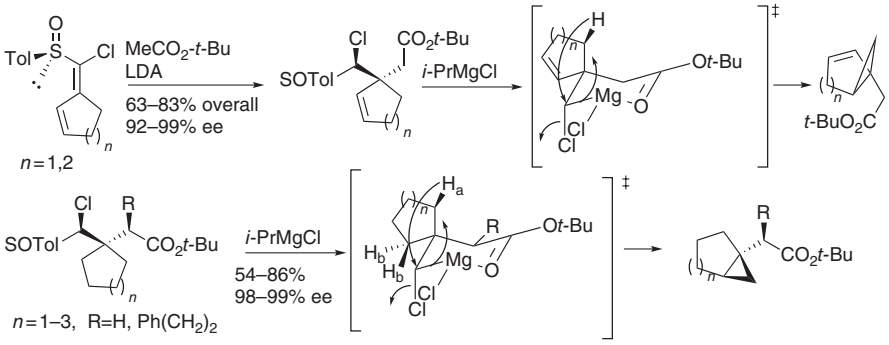
The reaction was also extended to the lithium enolate of *tert*-butyl 4-phenylbutyrate, and the absolute configuration of the carbon bearing the 2-phenylethyl group in the chlorosulfoxides was determined to be *R*. A detailed mechanistic investigation was conducted, and it was found that:

i) the sulfoxide–magnesium exchange took place remarkably with retention of configuration;

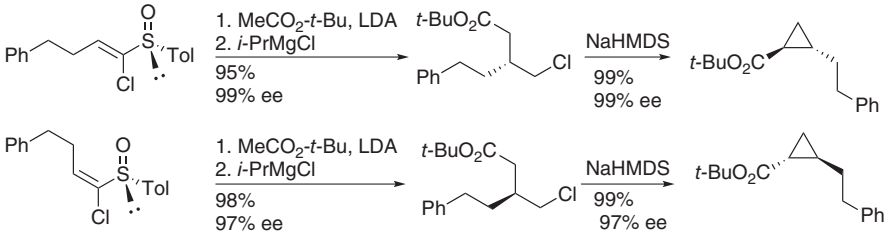


Scheme 1.200 Microwave decomposition of 6-alkylidenepenicillanates.

ii) the C—H bond on the methylene carbon of the cycloalkene attacked the chlorine atom from its backside to give the cyclopropane;
iii) the reaction occurred only at the methylene carbon on the cycloalkene, because the methylene carbon adjacent to the carbonyl has no hydrogen atoms on the backside of the chlorine atom;



Scheme 1.201 Asymmetric cyclopropanation via magnesium carbenoid 1,3-CH insertion reaction in cyclic compounds.

