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Transition Metal-Catalyzed Cycloadditions of Cyclopropanes for the Synthesis of Carbocycles: C–C Activation in Cyclopropanes

Yang Gao, Xu-Fei Fu, and Zhi-Xiang Yu

Abstract Transition metal-catalyzed cycloadditions of cyclopropanes have been well developed over the past several decades, leading to numerous new types of cycloadditions which are complementary to the traditional cycloadditions for the synthesis of carbocycles. Cycloadditions of vinylcyclopropanes (VCPs) and methylenecyclopropanes (MCPs) constitute two main aspects of this field. VCPs can act either as five-carbon synthons or three-carbon synthons, depending on whether the vinyl substituent is acting as an additional two-carbon synthon or not. As five-carbon synthons, VCPs are involved in [5+1], [5+2], [5+2+1], and [5+1+2+1] cycloadditions. As three-carbon synthons, VCPs are mainly involved in [3+2] and [3+2+1] cycloadditions. MCPs mostly act as three-carbon synthons and can have [3+2] cycloadditions with different π systems. Other types of cycloadditions involving MCPs are also reviewed, such as [3+1], [3+2+2], and [4+3+2]cycloadditions. Cycloadditions of some other unusual cyclopropane derivatives are also introduced briefly. The cycloadditions of VCPs and MCPs have found applications in total synthesis and some representative molecules are tabulated as selected examples.

Keywords C-C activation · Cycloaddition · Cyclopropane · Transition metal

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1 Introduction

Carbocycles can be accessed by many methods, among which the most important is perhaps the cycloaddition reaction. Due to its high efficiency and atom/step economy, the traditional cycloaddition reaction, which mostly involves (conjugated) unsaturated carbon–carbon bonds, has been widely used to synthesize carbocycles (or polycarbocycles). However, it also suffers from some notorious limitations, such as harsh conditions, poor selectivity, and limited substrate scope. Introducing activating functional groups and/or transition metal catalysis can overcome these disadvantages to a great extent, but there is still room to improve. For example, there are limited approaches to odd-membered carbocycles owing to restrictions of Woodward–Hoffman rules or even-membered synthons used. Therefore, introducing new synthons, especially odd-membered synthons, would provide opportunities to develop new reaction patterns to synthesize more types of carbocycles.

It has long been recognized that cyclopropanes have reactivities similar to alkenes, and cyclopropanes can be viewed as homologues of alkenes. Nevertheless, cyclopropanes, as unique three-membered synthons, were not able to participate in cycloaddition reactions via C-C activation strategy until the development of transition metal chemistry. The past several decades have witnessed the great advance of cycloaddition chemistry of cyclopropanes along with development of the transition metal-catalyzed organic chemistry. As a result, combinations of cyclopropanes and other new or traditional synthons in the presence of transition metals have led to many new types of cycloadditions, and C-C activation of cyclopropanes strategies in cycloadditions have also found many applications in the synthesis of complex molecules. Generally, a vinyl or a methylene substituent was necessary to activate (or direct) the C-C bond activation in cyclopropanes so vinylcyclopropanes (VCPs) and methylenecyclopropanes (MCPs) chemistries constitute the two main aspects of cycloadditions of cyclopropanes via the C-C activation mechanism. This chapter will mainly review the transition metal-catalyzed cycloadditions of VCPs and MCPs (via a metallacarbocycle intermediate) for synthesis of carbocycles, and is organized by the type of cyclopropanes (VCPs, MCPs, and others), including the illustration of selected examples of their applications in total synthesis. Given space limitations, cycloadditions of cyclopropanes with heteroatom-containing unsaturated partners leading to heterocycles,

cycloadditions of cyclopropanes via radical or dipolar intermediates, and cycloadditions of cyclopropenes and related compounds will not be included.

2 VCP Chemistry in Transition Metal-Catalyzed Cycloadditions

Vinylcyclopropane (VCP) can be viewed as the homologue of 1,3-butadiene, which is supported by theoretical computations and spectroscopy analysis [1]. However, it's the experimental fact that VCP can participate in cycloadditions as does 1,3-butadiene that may make the viewpoint more convincing. The vinyl substituent of VCP is usually essential to activate or direct the cyclopropane opening, but it does not have to participate in cycloadditions. As a result, VCP can act as either a five-carbon synthon or a three-carbon synthon. Combination of many other components with VCP (as a five- or three-carbon synthon) under transition metal catalysis or mediation has led to development of numerous new cycloaddition patterns. The cycloadditions of VCP introduced will be classified according to its role as a five- or three-carbon synthon. Under each category, further elaboration is arranged by different cycloaddition patterns and transition metals.

