Organic & Biomolecular Chemistry

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2018, **16**, 7315

Received 21st May 2018,
Accepted 5th September 2018

DOI: 10.1039/c8ob01187g

rsc.li/obc

Recent advances in the synthesis of cyclopropanes

Wanqing Wu, * Zhiming Lin and Huanfeng Jiang *

Cyclopropanes, one of the most important strained rings, have gained much attention for more than a century because of their interesting and unique reactivity. They not only exist in many natural products, but have also been widely used in the fields of organic synthesis, medicinal chemistry and materials science as versatile building blocks. Based on the sustainable development in this area, this review mainly focuses on the recent advances in the synthesis of cyclopropanes classified by the type of catalytic system, including regio-, diastereo-, and enantio-selective reactions.

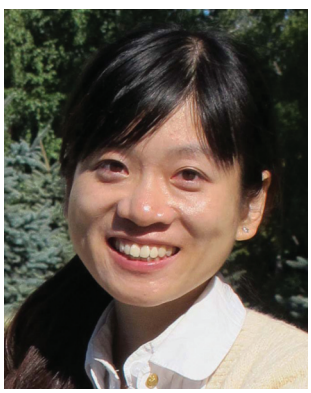
1. Introduction

As the smallest subset of a class of useful cycloalkanes, cyclopropanes play an indispensable role in the chemical world. A lot of attention has been given to the cyclopropane subunit, which is present in many natural products and pharmaceutical molecules, since the first synthesis of the cyclopropane ring by August Freund in 1882,[1] because of its unusual chemical skeleton structure. Relatively shorter C–C bonds,[2a] enhanced both the π-character of C–C bonds than normal,[2b] shorter and stronger C–H bonds than those in alkanes[2c] resulted in a higher reactivity than typical alkanes and there is significant kinetic stability under ring strain (27.5 kcal mol^{-1}).[3] As already stated, derived from their excellent reactivity and features, not only have a large number of methods for the synthesis of cyclopropanes been developed, but also numerous applications in which they act as precursors or key intermediates have been explored, such as the construction of macrocyclic compounds, heterocyclic compounds, bicyclo compounds, and even polysubstituted spiro compounds.[4]

Nature has given the biosphere a number of rich and diverse cyclopropane containing bioactive molecules and secondary metabolites.[5] In reality, related scientific communities have shown great interest in the natural products containing cyclopropane motifs, because they have versatile biological activities.[5c–e] Some drug research has discovered that the presence of the cyclopropane structure could enhance a drug's potency, while increasing the metabolic stability of an enzyme and even reducing, to a certain extent, the off-target effects.[6] Thus, research on cyclopropanes is still continuously developing in organic synthesis, medicinal chemistry, pharmacology, and even in materials science.

In the last decade, a number of reviews about the cyclopropane chemistry have been published, most of which focus on a special cyclopropane structure or a certain class of synthetic

Key Laboratory of Functional Molecular Engineering of Guangdong Province, Guangdong Engineering Research Center for Green Fine Chemicals, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, China. E-mail: cewuwq@scut.edu.cn, jianghf@scut.edu.cn



Wanqing Wu

Wanqing Wu received her PhD from Peking University with Professor Zhen Yang and Professor Chi-Sing Lee in 2010. Then she joined Professor Huanfeng Jiang's group as a postdoctoral researcher at the South China University of Technology (SCUT). In 2014, she was promoted to Professor and her research interests include the development and applications of new synthetic methods.

Zhiming Lin

Zhiming Lin received her BS degree from the Kunming University of Science and Technology (KMUST) in 2015. Currently she is doing research for her Masters degree under the guidance of Professor Wanqing Wu at the South China University of Technology (SCUT). Her research interests include the development and applications of new synthetic methods for strained rings.

methods.[7] This review highlights some of the recent progress on the development of efficient and practical synthetic methods for cyclopropanes from 2012 to 2017, with special emphasis placed on the reaction design and mechanistic aspects. It is hoped that this review will help to provide guidelines for researchers who are interested in this productive area.

2. Synthesis of cyclopropanes

Because the cyclopropane structure has been found in many biologically active compounds, much elegant research has been done on the cyclopropane ring construction. In this section, the recent progress based on transition metal catalysis and transition metal free systems for the formation of cyclopropane motifs, will be discussed.

2.1 Transition metal-catalyzed formation of cyclopropanes

Transition metal catalysis is one of the most efficient strategies for the construction of cyclopropanes. Except for the most commonly used transition metal reagents including copper (Cu), gold (Au), palladium (Pd), rhodium (Rh), and zinc (Zn) catalysts, other transition metal catalysts, such as ruthenium (Ru),[8] iron (Fe),[9] nickel (Ni),[10] cobalt (Co),[11] titanium (Ti)[12] and yttrium (Y)[13] also play an important role in the synthesis of cyclopropanes. It should be noted that the properties of the transition metals lead to the differences in the catalytic effects and the scope of applications, providing complementarity and orthogonality in cyclopropanation reactions. For example, because of their air and moisture stability, various precursors can effectively undergo the cyclopropanation process using Au catalysts, whereas some of the Rh-catalyzed cyclopropanation reactions are reported to be involved in the C–H activation process[14] and diverse chiral Rh catalysts also offer the possibility for stereoselectivity control. Additionally, Cu[15] and Zn[16] salts are both less toxic and inexpensive compared to the noble metals. In particular, the Zn catalytic system has been successfully used in the Simmons–Smith reaction. Recently, some new organozinc reagents have been found to efficiently cyclopropanate some traditionally unreactive alkenes, which expands the scope of alkene substrates for cyclopropanation.

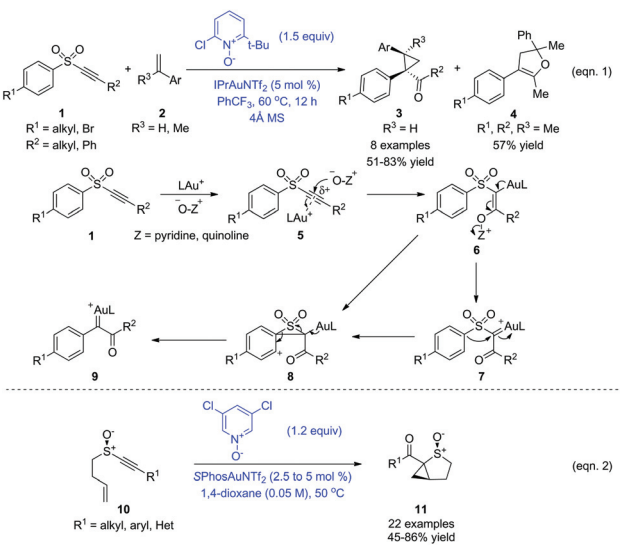
2.1.1 Au-Catalyzed formation of cyclopropanes. Generally, alkenes and alkynes are considered to be the most commonly used tools for the construction of cyclopropanes. Plus, the Au catalyst is a type of effective cyclopropanation reagent because of its air and moisture stability. Also, Au has also been recognized as a π-acid for the activation of enyne substrates for cyclopropanation reactions. Until now, the precursors were gradually developed and refined, which were then combined with Au to produce Au carbenoids, thus further widening the range of cyclopropanation reactions. Out of the Au carbenoids produced, three types of Au carbenoids for the synthesis of cyclopropanes from different precursors will be described, including the oxidation/nitrene transfer reactions of alkynes, cyclization of 1,*n*-enynes, and the decomposition of diazo compounds. However, there are certainly, far more Au-catalyzed cyclopropanation reactions than the ones mentioned here.

Recently, many examples of Au-catalyzed synthesis of functionalized carbo- and hetero-cycles from alkynes using an oxidation/nitrene transfer reaction have been reported. The key to the success of this type of reaction is the formation of an α-oxo Au carbenoid. This strategy uses alkynes as the safe precursor instead of α-diazoketones, and pyridine- or quinoline *N*-oxides were usually the most commonly used oxidants.

In 2015, Zhang's group[17a] developed an oxidative cyclopropanation reaction of alkynyl sulfone **1** and styrene **2**, giving a series of cyclopropyl ketones **3** in good yields with high selectivity using donor-substituted acyl Au carbenes (Scheme 1, eqn (1)). However, some electron-rich alkenes were unsuitable for this protocol. In this strategy, the α-oxo Au carbene intermediate **9** was first generated using a desulfonylation process.