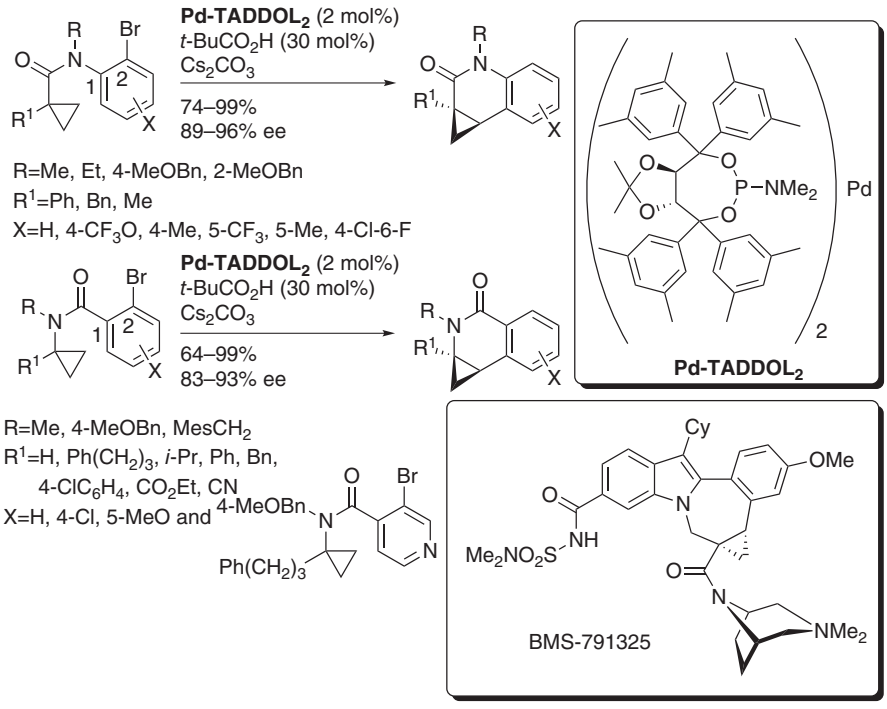


Scheme 1.202 Asymmetric cyclopropanation via magnesium carbenoid 1,3-CH insertion reaction in straight-chain compounds.

iv) (*Z*)-1-chlorovinyl-*p*-tolylsulfoxides, having no hydrogen atoms on the backside of the chlorine atom, because the carbon is sp^2 instead of sp^3, gave no reaction or intractable mixtures;
v) in saturated cyclic derivatives, only the C—H_b bond is placed almost vertically to the carbon—chlorine bond.

In straight-chain sulfoxides, the magnesium carbenoids were protonated before the 1,3-C–H insertion took place and the corresponding 4-chloro-substituted ester was obtained. Cyclopropanes were recovered after treatment with a base (Scheme 1.202) [659]. Both *E*- and *Z*-isomers reacted, because straight-chain sulfoxides are less conformationally demanding, leading to a 20 : 1 *trans*/*cis* mixture of the optically active *tert*-butyl cyclopropanecarboxylates.

At the end of this section, a reaction that is not properly an asymmetric synthesis of cyclopropanes should be mentioned. In fact, a TADDOL-based phosphoramidite palladium(0) complex enabled an enantioselective Friedel–Crafts reaction by C–H insertion on aryl cyclopropanes (Scheme 1.203) [660]. This method provided efficient access to cyclopropyl-dihydroquinolones and dihydroisoquinolones as well as the construction of the seven-membered ring of the cyclopropylindolobenzazepine core of BMS-791325. A substrate with another aryl bromide groups as the nitrogen substituent allowed for the synthesis of a pentacyclic dihydroquinolinone in 95% yield and 93% ee. Poor results were instead obtained with 3-ammi-



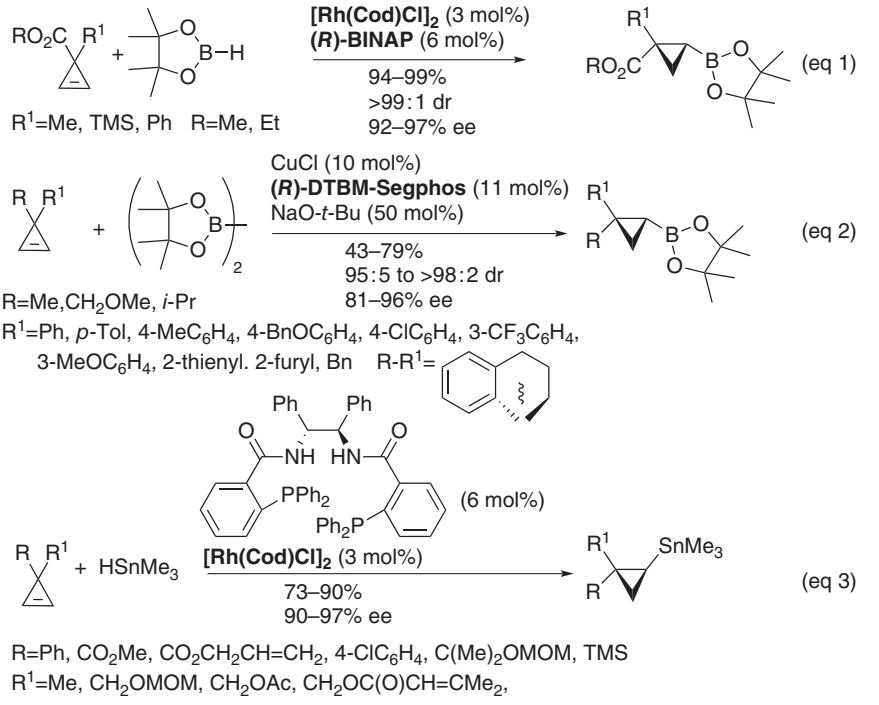
Scheme 1.203 Palladium(0)-catalyzed intramolecular cyclopropane functionalization.

