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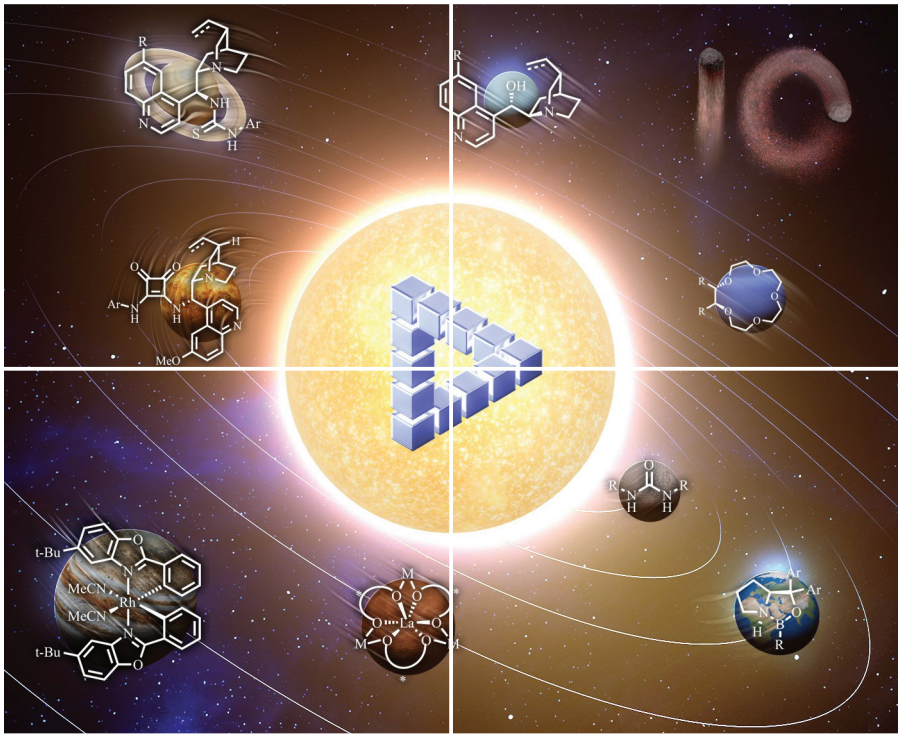

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Unveiling the beauty of cyclopropane formation: a comprehensive survey of enantioselective Michael initiated ring closure (MIRC) reactions

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This review presents a comprehensive overview of the synthesis of cyclopropanes using enantioselective Michael Initiated Ring Closure (MIRC) reactions. Cyclopropane-containing compounds possess unique structural and chemical properties that render them valuable in various fields, such as medicine, agrochemistry, and materials science. The MIRC approach has emerged as a versatile and efficient method for generating cyclopropane rings with excellent enantioselectivity. The review details fundamental concepts, reaction mechanisms, and synthetic strategies employed in MIRC reactions. A short introduction is provided to highlight the use of chiral substrates and nucleophiles to synthesize enantioenriched cyclopropanes. Additionally, recent advancements, challenges, and future prospects in the field are also discussed. This review serves as a valuable resource for researchers and practitioners interested in harnessing the potential of MIRC reactions for the synthesis of chiral cyclopropane derivatives, offering a comprehensive and up-to-date overview of the subject matter.

1. Introduction

Ever since August Freund first synthesized the cyclopropane ring in 1882,[1] it has held a crucial and flexible position in chemical synthesis and pharmacological research. The strained three-membered ring possesses a unique reactivity and serves as an important building block for the synthesis of complex compounds. The incorporation of cyclopropane ring into pharmacologically active drug molecules has enhanced metabolic stability and target binding through the modulation of molecular conformation.[2] The success of this approach is evident through numerous examples of structurally diverse

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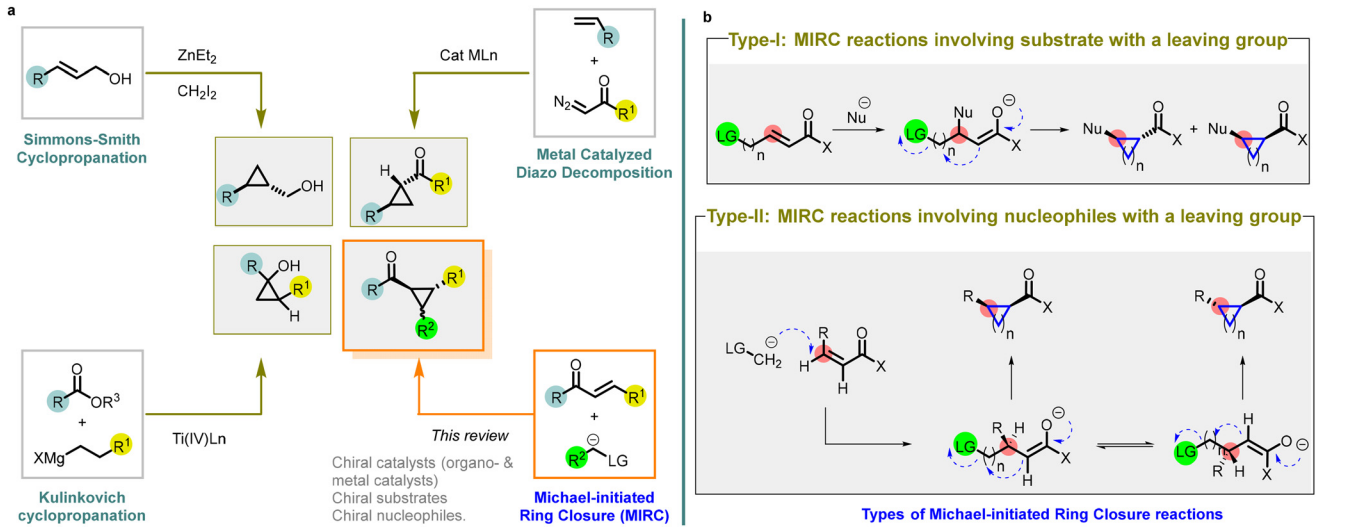

Fig. 1 (a) Different synthetic strategies utilized for the preparation of cyclopropanes; (b) different types of MIRC reactions.

cyclopropanes found in both developmental drug candidates and commercialized products.[3,4]

The ability to access enantioenriched cyclopropanes is of importance as it enables the synthesis of chiral molecules with a wide array of biological and functional properties. To address the specific synthetic challenges posed by the strained ring, various methods for constructing cyclopropanes have been developed. Among these methods, there are four major transformations described in the literature, with a focus on disconnections involving a formal [2 + 1] cycloaddition (Fig. 1).

The Simmons–Smith cyclopropanation is a widely used method for incorporating cyclopropane into compounds through the reaction of an organozinc carbenoid with an alkene or an alkyne[5,6] Achieving high reactivity and stereoselectivity often requires the presence of an oxygen or nitrogen-directing group. Asymmetric variations employing zinc- or boron-centered catalysts have expanded the options for stereoselective synthesis, leading to the desired stereochemical outcomes in cyclopropane synthesis (entry a, Fig. 1).

Diazo compound decomposition with transition metal catalysts is another popular method for cyclopropane synthesis.[7–10] It involves reacting a diazoalkane with a late transition metal catalyst, generating a nucleophilic metal carbenoid that can transfer to an electrophilic alkene, such as α,β-unsaturated carbonyl compounds. This versatile transformation allows for various substituents on both the diazo compound and the

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Prof. Mukund P Sibi earned his PhD from the City University of New York. After postdoctoral studies, he began his independent career at North Dakota State University where he is currently a University Distinguished Professor. His research focus is on radical chemistry, development of enantioselective reactions, total synthesis, and green chemistry. Prof. Sibi has received the prestigious Arthur C. Cope Scholar Award from the American Chemical Society in 2008 in recognition of his contributions to the field of radical chemistry. In 2021 he was elected as a Fellow of AAAS for his contribution to radical chemistry as well as building biomedical research infrastructure.

alkene substrate. Extensive research on asymmetric variations, resembling the Simmons–Smith cyclopropanation, has resulted in highly selective processes using readily accessible bisoxazoline and pyridine bisoxazoline ligands. These advances in asymmetric catalysis significantly expand the synthetic possibilities for accessing chiral cyclopropanes (entry a, Fig. 1).

The Kulinkovich cyclopropanation method is unique for cyclopropane synthesis.[11,12] It employs a titanium catalyst to combine an ester or an amide with a Grignard reagent containing an α-hydrogen, resulting in oxygen- or nitrogen-substituted cyclopropanes. Additionally, asymmetric variants enable the synthesis of enantioenriched cyclopropanes (entry a, Fig. 1).

Among these strategies, the utilization of Michael Initiated Ring Closure (MIRC) reaction (or Michael/alkylation cascade reaction) has emerged as a powerful approach to access chiral cyclopropanes with high stereoselectivity.[13–15] MIRC reaction involves Michael addition followed by a subsequent intramolecular cyclization, resulting in the formation of the cyclopropane ring. Little and Dawson were the pioneers who reported a MIRC reaction by combining a haloenolate with nitrogen and sulfur nucleophiles.[16] Their ground-breaking work involved the synthesis of disubstituted derivatives of cyclopropane, cyclopentane, cyclohexane, and cycloheptane through this reaction.

There are two types of Michael Initiated Ring Closure (MIRC) reactions (entry b, Fig. 1).

Type-I: MIRC reactions involving substrate with a leaving group

In type-I reaction, the formation of cyclopropanes is achieved through nucleophilic addition to electrophilic substrates that contain a leaving group.

A broad range of nucleophiles can be employed in these reactions, including alkoxides, thiolates, cyanides, enolates, Grignard reagents, hydrides, phosphites, and phosphonites.

Type-II: MIRC reactions involving nucleophile with a leaving group

In type-II reaction, the leaving group is located on the nucleophile itself.

The nucleophiles used in these reactions includes α-halo carbanions, but the heteroatom-derived ylides are the most effective reagents for transferring methylene to electron-deficient olefins. Ylides derived from sulfur, phosphorus, arsenic, and tellurium have all been successfully employed as precursors for cyclopropane formation.

Asymmetric variants of MIRC reactions have gained significant interest for their ability to generate enantiomerically enriched cyclopropane products. These reactions typically employ chiral catalysts or auxiliaries to control the stereochemistry during the Michael addition and subsequent ring closure steps. The development of efficient and selective enantioselective MIRC reactions has opened new avenues for synthesizing complex chiral cyclopropane derivatives.

Although previous reviews have covered cyclopropanation reactions,[17–38] there is currently no comprehensive account solely focused on Michael Initiated Ring Closure (MIRC) cyclopropanation. Therefore, we present a detailed account on enantioselective cyclopropanation, serving as a valuable resource for synthetic organic and medicinal chemists. In this review, we categorize MIRC cyclopropanation into three groups based on the chirality inducer employed: 1. chiral substrates, 2. chiral nucleophiles, and 3. chiral catalysts (including organocatalysts and metal catalysts). To facilitate readers understanding, we provide a concise description of substrate scope, putative reaction mechanisms, and any additional steps required to achieve the synthesis of the target natural product or its intermediate, if applicable. While we have made efforts to conduct an extensive literature search, we apologize in advance for any inadvertent omission of essential references.

2. Diastereoselective MIRC reactions leading to enantioenriched cyclopropanes

Stereoselectivity in Michael-initiated ring closing cyclopropanation reactions can be achieved by employing with chiral substrates (Michael acceptors) and chiral nucleophiles (Michael Donors). The presence of inherent structural asymmetry in chiral substrates which possess a chiral auxiliary (or a chiral center) is crucial for controlling the stereochemistry of the resulting cyclopropane product. On the other hand, chiral nucleophiles, which possess a chiral auxiliary or coordinating group, play a pivotal role in determining the stereochemistry of the cyclopropane product (Fig. 2). Previous reviews extensively discuss strategies involving chiral substrates and chiral nucleophiles. In this overview, we provide a concise summary of these types of cyclopropanations.

2.1. Chiral substrates (Michael acceptors)

Synthetic chemists employ the strategic addition of reagents to chiral substrates to achieve stereoselective reactions, and for this review, MIRC cyclopropanation reactions being extensively explored for a wide range of asymmetric Michael acceptors. These reactions involve the use of various auxiliaries (such as Evans's oxazolidinones,[39] Seebach's oxazolidine,[40,41] chiral lactams,[42–49] diphenyltetrahydrooxazinone,[50,51] pinanone-derived reagent, α,β-didehydroamino acid derivatives,[52] dehydroalanine[53]) and sulfoxides[54–61] attached to the substrate, which play a critical role in controlling the stereochemistry of the resulting cyclopropane product (entry a, Fig. 3). Careful selection of the

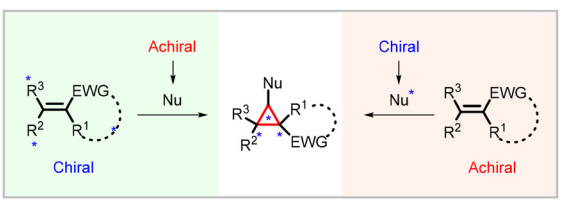


Fig. 2 General scheme for diastereoselective MIRC cyclopropanation using chiral substrate (Michael acceptors) and chiral nucleophile (Michael donors).

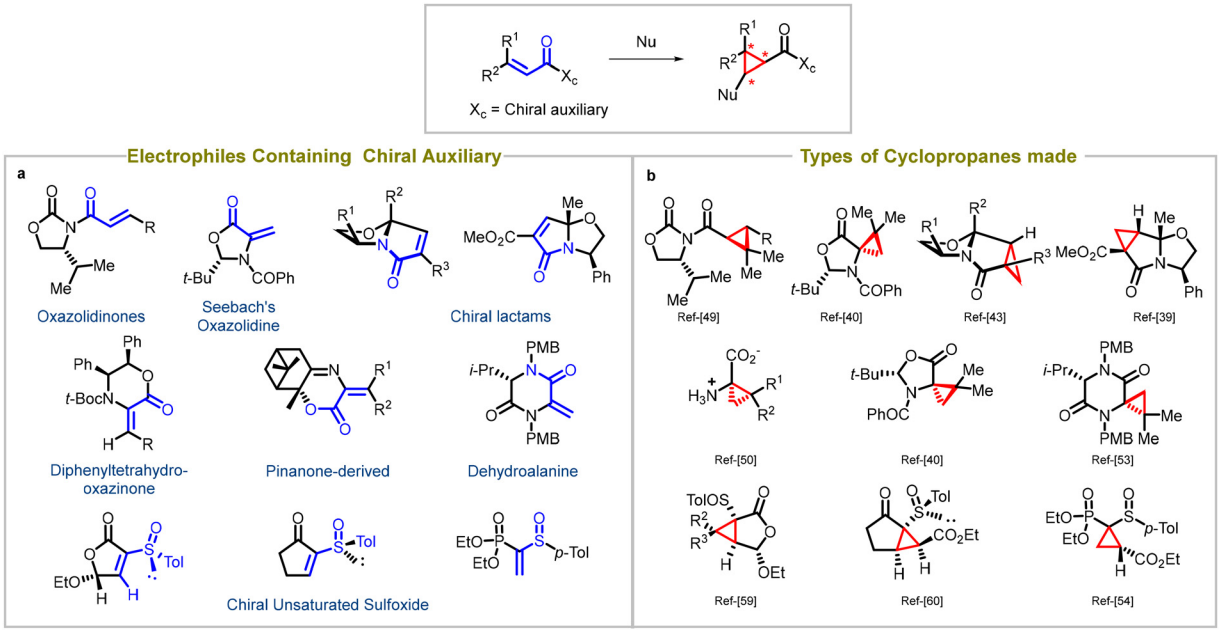


Fig. 3 Diastereoselective synthesis of cyclopropanes: (a) types of auxiliaries used in Michael acceptors, (b) different cyclopropanes synthesized using chiral auxiliaries.

appropriate chiral auxiliary or sulfoxide enables high diastereoselectivity, leading to the formation of enantioenriched cyclopropanes. Factors like steric hindrance, electronic effects, and non-covalent interactions guide the choice of auxiliary or sulfoxide. By strategically utilizing these chiral components, chemists can access a diverse array of enantioenriched cyclopropanes, enabling the synthesis of complex molecules with precise stereochemical control. Various types of cyclopropanes have been synthesized using these substrates (entry b, Fig. 3).

Enantioenriched cyclopropanes have also been successfully synthesized using a variety of chiral building blocks containing acyclic enones,[62–69] cyclic enones,[70–77] acyclic enoates,[78–92] unsaturated lactones,[93–95] and amides as electron-withdrawing groups, in addition to employing chiral auxiliaries. This versatile synthetic method serves as a crucial step in the synthesis of numerous biologically important compounds and natural products. Notable examples include the synthesis of potent taxol analogues,[62] glutamate analogues,[78] L-DCG-IV,[63] L-CCGI (selective activators of specific isotypes of metabotropic glutamate receptors),[89] 24,25-ethanovitamin D3 lactones (novel vitamin D receptor antagonists),[68] eicosanoids,[69] 17*S*,20*S*-methanofusidic acid (a fusidic acid antibiotic),[93] and majusculoic acid (an antifungal agent),[94] among many others (Fig. 4). This synthetic approach enables the efficient construction of diverse molecules with precise stereochemistry, facilitating the exploration of their biological activities and potential therapeutic applications.

2.2. Chiral nucleophiles

Chiral nucleophiles serve as a key reagent in an alternate strategy to obtain enantiomerically enriched cyclopropanes.[96] This

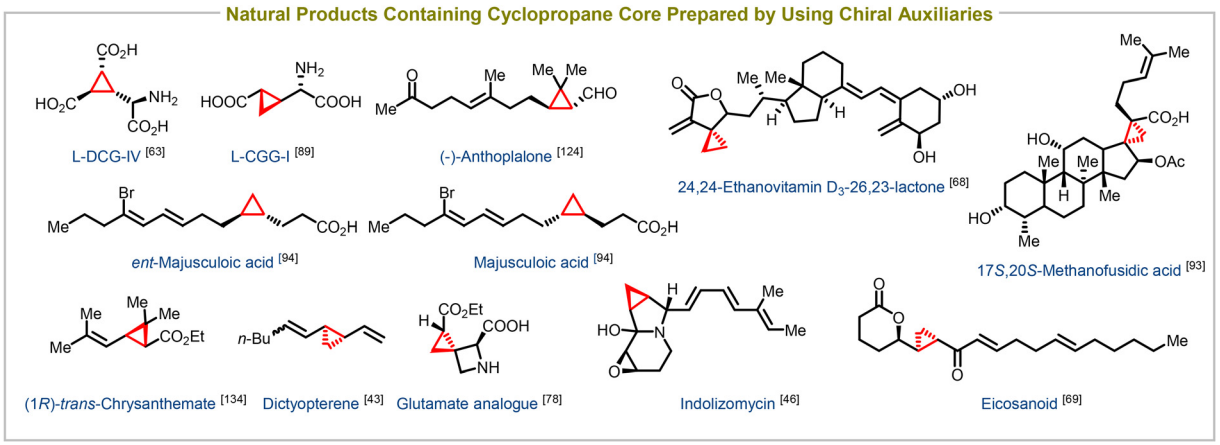


Fig. 4 Natural products containing cyclopropane core structure synthesized using chiral substrates and chiral nucleophiles.

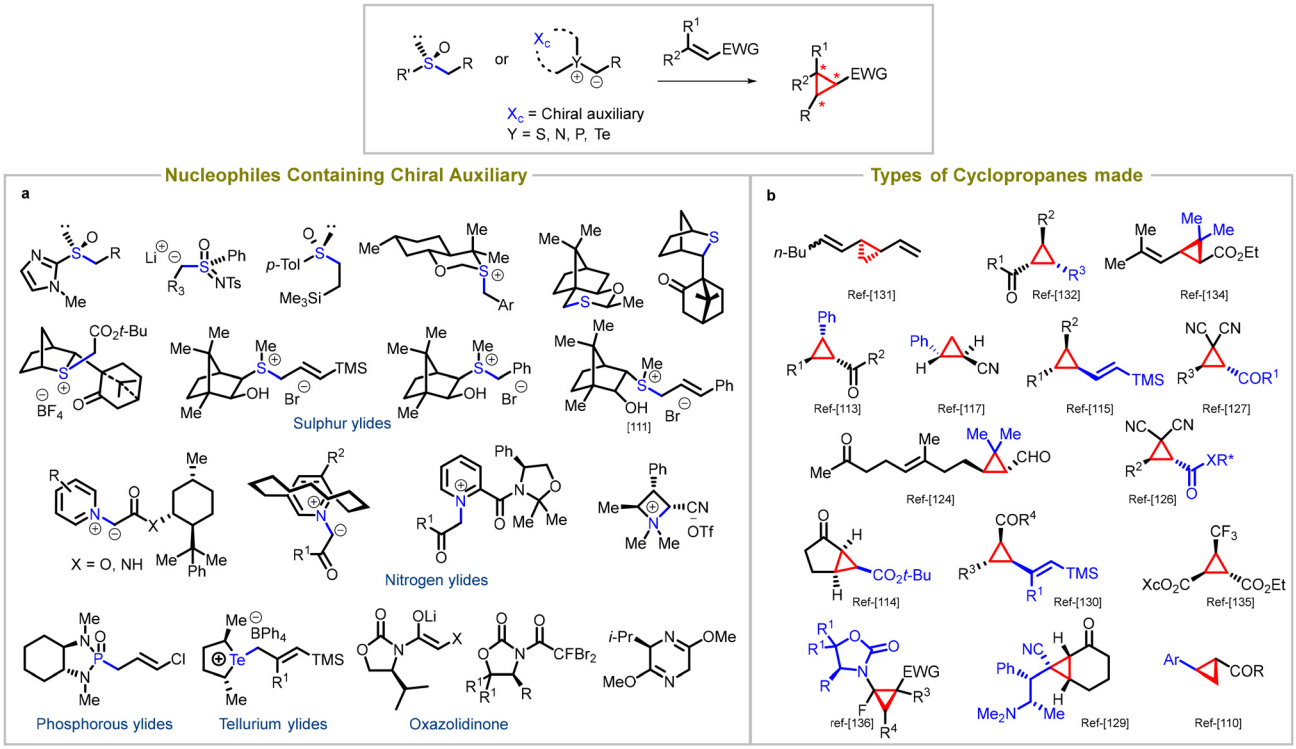


Fig. 5 Diastereoselective synthesis of cyclopropanes: (a) types of auxiliaries used in Michael acceptors, (b) different cyclopropanes synthesized using chiral auxiliaries.

approach involves the addition of nucleophiles that contain chiral auxiliaries to an achiral substrate. Initial studies involved chiral aminosulfoxonium ylides to access chiral cyclopropanes.[97–109] The nucleophiles possess chiral sulfur,[110–117] phosphorus,[118–124] nitrogen,[125–129] and tellurium ylides,[130] as well as chiral sulfoxides[131–134] and oxazolidinones[135,136] (entry a, Fig. 5). They possess a remarkable ability to undergo nucleophilic addition to electron-deficient Michael acceptors, resulting in the formation of chiral cyclopropane rings.

The literature showcases the synthesis of various types of cyclopropanes, some of which are illustrated in Fig. 5 (entry b). The chirality inherent in these nucleophiles allows for stereochemical control over the reaction, enabling selective formation of specific cyclopropane diastereomers. By utilizing chiral nucleophiles in Michael-initiated cyclopropanation reactions, chemists can access structurally diverse and stereochemically complex cyclopropane derivatives. These derivatives find applications in various fields, including medicinal chemistry and natural product synthesis.

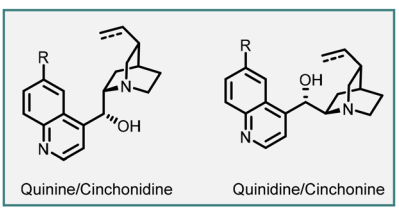
3. Chiral catalysts

3.1 Organocatalysts

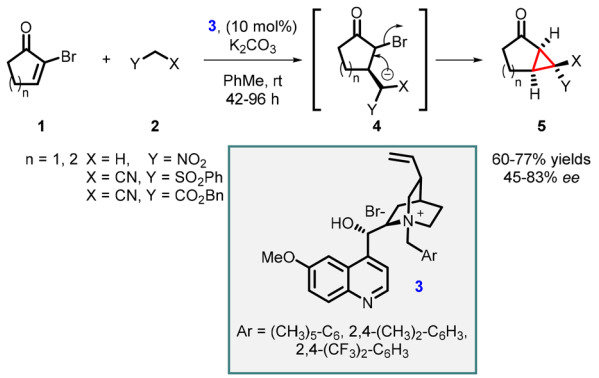
In the past two decades a large number of scientists including the recent Nobel laureates List and MacMillan have made significant contributions that has revitalized the field of organocatalysis, establishing it as a crucial component of asymmetric catalysis alongside organometallic and enzymatic catalysis.[137,138] The utilization of organocatalytic methods has proven to be highly effective in achieving efficient synthesis. These methods are characterized by their ability to accurately predict stereochemistry, accommodate diverse functional groups, and promote metal-free processes.

