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Recent developments in asymmetric cyclopropanation

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Abbreviations: Ac, acetyl; Acac, acetylacetone; Ar, aryl; BHT, 2,6-di-*tert*-butyl-4-methylphenyl; BINAP, 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; BINOL, 1,1′-bi-2-naphthol; BMIM, 1-butyl-3-methylimidazolium; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BSPIM, methyl-1-(*N*-benzenesulfonylproline)-2-oxaimidazolidine-4-carboxylate; Bu, butyl; Bz, benzoyl; CAN, ceric ammonium nitrate; Cbz, benzyloxycarbonyl; Cod, cyclooctadiene; Cp, cyclopentadienyl; Cy, cyclohexyl; DCE, dichloroethane; de, diastereomeric excess; DMAP, 4-dimethylaminopyridine; DME, 1,2-dimethoxyethane; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; DNA, desoxyribonucleic acid; DPTI, diphenyltriflylimidazolidinone; DTBM-SEGPHOS, 5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole; EDA, ethyl diazoacetate; ee, enantiomeric excess; EMA, ethyl methoxyacetate; Et, ethyl; EWG, electron-withdrawing group; FBNAZ, *p*-fluorobenzyl-2-azetidinone-4-carboxylate; Fu, furyl; Hept, heptyl; Hex, hexyl; HMCPIM, methyl 1-[3′-phenyl-2′-cyclopropanecarbonyl]-2-oxo-imidazolidine-4-carboxylate; HMDS, hexamethyldisilazide; HMDSA, hexamethyldisilazane; HMPA, hexamethylphosphoramide; Httl, *N*-1,8-naphthoyl-*tert*-leucine; L, ligand; LA, Lewis acid; LDA, lithium diisopropylamide; LIDAKOR, butyllithium/diisopropylamine/potassium *tert*-butoxide; LG, leaving group; LTMP, lithium 2,2,6,6-tetramethylpiperidine; M, metal; MCFs, mesocellular foams; Me, methyl; MEAZ, methyl-2-azetidinone-4-carboxylate; MEM, methoxyethoxymethyl; Menth, menthyl; MEPY, methyl-2-pyrrolidinone-5-carboxylate; MIB, 3-(morpholino)isoborneol; MIRC, Michael-initiated ring closure; MPPIM, methyl-1-(3-phenylpropanoyl)-2-oxaimidazolidine-4-carboxylate; MS, molecular sieves; Ms, mesyl; MOM, methoxymethyl; Naph, naphthyl; NMI, *N*-methylimidazole; NMO, *N*-methylmorpholine *N*-oxide; Nttl, 1,8-naphthanoyl-*tert*-leucine; Nu, nucleophile; Pent, pentyl; PG, protecting group; Ph, phenyl; PIB, polyisobutylene; Piv, pivalate; PMB, *p*-methoxybenzoyl; PMP, *p*-methoxyphenyl; PPTS, pyridinium 4-toluenesulfonate; Pr, propyl; Pro, proline; PS, polystyrene; Ptpa, *N*-phthaloylphenylalanine; Py, pyridyl; RNA, ribonucleic acid; Salen, 1,2-bis(salicylidenamino)ethane; SEM, 2-(trimethylsilyl)ethoxymethyl; TADDOL, α,α,α′,α′-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol; TBAF, tetra-*n*-butylammonium fluoride; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; TEA, triethylamine; TEBAC, triethylbenzylammonium chloride; TES, triethylsilyl; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; Thio, thiophene; THP, tetrahydropyranyl; TIPS, triisopropylsilyl; TMP, 2,4,6-trimethoxyphenyl; TMS, trimethylsilyl; Tol, tolyl; Tr, trityl; Ts, 4-toluenesulfonyl (tosyl); Val, valine.

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1. Introduction

The importance of chirality is well recognised, mainly in connection with the fact that nearly all natural products are chiral and their physiological or pharmacological properties depend upon their recognition by chiral receptors, which will interact only with molecules of the proper absolute configuration. Indeed, the use of chiral drugs in enantiopure form is now a standard requirement for virtually every new chemical entity and the development of new synthetic methods to obtain enantiopure compounds has become a key goal for pharmaceutical companies. Asymmetric synthesis constitutes one of the main strategies to gain access to enantioenriched compounds, involving the use of either chiral auxiliaries or catalysts.[1] The synthesis of chiral cyclopropanes remains a considerable challenge, especially due to the fact that cyclopropane rings are often found in a variety of natural products and biologically active compounds. Organic chemists have always been fascinated by the cyclopropane subunit,[2] which has played and continues to play a prominent role in organic chemistry.[3] Its strained structure, interesting bonding characteristics, and value as an internal mechanistic probe have attracted the attention of the physical organic community. While the cyclopropane ring is a highly strained entity, it is nonetheless found in a wide variety of naturally occurring compounds including terpenes, pheromones, fatty acid metabolites and unusual amino acids.[4] Cyclopropane subunits also occur in many natural products of primary and secondary metabolism. Indeed, the prevalence of cyclopropane-containing compounds with biological activity, whether isolated from natural sources or rationally designed pharmaceutical agents, has inspired chemists to find novel and diverse approaches to their synthesis.[5] Naturally occurring and synthetic cyclopropanes bearing simple or complex functionalities are endowed with a large spectrum of biological properties, including enzyme inhibition and insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumour, and antiviral activities.[6] For example, they constitute a common structural motif in pyrethroids,[7] the antidepressant, tranylcypromine,[8] papain and cysteine protease inhibitors,[9] potential antipsychotic substances,[10] anti-HIV agents,[11] and marine lactones.[12] Thousands of natural compounds and their derivatives carrying a cyclopropane group have been synthesised and described in the literature. Indeed, with representation in more than 4000 natural isolates and 100 therapeutic agents, the cyclopropane motif has long been established as a valuable platform for the development of new asymmetric technologies. In addition, the rigidity of the three-membered ring renders this group an appealing structural unit for the preparation of molecules with a defined orientation of pendant functional groups.[13] Indeed, the strain associated with the three-membered ring allows cyclopropanes to undergo a variety of synthetically useful ring-opening reactions.[14] In recent years, most of the synthetic efforts involving cyclopropanes have focused on the enantioselective synthesis of these compounds. This has remained a challenge since it was demonstrated that members of the pyrethroid class of compounds were effective insecticides.[15] New and more efficient methods for the preparation of these entities in enantiomerically pure form are still evolving, and this review will focus mainly on the new methods that have appeared in the literature since 2003. Indeed, the last four years have provided an impressive amount of developments of asymmetric cyclopropanation, clearly demonstrating the explosive growth and power of this particular field of organic chemistry. This fast-moving field was most recently reviewed in 2003.[5a] Prior to 2003, this area has been the subject of several excellent review articles.[5b–f] It must be noted that the stereoselective synthesis of cyclopropanols, in particular, was reviewed in 2006 by Martin et al.[16] Furthermore, the special synthesis of chiral cyclopropenes is not taken into account in this review.

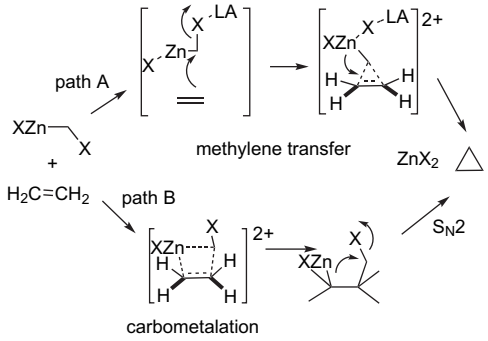
2. Simmons–Smith cyclopropanation

More than 49 years ago, Simmons and Smith discovered that the reaction of alkenes with diiodomethane in the presence of activated zinc afforded cyclopropanes in high yield.[17] The reactive intermediate is an $RZnCH_2I$ species. Several alternative methods for the preparation of this species have been developed such as those using $ZnEt_2$ or $IZnCH_2I$.[18] The features that have contributed to the popularity of the Simmons–Smith reagents include broad substrate generality, tolerance of a variety of functional groups, stereospecificity with respect to alkene geometry and the *syn*-directing/rate-enhancing effect observed with proximal oxygen atoms. These reactions have been shown to proceed through a 'butterfly-type' transition structure.[5g,19] In particular, the asymmetric cyclopropanation of various acyclic allylic alcohols has been widely developed, using a heteroatom as a directing group.[20] The Simmons–Smith reaction with an allylic alcohol has distinct advantages over the reaction with a simple olefin in relation to the reaction rate and stereocontrol. Indeed, these reactions have been shown to be much faster than those of simple olefins (>1000-fold) and, moreover, the reaction with a cyclic allylic alcohol took place in such a manner that the cyclopropane ring was formed on the same side as the hydroxyl group.[21]

2.1. Chiral auxiliaries

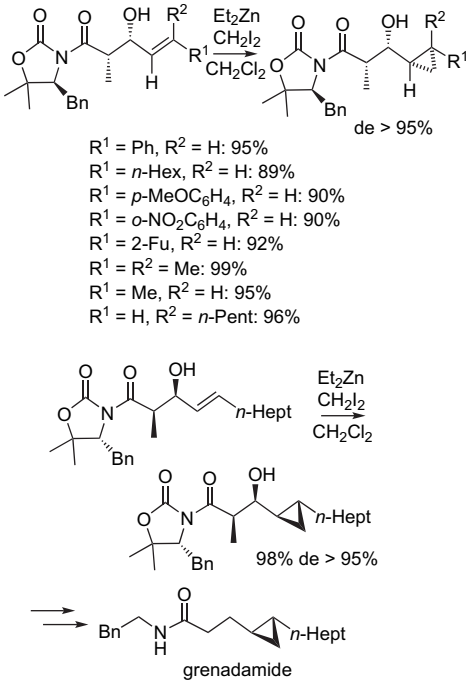
Numerous variants of the Simmons–Smith reagents have been explored, but little is known about their reaction pathways. Earlier mechanistic controversy focused on the dichotomy between a methylene-transfer mechanism and a carbometalation mechanism, in which the pseudotrigonal methylene group of iodomethylzinc iodide adds to an olefin π-bond and forms two new C–C bonds simultaneously, accompanying a 1,2-migration of the halide anion from the carbon atom to the zinc atom (path A of Scheme 1). There is experimental evidence for the Simmons–Smith reagent that contradicts path B, and path A has therefore been widely believed to represent the experimental reality. For lithium carbenoids, on the other hand, the alternative carbometalation/cyclisation pathway has received experimental support.[22] Actually, the factors that determine the reaction pathways of metal carbenoid addition to olefins are, therefore, still open to question.[23] In 2003, Nakamura

et al. studied the reaction pathways of cyclopropanation using the Simmons–Smith reagent by means of the B3LYP hybrid density functional method, confirming that the methylene-transfer pathway was the favoured reaction course.[24] 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 (Scheme 1).



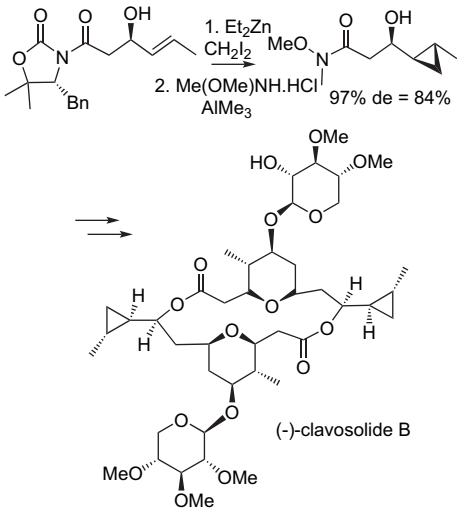
Scheme 1. Reaction pathways of Simmons–Smith reaction.

A number of auxiliary-based approaches have been reported, many of which offer the advantage of producing enantiomerically pure cyclopropyl derivatives after cleavage of the auxiliary. Various chiral auxiliaries have been developed in the past few years for the reaction with Simmons–Smith reagents, such as chiral allylic ethers, allylic amines, allylic alcohols, ketals, α,β-unsaturated carbonyl derivatives, enamines, enol ethers, and also unfunctionalised olefins. In particular, several examples implicating various chiral allylic alcohols have been developed in recent years, such as that reported in 2005 by Bull et al., in which the stereodirecting effect of the hydroxyl functionality was used to afford the corresponding chiral *syn* cyclopropanes in high des (Scheme 2).[25] This methodology was applied to an efficient total synthesis of grenadamide, a biologically active natural product having cannabinoid receptor binding activity as well as cytotoxicity towards cancer cells (Scheme 2).[26]



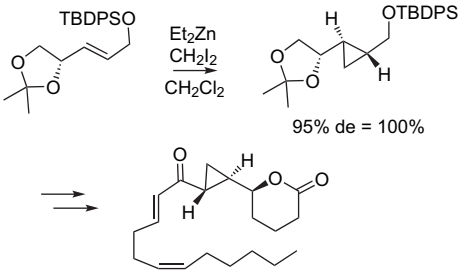
Scheme 2. Asymmetric cyclopropanations of aldols.

Another chiral oxazolidinone derivative was employed by Lee et al., in 2007, as a chiral auxiliary in a hydroxy-directed cyclopropanation, which constituted the key step of a total synthesis of (−)-clavosolide B, as shown in Scheme 3.[27]



Scheme 3. Synthesis of (−)-clavosolide B.

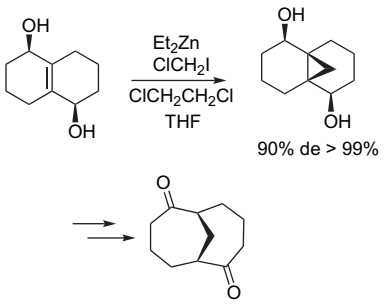
A similar methodology was applied by Mohapatra et al. to the total synthesis of an eicosanoid, b-[2-(2,b-dodecadienoyl)-cyclopropyl]tetrahydro-2*H*-pyran-2-one, a marine fatty acid metabolite having lipoxygenase-inhibiting activity (Scheme 4).[28] In this case, the Simmons–Smith reaction was performed in the presence of a chiral TBDPS ether derived from (*R*)-2,3-*O*-isopropylidene glyceraldehyde, providing diastereoselectively the corresponding cyclopropyl derivative in excellent yield. This compound was further converted into the desired eicosanoid, β-[2-(2,β-dodecadienoyl)cyclopropyl]tetrahydro-2*H*-pyran-2-one.



Scheme 4. Synthesis of b-[2-(2,b-dodecadienoyl)cyclopropyl]tetrahydro-2*H*-pyran-2-one.

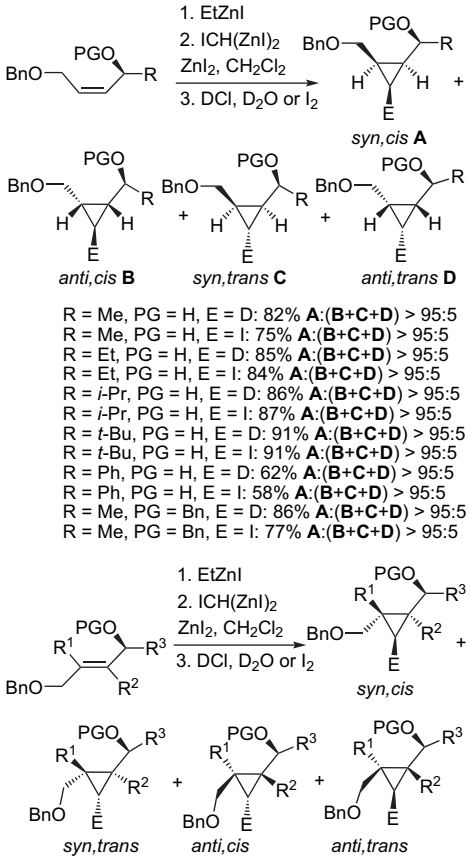
Among the group of small bridged bicyclic molecules, the bicyclo[4.4.1]undecane substructure is quite rarely encountered. In this context, Schmalz et al. have developed a novel and fully enantioselective synthesis of a C_2-symmetric diketone on the basis of a diastereoselective cyclopropanation.[29] While attempts to achieve cyclopropanation under the usual Simmons–Smith conditions failed, due to complete decomposition, the desired cyclopropanation was successfully achieved using a $ZnEt_2/ClCH_2I$ reagent, providing the corresponding tricyclic diol as a single diastereomer (Scheme 5).

In 2005, 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.[30] Thus, the zinco-cyclopropanation of several cis-disubstituted allylic alcohols bearing various sterically demanding substituents at the allylic position provided the corresponding



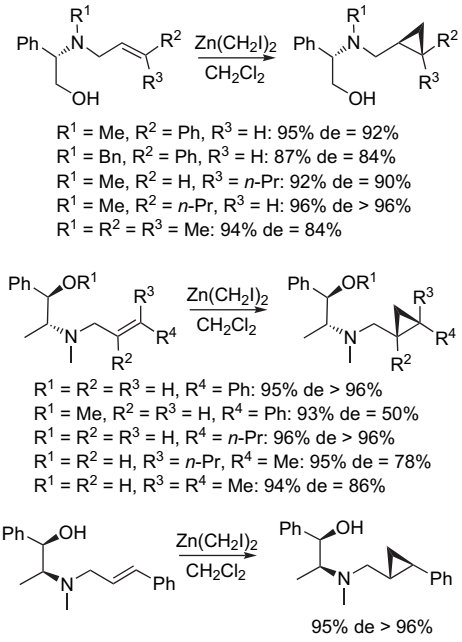
Scheme 5. Asymmetric cyclopropanation of C_2-symmetric diol.

syn,*cis* cyclopropyl derivatives in high diastereomeric ratios with a wide range of substituents. The facial selectivity for the attack of the *gem*-zinc carbenoid on the alkene was excellent in all of the cases. A high diastereoselectivity leading to the *cis*,*syn* isomer was also observed using a protected allylic alcohol. The zinco-cyclopropanation of the corresponding trans isomer led, however, to a mixture of stereoisomers. Moreover, introducing 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 6.



Scheme 6. Asymmetric cyclopropanations of allylic alcohols and ethers with *gem*-dizinc carbenoids.

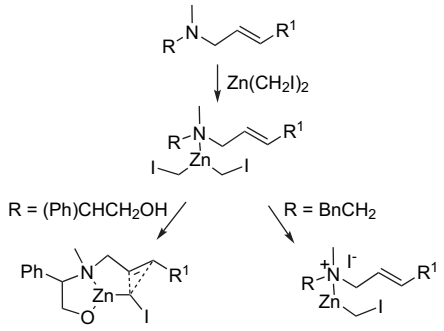
Much of the development of stereoselective cyclopropanation has relied on the directing effect of an allylic or homoallylic oxygen functional group, which provides an oxygen atom to chelate with the zinc reagent. Functional groups involved in substrate-controlled diastereoselective Simmons–Smith cyclopropanations include hydroxyl, acetal, amide and borate groups. Even though amines have, however, the same potential for binding with the zinc reagent as oxygen functional groups, allylic amines have been much less explored than their corresponding alcohols. In 2003, Aggarwal et al. reported the first highly diastereoselective cyclopropanation of allylic tertiary amines using the Simmons–Smith reagent by employing chelating groups in close proximity to the amine.[31] These groups promoted cyclopropanation at the expense of *N*-ylide formation by the formation of a stable chelating complex between the zinc reagent and the chiral amino alcohol of the allylic amines. The cyclopropanation process occurred with very high diastereoselectivity for a range of chiral amino alcohols such as phenylglycinol, pseudoephedrine and ephedrine, as shown in Scheme 7.



Scheme 7. Asymmetric cyclopropanations of allylic tertiary amines.

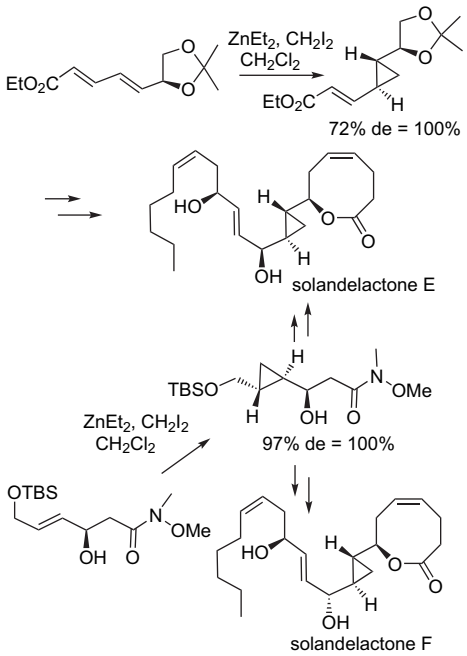
The divergent behaviour of allylic amines and those bearing additional chelating groups can be readily accounted for. In both cases, the reaction is initiated by complexation of the amine with the zinc reagent. In the case of a simple allyl-substituted amine (R=$BnCH_2$, Scheme 8), this species undergoes a 1,2-shift to furnish a zinc-complexed ammonium ylide. In the case of an amino alcohol (R=$(Ph)CHCH_2OH$), a more stable chelated zinc complex is considered to be formed that does not readily undergo the 1,2-shift. Because of the proximity of the olefin to the tightly held zinc carbenoid, however, cyclopropanation occurs instead (Scheme 8).

Very recently, a diastereoselective acetal-directed cyclopropanation has constituted the key step of a total synthesis of solandelactone E, a biologically active oxylipin (Scheme 9).[32] At the same time, White et al. have developed another total synthesis of this homoeicosanoid, having as the key step another



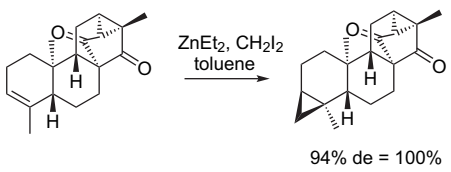
Scheme 8. Reaction pathways of Simmons–Smith reaction of allylic amines.

directed Simmons–Smith cyclopropanation leading to a single diastereoisomer, as shown in Scheme 9. Moreover, this cyclopropyl intermediate also allowed the total synthesis of solandelactone F to be achieved, confirming that the structures of the two solandelactones were epimeric at C11.[33] A similar methodology was previously applied by Smith et al. to the total synthesis of a marine diolide, (−)-clavosolide A.[34]



Scheme 9. Syntheses of solandelactones E and F.

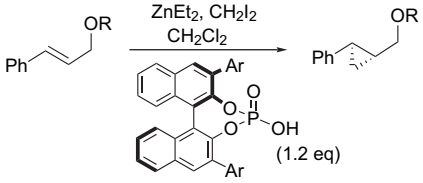
Finally, standard Simmons–Smith conditions were applied by Abad et al. to the cyclopropanation of a tetracyclic diterpene in 2006.[35] In spite of the absence of a directing group, the cyclopropanation took place stereoselectively from the less-hindered β-side of the double bond, affording the expected cyclopropane in excellent yield and diastereoselectivity (Scheme 10). This compound, having a tricyclo[3.2.1.0]octane moiety, was a key intermediate in the synthesis of trachylobane-, beyerane-, atisane- and kaurane-type diterpenes.



Scheme 10. Asymmetric cyclopropanation of unfunctionalised olefin.

2.2. Chiral catalysts

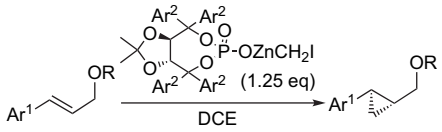
Several catalytic systems have been reported for the enantioselective Simmons–Smith cyclopropanation reaction and, among them, only a few could be used in catalytic amounts. In 2005, Charette et al. successfully employed a chiral phosphoric acid derived from a 3,3′-disubstituted BINOL derivative to design a novel chiral zinc phosphate reagent for the enantioselective cyclopropanation of protected allylic alcohols (Scheme 11).[36] Even when used in catalytic amounts, this chiral phosphoric acid allowed the corresponding chiral cyclopropanes to be obtained in high yield and up to 95% ee.



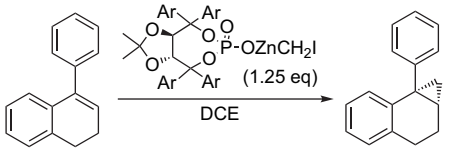
R = Me: > 95% ee > 95%
R = Bn: > 95% ee = 90%
R = PMB: 95% ee = 85%
R = MOM: 75% ee = 90%
R = TES: > 95% ee = 92%
R = CH_2OBn: > 95% ee = 93%
R = ZnEt: > 95% ee = 39%

Scheme 11. Asymmetric cyclopropanation in presence of BINOL-derived phosphoric acid.

In order to extend the scope of the cyclopropanation reaction, the same group developed, in 2006, a new family of chiral phosphates derived from TADDOL.[37] The use of these ligands in the asymmetric Simmons–Smith cyclopropanation of both functionalised and unfunctionalised olefins led to the formation of the desired cyclopropanes in good yields and good-to-moderate enantioselectivities, as shown in Scheme 12.



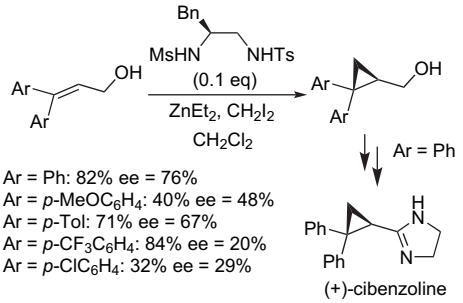
Ar^1 = Ph, Ar^2 = 2-Naph, R = Bn: 96% ee = 69%
Ar^1 = Ph, Ar^2 = 2-Naph, R = Me: 69% ee = 73%
Ar^1 = *p*-$MeOC_6H_4$, Ar^2 = 2-Naph, R = Bn: 87% ee = 69%
Ar^1 = *m*-$MeOC_6H_4$, Ar^2 = 2-Naph, R = Bn: 97% ee = 75%
Ar^1 = $Ph(CH_2)_2$, Ar^2 = 2-Naph, R = Bn: 88% ee = 69%



Ar = Ph: 38% ee = 40%
Ar = 2-Naph: 6% ee = 31%

Scheme 12. Asymmetric cyclopropanations in presence of TADDOL-derived phosphate ligands.

In 2006, Imai et al. reported the syntheses of (+)-cibenzoline, an antiarrhythmic agent, and its analogues via catalytic enantioselective cyclopropanation using simple chiral disulfonamides derived from α-amino acids such as (*S*)-phenylalanine-derived disulfonamides.[38] A catalytic amount of this catalyst was, therefore, successfully employed to cyclopropanate a range of 3,3-diaryl-2-propen-1-ols in the presence of Et_2Zn and CH_2I_2, providing the

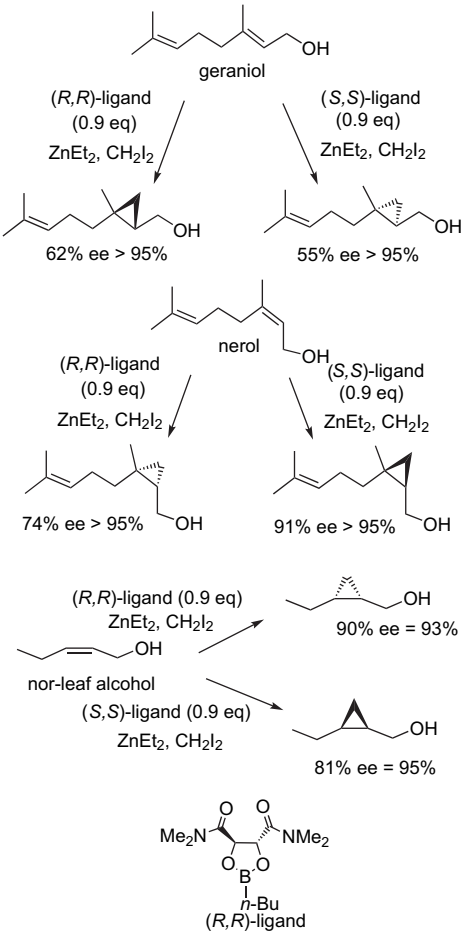


Scheme 13. Asymmetric cyclopropanation in presence of (*S*)-phenylalanine-derived disulfonamide.

corresponding cyclopropylmethanols with moderate-to-good enantioselectivity (Scheme 13). The chiral cyclopropane derived from 3,3-diphenyl-2-propen-1-ol was further converted into (+)-cibenzoline.

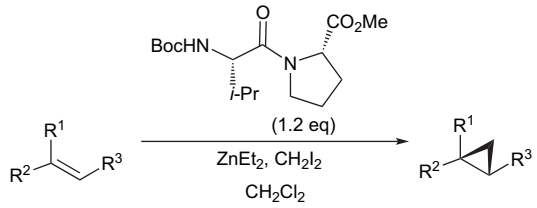
In order to evaluate their odour properties and to study the mechanism of human olfaction, both enantiomers of cyclopropanated analogues of geraniol were stereoselectively synthesised by Kiyota et al., in 2007, by using (*R*,*R*)- and (*S*,*S*)-dioxaborolane ligands.[39] The same methodology was also applied to nerol and nor-leaf alcohols in order to prepare the corresponding derivatives, as depicted in Scheme 14.

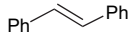
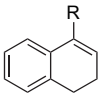
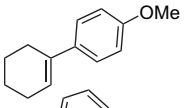
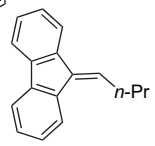
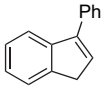
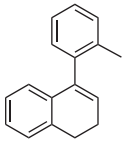
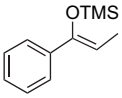
With the aim of developing a catalytic asymmetric cyclopropanation which does not require a specific directing functional group, Shi et al. have found that a simple chiral dipeptide, *N*-Boc–L-Val–L-Pro–OMe, combined with $ZnEt_2$ and CH_2I_2, led to an active



Scheme 14. Asymmetric cyclopropanations in presence of (*R*,*R*)- and (*S*,*S*)-dioxaborolane ligands.

cyclopropanation system for unfunctionalised olefins with an encouragingly high enantioselectivity (Scheme 15).[40]

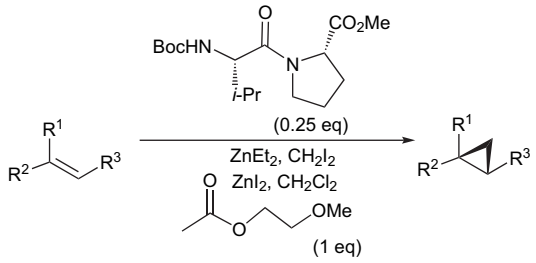


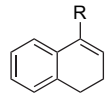
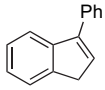
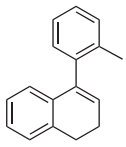
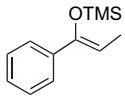
substrate		yield (%)	ee (%)
		83	75
	R = H	71	72
	R = Ph	83	90
	R = OBz	71	79
		71	75
		78	90
		84	78
		71	91
		68	85

Scheme 15. Asymmetric cyclopropanation of unfunctionalised olefins in presence of *N*-Boc–L-Val–L-Pro–OMe dipeptide.

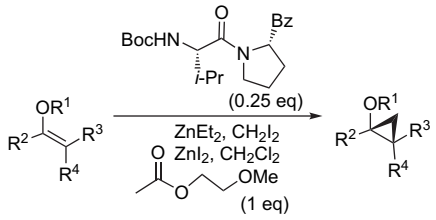
When these reactions were performed in the presence of substoichiometric amounts of the same chiral dipeptide, the enantioselectivity was decreased, due to an enhanced background reaction from $Zn(CH_2I)_2$. In this context, the authors surmised that an achiral additive could be used to coordinate with $Zn(CH_2I)_2$ and reduce the background cyclopropanation, thus enhancing the enantioselectivity. Indeed, when the reaction was carried out in the presence of ethyl methoxyacetate (EMA) as an additive, and a catalytic amount of *N*-Boc–L-Val–L-Pro–OMe dipeptide, the corresponding chiral cyclopropanes were obtained with comparable ees to those obtained by the original stoichiometric procedure (Scheme 16).[41]

In 2006, the same group reported the use of another chiral dipeptide as ligand to promote the asymmetric Simmons–Smith cyclopropanation of silyl enol ethers in the presence of EMA as additive, giving access to a variety of optically active cyclopropyl silyl ethers in high yield and with up to 96% ee (Scheme 17).[42] A plausible catalytic cycle is depicted in Scheme 17, in which intermediate **E** is generated from the dipeptide by deprotonation with $ZnEt_2$, followed by halogen exchange with CH_2I_2. The intermediate **E** then cyclopropanates the olefin to form the intermediate **F**, which regenerates **E** by exchange with $Zn(CH_2I)_2$ to complete the cycle.



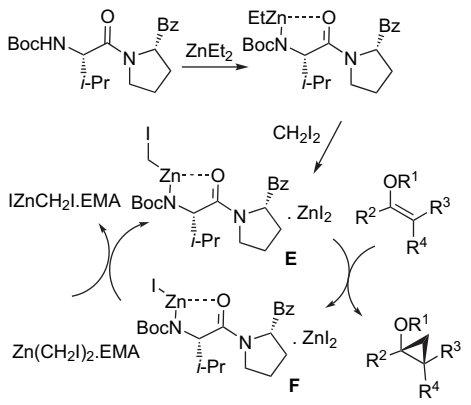
substrate		yield (%)	ee (%)
	R = Ph	87	89
	R = OBz	52	78
		85	77
		60	89
		96	87

Scheme 16. Asymmetric cyclopropanation of unfunctionalised olefins in presence of *N*-Boc–L-Val-L-Pro–OMe dipeptide and EMA as additive.



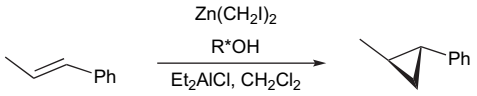
R^1 = TMS, R^2 = Ph, R^3 = Me, R^4 = H: 99% ee = 93%
R^1 = TMS, R^2 = *p*-$MeOC_6H_4$, R^3 = Me, R^4 = H: 97% ee = 93%
R^1 = TMS, R^2 = 2-Naph, R^3 = Me, R^4 = H: 80% ee = 95%
R^1 = TBS, R^2 = C≡C-Ph, R^3 = Me, R^4 = H: 89% ee = 86%
R^1 = TBS, R^2 = C≡C-*n*-Pent, R^3 = Me, R^4 = H: 86% ee = 86%
R^1 = TBS, R^2 = C≡C-Ph, R^3 = H, R^4 = Me: 91% ee = 93%
R^1 = TMS, R^2,R^4 = CH=CH-$(CH_2)_2$, R^3 = H: 79% ee = 92%
R^1 = TBS, R^2,R^4 = $(CH_2)_4$, R^3 = H: 90% ee = 72%
R^1 = TBDPS, R^2,R^4 = $(CH_2)_3$, R^3 = H: 77% ee = 89%

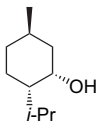
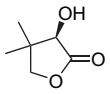
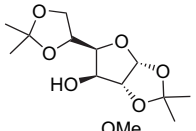
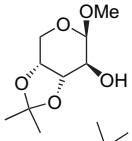
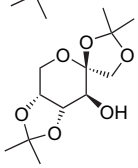
proposed catalytic cycle:



Scheme 17. Asymmetric cyclopropanation of silyl enol ethers in presence of chiral dipeptide.

Since zinc reagents modified by a covalent ligand ($RXZnCH_2I$) are effective for cyclopropanation, several chiral (iodomethyl)-zinc species, R^*XZnCH_2I, have been investigated by Shi et al. in order to induce enantioselectivity in cyclopropanation reactions.[43] A number of chiral alcohols were, therefore, tested using *trans*-β-methylstyrene as a substrate. Generally, the cyclopropanations were very sluggish, but they were accelerated by the addition of a catalytic amount of a Lewis acid. As shown in Scheme 18, an enantioselectivity of 51% ee was obtained for the cyclopropane product using fructose-derived alcohol as a modifier and Et_2AlCl as the Lewis acid.



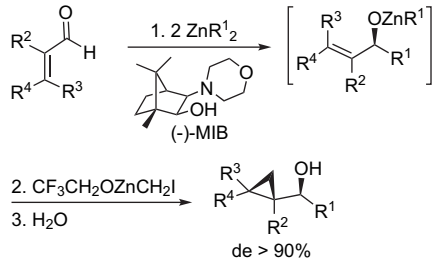
R*OH	yield (%)	ee (%)
	85	8
	91	17
	6	8
	19	20
	74	51

Scheme 18. Asymmetric cyclopropanation of *trans*-β-methylstyrene catalysed by R^*OZnCH_2I.

In addition, a highly enantio- and diastereoselective tandem generation of cyclopropyl alcohols with up to four contiguous stereocentres was reported by Walsh et al. in 2005.[44] This methodology consisted of generating a key allylic zinc alkoxide intermediate by asymmetric alkyl addition to α,β-unsaturated aldehydes in the presence of a catalytic amount of Nugent's (−)-MIB (Scheme 19).[45] The initial enantioselective C–C bond formation was followed by a diastereoselective cyclopropanation performed in the presence of 5 equiv of $ZnEt_2$ and CH_2I_2, affording the corresponding cyclopropyl alcohols in very high ees and des for almost all substrate classes (Scheme 19).

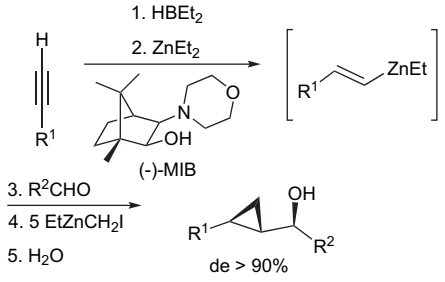
A second tandem addition/cyclopropanation sequence was developed by the same group on the basis of Oppolzer's hydroboration/transmetalation method,[46] generating an intermediate vinylzinc reagent. In the presence of (−)-MIB, a clean vinylation of an aldehyde proceeded to furnish the corresponding allylic alkoxide intermediate, which then cyclopropanated (Scheme 20).[44] Although these two novel tandem addition/cyclopropanation sequences gave similar stereoselectivities to the cyclopropanation of isolated chiral allylic alcohols, they were, however, demonstrated to be more efficient.

Finally, the scope of this methodology was extended to the synthesis of chiral iodocyclopropyl alcohols by using iodoform in place of diiodomethane to form the intermediate $CF_3CH_2OZnCHI_2$,



R^1 = Et, R^2,R^4 = $(CH_2)_4$, R^3 = H: 90% ee = 99%
R^1 = $(CH_2)_4$*i*-Pr, R^2,R^4 = $(CH_2)_4$, R^3 = H: 66% ee = 97%
R^1 = $(CH_2)_5$OTBDPS, R^2,R^4 = $(CH_2)_4$, R^3 = H: 75% ee = 98%
R^1 = R^3 = R^4 = Me, R^2 = H: 76% ee = 99%
R^1 = Et, R^3 = R^4 = Me, R^2 = H: 78% ee = 95%
R^1 = $(CH_2)_4$*i*-Pr, R^2 = H, R^3 = R^4 = Me: 64% ee = 96%
R^1 = R^2 = Me, R^3 = H, R^4 = Ph: 85% ee = 95%
R^1 = Et, R^2 = Me, R^3 = H, R^4 = Ph: 90% ee = 96%
R^1 = Et, R^2 = R^3 = H, R^4 = Ph: 87% ee = 89%
R^1 = Et, R^2 = R^4 = H, R^3 = CH_2OTBDPS: 80% ee = 98%
R^1 = Et, R^2 = R^4 = H, R^3 = CH_2OBn: 91% ee = 91%

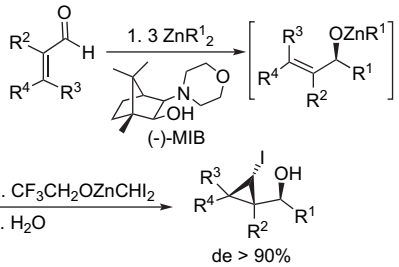
Scheme 19. Asymmetric tandem addition/cyclopropanation reaction of enals in presence of (−)-MIB.



R^1 = Ph, R^2= *i*-Pr: 75% ee = 99%
R^1 = *n*-Bu, R^2= *i*-Pr: 71% ee = 92%
R^1 = *t*-Bu, R^2= *i*-Pr: 78% ee = 87%
R^1 = Ph, R^2= Cy: 78% ee = 99%
R^1 = *n*-Bu, R^2= Cy: 84% ee = 93%
R^1 = *t*-Bu, R^2= Cy: 74% ee = 96%
R^1 = $(CH_2)_4$Cl, R^2= Cy: 80% ee = 94%
R^1 = $(CH_2)_2$OTr, R^2= Cy: 73% ee = 93%

Scheme 20. Asymmetric tandem addition/cyclopropanation reaction of alkynes in presence of (−)-MIB.

instead of $CF_3CH_2OZnCH_2I$, in the cyclopropanation step of the tandem sequence depicted in Scheme 19.[44] The intermediate allylic alkoxide formed upon alkyl addition to an enal was treated with $CF_3CH_2OZnCHI_2$, giving rise to the corresponding iodocyclopropyl alcohol with up to 99% ee (Scheme 21).



