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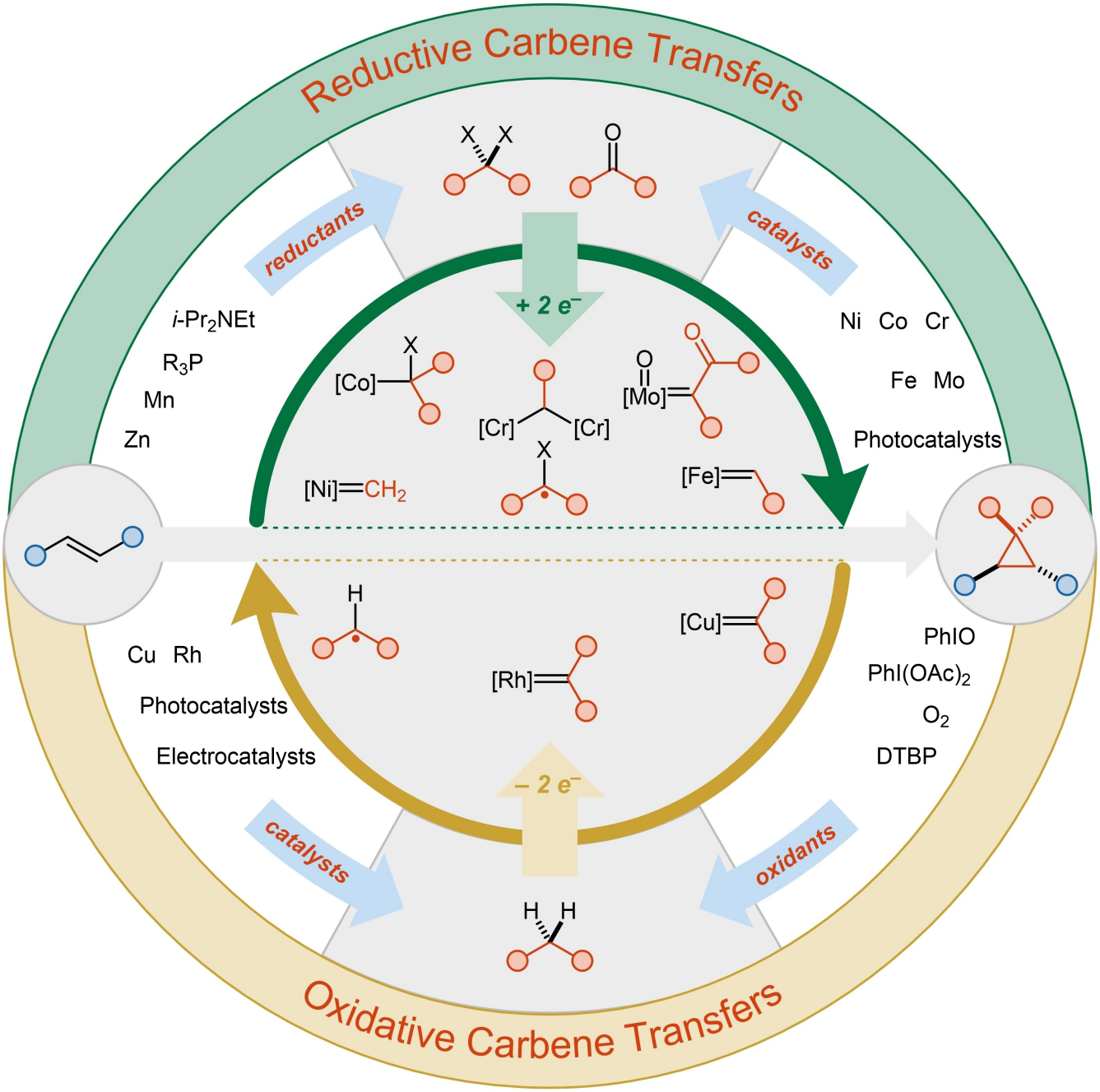
Cyclopropanation

Redox Approaches to Carbene Generation in Catalytic Cyclopropanation Reactions

*Mingxin Liu and Christopher Uyeda**



Abstract: Transition metal-catalyzed carbene transfer reactions have a century-old history in organic chemistry and are a primary method for the synthesis of cyclopropanes. Much of the work in this field has focused on the use of diazo compounds and related precursors, which can transfer a carbene fragment to a catalyst with concomitant loss of a stable byproduct. Despite the utility of this approach, there are persistent limitations in the scope of viable carbenes, most notably those lacking stabilizing substituents. By coupling carbene transfer chemistry with two-electron redox cycles, it is possible to expand the available starting materials that can be used as carbene precursors. In this Minireview, we discuss emerging catalytic reductive cyclopropanation reactions using either *gem*-dihaloalkanes or carbonyl compounds. This strategy is inspired by classic stoichiometric transformations, such as the Simmons–Smith cyclopropanation and the Clemmensen reduction, but instead entails the formation of a catalytically generated transition metal carbene or carbenoid. We also present recent efforts to generate carbenes directly from methylene (CR_2H_2) groups *via* a formal 1,1-dehydrogenation. These reactions are currently restricted to substrates containing electron-withdrawing substituents, which serve to facilitate deprotonation and subsequent oxidation of the anion.

1. Introduction

Metal-catalyzed decomposition reactions of diazo compounds were first investigated at the turn of the 20th century.[1] However, it was not until the 1960s that these reactions gained prominence in organic synthesis with the introduction of well-defined homogeneous copper catalysts.[2] These early studies established metal-bound carbenoids as catalytic intermediates and paved the way for the development of catalyst-controlled, rather than substrate-controlled, reactions. Diazo-based carbene transfer reactions have seen continuous development and are now extensively used in the synthesis of natural products and other complex bioactive molecules. The ability of Rh_2 catalysts to carry out regio-, diastereo-, and enantioselective carbene insertions into unactivated C–H bonds provides a modern showcase of diazo transfer chemistry.[3] Biocatalytic approaches based on engineered P450 enzymes have also extended the utility of these reactions by leveraging the techniques of directed evolution to accelerate the discovery of highly selective catalysts.[4]

While diazo-based carbene transfer reactions are commonly practiced on laboratory scales, there are perceived and real safety concerns that have limited their adoption in commercial pharmaceutical synthesis.[5] All diazo compounds have the potential for rapid heating and gas evolution due to the highly exothermic nature of N_2 elimination. Ethyl diazoacetate cannot sustain detonation, even in neat form. However, diazomethane, which lacks stabilizing substituents, is a shock-sensitive gas. There is limited information available on the sensitivity of diazo compounds exclusively containing electron-donating groups, such as alkyl, alkoxy, and amino groups (Figure 1A).

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1.1. In Situ Generation of Diazomethane Compounds

Despite these daunting technical challenges, there are ongoing efforts to design reactors suitable for the safe implementation of diazomethane chemistry on kilogram scales and beyond. For example, the synthesis of nelfinavir mesylate (**1**) employed a diazoketone intermediate (**3**) generated from the corresponding mixed anhydride **2** and diazomethane.[6] In a pilot-scale reactor, a DMSO solution of Diazald and an aqueous solution of KOH were fed into a continuously stirred tank reactor where a subsurface N_2 sparge swept CH_2N_2 (g) into a packed column containing the substrate (Figure 1B).

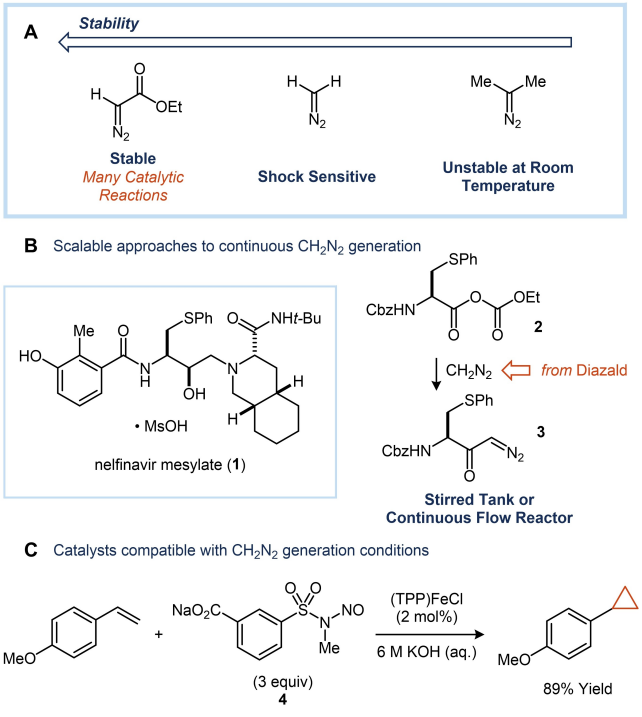


Figure 1. Preparative synthesis using non-stabilized diazoalkanes. (A) Stability trends in diazo compounds. (B) Processes involving the continuous generation of CH_2N_2. (C) Catalytic cyclopropanations compatible with the strongly basic conditions required for CH_2N_2 generation.

More recently, efforts have been directed at designing continuous flow systems that fully integrate the process of generating CH_2N_2 with a downstream reaction of interest.[7] For example, Kappe showed that the same transformation to generate **3** could be carried out using a tube-in-tube flow reactor in which the CH_2N_2 generated in the inner tube diffuses through a gas-permeable membrane into the outer tube where the reaction with **2** takes place (Figure 1B).[8] In a related strategy, CH_2N_2 separation could also be accomplished using a liquid-gas separator.[9] Both systems were successfully demonstrated in the Pd-catalyzed cyclopropanation of styrene, which is a reaction known to be inhibited by the organic byproducts of CH_2N_2 generation.