Organocatalysts play a crucial role in facilitating enantioselective Michael Initiated Ring Closure (MIRC) reaction.[139] These catalysts interact with the reactants to direct the synthesis of highly enantioselective cyclopropane derivatives through processes such as hydrogen bonding and Lewis acid/base interactions. An advantage of MIRC reaction is its capability to operate under mild reaction conditions without the need for metal catalysts. This characteristic significantly expands the possibilities for synthesizing complex chiral cyclopropanes.

3.1.1 Quinine/cinchonine, quinidine/cinchonidine organocatalysts



In 1999, Arai, Shioiri, and co-workers reported the first asymmetric cyclopropanation reaction using phase-transfer catalysis (PTC) (Scheme 1). They utilized α-bromocycloalkenones (**1**)



Scheme 1 PTC catalyzed asymmetric cyclopropanation of α-bromocycloalkenones.

and nitriles (**2**) in a Michael addition, proton transfer, and intramolecular alkylation sequence employing catalyst **3** (cinchona alkaloid derived quaternary ammonium salt) and potassium carbonate as base. The reaction proceeded through intermediate **4**, which yielded highly functionalized bicyclic compounds (**5**) with moderate to good enantioselectivities (45–83% ee).[140]

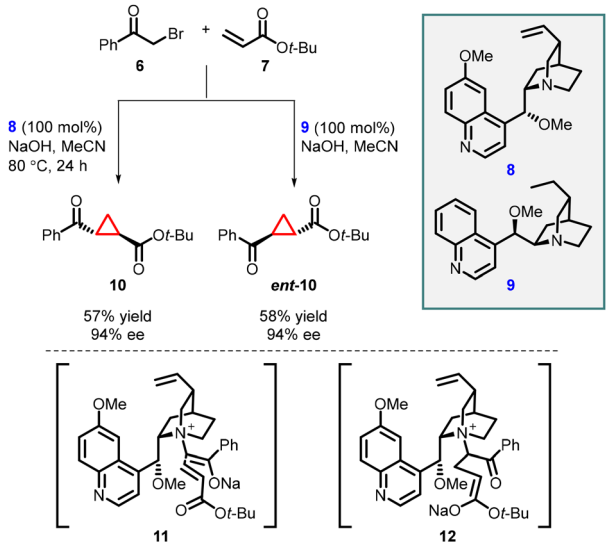
In 2003, Gaunt and co-workers reported enantioselective cyclopropanation utilizing a cinchona alkaloid derived quaternary ammonium salt. They achieved this by employing a Michael addition of a chiral ammonium ylide (**11**), derived from cinchona alkaloids (**8**, **9**), to an α,β-unsaturated carbonyl compound (**7**). This step was crucial in generating the cyclopropane structure with high stereoselectivity (Scheme 2).[141]

To accomplish asymmetric variation of MIRC reaction, they first formed a quaternary ammonium salt *in situ* using phenacyl bromine **6** and a stoichiometric amount of chiral cinchonine **8** through a nucleophilic substitution process. Subsequently, deprotonation with sodium hydroxide yielded the ammonium ylide. The chiral ammonium ylide was then reacted with *tert*-butyl acrylate **7** resulting in the formation of chiral cyclopropane (**10**) in 57% yield and good stereoselectivity (94% ee). Interestingly, when cinchonine **9** was used instead of cinchonine **8** under the same reaction conditions, the opposite enantiomer, *ent*-**10**, was obtained with a 58% yield and the same stereochemistry (94% ee) (Scheme 2).

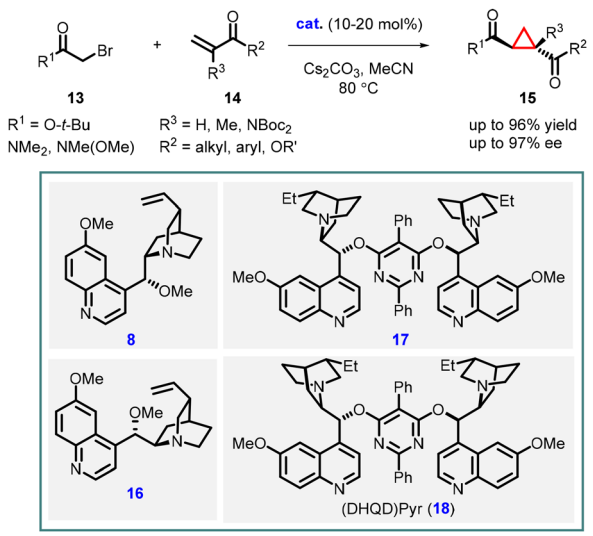
The reaction mechanism can be explained by a Michael addition of the ammonium ylide (**11**) to *tert*-butyl acrylate, followed by the release of a chiral *tertiary* amine during the 3-*exo*-*tet*-cyclization process (**12**) to yield cyclopropane **10**.

Following their initial report on stoichiometric asymmetric cyclopropanation, the Gaunt group went on to develop a catalytic enantioselective version using a series of cinchona alkaloid catalysts derived from quinine or quinidine. Through a thorough screening of bases, they discovered that using a larger metal cation (transitioning from Na to Cs) of the base resulted in improved yields of the cyclopropane product. This breakthrough allowed for the efficient utilization of a variety of easily accessible or commercially available cinchona alkaloid derivatives (**8**, **16**, **17**, **18**) in the asymmetric cyclopropanation reactions. These reactions involved α–bromo esters or amides (**13**) and vinyl ketones or ester (**14**), yielding the corresponding cyclopropanes (**15**) with good diastereo- and enantioselectivities (Scheme 3).[142]

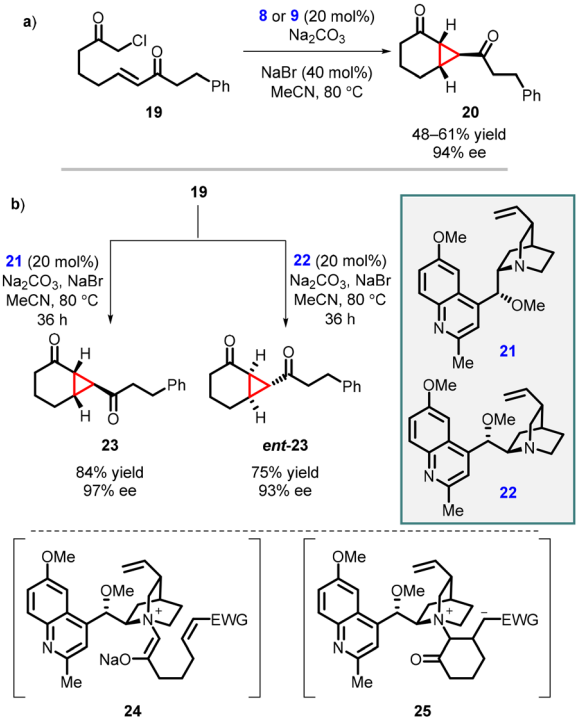
Gaunt and coworkers expanded MIRC reaction to enantioselective intramolecular cyclopropanation by utilizing substrate **19**. For the intramolecular variant, catalysts **8** and **9**, derived from cinchona alkaloids, were used for the reaction resulting in moderate yield and enantioselectivity 67% and 64% *ee* respectively. However, when NaBr was introduced to aid in the formation of the quaternary salt of the catalyst (Scheme 4, entry a) the reaction gave excellent enantioselectivity (94% ee).[143]



Scheme 2 Chiral ammonium ylide-mediated asymmetric cyclopropanation of *tert*-butyl acrylate.



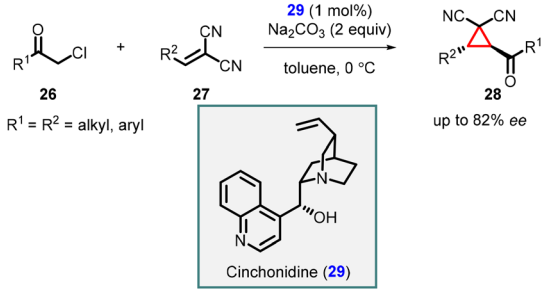
Scheme 3 Chiral ammonium ylide-mediated asymmetric cyclopropanation of α,β-unsaturated carbonyl compounds.



Scheme 4 Intramolecular asymmetric cyclopropanation using modified cinchona alkaloid.

Two years after their initial report on intramolecular MIRC reaction, Gaunt and coworkers used novel cinchona alkaloid derivatives **21** or **22** to improve the yield and enantioselectivity for substrate **19**. The reaction involves two steps: an intramolecular Michael addition (**24**) followed by an intramolecular cyclopropanation *via* nucleophilic substitution (**25**), taking place within a chiral ammonium ylide, resulting in the formation of [4.1.0]-bicycloalkane **23** (Scheme 4 entry b). The substrate **19** was treated with the modified cinchona catalyst **21** (20 mol%), in the presence of Na_2CO_3 and NaBr in MeCN at 80 °C for 36 h, resulting in the formation of cyclopropane **23** with an 84% yield and 97% enantiomeric excess. By using catalyst **22** under the same reaction conditions, enantiomer *ent*-**23** was obtained with a 75% yield and 93% ee (Scheme 4, entry b). The modified cinchona alkaloid derivatives **21** and **22** prevented side reactions caused by *N*-alkylation of the quinoline ring nitrogen atom thereby improving the yields of both **23** and *ent*-**23**.[144]

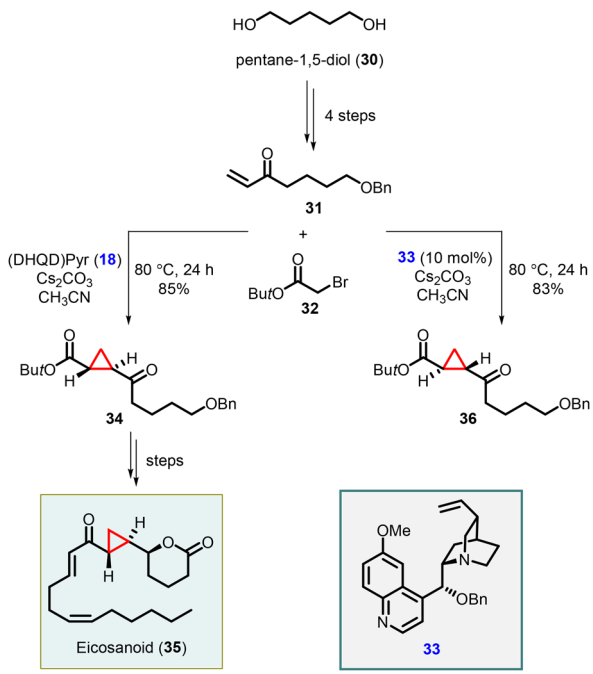
In 2006, Kojima and coworkers presented an enantioselective synthesis of tetra-substituted cyclopropanes by utilizing chiral cinchonidine catalyst **29** in MIRC reaction involving chloromethyl ketones (**26**) and β-substituted methylidenemalononitriles (**27**) (Scheme 5).[145] This reaction yielded *trans*-cyclopropanes (**28**) with good enantioselectivities up to 82% ee. Notably, the Cinchonidine catalyst functioned as a chiral Brønsted base catalyst, and the presence of hydrogen bonding played a crucial role in achieving high enantioselectivity. This innovative approach highlighted the versatility and effectiveness of cinchonidine in promoting asymmetric transformations.



Scheme 5 Enantioselective cyclopropanation of β-substituted methylidenemalononitriles.

Total synthesis of an eicosanoid was developed by Kumaraswamy and coworkers who adopted Gaunt's method of Michael-initiated ring closure reaction for the cyclopropanation step using the (DHQD)Pyr (**18**) as catalyst. They applied the protocol by functionalizing the vinyl ketone **31**, derived from pentane-1,5-diol (**30**), and *tert*-butyl bromoacetate, resulting in the formation of the key cyclopropyl moiety **34**. To access the opposite enantiomer **36**, they employed the cinchona alkaloid derivative **33** as catalyst. The cyclopropane intermediate **34** served as a pivotal building block for the synthesis of the natural product eicosanoid **35**. This was accomplished by subjecting compound **34** to catalytic asymmetric transfer hydrogenation, following Noyori's protocol, followed by subsequent manipulations of the functional groups (Scheme 6).[146]

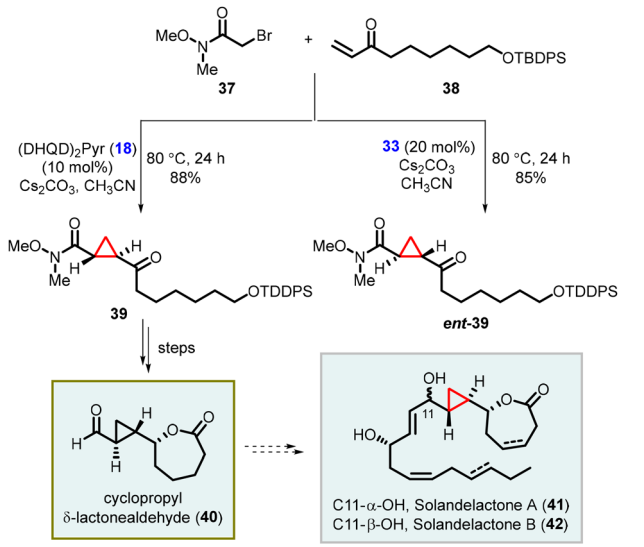
Kumaraswamy and coworkers have also reported the total synthesis of solandelactone A and B which involves the synthesis of cyclopropyl δ-lactonealdehyde **40** as a key intermedi-



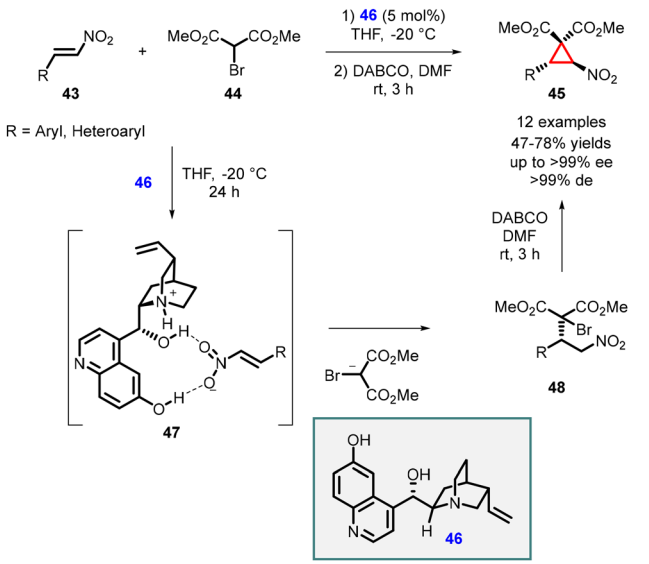
Scheme 6 Enantioselective cyclopropanation in total synthesis of eicosanoid.

ate. The cyclopropyl moiety of the intermediate **40** was synthesized using asymmetric MIRC reaction which involves reaction of 2-bromo-*N*,*O*-dimethylacetamide (**37**) and enone (**38**), utilizing organocatalyst **18** and **33** (Scheme 7).[147]

In 2009, Yan and coworkers showcased an enantioselective conjugate addition of dimethyl bromomalonate **44** to nitroalkenes (**43**) using the 6′-demethyl quinine (**46**) catalyst. The reaction was followed by an intramolecular cyclopropanation employing 1,4-diazabicyclo[2.2.2]octane (DABCO), resulting in the formation of nitrocyclopropanes **45** with 47–78% yields and high diastereoselectivity (>99% de) and enantioselectivity (>99% ee) (Scheme 8).[148]



Scheme 7 Synthesis of cyclopropyl δ-lactonealdehydes through enantioselective cyclopropanation.

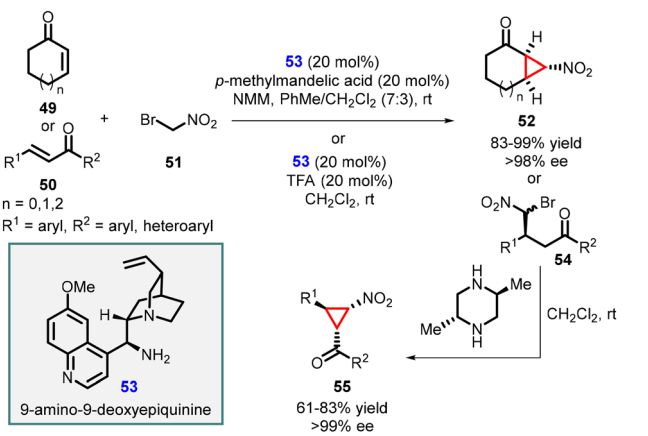


Scheme 8 6′-Demethyl quinine catalyzed enantioselective synthesis of nitrocyclopropanes.

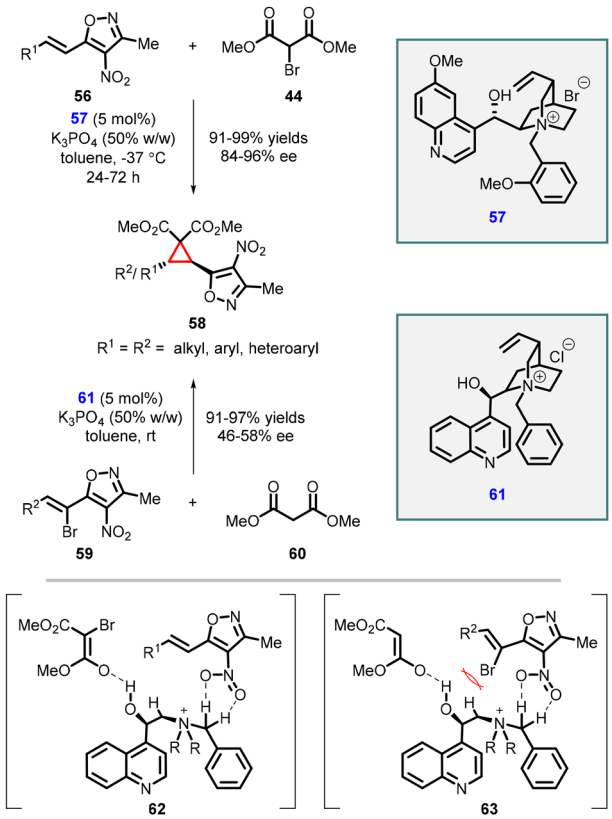
The cinchona alkaloid **46** played a crucial role as a bifunctional catalyst In the MIRC reaction. The nitrogen atom of the catalyst facilitated the abstraction of the α-proton from dimethyl bromomalonate **44**, while the hydroxyl groups of catalyst (**46**) formed hydrogen bonds with the nitro group of the β-nitroalkene **43** which is depicted in the transition state **47**. This interaction activated the β-nitrostyrene **43**, enabling an efficient asymmetric Michael addition. Subsequent treatment of the Michael-adduct (**48**) with DABCO in DMF at room temperature for 3 hours yielded *trans*-cyclopropane (**45**). Notably, no *cis*-cyclopropane was observed based on NMR analysis.

Wang and coworkers successfully synthesized enantiopure functionalized nitrocyclopropanes by utilizing a quinine-derived amine, specifically 9-amino-9-deoxyepiquinine (**53**), as an effective catalyst (Scheme 9).[149] The conjugate addition of bromonitromethane **51** to α,β-unsaturated enone systems was efficiently catalyzed by the salt derived from the combination of cinchona alkaloid **53** with mandelic acid. The reaction tolerated cyclic as well as aromatic enones (**49** and **50**) as substrates, resulting in high yields of nitrocyclopropane products (**52** and **55**) with excellent stereoselectivities (>98 and >99% ee). This approach demonstrated the effectiveness of the 9-amino-9-deoxyepiquinine as an organocatalyst in facilitating the synthesis of enantioenriched nitrocyclopropanes through MIRC reaction.

Adamo and coworkers have reported an efficient enantioselective synthesis of highly substituted cyclopropanes through MIRC reaction. The reaction involves 4-nitro-5-styrylisoxazoles (**56**), a class of cinnamate synthetic equivalent, with 2-bromomalonate esters (**44**) using a cinchona alkaloid derived phase-transfer catalyst (**57**) (Scheme 10).[150] Remarkably, this method yielded *trans*-cyclopropylisoxazoles (**58**) as a single diastereomer with excellent yields (up to 99%) and good to excellent enantiomeric excess (84–96% ee). The presence of a free hydroxy group of the catalyst **57** plays a vital role in achieving high enantioselectivity. This is attributed to the ability of the hydroxy group to form a hydrogen bond with the bromomalonate substrate (**44**).



Scheme 9 9-Amino-9-deoxyepiquinine catalyzed enantioselective synthesis of functionalized nitrocyclopropanes.

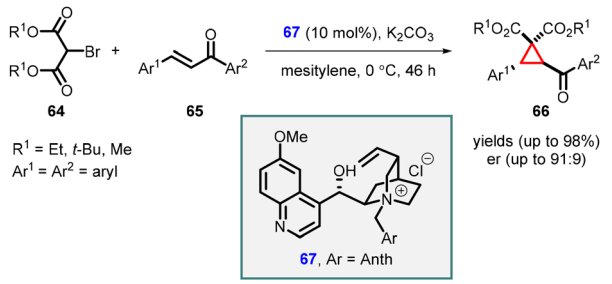


Scheme 10 Enantioselective cyclopropanation of 4-nitro-5-styrylisoxazoles.

In 2015, the study was extended to malonate esters **60** as a nucleophile resulting in the formation of the same cyclopropanes **58** with excellent yields (91–97%) and poor enantioselectivities (46–58% ee) (Scheme 10).[151]

The observed difference in enantioselectivity between these two approaches can be attributed to a comparison of transition states **62** and **63**. In compound **59**, the presence of a bromine atom shields the nitro group (NO_2), limiting its interaction with the phase-transfer catalyst (PTC). This interaction, which is absent in compounds **56**, is responsible for higher enantioselectivity. Therefore, the lower enantioselectivity observed can be correlated to the limited interaction between the nitro group and the PTC due to the presence of the bromine atom.

In a significant breakthrough, Waser and coworkers introduced an asymmetric MIRC reaction between bromomalonate (**64**) and chalcones (**65**). This transformation was achieved using Cinchona alkaloids (**67**) as chiral catalyst under phase transfer catalysis conditions, resulting in the synthesis of highly substituted cyclopropanes (**66**) (Scheme 11).[152] Catalyst **67**, derived from quinidine and 9-(chloromethyl)-anthracene proved to be highly effective in facilitating the reaction, leading to high yields (up to 98%) and enantioselectivity (up to 91 : 9 er). The successful outcome of the reaction relied on the utilization of a cinchona alkaloid ammonium salt catalyst containing a free OH group, along with the optimized liquid/liquid reaction conditions. Notably, the process demonstrated



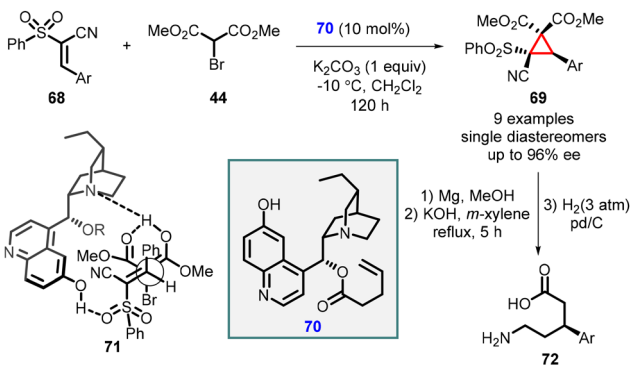
Scheme 11 Enantioselective cyclopropanation of chalcones.

excellent performance with both electron-donating and electron-deficient chalcones.

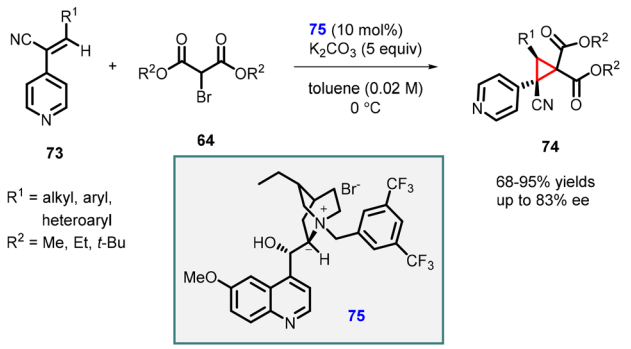
Cobb and coworkers have recently disclosed a remarkable finding regarding the enantioselective cyclopropanation of conjugated cyanosulfones (**68**). This transformation resulted in the formation of a single diastereomer with remarkably high enantioselectivity, reaching up to 96% enantiomeric excess (ee). The high stereoselectivity for the MIRC reaction was attributed to the development of a novel bifunctional catalyst based on the cinchona alkaloid framework, specifically the cupreine organocatalyst (**70**). The reaction proceeds through the simultaneous activation of the pronucleophile bromomalonate (**44**) and the electrophilic cyanosulfone (**68**), facilitated by coordination to the cupreine-derived catalyst which is shown in transition state (**71**) (Scheme 12).[153]

The resulting cyclopropanes (**69**) can be further transformed into the corresponding δ-amino acids (**72**) through a magnesium-initiated radical desulfonylation-ring opening process.