Huanfeng Jiang

Huanfeng Jiang received his PhD from the Shanghai Institute of Organic Chemistry (SIOC) with Professor Xiyan Lu in 1993. Then he joined the Guangzhou Institute of Chemistry as a research fellow. In 2003, he moved to the South China University of Technology (SCUT) as the Leading Professor of Chemistry. He received the Chinese Chemical Society-BASF Young Investigator's Award in 2002 and the National Natural Science Funds for a Distinguished Young Scholar in 2006. His research interests focus on synthetic methodology, green and sustainable chemistry.



Scheme 1 Au-Catalyzed intramolecular and intermolecular oxidative cyclopropanation.

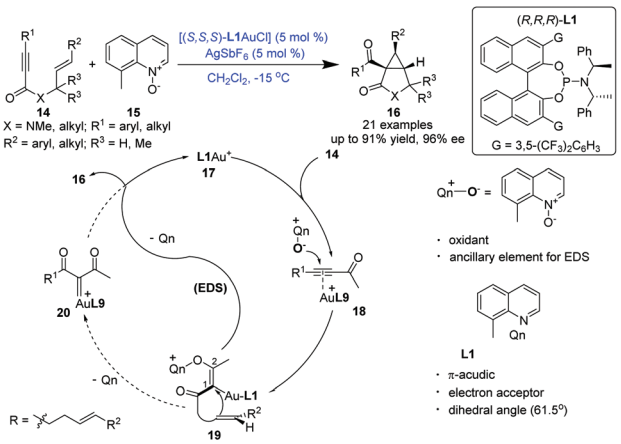
The β-C(sp) of the carbon–carbon triple bond which is polarized by the sulfonyl group was attacked by *N*-oxide upon its coordination to the Au catalyst, thus leading to intermediate **6**. Then intermediate **7** was formed through redox rearrangement, followed by the intramolecular reaction of the carbene moiety with the aryl/alkenyl group to give intermediate **8**. Alternatively, intermediate **8** could be obtained using 3-*exo*-*trig* cyclization of **6**. The desulfonylation fragmentation of episulfone intermediate **8** would finally give the key α-oxo Au carbene **9**. During this process, the desulfonylation rearrangement could be accelerated by the more electron-rich phenyl ring. When α-methylstyrene was used as a co-solvent, the dihydrofuran product **4** was obtained. The author supposed that the benzylic position of the styrene increased the steric hindrance and could better accommodate the positive charge, both of which caused the divergent reactivity.

Afterwards, Grainger and Davies *et al.*[17b] disclosed an intramolecular cyclopropanation reaction giving a series of cyclopropanes containing an α-sulfinyl carbonyl motif **11**. It should be noted that this method demonstrated the reactivity of an α-sulfinyl carbene-like compound for the first time (Scheme 1, eqn (2)).

Obviously, the alkynyl sulfoxides acted as α-sulfinyl metallocarbene synthons under oxidative Au catalysis, which could be engaged in the intra- and inter-molecular cyclizations, and further converted into the corresponding cyclopropane products. Furthermore, a useful 3-aza-bicyclo[3.1.0]-hexan-2-one derivative **13** could be obtained using Au-catalyzed oxidative cyclopropanation of *N*-allyl ynamides (Scheme 2).[18]

In recent years, asymmetric synthesis of cyclopropane compounds has gained great attention because the basic substances that make up life in nature have unique chiral characteristics. It is known that the metallocarbenes with olefins usually act as a common collocation to form asymmetric cyclopropanation (ACP). In 2014, Zhang's group[19] realized an asymmetric alkyne oxidation/cyclopropanation under Au(I)-catalysis for the construction of **16** with high enantioselectivity (up to an enantiomeric ratio (er) of 98 : 2) and up to 91% yield (Scheme 3). For this asymmetric oxidative cyclopropanation, two plausible pathways were found. From the mechanistic studies, β-Au vinyloxyquinolinium species were demonstrated to contribute to the enantioselectivity of this cyclopropanation.

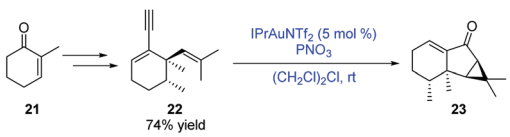
Unlike oxidation, nitrene transfer reactions of alkynes *via* Au catalysis usually generate α-imino Au carbenes. The common nitrene transfer reagents are pyridine *N*-oxides and imino-pyridinium ylides. In 2015, Zhang's group[20] developed a new chiral *P*,*N*-bidentate ligand, which could promote the



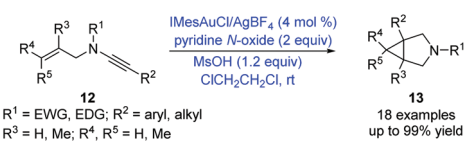
Scheme 3 Au(I)-Catalyzed asymmetric alkyne oxidation/cyclopropanation and a plausible mechanism.

enantio-selective intramolecular cyclopropanation through a reactive α-oxo Au carbene intermediate generated *in situ*. This new class of chiral ligands should have high value in asymmetric synthesis. In the same year, Echavarren[21] reported the first example of Au(I)-catalyzed oxidative cyclopropanation of enynes in a total synthesis, which could be applied for the efficient preparation of (−)-nardoaristolone B (**23**), exhibiting a certain level of protective activity for the injury of neonatal rat cardiomyocytes (Scheme 4). The cyclopropane derived indoloquinolin **25** could be also obtained *via* a cascade cyclization and the α-amidino Au carbenoid is supposed to be the key intermediate (Scheme 5).[22] Actually, different functional groups of (azido)ynamides would affect the cascade cyclization process.

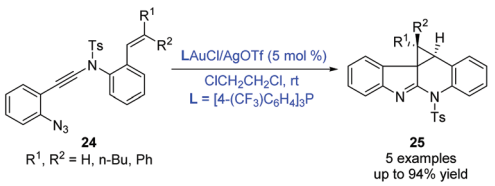
1,*n*-Enyne is a versatile building block for many transformations. Compared to the common alder-ene type rearrangements, 1,*n*-enynes usually undergo skeletal rearrangements under the treatment of an Au catalyst. In 2013, Yeom and Shin[23] developed an efficient intramolecular oxidative cyclopropanation of 1,6-enynes bearing propiolamide tethers **26**



Scheme 4 Enantio-selective total synthesis of (−)-nardoaristolone B using oxidative cyclization.



Scheme 2 Au-Catalyzed oxidative cyclopropanation of *N*-allyl ynamides.



Scheme 5 Synthesis of cyclopropane derivatives from ynamides.

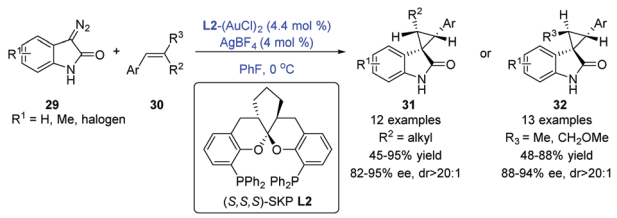
Scheme 6 Intramolecular oxidative cyclopropanation of 1,6-enynes.

with diphenyl sulfoxide **27** as oxidant (Scheme 6). This work was the first to yield the cyclopropane carboxaldehydes **28** which might have distinct applications because of their aldehyde functionality. It is worth mentioning that diphenyl sulfoxide rather than other oxidants, such as pyridine/quinoline *N*-oxides, performed as an excellent oxidant in this reaction.

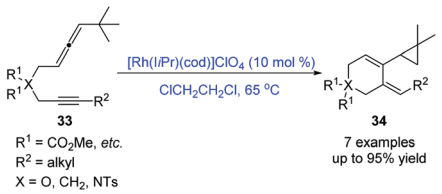
Diazo compounds have been widely used in many synthetic transformations *via* carbene intermediates generated *in situ* from their decomposition under transition metal catalysis. However, the first Au-based catalyst for the cyclopropanation of a diazo was reported by Pérez *et al.* in 2005.[24a] In 2013, Zhou's group[24b] developed the synthesis of substituted spiro cyclopropyl oxindoles **31** and **32** with high diastereo- and enantioselectivity, which are useful in medicinal research (Scheme 7). Importantly, the results implied that the spiroketal bisphosphine ligands might have more applications in Au-catalyzed asymmetric reactions, and that the Au-stabilized donor/acceptor carbenoids would have potential applications in asymmetric cyclopropanations.