2.1 VCP as a Five-Carbon Synthon in Transition Metal-Catalyzed Cycloadditions

2.1.1 [5+1] Cycloadditions

VCP as a five-carbon synthon participating in transition metal-catalyzed cycloadditions can date back to 1969 when Sarel reported the first example of [5+1] reaction involving VCP in the presence of $Fe(CO)_5$ under thermal conditions [2]. When 1,1-dicyclopropylethylene was heated with Fe(CO)₅ at a high temperature for a prolonged time, cyclohexenone-Fe complex was unexpectedly obtained, in addition to the desired diene π -complex (see (1)). The cyclohexenone-Fe complex arose from [5+1] carbonylation of 1,1-dicyclopropylethylene with CO from Fe(CO)₅ followed by opening of the second cyclopropane ring. The authors systematically studied the reaction under milder photochemical conditions to gain more mechanistic insights and to achieve cleaner conversion as well [3, 4]. They found that a wide range of vinylcyclopropanes performed well, giving the corresponding cyclohexenones as the major products together with minor quantities of π -complexes (see (2)). Based on their results, they also proposed a plausible mechanism, as described in Scheme 1. Vinylcyclopropane compound 1 undergoes an oxidative cycloaddition of an iron carbonyl bond [Fe=C=O] to form a labile, spectroscopically identifiable metallacyclic species 2. Then 2 could undergo



Scheme 1 The proposed mechanism of the photochemical [5+1] reaction by Sarel

reversible carbon monoxide dissociation to give a non-isolable metallacycloalkenone **3**, which gives cyclohexenone products **5** and/or **6** through reductive elimination or an isolable species **4** through bond reorganization. The σ , π -allyl species **4** could also reversibly lose carbon monoxide to give the isolable, wellcharacterized σ , π -allyl iron tricarbonyl complex **7**. Later in 1974, Aumann also reported the similar reactivities of vinylcyclopropane with Fe(CO)₅ under photochemical conditions [**5**]. The thermal iron-catalyzed [5+1] cycloaddition of VCP was also reported by Schulze in 1996 [**6**], and the mechanism under applied conditions was studied by deuterium labeled experiments [**7**].



The group of Taber studied the regioselectivity of opening of the unsymmetrically substituted cyclopropane ring in the iron-catalyzed photochemical [5+1] cycloaddition (Scheme 2) [8, 9]. They found the cleavage of the less hindered C– C bond (bond b in Scheme 2) was favored. Consequently, the stereogenic center of the cyclopropane in the [5+1] reaction would not be destroyed. As a result, 5-alkyl cyclohexenones with high enantiomeric purity can be prepared from enantiomerically pure alkenyl cyclopropanes using the [5+1] cycloaddition method. Since there are many available methods to prepare enantiomerically pure vinylcyclopropanes, this [5+1] cycloaddition may provide a versatile method for



Scheme 2 Enantiomerically pure cyclohexenones by Fe-catalyzed carbonylation of VCPs

the construction of cyclohexane derivatives. de Meijere's group disclosed another example of [5+1] cycloaddition involving VCP catalyzed by $Co_2(CO)_8$ (see (3)) [10]. They found that α -enyl cyclopropanes, including (cyclopropylmethylene) cyclopropanes and vinylcyclopropanes, can be converted into non-conjugated cyclohexenones in the presence of a stoichiometric quantity of $Co_2(CO)_8$. In some cases, the reaction can also be conducted catalytically under a CO atmosphere.

$$\begin{array}{c} & \stackrel{R^{5}}{\underset{R^{2}}{\overset{R^{6}}{\underset{R^{3}}{\overset{R^{6}}{\underset{R^{4}}{\overset{Co_{2}(CO)_{8}}{\underset{R^{4}}{\overset{R^{6}}{\underset{R^{4}}{\underset{R^{4}}{\overset{R^{6}}{\underset{R^{4}}{\underset{R^{4}}{\overset{R^{6}}{\underset{R^{4}}{\underset{R$$

In 2012, the first general example of Rh(I)-catalyzed [5+1] cycloaddition of vinylcyclopropanes with CO was reported by Yu's group [11]. The reaction was conducted under two different conditions (conditions **A** and **B**, Scheme 3) to provide selectively nonconjugated or conjugated products, respectively. The presence of 4-Å molecular sieves was found to be essential to the reactions. The reaction can accommodate VCP substrates with different functional groups and substitution patterns, as illustrated in Scheme 3.