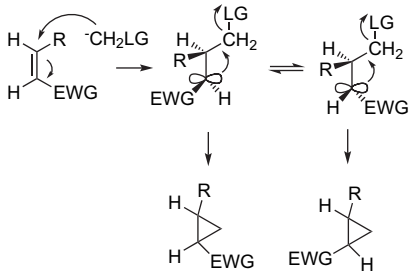
R^1 = Et, R^2,R^4 = $(CH_2)_4$, R^3 = H: 68% ee = 99%
R^1 = $(CH_2)_5$OTBDPS, R^2,R^4 = $(CH_2)_4$, R^3 = H: 70% ee = 98%
R^1 = R^3 = R^4 = Me, R^2 = H: 78% ee = 99%
R^1 = Et, R^3 = R^4 = Me, R^2 = H: 62% ee = 95%
R^1 = $(CH_2)_4$*i*-Pr, R^2 = H, R^3 = R^4 = Me: 60% ee = 96%
R^1 = Et, R^2 = R^3 = H, R^4 = Ph: 70% ee = 89%
R^1 = Et, R^2 = Me, R^3 = H, R^4 = Ph: 56% ee = 96%
R^1 = Et, R^2 = R^4 = H, R^3 = CH_2OTBDPS: 74% ee = 98%

Scheme 21. Synthesis of chiral iodocyclopropyl alcohols in presence of (−)-MIB.

3. Michael-initiated ring closure

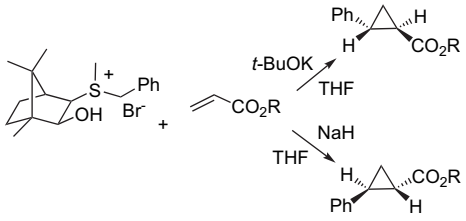
3.1. Chiral auxiliaries

Cyclopropanation reactions involving a conjugate addition to an electrophilic alkene to produce an enolate, which then subsequently undergoes an intramolecular ring closure, are defined as Michael-initiated ring-closure (MIRC) reactions. Although there are exceptions, cyclopropanations via the MIRC reaction of acyclic olefins are usually nonstereospecific, and both (*E*)- and (*Z*)-olefins give the corresponding *trans* cyclopropanes. 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 formation. Conversely, the formation of a configurationally stable tetrahedral intermediate after the first addition may also lead to a stereospecific process (Scheme 22).

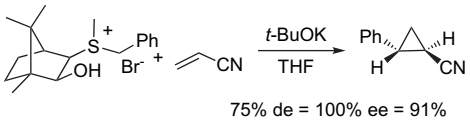


Scheme 22. Michael-initiated ring-closure cyclopropanation reaction.

A variety of stoichiometric chiral nucleophiles have been developed in recent years to perform enantio- and diastereoselective cyclopropanations of α,β-unsaturated carbonyl derivatives via MIRC processes. As an example, Huang et al. have developed a practical and controllable enantioselective synthesis of 2-phenyl-1-cyclopropane-carboxylates by using a camphor-derived sulfonium ylide as the chiral nucleophile.[47] Excellent diastereoselectivities were achieved, with the trans isomer dominant in all cases, combined with good yields and high enantioselectivities (Scheme 23). It



R = Et, base = *t*-BuOK: 84% de = 98% ee = 91%
R = Me, base = *t*-BuOK: 88% de = 100% ee = 90%
R = *n*-Bu, base = *t*-BuOK: 91% de = 98% ee = 91%
R = Bn, base = *t*-BuOK: 79% de = 96% ee = 95%
R = Et, base = NaH: 76% de = 98% ee = 80%
R = Me, base = NaH: 71% de = 96% ee = 85%
R = *n*-Bu, base = NaH: 80% de = 100% ee = 72%
R = Bn, base = NaH: 76% de = 96% ee = 82%

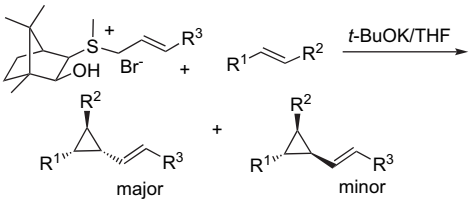


75% de = 100% ee = 91%

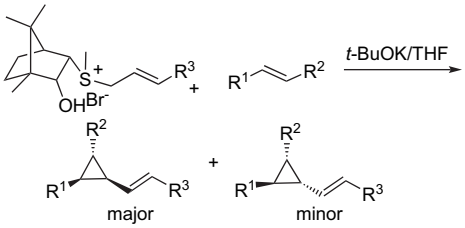
Scheme 23. Asymmetric cyclopropanations via camphor-derived sulfonium ylide.

was noteworthy that the starting chiral sulfide could be recovered almost quantitatively and re-used conveniently. Interestingly, the enantioselectivity could be tuned at will, just by changing the base. Indeed, when sodium hydride was used instead of potassium *tert*-butoxide, (1*S*,2*S*)-2-phenyl-1-cyclopropane-carboxylates were obtained with good opposite enantioselectivities. Moreover, the scope of the reaction was extended to the use of acrylonitrile as electrophile, providing the corresponding cyclopropane in high de and ee (Scheme 23).

In order to prepare a series of chiral 1,3-disubstituted-2-vinylcyclopropanes, Tang et al. reported similar reactions to those depicted in Scheme 23, but using other camphor-derived sulfur ylides in the presence of a variety of α,β-unsaturated carbonyl compounds (Scheme 24).[48] The use of *exo*-type sulfonium ylides allowed the corresponding cyclopropanes to be obtained with high diastereo- and enantioselectivities, whereas with the corresponding *endo*-type sulfonium ylides, the diastereoselectivities were not changed, but the absolute configurations of the products became opposite to those of the reactions of *exo*-type sulfonium ylides.



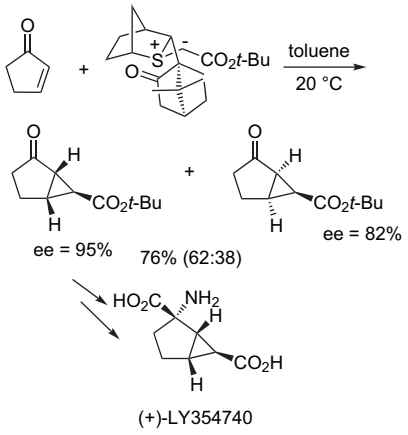
$R^1 = R^3 = Ph$, $R^2 = CO_2Me$: 77% de > 98% ee = 99%
$R^1 = R^3 = Ph$, $R^2 = Bz$: 83% de = 94% ee = 94%
$R^1 = p\text{-}ClC_6H_4$, $R^2 = COt\text{-}Bu$, $R^3 = Ph$: 91% de = 90% ee = 98%
$R^1 = R^3 = Ph$, $R^2 = CON(CH_2)_4$: 98% de > 98% ee = 94%
$R^1 = R^3 = Ph$, $R^2 = CON(CH_2)_2O$: 99% de > 98% ee = 98%
$R^1 = p\text{-}BrC_6H_4$, $R^2 = CN$, $R^3 = Ph$: 83% de > 98% ee = 96%
$R^1 = H$, $R^2 = CO_2Me$, $R^3 = Ph$: 90% de > 98% ee = 93%
$R^1 = H$, $R^2 = CON(CH_2)_4$, $R^3 = Ph$: 70% de = 94% ee = 90%
$R^1 = Ph$, $R^2 = CO_2Me$, $R^3 = TMS$: 85% de > 98% ee = 97%
$R^1 = Ph$, $R^2 = CO_2Et$, $R^3 = TMS$: 75% de > 98% ee = 97%
$R^1 = Ph$, $R^2 = CON(CH_2)_4$, $R^3 = TMS$: 70% de > 98% ee = 97%
$R^1 = Ph$, $R^2 = CON(CH_2)_2O$, $R^3 = TMS$: 66% de > 98% ee = 97%
$R^1 = p\text{-}BrC_6H_4$, $R^2 = CN$, $R^3 = TMS$: 79% de > 98% ee = 99%



$R^1 = R^3 = Ph$, $R^2 = CO_2Me$: 86% de > 98% ee = 98%
$R^1 = R^3 = Ph$, $R^2 = Bz$: 71% de = 84% ee = 92%
$R^1 = p\text{-}ClC_6H_4$, $R^2 = COt\text{-}Bu$, $R^3 = Ph$: 91% de = 98% ee = 98%
$R^1 = R^3 = Ph$, $R^2 = CON(CH_2)_4$: 87% de > 98% ee = 96%
$R^1 = R^3 = Ph$, $R^2 = CON(CH_2)_2O$: 97% de > 98% ee = 99%
$R^1 = p\text{-}BrC_6H_4$, $R^2 = CN$, $R^3 = Ph$: 75% de > 98% ee = 95%
$R^1 = H$, $R^2 = CO_2Me$, $R^3 = Ph$: 60% de > 98% ee = 91%
$R^1 = H$, $R^2 = CON(CH_2)_4$, $R^3 = Ph$: 78% de = 94% ee = 98%
$R^1 = Ph$, $R^2 = CO_2Me$, $R^3 = TMS$: 37% de > 98% ee = 74%
$R^1 = Ph$, $R^2 = CON(CH_2)_4$, $R^3 = TMS$: 72% de > 98% ee = 96%
$R^1 = Ph$, $R^2 = Bz$, $R^3 = TMS$: 78% de > 98% ee = 96%
$R^1 = p\text{-}ClC_6H_4$, $R^2 = COt\text{-}Bu$, $R^3 = TMS$: 87% de > 98% ee = 94%

Scheme 24. Synthesis of chiral 1,3-disubstituted-2-vinylcyclopropanes.

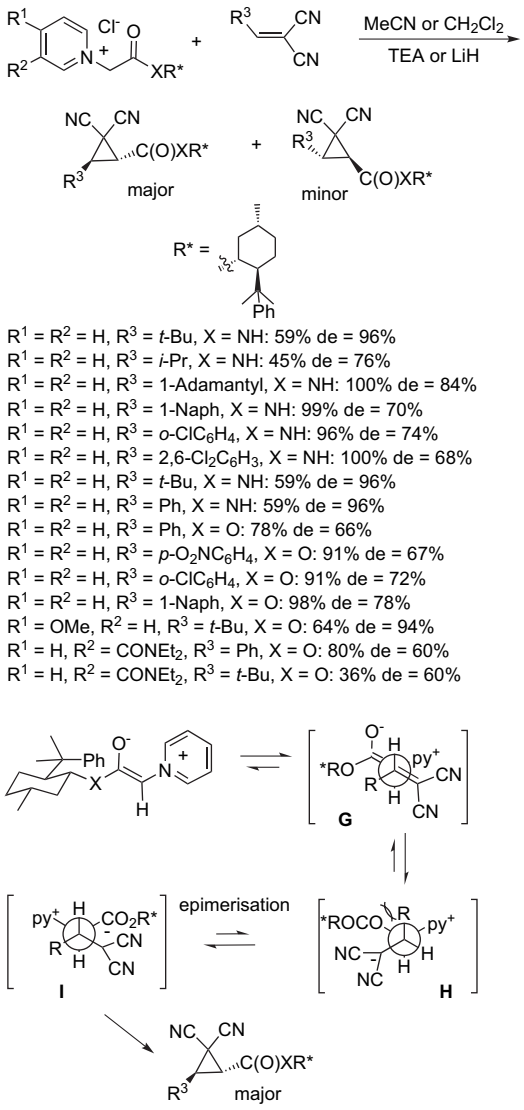
In 2006, Aggarwal et al. studied the reaction of chiral ester-stabilised sulfonium ylides with cyclopentenone, giving access to an important precursor to the pharmacologically important compound, (+)-LY354740.[49] It was found that the reaction conditions employed had a major influence over both the diastereo- and enantioselectivities. Thus, under catalytic conditions, a good enantioselectivity with a low diastereoselectivity was observed, but, under stoichiometric conditions, a low enantioselectivity with a high diastereoselectivity was observed. When the stoichiometric reactions were conducted at high dilution, the diastereoselectivity was reduced, indicating that base-mediated betaine equilibration was occurring. Based on these results, the conditions for achieving high enantioselectivity were established as the use of a preformed ylide, the absence of base, and the presence of a hindered ester, along with a low concentration. Under these conditions, a high enantioselectivity was achieved, albeit with a low diastereocontrol, as shown in Scheme 25.



Scheme 25. Asymmetric sulfonium ylide-mediated cyclopropanation.

Surprisingly, there are relatively few examples in the literature that employ nitrogen-derived ylides. As an example, Kojima et al. have demonstrated that chiral pyridinium ylides could be applicable for cyclopropanation.[50] Thus, the reaction between an α-pyridinium acetamide bearing an 8-phenylmenthyl group as the chiral auxiliary and β-substituted methylidenemalonitriles gave rise to the corresponding *trans* cyclopropanes with des of up to 96% (Scheme 26). A high diastereoselectivity was observed, especially for bulky Michael acceptor reactants, and the stereochemical course of the reaction turned out to be opposite to that of the ester series. The mechanism involving the selectivity could tentatively be assumed to be as follows.[51] The enolate, in which the large pyridyl and 8-phenylmenthyloxy groups are in a trans relationship, was expected to be predominant upon deprotonation, due to both steric factors and electrostatic interactions between the cationic pyridine and anionic oxide moieties. The reaction with the Michael acceptor was expected to occur upon the face of the enolate that was not sterically encumbered by the phenyl group of the 8-phenylmenthyl chiral auxiliary, and considering dipole cancellation as the driving force, it was proposed that the process involving the transition state **G** was the favoured and, thus, the primary stereodetermining step. Upon ring closure to give the cyclopropane product, however, the intermediate **H** experienced severe steric hindrance, due to the interaction between the carboxylate group and the R group and, thus, product formation was unfavourable. Due to the presence of the two carbanion-stabilising groups, the intermediate **H** should have a sufficient lifetime to allow the carbon between the pyridinium and carboxylate groups to undergo epimerisation under the basic reaction conditions. This afforded the intermediate **I**, in which hindrance in the ensuing cyclisation process was alleviated, and, thus, gave the major *trans* cyclopropane (Scheme 26).

In 2007, Yamada et al. reported an asymmetric cyclopropanation of electron-deficient olefins using another chiral pyridinium ylide, the conformation of which was fixed through a cation–π interaction.[52] The key feature of this process was that the cation–π

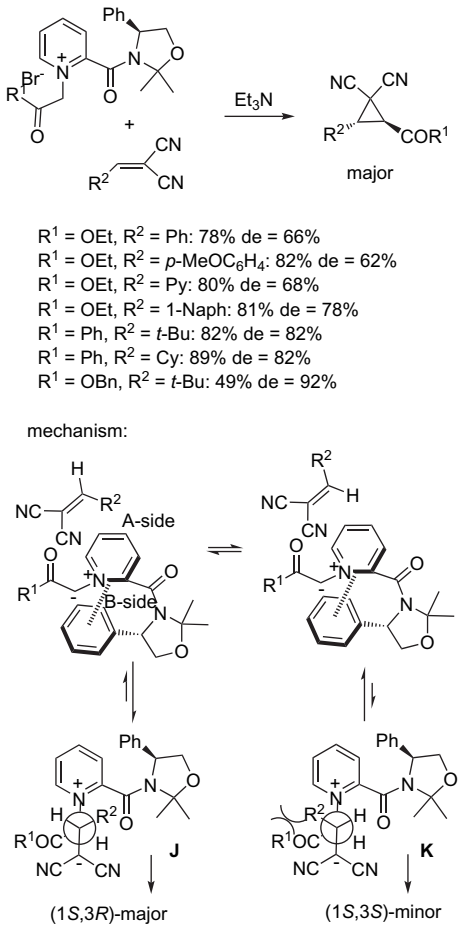


Scheme 26. Asymmetric pyridinium ylide-mediated cyclopropanation.

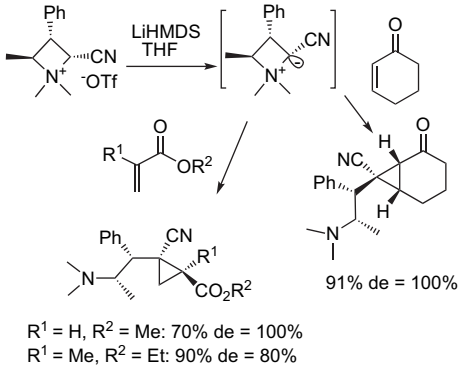
interaction allowed the production of a chiral environment around the active site, which enabled the *Re* and *Si* faces of olefins to be distinguished, although the chiral centre was apart from it. These studies led to a working model for the stereoselective formation of cyclopropanes, as outlined in Scheme 27. An electron-deficient olefin will approach the ylide from the less-hindered A-side. Two intermediates **J** and **K** would be produced, depending upon whether the ylide attacks the *Re* or *Si* face of the olefin. The equilibrium between the intermediates **J** and **K** would shift to the intermediate **J** in order to avoid severe steric repulsion between the COR^1 and R^2 groups in the intermediate **K** and, consequently, the cyclopropane bearing the (1*S*,3*R*)-configuration was produced as the major product.

In 2007, Couty et al. reported that chiral azetidinium ylides showed a remarkable ability to perform the cyclopropanation of Michael acceptors.[53] Thus, ephedrine-derived azetidinium ylides allowed the formation of tri- or tetrasubstituted cyclopropanes, bearing one or two quaternary carbon centres along with one or two tertiary centres, in good yields and at a high level of stereoselectivity (Scheme 28).

In addition, Tang et al. have found another class of chiral nucleophiles such as chiral allylic telluronium ylides, which could be condensed onto a range of α,β-unsaturated esters, amides and



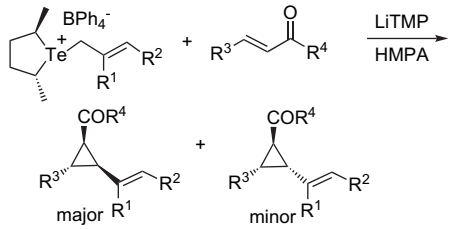
Scheme 27. Asymmetric pyridinium ylide-mediated cyclopropanation through cation–π interaction.



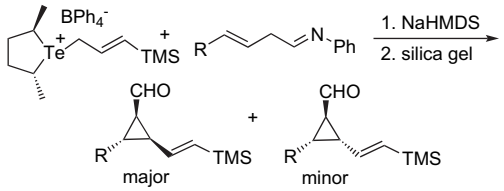
Scheme 28. Asymmetric azetidinium ylide-mediated cyclopropanation.

ketones, providing the corresponding 1,3-disubstituted 2-vinylcyclopropanes with high yields, des and ees, as shown in Scheme 29.[54] The scope of this methodology was extended, in 2005, to the use of α,β-unsaturated imines, leading to the formation of the corresponding vinylcyclopropanecarbaldehydes in one pot with both excellent diastereo- and enantioselectivities and in good yields (Scheme 29).[55]

On the other hand, it is also possible to use a chiral Michael acceptor instead of a chiral nucleophile, compared to the studies described above. As an example, Mikolajczyk et al. have developed asymmetric cyclopropanations of chiral (1-diethoxyphosphoryl)-vinyl *p*-tolyl sulfoxides with sulfur ylides that occur in a highly



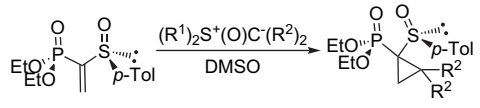
R^1 = H, R^2 = TMS, R^3 = Ph, R^4 = CO_2Me:
95% de = 92% ee = 96%
R^1 = H, R^2 = TMS, R^3 = Ph, R^4 = CO_2Et:
97% de = 96% ee = 97%
R^1 = H, R^2 = TMS, R^3 = *p*-$MeOC_6H_4$, R^4 = CO_2Me:
63% de = 94% ee = 94%
R^1 = H, R^2 = TMS, R^3 = *p*-Tol, R^4 = CO_2Me:
88% de = 96% ee = 97%
R^1 = H, R^2 = TMS, R^3 = *p*-BrC_6H_4, R^4 = CO_2Me:
97% de = 94% ee = 96%
R^1 = H, R^2 = TMS, R^3 = 2-Fu, R^4 = CO_2Et:
81% de = 88% ee = 97%
R^1 = H, R^2 = TMS, R^3 = Ph, R^4 = Bz:
95% de = 96% ee = 95%
R^1 = H, R^2 = TMS, R^3 = *p*-BrC_6H_4, R^4 = Bz:
99% de = 98% ee = 96%
R^1 = H, R^2 = TMS, R^3 = $Me(CH_2)_3$, R^4 = $CO(CH_2)_6Me$:
78% de = 96% ee = 99%
R^1 = H, R^2 = TMS, R^3 = Ph, R^4 = $CON(CH_2)_5$:
83% de = 98% ee = 93%
R^1 = Me, R^2 = H, R^3 = *p*-BrC_6H_4, R^4 = Bz:
81% de = 94% ee = 96%
R^1 = R^2 = H, R^3 = Ph, R^4 = CO_2Me:
42% de = 86% ee = 95%



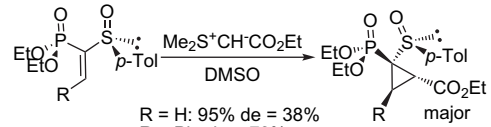
R = Ph: 85% de > 96% ee = 99%
R = *p*-ClC_6H_4: 73% de > 96% ee = 95%
R = *p*-$CF_3C_6H_4$: 83% de > 94% ee = 95%
R = *p*-$MeOC_6H_4$: 68% de > 98% ee = 95%
R = 2-Fu: 61% de > 98% ee = 95%

Scheme 29. Asymmetric allylic telluronium ylide-mediated cyclopropanations.

diastereoselective manner (Scheme 30).[56] One of the resulting chiral cyclopropanes has been further converted into a constrained analogue of the $GABA_B$ antagonist, phaclofen, whereas another was converted into chiral cyclopropylphosphonate analogue of purine nucleotides as the constrained form of antiviral 1-alkenylphosphonic acid derivatives of purines.



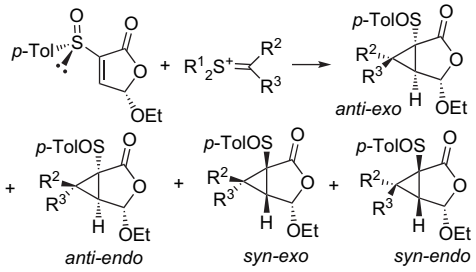
R^1 = Me, R^2 = H: 90% de = 100%
R^1 = CD_3, R^2 = D: 92% de = 100%



R = H: 95% de = 38%
R = Ph: de = 78%

Scheme 30. Asymmetric cyclopropanations of (1-diethoxyphosphoryl)vinyl *p*-tolyl sulfoxides with sulfur ylides.

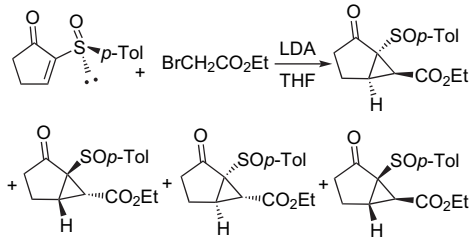
In 2004, Ruano et al. reported the asymmetric cyclopropanation of chiral sulfinylfuranones with sulfonium ylides, the stereochemistry of which was highly dependent upon the substituents bonded to the ylidic sulfur atom.[57] Indeed, the results clearly showed that the reaction of the furanone with nonstabilised ylides occurred in a completely stereoselective manner via the addition of the sulfur nucleophile to the double bond from the opposite face to that occupied by the OEt group (*anti* products). The formation of the *endo* or *exo* adducts depended upon the face of the ylide, which was attacked by the electrophile and was completely dependent upon the substituents at sulfur. Consequently, dimethylsulfonium derivatives yielded mainly the *exo* products, while, with the diphenylsulfonium ylides, the *endo* products predominated (Scheme 31).



R^1 = Ph, R^2 = R^3 = H: 59% *anti:syn* = 100:0
R^1 = Ph, R^2 = R^3 = Me: 91% *anti:syn* = 100:0
R^1 = Ph, R^2 = Me, R^3 = H: 77%
endo:exo = 78:22 *anti:syn* = 100:0
R^1 = Ph, R^2 = CO_2Et, R^3 = H: 68%
endo:exo = 96:4 *anti:syn* = 95:5
R^1 = Me, R^2 = CO_2Et, R^3 = H: 50%
endo:exo = 4:96 *anti:syn* = 66:34
R^1 = Me, R^2 = Ph, R^3 = H: 25%
endo:exo = 23:77 *anti:syn* = 90:10

Scheme 31. Asymmetric cyclopropanation of sulfinylfuranones with sulfonium ylides.

In the same context, Mikolajczyk et al. have shown that the cyclopropanation of chiral sulfinylcyclopentenones with the α-bromoacetate carbanion proceeded efficiently and with a high degree of stereocontrol.[58] The best facial and *endo*/*exo* selectivity was observed in the reaction of the sulfinylcyclopentenone depicted in Scheme 32 with the α-bromoacetate carbanion.

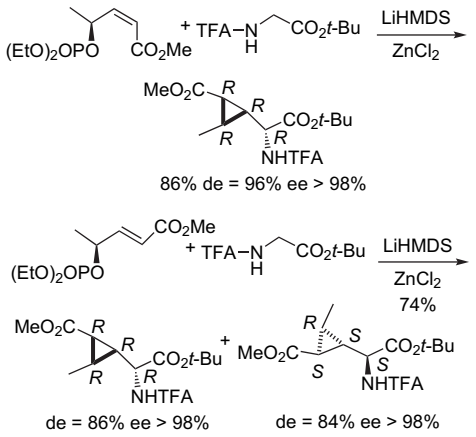


78% (85:4:8:3)
π-facial selectivity: 93:7
endo/exo = 89:11

Scheme 32. Asymmetric cyclopropanation of sulfinylcyclopentenone with α-bromoacetate carbanion.

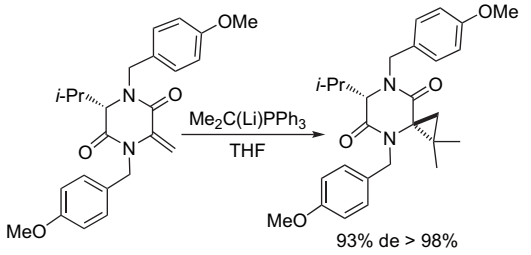
On the other hand, Kazmaier et al. have demonstrated that Zn-chelated glycine ester enolates were highly efficient nucleophiles for the synthesis of *trans*-methoxycarbonylcyclopropylglycines by domino sequences of Michael additions and subsequent ring closures. The reaction gave the *anti* isomers with high yields and excellent des, as shown in Scheme 33, allowing the creation of up to four stereogenic centres in one step.[59]

In addition, Davies et al. have developed the conjugate addition of an in situ-generated phosphonium-derived ylide to a chiral dehydroalanine acceptor, depicted in Scheme 34, giving access to



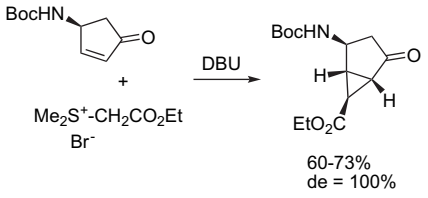
Scheme 33. Syntheses of chiral cyclopropyl amino acids.

the corresponding cyclopropane-substituted diketopiperazine in excellent yield and de.[60]



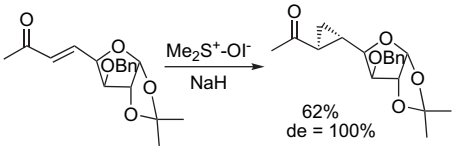
Scheme 34. Asymmetric cyclopropanation of dehydroalanine acceptor.

With the aim of developing concise total syntheses of 4-acylamino analogues of LY354740, the cyclopropanation of a chiral cyclopentenone was involved as a key step, providing the corresponding cyclopropane in good yield and de (Scheme 35).[61]



Scheme 35. Asymmetric cyclopropanation of chiral cyclopentenone.

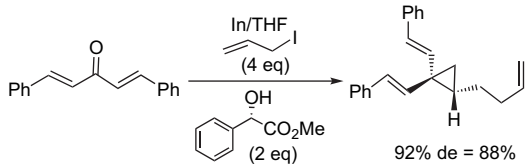
In 2006, a carbohydrate-based approach for the enantioselective synthesis of the polyketide acid unit present in nagahamide A was reported by Mohapatra et al.[62] The key step was the asymmetric cyclopropanation of a chiral olefin derived from D-glucose performed in the presence of trimethylsulfoxonium iodide and NaH, leading to the corresponding cyclopropane as a single product (Scheme 36).



Scheme 36. Asymmetric cyclopropanation of D-glucose-derived enone.

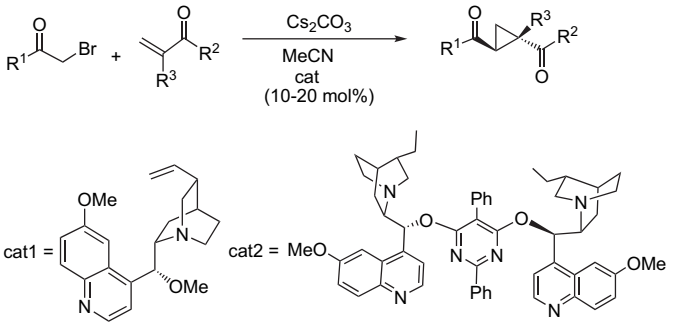
3.2. Chiral catalysts

In recent years, a strong emphasis has been placed on the development of catalytic methods to generate chiral cyclopropanes via Michael-initiated ring-closure reactions. In 2006, Lloyd-Jones et al. reported the asymmetric indium-mediated homoallyl-cyclopropanation reaction of dibenzylideneacetone performed in the presence of a chiral and cheap modifier such as (*S*)-methyl mandelate, as depicted in Scheme 37.[63] The reaction proceeded via stepwise cleavage of the C=O bond and delivery of two allyl fragments from the reagent, providing the corresponding cyclopropane in high de. This cyclopropane was further submitted to a Ru-catalysed ring-closing metathesis to generate the corresponding chiral norcarene.



Scheme 37. Asymmetric homoallyl-cyclopropanation of dibenzylideneacetone with modified allylindium halide.

On the other hand, a new class of catalytic asymmetric cyclopropanations has been developed in the last few years with the use of chiral organocatalysts.[64] As an example, Gaunt et al. reported, in 2003, the first example of enantioselective cyclopropanation based on the use of a chiral ammonium ylide as organocatalyst.[65] This highly efficient catalytic process produced a range of chiral functionalised cyclopropanes with excellent diastereo- and enantioselectivities, and as either enantiomer.[66] Moreover, this novel methodology had several advantages over its counterparts, e.g., transition metals are absent, the starting materials are readily available and conveniently handled and, furthermore, the number of known chiral amines represents a significant pool from which potential catalysts can be selected. The results obtained by using quinine or quinidine derivatives as chiral organocatalysts are collected in Scheme 38.

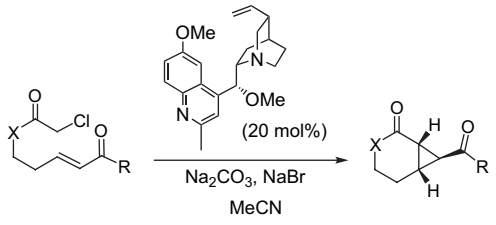


with cat = cat1:
R^1 = O*t*-Bu, R^2 = Ph, R^3 = H: 96% ee = 86%
R^1 = O*t*-Bu, R^2 = *p*-(Et_2N)C_6H_4, R^3 = H: 73% ee = 84%
R^1 = O*t*-Bu, R^2 = *p*-BrC_6H_4, R^3 = H: 83% ee = 85%
R^1 = NEt_2, R^2 = Ph, R^3 = H: 94% ee = 97%
R^1 = O*t*-Bu, R^2 = Ph, R^3 = Me: 63% ee = 92%
R^1 = O*t*-Bu, R^2 = OBn, R^3 = H: 75% ee = 80%
R^1 = O*t*-Bu, R^2 = OMe, R^3 = NHBoc: 90% ee = 97%
with cat = cat2:
R^1 = NMe(OMe), R^2 = *p*-BrC_6H_4, R^3 = H: 74% ee = 97%
R^1 = NMe(OMe), R^2 = *m*-BrC_6H_4, R^3 = H: 60% ee = 97%
R^1 = NMe(OMe), R^2 = *n*-Pent, R^3 = H: 77% ee = 92%

Scheme 38. Asymmetric organocatalytic cyclopropanation via ammonium ylides.

The scope of this powerful method was extended to the intramolecular version, allowing chiral [4.1.0]bicycloheptanes to be formed with high yields, as single diastereomers and with ee values that were usually over 95% (Scheme 39).[67]

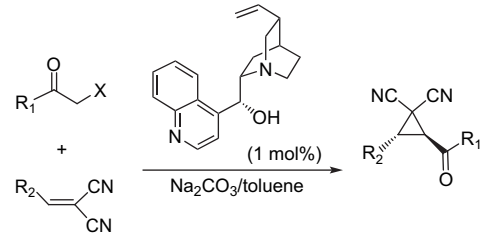
In 2006, Kojima et al. reported that an organocatalyst closely related to that used above was able to catalyse the



R = CH_2Bn, X = CH_2: 84% ee = 97%
R = Me, X = CH_2: 68% ee = 98%
R = Cy, X = CH_2: 79% ee = 95%
R = Ph, X = CH_2: 78% ee = 98%
R = *p*-BrC_6H_4, X = CH_2: 83% ee = 96%
R = *m*-$MeOC_6H_4$, X = CH_2: 77% ee = 99%
R = Et, X = NBn: 27% ee = 97%

Scheme 39. Asymmetric organocatalytic intramolecular cyclopropanation via ammonium ylide.

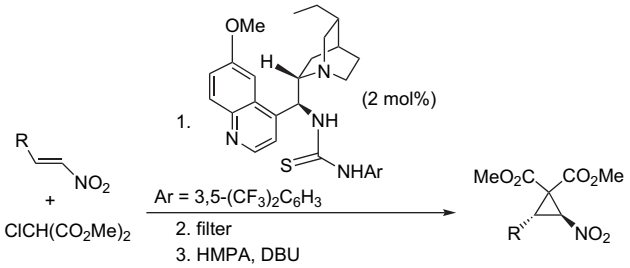
cyclopropanation between chloromethyl ketones and β-substituted methylidenemalononitriles to give the corresponding tetrasubstituted *trans* cyclopropanes with enantioselectivity of up to 82% ee (Scheme 40).[68]



R^1 = R^2 = Ph, X = Cl: 78% ee = 56%
R^1 = R^2 = Ph, X = Br: 45% ee = 20%
R^1 = Ph, R^2 = *o*-ClC_6H_4, X = Cl: 81% ee = 44%
R^1 = Ph, R^2 = *t*-Bu, X = Cl: 27% ee = 66%
R^1 = *o*-ClC_6H_4, R^2 = *t*-Bu, X = Cl: 65% ee = 82%

Scheme 40. Asymmetric organocatalytic cyclopropanation of methylidenemalononitriles.

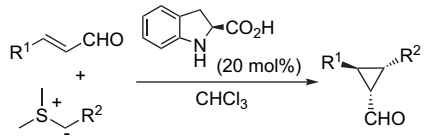
In 2006, Connon et al. reported the first asymmetric addition of dimethyl chloromalonate to a variety of nitroolefins catalysed by a chiral bifunctional cinchona alkaloid-based organocatalyst (Scheme 41).[69] The corresponding nitrocyclopropanes were obtained in good yields, with almost total diastereoselectivity, whereas the enantioselectivity was poor to moderate (≤47% ee).



R = Ph: 73% de > 98% ee = 38%
R = *p*-BrC_6H_4: 67% de > 98% ee = 47%
R = 2-Naph: 66% de > 98% ee = 25%
R = 2-Thio: 65% de > 98% ee = 31%

Scheme 41. Asymmetric organocatalytic cyclopropanation of nitroolefins.

In 2005, a novel class of iminium organocatalysts based upon directed electrostatic activation was proved by MacMillan et al. to be effective catalysts for the asymmetric cyclopropanation of α,β-unsaturated aldehydes (Scheme 42).[70] Thus, a chiral 2-carboxylic acid dihydroindole was found to be a useful catalyst for the reaction between a sulfonium ketone ylide and an α,β-unsaturated aldehyde, providing the corresponding cyclopropane with excellent levels of induction and yields. It was demonstrated that the organocatalyst and the ylide were engaged in electrostatic association via their pendant carboxylate and thionium substituents.

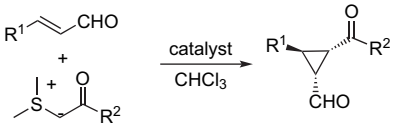


R^1 = *n*-Pr, R^2 = Bz: 85% de = 94% ee = 95%
R^1 = $CH_2Oallyl$, R^2 = Bz: 77% de = 90% ee = 91%
R^1 = Me, R^2 = Bz: 67% de = 90% ee = 90%
R^1 = allyl$(CH_2)_3$, R^2 = Bz: 74% de = 92% ee = 96%
R^1 = Ph, R^2 = Bz: 73% de = 94% ee = 89%
R^1 = *i*-Pr, R^2 = Bz: 63% de = 96% ee = 96%
R^1 = *n*-Pr, R^2 = *p*-BrC_6H_4: 67% de = 98% ee = 92%
R^1 = *n*-Pr, R^2 = *p*-$MeOC_6H_4$: 64% de = 84% ee = 93%
R^1 = *n*-Pr, R^2 = CO*t*-Bu: 82% de = 72% ee = 95%

Scheme 42. Asymmetric organocatalytic cyclopropanation of α,β-unsaturated aldehydes.

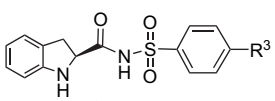
In 2007, Arvidsson et al. reported the preparation of novel chiral arylsulfonamides derived from (2*S*)-indoline-2-carboxylic acid and employed these organocatalysts for similar enantioselective cyclopropanations of α,β-unsaturated aldehydes with sulfur ylides such as those described above.[71] Although none of these new catalysts performed as well as the chiral indoline-2-carboxylic acid used in MacMillan's first disclosure of this reaction sequence (described in the preceding scheme), these sulfonamide-modified indole derivatives allowed enantioselectivities of up to 99% ee to be obtained, as shown in Scheme 43.

In 2007, the same workers described the development of another new chiral organocatalyst, a tetrazolic acid-functionalised



with catalyst 1:
R^1 = Me, R^2 = Ph: 45% de = 95% ee = 88%
R^1 = *n*-Pr, R^2 = Ph: 25% de = 96% ee = 94%
R^1 = *n*-Pr, R^2 = *p*-BrC_6H_4: 50% de = 96% ee = 95%
R^1 = R^2 = Ph: 20% de = 95% ee = 92%
R^1 = *n*-$PrOCH_2$, R^2 = Ph: 16% de = 97% ee = 93%
R^1 = *n*-$PrOCH_2$, R^2 = *p*-BrC_6H_4: 20% de = 95% ee = 91%
R^1 = *c*-Pent, R^2 = Ph: 43% de = 96% ee = 90%
R^1 = *c*-Pent, R^2 = *p*-BrC_6H_4: 48% de = 97% ee = 92%

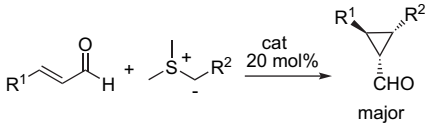
with catalyst 2:
R^1 = Me, R^2 = Ph: 55% de = 95% ee = 88%
R^1 = *n*-Pr, R^2 = Ph: 52% de = 97% ee = 98%
R^1 = *n*-Pr, R^2 = *p*-BrC_6H_4: 58% de = 96% ee = 99%
R^1 = R^2 = Ph: 28% de = 94% ee = 97%
R^1 = *n*-$PrOCH_2$, R^2 = Ph: 25% de = 96% ee = 99%
R^1 = *n*-$PrOCH_2$, R^2 = *p*-BrC_6H_4: 21% de = 94% ee = 99%
R^1 = *c*-Pent, R^2 = Ph: 52% de = 95% ee = 99%
R^1 = *c*-Pent, R^2 = *p*-BrC_6H_4: 57% de = 98% ee = 94%



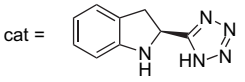
R^3 = NO_2: catalyst 1
R^3 = Me: catalyst 2

Scheme 43. Asymmetric organocatalytic cyclopropanation of α,β-unsaturated aldehydes.

dihydroindole, for the enantioselective cyclopropanation of α,β-unsaturated aldehydes with sulfur ylides.[72] This organocatalyst provided the best results so far reported for intermolecular enantioselective organocatalysed cyclopropanations, since excellent diastereoselectivities ranging from 96 to 98% de, along with enantioselectivities exceeding 99% ee, for all reacted α,β-unsaturated aldehydes were observed, as shown in Scheme 44. Indeed, these results, compared with those obtained with the normal carboxylic acid functionality (Scheme 42), convincingly showed that carboxylic acid substitution by the corresponding tetrazolic acid has a beneficial effect in terms of asymmetric induction.