Diazomethane must be generated from a stable precursor under strongly basic aqueous conditions, which are incompatible with most of the desired catalytic reactions of CH_2N_2. Thus, much of the engineering complexity associated with carrying out CH_2N_2 chemistry is the extraction of pure anhydrous CH_2N_2 from the conditions of its generation. One potential solution is to develop robust catalysts that are stable in basic water such that the entire process can be run in a single vessel. To that end, Carreira demonstrated that a (TPP)FeCl catalyst is capable of cyclopropanating styrenes and related olefins under the 6 M KOH (aq) conditions used to generate diazomethane from **4**, a water-soluble derivative of Diazald (Figure 1C).[10]

1.2. Redox Neutral Precursors for Substituted Carbenes

Substituted diazo compounds can be generated from the base-promoted decomposition of sulfonyl hydrazones (Figure 2). In one recent example, Zhang demonstrated asymmetric cyclopropanation reactions with trifluoromethylcarbenes using a cobalt metalloradical catalyst.[11,12] Related strategies include the oxidation of parent hydrazones[13] or conversions of primary amines to diazo compounds using $NaNO_2$.[14] *N*-Sulfonyl triazoles or 1,2,3-triazine 1-oxides may also be viewed as masked diazoalkanes *via* ring-opening processes.[15,16]

Ylides have also been explored as diazo-free carbene precursors in catalytic cyclopropanation reactions. The most common reagents for this purpose are sulfur ylides.[17] In most examples, the resulting carbenes bear electron-withdrawing substituents, which serve to facilitate the deprotonation of the sulfonium ions. Chen demonstrated that nitrogen ylides lacking stabilizing substituents could participate in nickel-catalyzed cyclopropanation reactions.[18] Methylene transfer was accomplished by deprotonation of Me_4N^+ using *n*-BuLi.

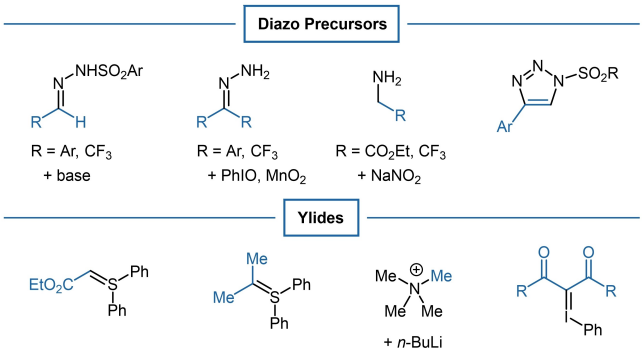
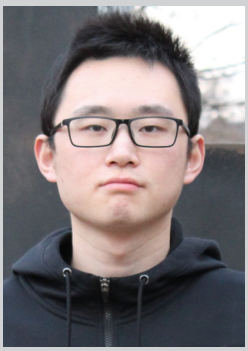


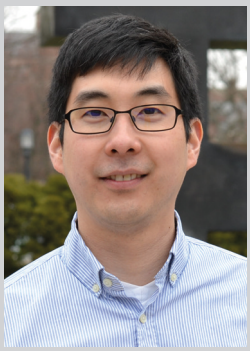
Figure 2. Examples of redox-neutral precursors to form substituted carbenes.

It is apparent from the body of literature on redox-neutral catalytic cyclopropanation reactions that there are significant limitations associated with carbenes that lack resonance-stabilizing substituents (Figure 3). In principle, the ability to unveil carbene intermediates in a two-electron redox process would greatly expand the precursors that would be available to carry out cyclopropanation reactions (Figure 3). Inspired by the Simmons–Smith reaction, two-electron reduction can generate carbenes from CR_2X_2 species. For the most part, such reactions use *gem*-dihaloalkanes. However, these reagents are often not commercially available in substituted forms. Thus, streamlined processes to carry out direct deoxygenative carbene transfer reactions using carbonyl compounds are an emerging area of research.

It is also attractive to consider two-electron oxidations of CR_2H_2 compounds to generate reactive carbene equivalents. Such processes are currently restricted to precursors bearing electron-withdrawing substituents, which serve to acidify the protons that need to be removed. Nonetheless, there may be future opportunities to combine C–H activation processes with α-H elimination to generate carbenes directly from unactivated methylene groups. In this review, we discuss ongoing efforts to develop catalytic redox carbene transfer



Mingxin Liu obtained his B.S. in chemistry at Jilin University in 2019. During his undergraduate studies, he spent a semester in Prof. Mingji Dai's group at Purdue University as a visiting student, where he worked on total synthesis of natural products. Choosing to stay at Purdue University for graduate studies, he is currently a Ph.D. candidate under the guidance of Prof. Uyeda. His graduate research focuses on transition metal-catalyzed carbene and vinylidene transfer reactions.



Chris Uyeda obtained his Ph.D. at Harvard University under the supervision of Prof. Eric Jacobsen and carried out postdoctoral research with Prof. Jonas Peters at Caltech. In 2013, he started his independent career at Purdue University and is currently the Herbert C. Brown Professor of Chemistry. His current research areas include the development of catalytic reductive carbene transfer reactions and the investigation of metal–metal bonds as catalytic active sites.

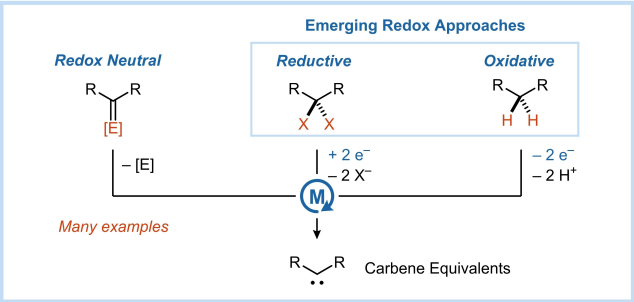


Figure 3. Redox-neutral, reductive, and oxidative approaches to carbene generations.

reactions as a complement to the expansive toolbox of diazo and related redox neutral processes.

2. Reductive Carbene Transfers

In the Simmons–Smith reaction,[19] zinc carbenoids, generated from diiodomethane and Zn, react with alkenes to form cyclopropanes. Historical efforts to develop catalytic variants of the Simmons–Smith reaction have focused on the use of Lewis acids, which can activate zinc carbenoids by assisting in the ionization of the halide leaving group.[20] This approach has led to the successful development of catalytic asymmetric Simmons–Smith reactions.[21] However, the substrate scope is largely restricted to allylic alcohols, because the alcohol directing group can pre-organize the chiral Lewis acid and the zinc carbenoid. The dipeptide catalyst reported by Shi is the singular exception.[22] However, only simple alkenes lacking functional groups have been demonstrated, presumably due to the reliance on abstraction of a weakly Lewis basic halide as the mode of activation.

Redox-active transition metal complexes provide a more general mode of catalysis for reductive cyclopropanation reactions. In these processes, a low-valent metal activates the *gem*-dihaloalkane by C–X oxidative addition. The resulting transition metal carbenoid transfers the carbene to an olefin, and two-electron reduction closes the catalytic cycle. Due to the abundance of supporting ligands that can be used to tune the steric and electronic properties of transition metals, there are ample opportunities to develop efficient reactions for different alkene types with control over stereoselectivity.

2.1. Nucleophilic Cyclopropanation Reactions using Nickel Catalysts

In the early 1980s, Kanai showed that $NiBr_2$ used in catalytic quantities can induce the cyclopropanation of electron-deficient alkenes under typical Simmons–Smith conditions (CH_2Br_2 or CH_2I_2 and Zn) (Figure 4A).[23] This finding was significant because zinc carbenoids are known to be electrophilic in character and do not typically react with electron-deficient alkenes such as α,β-unsaturated ketones. Kanai proposed the intermediacy of a nucleophilic nickel carbene derived from the oxidative addition of CH_2I_2 by a Ni(0) species. The initial scope of this reaction was largely restricted to simple mono-substituted alkenes. However, Duong later demonstrated that the scope could be extended to more substituted α,β-unsaturated carbonyl compounds using Et_2Zn as a reductant.[24]

Uyeda reported that PyBox ligand **5** can significantly improve the efficiency and generality of nickel-catalyzed reductive cyclopropanation reactions.[25] Less reactive

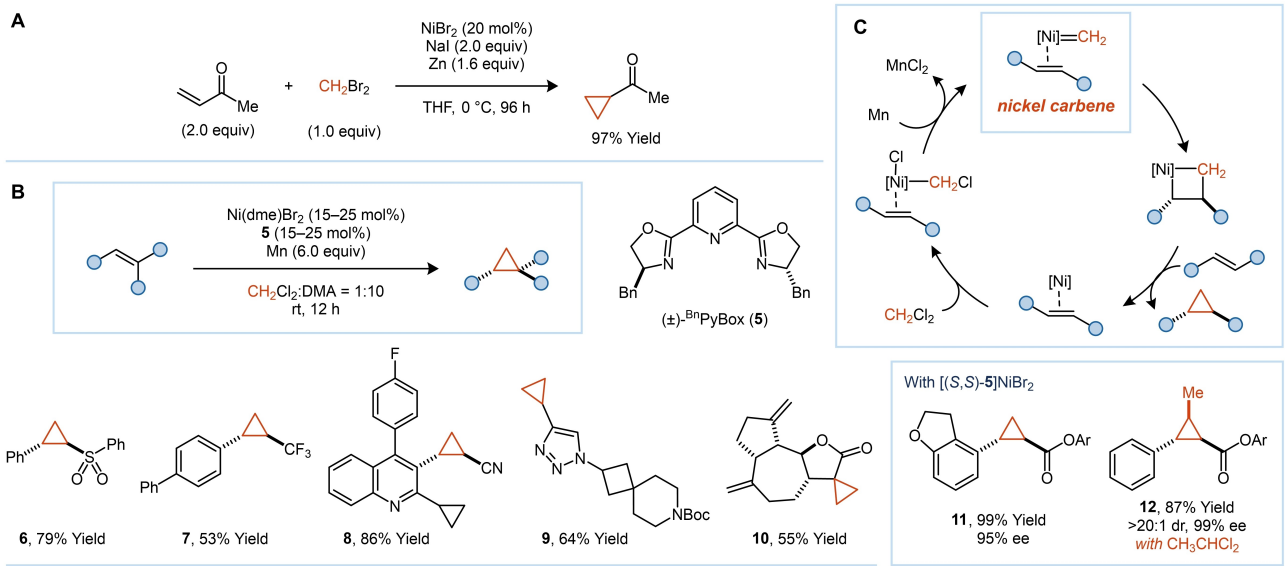


Figure 4. Nickel-catalyzed reductive cyclopropanation reactions. (A) $NiBr_2$-catalyzed cyclopropanations of monosubstituted enones using CH_2Br_2 and Zn. (B) Cyclopropanations of electron-deficient alkenes using a (PyBox)Ni catalyst and CH_2Cl_2. Asymmetric cyclopropanations using chiral PyBox ligands. Ar = 2,6-dimethylphenyl. (C) A proposed mechanism involving the formation of a Ni=CH_2 intermediate.