Related allenylcyclopropanes can also participate in the [5+1] cycloaddition. For example, Iwasawa and co-workers found that allenylcyclopropanols reacted with stoichiometric $Co_2(CO)_8$, giving hydroquinone derivatives in moderate to good yields (see (4)) [12, 13]. Murakami reported an example of iridium-catalyzed [5+1] cycloaddition of multisubstituted allenylcyclopropanes with carbon monoxide for synthesis of methylenecyclohexenones (see (5)) [14]. It was found that the presence of one, or preferably two, substituents at the allenic terminus was necessary.



Scheme 3 Rh(I)-catalyzed [5+1] cycloaddition of VCPs and CO



Scheme 4 Rh(I)-catalyzed [5+1] cycloaddition of allenylcyclopropanes and CO

Tang found that in the presence of $[Rh(CO)_2Cl]_2$, allenylcyclopropanes can be generated from 1,3-acyloxy migration of cyclopropyl propargyl ester in situ, which then underwent the [5+1] cycloaddition to produce highly functionalized cyclohexenones efficiently (see (6)) (Scheme 4) [15, 16]. Mostly, regioselective cleavage of the less substituted cyclopropane C–C σ -bond can be achieved for various substituted substrates and the stereogenic center on the cyclopropane can remain intact. Another type of cyclopropyl substituted propargyl esters with acyloxy placed between the cyclopropane and the alkyne can also undergo similar transformation (see (7)).



2.1.2 [5+2] Cycloadditions

Rhodium-Catalyzed [5+2] Cycloadditions

Developing a formal homologue of Diels–Alder reaction between VCPs and two-carbon π systems for synthesis of seven-membered rings had been a longterm pursuit of many chemists, but it was not until 1995 when Wender's group reported the first efficient and reliable example of rhodium-catalyzed [5+2] cycloaddition reaction of vinylcyclopropanes (VCPs) and alkynes [17]. Sevenmembered carbocycles can be obtained from the intramolecular [5+2] reaction in good to excellent yields, which can tolerate different tethers, various substituents on the alkyne or alkene, and both Z and E configuration of the double bond (see (8)) [17]. One limitation was the isomerization of the initially formed double bond from the opening of the cyclopropane ring, which was observed in some cases. The intramolecular [5+2] cycloaddition can also be applied to VCPs with alkenes (see (9)) [18, 19] and VCPs with allenes (see (10)) [20]. In the intramolecular [5+2] reactions of VCPs with alkenes as shown in (9), only the *cis* diastereoisomer was produced with the exception of four-atom tethered substrate which gave the *trans* diastereoisomer exclusively (see (9)). At this time, the authors found that [Rh $(CO)_2Cl]_2$ was a superb catalyst for the [5+2] reactions, benefiting from its high reactivity and suppression of double bond isomerization [21]. In the case of VCPs reacting with allenes, formation of a *cis* ring-fusion was favored, and the level of selectivity can be controlled and amplified by using different catalysts (see (10)) [20]. The reaction displayed complete selectivity for the internal double bond of the allene and it was also proved that the chirality of allene can be transferred to the cycloadduct completely (see (10)).



On the regio- and stereoselectivity of the Rh-catalyzed [5+2] cycloadditions with substituted cyclopropanes, Wender's group had conducted detailed studies [22]. For substrates with 1,2-disubstituted cyclopropanes, the isomer derived from cleavage of the less substituted cyclopropane carbon–carbon σ -bond was the major (if not the only) product for electron-neutral or electron-donating substituents, but for substrates with electron-withdrawing substituents, the regioselectivity was poorer and can even be reversed under different conditions. It was thus concluded that different regioselectivities in cyclopropane bond cleavage can be obtained through judicious selection of substituents and/or catalyst [22]. Additionally, for almost all these substrates, the relative stereochemistry of vicinal cyclopropane retained through the cycloaddition, translating substituents is into а 1,4-stereorelationship in the product (3,4(5))-stereorelationship to 1,4(5)stereorelationship; see (11)) [23].