Adamo and coworkers reported highly enantioselective MIRC reaction using (*Z*)-3-substituted-2-(4-pyridyl)-acrylonitrile (**73**), a reactive class of Michael acceptor, and 2-bromomalonate esters (**64**). The reaction was catalyzed by a Cinchona derived phase-transfer catalyst (**75**) which resulted in the rapid synthesis of highly functionalized cyclopropanes **74** with two quaternary centers (Scheme 13).[154] The transformation produced *cis*-cyclopropanes as single diastereoisomers, exhibiting excellent yields (68–95%) and good enantioselectivity (up to



Scheme 12 Enantioselective cyclopropanation of conjugated cyanosulfones.



Scheme 13 Enantioselective cyclopropanation of (*Z*)-3-substituted-2-(4-pyridyl)-acrylonitrile.

83% ee). The reaction demonstrated broad substrate scope and was successfully scaled up to gram level without compromising yield or stereochemical outcome. Additionally, a one-pot multicomponent procedure proved to be effective in this context.

Synthesis of cyclopropane-based purine analogues was reported by Xie and Guo using C_2-symmetric hydroquinidine (anthraquinone-1,4-diyl)diether (DHQN)$_2$AQN (**79**) as an organocatalyst. The system was efficient for enantioselective cyclopropanation of α-purine acrylate **76** and *tert*-butyl-2-bromoacetate **77**, leading to the formation of cyclopropyl purine analogs **78**. The reaction exhibited high yields (up to 98%), and excellent stereoselectivity (>20 : 1 dr, 97% ee) (Scheme 14).[155]

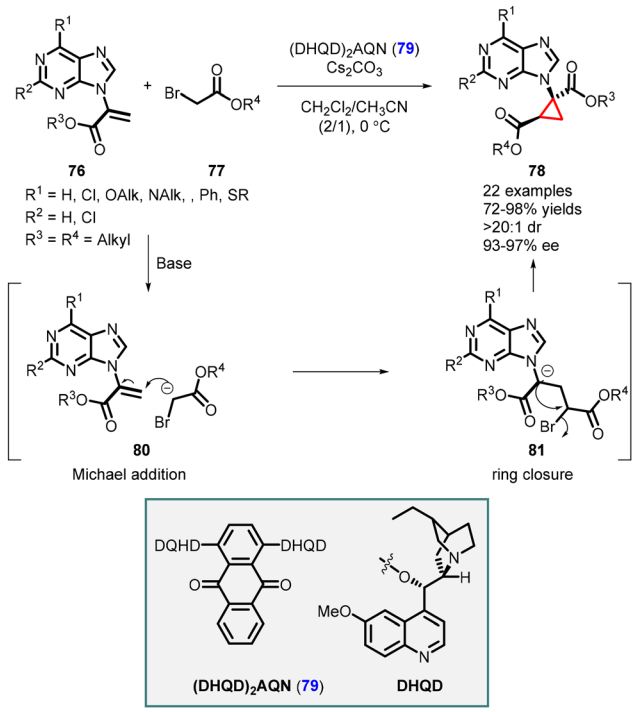
The mechanism involves the formation of a hydrogen bond between the enol form of *tert*-butyl-2-bromoacetate **77** and the catalyst **79**. This interaction facilitates a Michael addition (intermediate **80**) to the purine acrylate **76**, followed by intramolecular alkylation (intermediate **81**). The release of a bromine atom results in the formation of cyclopropyl purine analogue **78**, with two stereogenic centers, one of which is a quaternary center.

In an interesting development, Xie and Guo were able to extend the studies to cyclopropane-based pyrimidine analogues (**84**) containing a quaternary center. The asymmetric version of the MIRC reaction was achieved using (DHQD)$_2$AQN (**79**) as an organocatalyst and the reaction involves the coupling of α-pyrimidine substituted acrylates (**82**) with bromo-carboxylic esters (**83**) (Scheme 15).[156]

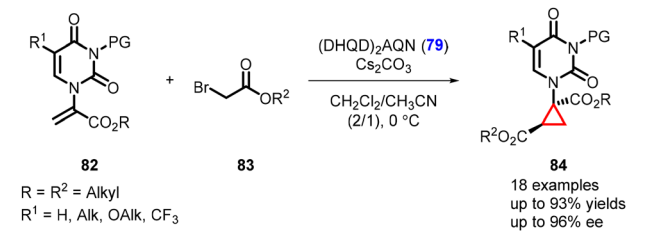
Notably, the cyclopropyl pyrimidine analogues synthesized exhibited axis chirality, which was observed for the first time in this context. This axis chirality arises from the rotationally restricted N–C bond in the N–COR$_3$ moiety of the molecules.

Roiser and Waser reported the synthesis of highly enantioenriched spirocyclopropanes (chiral spiro[2.5]octa-4,7-dien-6-ones) (**87**). The reaction involved the addition of cinchona alkaloid-based chiral ammonium ylides **86** to *para*-quinone methides **85** in the presence of Cs_2CO_3 (6 equiv.) as base in CH_2Cl_2 at reflux condition for 96 h (Scheme 16).[157] The reaction yielded spirocyclopropanes **87** with a high diastereomeric ratio of >95 : 5 and an enantiomeric ratio of >99.9 : 0.1, making it a valuable method for the synthesis of chiral spirocyclopropanes.

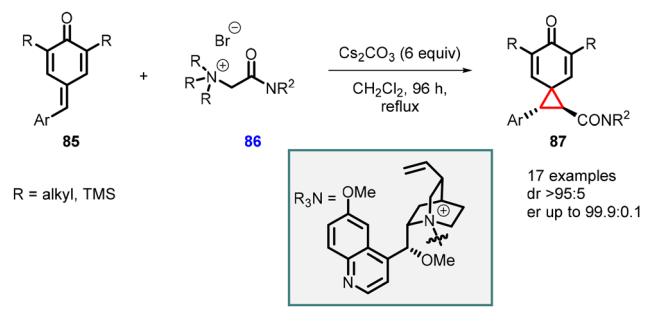
Ji, Peng, and Zeng reported the synthesis of highly functionalized cyclopropa[*c*]coumarin derivatives (**90**) through a MIRC reaction of 3-substituted coumarins (**88**) and 2-bromomalonate



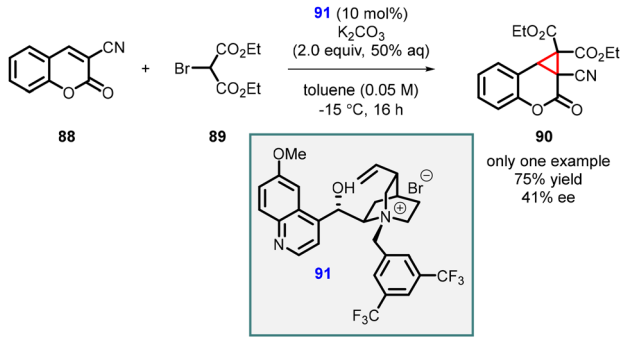
Scheme 14 Enantioselective cyclopropanation of α-purine acrylate.



Scheme 15 Enantioselective cyclopropanation of α-pyrimidine substituted acrylates.



Scheme 16 Enantioselective cyclopropanation of *para*-quinone methides.



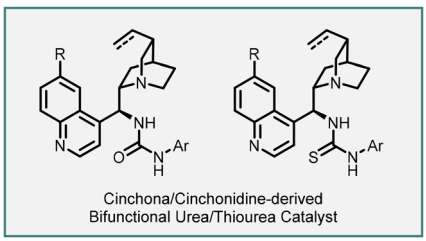
Scheme 17 Enantioselective cyclopropanation of 3-substituted coumarins.

(**89**), (Scheme 17).[158] The reaction utilized chiral phase-transfer catalyst (PTC) (**91**), which resulted in the desired cyclopropanation transformation in average yield (75%) and poor enantioselectivity (41% ee). It is important to note that the asymmetric version of the reaction was performed for only one substrate.

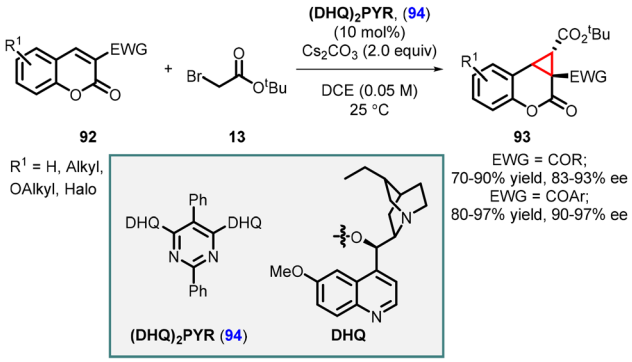
Sun and coworkers subsequently employed the catalyst $(DHQ)_2PYR$ **94** for the highly enantioselective synthesis of cyclopropa[*c*]coumarins (**93**). In this method, the catalyst $(DHQ)_2PYR$ **94** reacts with *tert*-butyl 2-bromoacetate **13**, leading to the formation of an ylide **96** with the assistance of the base Cs_2CO_3. The intermediate **96** then undergoes a Michael addition to the coumarin (**92**), followed by nucleophilic substitution, resulting in the formation of the corresponding cyclopropa[*c*]coumarins (**93**) with good to excellent yields of up to 97% and enantioselectivities of up to 97% ee (Scheme 18).[159]

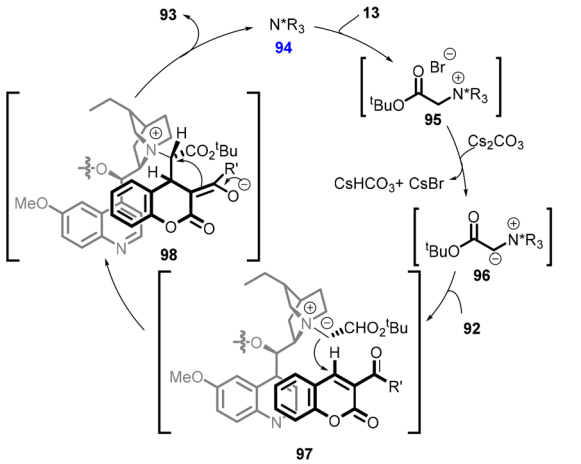
Recently, Blay, Vila, and coworkers have made significant progress in developing an asymmetric MIRC reaction. They successfully demonstrated the reaction between arylidenepyrazolones (**99**) and dialkyl 2-bromomalonates (**64**) (Scheme 19).[160] The catalyst employed in this process was a commercially available organocatalyst, $(DHQ)_2AQN$ (**79**). The reaction conditions were mild, leading to the formation of chiral spirocyclopropyl pyrazolones (21 examples) with yields ranging from 30–81%. The diastereoselectivity for the reaction varied from 60 : 40 to >95 : 5, and the enantioselectivity obtained was modest to high ranging from 26–93% ee.

3.1.2 Cinchona/cinchonidine-derived bifunctional urea/thiourea organocatalysts

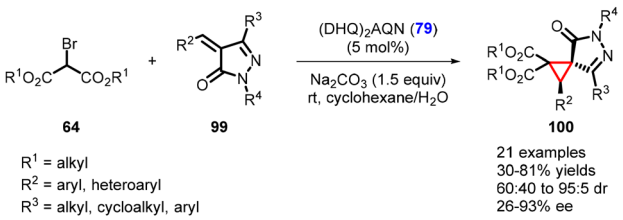


Singh and coworkers have recently introduced an efficient and practical method for the synthesis of highly enantioenriched





Scheme 18 $(DHQ)_2PYR$ catalyzed enantioselective MIRC cyclopropanation of coumarins.

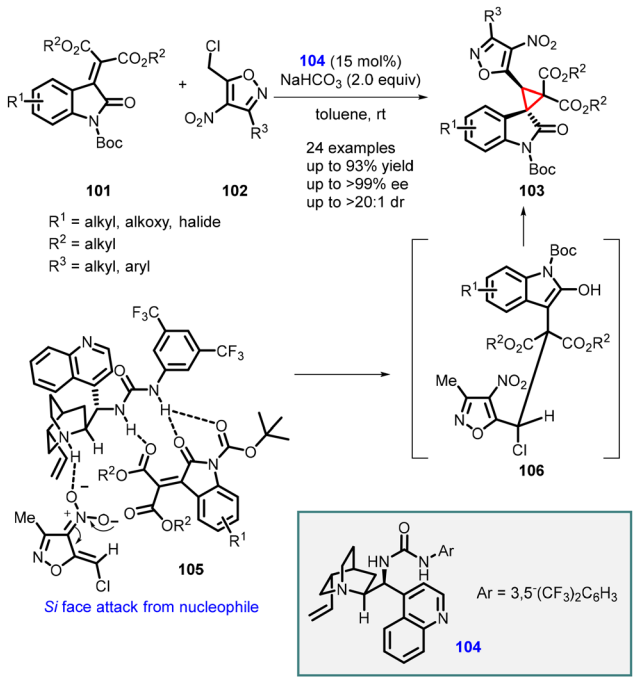


Scheme 19 Enantioselective MIRC cyclopropanation of arylidenepyrazolones.

spiro-cyclopropyl oxindole derivatives (**103**). This approach involves a cinchonidine-derived bifunctional urea catalyst **104** and employs an asymmetric vinylogous Michael addition of 4-nitroisoxazole derivatives (**102**) to *N*-Boc isatylidene malonates (**101**), followed by intramolecular alkylation.

The novel organocatalyst yielded highly substituted spiro-3,3′-cyclopropyl oxindoles (**103**) with *tert*-spiro quaternary stereogenic centers. The reaction exhibited excellent diastereoselectivity (>20 : 1, dr) and enantioselectivity (up to >99%). The desired products were obtained in high yields (up to 93%) (Scheme 20).[161]

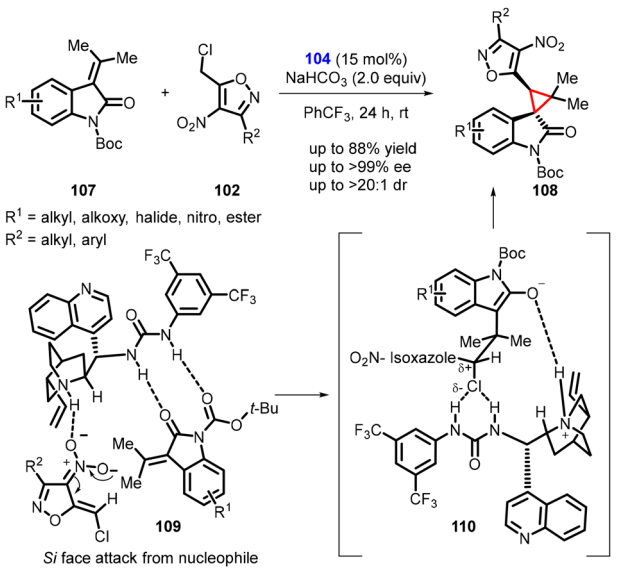
The observed stereochemical outcome of the vinylogous MIRC reaction was rationalized based on a transition state **105**. This transition state involves the simultaneous activation



Scheme 20 Asymmetric synthesis of spiro-3,3′-cyclopropyl oxindoles using cinchonidine-derived bifunctional urea catalyst.

of the reaction partners through H-bonding interactions facilitated by the bifunctional urea catalyst.

Singh and coworkers extended the idea in a subsequent study, involving the enantioselective synthesis of novel spirocyclopropyl oxindole (**108**) from *N*-boc-isopropylidene oxindole (**107**) and 5-(chloromethyl)-3-methyl-4-nitroisoxazole (**102**) (Scheme 21).[162] The reaction employed the same catalyst **104** and exhibited a similar stereochemical outcome. The catalyst



Scheme 21 Asymmetric cyclopropanation of *N*-boc-isopropylidene oxindole and 5-(chloromethyl)-3-methyl-4-nitroisoxazole.

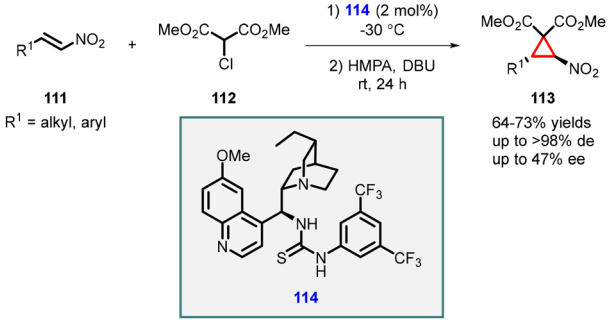
deprotonated compound **102**, generating an anionic nucleophile, while activating *tert*-butyl 2-oxo-3-(propan-2-ylidene) indoline-1-carboxylate (**107**) through H-bonding. The nucleophile then attacked substrate **107**, resulting in the formation of an enolate. The facilitation of the chiral catalyst **104** in the substitution step, and its anion binding activity promoted S_N2-type reactions, ultimately leading to the formation of the major stereoisomer of compound **108** (Scheme 21. See **109** and **110**).

In 2006, Connon developed an elegant and convenient MIRC reaction involving β-nitrostyrenes (**111**) and 2-chloromalonates (**112**). Chiral thiourea (**114**) served as a catalyst, and base was required for the final cyclization step. The reaction gave cyclopropanes (**113**) in good yields with excellent diastereoselectivities (>98% dr). Mechanistically, the reaction proceeded through the addition of chloromalonate to nitroalkenes, followed by base catalyzed intramolecular alkylation. However, the observed enantioselectivity for different substrates were modest, with values ranging from moderate to low, reaching a maximum of 47% ee (Scheme 22).[163]

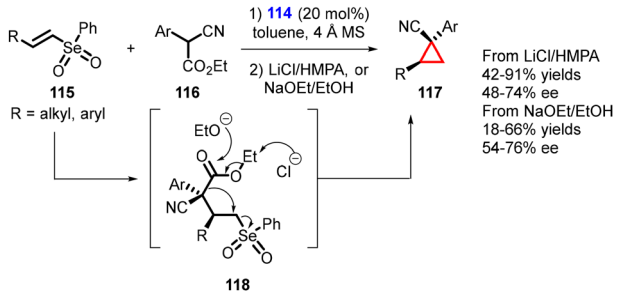
Marini and coworkers reported the synthesis of enantioenriched cyclopropanes containing vicinal tertiary and quaternary stereocenters using a MIRC reaction. The reaction involves the conjugate addition of α-substituted cyanoacetates (**116**) to readily accessible, less reactive β-substituted vinyl selenones (**115**) using a bifunctional thiourea catalyst (**114**). The reaction proceeds through formation of the Michael adduct (**118**), which undergoes intramolecular alkylation induced by a de-ethoxycarbonylation process.

Two distinct conditions were utilized for the de-ethoxycarbonylation step: (1) use of LiCl in HMPA (a Krapcho-type protocol), and (2) a more environmentally friendly strategy employing EtONa in EtOH (Scheme 23).[164] As a result, the *Z*-cyclopropanes were obtained as exclusive isomers with yields ranging from moderate to high, accompanied by moderate to good enantioselectivity (54–74% ee).

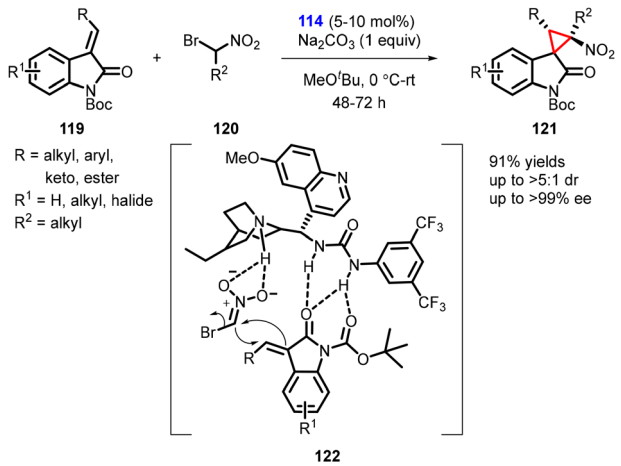
In 2011, Bencivenni and Bartoli described a new variant for the asymmetric synthesis of spirocyclopropyl oxindoles utilizing a MIRC strategy. The reaction involved treatment of 3-alkenyl oxindoles (**119**) with bromonitromethane (**120**) in presence of cinchona alkaloid-derived bifunctional thiourea catalyst (**114**). The reaction resulted in the formation of spiro



Scheme 22 Chiral thiourea catalyzed stereoselective synthesis of heavily functionalized nitrocyclopropanes.



Scheme 23 Organocatalyzed MIRC cyclopropanation reaction of β-substituted vinyl selenones.



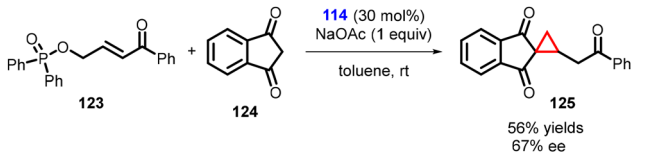
Scheme 24 MIRC cyclopropanation of 3-alkenyl oxindoles with bromonitromethane.

nitrocyclopropane oxindoles (spiro 3,3′-cyclopropyl oxindoles) (**121**) with moderate to high diastereoselectivity (>5 : 1) and excellent enantioselectivity (>99% ee) (Scheme 24).[165]

Catalyst **114** played a dual role by activating both the electrophilic oxindole and the Michael donor bromonitromethane. The activation occurred through hydrogen-bond interactions controlled by the thiourea moiety of the catalyst, which facilitated the formation of cyclopropane from the *Si*-face of the double bond.

Lattanzi and coworkers have developed a direct and efficient method to synthesize activated cyclopropanes containing homologated carbonyl groups. The method involves K_2CO_3-promoted tandem MIRC reaction between γ-hydroxyenone derived diphenylphosphinates (**123**) and 1,3-indandione (**124**). In preliminary studies, it was discovered that the cinchona alkaloids derived thiourea **114** served as a suitable catalyst for the development of an asymmetric version of this process (Scheme 25).[166]

Malkov and coworkers utilized Michael addition strategy for the synthesis of spirocyclopropanes containing two adjacent quaternary carbon centers. They employed α-chloro-β-dicarbonyl derivatives (**127**) in combination with alkylideneoxindoles (**126**) to generate the desired spirocyclopropanes



Scheme 25 Cinchona alkaloids derived thiourea catalyzed MIRC cyclopropanation containing homologated carbonyl groups.

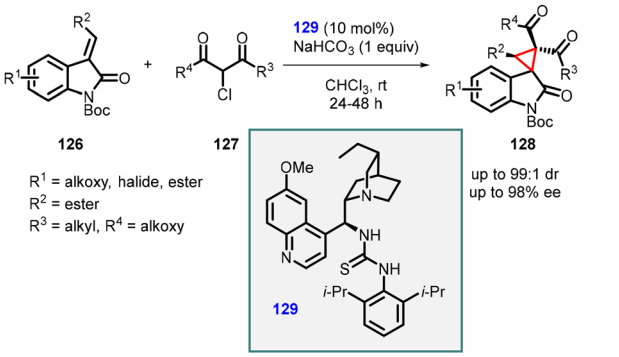
(**128**). These products featured valuable ketone or ester groups and exhibited excellent diastereomeric ratios (up to 99 : 1) and enantioselectivity (80–98% ee) (Scheme 26).[167]

Malkov group utilized **129** as a catalyst for the MIRC reaction, which is similar to the one employed by Bencivenni and Bartoli, thereby facilitating the formation of cyclopropane from *Si*-facial. The presence of 2′,5′-diisopropyl substitution on the aromatic ring of chiral catalyst **129** proved beneficial in restricting the rotation of the C–N bond, thereby enhancing the reaction's diastereoselectivity.

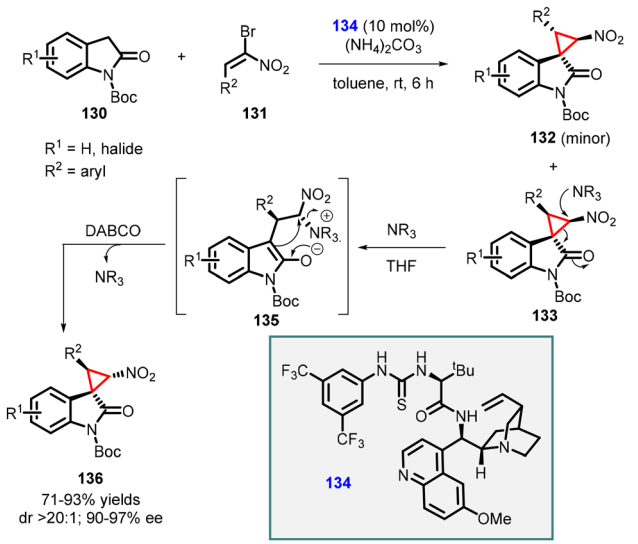
Lu and coworkers developed a MIRC strategy for the asymmetric synthesis of spirocyclopropyl oxindoles. The approach involves direct coupling of dinucleophilic oxindoles with a suitable dielectrophile, such as α-halogenated nitroolefins (Scheme 27).[168] The *N*-Boc oxindole **130** (serving as the dinucleophile C1 synthon) was reacted with bromonitroolefins **131** (acting as the dielectrophilic C2 synthon) in the presence of a novel thiourea catalyst **134** (10 mol%). Ammonium carbonate was used as an HBr scavenger to mitigate its generation during the reaction. This reaction resulted in the formation of two diastereoisomers, **133** and **132**, in good yields, moderate to excellent diastereoselectivity, and excellent enantioselectivity (90–97% ee).