CH_2Cl_2 could be used as a carbene precursor, and the reaction was viable for substrate classes beyond α,β-unsaturated carbonyl compounds. Alkenes bearing sulfones (**6**), trifluoromethyl groups (**7**), nitriles (**8**) and electron-deficient arenes (**9**) are cyclopropanated in high yield. The introduction of a PyBox ligand also provides a straightforward entry into enantioselective cyclopropanations (Figure 4B). For example, 2-arylcyclopropane carboxylates, which are key intermediates in the synthesis of pharmaceutical compounds, are generated efficiently and with high levels of enantioselectivity (**11**).

2.2. Cobalt Catalysts for Cyclopropanation Reactions with Alkyl-Substituted Carbenes

Cobalt complexes bearing tridentate nitrogen donor ligands are also effective reductive cyclopropanation catalysts. Unlike their nickel counterparts, cobalt catalysts are relatively insensitive to electronic effects and are effective for both electron-rich and electron-deficient alkenes.[26] One notable application of the cobalt-catalyzed reaction is in the synthesis of *gem*-dimethylcyclopropanes using 2,2-dichloropropane as a carbene precursor.[27] Carbenoids containing β-hydrogens are susceptible to rapid isomerization by a 1,2-hydride shift. Minimizing this side process to achieve high-yielding cyclopropanation has been challenging using main group carbenoids, and few examples are known.[28]

Asymmetric variants of dimethylcyclopropanation and spirocyclopropanation reactions were demonstrated using a C_1-symmetric oxazoline-iminopyridine (OIP) ligand (**13**) (Figure 5A).[29] Monosubstituted alkenes, internal alkenes, 1,1-disubstituted alkenes, and 1,3-dienes are effective substrates (**14**–**19**). In the proposed mechanism, the dichloroalkane reacts with the (OIP)CoCl complex by halogen-atom abstraction to generate a free $R_2(Cl)C^{\bullet}$ radical. This radical is captured by a second equivalent of Co(I) to give a $Co(Cl)CR_2Cl$ species. Halide abstraction by ZnX_2 generates cationic cobalt carbenoid **20**,[30] which is viable for carbene transfer.

As a demonstration of synthetic utility on manufacturing scales, the cobalt-catalyzed dimethylcyclopropanation reaction was applied to the synthesis of nirmatrelvir, a component of Paxlovid used as a treatment for COVID-19 (Figure 5B).[31] The cyclopropanation of protected dehydroproline **21** using 2,2-dibromopropane was carried out on a 300 kg scale to generate **22** in 73 % yield after Boc deprotection. The previous route to bicyclic amine **22** required a lengthy sequence starting from ethyl chrysanthemate.[32]

2.3. Chromium Catalyzed Halo-, Silyl-, Stannyl- and Borylcyclopropanation Reactions

Mid transition metals have also been investigated as reductive cyclopropanation catalysts. In a seminal contribu-

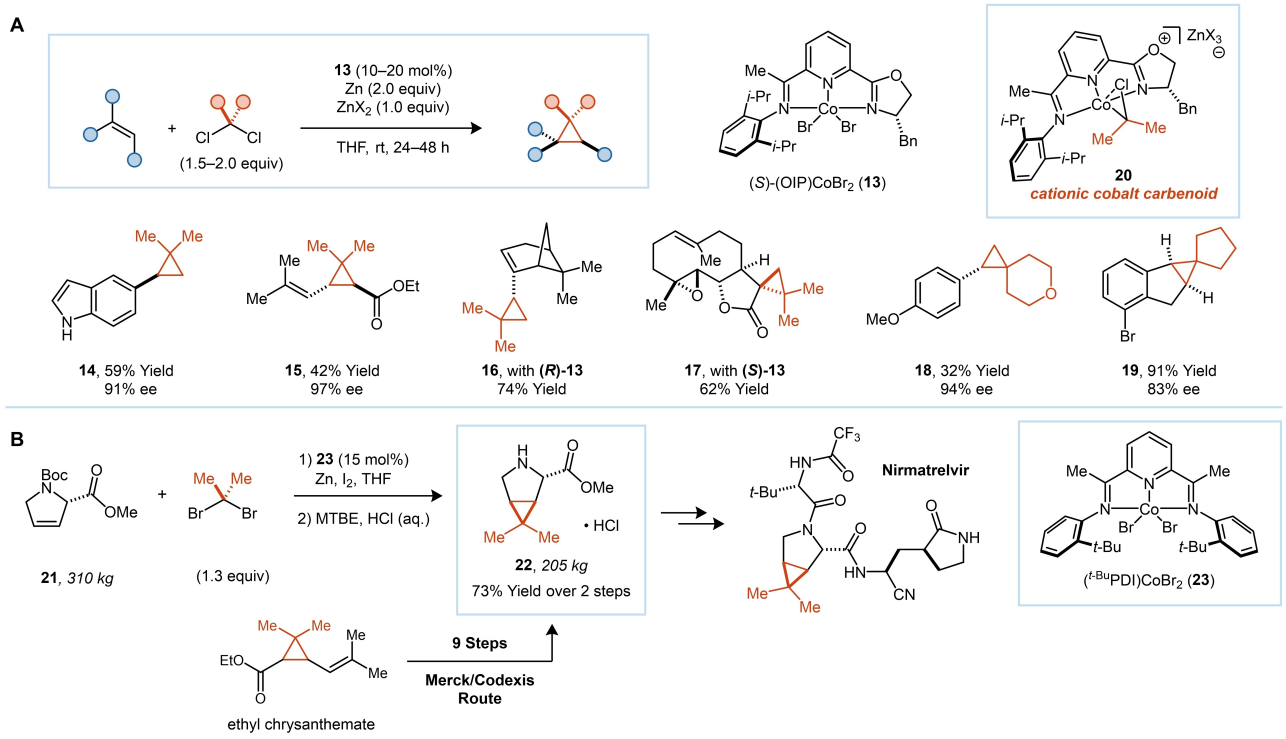


Figure 5. Cobalt-catalyzed reductive *gem*-dialkylcyclopropanation reactions. (A) Asymmetric *gem*-dimethylcyclopropanations and spirocyclopropanations using a C_1-symmetric OIP ligand. A cationic cobalt carbenoid intermediate (**20**) is proposed. (B) A commercial-scale cyclopropanation route to the bicyclic amine building block of nirmatrelvir.

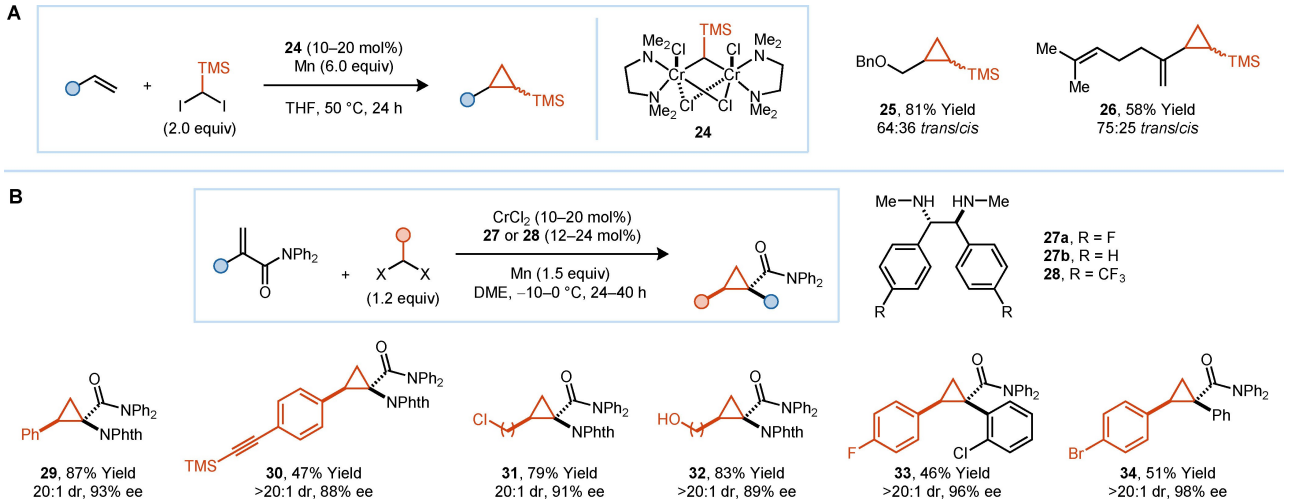


Figure 6. Chromium-catalyzed reductive cyclopropanation reactions. (A) Catalytic silylcyclopropanations involving a dichromium intermediate (**24**). (B) Chiral amine ligands (**27** and **28**) enable diastereo- and enantioselective cyclopropanations of terminal alkenes with substituted dihaloalkanes.

tion, Takai demonstrated that a (diamine)$CrCl_2$ complex can mediate the stoichiometric cyclopropanation of terminal alkenes using CHI_3. Similar reactivity was also observed for $(Me_3Si)CHI_2$, $(R_3Sn)CHI_2$, and $((RO)_2B)CHI_2$.[33] Mechanistic studies implicated a dichromium complex containing a bridging methylene ligand as the key intermediate in this process. The reaction could be rendered catalytic in Cr using Mn as a stoichiometric reductant (Figure 6A).[34]

Wang recently reported an asymmetric Cr-catalyzed reductive cyclopropanation using a chiral diamine ligand (**27** or **28**) (Figure 6B).[35] High levels of enantioselectivity and diastereoselectivity were observed for cyclopropanation reactions of α,β-unsaturated amides using aryl- and alkyl-substituted dibromomethanes or dichloromethanes (**29**–**34**). The cyclopropane products can be hydrolyzed to form chiral α,α-disubstituted amino acids.