Since Wender first employed the Wilkinson's catalysts $[RhCl(PPh_3)_3]$ and $[RhCl(CO)_2]_2$ to catalyze [5+2] cycloadditions, many other types of rhodium-based catalysts have been developed by Wender and others to effect the [5+2] reactions. These include $[Rh(CH_2Cl_2)_2(dppe)]SbF_6$ by Gilbertson [24], $[RhCl(dppb)]_2$ by Zhang [25], $[Rh(NHC)(cod)]SbF_6$ by Chung [26], $[Rh(cod)Cl]_2$ by Saito and Hanzawa [27], $[Rh(arene)(cod)]SbF_6$ [28], water-soluble $[Rh(nbd)L1]SbF_6$ [29], NHC complex Rh(NHC)(cod)Br [30], and rhodium dinaphthocyclooctatetraene (dnCOT) complex $[Rh(dnCOT)(MeCN)_2]SbF_6$ [31, 32] by Wender (Fig. 1). In particular, Rh(NHC)(cod)Br and $[Rh(dnCOT)(MeCN)_2]SbF_6$ proved to be most efficient so far, making the intramolecular or intermolecular [5+2] cycloadditions complete in just minutes at room temperature with high efficiency.

As early as 1998, Wender's group reported their preliminary studies towards an asymmetric version of the [5+2] cycloadditions, but the use of (2S,3S)-bis(diphenyl-phosphino)butane as a chiral bisphosphine ligand resulted in only moderate enantioselectivity (up to 63% *ee*) in a single substrate studied [19]. Eight years later they reported the first highly enantioselective [5+2] cycloadditions employing (*R*)-BINAP as the chiral ligand [33]. High enantioselectivity (up to >99% *ee*) was achieved for alkene-VCPs (see (12)) but only moderate enantioselectivity for alkyne-VCPs. In 2009, Hayashi and co-workers reported the Rh-catalyzed asymmetric [5+2] cycloaddition of alkyne-VCPs using a chiral phosphoramidite ligand to deliver the cycloadduct in excellent enantiomeric excess (up to >99.5% *ee*), thus addressing the shortcoming of Wender's protocol (see (13)) [34].



More effort from others has expanded the types of substrates involved in the [5+2] cycloadditions. For example, Saito and Hanzawa et al. reported the rhodium-catalyzed [5+2] cycloaddition of ester-tethered alkyne-VCPs using fluorinated alcohols as solvents (see (14)) [27]. Mukai's work demonstrated that alkyne-allenylcyclopropanes can also undergo rhodium-catalyzed [5+2] cycloaddition to give bicyclo[5.4.0] undecatrienes or bicyclo[5.5.0]dodecatrienes (see (15)) [35]. In related work from Yu's group, they found that the alkene-VCP with an internal cyclopropane with the *cis*-substitution can react well by following the [5+2] pathway (see (16)) while the *trans* isomer underwent the [3+2] process (see [3+2] section and (32)) [36].



Wender's group has also developed rhodium-catalyzed intermolecular [5+2] cycloadditions. At first, they found the catalysis system of Rh(PPh₃)₃Cl for the intramolecular reactions was not effective at all for the intermolecular reactions. To effect the intermolecular [5+2] cycloadditions, $[Rh(CO)_2Cl]_2$ must be used and oxygen substitution of the cyclopropane was necessary (see (17)) [37–39]. Then they successfully expanded the substrate to unactivated vinylcyclopropanes by adjusting the substituents. For monosubstituted alkynes, the substitution on the olefin terminus directs the formation of single isomer that minimized steric hindrance (see (18)) [40]. The [5+2] cycloadditions can also be applied to VCPs with allenes (see (19)) [41]. It should be noted that the alkyne substituent did not interfere with the reaction, indicating that allenes as reaction partners were superior to alkyne in the [5+2] cycloadditions. Curiously, the authors didn't report the corresponding intermolecular [5+2] cycloadditions of VCPs with alkenes.