2.1.2 Rh-Catalyzed formation of cyclopropanes. Rhodium complexes are not only well known to have the ability of C–H bond activation, but also to show effective catalytic ability in cyclopropanation reactions. Because of its particular atomic structure, Rh-carbenoids are much more susceptible to steric interference compared to the corresponding Au-carbenoids, which makes the chiral Rh catalysts show high regio-, diastereo-, and enantio-control in the cyclopropanation process. In this section, Rh-catalyzed cyclization of allenynes/alkenes, and the decomposition of diazo compounds for the construction of cyclopropanes will be introduced. Most notably, some cyclopropanation reactions are initiated by Rh-catalyzed C–H activation. Dual catalysis involving an Rh catalyst will also be discussed.

In 2012, Sato's group,[14a] developed a Rh(I)-catalyzed cyclization of allenynes **33** to construct cyclic compounds containing a cyclopropane structure **34**. Deuterium labeling experiments



Scheme 7 Enantio-selective formation of spiro-cyclopropyl-oxindoles *via* Au-catalyzed cyclopropanation.

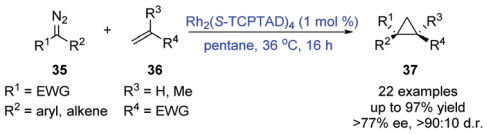


Scheme 8 Rh(I)-Catalyzed C_{sp^3}–H bond activation directed to the formation of cyclopropane compounds.

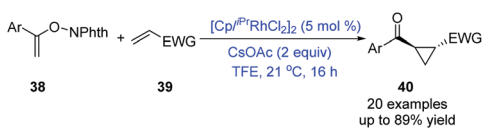
supported the fact that the rate-determining step was the cleavage of the C_{sp^3}–H bond, which triggered the cyclopropanation process (Scheme 8).

Generally, Rh-catalyzed cyclopropanation reactions occur in electron rich and electron neutral alkenes rather than electron deficient alkenes because of the electrophilic nature of Rh-bound carbenes. In 2013, Davies *et al.* developed a Rh_2(*S*-TCPTAD)$_4$-catalyzed, highly stereo-selective cyclopropanation reaction from the substituted aryldiazoacetates or vinyldiazoacetates with electron-deficient alkenes **36** (Scheme 9).[25] It is important to know, that computational studies suggested that the reaction was promoted by the weak interaction between the substrate carbonyl and the Rh-carbenoid, but the subsequent different pathways were dependent on the nature of the carbonyl group. This might account for the fact that acrylates and acrylamides transferred to the cyclopropanation products, whereas unsaturated aldehydes and ketones were converted to the epoxides. Later, Rovis *et al.*[14b] successfully developed the first Rh(III)-catalyzed cyclopropanation *via* C–H activation (Scheme 10). It is worth noting that the newly designed monosubstituted isopropylcyclopentadienyl ligand significantly improved the yield and diastereoselectivity, and this is also a rare example of carbocycle synthesis *via* Rh(III) catalysis.

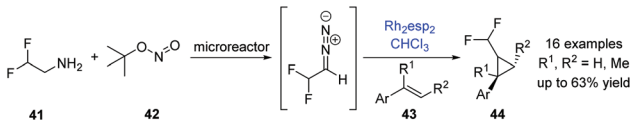
Diazo compounds, which are prone to generate a carbene intermediate under Rh catalysis, have been widely used in cyclopropanation reactions. However, the applications of difluoromethyl diazomethane in organic synthesis are still



Scheme 9 Rh_2(*S*-TCPTAD)$_4$-catalyzed formation of cyclopropane from electron-deficient alkenes.



Scheme 10 Rh(III)-Catalyzed carbocycle synthesis.

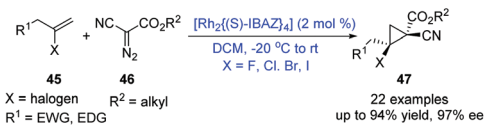


Scheme 11 Rh-Catalyzed synthesis of difluoromethyl cyclopropanes.

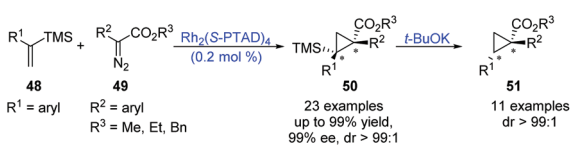
rare, even though the difluoromethyl group exhibits lower lipophilicity and increased polarity and the difluoromethyl-substituted cyclopropanes show medicinal value. In 2016, Koenigs *et al.*[26] disclosed the first protocol for the Rh(II)-catalyzed one-step synthesis of difluoromethyl cyclopropanes from difluoromethyl diazomethane with good yields. Interestingly, the key factor for the success of this method is the preparation of difluoromethyl diazomethane in continuous flow with high efficiency (Scheme 11). During the same time, Jubault's group[27] reported an asymmetric synthesis of halocyclopropanes **47** with good yields and moderate to good diastereoselectivities in the presence of $Rh_2\{(S)\text{-IBAZ}\}_4$ as a catalyst (Scheme 12). This is the first general method to yield highly functionalized halocyclopropanes from readily available materials, which could be applied for the construction of complex molecular architecture.

Whereas most Rh-catalyzed asymmetric cyclopropanations between stryenes and aryl diazoacetates are *trans*-selective, in 2016, Gu *et al.*[28] reported the preparation of unique optically active *cis*-cyclopropane carboxylates **51** using Rh-catalyzed cyclopropanation followed by desilylation (Scheme 13), in which the configuration inversion was observed. This synthetic strategy is useful for the preparation of chiral (*Z*)-1,2-diaryl-cyclopropane carboxylates, which are usually difficult to obtain using traditional methods.

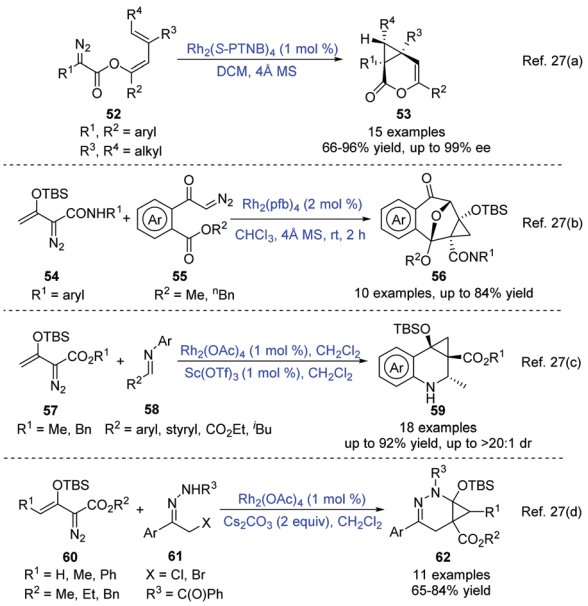
In particular, Doyle's group has expended much effort on researching Rh-catalyzed cyclopropanation reactions to build cyclopropane-fused cyclic compounds and heterocycles. Recently, Doyle's group[29a] developed an intramolecular cyclopropanation reaction of dienyl aryldiazoacetates **52** with high regio-, diastereo-, and enantio-selectivities using chiral dirhodium 2-phthalimide carboxylates as catalyst (Scheme 14). In particular, preferential cycloaddition occurred in the 3,4-double bond instead of the 1,2-double bond in this system. In addition, the cyclopropene cycloaddition reactions of enoldiazo compounds were also developed to build a series of highly strained cyclopropane-fused cyclic compounds, including [3 + 2]-cycloaddition[29b] and [4 + 2]-cycloaddition.[29c,d] The common key intermediates were supposed to be cyclopropenes, even if two molecules of diazo were involved in the reaction.



Scheme 12 A chiral Rh-catalyzed asymmetric synthesis of halocyclopropanes.