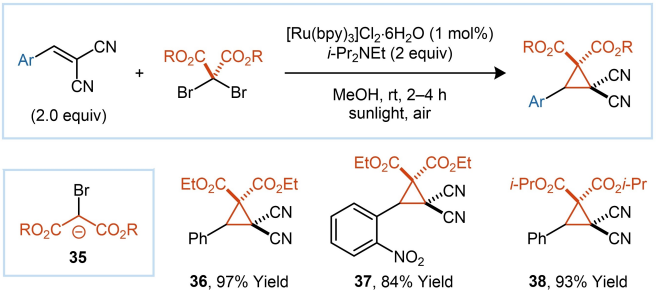


Figure 7. Photocatalytic reductive cyclopropanation reactions of electron-deficient alkenes with 2,2-dibromomalonate. Carbanion **35** is proposed as the carbene transfer reagent.

2.4. Photoredox Catalysts

A well-established elementary step in photoredox catalysis is the single electron reduction of an alkyl halide to generate a carbon-centered radical.[36] This radical can participate in a broad range of down-stream reactions, including further reduction to a carbanion, addition to a radical acceptor, and capture by a transition metal co-catalyst. When the same reduction is carried out using a *gem*-dihaloalkane, the resulting $CH_2X^{\bullet}$ intermediate can display carbene-like reactivity, for example by adding to an alkene and undergoing ring-closure to generate a cyclopropane.[37]

Guo utilized 2,2-dibromomalonate to cyclopropanate electron-deficient alkenes under photoredox conditions with $Ru(bpy)_3Cl_2$ (Figure 7).[38] Reduced to no reactivity was observed with electron-rich alkenes, and radical trapping reagents like TEMPO or BHT only resulted in slightly decreased yields. These results collectively suggest a double single-electron transfer (SET) process: the 2,2-dibromomalonate is first reduced to the radical carbenoid $[(RO_2C)_2CBr]^{\bullet}$, which is prone to further reduction to carbanion **35**. The carbanion then adds to the alkene, and subsequent ring-closure forms the cyclopropane.

Suero successfully extended this photoredox manifold to non-stabilized carbenes (Figure 8A).[39] In the proposed mechanism, photoexcited $[Ru(bpy)_3]^{2+}$ transfers one electron to CH_2I_2 to form a transient radical anion $[CH_2I_2]^{-\bullet}$, which then dissociates I^- to form the $CH_2I^{\bullet}$ radical carbenoid. $CH_2I^{\bullet}$ is subsequently trapped by an alkene and undergoes ring-closure by a radical substitution mechanism (Figure 8B). A characteristic feature of this process is the stereoconvergent formation of *trans*-disubstituted cyclopropanes from either the *E* or *Z* alkene starting material.

Photoredox approaches to reductive cyclopropanation reactions have been studied for other classes of *gem*-dihaloalkanes. Charette discovered that xanthone can serve as a photocatalyst for the borylcyclopropanation of styrene using $(PinB)CHI_2$.[40] The reaction was conducted under continuous flow conditions using a 350 nm UV light (Figure 9A). The key radical carbenoid $[(PinB)CHI]^{\bullet}$ (**43**) is proposed to be derived from either oxidative quenching of photoexcited xanthone by $(PinB)CHI_2$ or reduction of $(PinB)CHI_2$ by the xanthone radical anion. Ooi and Liu

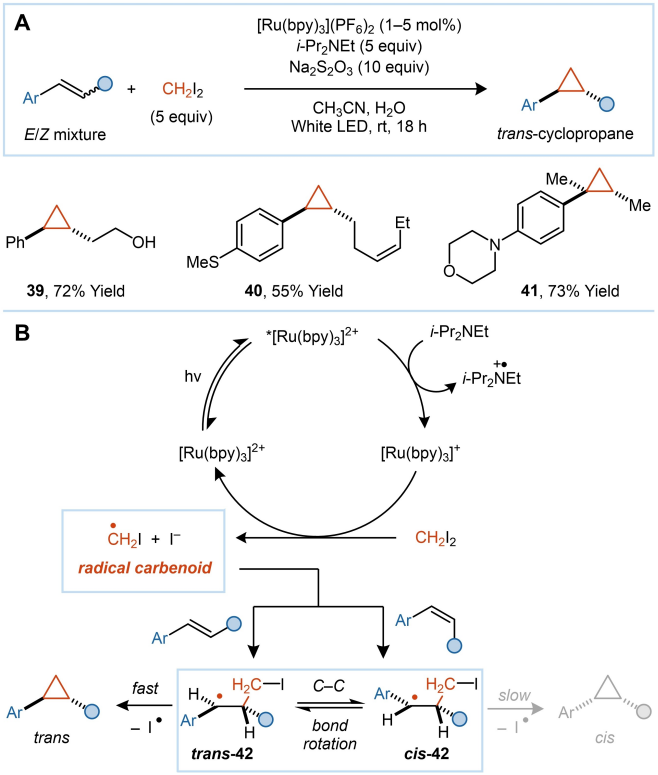


Figure 8. (A) Photocatalytic reductive cyclopropanation reactions of styrenes with CH_2I_2 under visible light irradiation. (B) Proposed catalytic cycle involving a radical carbenoid generated from the reduction of CH_2I_2.

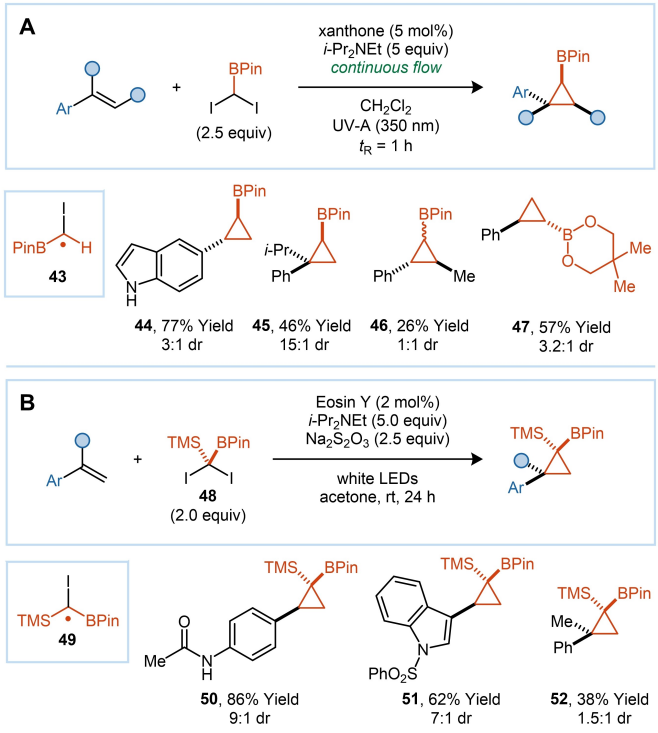


Figure 9. (A) Photocatalyzed borylcyclopropanations of styrene derivatives under continuous flow conditions. (B) Photocatalyzed *gem*-borylsilylcyclopropanations of styrene derivatives. Both reactions involve the addition of radical carbenoids (**43** and **49**) generated from photocatalyst.

found that similar transformations can also be carried out under batch conditions with blue LEDs.[41] *gem*-Borylsilylcyclopropanations of styrene derivatives can also be carried out with **48** using Eosin Y under white LED irradiation (Figure 9B).[42]

The photocatalytic processes described above require diiodoalkanes as carbenoid precursors due to their relatively accessible reduction potentials. Dichloroalkanes, which have more cathodic redox potentials and stronger C–Cl bonds, are comparatively inert, and CH_2Cl_2 has even been used as a solvent in several photocatalytic reductive cyclopropanation reactions.

Xie showed that dichloroalkanes can be activated by a dimeric gold photocatalyst (**53**) under blue light irradiation to effect additions to alkenes.[43] The reaction outcomes are substrate-dependent, and cyclopropanation occurs with 1,1-disubstituted styrene derivatives. Multi-substituted cyclopropanes (**54**–**59**) are accessible with various dichloroalkanes (Figure 10A). Although an adduct of **53** and Hantzsch ester was initially proposed to be the photosensitizer, a recent comprehensive computational report challenged this hypothesis.[44] Instead, ion pair **60** containing deprotonated Hantzsch ester and a guanidinium counterion was proposed to be the photosensitizer. Photoexcited **60*** can reduce the dimeric gold catalyst to provide **62**, which then reacts with dichloroalkanes to form adduct **63**. Subsequent inner-sphere SET generates the chloroalkyl radical carbenoid **65**. Intermediate **65** then adds to the alkene to form **66**, which can either undergo intramolecular radical substitution to form the cyclopropane, or hydrogen-atom transfer (HAT) from **60** to give the hydrochloromethylated product. DFT calculations indicate that, for 1,1-disubstituted alkenes, cyclopropane formation is favored, which is consistent with experimental results (Figure 10B).