nopyridine, trimethylsilylcyclopropane, and 3-thienylketone as the substrates and secondary amides are unreactive. Finally, it is worth noting that the destruction of the cyclopropane moiety in the synthesis of dihydroisoquinolones was never observed, conversely from similar Pd(0)-catalyzed *C*—H bond functionalization reactions [661].

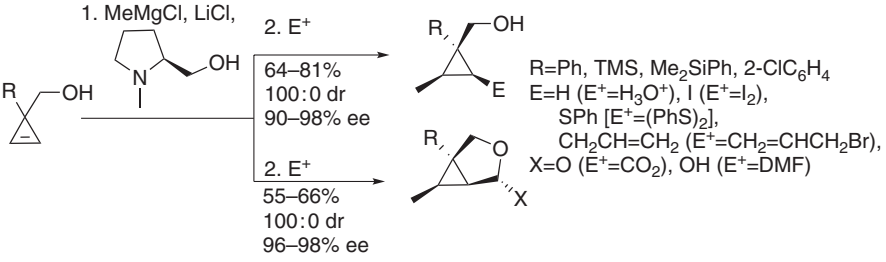
1.5.5 Addition to Cyclopropenes

The diastereoselective addition reactions of cyclopropenes constitute an attractive alternative to the more mainstream routes to chiral cyclopropanes [3, 662]. For example, enantiopure 2,2-disubstituted cyclopropylboronates could be easily prepared by hydroboration of cyclopropenes under rhodium catalysis. In the presence of a chiral ligand such as (*R*)-BINAP, (1*S*,2*R*)-cyclopropanes were the main product (Scheme 1.204, eq 1), while (*S*)-TolBINAP afforded the enantiomeric (1*R*,2*S*)-product in comparable yield and selectivity [663]. More recently, a diastereo- and enantioselective Cu-catalyzed hydroboration of cyclopropanes, which did not need a directing group, was described (Scheme 1.204, eq 2) [664]. Additionally, the capture of the cyclopropylcopper intermediate with electrophilic amines was possible, but the enantioselective version of this reaction has never been reported.

Under chiral rhodium catalysis, hydrostannation of cyclopropenes provided optically active cyclopropylstannanes [665]. The hydrostannation had a more



Scheme 1.204 Asymmetric hydroboration and hydrostannation of cyclopropenes.