In addition, a diastereodivergent approach was developed by subjecting compound **133** to DABCO which acts as a nucleophile. Upon the addition of DABCO, a conventional cyclopropane ring-opening and closing mechanism was observed. Interestingly, the presence of the nucleophile did not affect the other diastereomer **132**, thereby influencing the diastereoselectivity of the reaction.

Lin and coworkers reported a cascade reaction which involves Michael addition and intramolecular alkylation steps



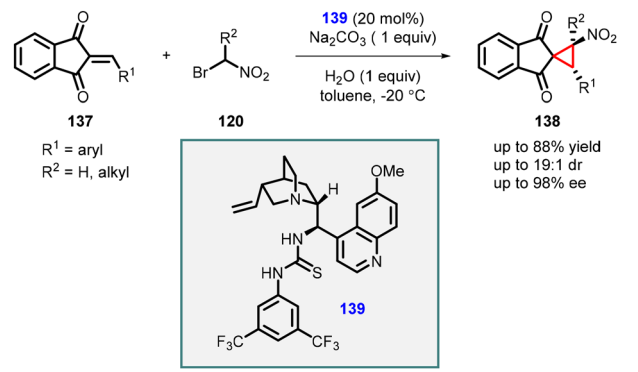
Scheme 26 Michael addition of α-chloro-β-dicarbonyl derivatives to alkylideneoxindoles.



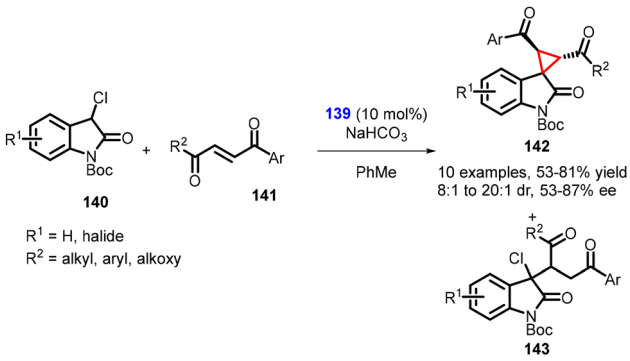
Scheme 27 Chiral amino acid-derived multifunctional thiourea catalyzed cyclopropanation of oxindoles with nitroolefins.

between 2-arylidene-1,3-indandiones (**137**) and 1-bromo nitroalkanes (**120**). The initial step of the cascade reaction involves Michael addition of nitro alkyl to the indandiones (**137**), followed by alkylation with the bromo group to the enolate resulting in spironitrocyclopropanes (**138**) formation (Scheme 28).[169] The reaction was efficiently catalyzed by a bifunctional tertiary amine/thiourea catalyst (**139**) derived from cinchona alkaloids. The reaction yielded good yields (63–88%) and with excellent stereoselectivities (up to 19 : 1 dr and 98% ee).

Kanger and coworkers reported the synthesis of spirocyclopropyl oxindoles using MIRC reaction. In this method, *N*-Boc-3-chlorooxindole **140**, unsaturated aromatic 1,4-diketone **141** and chiral thiourea catalyst **139** was used in the synthesis of spirocyclopropanes (**142**) (Scheme 29).[170] The chlorooxindole (**140**) underwent conjugate addition with the unsaturated 1,4-diketone (**141**), followed by an intramolecular nucleophilic chloride displacement to yield cyclopropane (**142**). The mechanism is similar to the one proposed by Malkov and coworkers.



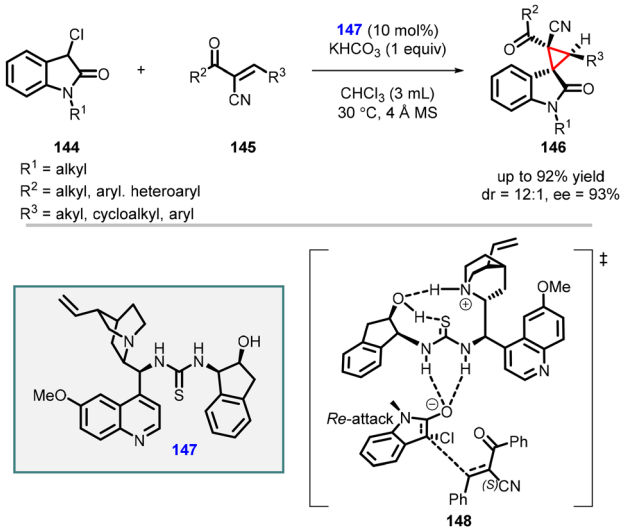
Scheme 28 MIRC cyclopropanation of 2-arylidene-1,3-indandiones with 1-bromo nitroalkanes.



Scheme 29 MIRC cyclopropanation of *N*-Boc-3-chlorooxindole with unsaturated aromatic 1,4-diketone.

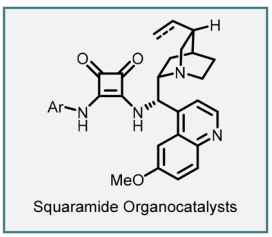
It is worth noting that the nucleophilic substitution reaction of chlorooxindole (**140**) to unsymmetrical, unsaturated 1,4-diketones (two reactive electrophilic centers) proceeded with regioselectivity. However, a small amount of uncyclized Michael adduct (**143**) was produced in all reactions. The reaction resulted in the desired cyclopropanes (**142**) in good yields (58–81%), diastereoselectivity (dr = 8 : 1 to 20 : 1), and enantioselectivity (87% ee).

In 2022 by Ouyang and Zheng reported stereoselective spirooxindoles synthesis by utilizing α-cyano chalcones (**145**) as the Michael acceptors, 3-chlorooxindole **144** as the nucleophile, and (**147**) derived from multifunctional quinine-based aminoindanol-thiourea as catalyst (Scheme 30).[171] The reaction yielded the desired product (**146**) with high yields (up to 92%), diastereoselectivity (up to 12 : 1), and enantioselectivity (93% ee). Density functional theory (DFT) calculations provided insights into the reaction mechanism, revealing the significance of potential intramolecular hydrogen bonds (**148**) within the chiral catalyst for effective stereocontrol.

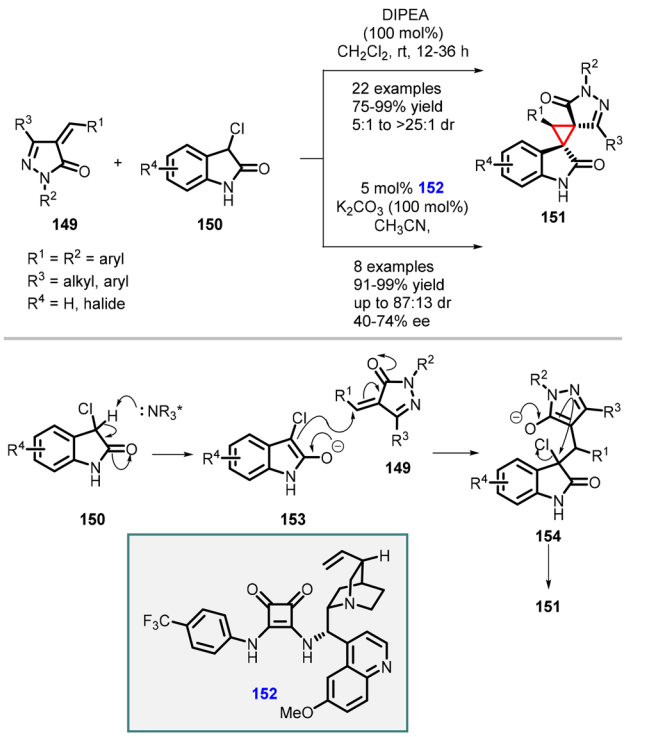


Scheme 30 MIRC cyclopropanation of chlorooxindole with α-cyano chalcones.

3.1.3 Squaramide organocatalyst. Squaramides, derivatives of squaric acid where the –OH groups are replaced with $–NH_2$ groups, have found wide application in MIRC reactions. They serve as isosteres and exhibit structural similarities to thioureas, although the interatomic distance between hydrogen atoms (H–H) in the squaramide system is 0.6 times greater than thiourea. Squaramides possess a higher acidity level in their NH bonds compared to thioureas. This characteristic enables squaramides to form stronger hydrogen bonds with functional groups such as nitro, carbonyl, carboxylates, and imino groups, which are particularly relevant in the context of thiourea-catalyzed reactions.



In 2005, Du and coworkers reported the synthesis of spiro-pyrazolone–cyclopropane oxindoles (**151**) through a tandem Michael addition/alkylation cascade reaction (Scheme 31).[172] The reaction involves 3-chlorooxindoles (**150**) and arylidene-pyrazolones (**149**) in the presence of DIPEA to yield the product (**151**) in excellent yield (75–99%) and diastereoselectivity (5 : 1 to >25 : 1).



Scheme 31 Michael/alkylation cascade cyclopropanation of chloroox-indole with arylidenepyrazolones.

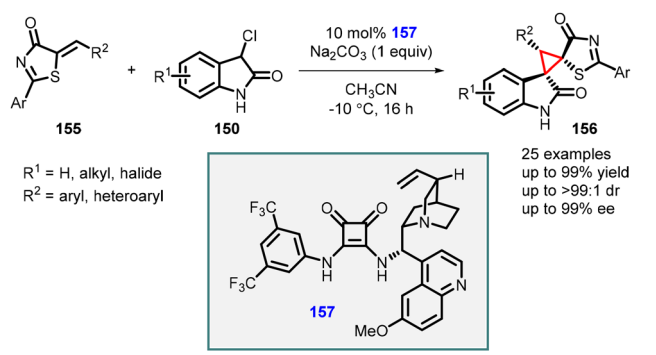
The proposed reaction mechanism involves the initial formation of an enolate by deprotonation of the halo oxindole derivative using DIPEA. The enolate then underwent a Michael addition on the β-carbon of the Michael acceptor (arylidene-pyrazolone) through a *Re*-face nucleophilic approach. Subsequently, an intramolecular nucleophilic displacement of the chlorine atom occurred in the presence of the base, resulting in the formation of the spiro-pyrazolone–cyclopropane-oxindole (**151**) product.

An enantioselective variant was demonstrated by employing a bifunctional squaramide catalyst (**152**). The reaction involves treating **149** and **150** with 5 mol% of the catalyst **152** and 100 mol% K_2CO_3, resulting in the cyclopropanes (**151**) bearing three contiguous stereocenters, including two vicinal quaternary centers. The reaction gave modest diastereoselectivity (87 : 13) and enantioselectivity (up to 74% ee), but the yields obtained were excellent ranging from 91% to 99%.

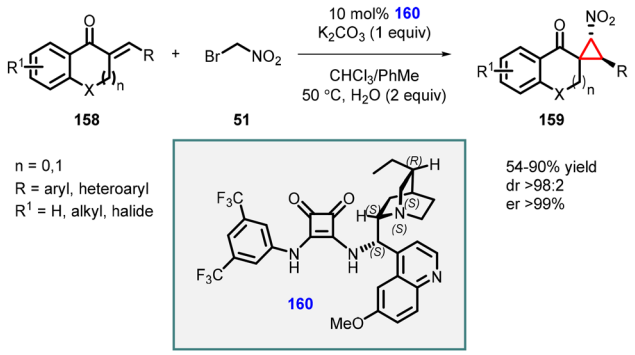
In a related study Du and coworkers, an asymmetric [2 + 1] cycloaddition reaction between 3-chlorooxindoles (**150**) and 5-alkenylthiazolones (**155**) was investigated (Scheme 32).[173] This reaction was catalyzed by hydroquinine squaramide **157**, with Na_2CO_3 as the base in acetonitrile at −10 °C. These optimized reaction conditions resulted in higher yields of the desired products, reaching up to 99%. Moreover, the reaction exhibited excellent diastereoselectivity (>99 : 1) and the enantioselectivity was also significantly improved, with enantiomeric excess (ee) values reaching up to 99%.

Du and coworkers extended the MIRC reaction for the asymmetric synthesis of spironitro-chromanonecyclopropanes (**159**) using bromonitroalkane **51** as nucleophile. The reaction proceeded through a Michael addition/alkylation cascade cyclization reaction, which involves unsaturated 4-chromanones (**158**), bromonitroalkane **51**, and chiral squaramide (**160**) as catalyst (Scheme 33).[174] The reaction resulted in the formation of highly substituted cyclopropanes with three contiguous stereocenters, with moderate to good yields (54–90%), excellent diastereoselectivity (98 : 2), and exceptional enantioselectivity, with an enantiomeric excess (ee) exceeding 99%.

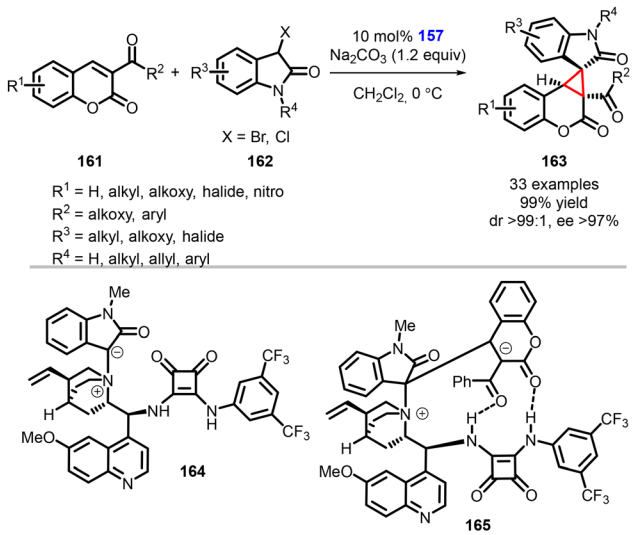
Yuan and coworkers reported an asymmetric synthesis of spirooxindole cyclopropa[*c*]coumarin compounds (**163**) achieved using a bifunctional squaramide catalyst (**157**)



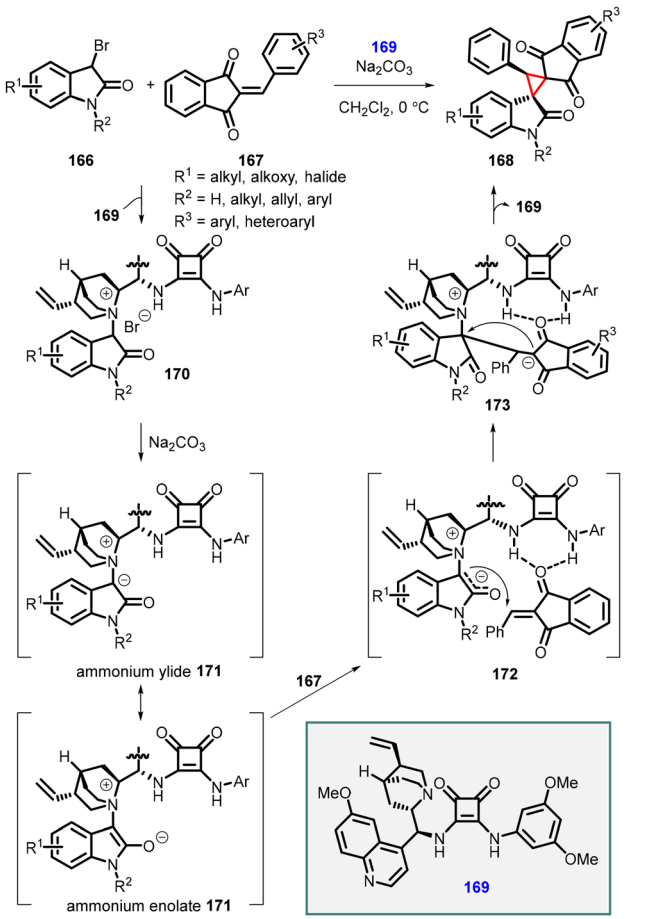
Scheme 32 Michael/alkylation cascade cyclopropanation of chloroox-indole with 5-alkenylthiazolones.



Scheme 33 Chiral squaramide catalyzed MIRC cyclopropanation cascade of unsaturated 4-chromanones with bromonitroalkane.



Scheme 34 Chiral squaramide catalyzed MIRC cyclopropanation of 3-acylcoumarins with 3-halooxindoles.



Scheme 35 Chiral squaramide catalyzed MIRC cyclopropanation of 2-arylidene-1,3-indanediones with 3-bromooxindoles.

through a [2 + 1] Michael/intramolecular cyclization cascade reaction (Scheme 34).[175] Notably, to confirm the formation of spirocyclic compounds, the authors conducted dynamic high-resolution mass spectrometry studies by treating 3-acylcoumarins (**161**) and 3-halooxindoles (**162**) with catalyst **157**.

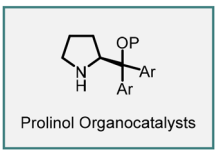
During the model reaction under standard conditions, it was observed that the reaction proceeded smoothly over a duration of 30 minutes. The dynamic high-resolution mass spectrometry analysis detected the presence of the ammonium ylide or ammonium enolate **164**, as well as the zwitterionic intermediate **165**. These observations provided further evidence and mechanistic insight for the formation of the desired spirocyclic compounds.

Lei and coworkers reported a similar approach involving the [2 + 1] annulation reaction with 2-arylidene-1,3-indanediones (**167**), 3-bromooxindoles (**166**), and a bifunctional squaramide catalyst (**169**). This reaction resulted in the formation of a series of novel bi-spiro[indanedione–oxindole–cyclopropane] (**168**) compounds through a tandem Michael addition/alkylation cascade reaction (Scheme 35).[176] Like the protocol described by Yuan *et al.*, high-resolution mass spectrometry (HRMS) studies were conducted to elucidate the mechanism of this tandem [2 + 1] annulation reaction, revealing the involvement of an *in situ* generated ammonium ylide followed by an intramolecular cyclization process.

The proposed mechanism for [2 + 1] annulation is as follows: step 1: substrate **166** reacts with catalyst (**169**), leading to the formation of ammonium salt **170**. Step 2: Na_2CO_3 deprotonates ammonium salt **170**, generating a nucleophilic ammonium ylide or enolate intermediate **171**. In **172**, the double hydrogen-bonding interaction involving the N–H in catalyst **164** facilitates a *Re*-face Michael addition of the 2-phenylidene-1,3-indanedione **167**, resulting in the formation of the zwitterionic intermediate **173**. Step 3: the intramolecular alkylation process occurs, with the *Re*-face attack at the C3-position of the oxindole moiety, leading to the formation of the desired chiral product **168** and concomitant release of catalyst **169**.

3.1.4 Prolinol organocatalysts. Prolinol and its derivatives are effective catalysts for enantioselective MIRC cyclopropanation. They facilitate the synthesis of chiral cyclopropanes through Michael addition and intramolecular cyclization. The

chiral centers and functional groups of prolinol derivatives activate substrates and control stereochemistry. These catalysts yield complex chiral cyclopropane compounds in high yields and excellent enantioselectivity.

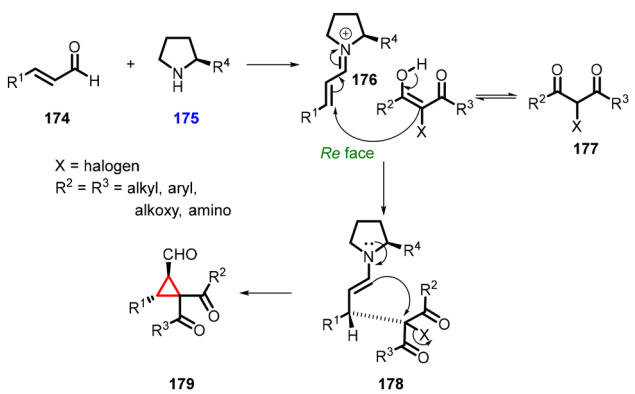


3.1.4.1 *Reactions of unsaturated aldehydes*

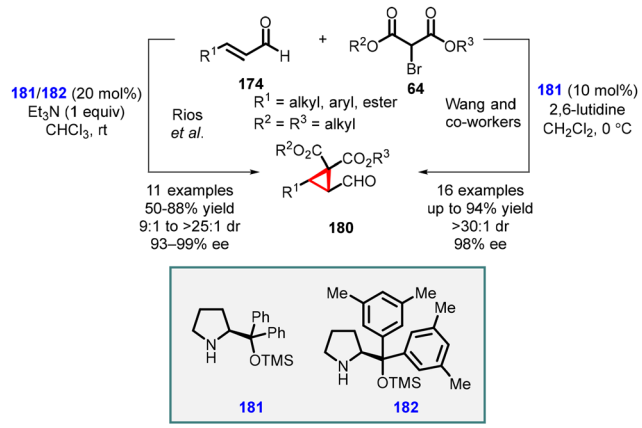
(a)The addition of α-halocarbonyl compounds to conjugated aldehydes (enals). **General reaction mechanism**: the halocarbonyl compounds, specifically Cl/Br-malonates, exhibit intriguing ambiphilic characteristics in their reactivity. They can act as both nucleophiles in Michael additions and electrophiles in alkylations (Scheme 36). This ambiphilicity is fundamental to understanding their mode of reactivity in MIRC reactions. The prolinol **175** activates the enal **174**, by generating the iminium ion **176**. The bulky TMS-protected diphenyl ether unit effectively shields the *Si* face of the iminium ion. As a result, the halomalonate attacks the *Re* face of the iminium ion, leading to the formation of an enamine intermediate. This enamine then undergoes intramolecular alkylation **178**, resulting in formation of the desired cyclopropane product **179**. Finally, the catalyst is regenerated through hydrolysis.

Córdova and coworkers made a significant discovery involving the TMS-protected prolinol (**181** and **182**) catalyzed MIRC reaction for synthesizing chemo- and enantioenriched 2-formylcyclopropanes (**180**) (Scheme 37).[177,178] The organocatalytic cyclopropanation of α,β-unsaturated aldehyde (**174**) was performed with bromomalonate (**64**) in $CHCl_3$ at room temperature, resulting in good yields (60–80%), excellent diastereoselectivity (ranging from 9 : 1 to >25 : 1), and enantioselectivity (93–99% ee). The use of triethylamine was crucial for achieving optimal reactivity in this process.

Wang and coworkers also reported MIRC reaction for synthesizing cyclopropanes, utilizing bromomalonates and enals. By employing catalyst (**181**) and 2,6-lutidine as a base,



Scheme 36 Proposed mechanism for the cyclopropanation of enals with halocarbonyl compounds.

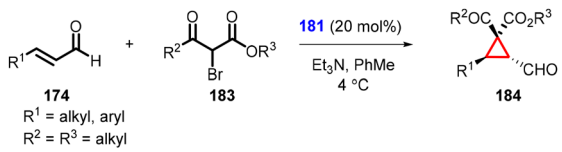


Scheme 37 Enantioselective MIRC cyclopropanation of enals with bromomalonates.

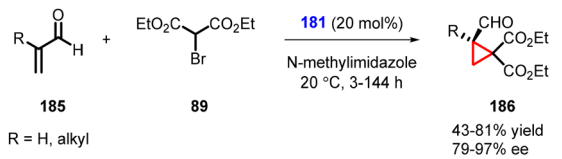
they successfully obtained highly functionalized chiral cyclopropanes (**180**) with good enantioselectivities (up to 98% ee).[179]

Rois and coworkers successfully utilized 2-bromo-3-keto esters (**183**) as nucleophiles for cyclopropanation (**184**). The reaction yielded excellent levels of chemo-, diastereo-, and enantioselectivity by using α,β-unsaturated aldehydes as substrates (**174**) (Scheme 38).[180] The cyclopropanes were obtained in high yields, excellent diastereoselectivity (>25 : 1) and enantioselectivity (99% ee). Interestingly, the studies revealed a predominant formation of the diastereomer where the ester group is positioned *cis* to the formyl group. This observation provides valuable insights into the stereochemical outcome of the cyclopropanation reaction.

Terrasson and coworkers expanded the MIRC cyclopropanation reaction for more challenging α-substituted α,β-unsaturated aldehydes (**185**) as substrates with bromomalonate (**89**) using catalyst **181** (Scheme 39).[181] The protocol enables the synthesis of cyclopropanes (**186**) with a quaternary carbon stereocenter, in high yields and excellent enantioselectivity (up to 97% ee). However, it is worth noting that this



Scheme 38 Enantioselective MIRC cyclopropanation of enals with 2-bromo-3-keto esters.