Pitre recently demonstrated that CH_2Cl_2 can also engage in reductive cyclopropanation reactions using a photoactivated vitamin B_{12} catalyst (Figure 11A).[45] Previously, it was established that vitamin B_{12} in its reduced Co(I) form reacts with CH_2Cl_2 to give Co(III)-CH_2Cl (**71**). Under electrochemical conditions, **71** can be reduced to release the $[CH_2Cl]^\bullet$ radical, which is able to cyclopropanate styrenes.[46] Under light irradiation, **71** is proposed to undergo direct homolysis to form the radical pair $[Co(II)^\bullet\cdots{}^\bullet CH_2Cl]$ **72**, which adds to the alkene to provide **73** (Figure 11B).

2.5. From Carbonyl Compounds

Whereas simple *gem*-dihaloalkanes are often commercially available, more complex derivatives must be synthesized by deoxydihalogenation reactions of carbonyl compounds. To streamline this process, it is attractive to consider the generation of carbenes from the direct deoxygenation of carbonyl compounds. In the Clemmensen reduction, a zinc carbenoid intermediate is formed from a ketone using

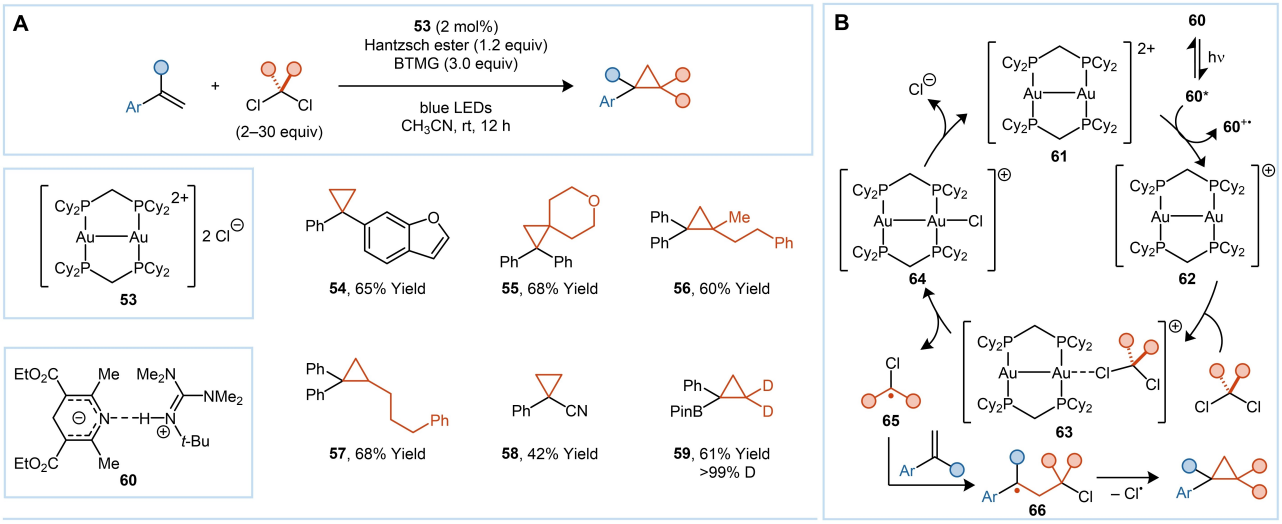


Figure 10. (A) Photocatalyzed cyclopropanation reactions of 1,1-disubstituted styrenes with dihaloalkanes by a dimeric gold catalyst. The adduct of Hantzsch ester and guanidine base **60** is proposed to be the photosensitizer (BTMG = 2-*tert*-butyl-1,1,3,3-tetramethylguanidine). (B) In the mechanism based on DFT calculations, a chloroalkyl radical carbenoid **65** is proposed from the inner-sphere SET of the catalyst and dichloroalkane.

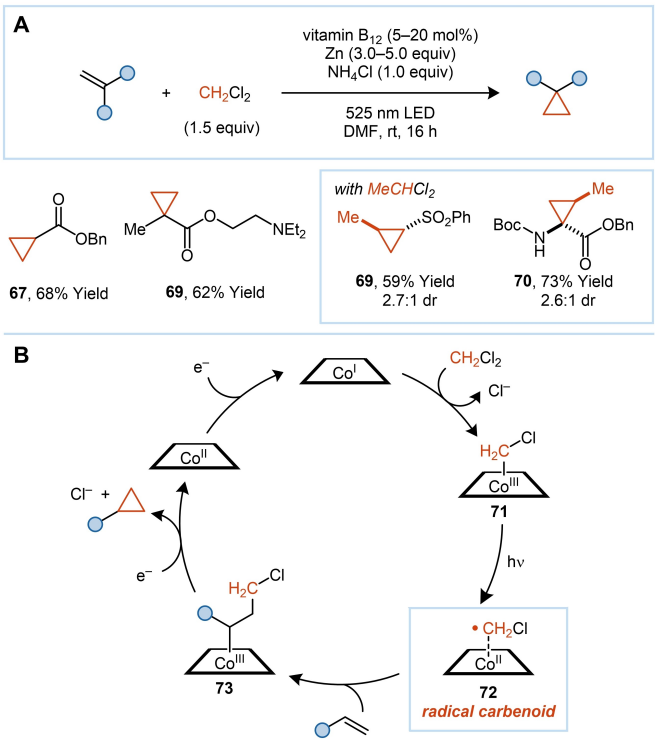


Figure 11. (A) Photocatalytic cyclopropanations using vitamin B_{12}. (B) A radical carbenoid (**72**) bound to Co(II) as a proposed catalytic intermediate.

Zn(Hg) and HCl. Elphimoff-Felkin, Ogawa, and Motherwell later demonstrated that alkenes can trap the carbene intermediate to generate the corresponding cyclopropanes.[47]

The conversion of an aldehyde to a *gem*-dihaloalkane generally requires a deoxydihalogenation reagent (e.g. $POCl_3$ or WCl_6) which generates a byproduct that is incompatible with catalytic cyclopropanation. Nagib demonstrated that the process of converting a carbonyl compound into a carbene equivalent can be telescoped through an α-acetoxy haloalkane intermediate. Intermolecular cyclopropanations of styrenes were demonstrated using $FeCl_2$ as a catalyst (Figure 12A).[48] The proposed iron carbene **77** (Figure 12B) displays electrophilic character and reacts selectively with electron-rich alkenes. Under modified reaction conditions, a broad range of substrates, including non-styrene terminal alkenes (**79**), alkenes substituted with heteroatoms (**80**), and endocyclic alkenes (**81**), were effectively cyclopropanated (Figure 12C).[49]

By leveraging the oxophilicity of low-valent Mo complexes, Zhuo showed that a 1,2-dicarbonyl group could be directly deoxygenated to carry out an intramolecular cyclopropanation (**85**–**87**) (Figure 13A).[50] A phosphine serves as the stoichiometric oxygen atom acceptor. An asymmetric variant was subsequently reported using a chiral salen ligand (**88**) (Figure 13B).[51] To elucidate the possible intermediates in the catalytic cycle, stoichiometric reactions of the isolated Mo(VI) species **89** were performed. Reduction of **89** using 6 equiv. of DPPB at 45 °C generates oxo-bridged Mo(V) complex **96**. Further increasing the temperature to 120 °C reduces **96** to a Mo(III) complex **94**. Complex **94** can convert substrates to cyclopropane products with concomitant formation of **96**. Together, these experiments indicate that **94** is likely the species that cleaves the C=O bond of the substrate to form the oxomolybdenum carbene intermediate **95** (Figure 13C).

Wang recently reported a Ti-catalyzed formal deoxygenative cyclopropanation of terminal alkenes with carboxylic acids and esters to form cyclopropanols (**97**–**98**) (Figure 14A).[52] This transformation can be viewed as a variant of the Kulinkovich reaction,[53] which uses a stoichiometric Grignard reagent. In the proposed mechanism, the carbonyl is not directly reduced by Mg. Instead, Mg reduces Ti(IV) to

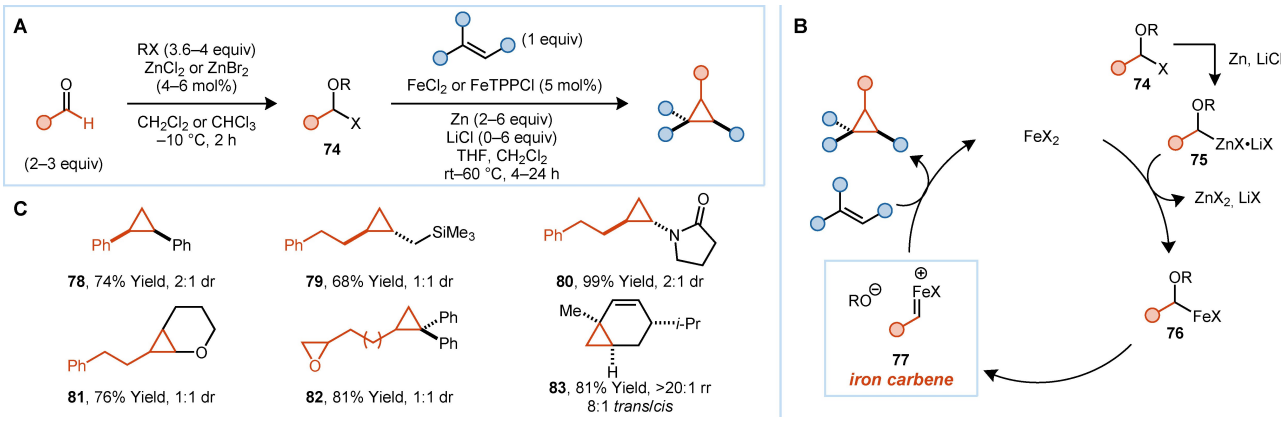


Figure 12. (A) Iron-catalyzed deoxygenative cyclopropanation reactions using aldehydes as carbene precursors. (B) Proposed mechanism involving the formation of an iron carbene (**77**). (C) Cyclopropanes derived from aryl aldehydes, alkyl aldehydes and formaldehydes.