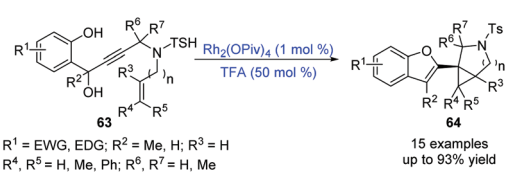


Scheme 13 Preparation of optically active *cis*-cyclopropane carboxylates.

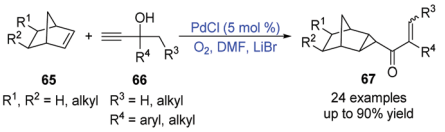


Scheme 14 Examples for Doyle's work on Rh(II)-catalyzed cyclopropanation.

Dual catalysis has also been proved to be a powerful strategy to generate and trap some highly reactive transient species. As shown in Scheme 11, Doyle's group[29c] reported a novel regio- and diastereo-selective Rh(II)/Lewis acid-catalyzed [4 + 2]-cycloaddition reaction between enoldiazoacetates **57** and imines **58** using a two-step, one-pot procedure. Significantly, no reaction occurred between the cyclopropene intermediate and imine without scandium(III) triflate [$Sc(OTf)_3$], indicating the critical role of the Lewis acid. In 2016, Zhu *et al.*[30] also reported an efficient proton/metal-catalyzed cyclopropanation for the construction of various benzofuryl-substituted cyclopropanes **64** (Scheme 15), and the key intermediates were supposed to be benzofuryl carbene and *o*-quinone methide (*o*-QM).



Scheme 15 Proton/Rh-catalyzed cyclopropanation reaction.



Scheme 16 Pd(II)-Catalyzed synthesis of 1,2,3-trisubstituted cyclopropanes.

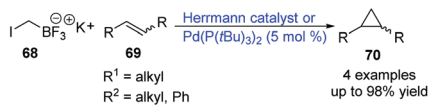
2.1.3 Pd-Catalyzed formation of cyclopropanes. Palladium catalyzed transformations have been also developed for the construction of cyclopropanes, and the most common Pd intermediates for these protocols are allylpalladium, alkylpalladium, as well as palladacycle. Furthermore, high valency Pd-catalyzed cyclopropanation has been achieved to give access to new types of complex compounds as well.[31] In addition, Pd(II) is inert to moisture and air, thus providing opportunities for cyclizations to build diverse cyclopropanes. In this section, the Pd-catalyzed oxidative cyclization of alkenes and decomposition of hydrazone compounds for the synthesis of cyclopropane rings will be introduced.

In 2012, Wu and Jiang[32] used a Pd(II) catalyst and molecular oxygen as the sole oxidant to achieve the cyclopropanation of norbornene derivatives, generating various 1,2,3-trisubstituted cyclopropanes **67** with single regio- and diastereo-selectivity (Scheme 16). In 2014, Chen *et al.*[33a] explored a new protocol to realize methylenation and cyclopropanation using versatile Pd catalysis and halomethylboronate reagents **68** which could be used as the methylene donors instead of Zn-carbenoids and diazomethane (Scheme 17). This protocol only preferred to norbornene, while other olefins exhibited lower reactivity. Furthermore, researchers are still looking for new methylene group sources to break the limitation of classic reaction mode. Nacci and Monopoli *et al.*[33b] discovered an unusual Pd(II)-catalyzed cyclopropanation reaction proceeding through a two-fold C–H activation with water as the sole by-product (Scheme 18). When ketones and alkenes with long aliphatic chains were used as the substrates, only the dehydrogenation by-products were obtained. According to the mechanistic studies, AcO^- was acting as a counterion of both the ionic liquid medium and the Pd(II) source.

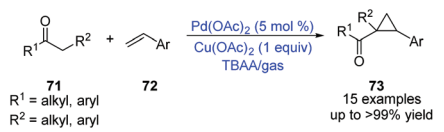
In effect, both the Pd catalyst and additive have influence on the selectivity of the cyclopropanation reactions. For instance, since Hou's group[34] reported the highly enantioselective cyclopropanation reaction of substituted allyl carbonates with acyclic amides using a Pd catalyst and SiOCPhox ligand in 2009. Further studies were done on the type of reaction in which the nucleophile would attack the central carbon of the Pd–ligand–allyl complex to construct cyclopropane rings and it was found that the ligand plays an important role. They developed a novel NHC-pyridine ligand for the cyclopropanation of substituted allyl carbonates under Pd catalysis in 2014 [35a] and 2017 [35b] (Scheme 19), which proved that the properties of the coordination atoms of the ligand played the major role in the selectivity control for the Pd-catalyzed cyclopropanation. Specifically, they[35b] used aliphatic ketones **77** as the nucleophile in the Pd-catalyzed cyclopropanation for the first time whereas carboxylic acid derivatives had been commonly used previously. Hou *et al.*[35c] also developed a Pd-catalyzed cyclopropanation of acyclic amides **79** and allyl and polyenyl carbonates **80** with high diastereo- and enantio-selectivities (Scheme 19). The related studies demonstrated that the presence of Li^+ and Cl^- had a great implication for the selectivity of cyclopropanation and allylic alkylation, as well as the diastereo-selectivity of the cyclopropanation process.

In 2016, Jiang's group[36] reported the controllable *O*-nucleometalation cyclization of 1,*n*-enynes **81** using Pd catalysis (Scheme 20), which was the first example of controllable regio-selective Heck annulation and cyclopropanation in which Cu(II) was an oxidant. It should be remembered that the amide moiety induced the divergent annulation processes.

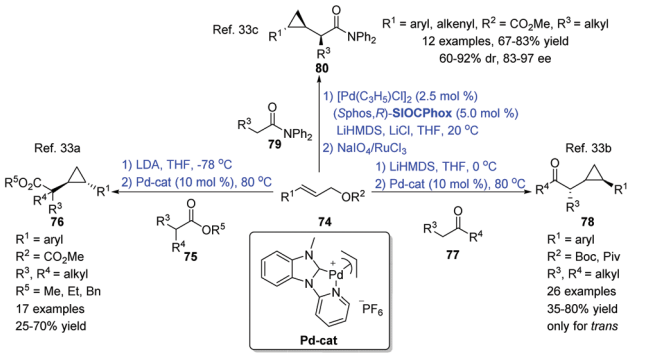
Though the diazo compound is known to be a class of important synthons to achieve cyclopropanation, some limitations such as instability in the substrate preparation still require to be resolved. Therefore, many groups have explored the precursor of diazo compounds to replace them, such as hydrazones, which are generally stable and easy to purify. In 2012, Jiang *et al.*[37a] developed an intermolecular cross-coupling reaction of *N*-tosylhydrazones **94** and acrylamides **95**



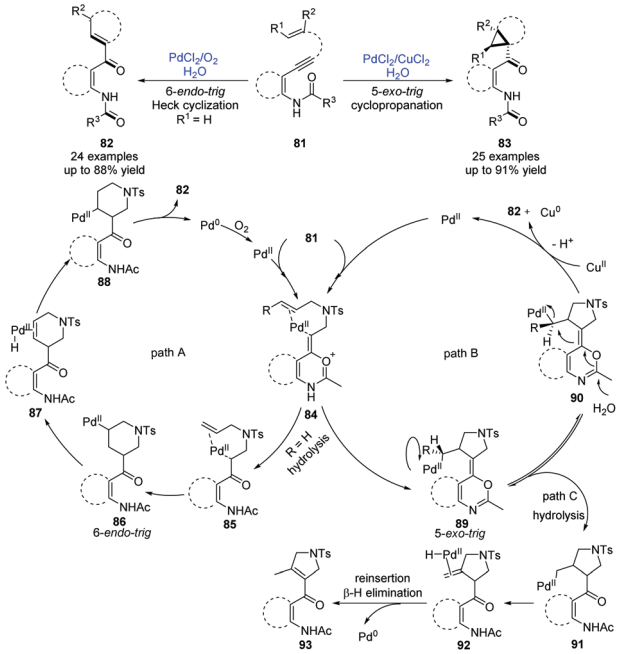
Scheme 17 Pd-Catalyzed methylenation and cyclopropanation using halomethylboronate.