The rhodium-catalyzed [5+2] cycloadditions have been used in cascade with other processes to synthesize molecules of more complexity in a single operation. The first example was reported by Martin who developed a cascade sequence involving allylic alkylation and [5+2] cycloaddition (see (20)) [42, 43]. The catalyst $[Rh(CO)_2CI]_2$ could be used to catalyze both the highly regioselective allylic alkylation and the following intramolecular [5+2] cycloaddition. As another example, Wender and co-workers combined intermolecular [5+2] cycloaddition with



Scheme 5 The mechanism of transition metal-catalyzed [5+2] cycloaddition

Nazarov reaction to develop a highly efficient construction of bicyclo[5.3.0]decane systems (see (21)) [44]. In addition, intermolecular [5+2] cycloadditions combined with Diels-Alder reactions have been used by Wender to construct polycyclic structures in one pot (see (22)) [45].



Generally there are two mechanistic considerations for the rhodium-catalyzed [5+2] cycloaddition (Scheme 5) [46]. One would proceed through initial formation of a rhodacyclohexene intermediate followed by alkyne insertion and reductive elimination (Path I) while the second would involve initial formation of a rhodacyclopentene followed by ring expansion assisted by release of the ring strain and reductive elimination (Path II). A DFT computational investigation taken up by Houk group revealed that pathway I involving a rhodacyclohexene intermediate is

favored [46]. Other computational and experimental studies have disclosed other aspects of the mechanism, including the origins of different reactivities associated with different substrates, the influence of substituents on the reactivities, and the electronic and steric control of regioselectivities in the rhodium-catalyzed [5+2] cycloadditions [47–49].

Ruthenium-Catalyzed [5+2] Cycloadditions

Trost's group successfully developed a [5+2] cycloadditions catalyzed by [CpRu (MeCN)₃]PF₆ in 2000 [50]. Though limited to tethered alkyne-VCPs, the [5+2] cycloadditions gave corresponding seven-membered ring products in good yields at room temperature efficiently with high regio- and stereoselectivity, and showed good compatibility with a variety of functional groups and different tethers between the alkynes and VCPs [50-53]. For substrates with 1,2-disubstituted cyclopropanes, the issue of regio- and stereoselectivity arose. With *cis* cyclopropyl substrates, steric effects appear to dominate and the less hindered bond of the cyclopropane was cleaved with high selectivity mostly (see (23)). With trans cyclopropyl substrates, the bond energy of the cleaving bond appears to be an important factor and the regioselectivity was usually poor as a result of both electronic and steric factor operating (see (24)). However, in both cases, the 1,2-disubstituted cyclopropyl stereochemistry was conserved and completely transferred to the product, as is same as the Wender rhodium-catalyzed [5+2] cycloaddition (see (11)). Good to excellent diastereoselectivities favoring the angular hydrogen to be anti to the homoallylic oxygen substituent were also observed for the substrates with an allylic stereogenic center (structure $\mathbf{8}$). This methodology can also be expanded to synthesize a wide range of tricyclic systems in good yields and diastereoselectivities [54, 55] (Fig. 2). In contrast to rhodium-catalyzed [5+2] reaction, the rutheniumcatalyzed [5+2] reaction was believed to proceed via a ruthenacyclopentene (Path II, Scheme 5) intermediate as was supported by experimental facts. A DFT investigation by Houk has also been conducted to verify the mechanism and rationalize the regio- and stereoselectivities [56].





Fig. 2 Some representative examples of Ru-catalyzed [5+2] cycloadducts



Iron- and Nickel-Catalyzed [5+2] Cycloadditions

Iron and nickel have also been used to catalyze the intramolecular [5+2] cycloadditions. Louie's group reported a nickel-promoted intramolecular [5+2] cycloaddition when studying the nickel-catalyzed rearrangement of cyclopropylen-ynes (see (25)) [57]. The reaction course strongly depended on the substituents of the substrates and the ligands used, and has also recently been studied theoretically by Houk and co-workers [58].



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

Two ferrate complexes **A** and **B** were used by Fürstner and co-workers to catalyze the intramolecular [5+2] cycloadditions of alkyne-VCPs to give the corresponding seven-membered products in good to excellent yields with a good substrate scope and diastereoselectivity (see (26)) [59].