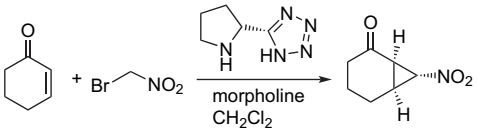


R^1 = *n*-Pr, R^2 = Ph: 82% de = 97% ee = 99%
R^1 = *n*-Pr, R^2 = *p*-BrC_6H_4: 74% de = 97% ee = 99%
R^1 = Me, R^2 = Ph: 85% de = 96% ee = 99%
R^1 = allylOCH_2, R^2 = Ph: 91% de = 98% ee = 99%
R^1 = allylOCH_2, R^2 = *p*-BrC_6H_4: 83% de = 98% ee = 99%
R^1 = *c*-Pent, R^2 = *p*-BrC_6H_4: 86% de = 97% ee = 99%
R^1 = R^2 = Ph: 74% de = 97% ee = 99%



Scheme 44. Asymmetric organocatalytic cyclopropanation of α,β-unsaturated aldehydes.

Using chiral 5-(pyrrolidin-2-yl)-1*H*-tetrazole as an organocatalyst, the asymmetric nitrocyclopropanation of 2-cyclohexen-1-one has been achieved by Ley et al., proceeding in high yield and with good enantioselective control, as shown in Scheme 45.[73]



80% ee = 77%

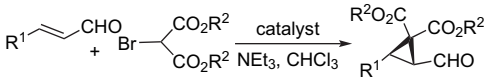
Scheme 45. Asymmetric organocatalytic nitrocyclopropanation of 2-cyclohexen-1-one.

In 2007, Cordova et al. reported a novel example of a highly chemo- and enantioselective organocatalytic cyclopropanation of α,β-unsaturated aldehydes.[74] The reaction was efficiently catalysed by simple chiral pyrrolidine derivatives and gave access to the corresponding 2-formylcyclopropanes in high yields, and diastereo- and enantioseselectivities, as shown in Scheme 46. Similar diastereoselective cascade Michael-alkylation processes were reported at the same time by Wang et al. by using chiral diphenylprolinol TMS ether as the organocatalyst (Scheme 46).[75]

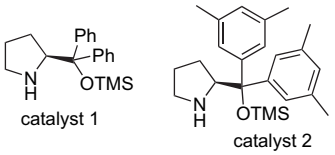
Finally, an ylide asymmetric cyclopropanation of chalcone derivatives with phenyl allylic bromide performed in the presence of a catalytic amount of a camphor-derived sulfonium salt has been developed by Tang et al.[48] The origin of the enantioselectivity and diastereoselectivity in this cyclopropanation has been studied both experimentally and by density functional theory calculations, revealing the importance of the hydrogen bonding between the side-arm hydroxyl group and the substrate. The results are collected in Scheme 47.

4. Transition-metal-catalysed decomposition of diazoalkanes

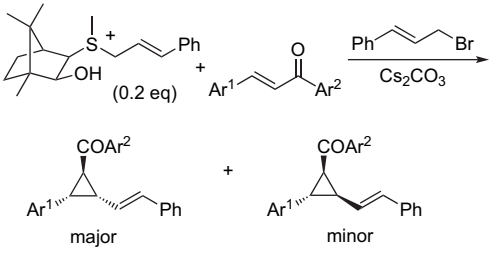
The cyclopropanation of olefins using the transition-metal-catalysed decomposition of diazoalkanes is one of the most



with catalyst 1:
R^1 = Ph, R^2 = Et: 83% de > 92% ee = 99%
R^1 = Ph, R^2 = Me: 88% de > 94% ee = 96%
R^1 = *n*-Pr, R^2 = Et: 80% de = 88% ee = 99%
R^1 = *n*-Pr, R^2 = Me: 74% de > 94% ee = 96%
R^1 = $BnCH_2$, R^2 = Et: 74% de = 92% ee = 94%
R^1 = Me, R^2 = Et: 88% de = 80% ee = 94%
R^1 = Et, R^2 = Me: 68% de > 94% ee = 95%
R^1 = CO_2Et, R^2 = Et: 50% de > 92% ee = 93%
R^1 = 2-Naph, R^2 = Et: 83% de > 92% ee = 96%
R^1 = *p*-ClC_6H_4, R^2 = Et: 60% de > 92% ee = 96%
R^1 = *p*-$NO_2C_6H_4$, R^2 = Me: 93% de > 94% ee = 94%
R^1 = *p*-$NO_2C_6H_4$, R^2 = Et: 87% de > 94% ee = 94%
R^1 = *p*-$NO_2C_6H_4$, R^2 = Bn: 88% de > 94% ee = 93%
R^1 = *p*-$NO_2C_6H_4$, R^2 = *i*-Pr: 42% de > 94% ee = 90%
R^1 = *o*-$NO_2C_6H_4$, R^2 = Me: 89% de > 94% ee = 96%
R^1 = *p*-$CF_3C_6H_4$, R^2 = Me: 84% de > 94% ee = 95%
R^1 = *p*-$MeOC_6H_4$, R^2 = Me: 85% de > 94% ee = 94%
R^1 = *o*-$MeOC_6H_4$, R^2 = Me: 72% de > 94% ee = 96%
with catalyst 2:
R^1 = Ph, R^2 = Et: 87% de > 92% ee = 99%
R^1 = *p*-$NO_2C_6H_4$, R^2 = Et: 81% de > 92% ee = 98%
R^1 = 2-Naph, R^2 = Et: 80% de > 92% ee = 93%



Scheme 46. Asymmetric organocatalytic cyclopropanation of α,β-unsaturated aldehydes.

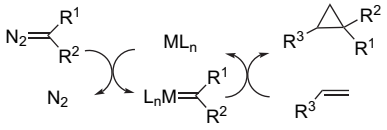


Ar^1 = Ar^2 = Ph: 92% de = 72% ee = 82%
Ar^1 = *p*-ClC_6H_4, Ar^2 = Ph: 86% de = 52% ee = 78%
Ar^1 = *p*-BrC_6H_4, Ar^2 = Ph: 89% de = 50% ee = 78%
Ar^1 = *p*-Tol, Ar^2 = Ph: 80% de = 72% ee = 81%
Ar^1 = *p*-$MeOC_6H_4$, Ar^2 = Ph: 66% de = 72% ee = 80%
Ar^1 = Ph, Ar^2 = CO(*p*-Tol): 87% de = 74% ee = 81%

Scheme 47. Asymmetric organocatalytic cyclopropanation of α,β-unsaturated ketones.

extensively studied reactions in the organic chemist's arsenal.[76,222] Indeed, the synthesis of cyclopropanes by transition-metal-mediated carbene transfer from aliphatic diazo compounds to carbon–carbon double bonds is not only a major method for the preparation of cyclopropanes, but is also among the best developed and most general methods available to the synthetic organic chemist.[23,77,222] Highly effective and stereocontrolled syntheses of functionalised cyclopropanes have been achieved, in particular, with catalysts based on copper, rhodium and, more recently, ruthenium. Palladium-based catalysts have advantages in special cases, and catalysts based on other late transition metals (e.g., iron and osmium) have been reported only occasionally. Outstanding levels of enantioselectivity have been achieved with some chiral catalysts such as copper(I) complexes with C_2-symmetric bisoxazoline ligands and dinuclear rhodium(II) complexes of the type $Rh_2L^*_4$, in which L* is

a chiral bidentate carboxylate, amidate or phosphate ligand.[23,78] On the other hand, the diastereocontrol of the intermolecular cyclopropanation reaction is more difficult to handle, because the cis/trans or *syn*/*anti* selective formation of cyclopropanes is most often controlled by the particular olefin/diazo compound combination. Nevertheless, catalysts with cleverly designed ligands have been developed, which did allow highly selective *trans*- or *cis*-cyclopropanation in particular cases. The catalytic cycle of the carbenoid cyclopropanation reaction is outlined in Scheme 48, involving interaction of the catalyst with the diazo precursor to afford a metallocarbene complex as the central intermediate with concomitant release of nitrogen and subsequent transfer of the carbene to an appropriate substrate such as an olefin. Enantiocontrol in the carbine-transfer step may be achieved by chiral ligands surrounding the metal centre of the catalyst. It must be noted that the cyclopropanation of styrene with ethyl diazoacetate (EDA) often serves as the bench-mark reaction for the evaluation of almost any new catalyst.

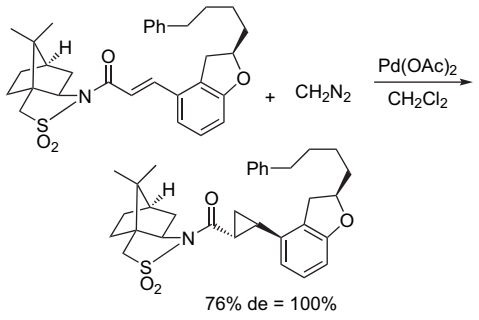


Scheme 48. Catalytic cycle of metal-catalysed carbenoid cyclopropanation reactions with diazo compounds.

4.1. Intermolecular cyclopropanation

4.1.1. Chiral auxiliaries

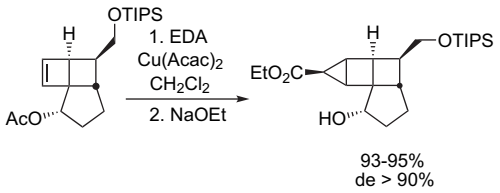
In the last few years, only a few chiral auxiliaries have been involved in cyclopropanation using the decomposition of diazoalkanes, whereas an explosive growth of similar reactions catalysed by chiral catalysts has been developed. As an example, a stereoselective, Pd-catalysed cyclopropanation of a chiral *N*-enoyl camphorsultam was accomplished by treatment with diazomethane, giving rise to an important intermediate for the syntheses of novel melatoninergic agents (Scheme 49).[79]



Scheme 49. Asymmetric cyclopropanation of *N*-enoyl camphorsultam.

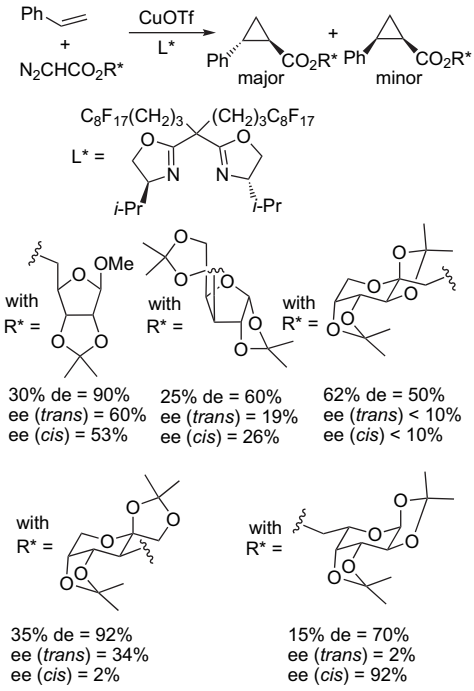
In 2006, Tanyeli et al. studied the asymmetric cyclopropanation of α′-acetoxy-α,β-unsaturated cyclopentanone and cyclohexanone in the presence of diazomethane and $Pd(OAc)_2$.[80] It was shown that the five-membered-ring enone afforded only the *anti* diastereomer in 98% yield, whereas the six-membered enone afforded both the *syn*- and *anti*-diastereomers (syn/anti=63:34) as the major and minor products, respectively. In the course of developing total asymmetric syntheses of pleocarpenene and pleocarpenone, Snapper et al. have observed a considerable stereochemical control in the ethyl diazoacetate cyclopropanation/deacetylation reaction of a chiral cyclobutene, using $Cu(Acac)_2$ as the catalyst (Scheme 50).[81]

Several carbohydrate derivatives have also been employed as chiral auxiliaries in asymmetric cyclopropanation, and the



Scheme 50. Asymmetric cyclopropanation of chiral cyclobutene.

relatively few examples of their use as chiral ligands in the Cu-catalysed reactions of olefins with diazoacetates show generally low trans/cis ratios and enantioselectivities.[82] In 2007, Ferreira et al. 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 51).[83] These authors studied the role of the chiral auxiliary and the effect of a chiral fluorous bisoxazoline as ligand, showing the remarkable importance of the carbohydrate-based chiral auxiliary on the enantioselectivities and the unexpected effect of this ligand on the trans/cis ratios, thus demonstrating that the stereoselectivity of the reaction was not attributed exclusively to the efficiency of the Cu-bisoxazoline complex.

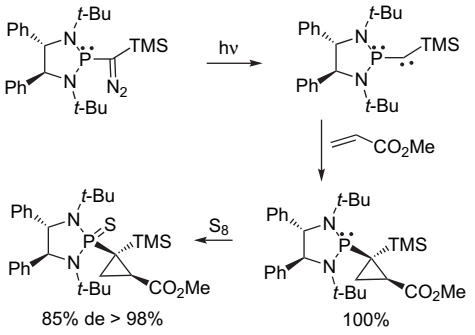


Scheme 51. Asymmetric cyclopropanation of carbohydrate-derived chiral auxiliaries in presence of chiral Cu(I) catalyst.

Finally, Bertrand et al. have reported the synthesis of the first stable optically pure phosphino(silyl)carbenes by photolysis of the corresponding diazo compounds, and their subsequent highly stereoselective cyclopropanations with methyl acrylate.[84] A total *syn* diastereoselectivity (with respect to the phosphino group) was observed, as shown in Scheme 52. It should be noted that the decomposition of the diazo compound was not initiated by the use of a transition-metal catalyst, but it was decided to discuss this result in this section.

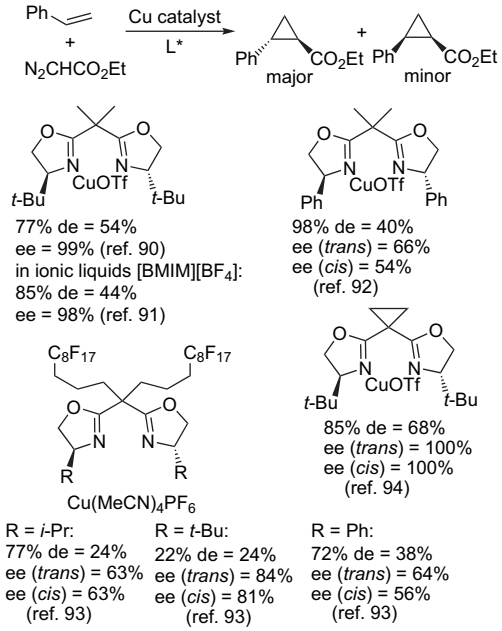
4.1.2. Chiral catalysts

4.1.2.1. Copper catalysts. Transition-metal-catalysed reactions of diazo compounds with alkenes have been widely used to prepare



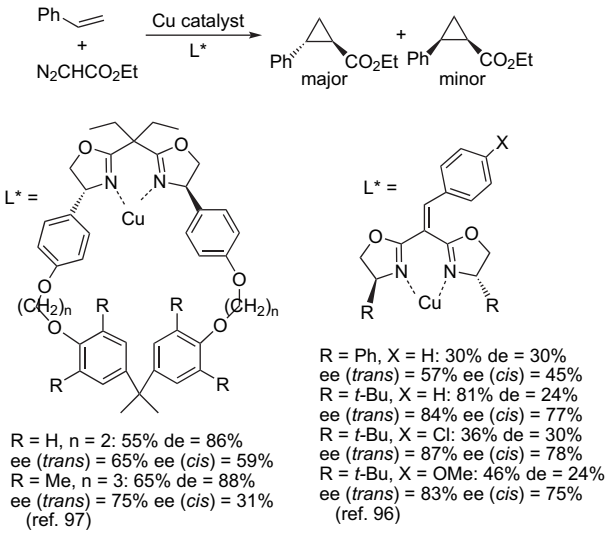
Scheme 52. Asymmetric cyclopropanation of chiral stable phosphino(silyl)carbene.

cyclopropanes, involving as the most common catalysts, copper,[85] rhodium or ruthenium complexes.[86] Most of the time (Cu, Rh, Ru, or Os), the mechanism of the transition-metal-catalysed decomposition of α-diazocarbonyl compounds is believed to initially proceed via the formation of a metal–carbene complex.[87] In particular, the Cu-catalysed enantioselective cyclopropanation of alkenes is now well established, and chiral C_2-symmetric bidentate bisoxazoline ligands[88] are the most widely used ligands.[89] 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. Some structural variations of the bisoxazoline ligands are represented in Scheme 53, which summarises several recent results obtained for the cyclopropanation of styrene with ethyl diazoacetate (EDA).[90–94] In 2004, Li et al. studied this reaction by means of density functional theory, showing that it was exothermic, and that the turnover-limiting step was the formation of metal catalyst–cyclopropyl carboxylate complexes.[95]



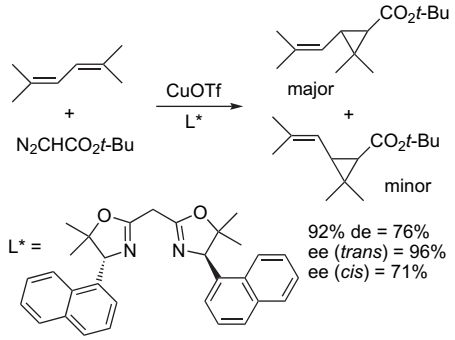
Scheme 53. Bisoxazoline ligands for Cu-catalysed cyclopropanation of styrene with EDA.

In 2005, a new family of chiral bisoxazolines containing an arylidene bridging unit (Arylid-Box) was developed by Burke et al., providing, for the same reaction as that described above, enantioselectivities of up to 87% ee (Scheme 54).[96] The scope of this methodology was extended to α-methylstyrene, giving lower diastereoselectivities (12% de, 52% yield and 86% ee). Examples in which the trans/cis-diastereoselectivity is higher than the most commonly observed ratios of 60:40 to 75:25 are, however, exceptionally rare. In 2007, Zinic et al. developed novel chiral macrocyclic bisoxazoline ligands having profound effects on the diastereoselectivity outcomes of the reaction, since 88% de could be obtained (Scheme 54).[97]



Scheme 54. Macrocyclic bisoxazoline and Arylid-Box ligands for Cu-catalysed cyclopropanation of styrene with EDA.

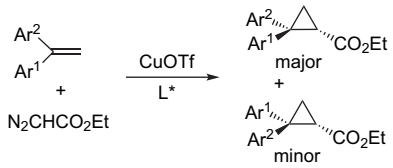
Alkenes other than styrene and its derivatives have also been involved in copper–bisoxazoline-catalysed cyclopropanation with diazoalkanes. As an example, Itagaki et al. have studied the cyclopropanation of 2,5-dimethyl-2,4-hexadiene with *tert*-butyl diazoacetate in the presence of a new bisoxazoline ligand bearing a naphthyl group (Scheme 55).[98]



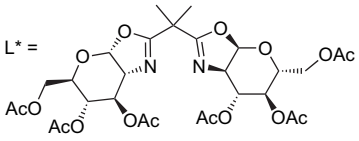
Scheme 55. Asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene.

In 2007, Boysen et al. reported a facile synthesis of a new carbohydrate-bisoxazoline ligand with a dimethylmethylene bridge (*gluco*Box) from D-glucosamine hydrochloride and its application in the Cu-catalysed cyclopropanation of various olefins with EDA.[99] The reaction of all alkenes proceeded in good yields with ees, for all trans as well as cis products, well above 70%, as shown in Scheme 56. In addition, these workers have prepared a novel carbohydrate-derived pyridyl-bisthiazoline ligand, which did not allow high enantioselectivities to be obtained in the cyclopropanation of styrene with EDA (ee≤28%).[100]

Another class of alkenes such as furans has been successfully involved by Reiser et al. in the presence of novel protected α-amino acid-containing bisoxazoline ligands, providing the corresponding cyclopropanes in 100% de in all cases and with up to 91% ee

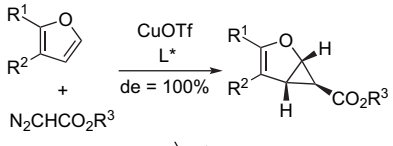


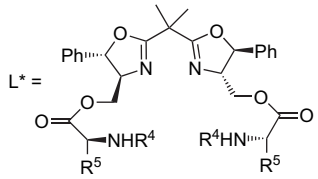
Ar^1 = Ph, Ar^2 = H: 60% de = 40%
ee (*trans*) = 82% ee (*cis*) = 82%
Ar^1 = *p*-$MeOC_6H_4$, Ar^2 = H: 72% de = 30%
ee (*trans*) = 77% ee (*cis*) = 80%
Ar^1 = Ar^2 = Ph: 85% ee (*trans*) = 75%



Scheme 56. Asymmetric cyclopropanation of alkenes with *gluco*Box ligand.

(Scheme 57).[101] This powerful process was applied to the total syntheses of paraconic acids,[102] and the core nucleus of xanthanolides, guaianolides and eudesmanolides.[103] In contrast, with substrates such as styrene and *N*-Boc-pyrrole, with which no secondary interactions with the ligands could occur, only moderate enantioselectivities were achieved (<50% ee). In addition, Reiser et al. have very recently reported the first total synthesis of arglabin, a natural product having antitumour activity, on the basis of the asymmetric cyclopropanation of methyl 2-furoate with EDA.[104] This reaction was performed in the presence of (*R*,*R*)-*i*-Pr-Box ligand and CuOTf, leading to the corresponding cyclopropane in 90% ee.



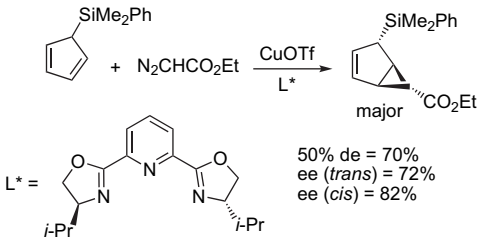


R^1 = CO_2Me, R^2 = H, R^3 = Me, R^4 = Cbz, R^5 = *i*-Pr: 41% ee = 62%
R^1 = CO_2Me, R^2 = H, R^3 = R^5 = Me, R^4 = Boc: 43% ee = 77%
R^1 = CO_2Me, R^2 = H, R^3 = R^5 = Me, R^4 = Ts: 39% ee = 88%
R^1 = CO_2Me, R^2 = H, R^3 = Et, R^4 = Boc, R^5 = Me: 42% ee = 83%
R^1 = CO_2Me, R^2 = H, R^3 = Et, R^4 = Ts, R^5 = Me: 33% ee = 85%
R^1 = H, R^2 = CO_2Me, R^3 = Et, R^4 = Boc, R^5 = Me: 36% ee = 91%
R^1 = H, R^2 = CO_2Me, R^3 = Et, R^4 = Ts, R^5 = Me: 31% ee = 68%

Scheme 57. Asymmetric cyclopropanation of furans.

In 2003, Landais et al. reported the first example of desymmetrisation based on an asymmetric cyclopropanation. Therefore, a cyclopentadienylsilane was desymmetrised by Cu-catalysed cyclopropanation in the presence of a PyBox ligand, providing the corresponding cyclopropane, bearing a useful allylsilane moiety, in up to 82% ee (Scheme 58).[105]

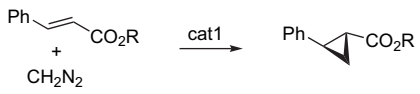
Similarly, diazoalkanes other than alkyl diazoacetates have also been employed in copper–bisoxazoline-catalysed cyclopropanations. As an example, Charette et al. have reported the reaction of diazomethane with *trans*-cinnamate esters, which occurred with good yields and ees, as shown in Scheme 59.[106] In 2003, France et al. found that the reaction of (TMS)diazomethane with olefins provided the corresponding cyclopropanes with greatly improved diastereoselectivities, compared to those obtained with

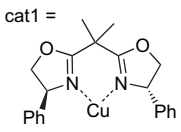


50% de = 70%
ee (*trans*) = 72%
ee (*cis*) = 82%

Scheme 58. Desymmetrisation of cyclopentadienylsilane.

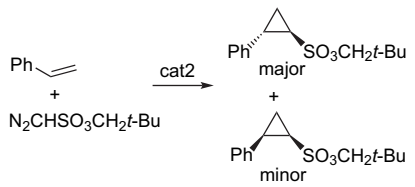
EDA in similar conditions (Scheme 59).[107] In addition, the cyclopropanation of styrene with diazosulfonate esters was investigated by Ye et al., giving an excellent result in the case of the *tert*-butyl ester, as shown in Scheme 59.[108]



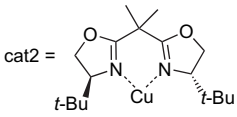


R = Me: 80% ee = 72%
R = Et: 80% ee = 73%
R = Bn: 79% ee = 75%
R = Ph: 80% ee = 72%
R = *i*-Pr: 43% ee = 69%
R = *p*-$O_2NC_6H_4$: 62% ee = 80%
R = *p*-$MeOC_6H_4$: 81% ee = 55%
R = *p*-Tol: 79% ee = 60%

Ar = Ph: 49% de > 94% ee (*trans*) = 63%
ee (*cis*) = 43%
Ar = *p*-BrC_6H_4: 86% de = 100% ee (*trans*) = 66%
Ar = *p*-ClC_6H_4: 80% de > 97% ee (*trans*) = 67%
ee (*cis*) = 48%
Ar = *p*-$MeOC_6H_4$: 80% de > 92% ee (*trans*) = 49%
ee (*cis*) = 61%



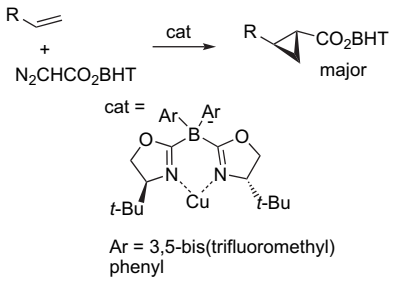
90% de = 72% ee (*trans*) = 92% ee (*cis*) = 79%



Scheme 59. Asymmetric cyclopropanations of diazomethane, (TMS)diazomethane and diazosulfonate *tert*-butyl ester.

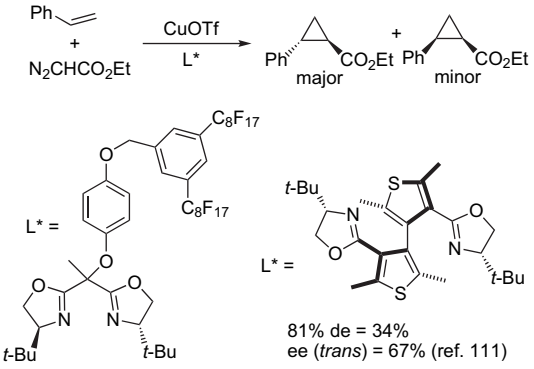
In 2005, a new class of anionic boron-bridged bisoxazoline ligands was developed by Pfaltz et al. and applied to the cyclopropanation of various alkenes with 2,6-di-*tert*-butyl-4-methylphenyl (BHT) diazoacetate, affording the corresponding cyclopropanes with almost perfect diastereoselectivity and excellent enantioselectivity (Scheme 60).[109]

A number of other bisoxazoline ligands with numerous structural diversities have been designed by several groups and involved in the cyclopropanation of styrene with EDA (Scheme 61). Therefore, perfluoroalkyl-substituted bisoxazolines were proposed by Benaglia et al., in 2003, providing up to 78% ee (Scheme 61).[110] These authors have also developed bisoxazolines displaying flexible and atropisomeric 3,3′-bithiophene backbones, giving similar results in terms of



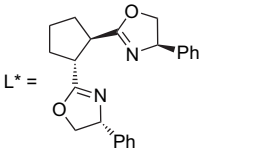
R = *p*-MeOC$_6$H$_4$: 65% de = 92% ee = 97%
R = Bn: 66% de = 84% ee = 97%
R = *n*-Hex: 68% de = 98% ee = 95%
R = Ph: 89% de = 98% ee = 98%

Scheme 60. Boron-bridged bisoxazoline ligands for Cu-catalysed cyclopropanation with BHT diazoacetate.

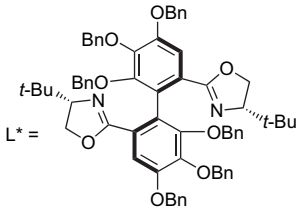


68% de = 30%
ee (*trans*) = 78% (ref. 110)

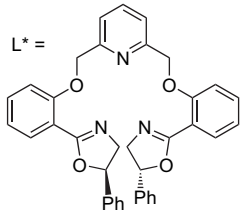
81% de = 34%
ee (*trans*) = 67% (ref. 111)



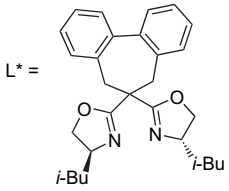
65% de = 44%
ee (*trans*) = 36%
ee (*cis*) = 26% (ref. 112)



41% de = 18%
ee (*trans*) = 82%
ee (*cis*) = 81% (ref. 113)



79% de = 52%
ee (*trans*) = 68%
ee (*cis*) = 61% (ref. 114)

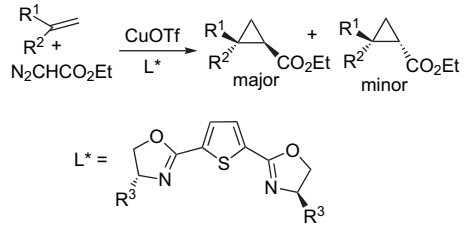


72% de = 22%
ee (*trans*) = 63%
ee (*cis*) = 54% (ref. 115)

Scheme 61. Other bisoxazoline ligands for Cu-catalysed cyclopropanation of styrene with EDA.

stereoselectivity (Scheme 61).[111] On the other hand, novel C_1- and C_2-symmetric bisoxazolines bearing a cyclic backbone have allowed a good diastereoselectivity to be obtained, but with low enantioselectivities (Scheme 61).[112] In 2006, Khanbabaee et al. investigated a series of novel bisoxazolines possessing biphenyl backbones, which gave a high enantioselectivity along with a moderate diastereoselectivity (Scheme 61).[113] Moreover, Wang et al. have developed a series of novel semi-crown ether-like bisoxazoline ligands, providing up to 84% ee for the trans product (Scheme 61).[114] In addition, bisoxazoline ligands containing dibenzo[*a*,*c*]cycloheptadiene units were studied by Du et al., leading to similar results (Scheme 61).[115]

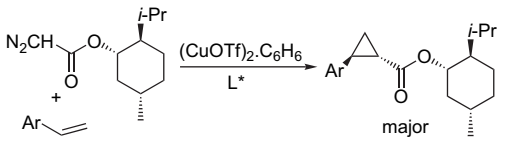
In 2005, You et al. reported the synthesis of novel bisoxazoline ligands derived from camphoric acid, which were evaluated in the Cu-catalysed cyclopropanation of styrene and 1,1-diphenylethylene with EDA.[116] Poor ee values were obtained for the former substrate, while up to 81% ee was obtained for the latter. A very good result was also observed by Gao et al. for the Cu-catalysed cyclopropanation of a range of olefins with EDA in the presence of novel sulfur-containing bisoxazoline ligands with thiophene as a backbone (Scheme 62).[117]



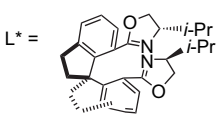
R^1 = R^2 = Ph, R^3 = Et: 84% ee = 91%
R^1 = H, R^2 = Ph, R^3 = *t*-Bu: 78% de = 78%
ee (*trans*) = 88% ee (*cis*) = 84%
R^1 = H, R^2 = *p*-ClC$_6$H$_4$, R^3 = *t*-Bu: 80% de = 76%
ee (*trans*) = 85% ee (*cis*) = 82%
R^1 = H, R^2 = *p*-MeOC$_6$H$_4$, R^3 = *t*-Bu: 76% de = 82%
ee (*trans*) = 90% ee (*cis*) = 87%

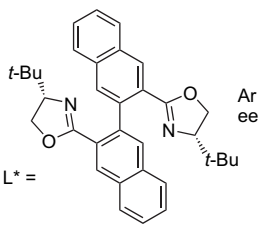
Scheme 62. Sulfur-containing bisoxazoline ligands for Cu-catalysed cyclopropanation of alkenes with EDA.

Another type of bisoxazoline ligands containing a chiral spirobiindane scaffold was applied, in 2006, by Zhou et al. to the Cu-catalysed cyclopropanation of styrenes with menthyl diazoacetate, furnishing the corresponding cyclopropanes in high des with moderate-to-good enantioselectivities (Scheme 63).[118] The reaction of menthyl diazoacetate with styrene was also performed by Ikeda et al., in 2006, in the presence of bisoxazolines with an axial-unfixed biaryl backbone and a copper complex. The best result was obtained with the ligand having a 2,2′-binaphthyl backbone and a *tert*-butyl group at the oxazoline ring, as shown in Scheme 63.[119]



Ar = Ph: 93% de = 78%
ee (*trans*) = 70% ee (*cis*) = 62%
Ar = *p*-CF$_3$C$_6$H$_4$: 56% de= 72%
ee (*trans*) = 82%
Ar = *p*-ClC$_6$H$_4$: 54% de = 70%
ee (*trans*) = 82%
Ar = *p*-BrC$_6$H$_4$: 61% de = 66%
ee (*trans*) = 72%
Ar = *p*-Tol: 67% de = 64%
ee (*trans*) = 55%
Ar = *p*-MeOC$_6$H$_4$: 55% de =70%
ee (*trans*) = 53%

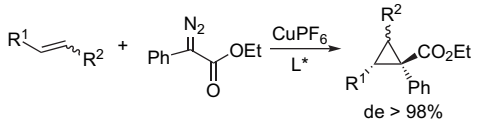




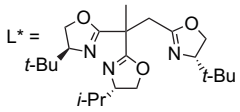
Ar = Ph: 49% de = 66%
ee (*trans*) = 89% ee (*cis*) = 96%

Scheme 63. Asymmetric cyclopropanation with menthyl diazoacetate.

Very recently, Tang et al. demonstrated that the introduction of a pendant oxazoline on a bisoxazoline greatly improved both the yield and enantioselectivity of the cyclopropanation of alkenes with ethylphenyldiazoacetate, furnishing an efficient method for the syntheses of tri- and tetra-substituted cyclopropane derivatives with high yields, des and ees (Scheme 64).[120]



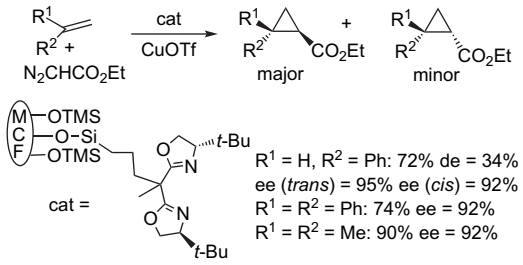
R^1 = Ph, R^2 = H, (*E*)-alkene: 92% ee = 92%
R^1 = *p*-ClC_6H_4, R^2 = H, (*E*)-alkene: 97% ee = 91%
R^1 = *p*-Tol, R^2 = H, (*E*)-alkene: 99% ee = 93%
R^1 = *p*-$MeOC_6H_4$, R^2 = H, (*E*)-alkene: 94% ee = 95%
R^1 = Ph, R^2 = $CH{=}CH_2$, (*E*)-alkene: 99% ee = 89%
R^1 = O-*n*-Bu, R^2 = H, (*E*)-alkene: 99% ee = 82%
R^1,R^2 = $(CH_2)_2O$, (*Z*)-alkene: 92% ee = 92%
R^1,R^2 = $(CH_2)_3O$, (*Z*)-alkene: 86% ee = 90%
R^1 = Ph, R^2 = H, (*Z*)-alkene: 51% ee = 82%



Scheme 64. Trisoxazoline ligand for Cu-catalysed cyclopropanation of alkenes with ethyl phenyldiazoacetate.

In addition, a new type of chiral dinitrogen ligands, chiral dihydrodinaphthazepinyloxazolines, were demonstrated by Zhou et al. to be effective ligands in the Cu-catalysed cyclopropanation of styrene and its derivatives.[121] The reaction was performed in the presence of various diazoacetates, providing the corresponding cyclopropanes with up to 90% ee.

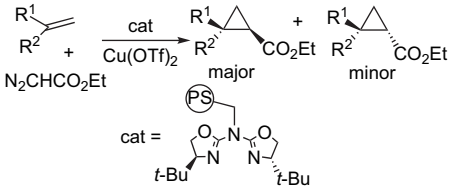
Interestingly, the Cu-catalysed cyclopropanation with bisoxazoline ligands has been successfully performed in the solid phase, giving, in some cases, stereoselectivities better than those observed in solution. Thus, a re-usable, insoluble polystyrene-supported bisoxazoline was developed, in 2003, by Salvadori et al., affording >90% ees, and up to 42% de in the heterogeneous cyclopropanation of styrene and 1,1-disubstituted alkenes with EDA.[122] At the same time, Mayoral et al. studied similar reactions in the presence of copper catalysts with bisoxazoline ligands immobilised on laponite by electrostatic interactions, demonstrating a previously unknown role of the catalyst surface, although the outcome was a lower enantioselectivity (≤55% ee).[123] In the same context, the same group has also studied the use of homopolymers of bisoxazoline ligands,[124] but the low accessibility to most bisoxazoline moieties led to a low copper loading. As a consequence, the transmission of the chiral information from the complexed polymer was usually not very efficient and only a few chiral cyclopropane molecules were obtained from each molecule of chiral ligand. The use of suitable dendrimers as cross-linkers in the polymerisation process allowed better copper functionalisation. As a consequence, the productivity of chiral cyclopropanes per molecule of chiral ligand greatly increased, which improved the ligand economy and the chirality transfer. In these conditions, enantioselectivities of up to 78% ee were obtained. In 2005, Ying et al. immobilised bisoxazoline ligands onto silicaceous mesocellular foams (MCFs), and studied the efficiency of these novel heterogenised catalysts for the cyclopropanation of styrene with EDA.[125] Both high enantioselectivity (up to 87% ee) and reactivity were observed, along with up to 28% de. In 2006, superior enantioselectivities (up to 95% ee) were reported by these authors by partially modifying the surface of these MCFs with TMS groups prior to the use of the bisoxazolines (Scheme 65).[126]



R^1 = H, R^2 = Ph: 72% de = 34%
ee (*trans*) = 95% ee (*cis*) = 92%
R^1 = R^2 = Ph: 74% ee = 92%
R^1 = R^2 = Me: 90% ee = 92%

Scheme 65. MCF-supported bisoxazoline-Cu catalyst for cyclopropanation of alkenes.

Due to the higher binding affinity towards copper, immobilised azabisoxazolines are far superior, compared to their corresponding bisoxazolines. In this context, azabisoxazoline ligands were attached by Mayoral et al. to various polymeric supports and the resulting immobilised ligands were evaluated in the Cu-catalysed cyclopropanation of olefins with EDA.[127] Up to 99% ee was obtained for the reaction of styrene, as shown in Scheme 66.

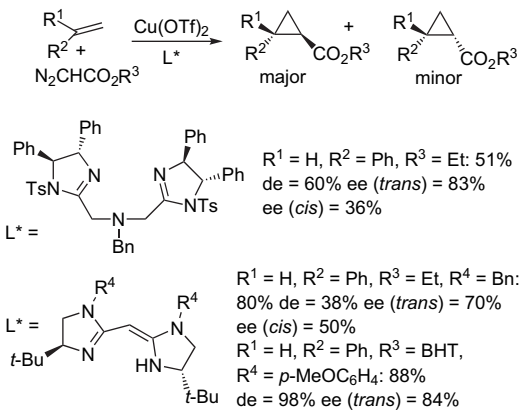


R^1 = H, R^2 = Ph: 94% de = 48%
ee (*trans*) = 99% ee (*cis*) = 90%
R^1 = H, R^2 = *n*-Hex: 32% de = 20%
ee (*trans*) = 90% ee (*cis*) = 82%

Scheme 66. Polystyrene-bound azabisoxazoline ligand for cyclopropanation of alkenes.