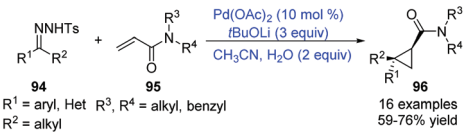
Scheme 18 Pd(II)-Catalyzed cyclopropanation reaction using two-fold C–H activation.



Scheme 19 Pd-Catalyzed cyclopropanation of substituted allyl carbonates with acyclic amides.

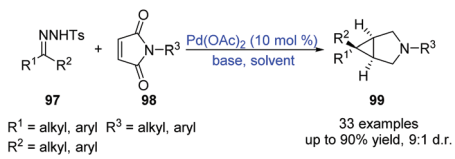


Scheme 20 Pd(II)-Catalyzed cyclizations using selective *O*-nucleometallation and proposed mechanisms.

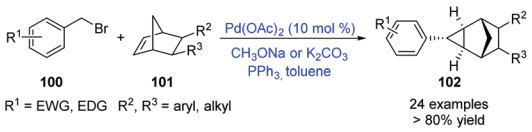


Scheme 21 Pd(II)-Catalyzed cross-coupling of *N*-tosylhydrazones and electron-deficient terminal alkenes.

using a Pd(II) catalyst (Scheme 21). Notably, the presence of water provided an additional proton source and promoted the cascade transformation. Later, the same group[37b] reported a Pd-catalyzed cyclopropanation of internal *N*-tosylhydrazones **97** which are readily available precursors of diazo compounds with alkenes **98** (Scheme 22). They proposed that the steric hindrance discrimination between the methyl group and the phenyl group made **99** the major product. It should be noted that the mu opioid receptor antagonist CP-866,087 could be easily achieved using this simple and environmentally friendly route.



Scheme 22 Pd-Catalyzed diastereo-selective synthesis of 3-azabicyclo [3.1.0]hexane derivatives.



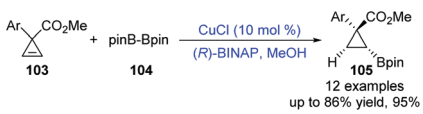
Scheme 23 Pd(0)-Catalyzed domino cyclopropanation reaction.

In 2014, Bao *et al.*[38] reported the first synthesis of cyclopropane derivatives **102** using Pd(0)-catalyzed cyclopropanation of bicyclic alkenes, which were involved in an intermolecular C(sp^3)–H bond activation and a Heck type coupling reaction (Scheme 23). The density functional theory (DFT) calculations revealed that the transformation underwent a four-membered palladacycle transition state. It is noteworthy, that only one example of Rh(I)-catalyzed intramolecular cyclopropanation *via* a C(sp^3)–H bond activation had been reported before,[14a] which was previously used relatively complex molecules with narrow functional group tolerance as the substrates.

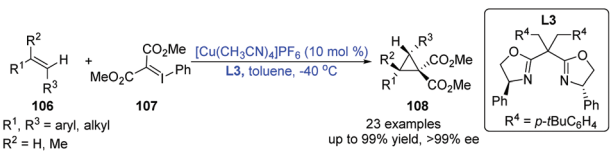
2.1.4 Cu-Catalyzed formation of cyclopropanes. Compared to precious metals, Cu is inexpensive and has low toxicity, it is easy to use, and has stable properties. In most cases, Cu-mediated cyclopropanation can be achieved under mild reaction conditions with good functional group tolerance and excellent chemical selectivity.

In 2014, Lin and co-workers[39] developed a Cu(I)-catalyzed enantio-selective hydroboration of 3,3-substituted cyclopropenes **103**, which gave optically active *trans*-cyclopropylboronates **105** with excellent enantio-selectivities superior to the early reports. It should be noted that when the Rh-catalytic system was used, *cis*-borylated cyclopropanes were obtained (Scheme 24).

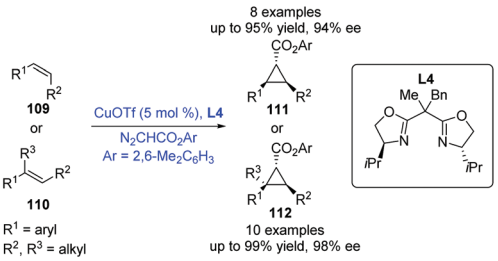
Tang *et al.*[40] have developed a newly designed and inexpensive bisoxazoline-Cu(I) complex for the synthesis of chiral 1,1-cyclopropane diesters **108** in excellent yields with high enantio-selectivity, a method which used Rh catalysts in previous reports (Scheme 25). Later, they[41] achieved the cyclopropanation of both *cis*- and *trans*-1,2-disubstituted alkenes **109** and **110**, respectively, with high diastereo- and enantio-selectivity using BOX/Cu(I) as the catalyst. The



Scheme 24 Cu-Catalyzed enantio-selective synthesis of cyclopropylboronates.



Scheme 25 Cyclopropanation of phenyliodonium ylide and nonterminal alkenes.

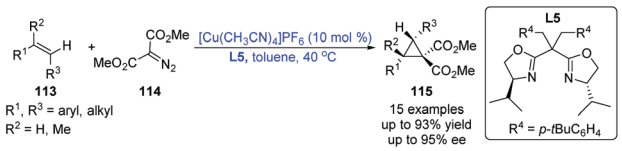


Scheme 26 Asymmetric cyclopropanation of *Z*- or *E*-alkenes.

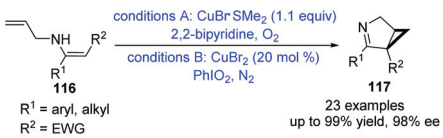
pendant group of BOX ligands was supposed to have a positive effect on the yield (Scheme 26). Recently, the same group[42] used another BOX ligand to achieve the first Cu-catalyzed enantio-selective cyclopropanation of diazomalonates with internal olefins, and the two identical substituents on substrates increased the difficulty in the asymmetric introduction of cyclopropanation (Scheme 27).

Chiba *et al.*[15b] established a novel cyclopropanation protocol for the synthesis of biologically and medicinally active azaheterocycles **117** from readily available *N*-allyl enamine derivatives **116** using two complementary Cu-catalyzed reactions (Scheme 28).

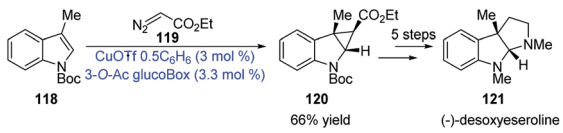
The indole alkaloid is recognized to be a type of organic molecule with significant biological activities, thus many research groups have been seeking variable synthetic methods for the construction of this skeleton. In 2012, Boysen *et al.*[43] first synthesized a valuable building block **120** for the indole alkaloid by using a copper catalyst. This newly formed product could be efficiently transformed to (−)-desoxyeseroline **121** using a five-step modification (Scheme 29).



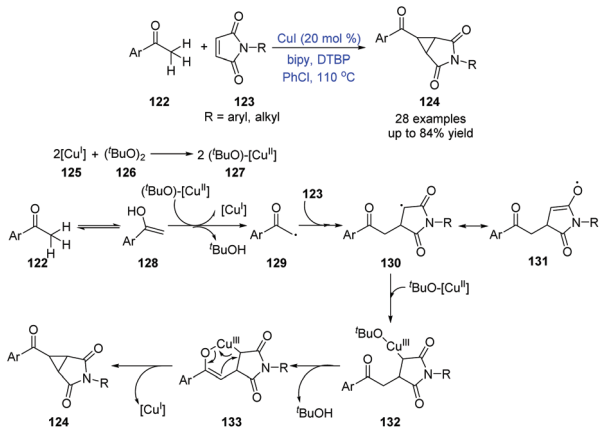
Scheme 27 Asymmetric cyclopropanation of *Z*- or *E*-alkenes.



Scheme 28 Two complementary conditions induced cyclopropanation to synthesise azaheterocycles.



Scheme 29 Cu-Catalyzed multi-step synthesis of (−)-desoxyeseroline.

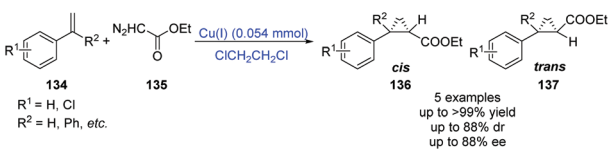


Scheme 30 Cu-Catalyzed [2 + 1] annulation for the direct synthesis of cyclopropanes.