Scheme 39 Enantioselective MIRC cyclopropanation of α-substituted α,β-unsaturated aldehydes.

method is limited to β-unsubstituted unsaturated systems, as the reactivity significantly decreases with β-substitution.

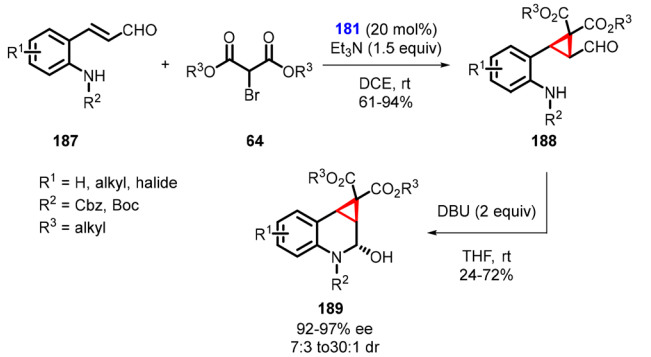
Kim and coworkers devised a complex one-pot domino strategy involving Michael addition/alkylation and sequential aza-cyclization for the synthesis of chiral cyclopropane-fused tetrahydroquinolines (**189**). The transformation utilizes aldehydes (**187**) and α-bromomalonic esters (**64**). The reaction proceeds in several steps: 1. an asymmetric domino Michael/alkylation reaction occurs between *N*-protected *ortho*-aminophenyl α,β-unsaturated aldehydes (**187**), utilizing triethylamine and chiral catalyst **181**. 2. Cyclization of dialkyl bromomalonates (**64**) resulting in the formation of intermediate (**188**). 3. The final product, cyclopropane-fused tetrahydroquinolines (**189**), was obtained through a DBU-induced intramolecular attack of the carbamate nitrogen onto the formyl group (Scheme 40).[182]

In 2015, Nishii and coworkers achieved a significant milestone by successfully completing the first enantioselective total synthesis of (+)-podophyllic aldehydes A (**192**), B (**193**), and C (**194**) belonging to the dihydronaphthalene-type lignans in overall yields of 30% (16 steps), 26% (16 steps), and 43% (8 steps) respectively. The starting materials used were α,β-unsaturated aldehyde (**190**) and α-bromomalonate (**44**).

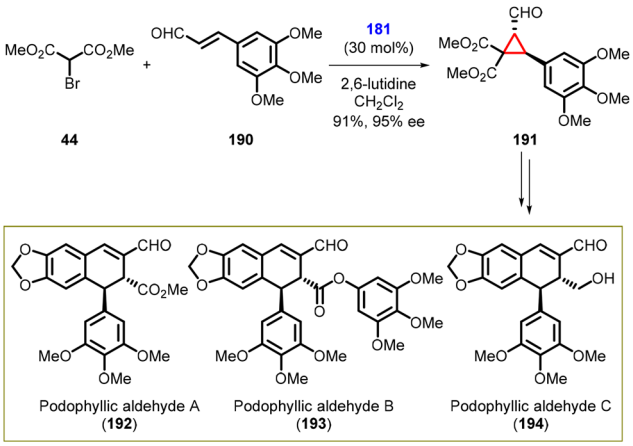
The cyclopropane synthesis by MIRC reaction was the key step in the total synthesis of (+)-podophyllic aldehydes A, B, and C. The reaction involved treating aldehyde (**190**) with α-bromomalonate **44** in the presence of Jørgensen-Hayashi amine catalyst **181**, 2,6-lutidine, and dichloromethane to yield cyclopropane intermediate (**191**) in high yield (91%) and excellent enantioselectivity (95% ee) (Scheme 41).[183]

Yang and coworkers made a recent breakthrough by introducing a small modification to the aldehyde used by Nishii *et al.* By using the aldehyde (*E*)-3-((*S*)-1-[(*R*)-1-phenylethyl)aziridin-2-yl]acrylaldehyde (**195**), they synthesized enantioenriched cyclopropylaziridine (**196**) using (**181**) as organocatalyst and diethyl bromomalonate **89** as nucleophile in good yield (68%) and excellent diastereoselectivity (>30 : 1) (Scheme 42).[184] This interesting design represents a significant advancement in the field of stereoselective synthesis.

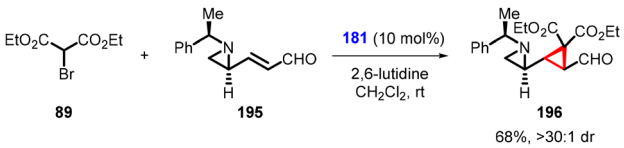
In 2013, Martínez and coworkers reported a reaction involving a novel catalyst derived from chiral diarylprolinols (**199**).



Scheme 40 MIRC reaction in the synthesis of cyclopropane-fused tetrahydroquinolines.



Scheme 41 MIRC cyclopropanation reaction in total synthesis of podophyllic aldehydes.

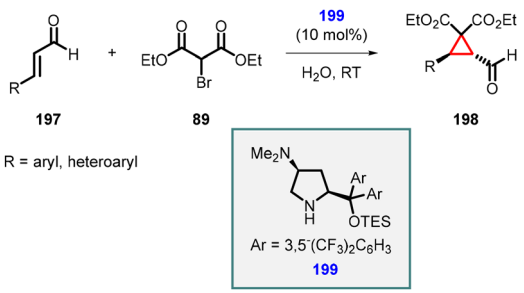


Scheme 42 Stereoselective synthesis of cyclopropylaziridines.

This new family of organocatalysts exhibited enhanced capabilities in catalyzing the enantioselective MIRC cyclopropanation of α,β-unsaturated aldehydes (**197**) with diethyl bromomalonate (**89**) in water.

The catalyst was specifically designed with the intention of incorporating a tertiary amino group at the 4-position of the pyrrolidine scaffold. This feature provides a basic site that can effectively deprotonate the pronucleophile. Additionally, a bulky diaryltrialkylsilyloxymethyl group was strategically placed at the 2-position to control the geometry of the iminium ion and introduce the necessary steric bias for stereoinduction.

Using catalyst **199**, Martínez *et al.*, successfully synthesized cyclopropanes (**198**) with remarkable levels of diastereoselectivity (>19 : 1) and enantioselectivity (>99% ee) (Scheme 43).[185]



Scheme 43 Asymmetric MIRC cyclopropanation using novel organocatalyst which acts as an external base.

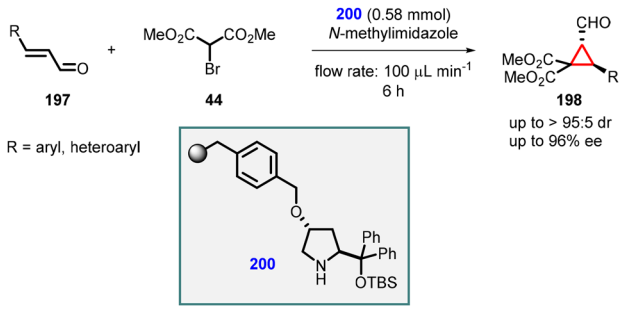
Pericàs and coworkers reported an organocatalytic enantioselective continuous-flow cyclopropanation reaction using α,β-unsaturated aldehydes. They introduced a solid-supported diarylprolinol catalyst (**200**) for this purpose. A series of cyclopropanes (**198**) were successfully synthesized with moderate yields, exceptional diastereoselectivity (>95 : 5), and enantioselectivity of up to 96% (Scheme 44).[186]

Phillips and Barros developed a noteworthy domino Michael addition/intramolecular alkylation reaction using α,β-unsaturated aldehyde (**202**) and α-bromophosphonoacetates (**201**) (Scheme 45).[187] This reaction enables the synthesis of α-cyclopropylphosphonates (**203**, **204**) using organocatalyst **181** in high yields, good diastereoselectivity (dr = 68 : 32 to 83 : 17) and high enantioselectivity (>99% ee). However, the reaction was limited to a narrow class of substrates.

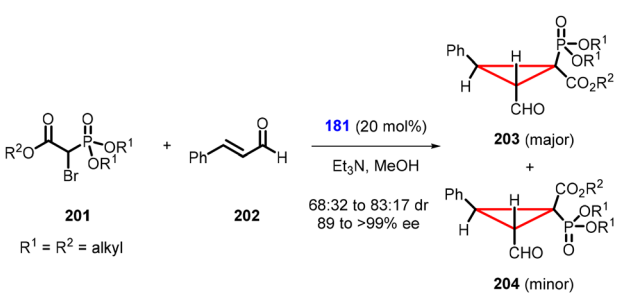
In 2021, Ye and coworkers employed chloroacetophenone as a nucleophile in the enantioselective cyclopropanation reaction with α,β-unsaturated aldehydes using prolinol organocatalyst **181** (Scheme 46).[188] The cyclopropanes (**206**) were successfully synthesized with excellent yields (up to 85%), exceptional diastereoselectivity (>30 : 1), and enantioselectivity (96% ee).

(b)The addition of α-halonitro compounds to conjugated aldehydes

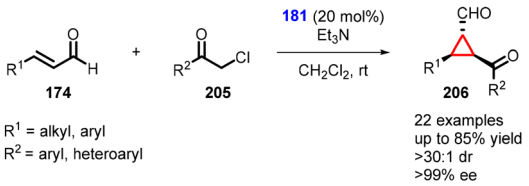
In 2008, Cordova and coworkers introduced a novel method for the nitrocyclopropanation of α,β-unsaturated aldehydes (**197**) using bromonitromethane (**51**) as a nucleophile and Jørgensen-Hayashi amine (**181**) as catalyst. The reaction furnished cyclopropanes (**207**) and (**208**) with moderate yields (29–63%), low diastereoselectivity (3 : 1) and excellent enantioselectivity (91–99% ee). (Scheme 47).[189]



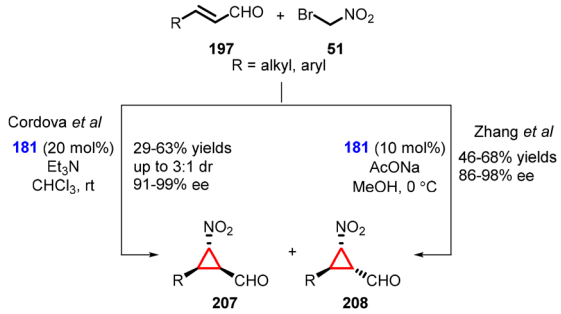
Scheme 44 Enantioselective MIRC cyclopropanation using flow chemistry.



Scheme 45 MIRC cyclopropanation of α,β-unsaturated aldehydes and α-bromophosphonoacetates.



Scheme 46 MIRC cyclopropanation of α,β-unsaturated aldehydes and chloroacetophenone.

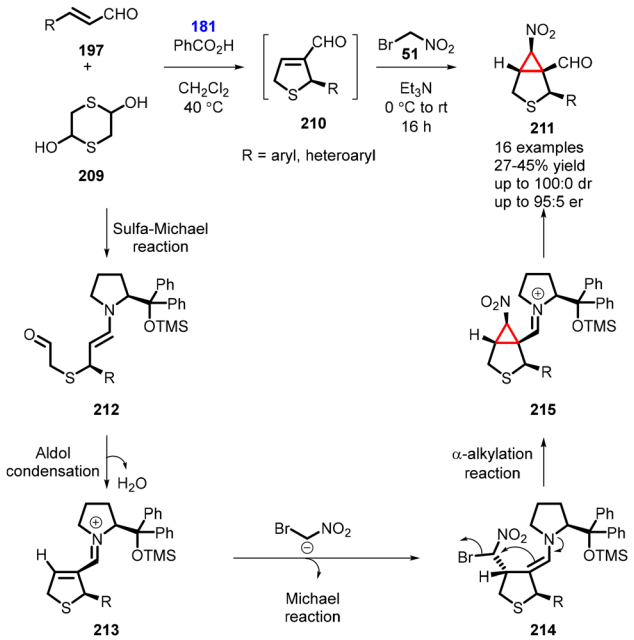


Scheme 47 MIRC cyclopropanation of α,β-unsaturated aldehydes with bromonitromethane.

Zhang and coworkers reported a similar transformation for the construction of cyclopropanes using MIRC reaction. The only difference was reaction conditions, AcONa was used as base and MeOH as solvent (Scheme 47).[190]

In 2015, Risi and coworkers reported an unprecedented one-pot four-step organocatalytic process for the synthesis of bicyclic nitrocyclopropane 6-nitro-3-thiabicyclo[3,1,0]hexane-1-carbaldehyde (**211**). The reaction involved the use of bromonitromethane as nucleophile. The reaction began with the unsaturated aldehyde (**197**) reacting with 1,4-dithiane-2,5-diol **209** in the presence of catalyst (**181**) (20 mol%) and benzoic acid (10 mol%) as additive in CH_2Cl_2 at 40 °C for 2 h, under an inert atmosphere. This step involved a domino sulfa-Michael-addition/aldol condensation reaction. Subsequently, a mixture of bromonitromethane and triethylamine was added, leading to a domino Michael-addition/α-alkylation reaction which yielded the bicyclic nitrocyclopropane (**211**) in moderate yields (of up to 45%) and high stereoselectivity (100 : 0 dr, 95 : 5 er) (Scheme 48).[191]

The plausible reaction mechanism involves the initial sulfa-Michael reaction between aldehyde (**197**) and *in situ* generated mercaptoacetaldehyde, forming the enamine intermediate (**212**). This intermediate then undergoes an intramolecular aldol reaction and subsequent dehydration, resulting in the formation of the iminium-ion intermediate (**213**). Bromonitromethane then adds to this intermediate, leading to the formation of **214**. The bromine atom is subsequently displaced *via* an intramolecular nucleophilic substitution, generating the second cycle. The chiral organocatalyst is regener-

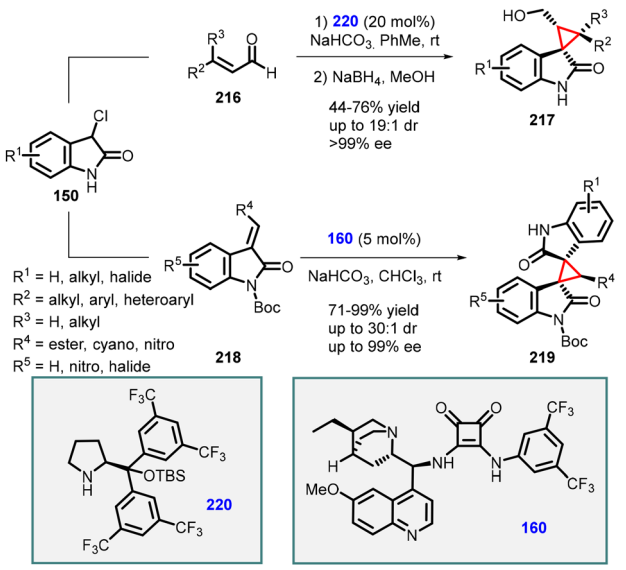


Scheme 48 One pot four-step MIRC cyclopropanation.

ated, ultimately leading to the formation of nitrocyclopropane **211** (Scheme 48).

(c)The addition of α-halooxindoles to conjugated aldehydes

Malkov and Kanger developed two distinct syntheses of spirocyclopropyl oxindole derivatives using 3-chlorooxoindoles (**150**) through a domino Michael-addition/substitution reaction (Scheme 49).[192] When the reaction was applied to enals **216**, the enamine catalyst **220** was utilized, resulting in the formation of desired spirocyclopropyl oxindole derivatives (**217**) with good to high yields (44–76%) and high stereoselectivities (>19 : 1 dr; >99% ee). Conversely, when the reaction involved



Scheme 49 MIRC cyclopropanation reaction with chlorooxoindoles.

Michael acceptors **218**, the hydroquinine-derived squaramide **160** emerged as the most effective catalyst, delivering the desired spirocyclopropyl oxindole derivatives **219** with excellent yields (71–99%) and high stereoselectivities (>30 : 1 dr; up to 99% ee).

Melchiorre and coworkers reported a fascinating reaction for the asymmetric synthesis of cyclopropane spirooxindoles (**222**) from 3-chlorooxindoles (**150**), dienals (**221**), and catalyst **181** through vinylogous organocatalytic cascade MIRC reaction. This reaction represents a rare example of highly regioselective and asymmetric 1,6-addition to 2,4-dienals. The presence of a bulky R^2 group at the β-site of the dienals is crucial for achieving δ-regioselective 1,6-addition, which is key to the successful outcome of the reaction. Various cyclopropanes (**222**) were synthesized with good to excellent yields (52–91%), along with excellent stereoselectivity (6 : 1 to 15 : 1 dr and 92–99% ee) (Scheme 50).[193]

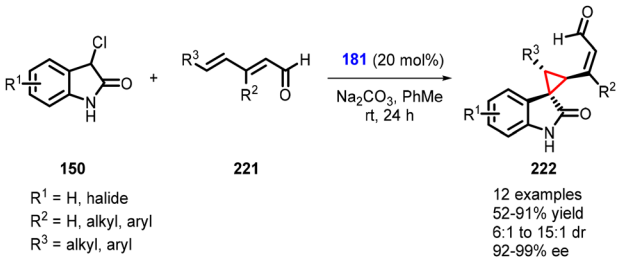
(d)The addition of benzyl and heterobenzyl halides to conjugated aldehydes

Rios and co-workers accomplished efficient synthesis of chiral trisubstituted diarylcyclopropane carbaldehydes (**224**, **225**, and **226**) using substituted benzyl chlorides as an ambiphilic (nucleophilic and electrophilic) reagents (**223**) and α,β-unsaturated aldehydes (**197**) as Michael acceptor (Scheme 51).[194] The transformation was carried out using Jørgensen-Hayashi amine **181** as catalyst.

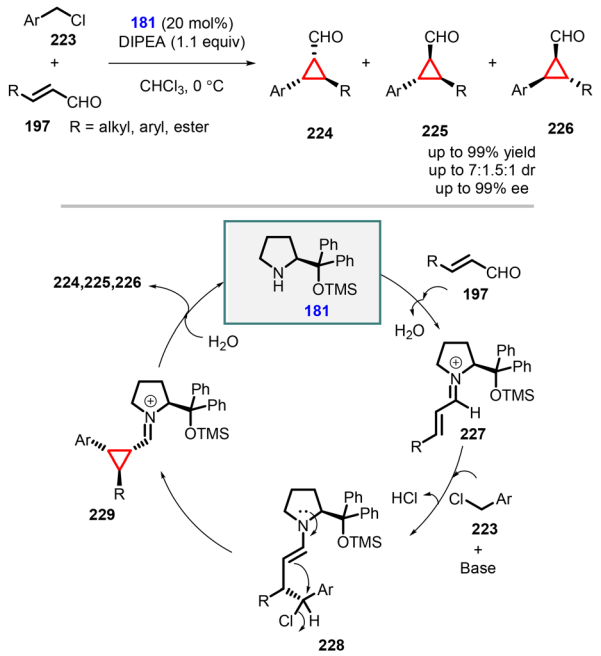
Mechanistic investigations revealed that the reaction proceeded through an initial activation of the α,β-unsaturated aldehyde (**197**) by catalyst **181**, forming the iminium species **227**. The Michael addition of the benzyl anion (derived from **223** using DIPEA as base) to **227** generated the enamine intermediate **228**, which underwent chloride displacement to yield the cyclopropane intermediate **229**. Finally, hydrolysis led to the formation of the desired products **224**, **225**, and **226**, while the catalyst was recovered. It is worth noting that the nucleophilic substitution could occur from both directions due to the presence of a chloride group at the achiral β position, resulting in relatively poor diastereoselectivity.

In the same year, Li and Wang reported a similar transformation by substituting the organocatalyst with chiral diphenylprolinol TBDMS ether (**234**) and using triethylamine as a base under mild reaction conditions (Scheme 52).[195]

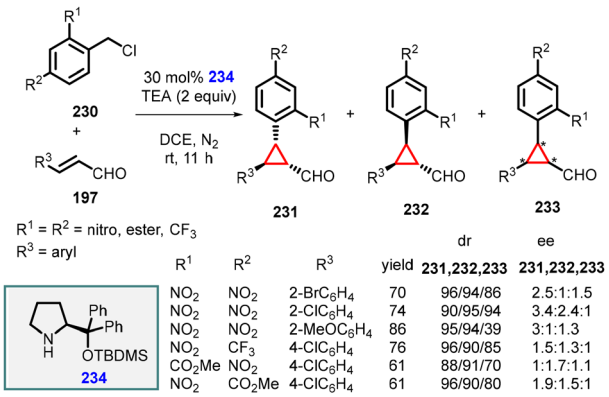
Veselý and coworkers applied a similar approach for the enantioselective synthesis of 1,2,3-trisubstituted cyclopropanes



Scheme 50 MIRC cyclopropanation of 2,4-dienals and oxindoles.



Scheme 51 MIRC cyclopropanation of benzyl chlorides and α,β-unsaturated aldehydes.

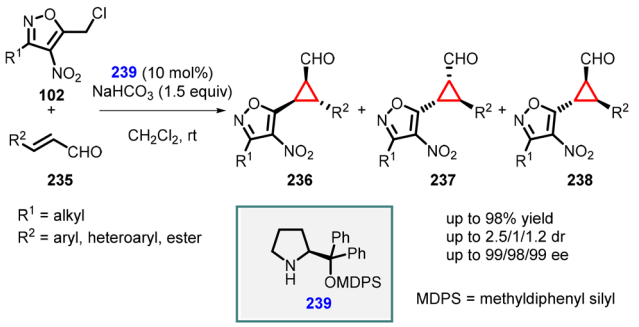


R1	R2	R3	yield	dr 231,232,233	ee 231,232,233
NO_2	NO_2	2-BrC_6H_4	70	96/94/86	2.5:1:1.5
NO_2	NO_2	2-ClC_6H_4	74	90/95/94	3.4:2.4:1
NO_2	NO_2	2-$MeOC_6H_4$	86	95/94/39	3:1:1.3
NO_2	CF_3	4-ClC_6H_4	76	96/90/85	1.5:1.3:1
CO_2Me	NO_2	4-ClC_6H_4	61	88/91/70	1:1.7:1.1
NO_2	CO_2Me	4-ClC_6H_4	61	96/90/80	1.9:1.5:1

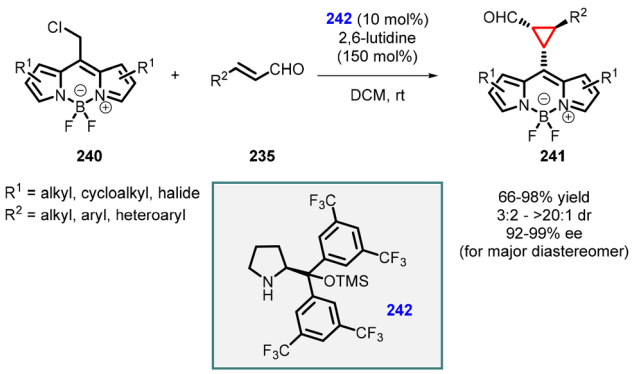
Scheme 52 MIRC cyclopropanation of benzyl chlorides and α,β-unsaturated aldehydes using catalyst **234**.

using heteroaryl chloride (**102**) as an ambiphilic reagent. In this method, the MIRC reaction was performed between 5-(chloromethyl)-3-methyl-4-nitroisoxazole (**102**) and α,β-unsaturated aldehydes (**235**), using catalyst **239** resulting in the formation of the desired cyclopropanes (**236**, **237**, **238**) in high yields (up to 98%), moderate diastereoselectivity and excellent enantioselectivity (99% ee), and (Scheme 53).[196]

Two years later, Veselý and coworkers published another noteworthy method for synthesizing cyclopropane carbaldehydes (**241**) derived from BODIPY (Scheme 54).[197] The approach involved a cascade reaction between readily available BODIPY derivatives (**240**), α,β-unsaturated aldehydes (**235**), and commercially available Jørgensen catalyst (**242**). The resulting BODIPY-derived cyclopropanes were obtained in high yields



Scheme 53 MIRC cyclopropanation of 5-(chloromethyl)-3-methyl-4-nitroisoxazole and α,β-unsaturated aldehydes.

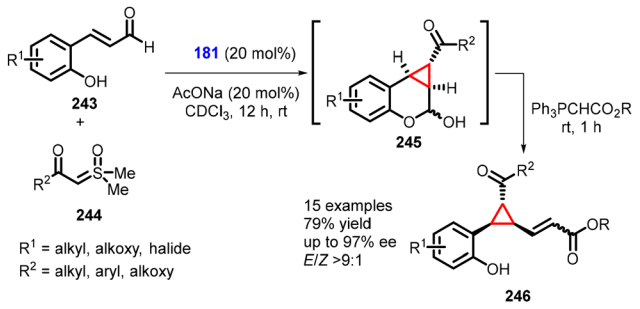


Scheme 54 MIRC cyclization to synthesize cyclopropane carbaldehydes derived from BODIPY.