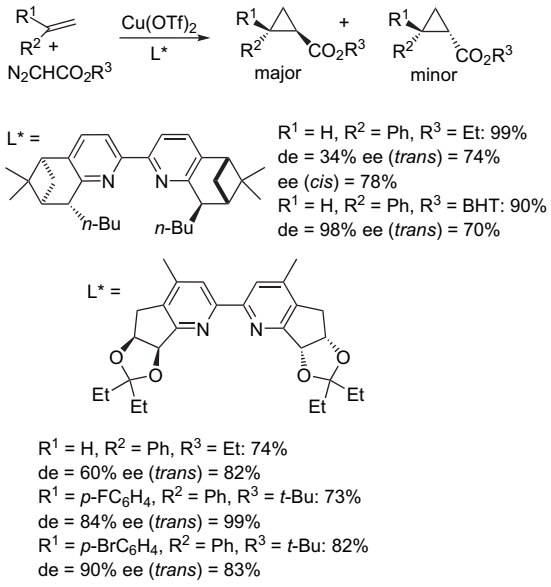
On the other hand, the use of ionic liquids offers the possibility of combining the positive aspects of both homogeneous and heterogeneous catalysis. The reaction takes place in a homogeneous phase with high activity and selectivity and, moreover, it is possible to easily separate the products after the reaction and re-use the catalyst, as in the case of heterogeneous catalysis.[128] In this context, Mayoral et al. have immobilised bisoxazolines in ionic liquids and evaluated these catalysts in cyclopropanation reactions.[129] The results, quite similar to those obtained in molecular solvents, were observed for the reaction of styrene with EDA with enantioselectivities of up to 92% ee. In addition, the azabisoxazolines depicted in Scheme 66 were also evaluated in ionic liquids by the same group, showing their clear advantages over bisoxazolines by increasing the stability of the copper complex and improving the re-usability of the catalyst solution.[130] Moreover, in all cases of alkenes, the enantioselectivity value was high, since the ees were between 83 and 98%.

Even with the striking success of the bisoxazoline ligands, however, regulating the electron density of the oxazoline ring has remained an unsolved problem. One way to overcome the limitation of electronic variation on the oxazoline ring has been by a rational design of a chemical analogue of oxazoline such as imidazoline. Indeed, the two *N*-substituents of imidazoline may serve as handles to tune the electronic and conformational properties of the ligand. In this context, Arai et al. reported, in 2005, the Cu-catalysed cyclopropanation of styrene with EDA performed in the presence of a novel *N*-tethered bisimidazoline ligand, providing the corresponding cyclopropanes in high yield with good ee (Scheme 67).[131] In addition, methylene-bridged bisimidazolines were very recently investigated by Pfaltz et al., inducing enantioselectivities, which were not as high as those reported for the best bisoxazolines (Scheme 67).



Scheme 67. Bisimidazoline ligands for cyclopropanation of alkenes.

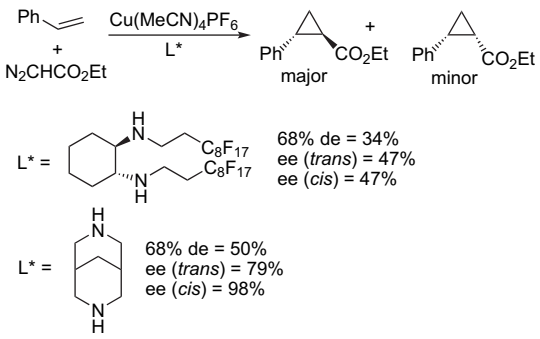
On the other hand, several types of ligands other than bisoxazolines and their derivatives have been investigated for the asymmetric cyclopropanation of alkenes. Thus, bipyridine-derived ligands have also produced some good results in these reactions. As an example, Kocovsky et al. reported, in 2003, the preparation of novel C_2-symmetrical 2,2′-bipyridines and their application in Cu-catalysed cyclopropanations, which proceeded with ≤78% ee and up to 98% de, as shown in Scheme 68.[132] In 2004, very high diastereo- and enantioselectivities were observed by Wilson et al. with another bipyridyl ligand, as depicted in Scheme 68.[133] These highest reported stereoselectivities for a bipyridyl ligand were rationalised in terms of the structural rigidification that was provided by the chiral acetal moieties of the C_2-symmetric bipyridyl ligand. On the other hand, the catalytic activity of new C_2-symmetric ligands containing two binaphthyl units linked by a 2,2′-bipyridyl bridge were studied by Gao et al. in 2005.[134] The corresponding cyclopropanes could be obtained in moderate diastereoselectivity (≤50% de) and enantioselectivity (≤51% ee). More recently, Levacher et al. designed new axially bridged 2,2′-bipyridines and pyridylmonooxazolines and evaluated these ligands in the cyclopropanation of styrene derivatives. While the 2,2′-bipyridine ligands afforded the corresponding cyclopropanes in up to 65% ee, the pyridylmonooxazoline ligands gave somewhat lower ees (up to 53%).[135] In 2003, Benaglia et al. prepared new chiral phenanthroline- and bipyridine-containing macrocycles and tested



Scheme 68. Asymmetric cyclopropanation with bipyridyl ligands.

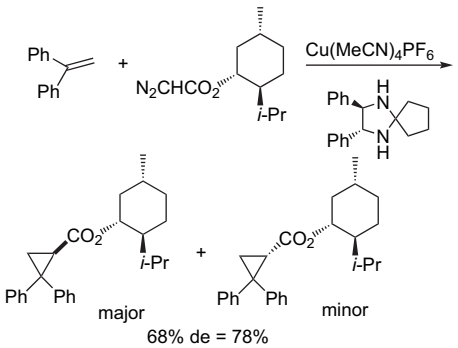
their Cu(I) complexes in the cyclopropanation of alkenes.[136] Although the level of enantioselectivity obtained with these new ligands was far from the best-performing known ligands (up to 97% ee), a simple structural modification of the chiral cavity allowed the successful control of the trans- or cis-diastereoselectivity of the reaction (up to 76% de). Other nitrogen-containing ligands with a (1*R*,2*R*)-*trans*-diaminocyclohexane core have been investigated by König et al. for the cyclopropanation of styrene with EDA, providing only low yields (≤52%) and poor enantioselectivities (≤8% ee).[137]

Various other chiral diamine and diimine ligands have been involved in promoting asymmetric cyclopropanations. As an example, Kwong et al. have designed a series of new chiral C_1-symmetric bidentate ligands, possessing two different nitrogen heterocycles comprising a 1,3-thiazolyl, 1-methylimidazolyl or pyrazinyl and a pyridyl group.[138] Applied to the cyclopropanation of styrene with EDA, these ligands gave the corresponding cyclopropane derivative with up to 38% ee. On the other hand, unsophisticated fluorous derivatives of (1*R*,2*R*)-diaminocyclohexane were investigated by Pozzi et al. in 2005.[139] These ligands showed similar activities, but lower enantioselectivities than those achieved using more synthetically demanding fluorous ligands such as fluorous bisoxazolines (Scheme 69). Very recently, Sacchetti et al. successfully applied a simple C_1-symmetric diamine ligand such as bispidine to the same reaction, and obtained up to 98% ee for the cyclopropanated product (Scheme 69).[140]



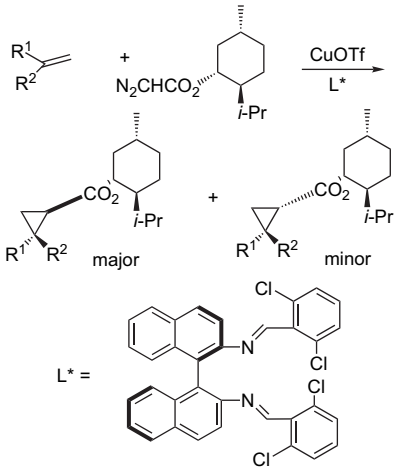
Scheme 69. Asymmetric cyclopropanation with diamine ligands.

In 2004, Cossy et al. reported the Cu-catalysed cyclopropanation of 1,1-diphenylethylene with menthyl diazoacetate performed in the presence of a chiral imidazolidine ligand, affording the corresponding cyclopropane in good yield and diastereoselectivity (Scheme 70).[141] This diazoacetate was also used by Baldwin et al. to react with isotopically labelled styrenes, providing the corresponding four isotopically labelled (1*R*)-menthyl (1*S*,2*S*)-2-phenylcyclopropanecarboxylates with better than 99% ee, in the presence of a very simple diamine ligand derived from (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine.[142]



Scheme 70. Asymmetric diamine-mediated cyclopropanation with menthyl diazoacetate.

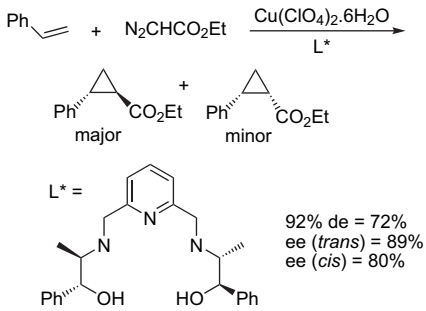
Diimine ligands have also been investigated in the context of the asymmetric cyclopropanation. In 2003, Suga et al. observed excellent enantioselectivities (up to 98% ee) for the reaction between menthyl diazoacetate and a range of olefins in the presence of binaphthyldiimine ligands, as depicted in Scheme 71.[143] On the other hand, C_2-symmetric diimines derived from (1*R*,2*R*)-diiminocyclohexane were studied by Pozzi et al., providing better enantioselectivities (up to 67% ee) than their corresponding diamines (see Scheme 69), but low diastereoselectivities (≤14% de).[139b]



R^1 = Ph, R^2 = H: 93% de = 80%
ee (*trans*) = 68% ee (*cis*) = 81%
R^1 = 2-Naph, R^2 = H: 89% de = 80%
ee (*trans*) = 76% ee (*cis*) = 62%
R^1 = Ph, R^2 = Me: 96% de = 44%
ee (*trans*) = 61% ee (*cis*) = 78%
R^1 = R^2 = Ph: 83% ee = 98%

Scheme 71. Asymmetric cyclopropanation with binaphthyldiimine ligand.

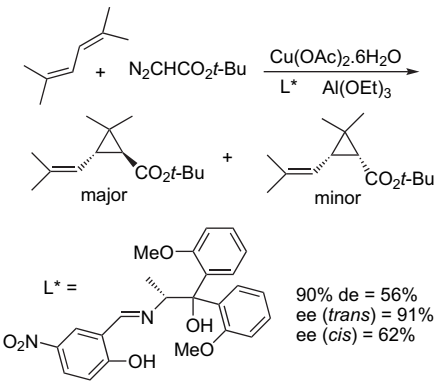
In addition, several Cu-catalysed cyclopropanations of alkenes with diazoalkanes have involved chiral amino alcohols as ligands.[144] As an example, Gao et al. have employed ligands derived from (1*R*,2*S*)-(−)-ephedrine for the cyclopropanation of styrene with EDA, which provided the expected cyclopropane with high ee, as depicted in Scheme 72.[145] In 2004, the same reaction was performed by Kwong et al. in the presence of various chiral *N*,*O*-pyridine alcohols, giving up to 56% ee.[146]



92% de = 72%
ee (*trans*) = 89%
ee (*cis*) = 80%

Scheme 72. Asymmetric cyclopropanation with ephedrine-derived ligand.

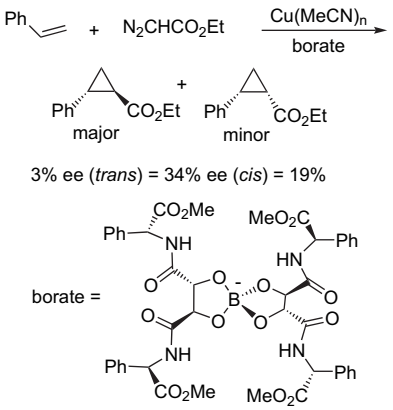
In addition, Itagaki et al. have reported very recently the asymmetric synthesis of chiral chrysanthemic acid esters by Cu-catalysed cyclopropanation of 2,5-dimethyl-2,4-hexadiene with *tert*-butyl diazoacetate in the presence of salicylaldimine ligands (Scheme 73).[147] The best result was obtained by combining the copper Schiff-base complex with a Lewis acid such as Al(OEt)$_3$, which enhanced the catalytic efficiency.



90% de = 56%
ee (*trans*) = 91%
ee (*cis*) = 62%

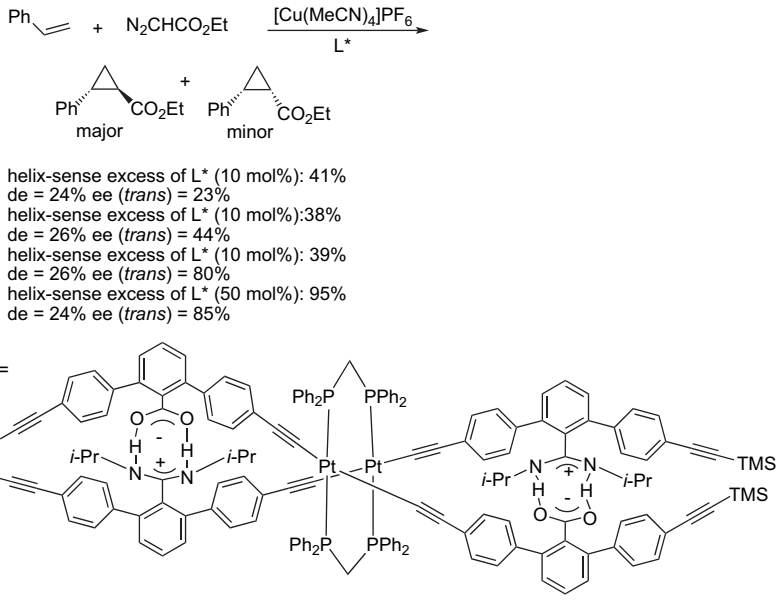
Scheme 73. Asymmetric cyclopropanation with salicylaldimine ligand.

On the other hand, Chelucci et al. have prepared a range of novel chiral thienylpyridines as *N*,*S*-ligands and tested their efficiency to induce chirality in the cyclopropanation of styrene with EDA.[148] These ligands provided effective copper catalysts offering, however, a low enantioselectivity (≤10% ee). Similarly, the use of chiral 2-(2-phenylthiophenyl)-5,6,7,8-tetrahydroquinolines as ligands did not lead to better results for the same reaction (≤5% ee).[149] In another context, Arndsten et al. have reported the preparation of the first example of a library of α-amino acid-bound borate anions.[150] Ion pairing of these anions to a copper cation could be used to induce enantioselectivity (up to 34% ee) in the Cu-catalysed cyclopropanation of styrene with EDA, as shown in Scheme 74.



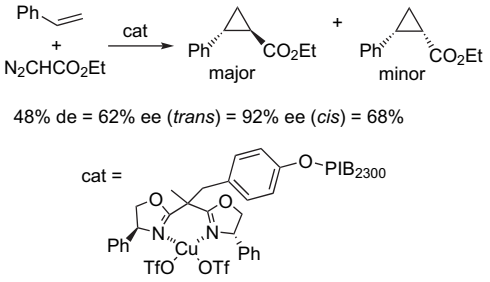
Scheme 74. Asymmetric cyclopropanation with α-amino acid-bound borate anion.

The double helix of DNA is one of the most attractive targets in organic and supramolecular chemistry because of its key biological structures and functions. Recent discoveries of DNA-based biocatalysts and metal-bound DNA hybrid catalysts[151] for enantioselective reactions imply the potential ability of double helices as promising chiral frameworks for enantioselective catalysis. In this context, Furusho et al. showed, in 2007, that complementary double-helical molecules showing optical activity owing to their helicity could be enantioselectively synthesised and could catalyse the asymmetric cyclopropanation of styrene with EDA in the presence of a copper catalyst.[152] The active copper catalyst was generated by the complexation of a bridged double-helix molecule of different helix-sense excesses with [(MeCN)$_4$Cu]PF$_6$. The results, presented in Scheme 75, show an almost linear relationship between the helix-sense excesses of the double-helix molecule and the ee values of *trans* cyclopropane. Moreover, the results suggest that the chiral space generated by the rigid double-helical structure of the double-helix molecule was effective and indispensable for the high enantioselectivity.



Scheme 75. Asymmetric cyclopropanation with chiral double-helical molecule.

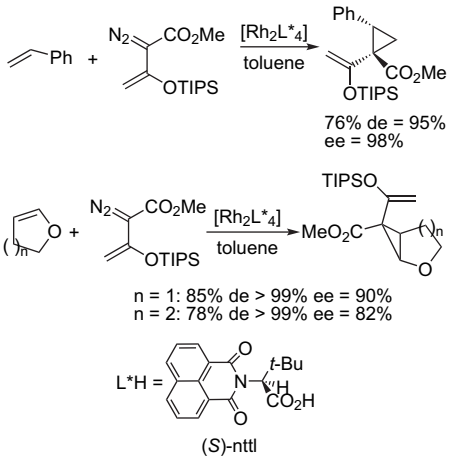
In 2007, Bergbreiter et al. reported the use of polyisobutylene (PIB) oligomers as soluble supports for the immobilisation of bisoxazoline-Cu(I) catalysts and their application to induce chirality in the cyclopropanation of styrene with EDA.[153] The chiral bisoxazoline depicted in Scheme 76 and prepared from phenylglycine provided the most effective stereocontrol and could be re-used 5–6 times.



Scheme 76. Asymmetric cyclopropanation with PIB-supported bisoxazoline-Cu(I) catalyst.

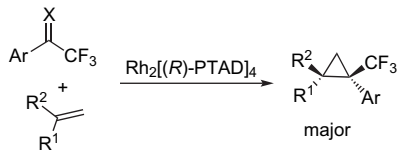
4.1.2.2. Rhodium catalysts. Rhodium catalysts have also proved to be effective catalysts for the cyclopropanation with diazo compounds. In particular, the development of dirhodium(II) carboxylate and carboxamidate catalysts has resulted in highly chemo-, regio- and stereoselective reactions of α-diazocarbonyl compounds via a variety of reactivity modes.[86] A number of chiral ligands have been applied to the Rh-catalysed cyclopropanation. Thus, Müller et al. have demonstrated the suitability of (*S*)-*N*-1,8-naphthanoyl-*tert*-leucine (nttl) as a ligand for the Rh-catalysed cyclopropanation of styrene with (silanyloxyvinyl)diazoacetates, proceeding with exceptional diastereo- and enantioselectivities (Scheme 77).[154] The scope of this reaction could be successfully extended to the use of other alkenes such as dihydrofuran and dihydropyran, as shown in Scheme 77.[155] This methodology has also been applied to alkyl diazo(trialkylsilyl)acetates, furnishing the corresponding cyclopropanes in good yields, but with modest enantioselectivity (<54% ee).[156] Hence, the use of ethyl diazo(triethylsilyl)acetate led to 69% yield, combined with 64% de and 54% ee.

As fluorine substituents are known to have a unique and often deep impact on the structure, energy, chemical reactivity and physical properties of organic compounds, an almost unlimited variety of fluorinated cyclopropanes have been synthesised.[157] In this context, Davies et al. have very recently described the reaction of 1-aryl-2,2,2-trifluorodiazoethanes with alkenes, catalysed by the adamantylglycine-derived dirhodium complex, $Rh_2[(R)\text{-PTAD}]_4$, generating the corresponding trifluoromethyl-substituted cyclopropanes with very high diastereo- and enantioselectivities, as shown in Scheme 78.[158]

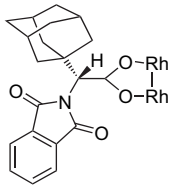


Scheme 77. Asymmetric cyclopropanations with (*S*)-nttl ligand.

In the same context, Müller et al. have reported the reaction of ethyl 3,3,3-trifluoro-2-diazopropionate with various olefins catalysed by dirhodium tetrakis((*R*)-(*N*-dodecylbenzenesulfonyl)prolinate), $Rh_2[(R)\text{-DOSP}]_4$.[159] Yields and enantioselectivities of up to 72% and 40% ee, respectively, were obtained for the reaction between this diazo compound and 1,1-diphenylethylene, whereas the cyclopropanation of monosubstituted olefins with this diazo compound led to cis/trans mixtures of the corresponding cyclopropanes with a maximum ee of 75% for 4-methoxystyrene. This catalyst was also used by Davies et al. to induce the decomposition of aryldiazoacetates in the presence of pyrroles or furans, resulting in the formation of mono- or biscyclopropanes of the heterocycle, but with opposite enantioinduction (Scheme 79).[160] Indeed, an interesting effect in these reactions was that the enantioinduction was markedly influenced by the structure of the heterocyclic



Ar = R^1 = Ph, X = NNH_2, R^2 = H: 71%
de > 94% ee > 98%
Ar = Ph, X = NNH_2, R^1 = *p*-Tol, R^2 = H: 72%
de > 94% ee = 90%
Ar = Ph, X = NNH_2, R^1 = *p*-$MeOC_6H_4$, R^2 = H: 76%
de > 94% ee = 88%
Ar = Ph, X = NNH_2, R^1 = *p*-ClC_6H_4, R^2 = H: 64%
de > 94% ee = 90%
Ar = Ph, X = NNH_2, R^1 = *p*-$CF_3C_6H_4$, R^2 = H: 61%
de > 94% ee > 94%
Ar = Ph, X = NNH_2, R^1 = 2-Naph, R^2 = H: 75%
de > 94% ee = 89%
Ar = *p*-Tol, X = O, R^1 = Ph, R^2 = H: 75%
de > 94% ee > 98%
Ar = *p*-FC_6H_4, X = O, R^1 = Ph, R^2 = H: 78%
de > 94% ee = 97%
Ar = *p*-BrC_6H_4, X = O, R^1 = Ph, R^2 = H: 77%
de > 94% ee = 98%
Ar = R^1 = *p*-BrC_6H_4, X = NNH_2, R^2 = H: 78%
de > 94% ee > 98%
Ar = *p*-BrC_6H_4, X = NNH_2, R^1 = *p*-$NO_2C_6H_4$, R^2 = H: 75%
de > 94% ee > 98%
Ar = *p*-BrC_6H_4, X = NNH_2, R^1 = 2-Naph, R^2 = H: 80%
de > 94% ee = 98%
Ar = *p*-BrC_6H_4, X = NNH_2, R^1 = R^2 = Ph: 75% ee > 98%



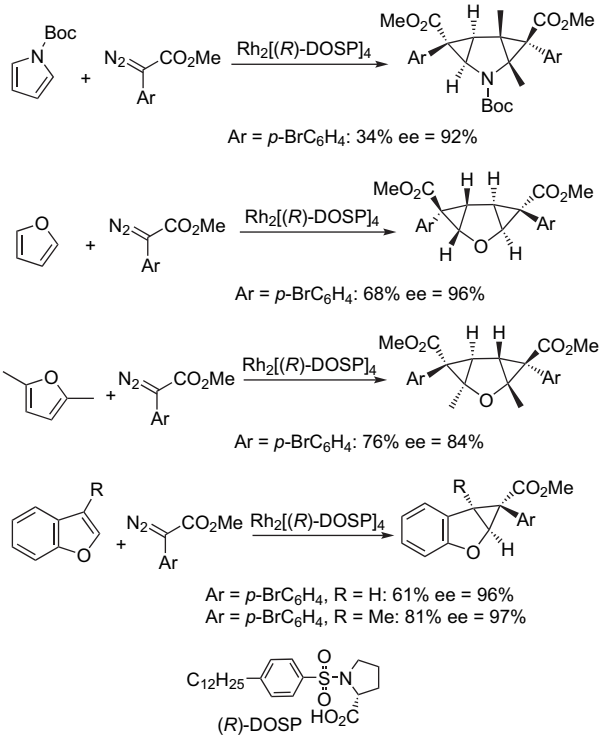
$Rh_2[(R)$-PTAD$]_4$

Scheme 78. Asymmetric cyclopropanation catalysed by $Rh_2[(R)$-PTAD$]_4$.

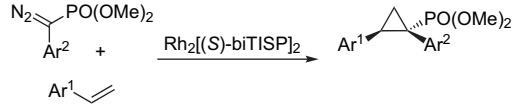
substrate. The cyclopropanation was considered to proceed in a concerted nonsynchronous manner and, depending upon which bond of the heterocycle initially interacted with the carbenoid, either face of the heterocycle can be attacked under the influence of the same chiral catalyst. The control was governed by a delicate interplay of steric and electronic influences. This methodology was applied to the total synthesis of a natural product, (+)-erogorgiaene, on the basis of the cyclopropanation of a dihydronaphthalene catalysed by $Rh_2[(S)$-DOSP$]_4$.[161]

In 2003, Davies et al. reported that a bridged dirhodium tetraprolinate, $Rh_2[(S)$-biTISP$]_2$, was able to catalyse the cyclopropanation of styrene with methyl phenyldiazoacetate with high turnover number (92,000) and turnover frequency (4000 h^{-1}).[162] With a substrate/catalyst ratio of 100,000, for example, 92% yield and 85% ee were obtained for the cyclopropanation of styrene with methyl phenyldiazoacetate on a large scale (crude=46 g). The same catalyst was applied to the stereoselective synthesis of cyclopropylphosphonates containing quaternary stereocentres by the reaction of dimethyl aryldiazomethylphosphonates, as shown in Scheme 80.[163] In addition, this catalyst could be immobilised on agitation in the presence of highly cross-linked polystyrene resins with a pyridine attachment.[164] The resulting heterogeneous complex was shown to be an effective catalyst for the cyclopropanation of styrene with methyl phenyldiazoacetate, providing up to 88% ee.

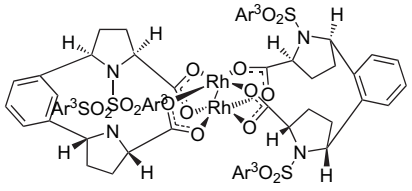
On the other hand, Doyle et al. have developed methyl 2-oxoimidazolidine-4(*S*)-carboxylate ligands, containing 2-phenylcyclo-



Scheme 79. Asymmetric cyclopropanations catalysed by $Rh_2[(R)$-DOSP$]_4$.



Ar^1 = Ar^2 = Ph: 89% de = 98% ee = 88%
Ar^1 = Ph, Ar^2 = 2-Naph: 85% de = 98% ee = 76%
Ar^1 = Ph, Ar^2 = *p*-$MeOC_6H_4$: 84% de = 98% ee = 92%
Ar^1 = Ph, Ar^2 = *p*-BrC_6H_4: 80% de = 98% ee = 89%
Ar^1 = Ph, Ar^2 = CH=CHPh: 76% de = 98% ee = 68%
Ar^1 = *p*-$MeOC_6H_4$, Ar^2 = Ph: 93% de = 98% ee = 89%
Ar^1 = *p*-ClC_6H_4, Ar^2 = Ph: 95% de = 98% ee = 85%
Ar^1 = 2-Naph, Ar^2 = Ph: 93% de = 98% ee = 87%
Ar^1 = *p*-ClC_6H_4, Ar^2 = Ph: 95% de = 98% ee = 85%
Ar^1 = CH=CHPh, Ar^2 = Ph: 96% de = 98% ee = 83%

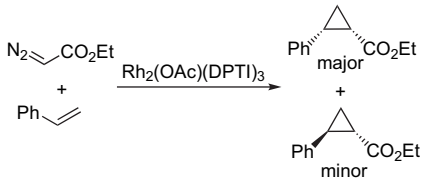


$Rh_2[(S)$-biTISP$]_2$

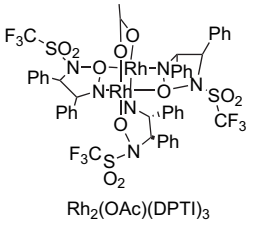
Scheme 80. Asymmetric cyclopropanation catalysed by $Rh_2[(S)$-biTISP$]_2$.

propane attached at the 1-*N*-acyl site such as the (4*S*,2′*R*,3′*R*-HMCPIM) ligand.[165] The resulting dirhodium complex led, for the cyclopropanation of styrene with EDA, to the corresponding cyclopropane with 68% ee and 59% yield, but with almost no diastereoselectivity. In 2004, Corey et al. reported the same reaction carried out in the presence of another dirhodium catalyst, Rh_2-(OAc)(DPTI)$_3$, prepared from (*R*,*R*)-1,2-diphenylethylenediamine, affording the corresponding product with high enantioselectivity, as shown in Scheme 81.[166] Surprisingly, the major diastereomer was the *cis* cyclopropane. In addition, a chiral fluorous complex,

tetrakis-dirhodium(II)-(*S*)-*N*-(*n*-perfluorooctylsulfonyl)prolinate, has been prepared by Biffis et al. and used as a catalyst in a homogeneous or fluorous biphasic fashion.[167] This catalyst displayed good chemo- and enantioselectivities in the cyclopropanation of styrene with ethyl phenyldiazoacetate, since 74% ee and 81% yield were obtained, when using perfluoro(methylcyclohexane) as the solvent.



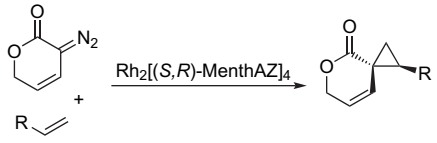
84% de = 34% ee (*cis*) = 99% ee (*trans*) = 94%



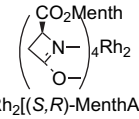
$Rh_2(OAc)(DPTI)_3$

Scheme 81. Asymmetric cyclopropanation catalysed by $Rh_2(OAc)(DPTI)_3$.

In 2003, Che et al. reported the use of a rhodium D_4-porphyrin to catalyse the cyclopropanation of various alkenes with EDA, providing high catalyst turnovers (>1000) and moderate enantioselectivities (up to 68% ee). The obtained trans/cis ratios were, however, low.[168] In 2006, Doyle et al. reported the use of divinyldiazolactone in cyclopropanation reactions with various alkenes in the presence of an azetidinone-ligated catalyst, Rh_2[(*S*,*R*)-MenthAZ]$_4$.[169] The corresponding cyclopropanes were obtained in high yields with notable diastereo- and enantioselectivities (up to 86% ee), as shown in Scheme 82. In the same context, these workers have prepared a series of chiral azetidinone-ligated dirhodium(II) catalysts and tested their efficiency to induce chirality in the cyclopropanation of various olefins with diazomalonates.[170] These reactions gave access to the corresponding cyclopropanes with enantioselectivities of up to 50% ee.



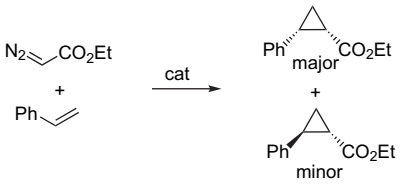
R = Ph: 74% de > 90% ee = 84%
R = (Me)C=CHPh: 81% de = 78% ee = 86%
R = CH=CHPh: 86% de = 66% ee = 73%



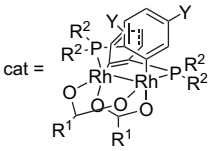
Rh_2[(*S*,*R*)-MenthAZ]$_4$

Scheme 82. Asymmetric cyclopropanation catalysed by Rh_2[(*S*,*R*)-MenthAZ]$_4$.

In recent years, Lahuerta et al. have demonstrated that dirhodium complexes bearing bulky *ortho*-metallated arylphosphines could produce high cis-diastereo- and enantioselectivities in the cyclopropanation of styrene with EDA (Scheme 83).[171] The influence of the substituents on the diastereoselectivity of the reaction was clearly demonstrated, increasing with the size of the substituents, Br<*t*-Bu<TMS, with cis/trans ratios going from 53:47 to 90:10. Moreover, Ubeda et al. showed, in 2006, that similar reactions could be performed in water as the solvent.[172]



$R^1 = CF_3$, R^2 = *p*-BrC_6H_4, Y = Br: 80%
de = 6% ee (*cis*) = 84% ee (*trans*) = 81%
$R^1 = CF_3$, R^2 = *p*-(*t*-Bu)C_6H_4, Y = *t*-Bu: 46%
de = 66% ee (*cis*) = 81% ee (*trans*) = 3%
$R^1 = CF_3$, R^2 = *p*-$TMSC_6H_4$, Y = TMS: 39%
de = 80% ee (*cis*) = 91% ee (*trans*) = 7%

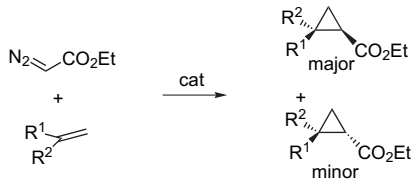


Scheme 83. Asymmetric cyclopropanation catalysed by dirhodium complexes with bulky *ortho*-metallated arylphosphines.

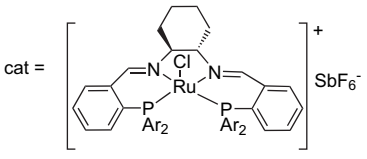
In 2003, Charette et al. screened a variety of structurally diverse chiral dirhodium catalysts for enantioselectivity of styrene with α-nitro-α-diazo carbonyl compounds and observed modest-to-high yields in a wide range of solvents, but only modest enantioselectivities (≤41% ee).[106b] A family of bisoxazoline 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.[173] In addition, Doyle et al. have demonstrated that chiral dirhodium catalysts could be immobilised on a polymer, providing yields and selectivities for cyclopropanations comparable to those with the homogeneous catalyst (up to 84% ee and 87% yield).[174] In the same context, Davies et al. have developed a universal strategy for the heterogenisation of chiral dirhodium catalysts. Indeed, the immobilisation was very effective, as a diverse range of catalysts could be immobilised, exhibiting all the reactivity features of the homogeneous catalysts, with the advantage of excellent recyclability.[175] In addition, Ubeda et al. have reported, very recently, the immobilisation of chiral *ortho*-metallated dirhodium(II) complexes on a cross-linked polystyrene resin.[176] These catalysts were applied to the cyclopropanation of styrene with EDA, giving higher yields, compared to those obtained with the standard homogeneous trifluoroacetate derivatives, whereas the diastereo- and enantioselectivities were generally lower. These differences could be attributed to electronic effects due to the substitution of CF_3CO_2 ligands by $C_6H_4(CH_2)_2CO_2$ groups.

4.1.2.3. Ruthenium catalysts. Ruthenium complexes have been more recently introduced in the field of catalytic cyclopropanation.[177] The resounding success of the rhodium complexes catalysing carbine-transfer reactions is somewhat tempered by the high price of this catalyst metal. In this respect, ruthenium, a direct neighbour of rhodium in the periodic table, offers an advantage, because it currently costs roughly one-tenth the price of rhodium. Another reason for focusing attention on ruthenium is the greater diversity of complexes to be evaluated, due to the larger number of oxidation states and the richer coordination chemistry, as compared to rhodium.[178] Indeed, in little more than a decade, ruthenium has emerged as the third important catalyst metal for the carbenoid chemistry of diazo compounds, besides copper and rhodium. On the other hand, a significant drawback of Ru-catalysed

cyclopropanation reactions 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 may be seen in the propensity of some ruthenium complexes to catalyse not only cyclopropanation, but also metathesis and alkene homologation reactions. In both inter- and intramolecular cyclopropanation reactions, where ruthenium catalysts work successfully, they often rival established rhodium catalysts in terms of effectiveness and relative, as well as absolute, stereochemistry. Several chiral diphosphines have been used as ligands of ruthenium to catalyse the cyclopropanations of alkenes. As an example, Mezzetti et al. have employed chiral tetradentate PNNP ligands, such as that depicted in Scheme 84, to prepare a ruthenium complex of the type $[RuCl(PNNP)]^+SbF_6^-$.[179] This catalyst was able to cyclopropanate various alkenes with EDA with unprecedented cis-diastereoselectivity (up to 98% de), as shown in Scheme 84. In 2006, these authors reported the first chiral bis(aqua) complexes of ruthenium, bearing the same PNNP ligands, and tested them in the cyclopropanation of styrene with EDA.[180] Both $[Ru(OH_2)_2(PNNP)]^{2+}$ and the chloride-free catalysts formed from $[RuCl_2(PNNP)]$ and $AgSbF_6$ were less effective in terms of cyclopropane yield and enantio- and diastereoselectivities than their monochloro-analogues, $[RuCl(PNNP)]^+SbF_6^-$. In 2005, Lopez et al. reported the use of another chiral bidentate ligand, (4*S*)-(2-diphenylphosphinophenyl)-4-isopropyl-1,3-oxazoline, for the cis-selective cyclopropanation of styrene with EDA.[181] In this case, an enantioselectivity of 74% ee for the cis isomer was obtained, along with 36% yield and 50% de.



R^1 = *n*-Hex, R^2 = H: 66% de = 70%
ee (*cis*) = 99% ee (*trans*) = 98%
R^1 = Ph, R^2 = H: 69% de = 98%
ee (*cis*) = 96% ee (*trans*) = 58%
R^1 = *p*-Tol, R^2 = H: 33% de = 84%
ee (*cis*) = 96% ee (*trans*) = 58%



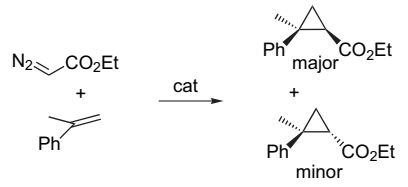
Ar = *p*-$CF_3C_6H_4$

$[RuCl(PNNP)]^+SbF_6^-$

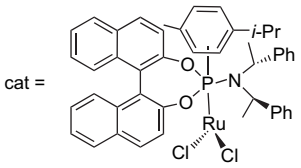
Scheme 84. Asymmetric cyclopropanation of alkenes catalysed by $[RuCl(PNNP)]^+SbF_6^-$.

On the other hand, Mezzetti et al. have investigated the possibility of controlling the absolute configuration at the metal centre by means of a monodentate chiral ligand.[182] Hence, piano-stool ruthenium complexes, bearing chiral monodentate phosphoramidite ligands, have been used to catalyse the cyclopropanation of styrene and α-methylstyrene with EDA after activation with $TlPF_6$ or $(Et_3O)PF_6$ as halide scavengers. In the case of α-methylstyrene, good enantioselectivities were observed, but the total yield and diastereoselectivity were generally low (Scheme 85).

In general, metalloporphyrins provide robust catalysts for group- and atom-transfer reactions, and their application to

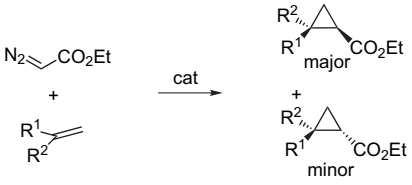


23% de = 14% ee (*cis*) = 86% ee (*trans*) = 87%

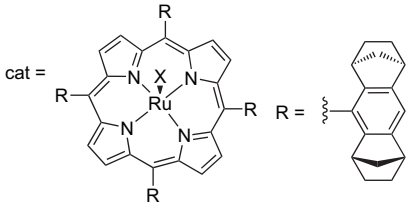


Scheme 85. Asymmetric cyclopropanation of α-methylstyrene catalysed by ruthenium complex of phosphoramidite ligand.

catalyse alkene cyclopropanations has made important advances in recent years.[183] In some cases, asymmetric cyclopropanations have been very successful. As an example, Berkessel et al. have reported the use of chiral ruthenium porphyrin catalysts for the cyclopropanation of alkenes with EDA, providing up to 90% ee and up to 90% de (Scheme 86).[184] In 2003, Che et al. reported a comparison between rhodium and ruthenium porphyrin complexes for similar reactions.[168] They showed that better trans/cis ratios were obtained with ruthenium complexes and higher ee values for the trans isomer than with the corresponding rhodium complexes. In addition, Berkessel et al. reported an example of a catalyst in which the axial CO ligand at ruthenium was exchanged for PF_3, resulting in the first chiral ruthenium porphyrin with a PF_3 ligand, allowing 95% ee, in the case of 1,1-diphenylethylene as the substrate, to be obtained.[184]



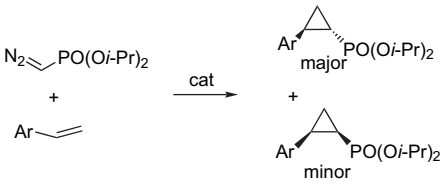
R^1 = Ph, R^2 = H, X = CO: 80% de = 92%
ee (*trans*) = 87% ee (*cis*) = 14%
R^1 = Ph, R^2 = Me, X = CO: 79% de = 32%
ee (*trans*) = 90% ee (*cis*) = 38%
R^1 = Ph, R^2 = OTMS, X = PF_3: 98% de = 40%
ee (*trans*) = 83% ee (*cis*) = 43%
R^1 = R^2 = Ph, X = PF_3: 45% de = 66%
ee (*trans*) = 96% ee (*cis*) = 34%



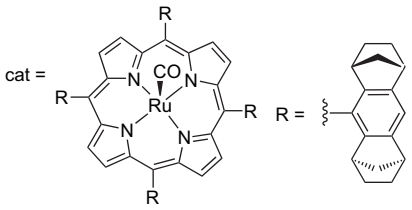
Scheme 86. Asymmetric cyclopropanation of alkenes with EDA catalysed by ruthenium porphyrin.