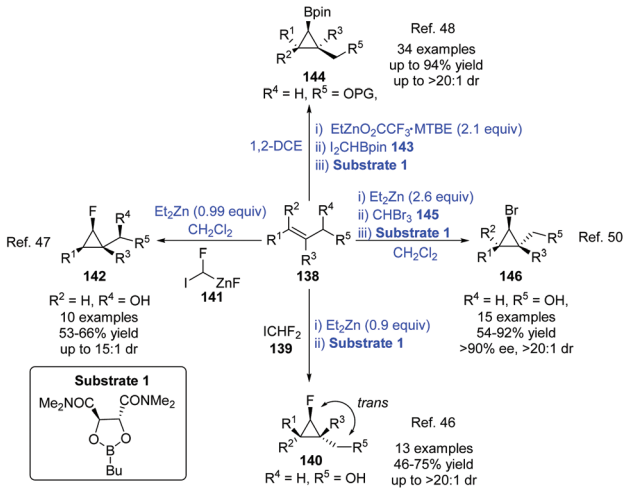
In 2015, Manna and Antonchick[44] developed a novel and practical Cu-catalyzed stereo-selective cyclopropanation of acetophenone **122** and maleimides **123** (Scheme 30). Different from classic cyclopropanation methods such as carbene reactions which require prefunctionalized reagents, this transformation underwent a Cu-catalyzed radical process. In addition, readily available starting materials without preliminary functionalization is one of the advantages in this reaction. This method provides another direction for the straightforward synthesis of strained cyclopropanes.

Compared to its heterogeneous counterpart, homogeneous catalysis has some inherent problems such as recyclability and difficulty of separation. Caselli *et al.*[45] have developed an acyclopropanation reaction using a new heterogenised catalytic system based on a chiral Cu(I) complex, and carbon dioxide (CO_2) as a vector (Scheme 31). In this new heterogenised system, the catalysts were stable and robust, and could be easily recycled, and so it should find its synthetic value in cyclopropane construction.

2.1.5 Zn-Catalyzed formation of cyclopropanes. Zinc reagents are different from other transition metals, and are usually used in the classic Simmon–Smith reaction for the construction of cyclopropane derivatives from alkenes. However, there are still some limitations, such as the use of unstable iodinated compounds in light and air, sluggish reactivity and poor selectivity, as well as the stoichiometric amount of the catalyst. In recent years, many new Zn reagents have been explored, and some of the unreactive unfunctionalized



Scheme 31 Continuous flow asymmetric cyclopropanation reactions using a Cu(I) catalyst and CO_2 as a vector.

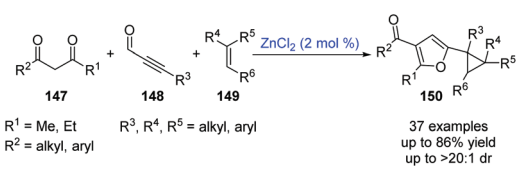


Scheme 32 Examples of Charette's work on Zn-catalyzed cyclopropanation.

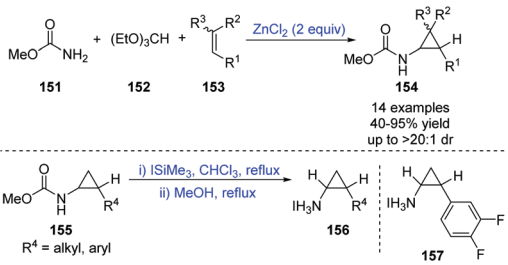
alkenes have been found to be suitable substrates in cyclopropanation using these novel organozinc species.[16]

Charette's group has done many elegant works on the Zn-catalyzed cyclopropanation reactions[46–50] (Scheme 32), most of which gave halo-substituted cyclopropanes. In 2013, Charette's group[46] reported the first protocol for the highly enantio-selective synthesis of monofluorocyclopropanes. Compared to the expensive carbenoid precursor fluoro(diiodo)methane ($FCHI_2$), difluoro(iodo)methane ($ICHF_2$) circumvented the ongoing restriction in the Simmons–Smith fluorocyclopropanations in this work. Later, chiral fluorocyclopropyl carbinols were synthesized in a one-pot reaction with high yields and diastereoselectivities.[47] Recently, Navuluri and Charette[48] have developed a highly efficient borocyclopropanation using a novel boromethylzinc carbenoid for the construction of 1,2,3-trisubstituted cyclopropane units.[49] Charette's group also improved the Zn-catalyzed Simmons–Smith reaction in 2015, and various 1,2,3-trisubstituted cyclopropanes could be obtained from free allylic alcohols without deprotonation.[50]

In 2012, López *et al.*[51] developed a new zinc carbene for the cyclopropanation reactions. They[52] used the Zn catalyst to realize three-component coupling for furyl-substituted cyclopropane derivatives **150**. In particular, it proved that zinc chloride ($ZnCl_2$) has the ability to promote the vinylcyclopropane/cyclopentene rearrangement, even with the loading as low as 0.02 mol% in this simple multicomponent protocol (Scheme 33). In 2013, Motherwell[53] reported the synthesis of



Scheme 33 $ZnCl_2$-catalyzed three component reaction for the construction of cyclopropanes.



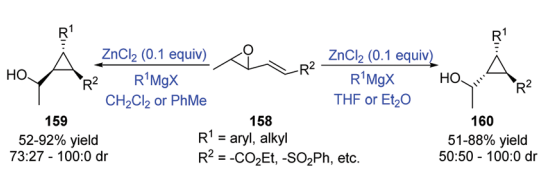
Scheme 34 Cyclopropanation reactions with methyl carbamate for the synthesis of aminocyclopropane HI salts.

carbamate-protected aminocyclopropanes using a novel carbamatoorganozinc carbenoid with the preference for the *cis*/*endo* isomer (Scheme 34). Interestingly, the aminocyclopropane hydrogen iodide (HI) salts were easily obtained using iodotrimethylsilane in the deprotection step. One of the HI salts **157** could be transformed into its *cis* isomer, which was the AstraZeneca drug candidate AZD6140, in only two steps with a 62% overall yield.

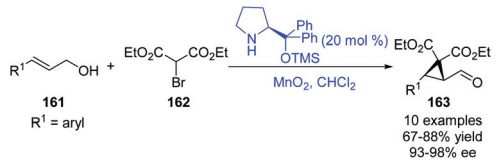
In addition, Dieter *et al.*[54] have developed a Zn-catalyzed cyclopropanation to give 1,2,3-trisubstituted cyclopropanes, which were supposed to undergo a Michael-initiated ring closure (MIRC) process in the presence of organozincates or Grignard reagents. The solvent also played an important role in the control of diastereo-selectivity (Scheme 35).

2.2 Transition metal free-catalyzed formation of cyclopropanes

Whereas use of transition metal catalysis, a powerful tool for carbon–carbon or/and carbon–hetero bond formations, has been great progress for use in cyclopropanation, transition metal free catalytic systems such as bases, Lewis acids, and ylides provide another possible route to realize cyclopropanation, which could not only avoid some limitations of transition metal catalysis, but also expand the synthetic scope of functionalized cyclopropanes. For example, some of the non-toxic and readily available reagents can be used instead of toxic and sensitive transition metal catalysts, and some catalysts provide a unique reactivity profile, which could reduce/cleave the C–O bond. Other advantages of this method include simplicity, convenient experimental conditions and low cost of the reagents. However, there are limited choices of mild and selective conditions to support unprotected and sensitive groups, which might narrow the applications in the functionalization of complex molecules.



Scheme 35 Zn-Catalyzed synthesis of 1,2,3-trisubstituted cyclopropanes using a MIRC process.

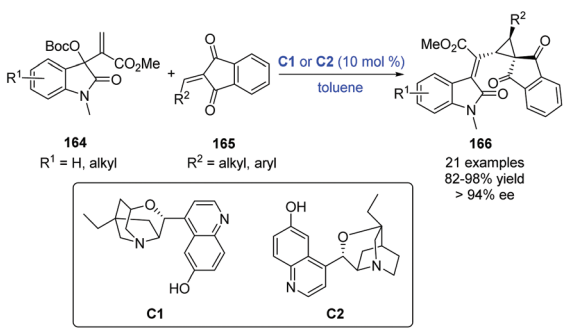


Scheme 36 Enantio-selective cyclopropanation of allylic alcohols.