Ti(II), which can mediate the oxidative coupling of an alkene and a carboxylate to form the oxatitanocyclopentane **100**. β-O elimination results in intermediate **101**, which undergoes intramolecular nucleophilic addition to give **102**. Reacting Me_2SiCl_2 with **102** releases the cyclopropane and regenerates the Ti(IV) complex to complete the catalytic cycle (Figure 14B).

3. Oxidative Approaches to Carbene Generation

It is attractive to consider the direct 1,1-dehydrogenation of an alkane to generate a carbene equivalent. Such an approach would obviate the need for prefunctionalized reagents and take advantage of the ubiquitous methylene groups found in organic molecules. In practice, such reactions have thus far only been demonstrated for CR_2H_2 compounds containing one, or more often two, electron-withdrawing substituents, and 1,1-dehydrogenation is accomplished through a stepwise sequence of deprotonation and oxidation.

3.1. Through Iodonium Ylides

Iodonium ylides have been explored as alternative carbene precursors to diazo compounds in cyclopropanation reactions.[54] Aiming to avoid having to pregenerate the iodonium ylide (Figure 15A), Dauban and Dodd found that dimethyl malonate can be directly used in the Cu-catalyzed cyclopropanation of styrene using PhIO as an oxidant (Figure 15B, top).[55] Cu catalysts supported by chiral bis(oxazoline) (Box) ligands (**105**) cyclopropanate styrene derivatives with high levels of enantio- and diastereoselectivity using methyl α-nitroacetate (Figure 15C, left).[56]

Charette investigated a related transformation using α-nitro and α-cyano carbonyl substrates (Figure 15B, bottom) under Rh catalyzed conditions.[57] The substrate scope includes both aryl- and alkyl-substituted terminal alkenes, in addition to activated internal alkenes such as indene. Müller demonstrated asymmetric cyclopropanations of terminal alkenes with dimethyl malonate and Meldrum's acid.[58] A Rh catalyst bearing chiral ligand **107** provided up to 98 % ee for cyclopropanes derived from alkyl- and aryl-substituted alkenes (Figure 15C, right). Finally, Xu showed that such transformations could also be carried out in an intramolecular fashion.[59] α-Cyanoacetamides (**109**) are converted to iodonium ylides, and cyclopropanation of a benzene ring followed by a Buchner reaction provides cycloheptatriene products (**111**) (Figure 15D).

3.2. Carbene Additions Proceeding via α-Carbonyl Radicals

As an alternative to the *in situ* formation of an iodonium ylide, the direct oxidation of an enolate can also generate a carbene equivalent. In early reports from Bertrand, stoichiometric Cu(II) or Mn(III) were shown to mediate cyclopropanation reactions of electron-deficient alkenes *via* radical carbenoid intermediates.[60] Antonchick demonstrated catalytic turnover in this process using DTBP as an oxidant. Acetophenone derivatives serve as carbene precursors for the cyclopropanation of maleimides (Figure 16A).[61] Mechanistically, it is proposed that acetophenone is converted to radical carbenoid **115**, which adds to the maleimide. Capture of the carbon-centered radical **116** by Cu(II) ultimately generates the cyclopropane after ring-closure (Figure 16B). An intramolecular variant of this reaction was demonstrated by Liu using cinnamyl 2-(phenylsulfonyl)acetate substrates (Figure 16C).[62]

Giri discovered a more general process using the photocatalyst 4CzIPN with O_2 as an oxidant and iodine as a co-catalyst (Figure 17A).[63] Under these conditions, various aliphatic terminal and internal alkenes are cyclopropanated in moderate to high yields. Regarding the carbene source, several dicarbonyl compounds, as well as cyano, sulfonyl and isocyanato-substituted methylene compounds, proved to be effective (**118**–**125**) (Figure 17B). In the proposed catalytic cycle, the photoexcited catalyst initially reduces O_2 to superoxide ($O_2^{-\bullet}$), which abstracts an H atom from the dicarbonyl compound to form the radical carbenoid **126**. Carbenoid **126** then reacts with the alkene substrate to form

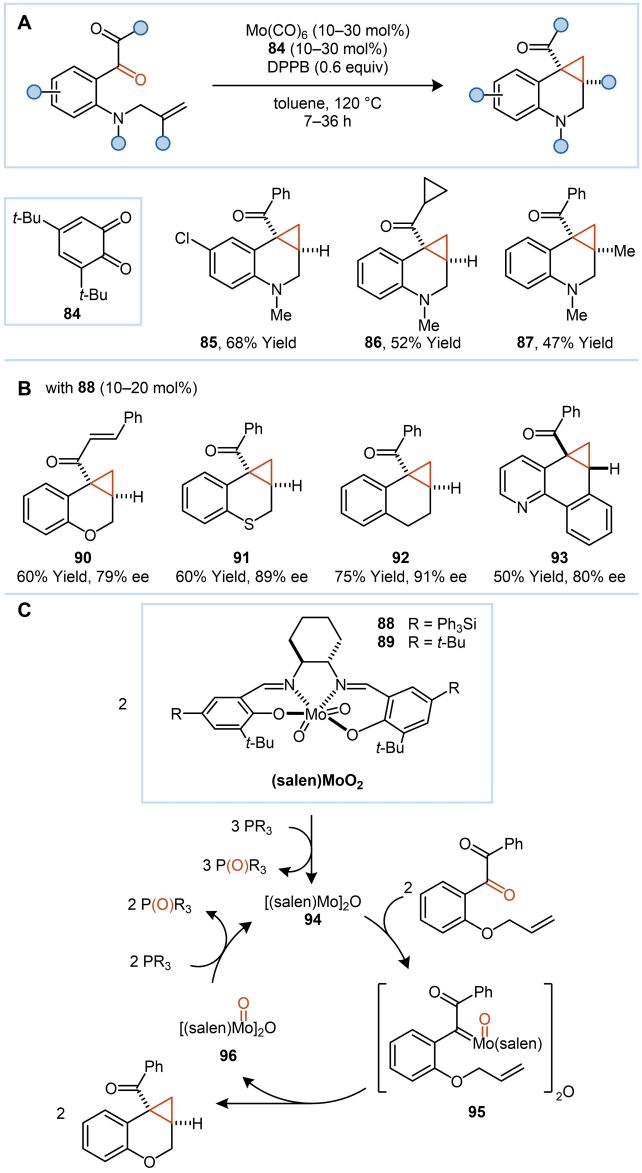


Figure 13. (A) Molybdenum-catalyzed deoxygenative cyclopropanations (DPPB = 1.4-bis(diphenylphosphino)butane). (B) Enantioselective deoxygenative cyclopropanations by using a chiral Mo(salen) catalyst (**88**). (C) A proposed Mo(III) species (**94**) undergoes C=O bond cleavage to form an oxomolybdenum carbene intermediate (**95**).

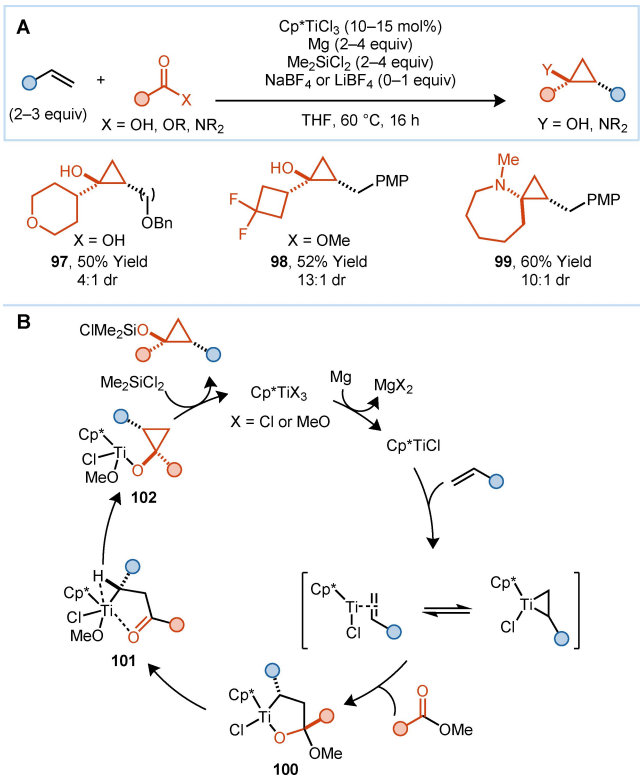


Figure 14. (A) Ti-catalyzed cyclopropanol and cyclopropylamine synthesis from carboxylic acids, esters and amides with terminal alkenes. (B) The proposed reaction mechanism indicates that the reduction occurs on the Ti catalyst.

127, which further reacts with O_2 to give **129**. Finally, radical ring-closure of **129** yields the cyclopropane product (Figure 17C).