The scope of this methodology was extended to the cyclopropanation of styrene and its derivatives with diisopropyl diazomethylphosphonate, affording the corresponding cyclopropyl esters in up to 92% ee, up to 98% de and high catalyst turnovers (Scheme 87).[185]

This catalyst was also applied, in 2006, to the cyclopropanation of styrene derivatives with 2,2,2-trifluorodiazoethane, providing the corresponding trifluoromethylphenylcyclopropanes with ee

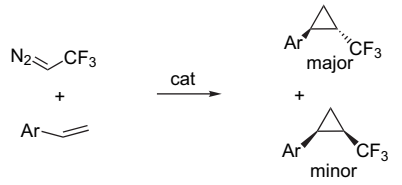


Ar = Ph: 97% de = 92%
ee (*trans*) = 90% ee (*cis*) = 34%
Ar = *p*-Tol: 93% de = 98%
ee (*trans*) = 87% ee (*cis*) = 23%
Ar = *p*-$MeOC_6H_4$: 96% de = 94%
ee (*trans*) = 90% ee (*cis*) = 23%
Ar = *p*-$CF_3C_6H_4$: 90% de = 90%
ee (*trans*) = 92% ee (*cis*) = 5%
Ar = *p*-ClC_6H_4: 92% de = 94%
ee (*trans*) = 88% ee (*cis*) = 27%

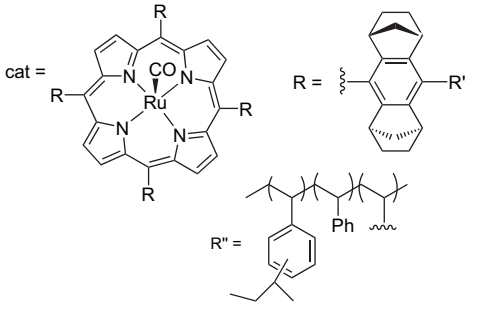


Scheme 87. Synthesis of cyclopropylphosphonates catalysed by ruthenium porphyrin.

values of up to 69%.[186] The reactions were also investigated under heterogeneous conditions with the corresponding metalloporphyrin polymers, giving similar results, as shown in Scheme 88.

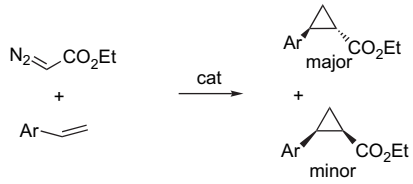


Ar = Ph, R' = H: 32% de = 96% ee (*trans*) = 58%
Ar = *p*-$MeOC_6H_4$, R' = H: 35% de = 98% ee (*trans*) = 30%
Ar = *p*-BrC_6H_4, R' = H: 24% de = 98% ee (*trans*) = 50%
Ar = Ph, R' = R": 33% de = 98% ee (*trans*) = 61%
Ar = *p*-$MeOC_6H_4$, R' = R": 35% de = 88% ee (*trans*) = 25%
Ar = *p*-BrC_6H_4, R' = R": 31% de = 92% ee (*trans*) = 39%

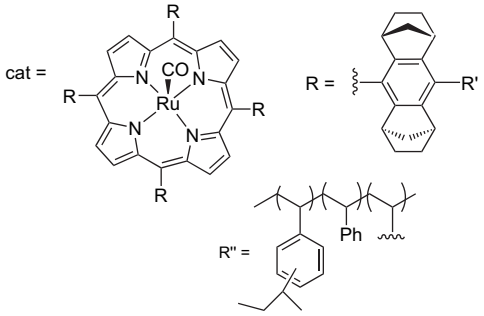


Scheme 88. Synthesis of trifluoromethylphenylcyclopropanes catalysed by homogeneous or heterogeneous ruthenium porphyrin.

These authors have also reported the use of chiral macroporous metalloporphyrin polymers for the heterogeneous diazoacetate addition to styrene derivatives.[187] Hence, a chiral ruthenium porphyrin complex, functionalised with four vinyl groups, has been polymerised with divinylbenzene to obtain the corresponding supported ruthenium complex. This polymer was applied to the cyclopropanation of EDA with styrene derivatives, leading to the corresponding *trans* cyclopropanes with good ees, as shown in Scheme 89.

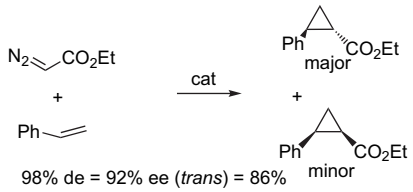


Ar = Ph: 77% de = 84% ee (*trans*) = 82%
Ar = *p*-$MeOC_6H_4$: 88% de = 84% ee (*trans*) = 80%
Ar = *p*-BrC_6H_4: 75% de = 86% ee (*trans*) = 90%

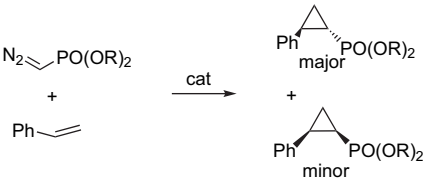


Scheme 89. Asymmetric cyclopropanation of alkenes with EDA catalysed by heterogeneous ruthenium porphyrin.

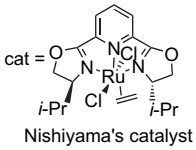
Another class of ligands such as chiral pyridine-bisoxazoline (Pybox) ligands has been demonstrated to be very efficient when complexed to ruthenium for cyclopropanation reactions. As an example, Nishiyama's catalyst, depicted in Scheme 90, was used by Deshpande et al., in 2003, to catalyse the cyclopropanation of styrene with EDA, providing the corresponding *trans* cyclopropane in high ee, de and yield.[188] In 2005, Charette et al. applied the success of this catalyst to prepare the corresponding cyclopropylphosphonates by cyclopropanation of styrene with α-diazomethylphosphonates, as shown in Scheme 90.[189]



98% de = 92% ee (*trans*) = 86%



R = Me: 65% de = 80% ee (*trans*) = 76%
R = Et: 65% de > 96% ee (*trans*) = 96%
R = *i*-Pr: 70% de > 96% ee (*trans*) = 96%
R = CH_2t-Bu: 79% de > 96% ee (*trans*) = 96%

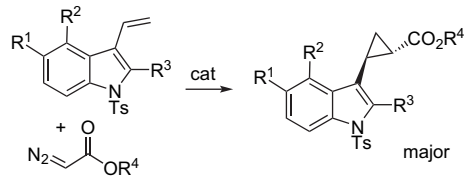


Nishiyama's catalyst

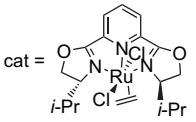
Scheme 90. Asymmetric cyclopropanations catalysed by Nishiyama's catalyst.

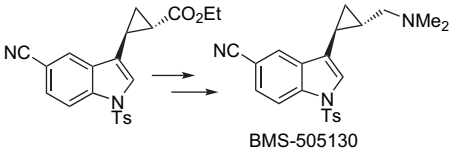
In 2005, Marcin et al. found that 1-tosyl-3-vinylindoles were excellent substrates for the Pybox-Ru-catalysed asymmetric diazoacetate cyclopropanation with ethyl and *tert*-butyl diazoacetates.[190] A good diastereoselectivity and a high enantioselectivity were observed for a variety of substituted 3-vinylindoles, as shown in

Scheme 91. The trans/cis-diastereoselectivity was notably improved when using *tert*-butyl as opposed to ethyl diazoacetate. Moreover, the utility of this method was demonstrated by the conversion of one of the resulting chiral cycloadducts into a selective serotonin reuptake inhibitor (SSRI), BMS-505130.



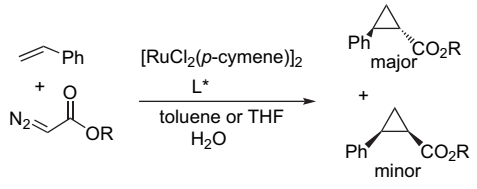
$R^1 = R^2 = R^3 = H$, R^4 = Et: 78%
de = 80% ee (*trans*) = 85%
$R^1 = R^2 = R^3 = H$, R^4 = *t*-Bu: 85%
de = 90% ee (*trans*) = 88%
R^1 = F, $R^2 = R^3 = H$, R^4 = Et: 84%
de = 78% ee (*trans*) = 84%
R^1 = CN, $R^2 = R^3 = H$, R^4 = Et: 82%
de = 80% ee (*trans*) = 86%
R^1 = OMe, $R^2 = R^3 = H$, R^4 = *t*-Bu: 76%
de = 92% ee (*trans*) = 86%
$R^1 = R^3 = H$, R^2 = Me, R^4 = Et: 73%
de = 88% ee (*trans*) = 81%



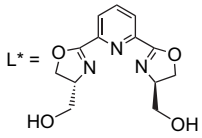


Scheme 91. Asymmetric cyclopropanation of 1-tosyl-3-vinylindoles.

In the same context, Nishiyama et al. have also developed a cyclopropanation process applicable in aqueous media, involving a water-soluble ruthenium catalyst with Pybox ligands bearing hydroxyl group moieties.[191] Hence, the hydroxymethyl derivative of Pybox could provide excellent stereoselectivities for the cyclopropanation of electron-rich terminal alkenes such as styrene, as shown in Scheme 92.



R = *d*-Menth: 57% de = 94% ee (*trans*) = 94% ee (*cis*) = 76%
R = *l*-Menth: 75% de = 92% ee (*trans*) = 83% ee (*cis*) = 54%
R = *i*-Pr: 24% de = 84% ee (*trans*) = 67% ee (*cis*) = 27%
R = *t*-Bu: 30% de = 84% ee (*trans*) = 57% ee (*cis*) = 26%



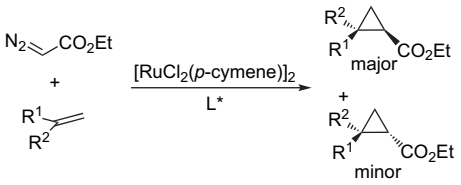
Scheme 92. Asymmetric cyclopropanation with Pybox ligand in aqueous media.

Since the substitution of an oxygen atom by sulfur in the five-membered ring of the chiral ligands could lead to a different situation with regard to the diastereoselectivity and enantioselectivity, Simmoneaux et al. have examined chiral 2,6-bis(thiazolinyl)pyridines as ligands for the Ru-catalysed cyclopropanation of olefins with diisopropyl diazomethylphosphonate and EDA.[192] Comparative evaluation of the enantiocontrol for the cyclopropanation of styrene with chiral ruthenium bisoxazoline and bisthiazoline showed many similarities with, in some cases, good enantiomeric excesses. Hence, enantioselectivities of up to 84% ee for the *trans* cyclopropylphosphonate were observed. In 2005, Mayoral et al. reported the immobilisation of 2,6-bis[(*S*)-4-isopropyloxazolin-2-yl]pyridine on polystyrene resins, both on a Merrifield-type resin by grafting and on supports prepared by the polymerisation of 4-vinyl-substituted ligands.[193] The corresponding ruthenium complexes have been tested as catalysts in the cyclopropanation of styrene with EDA, providing yields of over 60% with up to 91% ee in four successive reactions. It was shown that the catalytic activity, 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. In 2007, the same group reported the preparation of other supported catalysts having Pybox chiral moieties such as macroporous monolithic miniflow systems.[194] These catalysts were based on styrene-divinylbenzene polymeric backbones having different compositions and Pybox chiral moieties. The corresponding ruthenium complexes were tested for the continuous flow cyclopropanation reaction between styrene and EDA under conventional conditions and in supercritical carbon dioxide. Up to 83% ee could be obtained, demonstrating that these Ru-Pybox monolithic miniflow reactors not only provided a highly efficient and robust heterogeneous chiral catalyst, but also allowed the development of more environmentally friendly reaction conditions without sacrificing the global efficiency of the process. On the other hand, these authors have shown that chiral Pybox-Ru catalysts could be microencapsulated into linear polystyrene as a method to recover and recycle the valuable catalyst.[195] These catalysts allowed 60–68% yields to be achieved with enantioselectivities in the range 75–85% ee in the bench-mark cyclopropanation reaction between styrene and EDA. In addition, Pinel et al. reported, in 2006, the possibility of immobilising a chiral Pybox system on modified starch.[196] In these conditions, the cyclopropanation of styrene with EDA led to the corresponding cycloadduct in 67% yield, 78% de and 77% ee for the trans isomer.

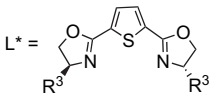
On the other hand, several kinds of C_2-symmetric chiral oxazolines have been investigated for Ru-catalysed cyclopropanations. As an example, Zingaro et al. have tested novel sulfur-containing chiral bisoxazolines with thiophene as the backbone as ligands in the Ru-catalysed cyclopropanation of alkenes with EDA.[197] Excellent enantio- and diastereoselectivities were obtained, as shown in Scheme 93, in particular with diphenylethene.

In 2003, Scialdone et al. reported the successful use of chiral (salen)Ru(II) catalysts for the cyclopropanation of styrene with EDA (Scheme 94). This reaction constituted the key step of the synthesis of chiral *trans* cyclopropyl β-amino acid derivatives.[198]

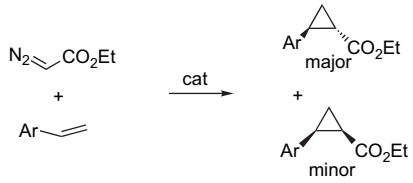
More recently, Nguyen et al. have reported the successful use of a chiral sulfoxide additive for the induction of asymmetry in the cyclopropanation of various olefins with EDA performed in the presence of an achiral (salen)Ru(II) catalyst, as shown in Scheme 95.[199] In order to explain the asymmetric induction, these authors proposed a mechanism involving the axial coordination of the chiral sulfoxide to the ruthenium centre as the key induction step. Initial reaction of EDA with the axial triphenylphosphine ligand caused the rapid formation of the corresponding phosphorus ylide, which did not bind significantly to the metal centre. This left the axial positions of the catalyst open to coordination by the chiral sulfoxide. The chiral additive could then bind preferentially to one of the two chiral conformers of the achiral (salen)ruthenium complex, thus effectively forcing the larger achiral salen ligand to



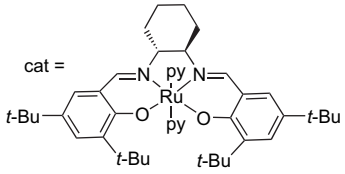
$R^1 = R^2 = Ph$, $R^3 = Et$: 70% ee (*trans*) > 99%
ee (*cis*) > 99%
$R^1 = H$, $R^2 = p\text{-}MeOC_6H_4$, $R^3 = t\text{-}Bu$: 78% de = 64%
ee (*trans*) = 91% ee (*cis*) = 85%
$R^1 = H$, $R^2 = p\text{-}ClC_6H_4$, $R^3 = t\text{-}Bu$: 82% de = 60%
ee (*trans*) = 87% ee (*cis*) = 83%
$R^1 = H$, $R^2 = Ph$, $R^3 = t\text{-}Bu$: 79% de = 58%
ee (*trans*) = 89% ee (*cis*) = 82%



Scheme 93. Asymmetric cyclopropanation with bis(oxazolinyl)thiophenes.



99% de = 84% ee (*trans*) = 99% ee (*cis*) = 96%



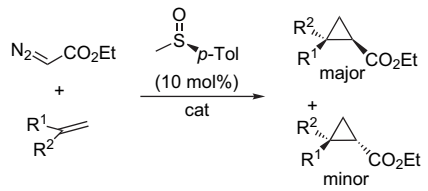
Scheme 94. Asymmetric cyclopropanation catalysed by (salen)Ru(II) catalyst.

adopt a preferred chiral conformation. Therefore, the asymmetry of the additive was transmitted and amplified to the opposite axial position, where a ruthenium carbene could interact stereoselectively with an olefin to complete the cyclopropanation cycle.

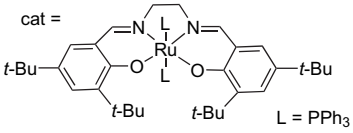
In addition, Katsuki et al. developed, in 2006, a metallosalen-catalysed highly cis-selective cyclopropanation reaction.[200] The reaction was performed under photo-irradiation in the presence of a ruthenium(NO)-salen complex as catalyst, providing good enantioselectivity and cis-diastereoselectivity, as shown in Scheme 96.

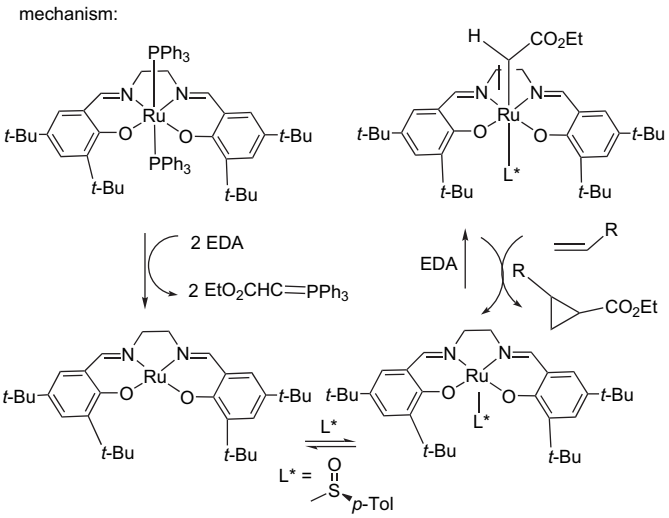
Another cis-diastereoselective cyclopropanation of a range of olefins with EDA was described by Kim et al. in 2007.[201] This reaction was catalysed by ruthenium complexes of chiral (iminophosphoranyl)ferrocenes, which proved to be excellent ligands, since up to 99% de and ee were observed, as shown in Scheme 97. Indeed, this new type of ligands was shown to be comparable to, or better than, the well-known ligands such as bisoxazolines or semicorrins in terms of asymmetric induction.

Finally, Garcia et al. reported an extensive comparison of full-QM (B3LYP) and QM/MM (B3LYP:UFF) levels of theory for two enantioselective catalytic systems, namely Pybox-Ru and Box-Cu complexes, in the cyclopropanation of alkenes with methyl diazoacetate.[202] 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. More importantly, the relative energies calculated at the QM/MM level were in good agreement with those calculated at the full-QM



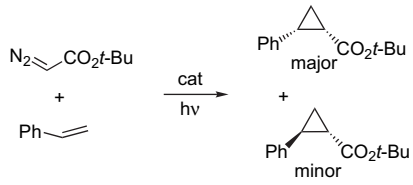
$R^1 = CO_2Me$, $R^2 = Me$: 98% de = 96%
ee (*trans*) = 68%
$R^1 = H$, $R^2 = p\text{-}MeOC_6H_4$: 97% de = 72%
ee (*trans*) = 87% ee (*cis*) = 89%
$R^1 = H$, $R^2 = p\text{-}(t\text{-}Bu)C_6H_4$: 97% de = 72%
ee (*trans*) = 87% ee (*cis*) = 89%
$R^1 = H$, $R^2 = p\text{-}FC_6H_4$: 86% de = 72%
ee (*trans*) = 83% ee (*cis*) = 80%
$R^1 = H$, $R^2 = p\text{-}Tol$: 98% de = 78%
ee (*trans*) = 86% ee (*cis*) = 79%



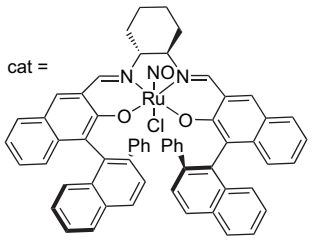


Scheme 95. Asymmetric cyclopropanation in presence of chiral sulfoxide additive.

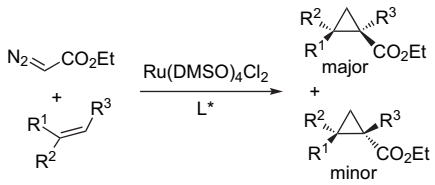
level in all cases. Furthermore, the QM/MM energies were often in better agreement with the stereoselectivity experimentally observed, and this suggested that QM/MM calculations could be superior to full-QM calculations, when subtle differences in inter- and



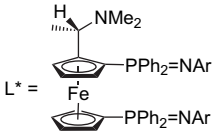
53% de = 60% ee (*cis*) = 81%



Scheme 96. Asymmetric cyclopropanation catalysed by Ru(NO)-salen catalyst.



R^1 = *n*-Bu, R^2 = R^3 = H: 79% de = 68%
ee (*cis*) = 94% ee (*trans*) = 92%
R^1 = *n*-Hex, R^2 = R^3 = H: 44% de = 68%
ee (*cis*) = 98% ee (*trans*) = 74%
R^1 = Me, R^2 = Ph, R^3 = H: 75% de = 90%
ee (*cis*) = 93% ee (*trans*) = 97%

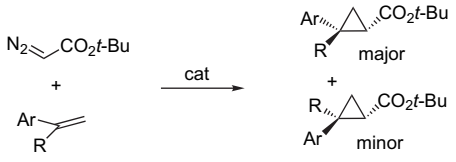


Ar = 2,6-$Me_2C_6H_3$

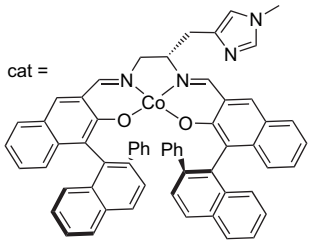
Scheme 97. Asymmetric cyclopropanation catalysed by Ru catalyst of chiral (iminophosphoranyl)ferrocene.

intramolecular interactions are important in determining the selectivity, as is the case in enantioselective catalysis.

4.1.2.4. Other metal catalysts. In recent years, several results concerning the asymmetric cyclopropanations of alkenes with diazo compounds have been reported, involving chiral cobalt complexes as catalysts. As an example, Katsuki et al. have recently developed the cyclopropanation of various alkenes with α-diazoacetates using chiral Co(II)-salen complexes as catalysts.[200,203] As shown in Scheme 98, all of these reactions proceeded with high cis-diastereo- and enantioselectivity.

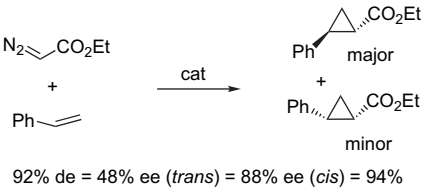


R = H, Ar = *p*-$MeOC_6H_4$: 95% de = 94% ee (*cis*) = 96%
R = H, Ar = *p*-Tol: 99% de = 98% ee (*cis*) = 94%
R = H, Ar = *p*-$NO_2C_6H_4$: 93% de = 78% ee (*cis*) = 93%
R = H, Ar = *p*-ClC_6H_4: 100% de = 94% ee (*cis*) = 96%
R = H, Ar = *o*-ClC_6H_4: 100% de = 84% ee (*cis*) = 96%
R = Me, Ar = Ph: 45% de = 10% ee (*cis*) = 97%

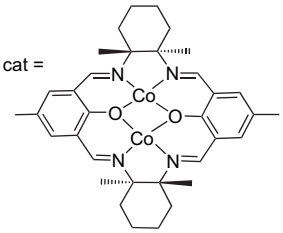


Scheme 98. Asymmetric cyclopropanation catalysed by cobalt–salen catalyst.

The corresponding dinuclear complexes, which are coupled salen complexes, represent a new type of effective catalyst. This is due to the fact that the substrate molecules will invariably be subjected to chiral induction by the chiral backbone as they approach the complex platform. In this context, Gao et al. have applied this type of catalyst to the cyclopropanation of styrene with EDA and obtained the trans cycloadduct as the major product with high enantioselectivity (Scheme 99).[204]

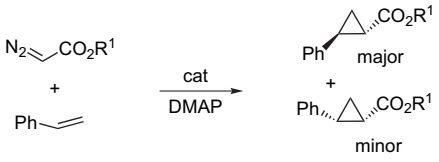


92% de = 48% ee (*trans*) = 88% ee (*cis*) = 94%

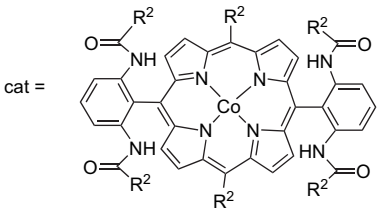


Scheme 99. Asymmetric cyclopropanation catalysed by dinuclear cobalt catalyst.

On the other hand, Zhang et al. have demonstrated that cobalt(II) porphyrin complexes were general and efficient catalysts for diastereo- and enantioselective cyclopropanation of alkenes.[205] As an example, cobalt(II) complexes of D_2-symmetric chiral porphyrins were successfully applied to the cyclopropanation of styrene with ethyl and *tert*-butyl diazoacetates, providing the corresponding trans cycloadducts in high yields, des and ees, as shown in Scheme 100.[206] It was shown that the use of DMAP as an additive allowed the enantioselectivities to be doubled and the production of the trans isomer to be boosted, suggesting a significant trans influence of potential coordinating ligands on the metal centre.[207] In 2007, the scope of this methodology was extended to a broad range of styrene derivatives, furnishing the corresponding cyclopropanes in good yield, and in up to 100% de and 98% ee.[208] Through comparative studies, these authors have demonstrated the superiority of cobalt over iron by performing the reactions with the same porphyrin ligand. Indeed, low yields (1–77%) and poor enantioselectivities (up to 28% ee) were obtained with the corresponding iron complex.



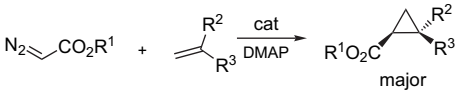
R^1 = Et: 86% de = 94% ee (*trans*) = 78%
R^1 = *t*-Bu: 88% de > 98% ee (*trans*) = 95%



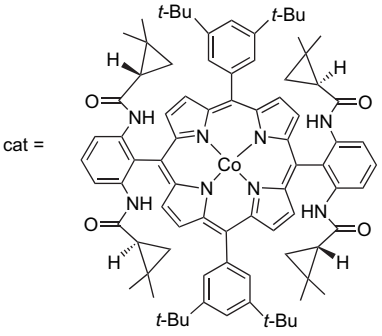
R^2 = 3,5-di-*t*-BuC_6H_3

Scheme 100. Asymmetric cyclopropanation catalysed by Co(II) complex of D_2-symmetric porphyrin.

In 2007, the same workers studied the asymmetric cyclopropanation of more challenging substrates such as electron-deficient non-styrenic olefins, using another Co(II) complex of a D_2-symmetric porphyrin.[209] Excellent yields and high stereoselectivities were obtained for most of the cyclopropanated products, as shown in Scheme 101, making this novel catalyst one of the most selective for asymmetric cyclopropanation of olefins in general.



R^1 = Et, R^2 = CO_2Et, R^3 = H: 78% de = 96% ee (*trans*) = 80%
R^1 = *t*-Bu, R^2 = CO_2Et, R^3 = H: 72% de = 98% ee (*trans*) = 90%
R^1 = *t*-Bu, R^2 = CO_2*t*-Bu, R^3 = H: 62% de = 96% ee (*trans*) = 84%
R^1 = Et, R^2 = Me, R^3 = CO_2Me: 73% de = 90% ee (*trans*) = 61%
R^1 = Et, R^2 = $CONH_2$, R^3 = H: 51% de = 98% ee (*trans*) = 88%
R^1 = *t*-Bu, R^2 = $CONH_2$, R^3 = H: 66% de = 98% ee (*trans*) = 97%
R^1 = Et, R^2 = $CONMe_2$, R^3 = H: 85% de = 98% ee (*trans*) = 77%
R^1 = *t*-Bu, R^2 = $CONMe_2$, R^3 = H: 86% de = 98% ee (*trans*) = 96%
R^1 = *t*-Bu, R^2 = CONH*i*-Pr, R^3 = H: 44% de = 98% ee (*trans*) = 97%
R^1 = R^2 = Et, R^3 = H: 89% de = 92% ee (*trans*) = 80%
R^1 = *t*-Bu, R^2 = Et, R^3 = H: 81% de = 98% ee (*trans*) = 94%
R^1 = Et, R^2 = *n*-Pent, R^3 = H: 92% de = 96% ee (*trans*) = 79%
R^1 = *t*-Bu, R^2 = *n*-Pent, R^3 = H: 94% de = 98% ee (*trans*) = 96%
R^1 = *t*-Bu, R^2 = Me, R^3 = Ac: 40% de = 96% ee (*trans*) = 90%
R^1 = *t*-Bu, R^2 = CN, R^3 = H: 83% de = 52% ee (*trans*) = 93%
R^1 = *t*-Bu, R^2 = Me, R^3 = CN: 87% de = 24% ee (*trans*) = 95%



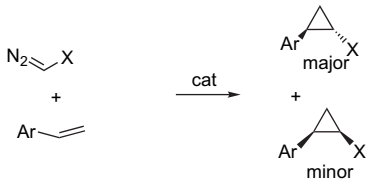
Scheme 101. Asymmetric cyclopropanation of electron-deficient olefins catalysed by Co(II) complex of D_2-symmetric porphyrin.

In 2005, Zhang's group also developed a series of novel *meso*-chiral porphyrins and used the cobalt complexes of these ligands to catalyse the cyclopropanation of styrene with EDA, affording the desired cyclopropane ester as a trans-dominant form in excellent yields.[210] Due to the orientation and flexibility of the chiral appendages, however, only low enantioselectivities were observed ($\leq$12% ee). In addition, these authors have found that similar reactions could be efficiently catalysed by vitamin B_{12} derivatives such as aquocobalamin.[211] This catalyst was shown to be the most effective for a variety of alkenes, providing the corresponding cis-dominant cyclopropanes in excellent yields and moderate enantioselectivities (up to 68% ee).

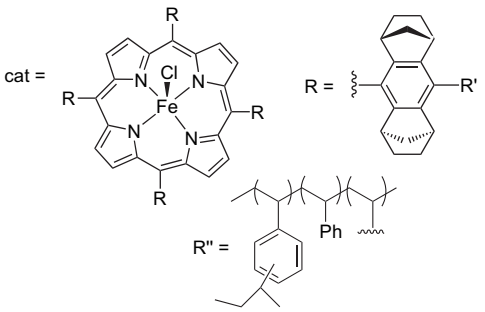
On the other hand, cheaper, non-toxic and environmentally benign metals such as iron have also been employed to catalyse cyclopropanations in the presence of chiral porphyrins. As an example, Wong et al. reported, in 2006, the use of Halterman iron porphyrin for inducing the cyclopropanation of alkenes with EDA, providing the corresponding trans cycloadducts with high des and ees, as shown in Scheme 102.[212] At the same time, similar conditions were applied by Simmoneaux et al. to the cyclopropanation of styrene derivatives with 2,2,2-trifluorodiazoethane, giving rise to the corresponding chiral trifluoromethylphenylcyclopropanes.[186] As shown in Scheme 102, the scope of this methodology was extended to the use of heterogeneous experimental conditions by employing the corresponding macroporous metalloporphyrin polymers as catalysts.

In 2005, Patti et al. showed that a chiral ferrocenyl-bisoxazoline derivative, possessing a biphenyl unit, could be used as a ligand of the Cu-catalysed 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.[213]

Very recently, Katsuki et al. have developed highly cis-diastereo- and enantioselective cyclopropanations of styrene and its

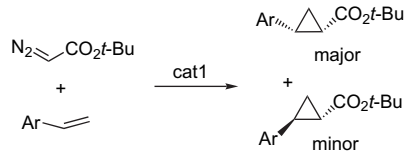


Ar = Ph, X = CO_2Et, R' = H: 70% de = 92% ee (*trans*) = 86%
Ar = *p*-ClC_6H_4, X = CO_2Et, R' = H: 57% de = 90% ee (*trans*) = 75%
Ar = *p*-Tol, X = CO_2Et, R' = H: 56% de = 84% ee (*trans*) = 79%
Ar = *p*-$MeOC_6H_4$, X = CO_2Et, R' = H: 65% de = 86% ee (*trans*) = 74%
Ar = Ph, X = CF_3, R' = H: 60% de = 86% ee (*trans*) = 75%
Ar = *p*-$MeOC_6H_4$, X = CF_3, R' = H: 96% de = 90% ee (*trans*) = 73%
Ar = *p*-BrC_6H_4, X = CF_3, R' = H: 88% de = 80% ee (*trans*) = 71%
Ar = Ph, X = CF_3, R' = R'': 52% de = 94% ee (*trans*) = 56%
Ar = *p*-$MeOC_6H_4$, X = CF_3, R' = R'': 51% de = 92% ee (*trans*) = 17%
Ar = *p*-BrC_6H_4, X = CF_3, R' = R'': 42% de = 94% ee (*trans*) = 37%

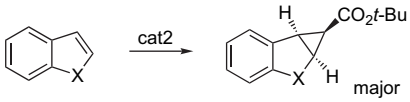


Scheme 102. Asymmetric cyclopropanation catalysed by Fe(III) complex, Halterman iron porphyrin.

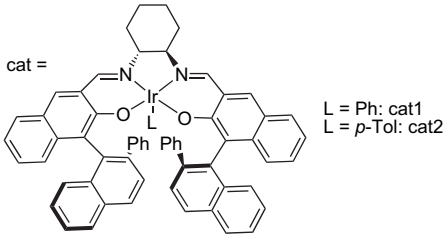
derivatives with *tert*-butyl α-diazoacetate performed in the presence of a new chiral aryliridium–salen complex (Scheme 103).[214] The scope of the reaction was extended to the use of cyclic olefins such as indene and benzofuran, giving access, with unprecedently very high cis-diastereo- and enantioselectivities, to the corresponding chiral cyclopropanes (Scheme 103).



Ar = Ph: > 99% de > 98% ee (*cis*) = 98%
Ar = *o*-$MeOC_6H_4$: 90% de = 94% ee (*cis*) = 99%
Ar = *m*-$MeOC_6H_4$: 88% de > 98% ee (*cis*) = 97%
Ar = *p*-$MeOC_6H_4$: > 99% de > 98% ee (*cis*) = 97%
Ar = *o*-ClC_6H_4: 90% de = 98% ee (*cis*) = 98%
Ar = *m*-ClC_6H_4: 91% de > 98% ee (*cis*) = 98%
Ar = *p*-ClC_6H_4: > 99% de > 98% ee (*cis*) = 98%



X = CH_2: 51% de > 98% ee = 97%
X = O: 46% de > 98% ee = 99%



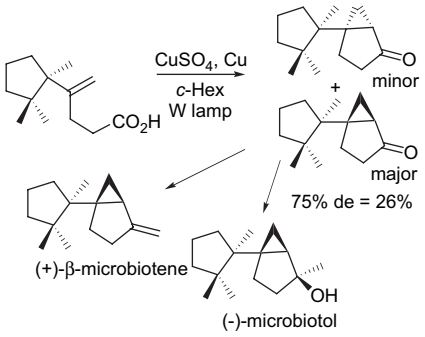
Scheme 103. Asymmetric cyclopropanations catalysed by aryliridium–salen catalysts.

In addition, Che et al. have reported the cyclopropanation of substituted styrenes with EDA performed in the presence of chiral osmium complexes bearing sterically bulky Schiff-base ligands such as bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine.[215] The corresponding cycloadducts were obtained in moderate-to-good enantioselectivity (up to 79% ee) and moderate trans-selectivity (up to 66% de). Finally, Llusar et al. reported, in 2006, an unprecedented synthesis of chiral Mo_3CuS_4 clusters and investigated the catalytic activity of these clusters for the asymmetric cyclopropanation of styrene and its derivatives with EDA.[216] Both diastereo- and enantioselectivities were, however, only moderate for both inter- and intramolecular processes.

4.2. Intramolecular cyclopropanation

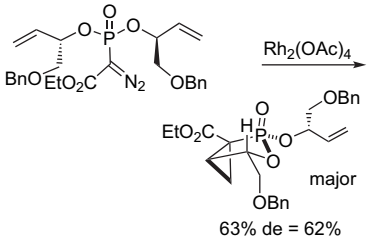
4.2.1. Chiral auxiliaries

The intramolecular cyclopropanation of alkenes via the transition-metal-catalysed decomposition of diazo derivatives is a simple and convenient method to generate synthetically versatile [*n*.1.0]bicycloalkanes. Indeed, when both functionalities, the diazo unit and the alkene, are in the same molecule, an intramolecular cyclopropanation is possible in the presence of an appropriate catalyst, thus producing bicyclic products.[217] In recent years, only a few chiral auxiliaries have been used to generate intramolecularly chiral cyclopropanes. As an example, Srikrishna et al. developed, in 2005, the first enantioselective syntheses of (−)-microbiotol and (+)-β-microbiotene, which are cyclocuparane sesquiterpenes containing three contiguous quaternary carbon atoms, on the basis of an asymmetric Cu-catalysed intramolecular cyclopropanation of a chiral diazo ketone derived from the readily available cyclogeraniol (Scheme 104).[218]



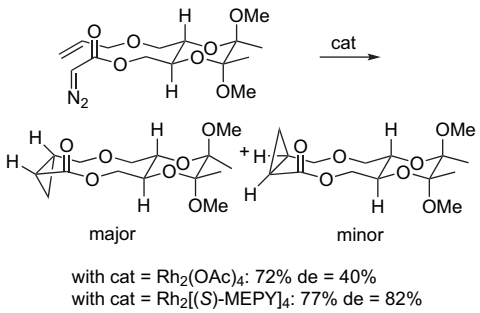
Scheme 104. Total syntheses of (−)-microbiotol and (+)-β-microbiotene.

In 2003, Hanson et al. demonstrated that substituents played an important role in the double diastereotopic differentiation strategy of α-diazophosphonate templates using $Rh_2(OAc)_4$-catalysed intramolecular cyclopropanation employing the (*R*)-pantolactone auxiliary.[219] Furthermore, the double diastereoselective intramolecular cyclopropanation of a pseudo-C_2-symmetric phosphonate was performed with excellent diastereoselectivity, as shown in Scheme 105.



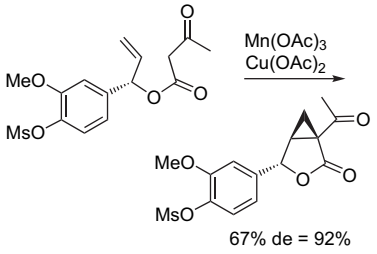
Scheme 105. Asymmetric cyclopropanation of chiral diazophosphonoacetate.

In 2006, Doyle et al. studied the intramolecular cyclopropanation of diazoacetates prepared from butane-2,3-diacetals of (L)- and (D)-threitol.[220] In the presence of $Rh_2(OAc)_4$ as catalyst, the reaction of the (L)-threitol-derived diazoacetate afforded two cyclopropane diastereoisomers in a ratio of 70:30, whereas up to 82% de was obtained in the presence of a chiral catalyst such as $Rh_2[(S)\text{-MEPY}]_4$, which demonstrated a double diastereoselectivity and 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 106).



Scheme 106. Asymmetric cyclopropanation of butane-2,3-diacetal of (L)-threitol.

In addition, Brown et al. have described a Mn(III)-mediated cyclopropanation of a chiral allyl acetoacetate, affording the corresponding 3-oxabicyclo[3.1.0]hexan-2-one in good yield and high diastereoselectivity, as shown in Scheme 107.[221] The utility of this approach has been illustrated by the syntheses of several furofuranones and furofuran lignans.

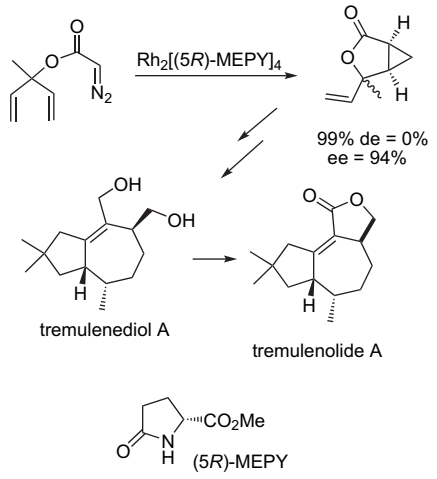


Scheme 107. Asymmetric cyclopropanation of chiral allyl acetoacetate.