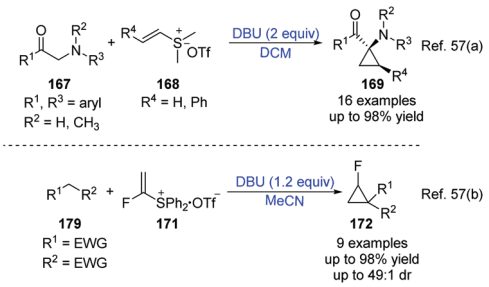
2.2.1 Base-promoted formation of cyclopropanes. In 2012, Rueping's group[55] reported an enantio-selective cyclopropanation of allylic alcohols with the use of chiral trimethylsilyl (TMS)-prolinol ether as the catalyst, providing the first asymmetric construction of **163** (Scheme 36). This work also further developed enantio-selective covalent catalysis. Recently, Chen and co-workers[56] discovered a chiral Lewis base-catalyzed [2 + 1] annulation of the Morita–Baylis–Hillman (MBH) carbonates **164** and **165** to synthesize densely substituted cyclopropanes **166** with excellent chemoselectivity and stereoselectivity (Scheme 37). The related DFT calculation also benefitted other asymmetric cyclopropanation reactions involving MBH carbonates.

Vinyl sulfonium salts have been regarded as a type of important intermediate in organic synthesis. In 2012 and 2013, Lin's and Hanamoto's group, respectively, developed simple and efficient methods to build disubstituted cyclopropanes from vinyl sulfonium salts using 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) as base (Scheme 38).[57]

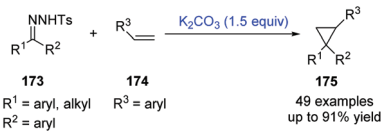
It is known that *N*-tosylhydrazones, the precursor of diazo compounds, have been successfully transformed to various cyclopropanes using different transition metal catalyzed processes. However, the transition metal-free catalytic systems exhibiting the same levels of efficiency and selectivity are also highly desirable, which could solve the problems associated with the need to handle the potentially toxic metals. Cabal and co-workers[58] first described a general method for the transition metal-free cyclopropanation of alkenes and non-stabilized diazo compounds in the presence of potassium carbonate (K_2CO_3) (Scheme 39). Also, Kamal and Maurya[59] reported a highly diastereo-selective synthesis of cyclopropanes **178** using a one-pot, two-step and three-component transformation of



Scheme 37 Various chiral Lewis base catalyzed asymmetric cyclopropanation reactions.



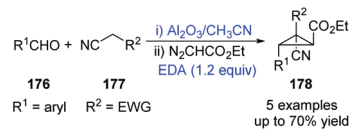
Scheme 38 Examples for cyclopropanation reactions from sulfonium salts under basic conditions.



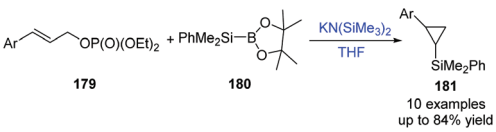
Scheme 39 Base-mediated cyclopropanation of diazo compounds.

aldehyde, malononitrile/ethyl cyanoacetate, and ethyl diazoacetate with a basic alumina catalyst (Scheme 40). In 2014, Nozaki[60] developed a potassium-bis(trimethylsilyl) amide-mediated cyclopropanation of allyl phosphates **179** with silylboronates **180** (Scheme 41). This method gave the silicon-containing cyclopropanes high selectivity. The β-position of the allylic substrates was selectively attacked by the nucleophile, which was a different result when compared to the results from previous reports on Cu-catalyzed allylic substitution processes.

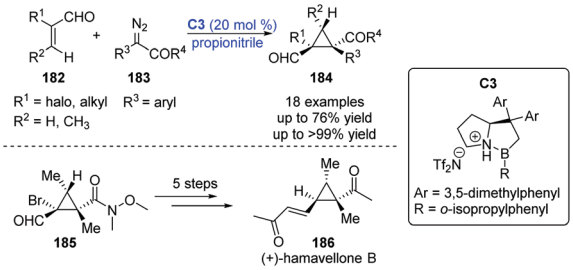
2.2.2 Lewis acid-promoted formation of cyclopropanes. The Lewis acid catalyzed Michael addition–cyclization of diazo compounds and electron deficient olefins provides a complementary approach to functionalized cyclopropanes. Ryu and Hwang[61] have developed a chiral oxazaborolidinium ion-catalyzed asymmetric cyclization of α- or α,β-substituted acroleins **182** and α-alkyl-α-diazoesters **183**. Functionalized cyclopropanes bearing a quaternary stereogenic center **184** were



Scheme 40 One-pot, two-step and three-component cyclopropanation reaction.



Scheme 41 Cyclopropanation of allyl phosphates and silylboronates.

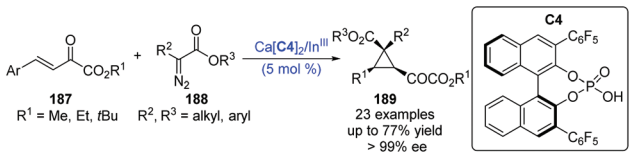


Scheme 42 Chiral oxazaborolidinium ion catalyzed asymmetric cyclopropanation.

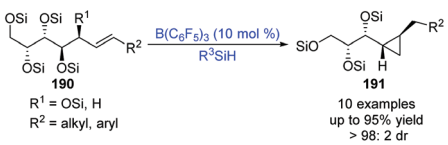
obtained with excellent enantioselectivities, especially for the total synthesis of (+)-hamavellone B (**186**) (Scheme 42). In addition, Luo and Lv[62] have developed an unprecedented enantio-selective cyclopropanation of β,γ-unsaturated α-ketoesters **187** and diazoacetates **188** with a type of binary Lewis acid catalyst $InBr_3/Ca[C4]_2$ (Scheme 43), which used a weak π-interaction for stereocontrol.

In 2016, Gagné[63] disclosed a tris(pentafluorophenyl)borane $[B(C_6F_5)_3]$ catalyzed cyclopropanation of unsaturated carbohydrates to generate cyclopropane **191**. The key intermediates to facilitate this carbocyclization were sila-tetrahydrofuran (THF) cations which caused the diastereo-selective C–C bond formation (Scheme 44).

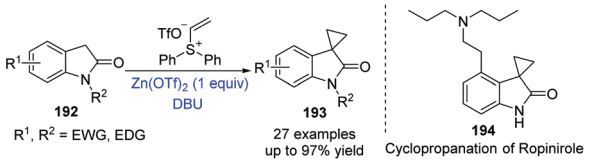
Recently, Qian *et al.*[64] first used zinc triflate $[Zn(OTf)_2]$ as a catalyst to realize the cyclopropanation of **192**. Cyclopropanation on medicinally relevant compounds was demonstrated in late-stage functionalization, and the cyclopropanation of some pharmaceutical molecules such as **194**, the cyclopropanation product of Ropinirole which is a dopamine agonist, were achieved using this strategy (Scheme 45). In particular, the presence of $Zn(OTf)_2$ could prevent the formation of an *N*-alkylation byproduct by using *N*-nonsubstituted oxindoles, which could be applied in other protocols where a regio-selectivity issue exists.



Scheme 43 Binary Lewis acid catalyzed cyclopropanation of an unsaturated keto ester.



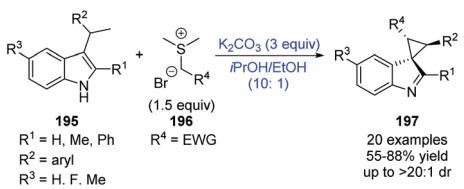
Scheme 44 $B(C_6F_5)_3$ catalyzed cyclopropanation of unsaturated carbohydrates.



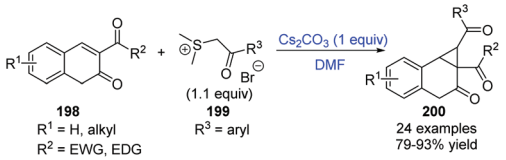
Scheme 45 $Zn(OTf)_2$ mediated cyclopropanation of oxindoles.