In addition to metal catalysts and photocatalysts, electrocatalysts can also be used in oxidative carbene transfer reactions.[64] A phenothiazine-based organocatalyst, **130** or **131**, mediates intramolecular cyclopropanations of activated methylene compounds containing tethered alkenes (Figure 18A). Multisubstituted cyclopropane-fused lactams, lactones, and ketones (**132**–**138**) can be obtained by this method (Figure 18B). In the proposed electrocatalytic cycle, radical cation **139**, generated from the oxidation of phenothiazine **130** or **131**, oxidizes substrate **140** to form the radical intermediate **141**. Subsequent ring-closure generates **142**, which can combine with another equivalent of radical cation **139** to give **143**. Deprotonation and ring-closure yields the cyclopropane (Figure 18C).

3.3. Organometallic Mechanisms for Oxidative Cyclopropanation

In some catalytic oxidative cyclopropanation reactions of carbonyl substrates, addition to the alkene and subsequent ring-closure proceed by an organometallic mechanism rather than through discreet radical intermediates. Lambert reported a Pd-catalyzed intramolecular vinylcyclopropane synthesis from β-keto esters and dienes (Figure 19A).[65] In the proposed mechanism, the cyclopropane is formed by nucleophilic addition of β-keto esters to a π-allylpalladium species. $(i\text{-PrCO}_2)_2$Cu is the stoichiometric oxidant, which regenerates Pd(II) to complete the catalytic cycle (Figure 19B).

Nacci showed that acetophenone derivatives can also cyclopropanate styrenes with a Pd catalyst and stoichiometric O_2 (Figure 20A).[66] In contrast to Antonchick's report, a Pd(II) enolate adds to the alkene to form palladacycle **148**. A second deprotonation followed by C–C reductive elimination affords the cyclopropane product. The reduced Pd(0)

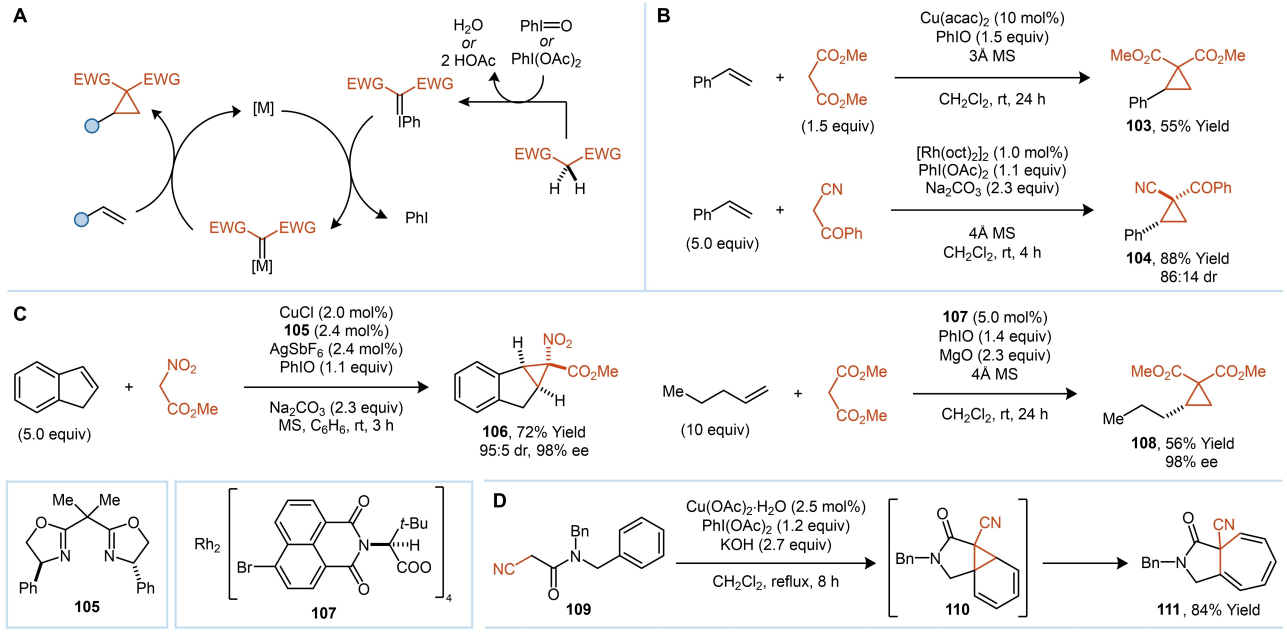


Figure 15. Oxidative cyclopropanations *via in situ* generated iodonium ylides. (A) General mechanistic proposal. (B) Cyclopropanations with dimethyl malonate and α-cyano carbonyl compounds. (C) Asymmetric cyclopropanations with chiral ligands. (D) An intramolecular cyclopropanation followed by a Buchner reaction.

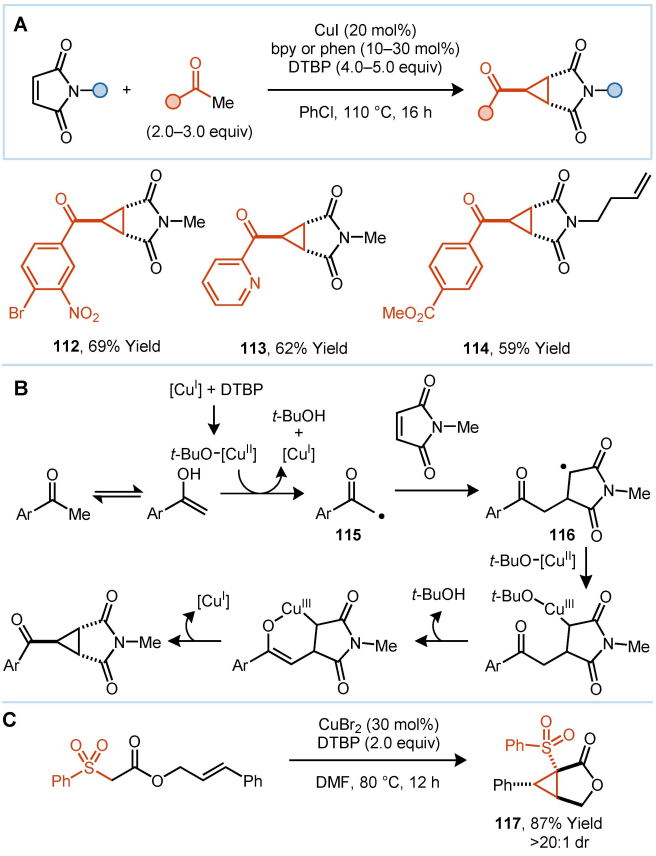


Figure 16. (A) Cu-catalyzed intermolecular cyclopropanations with acetophenone derivatives (DTBP = di-*tert*-butyl peroxide). (B) A radical carbenoid (**115**) is proposed in the catalytic cycle. (C) An intramolecular variant using α-sulfonyl esters.

is oxidized back to Pd(II) by O_2 using a Cu co-catalyst (Figure 20B).

Engle reported a Pd-catalyzed oxidative cyclopropanation of alkenyl amides with activated methylene compounds (Figure 21A).[67] Interestingly, (*Z*)-alkenes favor the formation of *trans*-cyclopropanes, while (*E*)-alkenes favor the formation of *cis*-cyclopropanes (Figure 21B). This unique selectivity suggests that the cyclopropanation mechanism is distinct from other processes described above. Iodoalkane **149** is proposed to undergo *anti*-nucleopalladation, followed by intramolecular oxidative addition/C–C reductive elimination to give the cyclopropane product.

4. Conclusions

The Simmons–Smith reaction continues to be one of the most general methods available to carry out alkene cyclopropanation reactions using a simple methylene group (CH_2). Nevertheless, efforts to develop general modes of catalysis for this classic transformation have been met with limited success. In most cases, Lewis acid catalysts are only viable for substrates possessing directing groups, which has largely restricted the scope of catalytic enantioselective reactions to allylic alcohol substrates.

As an alternative to Lewis acid catalysis, transition metal redox catalysts can activate *gem*-dihaloalkanes by oxidative addition mechanisms to generate metal carbene and carbenoid intermediates. A variety of first-row metal catalysts (e.g., Cr, Fe, Ni, and Co) have proven to be effective in this mode of activation, culminating in a broad range of cyclopropanation reactions using carbenes substituted with alkyl, halo, silyl, and boryl substituents. Furthermore, the use of

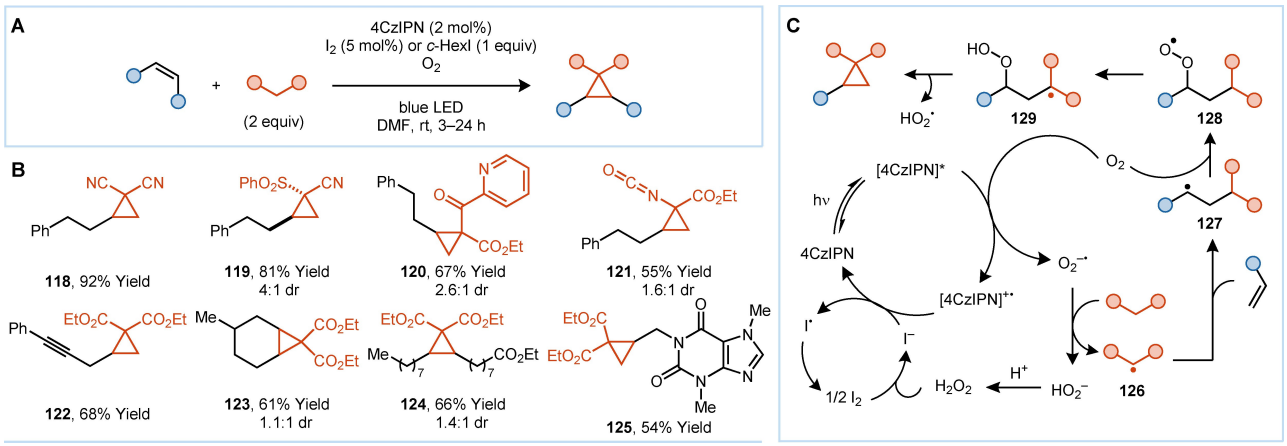


Figure 17. (A) Photocatalytic oxidative cyclopropanations with O_2 as the oxidant. (B) Representative substrate scope. (C) Proposed mechanism.