4.2.2. Chiral catalysts

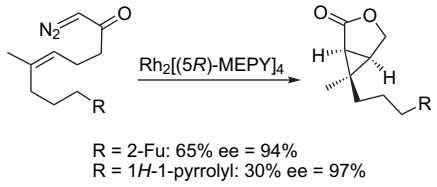
Chiral catalyst development within the dirhodium core has mainly centred on the use of chiral carboxylate and carboxamidate ligands. In most cases, C_1-symmetric ligands from simple amino acids are coordinated around the dirhodium core to give the chiral rhodium catalysts. Doyle has introduced chiral carboxamidate ligands, which coordinate to the dirhodium core through amide bonds. Generally, these catalysts, such as $Rh_2[(5R)\text{-MEPY}]_4$, are more electron rich than the tetracarboxylates and have a different reactivity profile.[222] In 2006, Martin et al. reported the use of this catalyst to promote the intramolecular cyclopropanation of a divinyl diazoacetate, providing the corresponding cyclopropyl lactone as an equimolecular mixture of diastereomers in excellent yield and enantioselectivity for each diastereomer (Scheme 108).[223] This reaction was the key step of a concise entry to the skeleton of the tremulane sesquiterpenes, since it culminated in the first enantioselective syntheses of tremulenediol A and tremulenolide A.[224] In addition, these workers have applied this methodology to the total synthesis of a novel antifungal agent, ambruticin S,[225] and to the syntheses of various cyclopropane-derived peptidomimetics.[226]

In addition, $Rh_2[(5R)\text{-MEPY}]_4$ was used as a catalyst by Fillion et al. to cyclopropanate various allylic diazoacetates, providing the



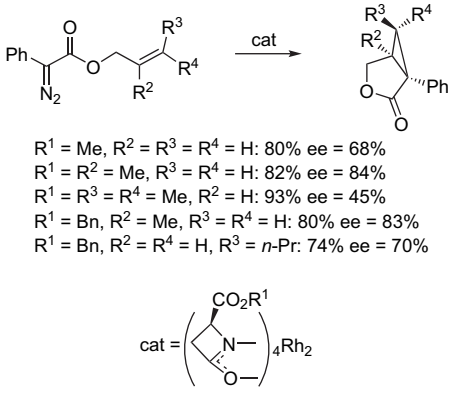
Scheme 108. Asymmetric intramolecular cyclopropanation of divinyl diazoacetate catalysed by $Rh_2[(5R)\text{-MEPY}]_4$.

corresponding cycloadducts with up to 97% ee, as shown in Scheme 109.[227]



Scheme 109. Asymmetric intramolecular cyclopropanation of allylic diazoacetates catalysed by $Rh_2[(5R)\text{-MEPY}]_4$.

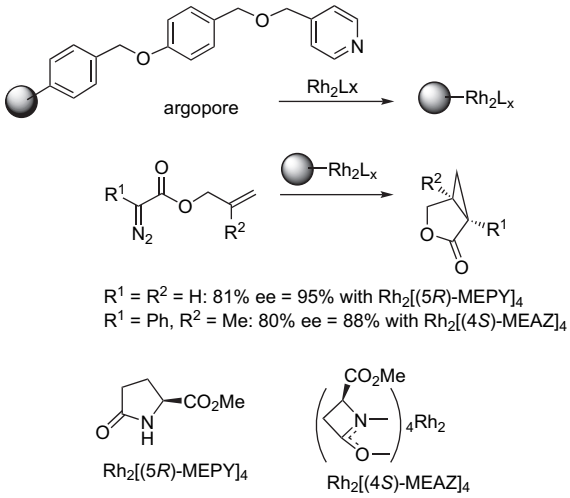
Another class of chiral dirhodium(II) carboxamidate-ligated catalysts, the bridging ligand of which was a chiral azetidinone-carboxylate, has been developed by Doyle et al., and applied to the intramolecular cyclopropanation of allyl phenyldiazoacetates, providing high yields and enantioselectivities, as shown in Scheme 110.[228]



Scheme 110. Asymmetric intramolecular cyclopropanation of allyl phenyldiazoacetates catalysed by dirhodium(II) azetidinone-carboxylates.

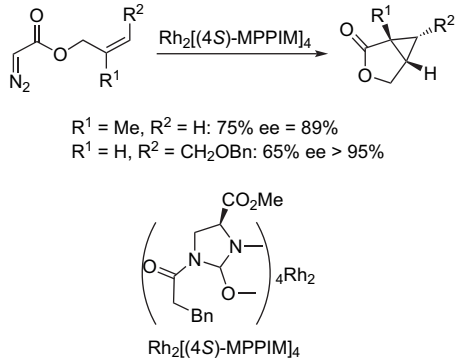
In 2005, the scope of the preceding methodology was extended to the use of immobilised rhodium catalysts.[175] Hence, the immobilisation of catalysts, such as $Rh_2[(4S)\text{-MEAZ}]_4$ or $Rh_2[(5S)\text{-MEPY}]_4$, using an argopore resin as the solid support, allowed enantioselectivities of up to 95% ee to be obtained for the intramolecular cyclopropanation of allyl diazoacetates (Scheme 111).

Another highly efficient dirhodium catalyst, $Rh_2[(4S)\text{-MPPIM}]_4$, has been investigated for the asymmetric intramolecular



Scheme 111. Asymmetric intramolecular cyclopropanation of allyl diazoacetates using immobilised dirhodium catalysts.

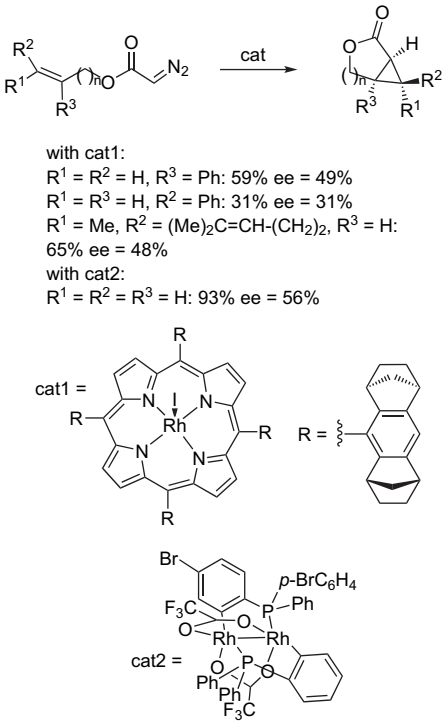
cyclopropanation of allyl diazoacetates, providing the corresponding chiral cyclopropanes in high ees, as shown in Scheme 112.[165,229] One of the resulting cyclopropanated products was further converted into a highly potent group 2 and 3 glutamate receptor agonist.[165]



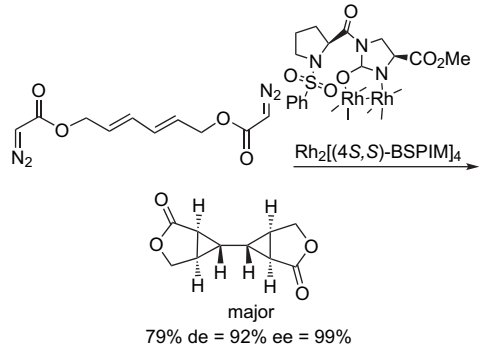
Scheme 112. Asymmetric intramolecular cyclopropanation of allyl diazoacetates catalysed by $Rh_2[(4S)\text{-MPPIM}]_4$.

Furthermore, the asymmetric intramolecular cyclopropanation of various allyl diazoacetates has been performed by Che et al. in the presence of a rhodium D_4-porphyrin catalyst, leading to the corresponding cyclopropanated products with moderate enantioselectivities, as shown in Scheme 113 (cat1).[168] In addition, Lahuerta et al. have developed similar reactions in the presence of dirhodium complexes bearing bulky *ortho*-metallated arylphosphines as catalysts, furnishing the corresponding cycloadducts in high yield and moderate enantioselectivity (Scheme 113, cat2).[171c,230] In 2006, Pérez-Prieto et al. reported the use of other chiral dirhodium(II) catalysts, bearing *ortho*-metallated arylphosphane ligands, in the enantioselective intramolecular cyclopropanation of 1-diazo-6-methyl-3-(2-propenyl)-5-hepten-2-one.[231] An excellent enantiocontrol was observed, since ee values of up to 90% were obtained. A similar methodology was previously employed by these workers to elaborate a total synthesis of sabina lactone.[232]

In 2005, Doyle et al. reported an original sequence of two successive intramolecular cyclopropanations involving a bis-diazoacetate, using a sterically encumbered oxaimidazolidine carboxylate dirhodium(II) catalyst, $Rh_2[(4S,S)\text{-BSPIM}]_4$.[233] An excellent result, depicted in Scheme 114, was obtained resulting from a double diastereoselection.



Scheme 113. Asymmetric intramolecular cyclopropanation of allyl diazoacetates catalysed by rhodium(I) porphyrin catalyst or dirhodium catalyst with bulky *ortho*-metallated arylphosphines.

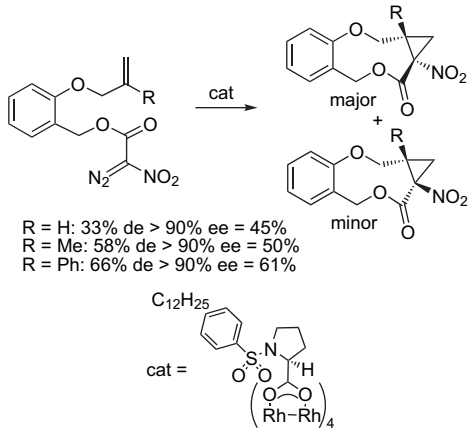


Scheme 114. Double intramolecular cyclopropanation of bis-diazoacetate catalysed by $Rh_2[(4S,S)\text{-BSPIM}]_4$.

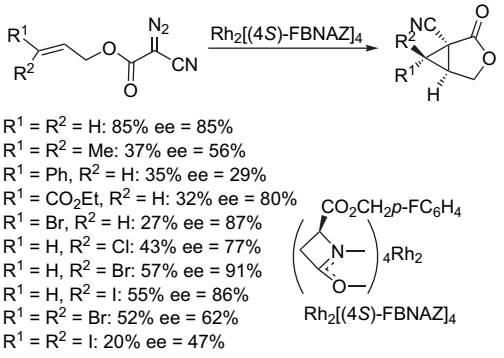
In recent years, the variety of useful diazo substrates for asymmetric intramolecular cyclopropanation processes has expanded. As an example, Charette et al. have reported the first example of an intramolecular cyclopropanation involving α-nitro-α-diazo carbonyl compounds.[106b] The reaction, catalysed by a Rh(II) carboxylate complex, led to the formation of nine-membered nitrocyclopropyl lactones in good yield and enantioselectivity with extremely high diastereoselectivity (Scheme 115). This novel methodology constitutes an effective entry into chiral functionalised macrocyclic-fused cyclopropane α-amino acids.

In 2005, Charette et al. demonstrated that the Rh-catalysed intramolecular cyclopropanation of 3-substituted-2-propenyl cyanodiazoacetates occurred cleanly to form the corresponding cyclopropane derivatives in high yields. Enantioselectivity of up to 91% ee was observed when using $Rh_2[(4S)\text{-FBNAZ}]_4$ as the chiral catalyst (Scheme 116).[234] The level of enantioselection was shown to be greatly dependent upon the substitution of the alkene.

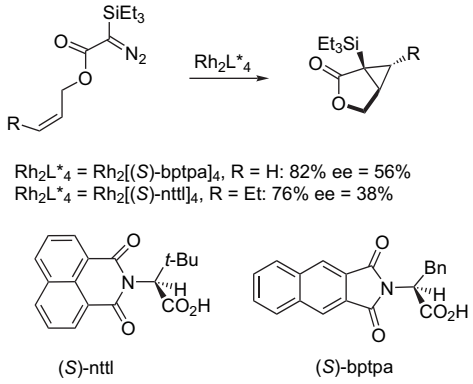
In 2004, Müller et al. reported the Rh-catalysed cyclopropanation of several (triethylsilyl)-substituted allyl diazoacetates.[156] As shown in Scheme 117, the use of chiral Rh(II) carboxamidate catalysts



Scheme 115. Asymmetric intramolecular cyclopropanation of α-nitro-α-diazo carbonyl compounds.



Scheme 116. Asymmetric intramolecular cyclopropanation of 3-substituted-2-propenyl cyanodiazoacetates.

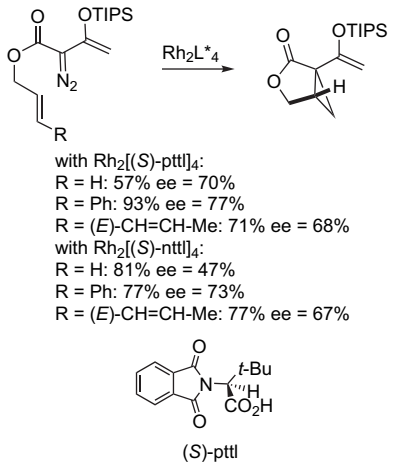


Scheme 117. Asymmetric intramolecular cyclopropanation of (triethylsilyl)-substituted allyl diazoacetates.

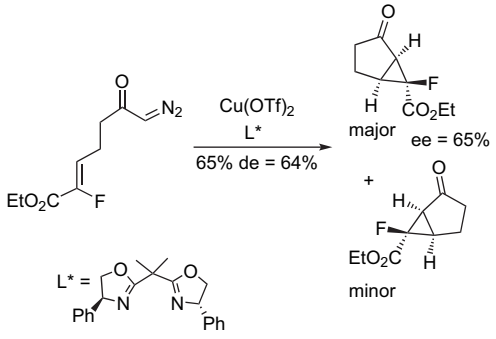
allowed enantioselectivities comparable to those resulting from the unsilylated analogues (up to 56% ee) to be reached.

In 2005, the scope of this methodology was extended to allyl 2-diazo-3-silanyloxybut-3-enoates, providing the corresponding lactones with good enantioselectivity, as shown in Scheme 118.[154b,235]

On the other hand, several Cu-catalysed enantioselective intramolecular cyclopropanations have been described in recent years, most of which have involved chiral bisoxazoline ligands. As an example, Wong et al. have developed the preparation of an enantiopure fluorobicycloketone on the basis of a Cu-catalysed intramolecular cyclopropanation of the corresponding fluorodiazoketone in the presence of a bisoxazoline ligand (Scheme 119).[236]



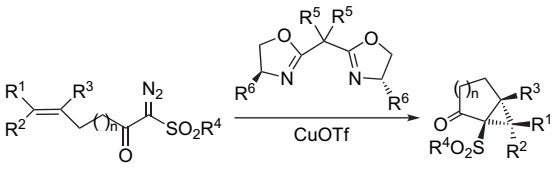
Scheme 118. Asymmetric intramolecular cyclopropanation of allyl 2-diazo-3-silanyloxybut-3-enoates.



Scheme 119. Asymmetric intramolecular cyclopropanation of a fluorodiazoketone.

In the same context, Nakada et al. have reported a number of highly enantioselective Cu-catalysed intramolecular cyclopropanations of a range of α-diazo-β-keto sulfones.[237] As shown in Scheme 120, high enantioselectivities were obtained for all the substrates.

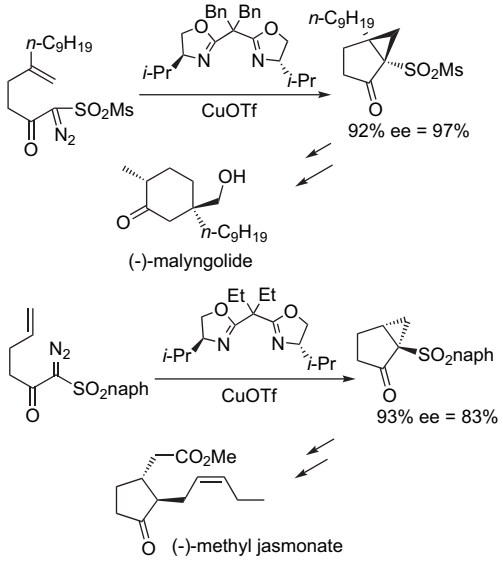
Furthermore, the success of this methodology has been applied to the total syntheses of several natural biologically active products,



$R^1 = R^2 = R^3 = H$, $R^4 = Ph$, $R^5 = Bn$, $R^6 = i\text{-Pr}$,
n = 1: 61% ee = 73%
$R^1 = R^2 = R^3 = H$, $R^4 = Ms$, $R^5 = Bn$, $R^6 = i\text{-Pr}$,
n = 1: 87% ee = 93%
$R^1 = R^2 = H$, $R^3 = R^5 = Me$, $R^4 = Ms$, $R^6 = i\text{-Pr}$,
n = 1: 96% ee = 81%
$R^1 = R^2 = H$, $R^3 = Br$, $R^4 = Ms$, $R^5 = Me$, $R^6 = i\text{-Pr}$,
n = 1: 68% ee = 92%
$R^1 = R^2 = R^5 = Me$, $R^3 = H$, $R^4 = Ms$, $R^6 = i\text{-Pr}$,
n = 1: 74% ee = 74%
$R^1 = R^2 = H$, $R^3 = CH_2OTr$, $R^4 = Ms$, $R^5 = Me$, $R^6 = i\text{-Pr}$,
n = 1: 91% ee = 78%
$R^1 = R^2 = R^3 = H$, $R^4 = Ph$, $R^5 = Me$, $R^6 = i\text{-Pr}$,
n = 2: 58% ee = 92%
$R^1 = R^2 = H$, $R^3 = Me$, $R^4 = Ph$, $R^5 = Bn$, $R^6 = i\text{-Pr}$,
n = 2: 62% ee = 93%
$R^1 = R^2 = R^3 = H$, $R^4 = Ms$, $R^5 = Bn$, $R^6 = i\text{-Pr}$,
n = 2: 31% ee = 98%
$R^1 = R^2 = H$, $R^3 = Me$, $R^4 = Ms$, $R^5 = Bn$, $R^6 = i\text{-Pr}$,
n = 2: 43% ee = 98%

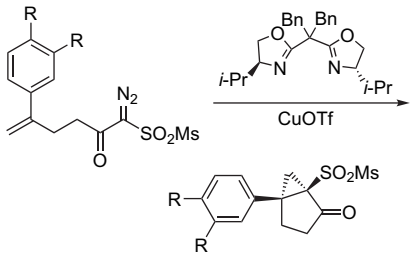
Scheme 120. Asymmetric intramolecular cyclopropanation of α-diazo-β-keto sulfones.

such as (−)-allocyathin B_2,[238] (−)-malyngolide[239] and (−)-methyl jasmonate (Scheme 121).[240]



Scheme 121. Syntheses of (−)-malyngolide and (−)-methyl jasmonate.

In 2005, Nakada et al. examined the intramolecular cyclopropanation of 5-aryl-1-diazo-1-mesitylsulfonyl-5-hexen-2-ones, and found that the substituent of the 5-aryl group dramatically changed the enantioselectivity.[241] Thus, no selectivity was observed when the substituent was a methoxy group, but the enantioselectivity was moderate when the substituent was a methylenedioxy or a *tert*-butyldimethylsilyloxy group, and dramatically increased when the substituent was lacking (96% ee) or was a benzoyloxy group (93% ee), as shown in Scheme 122.

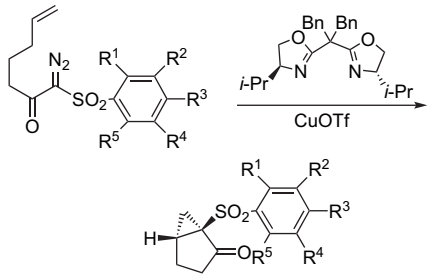


R = H: 95% ee = 96%
R = OBz: 96% ee = 93%
R,R = OCH_2O: 86% ee = 55%
R = OMe: 55% ee = 0%
R = OTBS: 77% ee = 55%

Scheme 122. Asymmetric intramolecular cyclopropanation of 5-aryl-1-diazo-1-mesitylsulfonyl-5-hexen-2-ones.

In 2006, other studies on structure–enantioselectivity relationships in the intramolecular cyclopropanation of α-diazo-β-keto sulfones bearing a methyl-substituted phenyl group were reported by the same group.[242] It was shown that the enantioselectivity of the reaction was varied by the position of the methyl group on the phenyl sulfone, and the 2-methyl group of the phenyl sulfonyl group was important to attain a high enantioselectivity (Scheme 123).

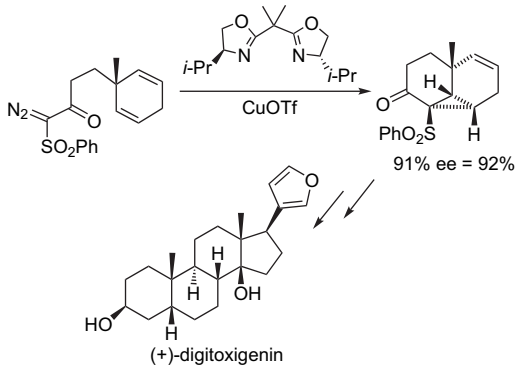
As an application of this methodology, Nakada et al. reported, in 2007, an enantioselective total synthesis of (+)-digitoxigenin, on the basis of an intramolecular cyclopropanation of an α-diazo-β-keto



$R^1 = R^2 = R^3 = R^4 = R^5 = H$: 61% ee = 73%
$R^1 = Me$, $R^2 = R^3 = R^4 = R^5 = H$: 98% ee = 86%
$R^2 = Me$, $R^1 = R^3 = R^4 = R^5 = H$: 97% ee = 77%
$R^1 = R^2 = R^4 = R^5 = H$, $R^3 = Me$: 95% ee = 69%
$R^1 = R^2 = Me$, $R^3 = R^4 = R^5 = H$: 82% ee = 91%
$R^1 = R^4 = Me$, $R^2 = R^3 = R^5 = H$: 90% ee = 82%
$R^1 = R^5 = Me$, $R^2 = R^3 = R^4 = H$: 98% ee = 86%

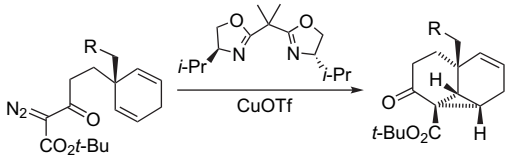
Scheme 123. Asymmetric intramolecular cyclopropanation of α-diazo-β-keto sulfones.

sulfone bearing a cyclohexadiene moiety (Scheme 124).[243] This reaction provided highly efficiently a chiral tricyclic cyclopropane, which was further converted into the desired natural cardenolide.

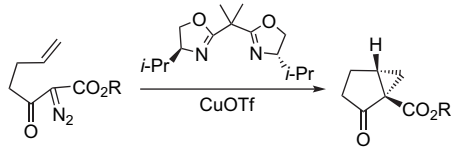


Scheme 124. Total synthesis of (+)-digitoxigenin.

In the same context, Nakada et al. developed, in 2007, the enantioselective preparation of tricyclo[4.4.0.0^{5,7}]dec-2-ene derivatives via catalytic asymmetric intramolecular cyclopropanation of α-diazo-β-keto esters with excellent enantioselectivity (95–98% ee), as shown in Scheme 125.[244] The resulting chiral cyclopropanes could be utilised as versatile intermediates for enantioselective natural product syntheses, including the preparation of



R = H: 78% ee = 95%
R = OTBS: 84% ee = 95%

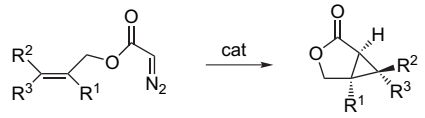


R = Me: 68% ee = 56%
R = MeCHBn: 77% ee = 48%
R = 2,4,6-$(Me)_3C_6H_2$: 74% ee = 53%
R = 2,6-$(t\text{-}Bu)_2$-4-MeC_6H_2: 92% ee = 77%

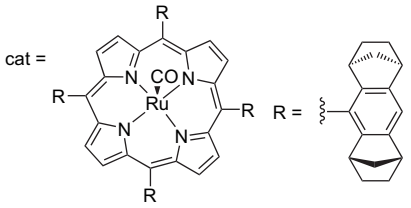
Scheme 125. Asymmetric intramolecular cyclopropanation of α-diazo-β-keto esters.

(+)-busidarasin C and acetoxytubipofuran. The same methodology was also applied to the intramolecular cyclopropanation of various 2-diazo-3-oxo-6-heptenoic acid esters, affording the corresponding bicyclic cyclopropanes in low-to-high ees, depending upon the nature of the ester group.[245] Indeed, the best enantioselectivities were obtained in the case of substrates bearing a bulky ester group (Scheme 125).

On the other hand, several chiral ruthenium complexes have been used, in recent years, to catalyse the intramolecular cyclopropanation of allyl diazoacetates. As an example, Che et al. have studied the cyclopropanation of allyl diazoacetates in the presence of a ruthenium D_4-porphyrin, leading to the corresponding lactones in moderate-to-high enantioselectivities, as shown in Scheme 126.[168]

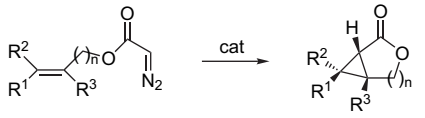


$R^1 = R^2 = H$, $R^3 = Ph$: 77% ee = 85%
$R^1 = H$, $R^2 = R^3 = Me$: 65% ee = 36%
$R^1 = H$, $R^2 = i\text{-}Pr\text{-}(CH_2)_2$, $R^3 = Me$: 85% ee = 30%

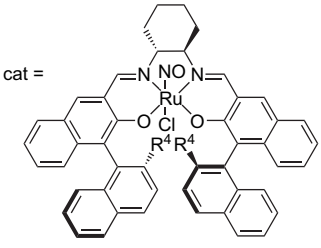


Scheme 126. Asymmetric intramolecular cyclopropanation of allyl diazoacetates.

A few types of chiral salen ligands have been demonstrated by Katsuki et al. to be efficient ligands of ruthenium to induce chirality for the intramolecular cyclopropanation of various alkenyl α-diazoacetates (Scheme 127).[200,246] It was demonstrated that the



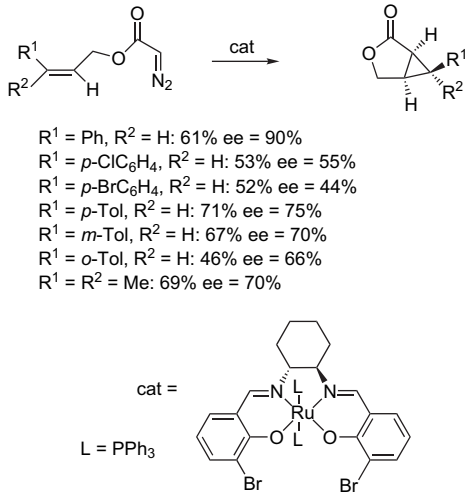
$R^1 = p\text{-}BrC_6H_4$, $R^2 = R^3 = H$, $R^4 = Me$, n = 1: 56% ee = 87%
$R^1 = p\text{-}MeOC_6H_4$, $R^2 = R^3 = H$, $R^4 = Me$, n = 1: 63% ee = 87%
$R^1 = Ph\text{-}C{\equiv}C$, $R^2 = R^3 = H$, $R^4 = Me$, n = 1: 51% ee = 79%
$R^1 = p\text{-}ClC_6H_4$, $R^2 = R^3 = H$, $R^4 = Me$, n = 3: 44% ee = 89%
$R^1 = p\text{-}MeOC_6H_4$, $R^2 = R^3 = H$, $R^4 = Me$, n = 3: 72% ee = 77%
$R^1 = R^2 = R^3 = H$, $R^4 = Me$, n = 3: 46% ee = 33%
$R^1 = Ph$, $R^2 = R^3 = H$, $R^4 = Me$, n = 3: 63% ee = 88%
$R^1 = (Me)_2C{=}CH(CH_2)_2$, $R^2 = Me$, $R^3 = H$, $R^4 = Ph$, n = 2: 44% ee = 89%
$R^1 = R^2 = Me$, $R^3 = H$, $R^4 = Ph$, n = 2: 65% ee = 87%
$R^1 = Ph\text{-}C{\equiv}C$, $R^2 = R^3 = H$, $R^4 = Ph$, n = 2: 82% ee = 84%
$R^1 = R^3 = H$, $R^2 = R^4 = Ph$, n = 2: 62% ee = 79%



Scheme 127. Asymmetric intramolecular cyclopropanation of alkenyl α-diazoacetates.

cyclisation was strongly affected by several factors, such as the substitution pattern of the alkenyl group of the substrate and the length and the nature of the linker connecting the alkenyl and diazomethyl moieties.

In the same context, Che et al. examined, in 2006, the efficiency of another ruthenium–salen complex containing a PPh_3 ligand for the intramolecular cyclopropanation of cis-substituted allylic diazoacetates.[247] The corresponding cycloadducts were obtained in up to 90% ee, as shown in Scheme 128.

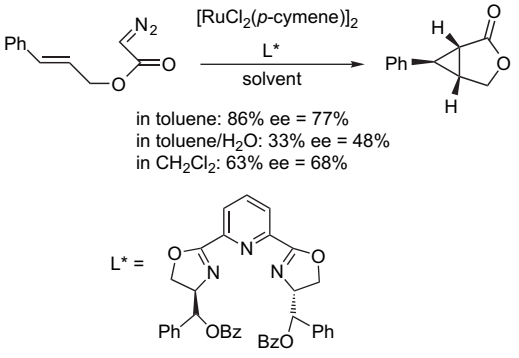


Scheme 128. Asymmetric intramolecular cyclopropanation of cis-substituted allylic diazoacetates.

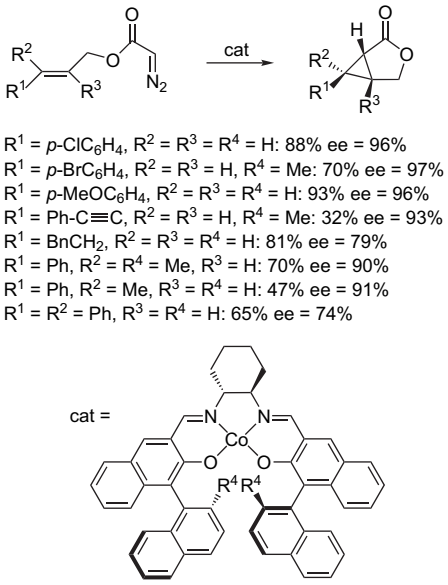
On the other hand, Nishiyama et al. have performed the intramolecular cyclopropanation of a *trans* cinnamyl diazoester in the presence of a Ru(Pybox) catalyst, which allowed enantioselectivities of up to 77% ee to be obtained (Scheme 129).[191] This catalyst could be used in biphasic media, but with a lower enantioselectivity.

Furthermore, asymmetric intramolecular cyclopropanations of diazo compounds have also involved chiral cobalt catalysts. These catalysts were found to be superior to the corresponding Ru(II)-(salen) complexes, since high enantioselectivities (up to 97% ee) were observed in almost all of the substrates studied, as shown in Scheme 130.[246]

Finally, Llusar et al. have investigated novel chiral Mo_3CuS_4 clusters for the asymmetric intramolecular cyclopropanation of 1-diazo-5-hexen-2-one.[216] The corresponding cyclopropanated product was obtained in 84% yield, but with only 25% ee.



Scheme 129. Asymmetric intramolecular cyclopropanation of *trans* cinnamyl diazoester.



Scheme 130. Asymmetric intramolecular cyclopropanation of alkenyl α-diazoacetates catalysed by Co(II)(salen) complexes.

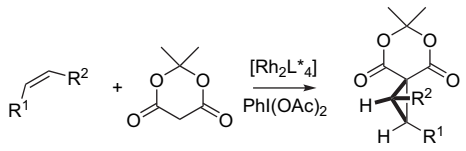
5. Miscellaneous methods

Various other methods have been developed over the last few years to access chiral enantioenriched cyclopropanes. This section describes these unrelated reactions, which cannot be included in Sections 2–4, because of their different mechanisms.

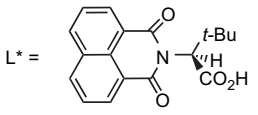
5.1. Asymmetric transfer of carbenes with phenyliodonium ylides

Asymmetric carbene transfer involving diazo decomposition is almost exclusively restricted to the research laboratory, and only a few industrial large-scale processes are known.[248] A possible reason for this lack of applications may be the often unjustified prejudice with regard to diazo compounds and the reagents used to prepare them, which are believed to be toxic, carcinogenic and potentially explosive. The development of carbine-transfer reactions avoiding diazo precursors is therefore of considerable interest. Several approaches to circumvent the isolation of these carbene precursors have been proposed, such as thermolysis of tosylhydrazone salts of carbonyl compounds,[249] and in situ diazotisation/decomposition of amino compounds in the presence of transition-metal catalysts.[250] These methods have, however, not found general application to date. Over the past few years, Müller and Ghanem have investigated phenyliodonium ylides as potential substitutes for diazo compounds in the transition-metal-catalysed transfer of carbenes.[154b,251] These authors have shown that phenyliodonium ylides, prepared in situ from 1,3-dicarbonyl compounds, react upon decomposition with Rh(II) catalysts via the same reactive intermediates as the corresponding diazo compounds, and exhibit the typical characteristics of carbine-transfer reactions. The chemo- and enantioselectivities of these reactions are identical to those of the corresponding diazo compounds, indicating metallocarbene intermediates with both precursors. An exception to this rule occurs in the intramolecular cyclopropanation of phenyliodonium ylides, in which a competing uncatalysed and unselective pathway occurs at room temperature. Furthermore, phenyliodonium ylides are readily accessible by the reaction of C–H acidic compounds with iodobenzene diacetate, or iodosylbenzene, and their decomposition occurs at temperatures well below those required for diazo decomposition. In 2003, Müller

et al. reported that the phenyliodonium ylide derived in situ from Meldrum's acid reacted with olefins in the presence of a chiral Rh(II) carboxylate catalyst to afford the corresponding cyclopropanes in good yields and with enantioselectivities of up to 72% ee (Scheme 131).[251a,252] These results were comparable to those resulting from cyclopropanation with the isolated ylide.



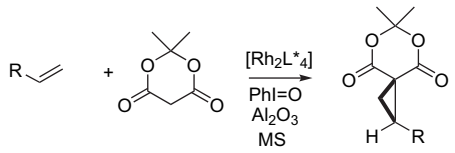
R^1 = Ph, R^2 = H: 90% ee = 43%
R^1 = H, R^2 = *n*-Pr: 56% ee = 70%
R^1 = Me, R^2 = CH=CH_2: 50% ee = 33%
R^1 = Me, R^2 = Et: 93% ee = 63%
R^1 = H, R^2 = CH=CH_2: 70% ee = 72%



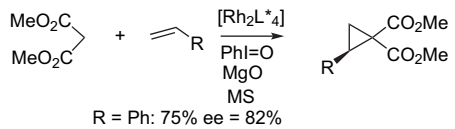
(*S*)-nttl

Scheme 131. Asymmetric cyclopropanation with phenyliodonium ylide derived from Meldrum's acid.

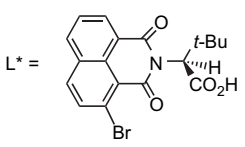
More satisfactory results were obtained by these authors by using iodosylbenzene instead of iodobenzene diacetate in the presence of either MgO or Al_2O_3 and molecular sieves as the oxidant for the generation of the ylide.[253] The reactions were performed in the presence of (*S*)-*N*-4-bromo-1,8-naphthanoyl-*tert*-leucine as the chiral ligand. The olefin cyclopropanation with Meldrum's acid gave, in these conditions, the corresponding cyclopropanes with enantioselectivities of up to 92% ee, as shown in Scheme 132. Moreover, the scope of this methodology was extended to the use of dimethyl malonate as a precursor of the phenyliodonium ylide, providing the corresponding cyclopropane-1,1-dicarboxylates in high yields and enantioselectivities in almost all of the olefins studied (Scheme 132). On the other hand, a low



R = Ph: 76% ee = 92%
R = CH=CH_2: 65% ee = 87%



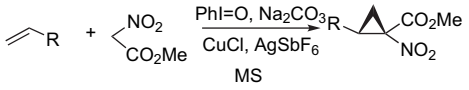
R = Ph: 75% ee = 82%
R = *p*-ClC_6H_4: 71% ee = 65%
R = *p*-BrC_6H_4: 65% ee = 90%
R = *p*-$CF_3C_6H_4$: 63% ee = 87%
R = *p*-Tol: 62% ee = 87%
R = *n*-Pr: 56% ee = 98%



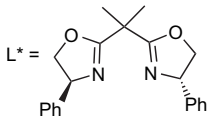
Scheme 132. Asymmetric cyclopropanations with phenyliodonium ylides derived from Meldrum's acid or dimethyl malonate in the presence of PhI=O.

enantioselectivity (26% ee) was obtained for the cyclopropanation of the dihydrofuranyl phenyliodonium ylide derived from Meldrum's acid in the presence of Rh_2[(*S*)-nttl]$_4$.[254]

In 2005, Charette et al. reported the highly efficient use of a Cu(I) catalyst bearing a chiral bisoxazoline as ligand for the asymmetric cyclopropanation of a range of alkenes with the phenyliodonium ylide derived from methyl nitroacetate.[255] The corresponding cyclopropanes were obtained in good yields, and with excellent diastereo- and enantioselectivities in all of the substrates studied (Scheme 133), whereas the involvement of a chiral Rh(II) catalyst, such as Rh_2[(*S*)-ptpa]$_4$, in the presence of iodobenzene diacetate, gave rise to low enantioselectivities.[256] Hence, the reaction of styrene gave, in these conditions, the corresponding cyclopropane in 74% yield and with 30% ee (for *E*-isomer). This novel methodology constituted a convenient synthesis of cyclopropane α-amino acids.



R = Ph: 82% de = 88% ee = 91%
R = *p*-ClC_6H_4: 45% de = 84% ee = 91%
R = *p*-$MeOC_6H_4$: 71% de = 86% ee = 68%
R = *p*-Tol: 76% de = 86% ee = 92%
R = 1-Naph: 53% de = 86% ee = 91%
R = 2-Naph: 74% de = 82% ee = 91%
R = 2,4,6-$(Me)_3C_6H_2$: 54% de = 90% ee = 93%
R = *p*-(*t*-Bu)C_6H_4: 80% de = 86% ee = 90%
R = CH=CH_2: 84% de = 64% ee = 90%



Scheme 133. Asymmetric cyclopropanation with phenyliodonium ylide derived from methyl nitroacetate.

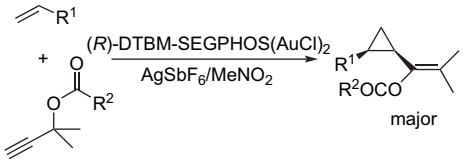
5.2. Chiral metal stoichiometric carbenes

Transfer of carbene ligands from optically active transition-metal–carbene complexes to alkenes represents a potentially useful and general method for the enantioselective synthesis of cyclopropanes.[257] Although not used extensively, success has been achieved with iron-,[258] chromium-, gold- and tungsten-derived carbene systems. In 2005, Dean Toste et al. developed an asymmetric Au-catalysed cyclopropanation of alkenes, using propargyl esters as Au(I)-carbene precursors.[259] A ligand optimisation identified DTBM-SEGPHOS-Au(I) as the catalyst of choice for the enantioselective preparation of vinylcyclopropanes with high cis-selectivity and enantioselectivity, as shown in Scheme 134.

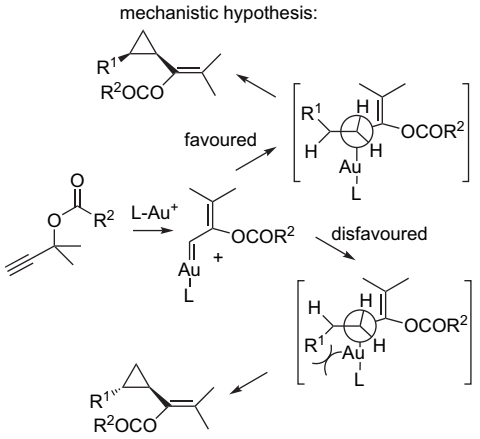
In 2007, Barluenga et al. examined the reactivity of chiral Fischer carbene complexes derived from tungsten in the cyclopropanation of 2-methoxyfuran, providing the corresponding polyfunctionalised cyclopropylcarbenes with good stereoselectivity.[260] The reaction involved the conjugate nucleophilic addition of 2-methoxyfuran to the carbene complex, followed by ring closure of the resulting zwitterionic intermediate species. A further oxidation of the resulting carbene gave rise to the formation of the corresponding enantiopure 1,2,3-trisubstituted cyclopropane (Scheme 135).