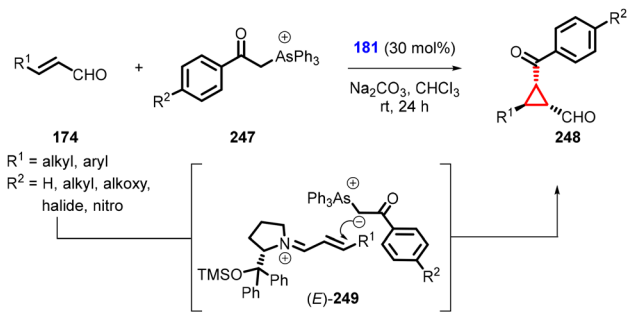
(66–98%), diastereomeric ratios ranging from 3/2 to >20/1, and high enantiomeric excess (92–99%) for the major diastereomer. The stereochemistry of the final product was investigated in detail through density functional theory (DFT) calculations of the intermediates involved in the reaction. These findings provide valuable insights into the mechanism and stereochemistry of the cascade reaction for the synthesis of BODIPY-derived cyclopropane carbaldehydes.

(e)The addition of ylides to conjugated aldehydes

Fochi and Bernardi recently introduced a novel approach for synthesizing the 1,1a,2,7b-tetrahydrocyclopropa[*c*]chromene scaffold (**245**) through enantioselective aminocatalytic Corey–Chaykovsky-type cyclopropanation reactions with unsaturated aldehydes (**243**), utilizing sulfoxonium ylides (**244**). This method represents a convenient utilization of sulfoxonium ylides in asymmetric amino-catalysis (**181**). The reaction yielded several ring-fused derivatives (specifically, cyclopropane-fused chromanes) (**245**). The chromanol derivative (**245**) was subjected to derivatization through Wittig olefination, resulting in the formation of **246** in moderate yields (up to 79%), excellent diastereoselectivity (*E*/*Z* > 9 : 1), and excellent enantioselectivities (up to 97% ee) (Scheme 55).[198] The product obtained predominantly existed as the *E*-isomer, which allowed for easy isolation and accurate determination of the enantiomeric excess.



Scheme 55 MIRC cyclopropanation of unsaturated aldehydes and stabilized sulfoxonium ylides.



Scheme 56 MIRC cyclopropanation using arsonium ylide.

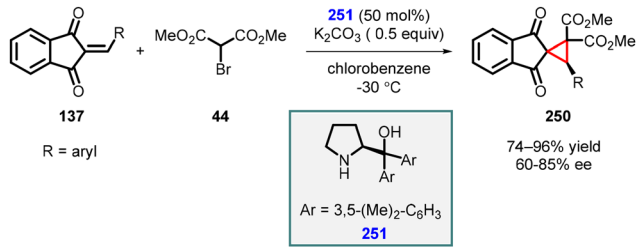
Zhao and Cao reported the synthesis of chiral cyclopropanes (**248**) utilizing α,β-unsaturated aldehydes, arsonium ylide (**247**) and diphenylprolinol silylether (**181**) as a catalyst (Scheme 56).[199] The configuration of these compounds was determined by the intermediate (*E*)-iminium **249** and the steric approach control, which are both influenced by the bulky diarylcarbinol silyl ether moiety in the catalyst.

Apart from enals, other unsaturated carbonyl compounds such as ketones, nitro compounds, and amides are also valuable substrates in the MIRC reaction when prolinol organocatalysts are employed.

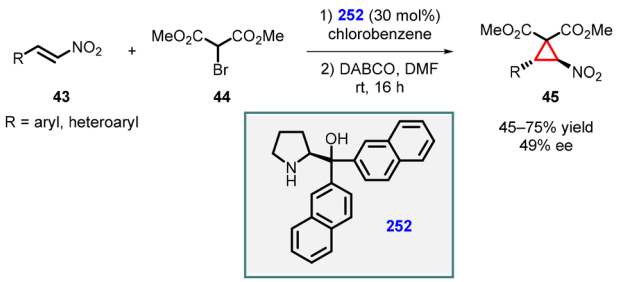
3.1.4.2 Reactions of unsaturated ketones. Lattanzi and coworkers conducted a study in which they employed 2-arylidene-1,3-indandiones (**137**) as Michael acceptors, along with α-bromo-methylmalonate (**44**), in the presence of diarylprolinol derivative (**251**) as the catalyst. This innovative approach led to the synthesis of spirocyclopropanes (**250**) with high yields (74–96%) and moderate to good enantioselectivity (60–85%) (Scheme 57).[200]

3.1.4.3 Reactions of unsaturated nitro compounds. Lattanzi and coworkers demonstrated MIRC reaction utilizing nitroalkenes (**43**) as Michael acceptor and α-bromo-methylmalonate (**44**) as nucleophile for the synthesis of chiral nitrocyclopropanes (**45**). In this study, α,α-(2-naphthyl) prolinol silyl ether **252** was used as catalyst at 30 mol% loading. The reaction exhibited complete *trans*-diastereoselectivity, although the enantioselectivity was relatively low (≤49% ee) (Scheme 58).[201]

Alemán and coworkers presented an interesting one-pot transformation utilizing bromonitroalkenes (**253**) as Michael



Scheme 57 MIRC cyclopropanation of 2-arylidene-1,3-indandiones and α-bromo-methylmalonate.

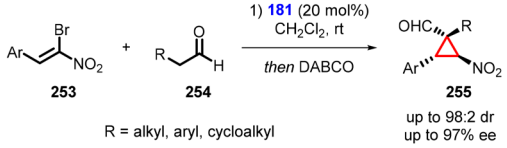


Scheme 58 MIRC cyclopropanation of nitroalkenes using α,α-(2-naphthyl) prolinol silyl ether catalyst.

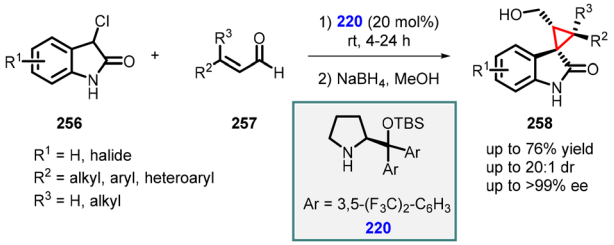
acceptor. This transformation resulted in the formation of cyclopropanes (**255**), with aldehyde (**254**), which exhibited good yields and excellent diastereoselectivity (up to 98 : 2) and enantioselectivity (up to 97% ee) (Scheme 59).[202] The one-pot reaction involves a two-step process: 1. an aminocatalytic reaction between aldehydes and bromonitroalkenes; and 2. an intramolecular bromo substitution catalyzed by DABCO as a base.

3.1.4.4 Reactions of unsaturated amides. Noole and coworkers developed three straightforward and effective approaches for accessing the spiro-cyclopropane framework. Among these strategies, one involves a MIRC reaction between unsaturated aldehydes (**257**) and 3-chlorooxindoles (**256**) utilizing prolinol (**220**) as the preferred catalyst. This method exhibits remarkable activity, favorable selectivity, and smooth conversion within a time frame of 4–24 hours (Scheme 60). The desired spiro-cyclopropane compounds are synthesized by employing iminium catalysis with catalyst **220**. These reactions proceed in high yields while demonstrating excellent diastereoselectivity (>20 : 1 dr) and enantioselectivity (>99% ee).[203]

3.1.5 Urea/thiourea organocatalyst. Urea and thiourea-based bifunctional base catalysts have emerged as efficient reagents in asymmetric catalysis of MIRC cyclopropanation by

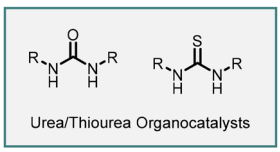


Scheme 59 One pot MIRC cyclopropanation of nitroalkenes.



Scheme 60 Strategies utilized in the synthesis of spiro-cyclopropane scaffold.

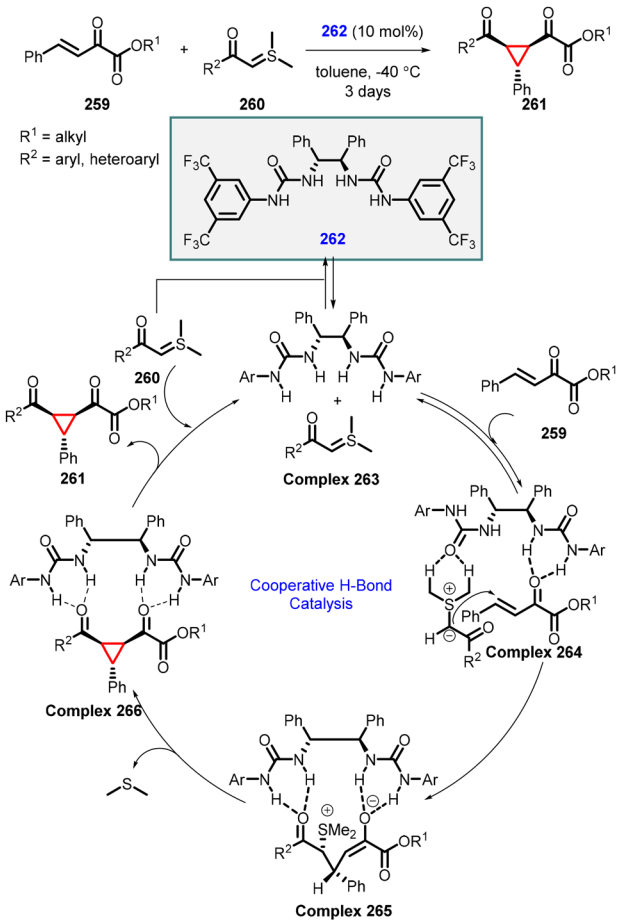
activating substrates through hydrogen bonding interactions. These catalysts enhance ring closure reaction by interacting with both the nucleophile and the electrophile. The urea or thiourea molecule boosts the reactivity of the nucleophile while simultaneously engaging with the electrophile to promote the desired stereochemistry *via* hydrogen bonding. Due to their ability to facilitate efficient and selective synthesis of cyclopropane products, urea and thiourea derivatives serve as valuable catalysts for enantioselective MIRC reactions.



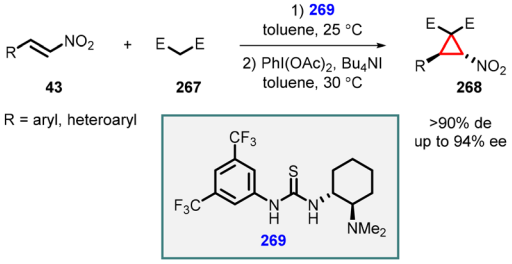
In 2011, Xiao and coworkers developed an enantioselective MIRC cyclopropanation reaction of β,γ-unsaturated α-ketoesters with sulfur ylides using a hydrogen-bonding urea catalyst (**262**) (Scheme 61).[204] The reaction mechanism involves the formation of hydrogen bond between catalyst **262** and ylide (**260**), resulting in the formation of complex **263**. Complex **263** then reacts with unsaturated ketoester (**259**) to form a ternary complex **264**, where the hydrogen bonds guide the reactant into the appropriate position and induce the observed face selectivity in intermediate **265**. Finally, intermediate **265** undergoes intramolecular S_N2 displacement to yield the desired cyclopropane (**261**) while regenerating urea catalyst **262** for the subsequent catalytic cycle. A diverse array of cyclopropanes can be synthesized with moderate to good yields, and enantioselectivity (up to 80% ee).

Fan and coworkers demonstrated organocatalyzed one-pot asymmetric synthesis of a range of functionalized cyclopropanes (**268**) through an efficient oxidative cyclopropanation of Michael adducts of nitroalkenes (**43**) with activated methylene compounds (**267**). This transformation was achieved by employing a combination of iodobenzene diacetate and tetrabutylammonium iodide. The highly efficient thiourea organocatalyst **269** was utilized for this reaction, leading to the synthesis of functionalized nitrocyclopropanes (**268**) in moderate to good yields, along with excellent diastereoselectivity (>90% de) and enantioselectivity (up to 94%ee) (Scheme 62).[205]

In a separate study, Inokuma and coworkers reported asymmetric MIRC reaction using bifunctional thiourea catalyst (**269**) to synthesize a wide range of cyclopropanes (**271** and



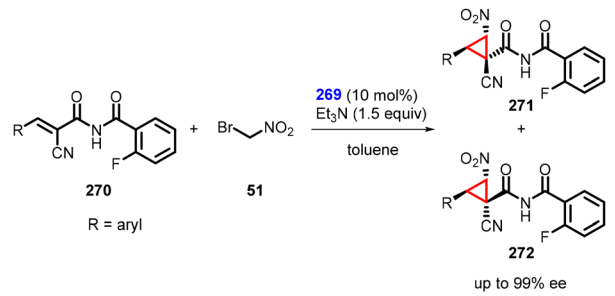
Scheme 61 Urea catalyzed asymmetric MIRC cyclopropanation of β,γ-unsaturated α-ketoesters and sulfur ylides.



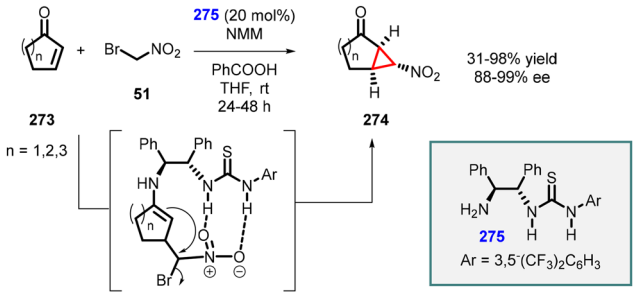
Scheme 62 Oxidative MIRC cyclopropanation of the Michael adduct of nitroalkenes with activated methylene compounds catalyzed by thiourea.

272) from α-cyano-α,β-unsaturated imides (**270**) and bromonitromethane (**51**). The reaction gave outstanding enantioselectivity (up to 99%) (Scheme 63).[206] Notably, the catalyst also demonstrated remarkable efficacy in facilitating the preparation of these α-cyanoimides through Knoevenagel condensation.

An intriguing study was conducted by Yan and coworkers utilizing chiral bifunctional thiourea–primary amine (**275**) catalyst to address the issue of poor diastereoselectivity in the



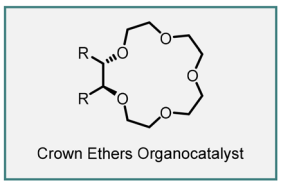
Scheme 63 MIRC cyclopropanation of α-cyano-α,β-unsaturated imides and bromonitromethane catalyzed by thiourea.



Scheme 64 MIRC cyclopropanation of cyclic enones and bromonitromethane catalyzed by chiral bifunctional thiourea–primary amine catalyst.

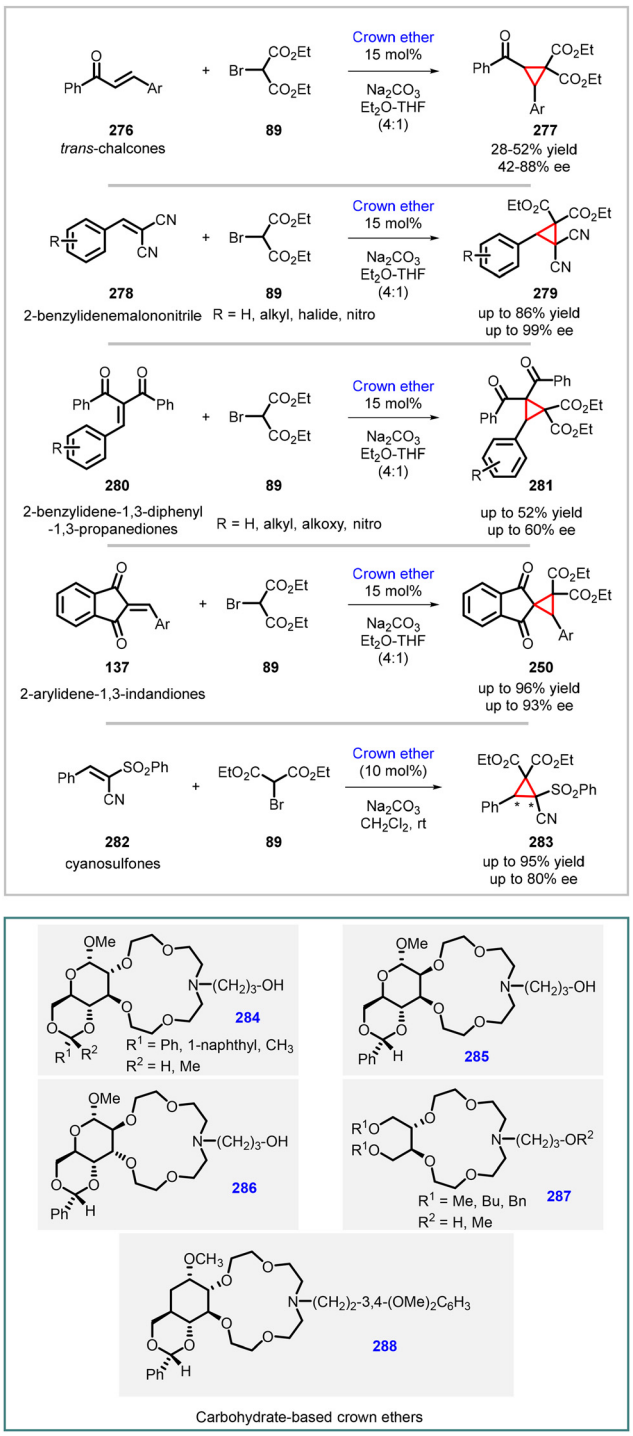
synthesis of asymmetric nitro cyclopropanes from cyclic enones (**273**) (Scheme 64).[207] The reaction demonstrated a limited scope; however, it achieved excellent enantioselectivity (88–99% ee). Notably, the presence of both acid ($PhCO_2H$) and base (NMM) additives was found to be crucial for the success of the reaction. The inclusion of $PhCO_2H$ enhances both enantioselectivity and yield, while NMM is essential for product **274** formation.

3.1.6 Crown ethers as organocatalyst. Crown ethers have been successfully used in enantioselective MIRC cyclopropanation reaction. They enhance enantioselectivity by facilitating appropriate alignment and activation of the reactants as phase transfer catalysts. Crown ethers create a controlled environment that allows stereochemical induction, resulting in superior enantioselectivity by encapsulating the reaction components within their cavities.



Bakó and co-workers attempted enantioselective MIRC cyclopropanation reactions using innovative chiral phase-transfer catalysts, including carbohydrate-based crown ethers (**284–288**). The MIRC cyclopropanation reaction was studied between diethyl bromomalonate (**89**) and different types of Michael acceptors, such as chalcones (**276**), 2-arylidenemalononitriles (**278**), 2-benzylidene-1,3-diphenyl-1,3-propanediones (**280**), 2-arylidene-1,3-indandiones (**137**), and cyanosulfones (**282**) under solid–liquid phase transfer catalytic conditions (Scheme 65).[208–211]

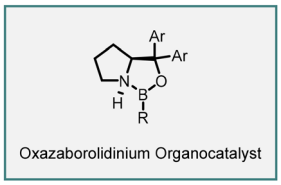
The reactions were carried out in a solvent mixture of THF and diethyl ether (in a 4 : 1 ratio) or DCM. Dry Na_2CO_3 served



Scheme 65 MIRC cyclopropanation using chiral α-D-glucopyranoside-based crown ether.

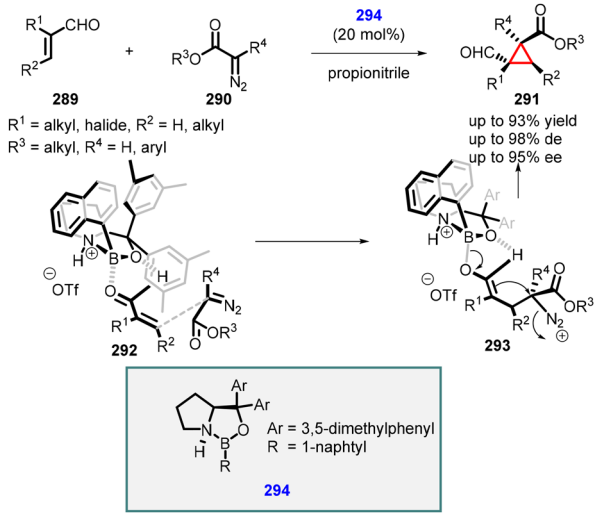
as the base, added in twofold excess, while 10/15 mol% of the crown ether catalyst was employed at room temperature. The results showed that enantioenriched cyclopropanes were obtained with moderate to good yields with varying levels of enantioselectivity. This research shed light on the potential of these novel chiral phase-transfer catalysts for controlling the stereoselectivity of MIRC cyclopropanation reactions.

3.1.7 Oxazaborolidinium organocatalyst

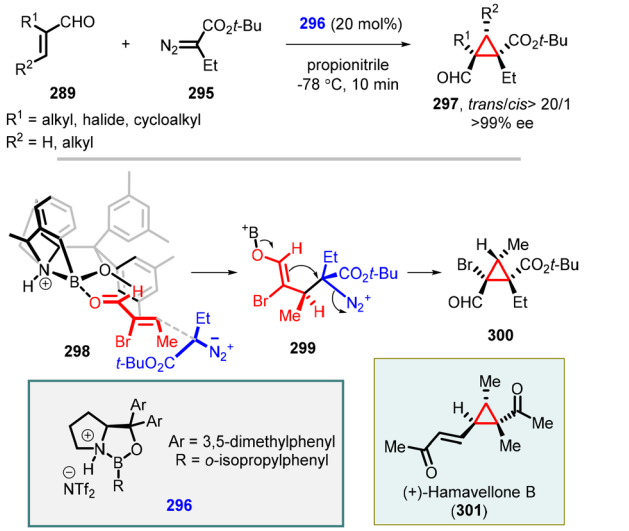


In 2011, Ryu reported the novel use of chiral oxazaborolidinium **294** as an organocatalyst for MIRC cyclopropanation reaction between α,β-unsaturated aldehydes (**289**) with aryl- and alkyl diazoacetates (**290**) as ylides (Scheme 66).[212] The catalyst coordinates with the oxygen atom of aldehyde (**289**), shielding the *re* face and enabling the attack of diazoacetate (**290**) from the *si* face, leading to intermediate (**293**). Subsequent cyclization, accompanied *via* nitrogen loss, yields formyl cyclopropanes **291** with moderate to excellent yields (up to 93%), excellent diastereoselectivity (up to 98%) and enantioselectivity (up to 95% ee).

Building upon the successful outcomes achieved with α-aryl diazo compounds, Ryu and coworkers expanded the asymmetric MIRC cyclopropanation reaction to α-alkyl diazo compounds (**295**). The reaction resulted in a series of highly functionalized cyclopropanes (**297**) with high *trans*-diastereoselectivity and exceptional enantioselectivity (up to >99% ee) when employing **296** as catalyst (Scheme 67).[213] Notably, the methodology was successfully applied in the total synthesis of (+)-hamavellone B, marking an important milestone in the field.



Scheme 66 MIRC cyclopropanation of α,β-unsaturated aldehydes and alkyl-and aryl diazoacetates catalyzed by chiral oxazaborolidinium.

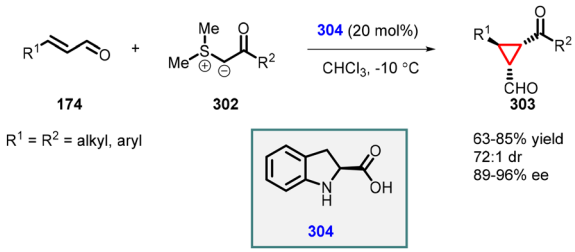


Scheme 67 MIRC cyclopropanation of alkyl diazoacetates catalyzed by chiral oxazaborolidinium catalyst and application in total synthesis.

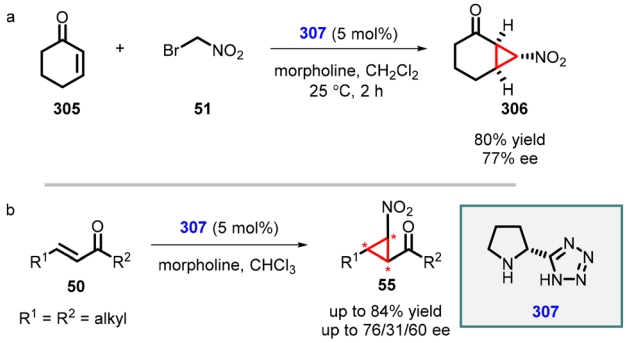
3.1.8 Other organocatalysts in MIRC reaction. In 2005, MacMillan and coworkers reported an elegant enantioselective Johnson–Corey–Chaykovsky cyclopropanation. This reaction involves a Michael addition/alkylation cascade reaction and was performed between α,β-unsaturated aldehydes (**174**) and dimethyl sulfonium ylides (**302**) using a chiral secondary amine as catalyst (2-carboxylic acid dihydroindole) (**304**) (Scheme 68).[214] Highly functionalized cyclopropanes (**303**) were obtained in good yields (63–85%) and excellent diastereo- (72 : 1) and enantioselectivity (89–96% ee).