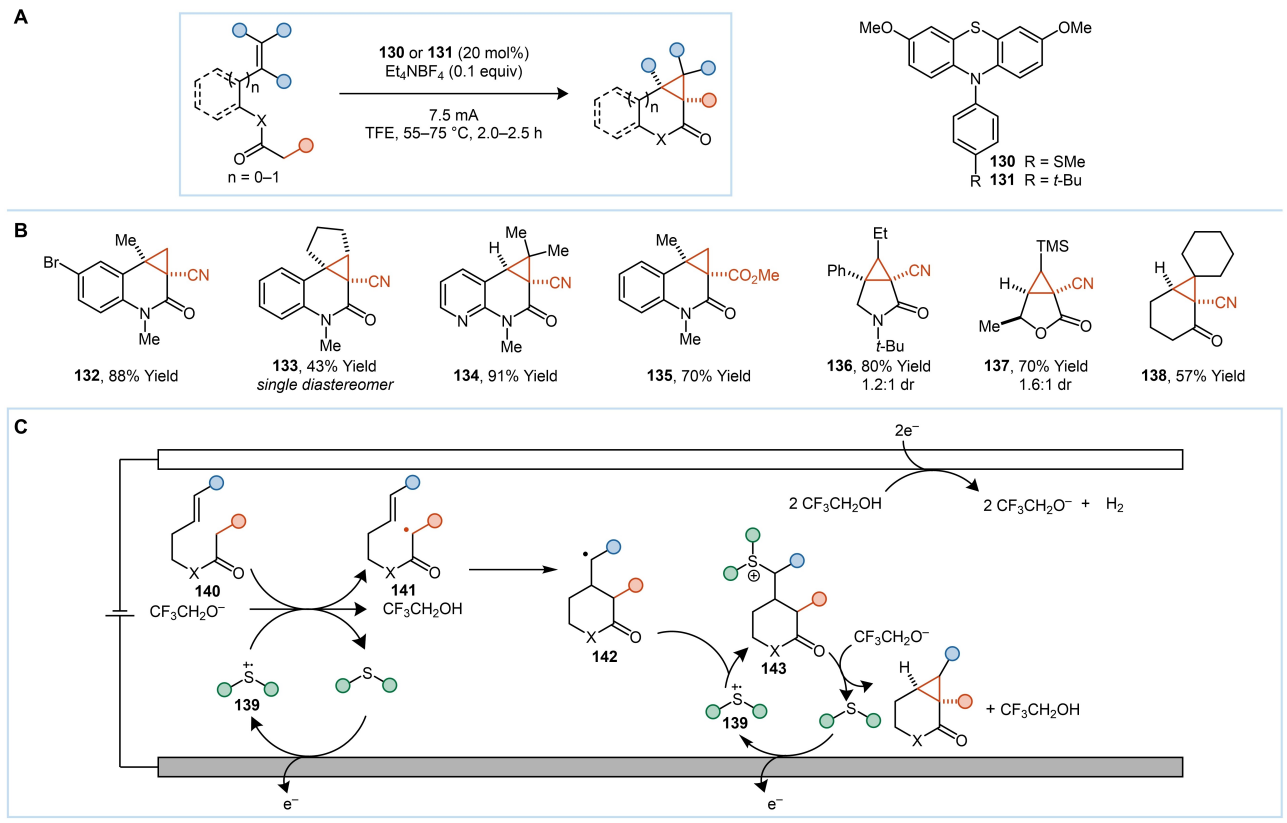


Figure 18. (A) Electrocatalytic intramolecular oxidative cyclopropanations. (B) Representative substrate scope. (C) Proposed electrocatalytic cycle.

chiral ligands provides a straightforward entry into catalytic asymmetric reactions, and it is now possible to carry out highly enantioselective cyclopropanation reactions without the restriction of directing groups. Because complex *gem*-dihaloalkanes must be synthesized from carbonyl compounds, it is also attractive to consider deoxygenative strategies for carbene generation. This process has been accomplished either in a telescoped two-step fashion *via* α-acetoxy haloalkane intermediates or through a direct O-atom abstraction using an oxophilic transition metal.

To avoid the need for prefunctionalized carbene precursors altogether, there is emerging interest in the formal dehydrogenation of simple methylene compounds to generate carbenes. Thus far, successful examples have been restricted to CR_2H_2 compounds where R is an electron-withdrawing group, such that the relatively acidic C–H bonds can be activated through sequential deprotonation and oxidation mechanisms. In the future, it may be possible to consider combining recent advances in C–H bond activation with an α-hydride elimination step to generate carbenes for cyclopropanation reactions.

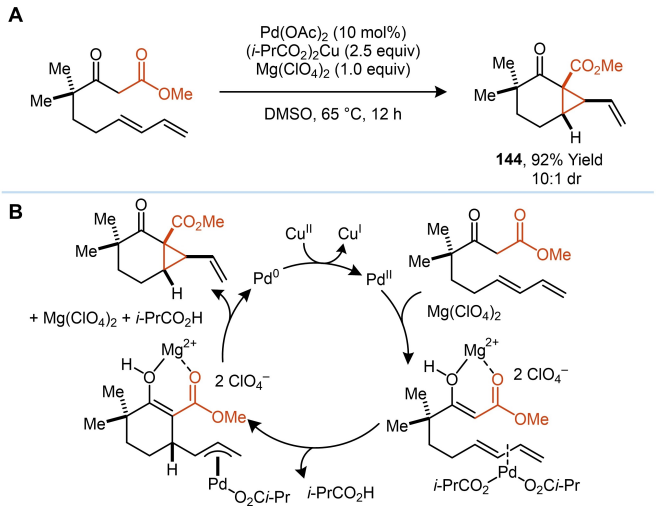


Figure 19. (A) Pd-catalyzed oxidative intramolecular cyclopropanations of dienes and β-keto esters. (B) An organometallic mechanism for oxidative cyclopropanation.

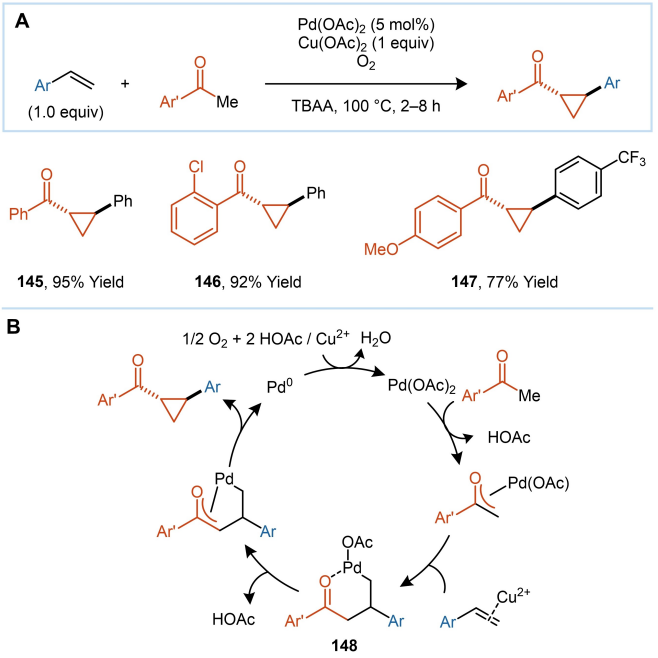


Figure 20. (A) Pd-catalyzed oxidative cyclopropanations of styrenes and acetophenones. TBAA = tetrabutylammonium acetate. (B) The oxidation is proposed to occur on the Pd catalyst.

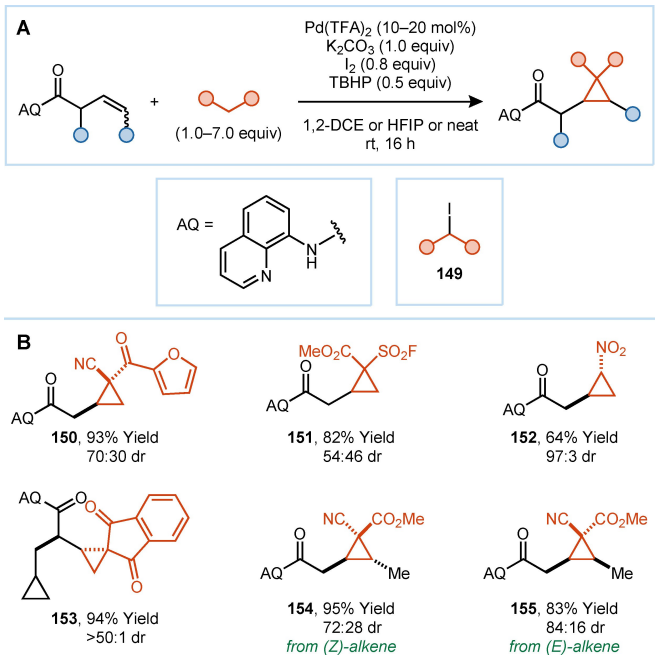


Figure 21. (A) Pd-catalyzed intermolecular oxidative cyclopropanations of aliphatic alkenes and active methylene compounds (TBHP = *tert*-butyl hydroperoxide, HFIP = 1,1,1,3,3,3-hexafluoroisopropanol). (B) Representative substrate scope.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: carbenes · cyclopropanes · homogeneous catalysis · asymmetric catalysis · redox chemistry

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Conflict of Interest

The authors declare no conflict of interest.

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