5.3. Rearrangement of chiral oxiranes

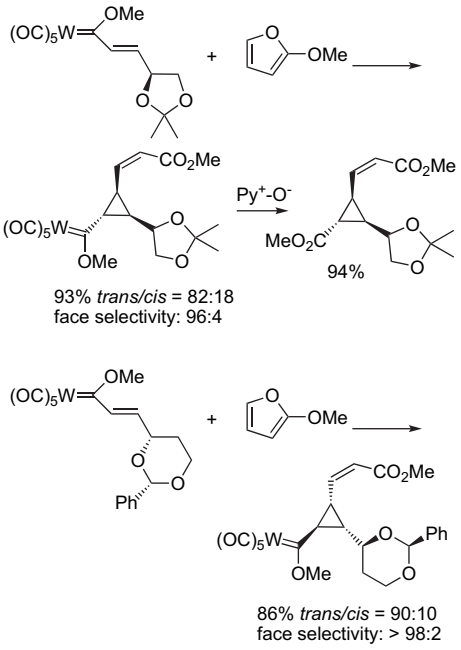
Chiral cyclopropanes have also been elaborated from chiral 1,2-electrophiles such as epichlorohydrins by reaction with a nucleophile such as a stabilised carbanion. Two pathways are possible for



R^1 = Ph, R^2 = Me: 72% de > 90% ee = 60%
R^1 = R^2 = Ph: 73% de > 90% ee = 68%
R^1 = Ph, R^2 = *t*-Bu: 70% de > 90% ee = 81%
R^1 = *o*-Tol, R^2 = Piv: 83% de > 90% ee = 81%
R^1 = *p*-(*t*-Bu)C_6H_4, R^2 = Piv: 82% de > 90% ee = 81%
R^1 = *o*-BrC_6H_4, R^2 = Piv: 60% de > 90% ee = 76%
R^1 = *m*-ClC_6H_4, R^2 = Piv: 69% de > 90% ee = 76%
R^1 = *p*-FC_6H_4, R^2 = Piv: 85% de > 90% ee = 82%
R^1 = 2,6-$(Me)_2$-4-(*t*-Bu)C_6H_2, R^2 = Piv: 71% de > 90% ee = 94%
R^1 = 1-Naph, R^2 = Piv: 79% de > 90% ee = 85%
R^1 = CH_2TMS, R^2 = Piv: 74% de = 66% ee = 78%

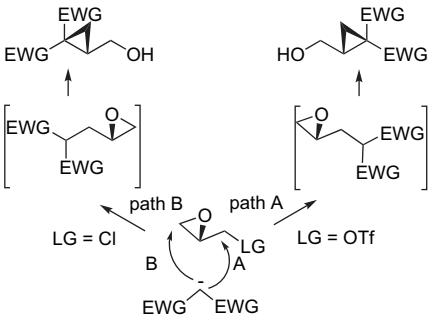


Scheme 134. Au-catalysed cyclopropanation of olefins with propargyl esters.



Scheme 135. Asymmetric cyclopropanations with Fischer tungsten-derived carbene complexes.

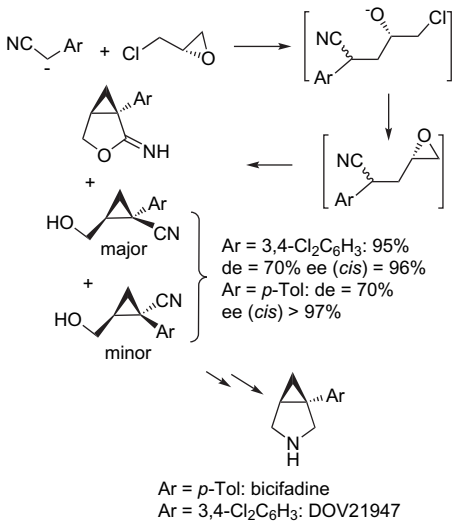
the double displacement of epichlorohydrins, which are dependent upon the nature of the leaving group. In path A of Scheme 136, the direct displacement of the leaving group is followed by the ring



Scheme 136. Synthesis of chiral cyclopropanes from chiral epoxides.

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

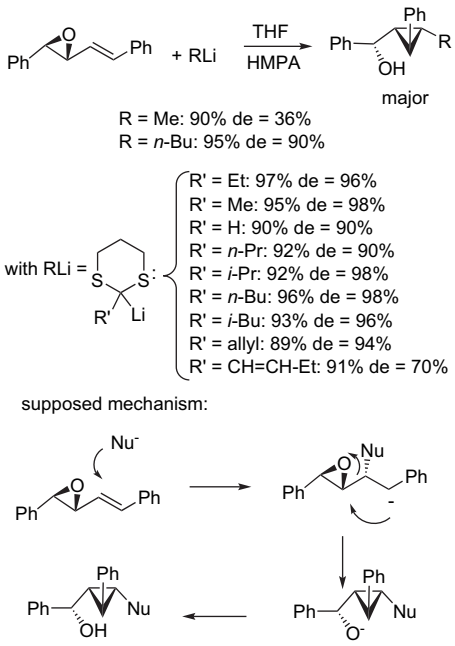
In 2006, Xu et al. reported the coupling of arylacetonitriles with chiral halohydrins, affording the corresponding hydroxyl nitriles in high ees and yields according to path B, in which the stereocontrol was achieved through manipulating the nitrile anion aggregation state (Scheme 137).[261] This methodology was successfully applied to the total syntheses of two neurotransporters, bicifadine and DOV21947, in a single-stage process without the isolation of any intermediates.



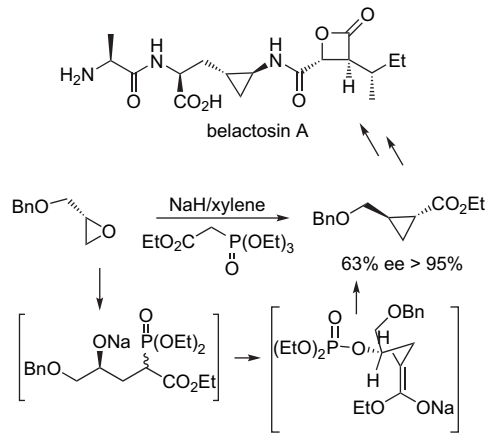
Scheme 137. Asymmetric epoxy nitrile coupling.

On the other hand, She et al. have shown that the reaction of a chiral phenylvinyl epoxide with a lithiated 2-alkyl-1,3-dithiane or a lithiated alkyl carbanion in the presence of HMPA led to the formation of the corresponding cyclopropanes bearing stereochemistry at all three positions on the ring in high yields and des (Scheme 138).[262] The reaction was considered to be a tandem conjugation addition–epoxide opening sequence.

In 2003, Armstrong et al. reported a Wadsworth–Emmons cyclopropanation reaction of (*S*)-glycidol benzyl ether, which led to the corresponding enantiopure cyclopropane in good yield and high enantioselectivity, as shown in Scheme 139.[263] 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. A total synthesis of a potent



Scheme 138. Asymmetric cyclopropanation of phenylvinyl epoxide with lithiated carbanions.



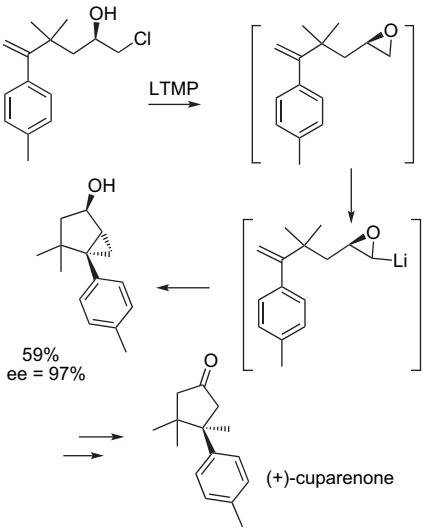
Scheme 139. Asymmetric Wadsworth–Emmons cyclopropanation reaction.

antitumour agent, belactosin A, could be developed by the application of this process.

In addition, several examples of intramolecular opening of chiral epoxides have been recently reported, such as the Et_3Al-mediated intramolecular epoxide opening with a fluoro ester enolate, as shown in Scheme 140.[264] This transformation provided highly functionalised bicyclo[3.1.0]hexane systems in high efficiency and with perfect F-*endo* selectivity. This procedure was applied to the total syntheses of metabotropic glutamate receptor agonists (mGluR2/3 agonists).

Scheme 140. Asymmetric Et_3Al-mediated intramolecular opening of epoxide.

In 2007, Hodgson et al. developed intramolecular cyclopropanations of unsaturated terminal epoxides and chlorohydrins induced by treatment with LTMP.[265] Thus, the chiral chlorohydrin depicted in Scheme 141 was converted into the corresponding cyclopropanol using LTMP, presumably via an in situ epoxide formation. This epoxide formed the corresponding lithiated epoxide, which reacted with the tethered alkene, affording the final cyclopropanol. The synthetic utility of this methodology was demonstrated in the elaboration of a concise total synthesis of (+)-cuparenone.



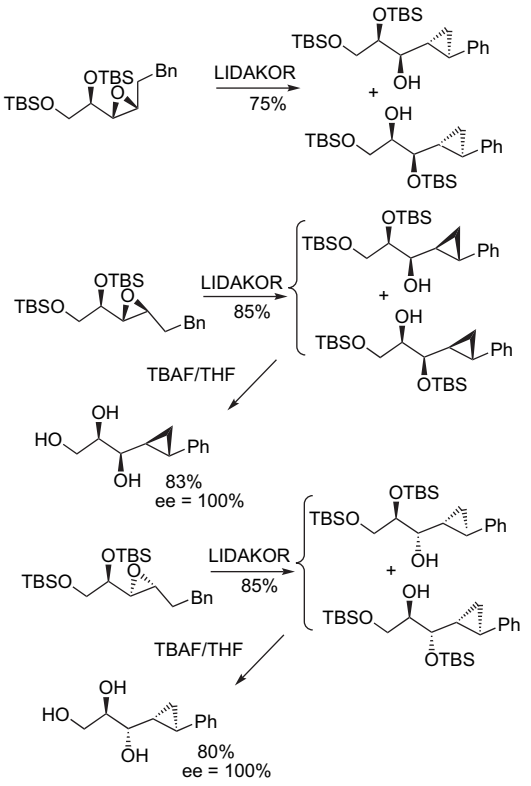
Scheme 141. Asymmetric LTMP-mediated intramolecular cyclopropanation of chlorohydrin.

On the other hand, Mordini et al. have demonstrated that superbasic mixtures such as LIDAKOR could be conveniently used for the 3-*exo* cyclisation of suitably substituted oxiranes lacking strong electron-withdrawing substituents.[266] The reaction was highly stereoselective, leading to the corresponding *trans* cyclopropanes. As depicted in Scheme 142, changes in the configuration of the starting chiral oxirane ring, or in the relative stereochemistry of the silyloxy substituent, did not affect the outcome of the rearrangement process. Indeed, in all cases, the reaction mixture actually contained two isomers, which turned out to be those derived from a *tert*-butyldimethylsilyl group migration from one oxygen to the neighbouring oxygen during the isomerisation process. This was further demonstrated by fluoride deprotection of all the silylated hydroxyl groups of the products, affording the corresponding triols (Scheme 142).

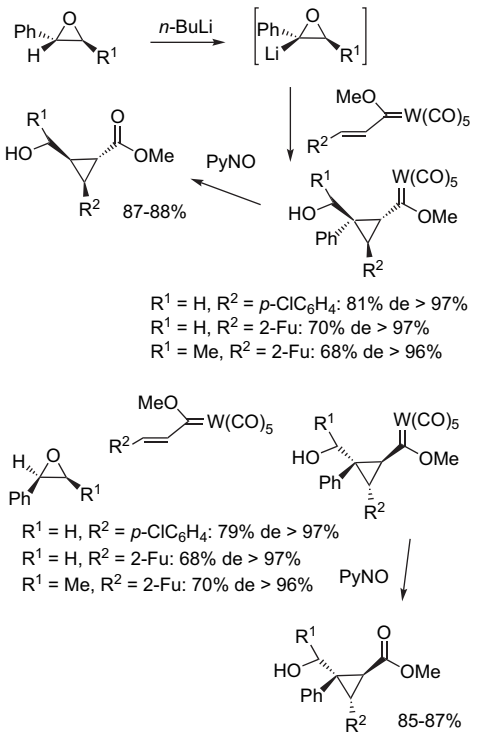
The utility of lithiated chiral oxiranes as nucleophiles was also exploited by Florio et al., in 2005, by condensing these species onto α,β-unsaturated Fischer tungsten-derived carbene complexes, diastereo- and enantiospecifically, providing the corresponding tetrasubstituted cyclopropane carbenes, which were further converted into the corresponding cyclopropanecarboxylates (Scheme 143).[267]

5.4. Denitrogenation of chiral pyrazolines

The decomposition of pyrazolines has proved to be an excellent method for the preparation of cyclopropanes.[268] In particular, the photochemical denitrogenation of chiral pyrazolines is a method extensively used in organic synthesis to prepare chiral cyclopropane derivatives. The mechanism of these reactions has been controversial for long time. At present, it is accepted that these processes generally involve diradicals, although the mode of

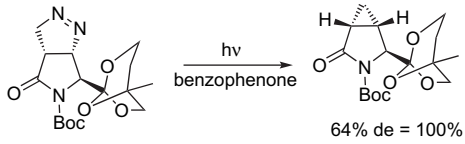


Scheme 142. LIDAKOR-promoted rearrangements of oxiranes to cyclopropanes.



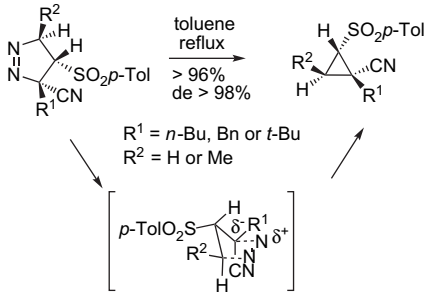
Scheme 143. Asymmetric cyclopropanations of α,β-unsaturated Fischer carbene complexes with lithiated oxiranes.

formation and their structure as singlets or triplets may vary with the substrate and the reaction conditions.[269] The presence of a photosensitiser is often required for the reaction to take place efficiently and to avoid the formation of byproducts such as cycloreversion or insertion olefins. As an example, Oba et al. have reported the photolysis of a chiral pyrazoline, performed in the presence of benzophenone as a photosensitiser, affording the corresponding cycloadduct as a unique isomer (Scheme 144).[270] This reaction was applied to the syntheses of pharmacologically important cyclopropane amino acids, such as L-(carboxycyclopropyl)glycines and 3,4-didehydro-L-prolines.



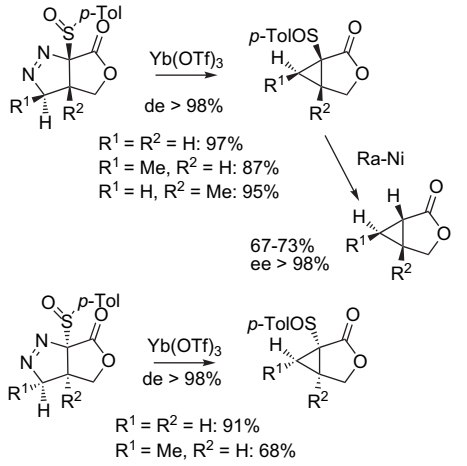
Scheme 144. Photolysis of pyrazoline.

Although the thermal extrusion of nitrogen from pyrazolines mainly gives olefins, examples are also known yielding cyclopropanes as the main products. The use of these processes in asymmetric synthesis has, however, only been occasionally exploited, because of their usually low stereoselectivity. In this context, Garcia Ruano et al. have developed a successful thermolysis of chiral sulfonylpyrazolines containing a quaternary carbon bearing an electron-withdrawing group (CN), providing completely stereoselectively the corresponding cyclopropanes containing a quaternary chiral centre.[271] This extrusion took place in very high yield and with complete retention of configuration of all the chiral centres, in all of the substrates studied, as shown in Scheme 145. These results were consistent with the concerted thermal decomposition, proposed by McGreer, of a series of 4- and 5-alkyl-substituted 3-methyl-3-methoxycarbonyl-Δ^1-pyrazolines, which afforded the corresponding cyclopropanes by extrusion of nitrogen through a polar transition state (Scheme 145).

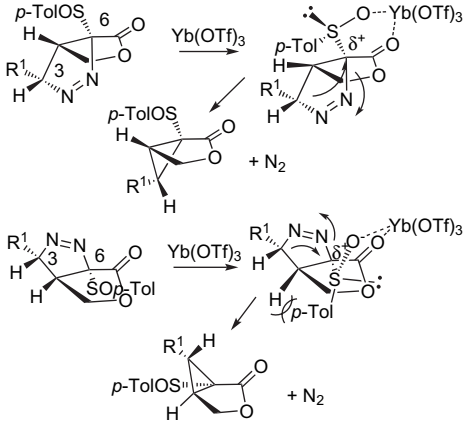


Scheme 145. Thermolysis of sulfonylpyrazolines.

In addition, these authors have described the completely stereoselective denitrogenation of chiral sulfinylpyrazolines into the corresponding cyclopropanes, performed in the presence of a substoichiometric amount of $Yb(OTf)_3$ under very mild conditions and in almost quantitative yields (Scheme 146).[272] The reaction evolved with complete retention of configuration at both carbons flanking the nitrogen atoms, resulting in the formation of enantiomerically pure polysubstituted cyclopropanes, containing up to five substituents, which could be further desulfinylated by treatment with Ra-Ni, providing chiral polysubstituted cyclopropanecarboxylic acid derivatives. This cyclopropane formation could be explained as depicted in Scheme 146. Initially, the metal forms a chelated species with the sulfinyl and carbonyl oxygens, which increases the electronic deficiency at C6 and provokes the concerted migration of C3 (from nitrogen to C6) with extrusion of nitrogen. Indeed, this process affords cyclopropanes with retention of configuration at the migrating carbon.



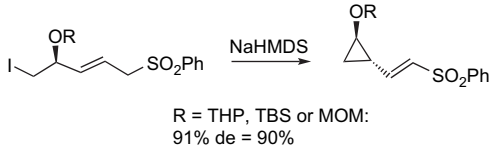
stereochemical course of denitrogenation:



Scheme 146. $Yb(OTf)_3$-catalysed denitrogenations of sulfinylpyrazolines.

5.5. Other ring-closing reactions of chiral precursors

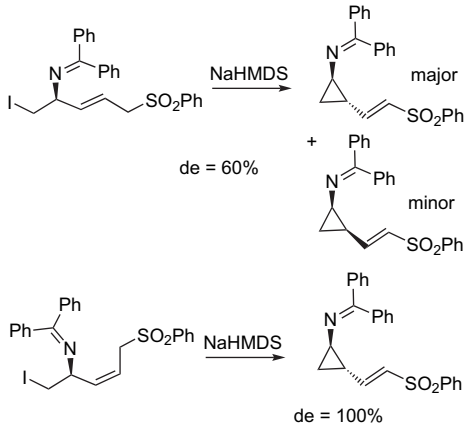
Various other ring-closure reactions forming chiral cyclopropanes have been recently reported. As an example, Diez et al. have developed a highly diastereoselective synthesis of chiral cyclopropanols substituted with a vinyl sulfone by treatment of allylic sulfones, depicted in Scheme 147, with a base such as LDA,[273] or HMDSA.[274] This methodology has opened the way for the synthesis of a large variety of cyclopropanol amino acids due to its simplicity, high yield and high diastereocontrol.[275]



Scheme 147. Asymmetric cyclopropanation of alkoxy allylic sulfones.

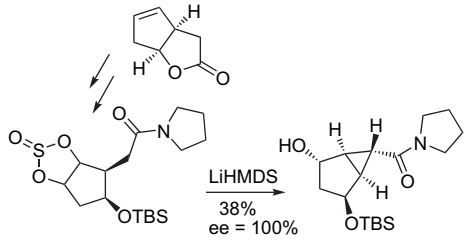
The scope of this methodology was extended to the preparation of chiral *N*-diphenylmethylene-2-vinyl-substituted cyclopropylamines, starting from the corresponding aminoallyl sulfones.[276] Hence, chiral aminocyclopropanes bearing a vinyl sulfone were obtained with high diastereoselectivity, as shown in Scheme 148.

On the other hand, Yoshikawa et al. have described the syntheses of bicyclo[3.1.0]hexane carboxylic acid derivatives by



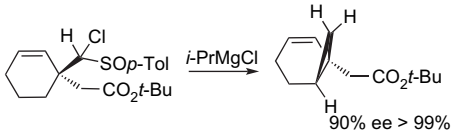
Scheme 148. Asymmetric cyclopropanations of aminoallyl sulfones.

intramolecular cyclopropanation of chiral cyclic sulfites as the key step.[277] Thus, the treatment of a chiral cyclic sulfite, depicted in Scheme 149, with LiHMDS afforded the corresponding enantiomerically pure bicyclic alcohol.



Scheme 149. Asymmetric cyclopropanation of cyclic sulfite.

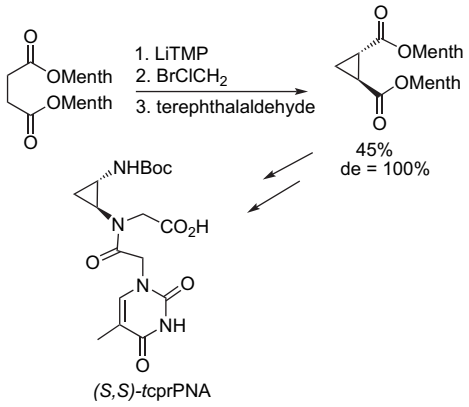
In 2006, Satoh et al. reported the synthesis of bicyclo[*n*.1.0]-alkanes via magnesium carbenoid 1,3-CH insertion as a key reaction.[278] Hence, treatment of a chiral sulfoxide, depicted in Scheme 150, with *i*-PrMgCl led to the formation of the corresponding optically active bicyclo[4.1.0]hept-2-ene derivative as a single product, which demonstrated that the magnesium carbenoid 1,3-CH insertion reaction occurred only at the methylene carbon on the cyclohexene.



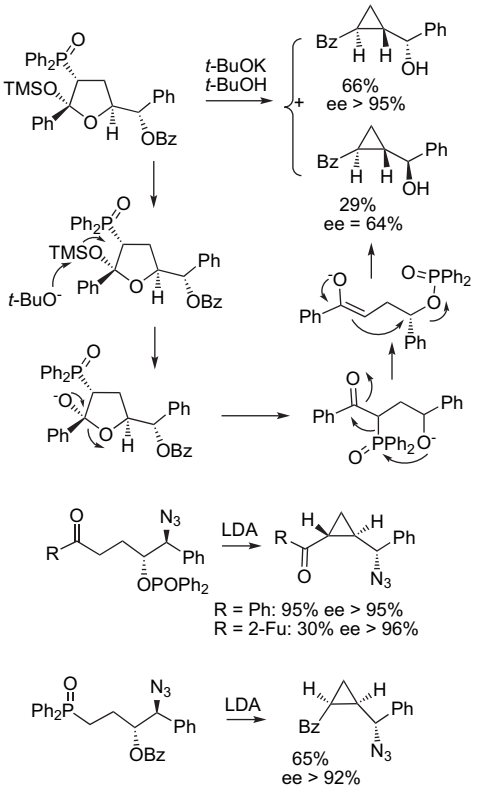
Scheme 150. Asymmetric cyclopropanation via magnesium carbenoid 1,3-CH insertion reaction.

In 2005, Appella et al. developed the synthesis of the first peptide nucleic acid (PNA) with a cyclopropane in the backbone (Scheme 151), in order to study the effects of the ring on the DNA/RNA-binding properties of the PNA.[279] The key step of the synthesis was Yamamoto's asymmetric alkylation of (−)-dimenthyl succinate with bromochloromethane, affording the corresponding cyclopropane dimenthyl ester as a single diastereomer (Scheme 151).

On the other hand, Warren et al. have recently developed an asymmetric cyclopropane synthesis via phosphine oxide-mediated cascade reactions.[280] When treated with KO*t*-Bu in *tert*-butanol, a chiral silyloxy-THF, depicted in Scheme 152, yielded a mixture of two *trans* cyclopropanes with a poor diastereoselectivity. In



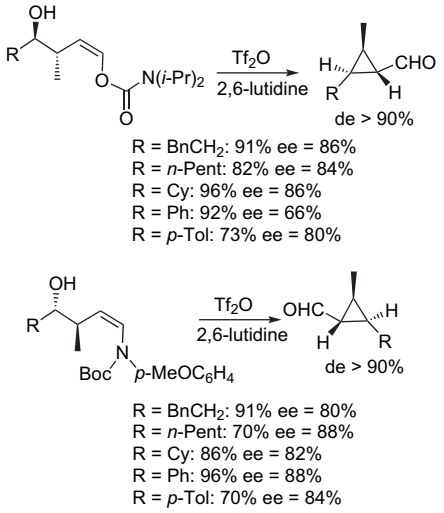
Scheme 151. Yamamoto's asymmetric alkylation of (−)-dimenthyl succinate with bromochloromethane.



Scheme 152. Phosphine oxide-mediated asymmetric cyclopropanations.

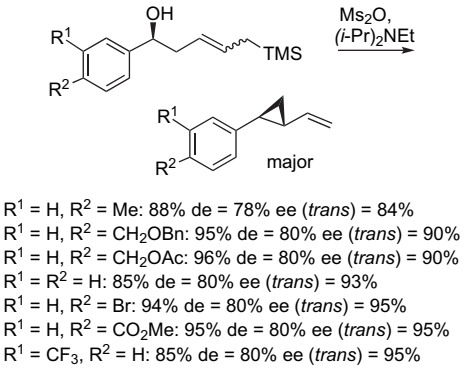
addition, these authors have reported the asymmetric synthesis of *trans* cyclopropane γ-azido ketones, in which the cyclopropane was formed via intramolecular ring closure by a chiral ketone enolate to displace a diphenylphosphinate leaving group (Scheme 152).[281]

On the other hand, the synthesis of chiral cyclopropanes through cationic pathways has been less widely explored.[282] As an example, Taylor et al. have developed an asymmetric synthesis of 1,2,3-trisubstituted *trans* cyclopropylaldehydes, based on the treatment of chiral *O*-enecarbamates with Tf_2O.[283] In particular, the aliphatic systems provided high yields and diastereoselectivity for the corresponding cyclopropylaldehyde products, as shown in Scheme 153. In each case, the ring closure took place with inversion of configuration at the alcohol centre in a stereospecific manner. In order to prepare both enantiomers of the cyclopropylaldehyde products, similar reactions were performed with the corresponding *N*-enecarbamates (Scheme 153).



Scheme 153. Asymmetric cyclopropanations of *O*- and *N*-enecarbamates.

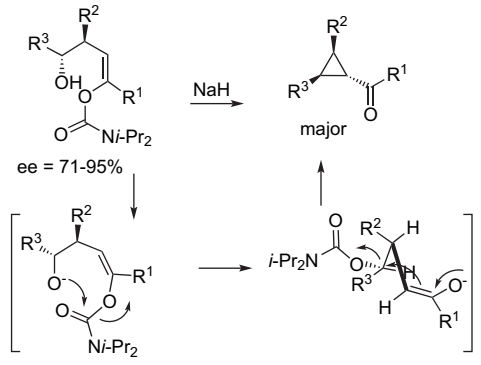
In 2007, Taylor et al. investigated the use of allylsilane homoallylic alcohols as a source of vinylcyclopropanes through an intermediate β-silylcyclopropylcarbinyl cation.[284] Indeed, these authors demonstrated the ability of this method to produce diastereomerically and enantiomerically pure 1,2-disubstituted cyclopropanes from homoallylic alcohols in excellent yields (Scheme 154). A series of substituted phenyl rings showed higher enantiospecificity for the cyclisation as the electron-withdrawing ability of the group increased, whereas an appreciable loss of enantiomeric purity was observed with electron-rich systems.



Scheme 154. Asymmetric cyclopropanation of allylsilane homoallylic alcohols.

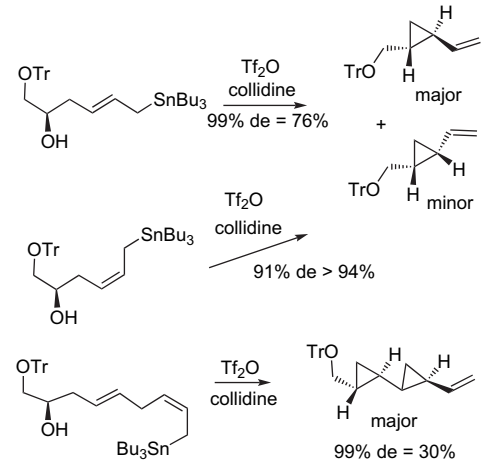
In 2004, Hoppe et al. observed that the simple treatment of chiral homoallylic alcohols with NaH furnished the corresponding cyclopropanes with excellent diastereoselectivity, complete chirality transfer and with high efficiency, as shown in Scheme 155.[285] Apparently, the *N*,*N*-diisopropylcarbamoyl group in the first intermediate alkoxide of Scheme 155 migrates to the O4 atom, forming a (*Z*)-enolate, which undergoes cycloalkylation by nucleophilic substitution of the carbamate group with strict stereoinversion. The enolate moiety occupies an *anti* position in the second transition state in order to avoid steric repulsion with R^2 and R^3.

In addition, White et al. have studied the exposure of a chiral homoallylic alcohol bearing a terminal tributylstannyl substituent to Tf_2O in base.[286] The treatment of this (*E*)-olefin resulted in rapid solvolysis of the transient homoallylic triflate to produce a mixture of two chiral cyclopropanes in quantitative yield and good diastereoselectivity, as shown in Scheme 156. In order to study the



R^1 = H, R^2 = Me, R^3 = Ph: 71% de = 90% ee = 71%
R^1 = R^3 = Ph, R^2 = Me: 98% de = 96% ee = 91%
R^1 = Ph, R^2 = Me, R^3 = *t*-Bu: 64% de = 96% ee = 94%
R^1 = Ph, R^2 = Me, R^3 = *p*-BrC_6H_4: 91% de = 96% ee = 93%
R^1 = H, R^2 = Me, R^3 = *n*-Pent: 62% de = 96% ee > 80%
R^1 = Ph, R^2 = Me, R^3 = naph: 84% de = 96% ee = 92%
R^1 = Ph, R^2 = Me, R^3 = 2-Fu: 98% de = 96% ee = 92%
R^1 = Ph, R^2 = R^3 = Me: 84% de = 96% ee = 91%
R^1 = Ph, R^2 = Me, R^3 = Et: 96% de = 96% ee = 95%
R^1 = Ph, R^2 = Me, R^3 = *i*-Pr: 62% de = 96% ee = 96%
R^1 = Ph, R^2 = Me, R^3 = *c*-Pr: 74% de = 96% ee = 95%
R^1 = Ph, R^2 = Me, R^3 = Cy: 78% de = 96% ee = 95%

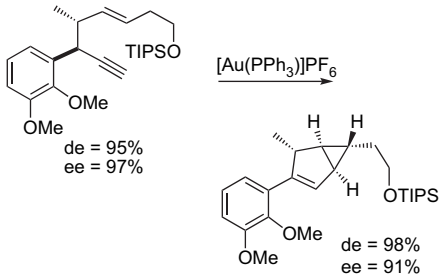
Scheme 155. Asymmetric cyclopropanation of homoallylic alcohols.



Scheme 156. Asymmetric cyclopropanations of homoallylic alcohols bearing terminal tributylstannyl substituent.

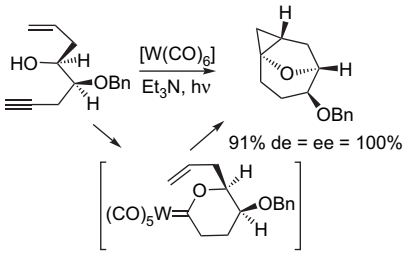
effect of the double-bond geometry on the homoallyl-to-cyclopropylcarbinyl cyclisation, the corresponding (*Z*)-olefin was submitted to the same methodology, affording the same products with a higher diastereoselectivity. An extension of this methodology to a system containing a skipped diene, in which a second contiguous cyclopropane could be formed in a cascade process, was undertaken. This methodology led to the quantitative formation of three enantiomerically pure, stereoisomeric bicyclopropanes (Scheme 156). It was shown that the major isomer possessed the relative *trans*,*syn*,*trans*-configuration, the utility of which was proved by its conversion into an intermediate employed by Falck et al. in the synthesis of FR-900848.[287]

Another entry into the asymmetric synthesis of chiral cyclopropanes is constituted by ring-closing reactions catalysed by metals. Transformations of enynes in the presence of transition-metal catalysts have played an important role in the preparation of a variety of cyclic compounds such as cyclopropanes.[288] As an example, Toste et al. have reported the cycloisomerisation of 1,5-enynes into bicyclo[3.1.0]hexane derivatives performed in the presence of a gold catalyst.[289] Scheme 157 presents the highly stereoselective reaction of a chiral 1,5-enyne in the presence of a cationic gold precursor, such as $[Au(PPh_3)]PF_6$, which affords the corresponding enantiomerically pure polycyclic cyclopropane.



Scheme 157. Au-catalysed asymmetric cyclopropanation of 1,5-enyne.

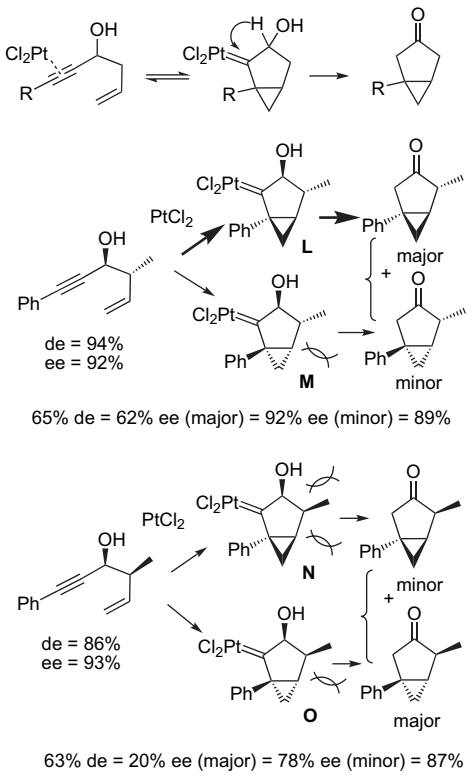
In 2005, Barluenga et al. reported another example of an asymmetric metal-catalysed cycloisomerisation reaction, involving a chiral hydroxylated enyne.[290] This substrate was irradiated in the presence of $[W(CO)_6]$ to provide the corresponding tricyclic product as a single stereoisomer (Scheme 158).



Scheme 158. W-catalysed asymmetric cyclopropanation of hydroxylated enyne.

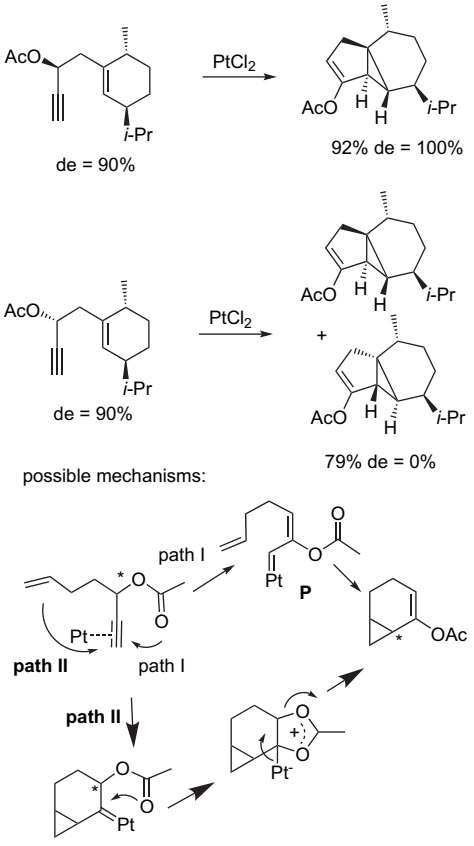
In 2004, Fürstner et al. showed that this class of reactions could also be catalysed by a platinum catalyst such as $PtCl_2$.[291] In this case, the chiral hydroxylated enyne bore the hydroxyl group at the propargylic position. The authors envisaged that the evolving platinum carbene triggered an irreversible 1,2-hydrogen shift with the formation of a bicyclo[3.1.0]hexanone skeleton, as shown in Scheme 159. The reactions of the diastereomeric *syn*- and *anti*-substrates were performed, furnishing the enantiomeric corresponding cyclopropanes. The most likely explanation for the significantly higher de in the *syn* series was the fact that only the carbene **L** was devoid of eclipsing the interactions between the methyl branch, the adjacent alcohol, and the incipient cyclopropyl ring and should therefore be more favoured over **M** than the diastereomeric intermediate **O** (was favoured) over **N**.

In 2006, Fürstner et al. reported the Pt-catalysed cycloisomerisation of a chiral propargyl acetate, affording the corresponding tricyclic product in high yield (Scheme 160).[292] While the diastereoselective reaction of the (*S*)-propargyl acetate paved an efficient route to cubebane sesquiterpenes, such as (−)-cubebol, the corresponding reaction of its (*R*)-configured isomer provided valuable mechanistic information. Indeed, under the same conditions, this substrate afforded a mixture of the same product obtained from the (*S*)-configured substrate, along with a diastereomeric compound in a 50:50 ratio. The striking differences between the stereoselective reactions of the (*R*)-configured isomer on the one hand, and the unselective reaction of the (*S*)-configured isomer on the other, showed that the configuration of the stereogenic centre carrying the acetate unit translated into the



Scheme 159. Pt-catalysed asymmetric cyclopropanations of hydroxylated enynes.

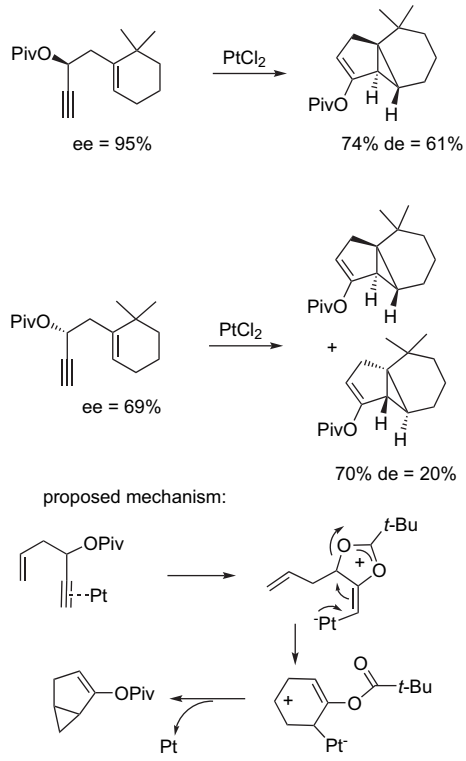
stereochemistry of the product. Thus, this position could not be rendered planar before cyclopropanation. Path I of Scheme 160 involves a vinylcarbene intermediate **P** prior to cyclisation and



Scheme 160. Pt-catalysed asymmetric cyclopropanations of propargyl acetates.

hence implies that both isomers lead to the same product distribution, whereas path II is consistent with the observed stereodivergent behaviour.

In an independent study, Fehr et al. have used this strategy for the same target and have described the Pt-catalysed cycloisomerisation of related pivaloates, providing similar results (Scheme 161).[293] Meanwhile, in order to justify their results, these authors have postulated a concerted C–C bond-formation/C–O bond-breaking pathway, as depicted in Scheme 161. In 2007, Soriano et al. reported an account of the stereocontrol of these reactions by computational methods, showing, however, that the concerted mechanism proposed by Fehr et al. (path I of Scheme 160) could be excluded as the operative mechanism.[294] Indeed, these authors have performed a detailed relaxed PES (potential energy surface) scan, selecting the involved C–C and C–O distances as independent coordinates, and varying these distances from 1.6 to 3.0 Å. The results have clearly revealed that a transition structure, involving the concerted C–O bond cleavage/C–C bond formation, could not be found, even supposing a high asynchronicity. In this context, the mechanism proposed by Fürstner et al. (path II of Scheme 160) was retained as the most plausible to justify the stereochemical outcome of the reactions.

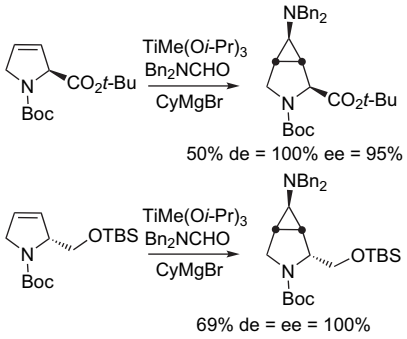


Scheme 161. Pt-catalysed asymmetric cyclopropanations of propargyl pivaloates.