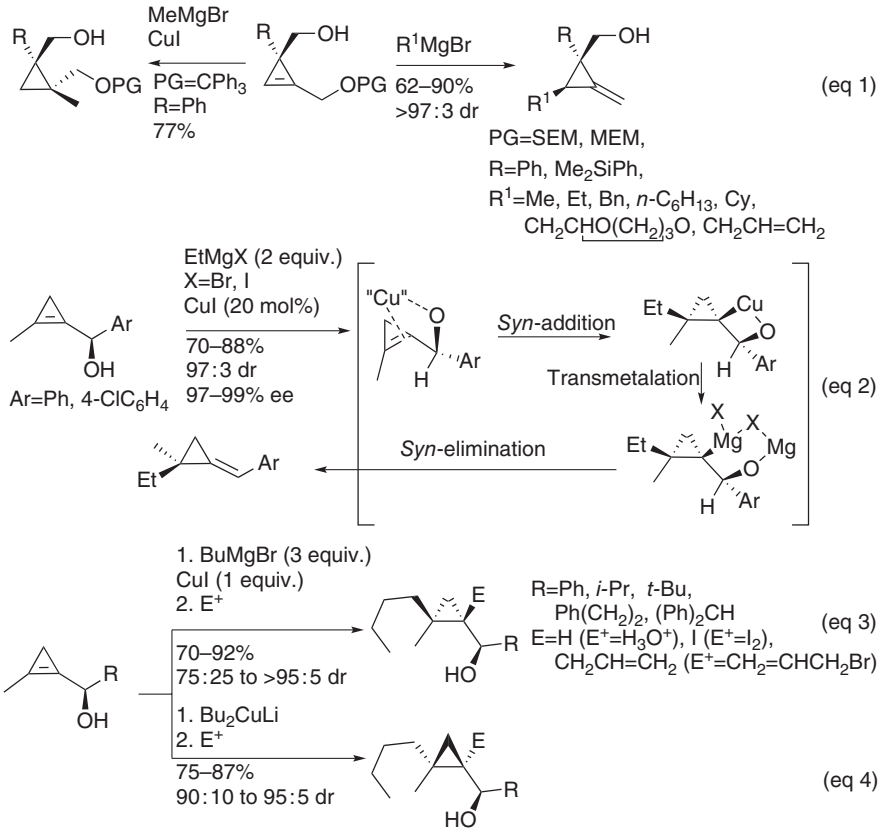


Scheme 1.205 Asymmetric carbomagnesations of cyclopropenes.

general scope than hydroboration under similar catalysis, because also in this case, no directing group was required (Scheme 1.204, eq 3). All these reactions allowed further functionalization, by selective removing of boron or tin groups.

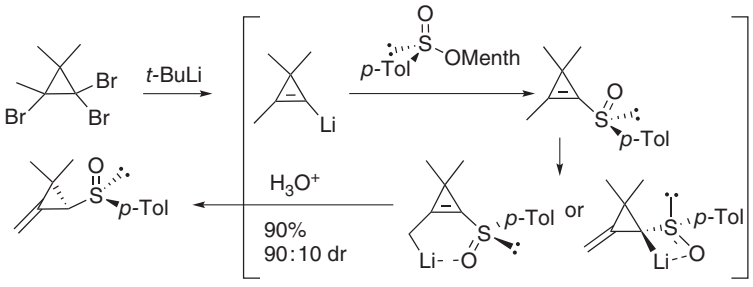
In the presence of *N*-methylprolinol as a chiral ligand, the addition of MeMgCl allowed an enantio- and facially selective carbomagnezation of cyclopropanes (Scheme 1.205) [666]. The introduction of electrophiles created three stereocenters with high enantioselectivity.

Chiral cyclopropene derivatives, obtained by reaction of alkynes and diazoalkanes under $Rh_2(DOSP)_4$ catalysis (see Section 1.3.1.4), and Grignard reagents allowed a regio- and diastereoselective synthesis of chiral methylenecyclopro-

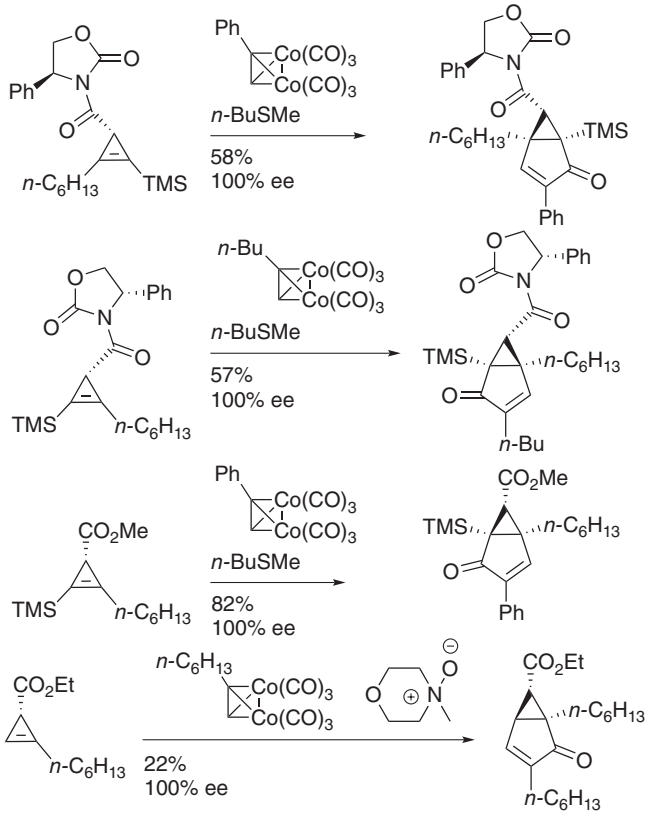


Scheme 1.206 Asymmetric carbometallation of cyclopropenylcarbinols.