2.2.3 Other methods. Although many methods are available for cyclopropanations under acidic or basic conditions, parts of the substrates may be unsuitable in these reaction systems, and would cause the decomposition of starting materials or products. Consequently, other transition metal free catalysts including ylide reagents,[65–68] phase transfer reagents,[69–72] and iodine reagents[73] provide efficient access to the construction of cyclopropane rings.

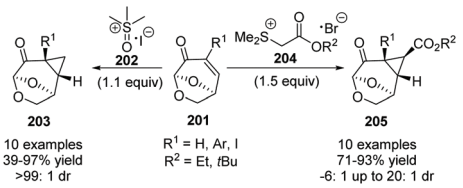
Ylide as a class of versatile synthons is widely used in synthetic chemistry because of its particular properties. In 2014, Zhou *et al.*[65] developed an efficient dearomatization strategy to construct spiro-cyclopropane compounds **197** using arenesulfony-lindoles **195** and sulfonium salts **196** as reaction partners (Scheme 46). Furthermore, the re-aromatized indole derivatives could be conveniently obtained from the spirocyclopropanes under acidic conditions. Shi[66] reported a stabilized sulfur ylide-mediated cyclopropanation of 3-acyl-2*H*-chromenones **198**, which gave **200** in moderate to excellent yields (Scheme 47). Greatrex[67] used sulfoxonium ylides to realize the stereo-selective cyclopropanation of (−)-levoglucosenone derivatives **201** (Scheme 48). Not limited to the sulfur ylide, other ylide reagents such as *N*-ylides and iron ylides have also received much attention recently. Namboothiri[68] and Deng *et al.*[69] disclosed the synthesis of cyclopropane derivatives *via* *N*-ylide and iron ylide, respectively. Notably, the cyclopropanation reactions using the iron ylide are applicable for the alkenes bearing either electron withdrawing or electron donating groups.



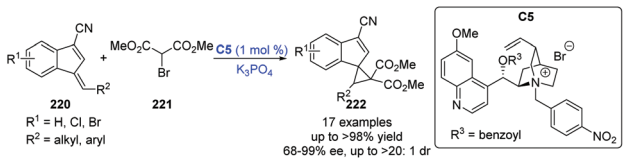
Scheme 46 De-aromatization strategy to construct spiro-cyclopropane compounds.



Scheme 47 Stabilized sulfur ylide mediated cyclopropanation.



Scheme 48 Cyclopropanation of (–)-levoglucosenone derivatives.

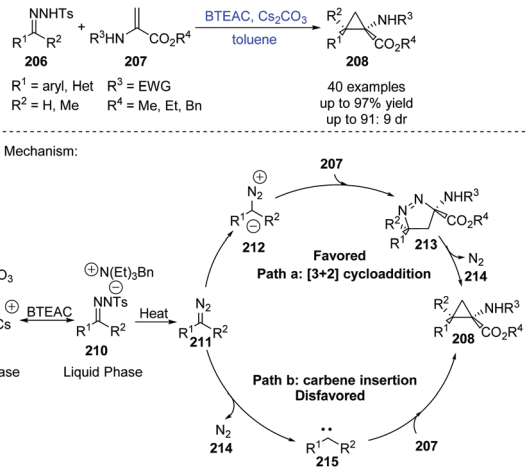


Scheme 51 PTC catalyzed cyclopropane spiroindenes from benzofulvenes.

As a type of effective catalyst and catalysis promoter, a phase transfer catalyst (PTC) offers attractive features including low cost, scale-up viability, and operational simplicity. In 2014, Maurya[70] developed the diastereo-selective synthesis of a series of spiro compounds from tosylhydrazone salts using benzyltriethylammonium chloride (BTEAC) as the catalyst.

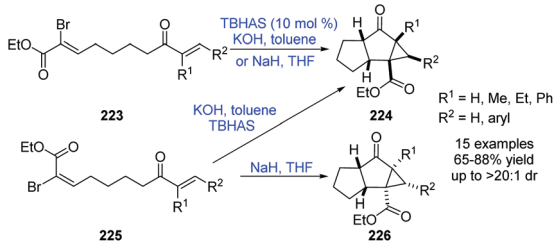
In 2016, Wu and Jiang[71] reported the cyclopropanation of *N*-tosylhydrazones **206** and 2-aminoacrylates **207** using a [3 + 2] cycloaddition process (Scheme 49), which gave cyclopropane products **208** bearing contiguous quaternary carbon centers with excellent yields and high diastereoselectivities. Recently, Wu and Jiang[72] developed a protocol for the construction of aminocyclopropanephosphonates with adjacent quaternary tetrasubstituted carbon centers **218** and **219** using a one-pot method and PTC was used as the important additive (Scheme 50).

In 2016, Jørgensen[73] successfully built the cyclopropane spiroindenes **222** with high selectivity and yields using PTC,



Scheme 49 PTC catalyzed cyclopropanation of aminoacrylates and *N*-tosylhydrazones.

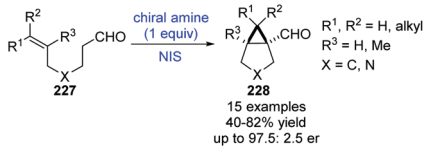
Scheme 50 The synthesis of aminocyclopropane phosphonates with adjacent quaternary tetrasubstituted carbon centers.



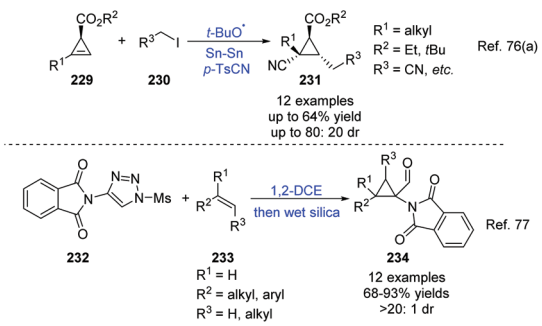
Scheme 52 Tetrabutylammonium hydrogen sulafte (TBAHS) catalyzed synthesis of tricyclic fused cyclopropanes.

which only required 0.1–1.0 mol% of catalyst loading (Scheme 51). Smith and Paton[74] delivered the synthesis of 5,5,3-fused tricyclic rings **224** and **226** using phase transfer mediated cascade cyclizations with excellent diastereoselectivity (Scheme 52).

Huang and co-workers[75] have reported the first example of asymmetric intramolecular α-cyclopropanation using a chiral amine promoter (Scheme 53). This protocol achieved the asymmetric double α-alkylation of aldehydes and the authors expect that the α-iodoaldehyde might have potential applications in asymmetric di-functionalization of carbonyl compounds.



Scheme 53 Intramolecular cyclopropanation promoted by a chiral amine.



Scheme 54 Some special cyclopropanation reactions.

Except for the previous reports, cyclopropanation *via* a free radical process[76] or outside thermal source[77] have also been developed (Scheme 54).

In the last decades, a number of reviews about the application of cyclopropane substrates have been published.[78] because of the inherent strain in the cyclopropane core, it usually acts as an indispensable synthon and is widely applied in various types of transformations, including ring-opening reactions, ring-expansion reactions and cycloaddition reactions. Using these processes, chain compounds, heterocycles and carbocycles could be obtained.

3. Conclusions

Despite the fact that the history of research about cyclopropanes spans over 100 years, numerous approaches have been established, whether the catalytic system is traditional transition metals with a ligand or Lewis acids and ylides, or even other mediums such as photo[79] and enzymes.[80] However, there are still some challenges including: (i) better understanding of the reaction mechanism to further expand the scope and reaction design, (ii) applying different modes of reaction systems for asymmetric synthesis to improve the enantioselectivity and diastereo-selectivity, and (iii) lowering the catalyst loading to not only meet the requirements of green chemistry, but also to facilitate the conversion to industrialization. It is also believed that the synthetic methods for cyclopropanes can be further developed in more eco-friendly and economical ways and the progress on cyclopropane research will never stop in the fields of organic chemistry, pharmaceuticals and advanced materials.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The Authors wish to thank the National Key Research and Development Program of China (2016YFA0602900), the National Natural Science Foundation of China (21472051 and 21420102003), and the Guangdong Province Science Foundation (2017B090903003) for financial support.

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