In addition, de Meijere et al. have developed Ti-mediated reductive cyclopropanation reactions[295] of chiral 3,4-dehydroprolinol derivatives in the presence of dibenzylformamide, providing diastereoselectively the corresponding enantiomerically pure cyclopropylated diamino acids (Scheme 162).[296] Similar conditions were applied to L-*N*-allyl-(*N*,*N*-dibenzyl)prolineamide, leading to the corresponding tricyclic cyclopropylamine in 70% yield and moderate de (48%).[297]

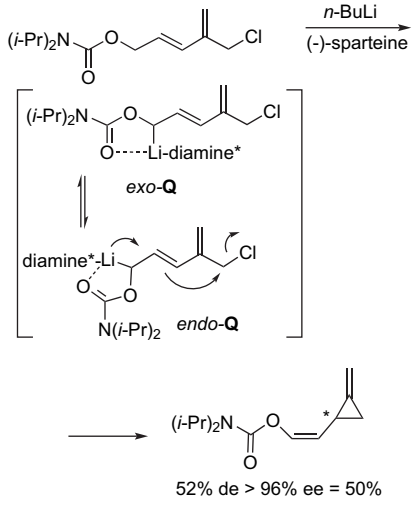
5.6. Other ring-closing reactions using chiral catalysts

In recent years, only a few methods of synthesis of chiral cyclopropanes via other ring-closing reactions based on the use of



Scheme 162. Ti-catalysed reductive asymmetric cyclopropanation reactions.

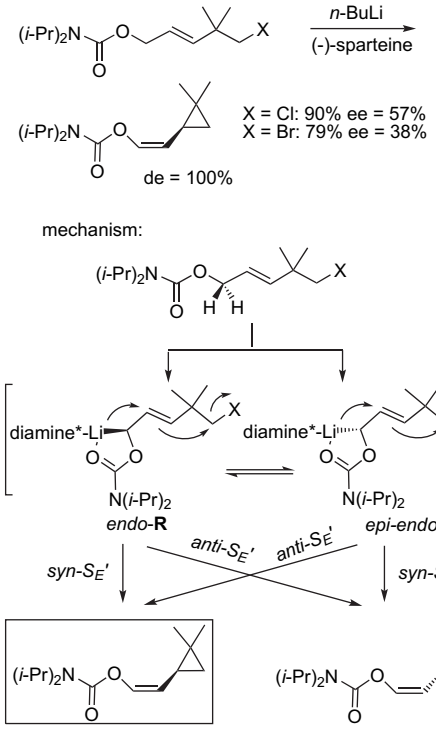
a chiral catalyst have been developed. As an example, Hoppe et al. have reported an asymmetric synthesis of 1-methylene-2-vinylcyclopropanes by intramolecular S'_E-cycloalkylation reaction, involving a 4-chloromethyl-2,4-dienyl carbamate, and using (−)-sparteine as a chiral inductor.[298] Indeed, the α-deprotonation of the substrate performed in the presence of *n*-BuLi associated with (−)-sparteine, followed by the intramolecular cycloalkylation reaction, led to the formation of the corresponding diastereomerically pure cyclopropane in moderate enantioselectivity, as shown in Scheme 163. The stereoselectivity of the reaction was explained by the fact that the α-lithiated intermediate **Q** reacted from the (2*E*)-*endo*-conformation, *endo*-**Q**, to form by intramolecular S'_E-cycloalkylation the (*Z*)-configured cyclopropane.



Scheme 163. Asymmetric synthesis of 1-methylene-2-vinylcyclopropane via (−)-sparteine-induced intramolecular S'_E-cycloalkylation reaction.

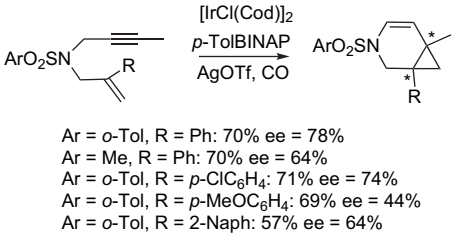
A similar methodology was applied to allyl carbamates, providing the corresponding enantioenriched, diastereomerically pure (2-carbamoyloxy-1-alkenyl)cyclopropanes.[299] In order to explain the stereoselectivity of the process, these authors proposed that the enantiotopes-differentiating deprotonation of ω-substituted 2-pentenyl carbamates by the *n*-BuLi/(−)-sparteine system proceeded in a highly stereoselective manner, whereas the epimeric (−)-sparteine/allyllithium complexes were configuratively labile. It was presumed that the lithium species **R** underwent a dynamic kinetic resolution to form, in an *anti*-S'_E reaction, the (*Z*)-configured enantioenriched (*S*)-vinylcyclopropane (Scheme 164).

In addition, Shibata et al. have developed a cationic iridium-chiral diphosphine complex-catalysed enantioselective cycloisomerisation of nitrogen-bridged 1,6-enynes, which afforded chiral cyclopropanes fused by a six-membered-ring system.[300] These



Scheme 164. Asymmetric synthesis of (2-carbamoyloxy-1-alkenyl)cyclopropane via (−)-sparteine-induced intramolecular S'_E-cycloalkylation reaction.

workers used *p*-TolBINAP as a chiral ligand in the presence of $[IrCl(cod)]_2$, which allowed enantiomerically enriched 3-azabicyclo[4.1.0]heptenes to be obtained in good yields and ees, as shown in Scheme 165.

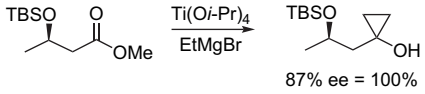


Scheme 165. Asymmetric synthesis of 3-azabicyclo[4.1.0]heptenes via cycloisomerisation catalysed by iridium-chiral diphosphine complex.

5.7. Other methods

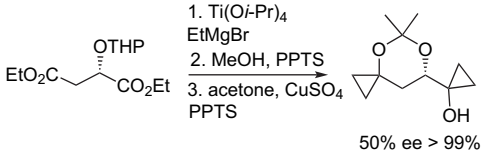
In 1989, the group of Kulinkovich found that the treatment of an ester with a mixture of Ti(O*i*-Pr)$_4$ and an excess of a Grignard reagent achieved the corresponding 1-substituted cyclopropanol in good-to-excellent yields.[301] Casey et al. have recently reported a study on the mechanism of the Kulinkovich reaction in order to explain the observed diastereoselectivity.[302] In recent years, the use of chiral auxiliaries in the enantioselective synthesis of cyclopropanols via the Kulinkovich method has been investigated. As an example, Singh et al. have applied the Kulinkovich methodology to a chiral ester, which afforded in the presence of EtMgBr and Ti(O*i*-Pr)$_4$ the corresponding enantiomerically pure cyclopropanol in excellent yield (Scheme 166).[303] This compound was further converted into all the stereoisomers of tarchonanthuslactone.

In 2005, Kulinkovich et al. reported the asymmetric reductive cyclopropanation of chiral THP-protected diethyl malate, which was converted, under Kulinkovich reaction conditions, and



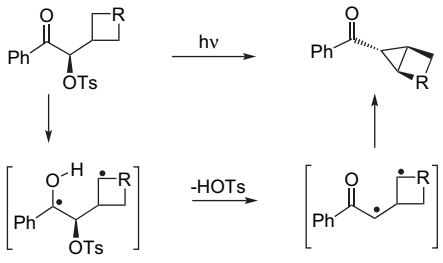
Scheme 166. Kulinkovich reaction of chiral β-alkoxy ester.

subsequent selective cleavage of one of the cyclopropyl groups, into the corresponding bis-cyclopropanol with more than 99% ee (Scheme 167).[304]



Scheme 167. Kulinkovich reaction of chiral THP-protected diethyl malate.

In 2005, Wessig et al. developed an entirely novel concept concerning the synthesis of enantiomerically enriched cyclopropanes based on a photochemically induced intramolecular 1,2-chirality transfer.[305] Hence, the irradiation of a chiral ketone, depicted in Scheme 168, led to the formation of the corresponding *exo* cyclopropylated product with complete stereoselectivity, in agreement with the concept of spin-centre shift. As shown in Scheme 168, at the stage of the 1,4-diradical generated by irradiation, this results in a shift of the radical centre from the carbonyl C atom to the adjacent C atom as a result of HOTs elimination. The resulting 1,3-diradical cyclises with complete diastereoselectivity and good yield to give the final cyclopropane. The mechanistic basis was the preferred co-linear arrangement of the leaving group and the π system of the photochemically excited carbonyl group, which could be explained by stereoelectronic effects.

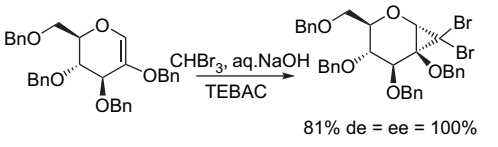


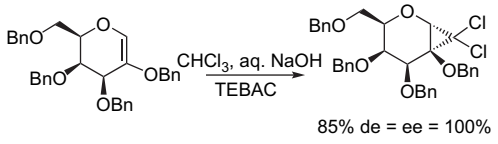
R = CH_2OCH_2: 74% de = 100% ee = 28%
R = $CH_2N(Ts)CH_2$: 78% de = 100% ee = 38%
R = $CH_2N(Boc)CH_2$: 69% de = 100% ee = 23%
R = $CH_2CH(t\text{-}Bu)CH_2$: 79% de = 100% ee = 52%

Scheme 168. Asymmetric photochemical cyclisation of ketones.

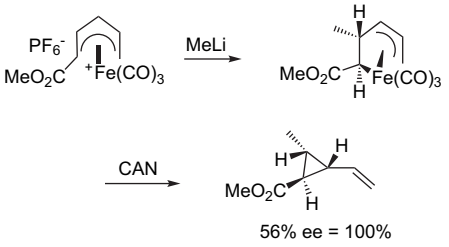
In order to prepare unnatural septanoside derivatives, Jayaraman et al. have very recently developed a novel methodology including an asymmetric cyclopropanation of a glycal performed with bromoform or chloroform.[306] Indeed, the reaction occurred with total diastereoselectivity under phase-transfer conditions, as shown in Scheme 169.

In 2005, Donaldson et al. reported a novel process to prepare vinylcyclopropanecarboxylates on the basis of organoiron methodology.[307] This methodology relied on the nucleophilic addition of stabilised carbon nucleophiles to a (1-methoxycarbonylpentadienyl)iron cation to generate (pentenediyl)iron complexes. The subsequent oxidative induced-reductive elimination of these complexes afforded vinylcyclopropanecarboxylates. Hence, the reaction of a chiral (1-methoxycarbonylpentadienyl)iron cation, depicted in Scheme 170, with MeLi gave predominantly the corresponding





Scheme 169. Asymmetric cyclopropanations of glycals.



Scheme 170. Asymmetric synthesis of vinylcyclopropane via organoiron methodology.

(pentenediyl)iron complex, which afforded by treatment with excess ceric ammonium nitrate (CAN) the corresponding enantiomerically pure vinylcyclopropane in good yield.

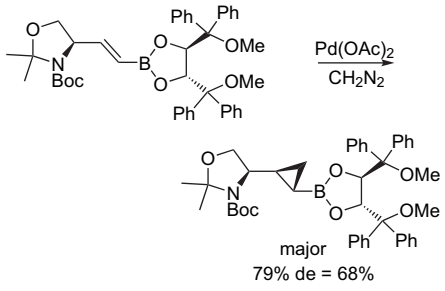
In 2003, Pietruszka et al. developed a synthetic route to chiral cyclopropylboronic esters on the basis of the cyclopropanation of the corresponding alkenylboronic esters performed by Pd-catalysed decomposition of diazomethane.[308] Good yields and diastereoselectivities of up to 84% de were obtained, as summarised in Scheme 171.

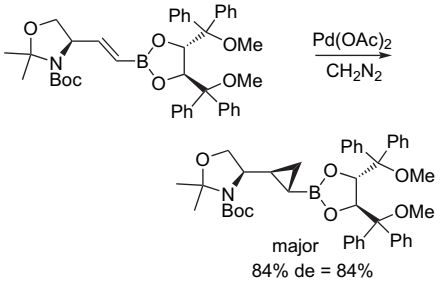
On the other hand, enantiomerically pure [60]fullerene tris-adducts with an *e*,*e*,*e*-addition pattern have been prepared by Hirsch et al. via the cyclopropanation of C_{60} with chiral D_3-symmetrical *cyclo*-tris(malonate) tethers bearing chiral C_8-spacers connecting the reactive malonate.[309] In addition, Tang et al. reported, in 2007, a highly diastereo- and enantioselective catalytic cycloaddition of 2-substituted cyclopropane-1,1-dicarboxylates with nitrones in the presence of a trisoxazoline-Ni(II) catalyst.[310] Furthermore, this reaction could be employed for the kinetic resolution of 2-substituted cyclopropane-1,1-dicarboxylates to furnish these compounds in an optically active form with excellent ee values, as shown in Scheme 172.

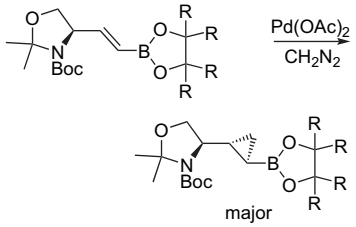
The diastereoselective addition reactions of cyclopropenes constitute an attractive alternative to the more mainstream routes to chiral cyclopropanes.[311] As an example, Gevorgyan et al. have developed a catalytic enantioselective hydroboration of cyclopropenes.[312] Thus, enantiopure 2,2-disubstituted cyclopropylboronates could be easily prepared in almost quantitative yield and very high diastereo- and enantioselectivities in the presence of a chiral ligand such as (*R*)-BINAP (Scheme 173).

In 2004, these workers reported the first catalytic enantioselective hydrostannation of cyclopropenes,[313] providing a straightforward approach to optically active cyclopropylstannanes.[314] Compared with the preceding hydroboration, the hydrostannation of cyclopropenes had a more general scope, as it did not require directing groups for achieving high degrees of enantioselectivity, as shown in Scheme 174. In this case, the best results were obtained in the presence of a chiral stilbene-derived ligand.

In 2006, Fox et al. reported the enantioselective, facially selective carbomagnesation of cyclopropenes performed in the presence of *N*-methylprolinol as a chiral ligand.[315] In all of the cyclopropenes

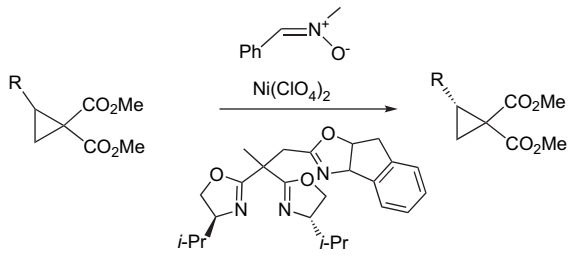






R = Me: 69% de = 56%
R = Ph: 61% de = 52%

Scheme 171. Asymmetric cyclopropanations of alkenylboronic esters.



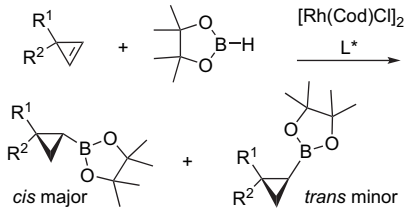
R = Ph: ee = 91%
R = *p*-Tol: ee = 96%
R = *p*-BrC_6H_4: ee = 95%
R = *p*-$CF_3C_6H_4$: ee = 96%
R = *p*-$NO_2C_6H_4$: ee = 97%
R = *p*-ClC_6H_4: ee = 94%
R = *p*-$MeOC_6H_4$: ee = 92%

Scheme 172. Kinetic resolution of 2-substituted cyclopropane-1,1-dicarboxylates.

studied, the addition of MeMgCl led to the formation of only one diastereomer in high yield and enantioselectivity, as shown in Scheme 175. The introduction of electrophiles created all three stereocentres in high enantioselectivity for diverse types of tetrasubstituted cyclopropanes.

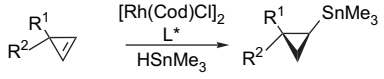
At the same time, these workers have reported a regio- and diastereoselective synthesis of chiral methylenecyclopropanes by reaction between chiral cyclopropene derivatives and Grignard reagents.[316] As shown in Scheme 176, a single stereoisomer was obtained in all cases when using bromide as the Grignard counterion.

Similar reactions were also successfully developed by Marek et al. in the presence of a catalytic amount of CuI (Scheme 177).[317]

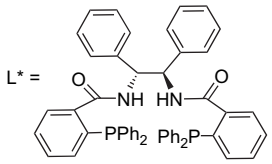


with L* = (*R*)-BINAP:
R^1 = Me, R^2 = CO_2Me: 94% de > 98% ee (*cis*) = 94%
R^1 = TMS, R^2 = CO_2Et: 99% de > 98% ee (*cis*) = 97%
R^1 = Ph, R^2 = CO_2Me: 99% de > 98% ee (*cis*) = 92%
with L* = (*S*)-Tol-BINAP:
R^1 = R^2 = CO_2Me: 99% ee > 98%

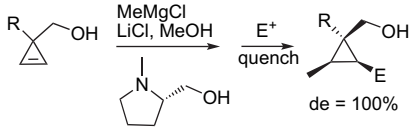
Scheme 173. Asymmetric hydroboration of cyclopropenes.



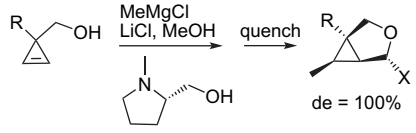
R^1 = Me, R^2 = CO_2Me: 90% ee = 94%
R^1 = Me, R^2 = Ph: 87% ee = 90%
R^1 = CH_2OMOM, R^2 = Ph: 86% ee = 93%
R^1 = Me, R^2 = CO_2allyl: 79% ee = 97%
R^1 = CH_2OAc, R^2 = Ph: 88% ee = 95%
R^1 = CH_2OAc, R^2 = *p*-ClC_6H_4: 83% ee = 96%
R^1 = Me, R^2 = $C(Me)_2OMOM$: 77% ee = 92%
R^1 = CH_2OAc, R^2 = TMS: 73% ee = 96%
R^1 = $CH_2OC(O)CH{=}CMe_2$, R^2 = TMS: 87% ee = 94%



Scheme 174. Asymmetric hydrostannation of cyclopropenes.



R = Ph, E = H, H^+ quench: 73% ee = 93%
R = Ph, E = I, I_2 quench: 64% ee = 98%
R = Ph, E = SPh, $(PhS)_2$ quench: 66% ee = 91%
R = Ph, E = allyl, allyl-Br quench: 65% ee = 94%
R = TMS, E = H, H^+ quench: 81% ee = 91%
R = Me_2SiPh, E = H, H^+ quench: 79% ee = 90%
R = *o*-ClC_6H_4, E = H, H^+ quench: 81% ee = 94%



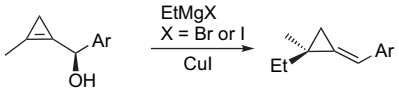
R = Ph, X = O, CO_2 quench: 55% ee = 96%
R = Ph, X = OH, DMF quench: 66% ee = 98%

Scheme 175. Asymmetric carbomagnesations of cyclopropenes.

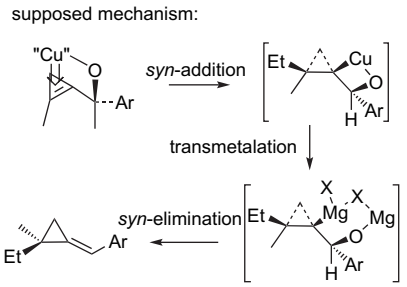
The reaction proceeded with an excellent transfer of chirality from chiral cyclopropenylcarbinol to alkylidenecyclopropane, regardless of the nature of the alkylmagnesium halides. The stereoselectivity

R^1 = Me_2SiPh, R^2 = SEM, R^3 = Me: 87%
R^1 = Me_2SiPh, R^2 = SEM, R^3 = Bn: 66%
R^1 = Ph, R^2 = MEM, R^3 = Me: 86%
R^1 = Ph, R^2 = MEM, R^3 = *n*-Hex: 64%
R^1 = Ph, R^2 = MEM, R^3 = $CH_2CHO(CH_2)_3O$: 62%
R^1 = Ph, R^2 = MEM, R^3 = allyl: 90%
R^1 = Ph, R^2 = MEM, R^3 = Bn: 65%
R^1 = Ph, R^2 = MEM, R^3 = Cy: 78%
R^1 = Ph, R^2 = MEM, R^3 = Et: 87%

Scheme 176. Synthesis of chiral methylenecyclopropanes.



Ar = Ph: 70% de = 94% ee = 97%
Ar = *p*-ClC_6H_4: 88% de = 94% ee = 99%

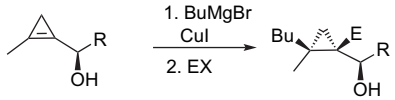


Scheme 177. Asymmetric Cu-catalysed carbomagnesation of cyclopropenecarbinols.

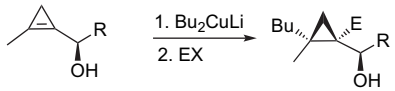
of the process was explained by the occurrence of an overall *syn* S_N2' displacement of the alcohol moiety. As the deprotonation of the alcohol precedes the addition, the most stable conformer of the cyclopropenylcarbinolate is given in Scheme 177, with the smallest substituent (hydrogen) at the pre-existing orientation 'inside' and the aryl group 'outside', away from the allylic methyl substituent (minimum 1,3-strain). Thus, this catalytic reaction proceeded through a *syn* addition/*syn* elimination mechanism.

In 2007, these workers demonstrated that it was possible to avoid the transmetalation depicted in the preceding scheme by using a stoichiometric amount of a copper salt.[318] Thus, when such a transmetalation reaction was avoided, the carbometallated product then became more stable towards β-elimination (the carbon–copper bond is usually less prone to β-elimination than the carbon–magnesium bond), and could react with different electrophiles to give the corresponding chiral functionalised cyclopropylcarbinol derivatives (Scheme 178). Surprisingly, these workers observed, in the course of their studies, that, when the same reaction was performed with an organocuprate derived from *n*-BuLi (instead of *n*-BuMgBr) with the same copper salt, the observed diastereomeric ratio was reversed in favour of the *syn* isomer (Scheme 178). Consequently, the combined two methodologies allowed the formation of each of the two possible diastereoisomers of polysubstituted cyclopropylcarbinols from cyclopropenylcarbinol derivatives, from a unique precursor simply by variation of the organometallic species, as shown in Scheme 178.

Chiral methylenecyclopropane derivatives were also prepared by Marek et al. via a three-component reaction from 1,1,2-tribromocyclopropanes, a chiral sulfinyl ester and electrophiles.[319] Thus, a cyclopropenyllithium was obtained from the corresponding



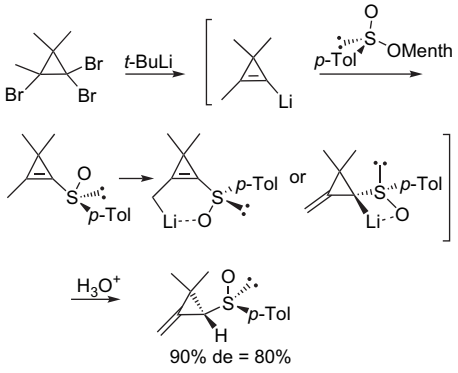
R = CH_2Bn, EX = H_3O^+, E = H: 76% de = 50%
R = *i*-Pr, EX = H_3O^+, E = H: 82% de > 90%
R = $CH(Ph)_2$, EX = H_3O^+, E = H: 73% de > 90%
R = *t*-Bu, EX = H_3O^+, E = H: 92% de > 90%
R = Ph, EX = H_3O^+, E = H: 70% de = 70%
R = $CH(Ph)_2$, EX = I_2, E = I: 84% de > 90%
R = $CH(Ph)_2$, EX = allylBr, E = allyl: 81% de > 90%



R = CH_2Bn, EX = H_3O^+, E = H: 78% de = 90%
R = *i*-Pr, EX = H_3O^+, E = H: 87% de = 80%
R = $CH(Ph)_2$, EX = H_3O^+, E = H: 81% de = 88%
R = *t*-Bu, EX = H_3O^+, E = H: 83% de = 90%
R = Ph, EX = H_3O^+, E = H: 75% de = 80%
R = $CH(Ph)_2$, EX = I_2, E = I: 86% de = 88%
R = $CH(Ph)_2$, EX = allylBr, E = allyl: 77% de = 88%

Scheme 178. Asymmetric carbometalations of cyclopropenecarbinols.

1,1,2-tribromocyclopropane by a successive 1,2-dehalogenation reaction followed by a halogen–lithium exchange, as described in Scheme 179. Next, after the addition of (−)-menthyl (*S*)-*p*-toluenesulfinate, the corresponding cyclopropenyl sulfoxide was formed as an intermediate. This intermediate then self-deprotonated, with the concomitant formation of the volatile 1,2,2-trimethylcyclopropene derivative. After the addition of water, the corresponding final chiral methylenecyclopropane was obtained in excellent yield and de (Scheme 179).

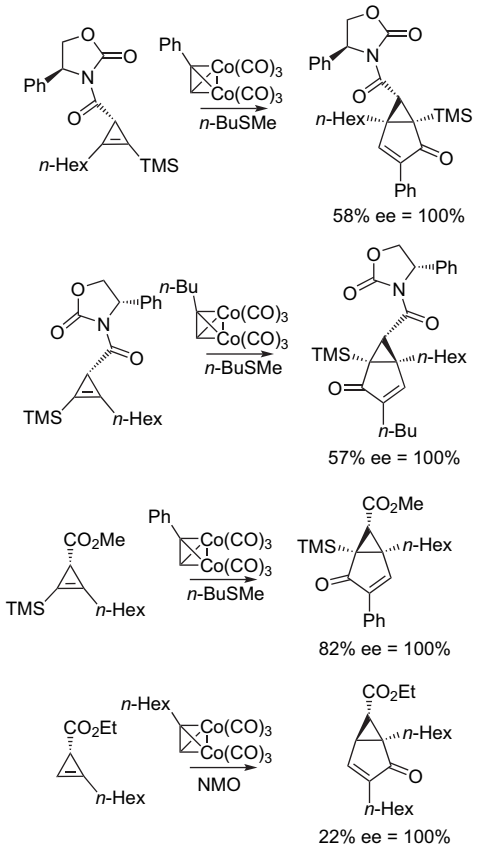


Scheme 179. Synthesis of chiral methylenecyclopropane via three-component reaction.

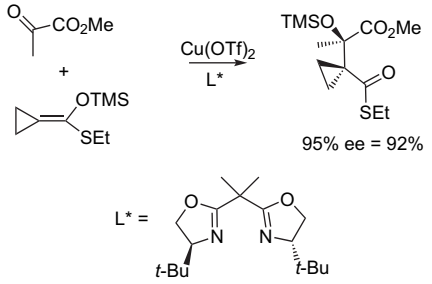
Finally, chiral cyclopropenes, depicted in Scheme 180, were proved by Fox et al., in 2005, to be a powerful tool for promoting regio- and stereoselective intermolecular Pauson–Khand reactions.[320] A single enantiomerically pure cyclopentenone was isolated in each of the reactions performed in the presence of a sulfide (*n*-BuSMe) or a *N*-oxide (*N*-methylmorpholine *N*-oxide (NMO)).

In the course of developing a total synthesis of the potent anticancer agent, (−)-irofulven, Movassaghi et al. have achieved the addition of a strained ketene hemithioacetal, depicted in Scheme 181, to a solution of methyl pyruvate in the presence of a chiral copper catalyst, which furnished the corresponding chiral polyfunctionalised cyclopropane in high yield and enantioselectivity (Scheme 181).[321]

In recent years, the use of biocatalysts for organic transformations has become an increasingly attractive alternative to

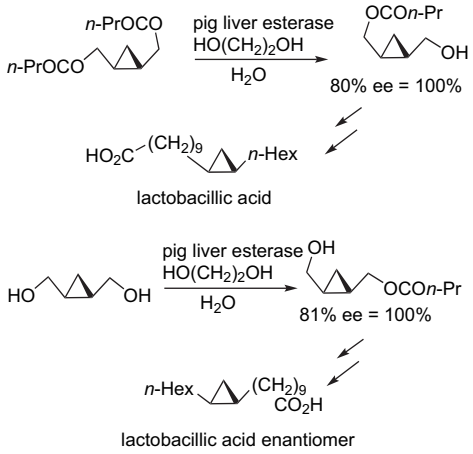


Scheme 180. Asymmetric Pauson–Khand reactions of cyclopropenes.



Scheme 181. Asymmetric aldol reaction of cyclopropanated ketene hemithioacetal.

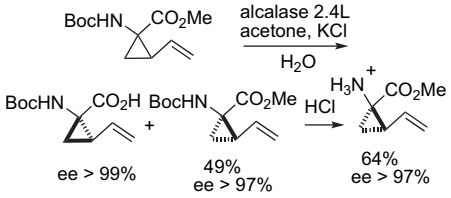
conventional chemical methods.[322] Enzymes and microorganisms have been extensively used for the resolution of racemates and the desymmetrisation of *meso* compounds, thus producing enantioenriched building blocks.[323] In particular, a number of chiral cyclopropane derivatives have been prepared from the enzymatic resolution of efficient precursors. Among these enzymes, the hydrolases such as lipases and esterases have been frequently used in the synthesis of chiral cyclopropanes.[5a] As an example, Minnikin et al. have developed an asymmetric synthesis of lactobacillic acid, in which the stereoselectivity was obtained through enzymatic desymmetrisation of *cis*-1,2-bis(butyroyloxymethyl)cyclopropane.[324] Indeed, this compound was treated with pig liver esterase in ethylene glycol and water to give the corresponding monoester in high yield, as shown in Scheme 182. This product was further converted into (11*R*,12*S*)-lactobacillic acid. In addition, when a solution of 2,2,2-trifluoroethyl butyrate in isopropyl ether was mixed with *cis*-1,2-bis(hydroxymethyl)-cyclopropane in the presence of pig liver esterase, it produced the corresponding half-ester in high yield, which was further converted into the (11*S*,12*R*)-lactobacillic



Scheme 182. Enzymatic desymmetrisations of *cis*-cyclopropanes.

acid enantiomer (Scheme 182). These results were used by Baird et al. in order to determine the absolute stereochemistry of grenadamide.[325]

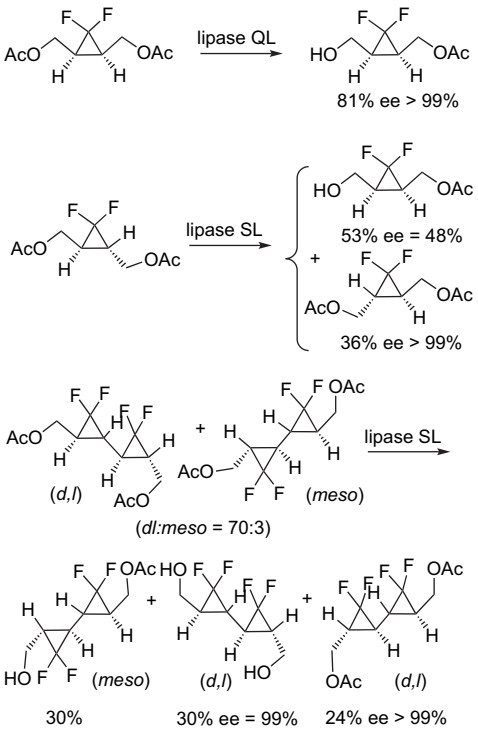
(1*R*,2*S*)-1-Amino-2-vinylcyclopropanecarboxylic acid (vinyl-ACCA) is a key building block in the synthesis of potent inhibitors of the hepatitis C virus NS3 protease. In 2005, Beaulieu et al. reported a scalable process that delivered derivatives of this unusual amino acid in >99% ee.[326] The key step of the process was the resolution of the methyl ester of this amino acid, using a readily available, inexpensive esterase enzyme, Alcalase 2.4L. Indeed, the enzymatic resolution of *N*-Boc-vinyl-ACCA led to the corresponding chiral ester in 49% yield and >97% ee, along with the corresponding chiral enantiomeric carboxylic acid in >99% ee, as shown in Scheme 183.



Scheme 183. Enzymatic resolution of *N*-Boc-vinyl-ACCA.

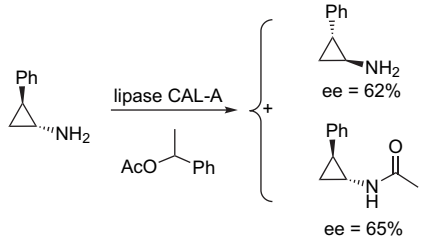
In 2004, Itoh et al. described the synthesis of optically active *gem*-difluorocyclopropanes using lipase technology.[327] As shown in Scheme 184, the diacetate of *cis*-1,3-bishydroxymethyl-2,2-difluorocyclopropane was converted into the corresponding chiral monoacetate by the *Alcaligenes* lipase (lipase QL)-catalysed hydrolysis with >99% ee. On the other hand, the corresponding *trans*-diacetate was reacted with lipase SL (*Pseudomonas cepacia* SL-25), affording the corresponding monoacetate in modest ee, along with remaining *trans*-diacetate with >99% ee. In addition, the syntheses of chiral *trans*,*trans*-bis-*gem*-difluorocyclopropane derivatives were succesfully accomplished using the same methodology (Scheme 184).

In 2005, Gotor et al. reported the kinetic resolution of some 2-phenylcycloalkanamines by means of aminolysis reactions catalysed by lipases.[328] They showed that the size of the ring and the stereochemistry of the stereogenic centres of the amines had a strong influence on both the enantiomeric ratio and the reaction rate of the aminolysis processes. Lipase CAL-B (from *Candida antarctica*) showed excellent enantioselectivities towards *trans*-2-phenylcyclohexanamine in a variety of reaction conditions, whereas lipase CAL-A (from *Candida antarctica*) was the best



Scheme 184. Enzymatic hydrolysis of *gem*-difluorocyclopropanes.

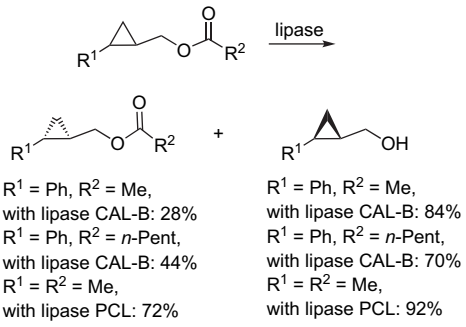
catalyst for the acylation of *cis*-2-phenylcyclohexanamine. Low enantioselectivities were, however, observed for the enzymatic resolution of *trans*-2-phenylcyclopropanamine, as shown in Scheme 185.



Scheme 185. Enzymatic acylation of 2-phenylcyclopropanamide.

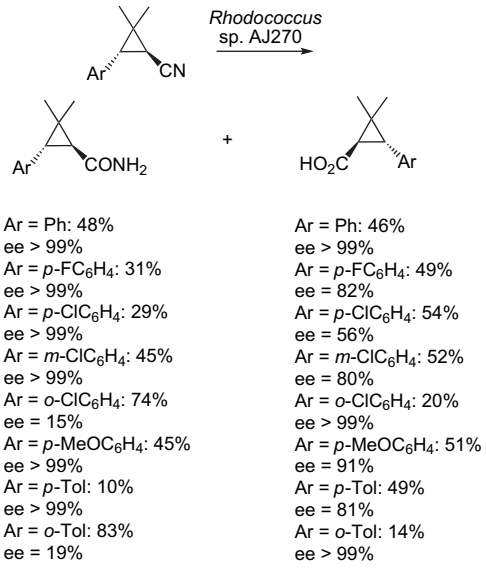
The enzymatic hydrolysis of various cyclopropylmethyl esters has been studied by Pietruszka et al., providing the corresponding chiral cyclopropylmethanols with up to 92% ee, when using *Pseudomonas cepacia* lipase (PCL), as shown in Scheme 186.[329]

Nitrile and amide biotransformations have been widely studied by Wang et al., employing a nitrile hydratase/amidase-containing



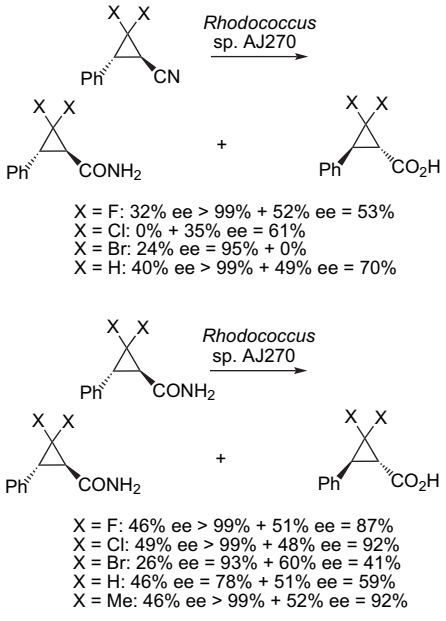
Scheme 186. Enzymatic hydrolysis of cyclopropylmethyl esters.

Rhodococcus sp. AJ270 whole-cell catalyst under very mild conditions. This catalyst induced the hydrolysis of *trans*-3-aryl-2,2-dimethylcyclopropanecarbonitriles to form the corresponding chiral 2,2-dimethyl-3-arylcyclopropanecarboxylic acids and 2,2-dimethyl-3-arylcyclopropanecarboxamides in excellent yields with high enantiomeric excesses (Scheme 187).[330] This biotransformation process provided effective and convenient syntheses of optically geminally dimethyl-substituted cyclopropanecarboxylic amides and acids such as chrysanthemic acids.



Scheme 187. Biotransformation of *trans*-3-aryl-2,2-dimethylcyclopropanecarbonitriles.

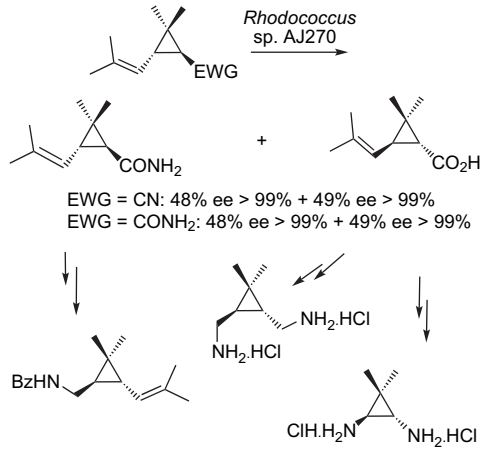
As *gem*-dihalocyclopropanes play an important role in organic synthesis,[331] the scope of this highly efficient methodology was extended to the synthesis of enantiopure *gem*-dihalocyclopropane derivatives.[332] Hence, catalysed by *Rhodococcus* sp. AJ270 microbial cells, *trans*-2,2-dihalo-3-phenylcyclopropanecarbonitriles and -carboxamides underwent enantioselective hydrolysis, as shown in Scheme 188. Both the efficiency and the enantioselectivity of the



Scheme 188. Biotransformations of *trans*-3-phenyl-2,2-dihalocyclopropanecarbonitriles and -carboxamides.

nitrile hydratase and amidase involved in the cells were strongly governed by the nature of the halogen substituent.

Finally, these authors applied, in 2006, this methodology to the chemoenzymatic construction of enantiopure geminally dimethylated cyclopropane-based C_2- and pseudo-C_2-symmetric diamines.[333] The key step of the synthesis was the highly enantioselective biotransformation of chrysanthemic nitriles and amides, yielding the corresponding enantiopure chrysanthemic acids and amides, as shown in Scheme 189.



Scheme 189. Syntheses of C_2- and pseudo-C_2-symmetric diamines by biotransformation of chrysanthemic nitriles and amides.

6. Conclusions

Since cyclopropane rings are often found in a wide variety of natural products and biologically active compounds, the synthesis of chiral cyclopropanes remains a considerable challenge, even 120 years after the synthesis of the first cyclopropane derivative. This review updates the principal and very versatile methods employed to obtain chiral cyclopropanes, reported in the literature since 2003, by either enzymatic or non-enzymatic methods and illustrates the diversity of useful products that can be obtained through this powerful concept. Indeed, the last 4 years have witnessed significant developments in the efficiency and scope of the asymmetric cyclopropanation. Thus, a number of enantioselective organocatalysed Michael-initiated ring-closure reactions have recently appeared in the literature, along with a wide variety of novel chiral metal catalysts applied to the versatile methods. The asymmetric cyclopropanation is therefore well represented as an important tool for organic synthesis.

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Biographical sketch

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