panes (Scheme 1.206, eq 1) [667]. It should be noted that a single stereoisomer was obtained only when using bromide as the Grignard counterion and that trityl protection reversed the regioselectivity. In addition, unprotected chiral cyclopropenylcarbinol led to elimination of alkylidenecyclopropane, regardless of the nature of the alkylmagnesium halides in the presence of a catalytic amount of CuI (Scheme 1.206, eq 2) [668]. It is worth noting that, as discussed in the previous reaction, CuI was essential to reverse regioselectivity of the addition (Scheme 1.206, eq 1 arrow leftward). The stereoselectivity of this process was explained by envisaging that the most stable conformer of the cyclopropenylcarbinolate had the smallest hydrogen "inside" and the largest aryl group "outside" to minimize $A^{1,3}$-strain. Then, the reaction proceeded through a *syn*-addition/*syn*-elimination mechanism. Later, this research group demonstrated that the carbon—copper bond was less prone to β-elimination compared to the carbon—magnesium bond [669]. Thus, a stoichiometric addition of CuI allowed for quenching of the metallated species with different electrophiles to give the corresponding chiral functionalized cyclopropylcarbinol derivatives (Scheme 1.206, eq 3). Interestingly, the use of an organocuprate reversed the observed diastereomeric ratio in favor of the *syn*-isomer (Scheme 1.206, eq 4).



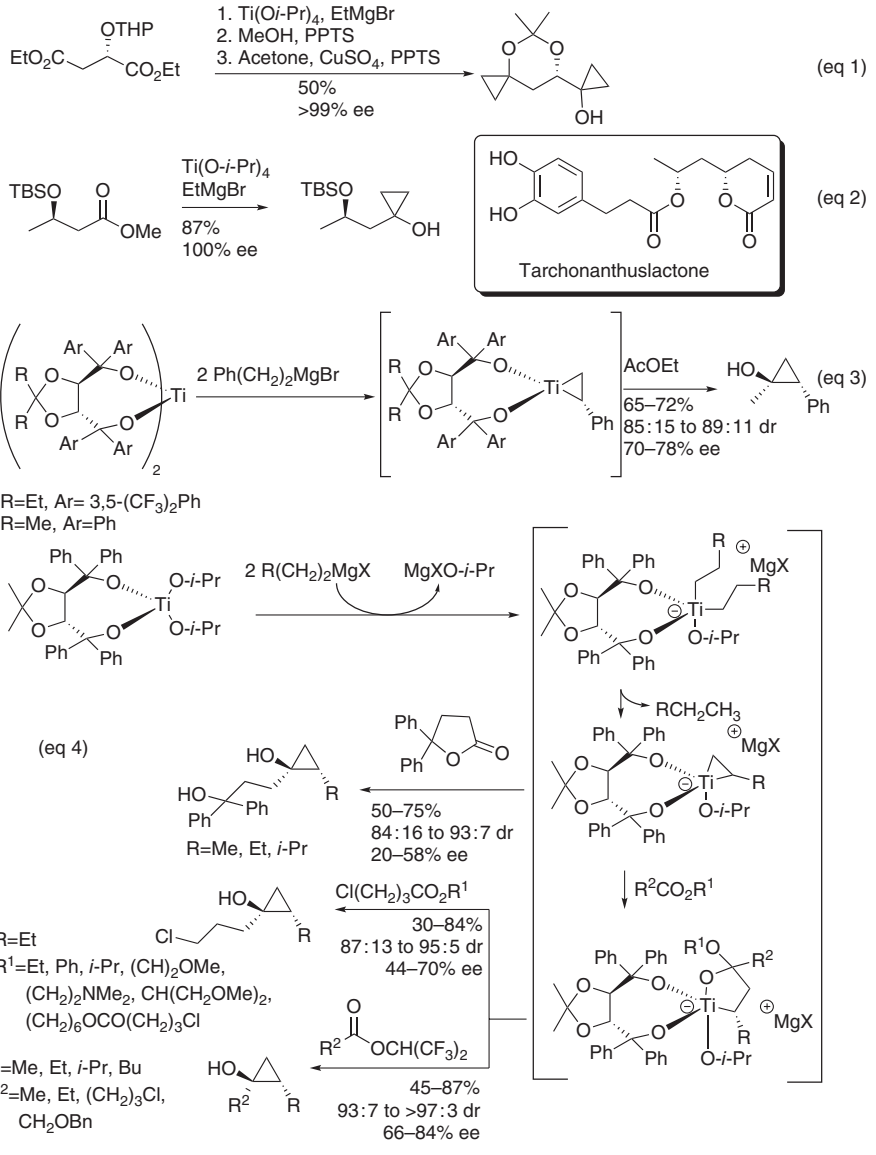
Scheme 1.207 Synthesis of chiral methylenecyclopropane via three-component reaction.