Ley and coworkers have reported an enantioselective MIRC cyclopropanation reaction involving cyclohexenone and bromonitromethane employing chiral 5-(pyrrolidin-2-yl)-1*H*-tetrazole (**307**) as organocatalyst. Chiral nitrocyclopropanes (**306**) were synthesized in high yield (80%) and good enantioselectivity (77% ee). The efficiency of the reaction was further aided by the addition of morpholine as an additive (entry a, Scheme 69).[215]

Subsequently, they explored MIRC reaction by expanding the scope of Michael acceptor to various cyclic and acyclic enones. However, the reaction resulted in poor to average diastereo- and enantioselectivity (entry b Scheme 69).[216]



Scheme 68 Johnson–Corey–Chaykovsky cyclopropanation using chiral secondary amine catalyst (2-carboxylic acid dihydroindole).

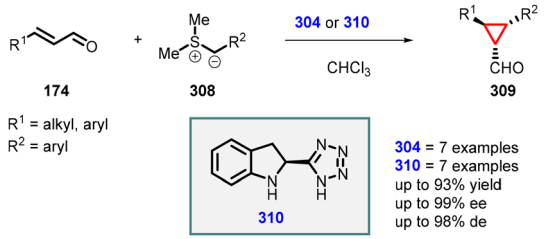


Scheme 69 MIRC cyclopropanation of cyclohexenones and bromonitromethane using proline tetrazole catalyst.

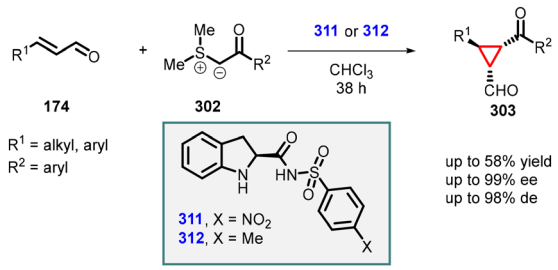
In 2007, Arvidsson and coworkers made significant advancement in the enantioselective Corey–Chaykovsky cyclopropanation process by modifying the organocatalyst 2-carboxylic acid dihydroindole (**304**). They replaced the carboxylic acid with a tetrazole group, leading to the development of novel organocatalyst (**310**). The MIRC reaction performed with the new catalyst significantly improved the yields (up to 93%), diastereoselectivity (up to 98% dr), and enantioselectivity (up to 99% ee). The larger size of the tetrazole group, in comparison to the carboxylic acid, created steric hindrance during the nucleophilic attack step by the sulfonium ylide, consequently increasing the enantioselectivity of the reaction (Scheme 70).[217]

In the same year, Arvidsson and coworkers further modified the organocatalyst by incorporating a sulfonamide group resulting in a new organocatalyst. A comparison of their findings with previously reported work showed newly developed organocatalysts (**311** and **312**) gave excellent diastereoselectivity (up to 98% dr) and enantioselectivity (up to 99% ee) for the cyclopropanes (**303**). However, the yields achieved with these modified catalysts were relatively low (58%) (Scheme 71).[218]

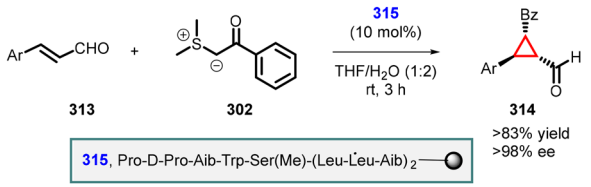
In an important contribution by Kudo and coworkers, it was demonstrated that resin-supported N-terminal Pro-containing peptide (**315**) as catalyst in the asymmetric cyclopropanation reaction of α,β-unsaturated aldehydes (**313**) with sulfur ylides (**302**) under aqueous conditions resulted in good yield (>83%) and excellent enantioselectivity (>98% ee) (Scheme 72).[219]



Scheme 70 Tetrazole-organocatalyst catalyzed MIRC cyclopropanation of unsaturated aldehydes and sulfur ylide.



Scheme 71 Sulfonamide-organocatalyst catalyzed MIRC cyclopropanation.

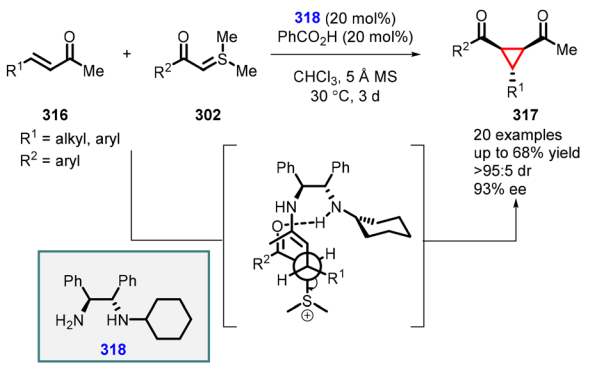


Scheme 72 Peptide-catalyzed MIRC cyclopropanation of α,β-unsaturated aldehydes with sulfur ylides.

Feng and coworkers successfully developed an asymmetric cyclopropanation method for α,β-unsaturated ketones (**316**) using stabilized ylides (**302**) as nucleophiles. The reaction was carried out in the presence of 20 mol% diamine catalyst (**318**) and benzoic acid as additive. The MIRC reaction yielded chiral cyclopropanation adducts (**317**) in moderate yields (up to 68%) and excellent enantioselectivity (up to 93% ee) (Scheme 73).[220]

To understand the stereoinduction of the MIRC reaction, the authors proposed a transition state where the primary amine of the catalyst formed an enamine with the ketone, while the secondary amine guided the ylide through hydrogen bonding. This cooperative interaction between the catalyst and reactants played a significant role in achieving excellent stereo- and enantioselectivity in the reaction.

Chein and coworkers introduced a series of novel chiral tetrahydroselenophenes (**321**) as organocatalysts derived from (*S*)-diphenyl(tetrahydroselenophen-2-yl)methanol. The authors demonstrated their efficacy as chiral organocatalysts in the



Scheme 73 Chiral diamine-catalyzed MIRC cyclopropanation of α,β-unsaturated ketones.

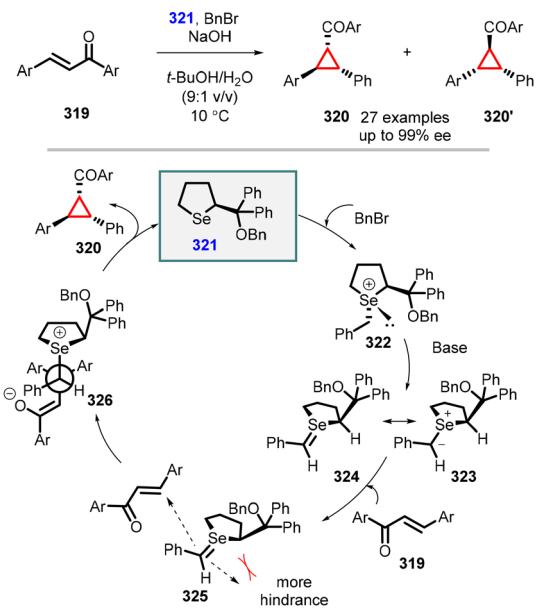
first organoselenium-catalyzed asymmetric cyclopropanation reactions. These selenium-containing catalyst generate selenonium ylide intermediates by reacting with benzyl bromide, which further reacts with (*E*)-chalcones (**319**) to generate a diverse array of cyclopropanes (**320**) (27 examples), exhibiting exceptional enantioselectivity (99% ee) (Scheme 74).[221]

The mechanism of this reaction involves the initial conversion of the selenide catalyst (**321**) into the selenonium salt **322** by reacting with benzyl bromide under basic conditions. Salt **322** then forms the corresponding ylide **323**/**324**. The bulky side chain in **324** is strategically positioned to shield the *si* face of the ylide carbon, directing the approach of the Michael acceptor from the *re* face. This leads to the formation of intermediate **326**, adopting the favorable *anti–anti* conformation. Subsequent intramolecular cyclization of the Michael adduct produces the major diastereomer, yielding the (*R*,*R*)-cyclopropane product.

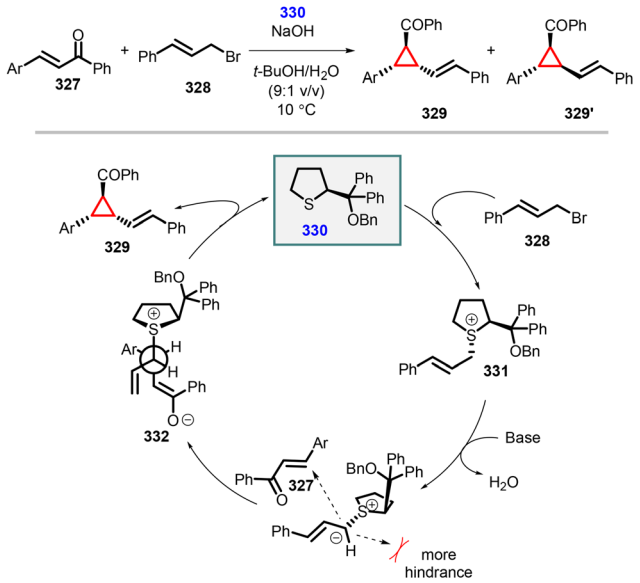
Chein and coworkers subsequently expanded their MIRC reaction by developing an innovative and environmentally friendly approach for the synthesis of enantioselective cyclopropane scaffolds using (*S*)-(thiolan-2-yl)diphenylmethanol benzyl ether (**330**) as an organocatalyst. This method utilizes a solvent system comprising *t*-BuOH/H_2O, a low-cost base (NaOH), and a reusable catalyst, making it a greener alternative.

In this process, a sulfur ylide, generated *in situ*, reacts with (*E*)-chalcones *via* a Johnson–Corey–Chaykovsky reaction. This transformation affords a range of cyclopropanes with excellent yields and enantioselectivity (up to 95% ee) (Scheme 75).[222]

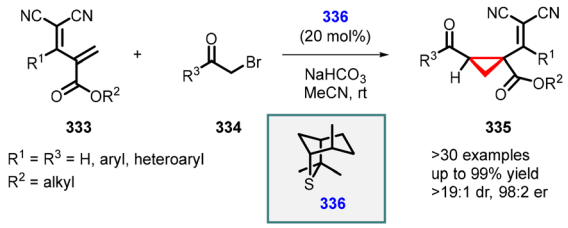
Li and coworkers developed a novel methodology for enantioselective cyclopropanation utilizing chiral sulfide (**336**) as an organocatalyst (Scheme 76).[223] In this process, the electron-deficient diene **333** is treated with bromides **334** in the presence of a chiral catalyst, namely (1*R*,4*R*,5*R*)-4,7,7-trimethyl-6-thiabicyclo[3.2.1]octane **336**, and $NaHCO_3$ in acetonitrile. The reaction yielded the desired product, vinylcyclopropanes (**335**) with a high yield (99%) and excellent stereoselectivity (>19 : 1 dr, 98 : 2 er).



Scheme 74 Organoselenium-catalyzed MIRC cyclopropanation.



Scheme 75 (Thiolan-2-yl)diphenylmethanol benzyl ether-catalyzed MIRC cyclopropanation of chalcones.

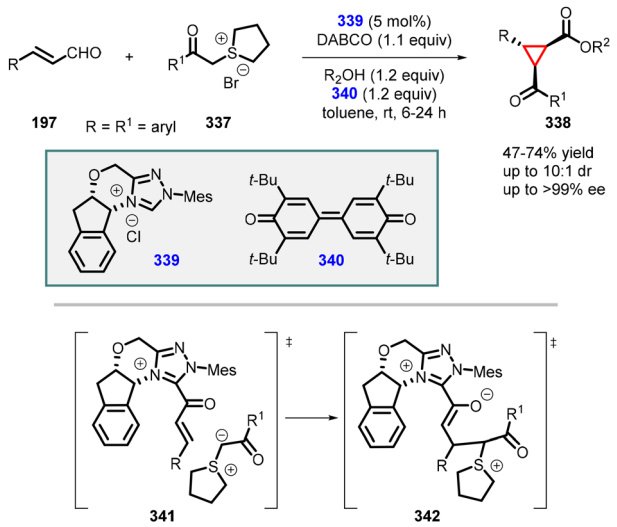


Scheme 76 (1*R*,4*R*,5*R*)-4,7,7-Trimethyl-6-thiabicyclo[3.2.1]octane catalyzed cyclopropanation.

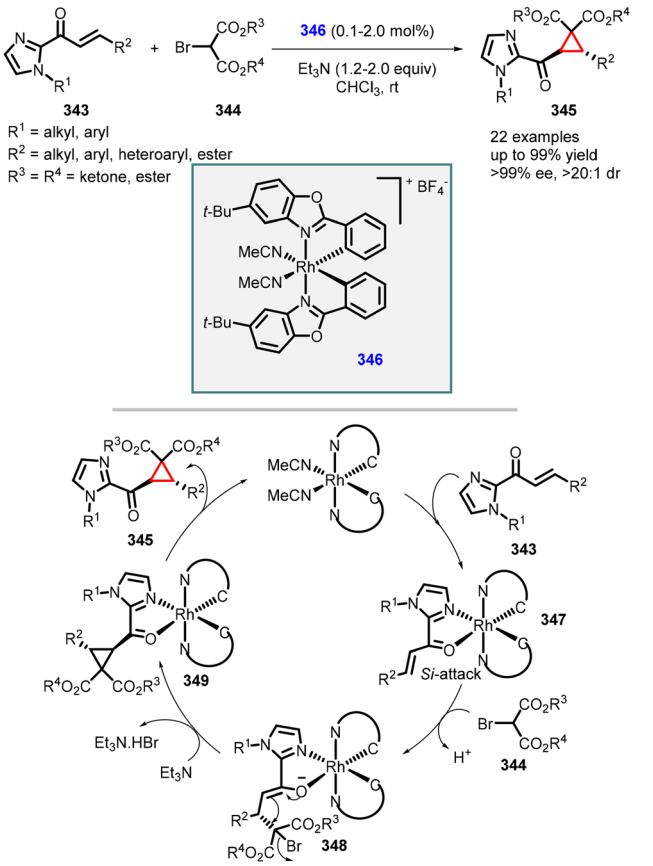
Studer and coworkers have developed an asymmetric cyclopropanation of α,β-unsaturated aldehydes (**197**) using stabilized sulfonium ylides (**337**) (Scheme 77).[224] This method employs a chiral NHC catalyst precursor (**339**), DABCO as base, and benzoquinone **340** as the oxidant. The reaction enables the synthesis of a diverse range of highly functionalized chiral cyclopropanes (**338**) with moderate yields (47–74%) and excellent diastereoselectivity (10 : 1 dr) and enantioselectivity (>99% ee).

The reaction mechanism begins with the formation of an acylazolium ion intermediate (**341**) by the reaction between carbene catalyst (**339**) and enal (**197**) in the presence of a mild oxidant (**340**). This intermediate, **341**, then undergoes a stereo-

The reaction proceeds *via* the formation of a chiral sulfur ylide through the combination of 2-bromoalkyl ethanone (**334**) with the sulfide catalyst (**336**). Subsequently, the ylide undergoes vinylogous addition to diene (**333**), followed by an intramolecular nucleophilic substitution, leading to the release of catalyst (**336**) and formation of vinylcyclopropane moiety (**335**).



Scheme 77 NHC catalyzed enantioselective MIRC cyclopropanation.



Scheme 78 Chiral Rh(III) complex-catalyzed cascade MIRC reactions for enantioselective synthesis of cyclopropanes.

selective Michael addition using ylide **337**, followed by an intramolecular alkylation reaction leading to the formation of intermediate (**342**). Finally, after the removal of NHC with isopropanol, the desired cyclopropane product (**338**) is obtained.

3.2 Metal catalysts

Metal catalysts play a crucial role in Michael-initiated ring-closing cyclopropanation, a key process in organic chemistry. These catalysts, including metals like ruthenium, magnesium, copper, lanthanum, nickel, indium, palladium, rhodium, and others in the form of complexes, are essential for accelerating the formation of the cyclopropane ring. By utilizing these catalysts, chemists can not only increase the efficiency of the reaction but also exert control over its yield, stereochemistry, and regioselectivity. This ability to activate and interact with the reactants enables the generation of highly valuable molecules containing cyclopropane unit. The discovery of metal catalysts in Michael-initiated ring-closing cyclopropanation has significantly expanded the synthetic toolkit available to chemists, providing them with a diverse range of methods for creating complex and valuable compounds.

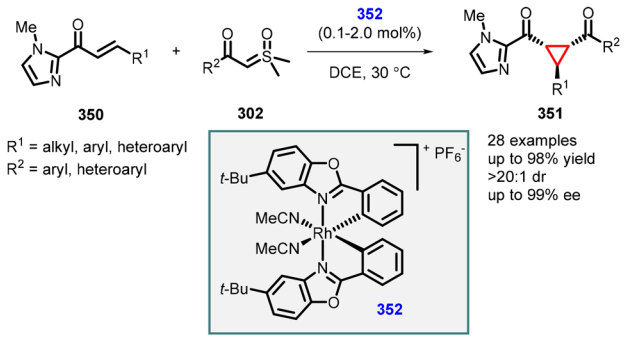
3.2.1 Rhodium-catalyzed MIRC cyclopropanation. In 2017, Kang and coworkers showcased the effectiveness of the chiral rhodium complex (**346**) in catalyzing the cascade Michael addition/alkylation reaction. Their work demonstrated the successful application of this process in the enantioselective cyclopropanation of α,β-unsaturated 2-acyl imidazoles (**343**) with 2-bromomalonate (**344**). The reaction resulted in the formation of highly substituted cyclopropanes (**345**) with moderate to high yields (70–99%) and high enantioselectivity (93–99% ee) (Scheme 78).[225]

The reaction proceeds through several key steps. First, substrate (**343**) was activated by the rhodium catalyst, forming an intermediate **347** through bidentate *N*,*O*-coordination. The bulky *t*-Bu group on the ligand shields the *Re* face of **347**, allowing nucleophilic attack of diethyl α-bromomalonate **344** to occur from the *Si* face. This leads to the formation of an enolate anion, intermediate **348**. Next, intermediate **348** undergoes cyclization, resulting in the formation of a coordinated intermediate **349** with a cyclopropane skeleton. The desired cyclopropane adduct (**345**) was released from the coordinated intermediate **349** through ligand exchange with substrate (**343**), initiating a new catalytic cycle.

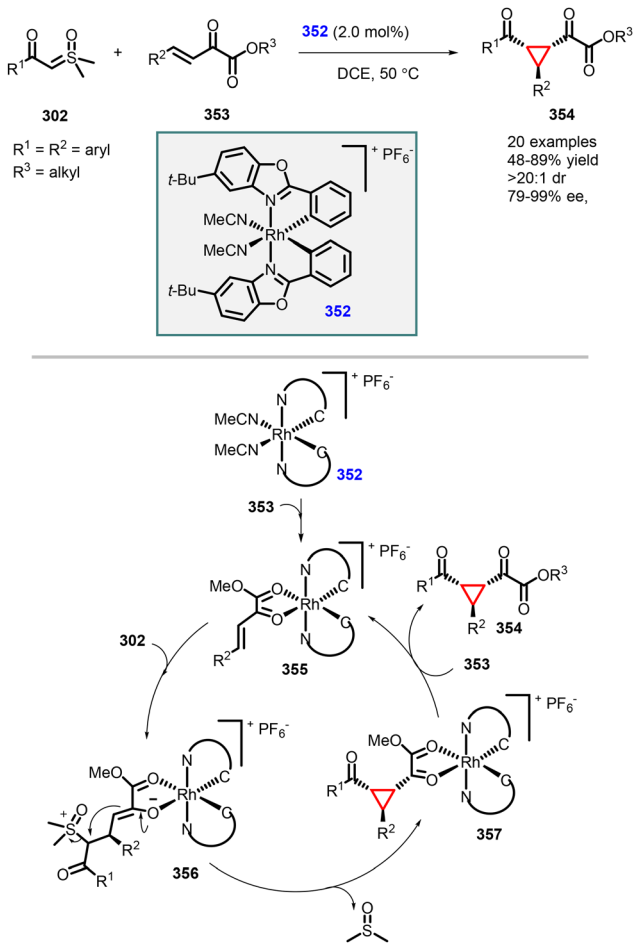
Gong and coworkers pursued a similar approach by employing sulfoxonium ylides (**302**) as nucleophiles in conjunction with α,β-unsaturated 2-acyl imidazoles (**350**). The reaction was catalyzed by a chiral rhodium complex (**352**) and the reaction gave favorable outcomes, as demonstrated in Scheme 79,[226] with a mechanism similar to the previously mentioned by Kang *et al.*

Li and coworkers reported an enantioselective MIRC reaction between sulfoxonium ylides (**302**) and β,γ-unsaturated ketoesters (**353**) using the same catalytic system (**352**) (Scheme 80).[227] The reaction furnished 1,2,3-trisubstituted cyclopropanes (**354**) in moderate to high yields (48–89%) and excellent diastereo- and enantioselectivity (dr >20 : 1 and up to 99% ee).

Mechanistic studies demonstrated the key role of a weak coordination mode between the chiral rhodium catalyst (**352**) and the β,γ-unsaturated carbonyl esters (**353**) in achieving high levels of diastereoselectivity and enantioselectivity for the product formation as shown in the Scheme 80.

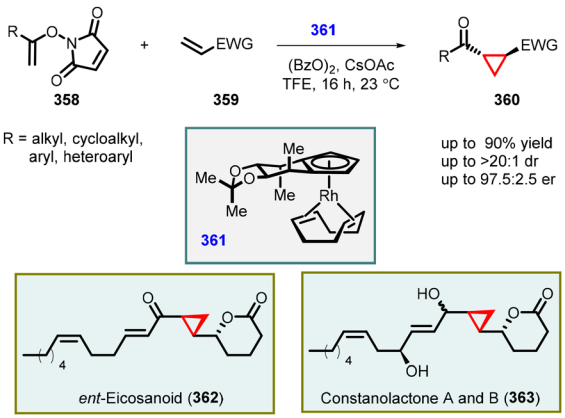


Scheme 79 Chiral Rh(III) complex-catalyzed cascade MIRC cyclopropanation of α,β-unsaturated 2-acyl imidazoles with sulfoxonium ylides.



Scheme 80 Chiral Rh(III) complex-catalyzed cascade MIRC cyclopropanation of sulfoxonium ylides and β,γ-unsaturated ketoesters.

In the synthesis of chiral functionalized cyclopropanes (**360**), Cramer and coworkers employed chiral cyclopentadienyl Rh(III) complexes **361** as catalysts. The substrates used were olefins with *N*-enoxyphthalimides (**358**) and electron-deficient olefins (**359**). The MIRC cyclopropanation yielded chiral cyclopropanes (**360**) in high yields (up to 90%), excellent diastereoselectivity (>20 : 1), and excellent enantiomeric excesses of 95%



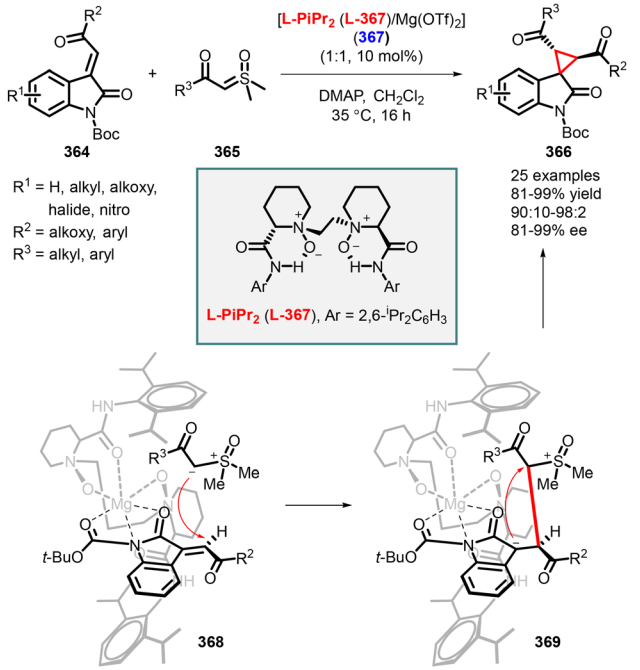
Scheme 81 Chiral Rh(III) complex-catalyzed cyclopropanation of *N*-enoxyphthalimides and electron-deficient olefins.

(Scheme 81).[228] The reaction involves enantioselective alkenyl C–H bond functionalization, providing an avenue for accessing chiral cyclopropanes under mild, open-flask reaction conditions. To demonstrate the synthetic applicability of this method, the authors successfully utilized cyclopropanation as a crucial step in synthesizing both the oxylipin family of natural products and the kynurenine 3-monooxygenase inhibitor UPF-648.