Scheme 1.208 Asymmetric Pauson–Khand reactions of cyclopropenes.

Chiral methylenecyclopropane derivatives were also prepared via a three-component reaction from 1,1,2-tribromocyclopropanes, (–)-menthyl (*S*)-*p*-toluenesulfinate, and electrophiles (Scheme 1.207) [670].

Chiral cyclopropanes also promoted regio- and stereoselective intermolecular Pauson–Khand reactions [671]. A single enantiomerically pure bicyclohexene was always isolated (Scheme 1.208).



Scheme 1.209 Asymmetric Kulinkovich reaction.

1.5.6 Other Methods

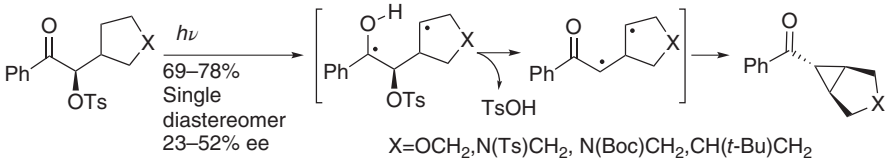
Since 1989, Kulinkovich's group discovered that the reaction of esters with a mixture of Ti(O-*i*-Pr)$_4$ and an excess of a Grignard reagents led to the corresponding substituted cyclopropanols [672].

More recently, enantioselective synthesis of cyclopropanols by the Kulinkovich method has been investigated. The use of either chiral substrates or chiral titanium ligands was successfully tested. As an example, Kulinkovich's group itself reported

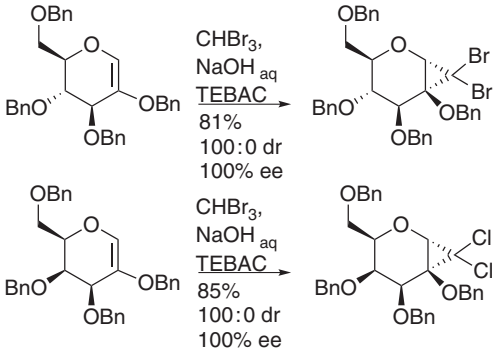
the asymmetric reductive cyclopropanation of chiral THP-protected diethyl malate (Scheme 1.209, eq 1) [673]. Almost at the same time, Singh and coworkers reported that, under Kulinkovich reaction conditions, a chiral β-alkoxy ester afforded the corresponding enantiomerically pure cyclopropanol, which was the key intermediate for all the stereoisomers of tarchonanthuslactone (Scheme 1.209, eq 2) [674]. Moreover, titanium TADDOLates mediated the asymmetric Kulinkovich reaction (Scheme 1.209, eqs 3 and 4) [675]. In order to rationalize the stereochemical outcome of the reaction, a mechanistic study was undertaken by Kulinkovich and coworkers [675c].