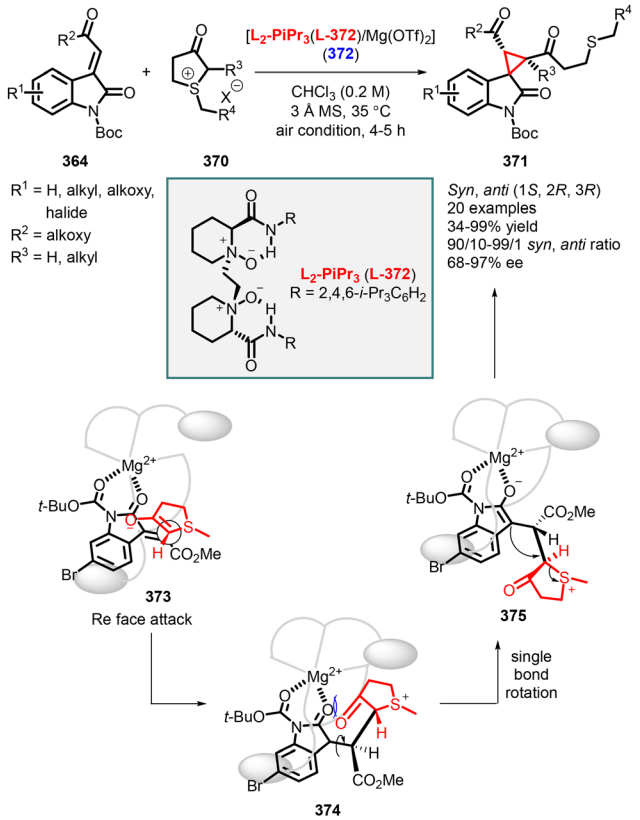
3.2.2 Magnesium-catalyzed MIRC cyclopropanation. In 2018, Feng and coworkers conducted a study on the synthesis of a series of spiro-cyclopropyl oxindoles (**366**) from 3-alkenyloxindoles (**364**) using sulfoxonium ylides (**365**) as substrates. The reaction was catalyzed by a chiral *N*,*N*′-dioxide [(**L-PiPr$_2$**)(**L367**)/Mg(OTf)$_2$] (**367**) complex (Scheme 82).[229] Although the authors did not provide an in-depth mechanistic explanation for the cyclopropanation reaction, they substantiated their findings with X-ray data and control experiments. The X-ray data and control experiments demonstrated that the [**L-PiPr$_2$**(**L367**)/Mg(OTf)$_2$] (**367**) complex effectively decreased the LUMO energy of the electron-deficient 3-alkenyl oxindole (**364**), thereby enhancing its electrophilicity. Furthermore, the complex also reduced the nucleophilicity of the sulfoxonium ylide (**365**), indicating that the nucleophilic attack step was hindered compared to other steps in the reaction.

Feng and coworkers expanded their study to a chiral sulfur ring-opening/cyclopropanation reaction involving 1-alkyl-3-oxotetrahydro-1*H*-thiophen-1-ium salts (cyclic sulfur ylides) **370** and (*E*)-3-(oxyethylidene)-2-oxoindolines **364**. Notably, this reaction was catalyzed by a chiral *N*,*N*′-dioxide (**L$_2$-PiPr$_3$**) (**L-372**) complex, featuring a slightly different aromatic substituent, in combination with Mg(OTf)$_2$. The reaction resulted in the formation of sulfur-containing *syn*, *anti* spirocyclopropyloxindoles (**371**) that possesses three contiguous chiral centers (Scheme 83).[230]

The authors proposed transition-state models to explain the origin of stereoselectivity. In this process, the chiral *N*,*N*′-dioxide ligand (**L$_2$-PiPr$_3$**) coordinates with Mg(II), adopting an octahedral geometry with four oxygens. Following this, the two



Scheme 82 *N,N′*-Dioxide (**L-PiPr$_2$**)/Mg(OTf)$_2$ complex catalyzed cyclopropanation of 3-alkenyl-oxindoles and sulfoxonium ylides.



Scheme 83 Ring opening cyclopropanation of cyclic sulfur ylides using Mg metal mediated catalyst.

oxygens of (*E*)-3-(oxyethylidene)-2-oxoindolines **364** coordinates with Mg(II) in a bidentate manner. The neighboring amide group of the ligand provides shielding to the *Si* face of compound (**364**). Consequently, the *Re* face of the nucleophilic ylide (**370**) approaches the *Re* face of compound (**364**).

During the ring-closing step, which proceeds through an S$_N$2 reaction, the enolate anion must attack from the opposite position as the releasing sulfur salt. If the enolate approaches the thianone (**370**) with its *Si* face (intermediate **374**), the repulsive effect intensifies. This prompts a rotation of the C–C single bond connected to the enolate, allowing the enolate anion's *Re* face to attack the thianone (**370**). The resulting process is an S$_N$2 reaction that yields the (1*S*,2*R*,3*R*)-product (**371**).

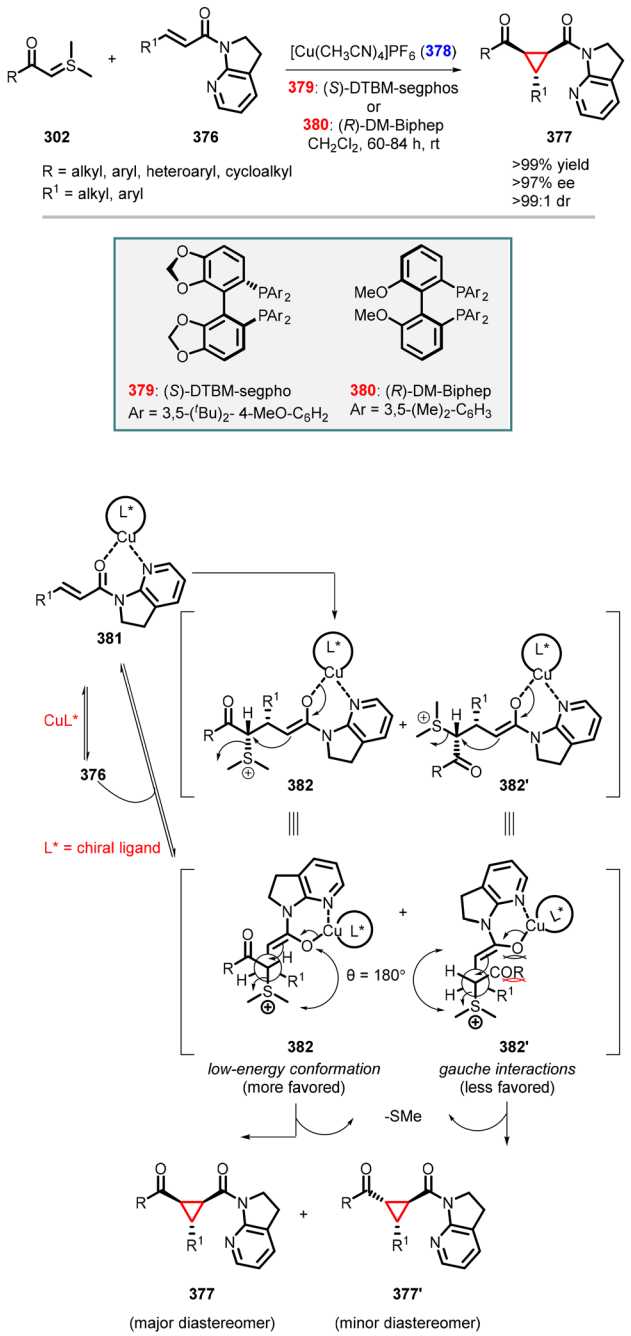
3.2.3 Copper-catalyzed MIRC cyclopropanation. Kumagai and Shibasaki achieved a highly selective synthesis of 1,2,3-trisubstituted cyclopropanes using a Cu(I) complex with chiral ligands, specifically (*S*)-DTBM-segphos (**379**) or (*R*)-DM-Biphep (**380**). Their method involved the MIRC reaction of α,β-unsaturated carbonyl compounds (**376**) in the carboxylic acid oxidation state (specifically 7-azaindoline amides, **376**) with stabilized sulfur ylides (**302**) (Scheme 84).[231]

Michael acceptor (**376**) reacts with the Cu(I)/L* complex, forming a *Z*-configured complex **381**. This complex enhances the electrophilicity of (**376**) for the nucleophilic attack by the ylide (**302**) in a chiral environment. Through an irreversible process, the initial asymmetric C–C bond formation occurs at the β-position. The resulting major Cu enolate intermediate **382** undergoes intramolecular S$_N$2 displacement, leading to the formation of the major diastereomer (**377**). In contrast, the minor diastereomer (**377′**) is formed from the minor Cu-enolate intermediate **382′**. The formation of the major diastereomer (**377**) is favored because it involves a more stable intermediate **382**, whereas intermediate **382′** experiences significant steric interactions, resulting in the formation of the minor diastereomer (**377′**) through a higher-energy transition state.

For β-alkyl and β-aryl substrates, two different ligand systems were used. These systems successfully produced the desired products in high yields (>99%) and selectivity (>99 : 1, >97% ee), with 1–2 mol% of catalyst loading.

In 2010, Feringa and coworkers reported an enantioselective copper-catalyzed domino reaction for synthesizing *trans*-1-alkyl-2-substituted cyclopropanes (**385**) (Scheme 85).[232] The reaction involves a combination of Grignard reagents and 4-chloro-α,β-unsaturated esters/thioesters/ketones (**383**) in the presence of the chiral ligand (*R*)-Tol-BINAP and CuI as the pre-catalyst. The presence of the internal chloro as a leaving group enabled a tandem conjugate addition-enolate trapping process, resulting in the formation of *trans*-1-alkyl-2-substituted cyclopropanes (**385**) with moderate to high yields (50–95%) and good to excellent enantiomeric excess values (up to 98%). This versatile reaction demonstrated its utility by producing key intermediates for the formal syntheses of cascarillic acid (**386**) and grenadamide (**387**).

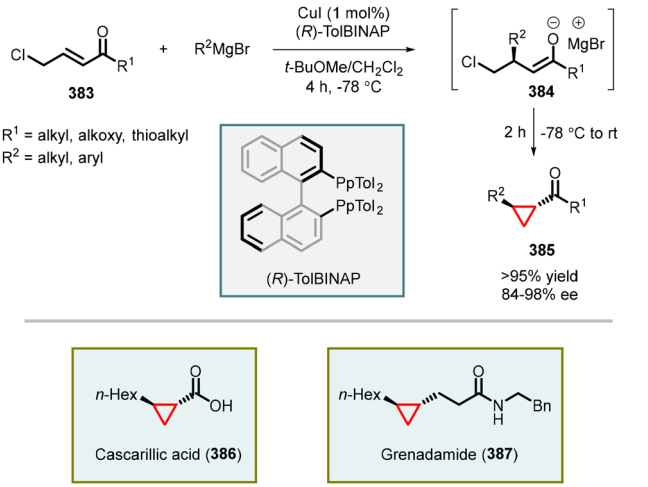
3.2.4 La-catalyzed MIRC cyclopropanation. Matsunaga and Shibasaki reported a catalytic asymmetric cyclopropanation



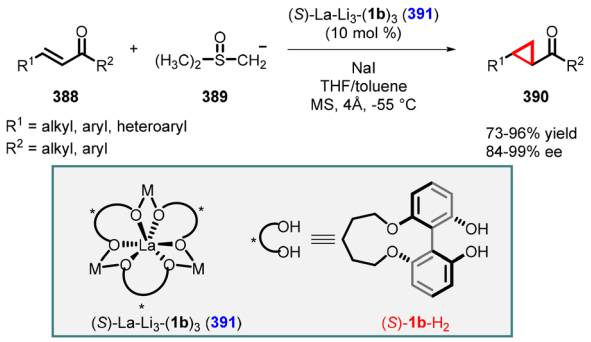
Scheme 84 Cu(I) complex catalyzed MIRC cyclopropanation of 7-azaindoline amides, with stabilized sulfur ylides.

reaction involving enones or *N*-acyl pyrrole (**388**) and dimethyloxosulfonium methylide **389**. The catalyst employed in this reaction was the La-Li$_3$-(biphenyldiolate)$_3$/NaI complex (**391**), which acted as a chiral Lewis acid. During this process, enantio-enriched cyclopropane products (**390**), featuring a wide range of functional groups, were successfully obtained in high yields (73–96%), and excellent enantioselectivity (84–99% ee) with a low catalyst loading (Scheme 86).[233]

Feng and coworkers reported a significant advancement in the synthesis of highly functionalized cyclopropanes through a

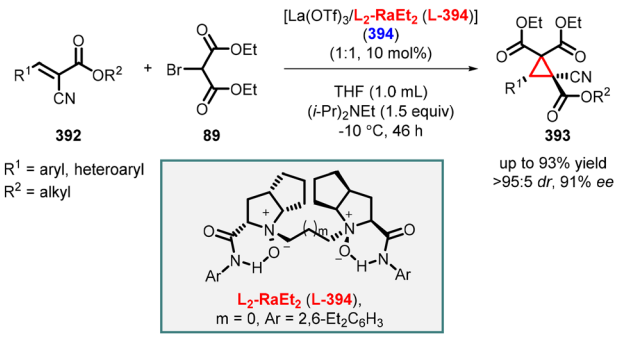


Scheme 85 MIRC cyclopropanation of 4-chloro-α,β-unsaturated esters/thioesters/ketones with Grignard reagents.



Scheme 86 La-Li$_3$-(biphenyldiolate)$_3$/NaI complex catalyzed MIRC cyclopropanation of enones with dimethyloxosulfonium methylide.

La-catalyzed enantioselective MIRC reaction. In this process, 2-cyano-3-arylacrylates (**392**) was reacted with 2-bromomalonates **89**, utilizing a *N*,*N*′-dioxide **L$_2$-RaEt$_2$**–lanthanum(III) complex (**394**) as a Lewis acid catalyst. The desired highly functionalized chiral cyclopropanes (**393**) were obtained in high yields (up to 93%), excellent diastereomeric ratios (>95 : 5 dr) and high enantiomeric excess (up to 91% ee) (Scheme 87).[234]



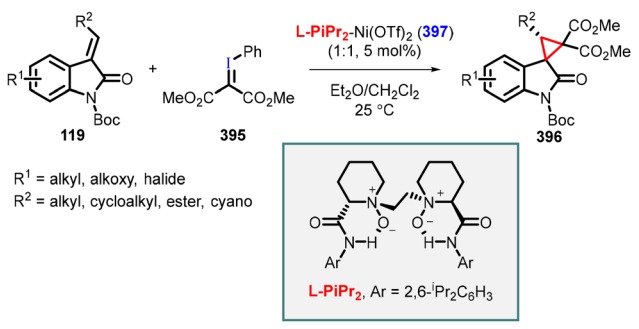
Scheme 87 *N*,*N*′-Dioxide–lanthanum(III) complex catalyzed enantioselective MIRC cyclopropanation.

3.2.5 Ni/In/Sc/Ti-catalyzed MIRC cyclopropanation. Feng and coworkers also published a study on a Ni-catalyzed cyclopropanation reaction involving 3-alkenyl-oxindoles (**119**) and phenyliodonium ylides (**395**). The reaction initiates with the mild thermal decomposition of phenyliodonium ylide malonate, resulting in the generation of a free singlet carbene. Subsequently, the carbene engages in a reaction with the 3-alkylidene oxindole, facilitated by an *N*,*N*′-dioxide **L-PiPr$_2$**-nickel complex (**397**). This process leads to the formation of spirocyclopropanes (**396**) with high yields, (82–99%), complete diastereoselectivity and excellent enantiomeric excess (up to 99% ee) (Scheme 88).[235]

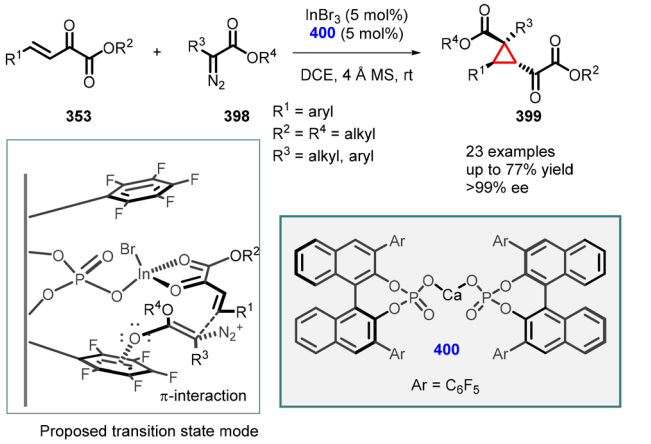
A domino Michael addition/cyclization reaction was reported by Luo and co-workers for the enantioselective synthesis of functionalized chiral cyclopropanes from β,γ-unsaturated α-keto esters (**353**) and diazo esters (**398**). This transformation was achieved using a binary Lewis acid catalyst consisting of 5 mol% $InBr_3$ and an equivalent quantity of chiral calcium phosphate (**400**). The reaction was carried out in dichloroethane (DCE) at room temperature. The resulting cyclopropanes (**399**) were obtained in moderate to good yields (50–77%) and as a single diastereomer and with excellent enantiomeric excess (>99% ee). In this process, the bidentate coordination of the β,γ-unsaturated α-keto esters with the cationic indium complex creates a rigid system for chiral identification. It was proposed that weak π-interactions between the chiral phosphoric acid and the diazo ylide facilitates a facial attack, followed by backside attack for the cyclization with the loss of nitrogen (Scheme 89).[236]

in 2018, Feng, Liu and coworkers developed a diastereodivergent asymmetric Michael addition-alkylation reaction using 3-Cl oxindoles (**150**) and β,γ-unsaturated α-ketoesters (**401**) (Scheme 90).[237] They achieved high yields (50–99%) and excellent enantioselectivity (72–99% ee) of *rel*-(1*R*,2*S*,3*R*) spiro cyclopropane oxindoles by modifying metal catalysts, ligands, and temperature. Different metal catalysts resulted in the formation of distinct diastereoisomers: *rel*-(1*S*,2*S*,3*R*) *via* intramolecular trapping and (iso)-**402** through a direct substitution pathway. These findings shed light on the reaction mechanism and provide valuable insights for future applications.

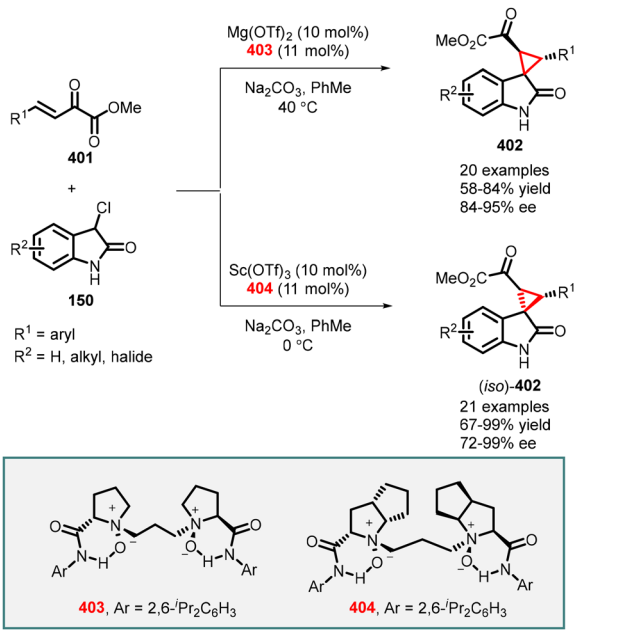
In a subsequent publication, the same research group employed a scandium complex derived from a chiral *N*,*N*′-dioxide ligand **409** as a catalyst in the enantioselective Michael-initiated addition between α-substituted vinyl ketones **406** and α-substituted α-diazoesters **405**. The reactions were conducted at 0 °C, and compounds **406** and **405** underwent a MIRC reaction, leading to the formation of chiral tetrasubstituted cyclopropanes **407** as exclusive diastereomers.[238] The reactions exhibited moderate to good yields (42–65%) and consistently excellent enantioselectivities (94–99% ee) (Scheme 91). In addition to the cycloadducts, a competing C–H insertion pathway resulted in the production of chiral *E*-enone derivatives **408**. These compounds were also obtained with high enantioenrichment (72–95% ee) and modest yields (24–57%).



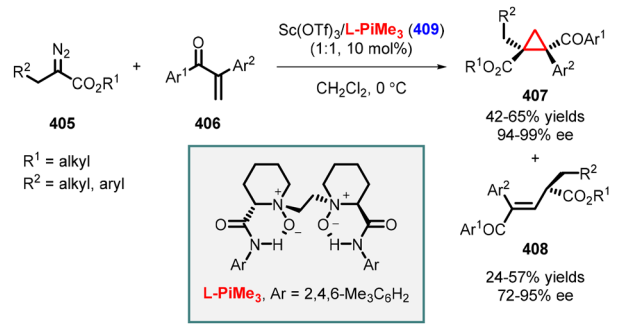
Scheme 88 *N*,*N*′-Dioxide–Ni(II) complex catalyzed enantioselective MIRC cyclopropanation.



Scheme 89 Binary Lewis acid ($InBr_3$ and chiral calcium phosphate) catalyzed enantioselective MIRC cyclopropanation.



Scheme 90 Catalytic enantioselective MIRC cyclopropanation of β,γ-unsaturated α-ketoesters.



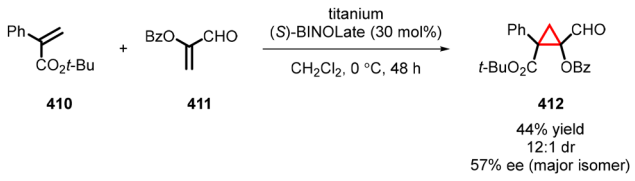
Scheme 91 *N,N′*-Dioxide–Sc(III) complex catalyzed enantioselective MIRC cyclopropanation.

In 2007, Maruoka and coworkers demonstrated the effectiveness of acid-catalyzed Michael-initiated cyclopropanation reactions with aryldiazoacetates as reactive nucleophiles and α-substituted acroleins (Scheme 92). The aim was to prepare sterically congested cyclopropanes with high diastereoselectivity. The authors investigated the viability of an asymmetric variation utilizing (*S*)-BINOL-Ti(Oi-Pr)$_4$ (2 : 1 molar ratio) as the catalyst. The cyclopropanation reactions between *tert*-butyl phenyldiazoacetate (**410**) and α-benzoyloxyacrolein (**411**) yielded a cyclopropane product (**412**) with good diastereoselectivity (12 : 1 dr) but poor enantioselectivity (57% ee for the major isomer).[239]

3.3 Guideline for catalyst selection for the enantioselective construction of cyclopropane rings

In this review, we have summarized catalytic MIRC reactions for the stereoselective construction of cyclopropane rings. Catalytic methodologies ranging from organocatalysis to metal based chiral Lewis-acid catalysis have been discussed in this review. Given the extensive amount of literature covered, it is appropriate to inform the readers which methodology would be appropriate while planning a synthesis. The chirality in these catalytic MIRC reactions is achieved through chiral electrophiles (acceptors) or through chiral Michael nucleophiles (donors). For chiral electrophiles, especially α,β-unsaturated aldehydes or ketones, organocatalysis based on chiral secondary amines (prolinol or imidazolidinone derived) (see section 3.1.4) could be the method of choice. The electrophiles can also be activated through chiral Lewis acid catalysis (see section 3.2). In this case, an auxiliary group capable of chelating to the metal center is often a requirement. For reactions with chiral nucleophiles, organocatalysis based on cinchona alkaloid derived catalysts (for the generation of ammonium ylide as a Michael initiator) (see section 3.1.1) could be the method of choice.

This review aims to guide researchers in selecting the most effective method for their specific cyclopropane targets. The analysis of enantioselectivity, substrate scope, synthetic efficiency, and reproducibility serves as a valuable resource for the selection.



Scheme 92 Titanium/(*S*)-BINOLate catalyzed enantioselective MIRC cyclopropanation.

4. Conclusions

This comprehensive review is focused on catalytic enantioselective Michael initiated ring closure (MIRC) cyclopropanation reaction. The review highlights the relevance of MIRC reactions in achieving high enantioselectivity for the product cyclopropanes and provides insights into the various methods, catalysts, substrates, and nucleophiles utilized in this transformation. Furthermore, the analysis delves into the examination of factors that influence reactivity and selectivity, including catalyst selection, reaction conditions, and functional groups. Despite notable advancements in cyclopropane synthesis, there are persistent obstacles that need to be addressed. These include gaining a better understanding of the reaction mechanism, exploring alternative systems to enhance selectivity, and reducing catalyst loading to promote environmentally friendly practices. Ongoing efforts are crucial to tackle these challenges and drive advancements in the field of asymmetric cyclopropanation, which holds significant importance in the synthesis of pharmaceuticals, and advanced materials.

Conflicts of interest

There are no conflicts to declare.

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