They proposed a model for the cyclopropanation involving the participation of five-coordinated alkyltitanium species (Scheme 1.209, eq 4), unlike Corey's idea (Scheme 1.209, eq 3) [675a]. Under this hypothesis, the stereogenic carbon in titanacyclopropane intermediates could occupy either apical or equatorial positions, but, in both cases, the (*S*)-diastereomers were less sterically hindered compared to the corresponding (*R*)-diastereomers, in agreement with Corey's suggestion.

In fact, in the most stable diastereomers, the R group was far from the pseudoaxial phenyl groups of the catalyst. The formation of titanium alkoxides by-products should be avoided, because they were more reactive compared to the TADDOLate and, catalyzing the background reaction, strongly affected the reaction stereoselectivity. The influence of the structure of the leaving alkoxy group on the stereoselectivity of cyclopropanation of methyl 4-chlorobutanoate was tentatively rationalized by introducing an oxatitanacyclopentane species, which could in turn undergo transformation with retention of configuration at the stereogenic carbanion center. In fact, the mechanism of the three-carbon ring for-



Scheme 1.210 Asymmetric photochemical cyclization of ketones.



Scheme 1.211 Asymmetric cyclopropanations of glycals.

mation did not explain the leaving alkoxy group influence, since it departed before the cyclopropane ring-forming step.

The irradiation of a chiral ketone led to the formation of the corresponding *exo* cyclopropylated product with complete stereoselectivity, in agreement with the concept of spin-center shift [676]. The 1,4-diradical generated by irradiation shifted the radical center from the carbonyl to the adjacent carbon atom with *p*-toluenesulfonic acid elimination. The resulting 1,3-diradical cyclized with complete diastereoselectivity to give the final cyclopropane (Scheme 1.210).

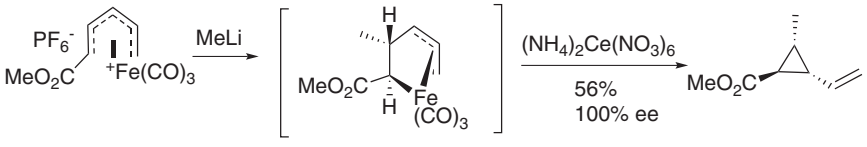
Another diastereoselective methodology to form cyclopropane was performed with bromoform or chloroform on glycal under phase-transfer conditions (Scheme 1.211), in order to prepare unnatural septanoside derivatives [677].

Vinylcyclopropanecarboxylates could be prepared on the basis of an organoiron methodology (Scheme 1.212) [678]. In fact, a chiral (1-methoxycarbonylpentadienyl) iron cation treated with MeLi predominantly gave the corresponding (pentenediyl) iron complex, which afforded the corresponding enantiomerically pure vinylcyclopropanes by treatment with excess ceric ammonium nitrate. The synthesis was applied to the synthesis of the C9–C16 segment of ambruticin (Scheme 1.107 for the structure) [678b].

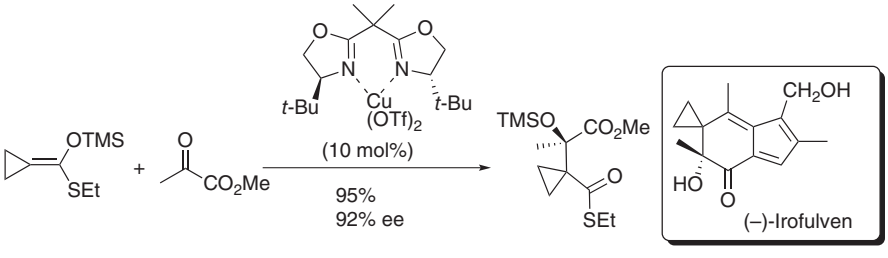
In the same period, enantiomerically pure [60]fullerene tris-adducts with an *e,e,e*-addition pattern have been prepared by cyclopropanation of C_{60} with chiral D_3-symmetrical cyclo-tris(malonate) tethers bearing chiral C_8-spacers connecting the reactive malonate [679].

A strained ketene hemithioacetal underwent the addition of methyl pyruvate in the presence of a chiral copper catalyst. The obtained chiral product was the key intermediate in a total synthesis of (–)-acylfulven and (–)-irofulven (Scheme 1.213) [680].

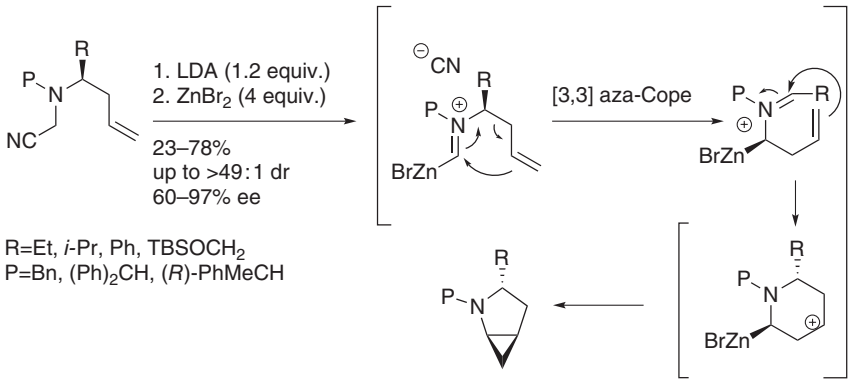
Enantioenriched α-*N*-homoallylaminonitriles could be stereoselectively cyclized to azabicyclo[3.1.0]hexanes in the presence of a base and zinc bromide.



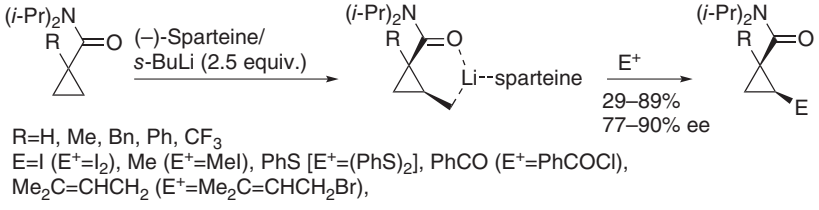
Scheme 1.212 Asymmetric synthesis of vinylcyclopropane via organoiron methodology.



Scheme 1.213 Asymmetric aldol reaction of cyclopropanated ketene hemithioacetal.



Scheme 1.214 Synthesis of enantiopure 3-substituted 2-azabicyclo[3.1.0]hexanes.



Scheme 1.215 Enantioselective synthesis of cyclopropylcarboxamides by metallation.

It is worth noting that the stereospecific inversion of the homoallylic stereogenic center with substrates derived from α-branched nitrogen-protecting groups (Scheme 1.214) [681]. However, benzyl-protected substrates showed a different stereochemical outcome for the cyclization, indicative of a not-explained mechanistic difference.

The last example of synthesis of chiral cyclopropanes reported here is the chiral-base-mediated desymmetrization reaction of β-metallated cyclopropylcarboxamides (Scheme 1.215) [682]. In the presence of (–)-sparteine (Scheme 1.172 for the structure), the *syn*-metallation of the cyclopropane with respect to the directing amide substituent asymmetrically occurred. The predominant β-metallation even in the presence of possible enolate formation (R=H) was noteworthy. The tendency of the lithiated cyclopropanes to undergo decomposition and self-condensation represented a serious drawback.

1.6 Conclusions

As cyclopropane rings are widespread in natural and biologically active compounds, their synthesis remains a considerable challenge, even over a century after the synthesis of the first cyclopropane derivative, and new syntheses appear in the literature. With the development of asymmetric synthesis, strategies involving chiral pools, chiral auxiliaries, chiral metal catalysts, and organocatalysts have led to other significant developments in the scope of the cyclopropanation reaction.

Enzymatic methods cannot be forgotten, but they are not considered here. The asymmetric cyclopropanation is therefore a very important tool for organic synthesis, and significant contributions are still needed.

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