2.1.3 [5+2+1] and [5+1+2+1] Cycloadditions

In 2002, Wender's group first realized the rhodium-catalyzed three-component intermolecular [5+2+1] cycloaddition of VCPs, carbonyl-substituted alkynes, and CO [60]. Initially, they envisioned that the rhodacyclooctene intermediate of the [5+2] cycloaddition may be intercepted by CO, thus leading to eight-membered rings, but instead they got bicyclo[3.3.0] octenones arising from transannular closure of the intended eight-membered products (see (27)). The reaction proceeded in good to excellent yields and with high or complete regioselectivity for unsymmetrical alkynes. However, when the [5+2+1] conditions were applied to terminal alkynes, a four-component [5+1+2+1] pathway involving two units of CO operated, giving hydroxyindanones putatively from the initially formed nine-membered ring intermediate through tautomerization, electrocyclic closure, and elimination (see (28)) [61]. The three-component [5+2+1] reaction can also be applied to allenes (see (29)), as was demonstrated that the allene **9** without a carbonyl substitution (the allenes with carbonyl substitutions; see (19)), VCP and CO reacted well to give a mixture of cyclooctanedione and its transannular aldol product [41].

$$\begin{array}{c} & & & \\ &$$

 $R_1 = COCH_3$, CO_2Et , $CONH_2$, CHO, CO_2Me $R_2 = Et$, TMS, Ph, Me, CO_2Me



Another impressive example of rhodium-catalyzed [(5+2)+1] cycloaddition was reported by Yu's group in 2007 [49]. Their DFT calculation results indicated the activation energy of reductive elimination step in the [5+2] cycloaddition of ene-VCPs was about 25-30 kcal/mol, while the CO insertion and migratory reductive elimination had activation energies of about 13-14 and 23-24 kcal/mol, respectively. They ascribed this to the more facile reductive elimination of (sp^2) $C-M-(sp^3)C$ in the [(5+2)+1] process compared to the reductive elimination of (sp^3) $C-M-(sp^3)C$ in the [5+2] reaction. Therefore they hypothesized that ene-VCPs, which are less reactive in the [RhCl(CO)₂]₂-catalyzed [5+2] cycloaddition reported by Wender [21], can be made reactive either by reacting at higher temperature or by introducing CO as an additional component (see (30)). Experimental results were in agreement with their hypothesis. The intramolecular [(5+2)+1] cycloaddition of ene-VCPs and CO worked well in good to excellent yields, compatible with a variety of tether types and substitution patterns, and allowed for the preparation of 5/8- and 6/8-fused ring systems even containing quaternary centers. Thus the new computationally designed and experimentally verified Rh(I)-catalyzed [(5+2)+1] cycloaddition provided a convenient and efficient method for constructing bicyclic cyclooctenones. Furthermore, Yu's group expanded this strategy to build [5-8-5]/ [6-8-5] tricyclic cyclooctenones which are important skeletons of natural products (see (31)) [62]. Recently, Yu and coworkers used both DFT calculations and experiments to study the mechanism of the [(5+2)+1] reaction and provided rationalization of the stereochemistry and reactivities of substrates with different configurations (Scheme 6) [63].



Scheme 6 The proposed mechanism of Rh-catalyzed [(5+2)+1] cycloaddition of VCPs



2.2 VCP as a Three-Carbon Synthon in Transition Metal-Catalyzed Cycloaddition

2.2.1 [3+2] Cycloadditions

VCP derivatives were first found by Tsuji and co-workers as three-carbon components to undergo a palladium-catalyzed intermolecular formal [3+2] cycloaddition with α,β -unsaturated esters and ketones in 1985, leading to vinyl-substituted cyclopentane derivatives in good yields [64]. This cycloaddition was proposed to proceed through a stepwise ionic mechanism in which two zwitterionic intermediates **10** and **11** of π -allyl palladium complex were involved (Scheme 7). Plietker's group recently reported that nucleophilic ferrate Bu₄N[Fe(CO)₃(NO)] with ligand L3 can act as an alternative catalyst for this transformation [65]. Since the discovery of the Tsuji's [3+2] cycloaddition, much effort has been devoted to developing



Fig. 3 Ligands of Pd catalyst

asymmetric variants. For example, Trost's group developed a high diastereo- and enantioselective dynamic kinetic asymmetric palladium-catalyzed [3+2] cycloaddition of VCPs and azlactone- or Meldrum's acid alkylidenes using the chiral ligand **L4** and **L5** [66, 67]. Shi also reported a palladium-catalyzed asymmetric formal [3 +2] cycloaddition of VCPs and β , γ -unsaturated α -keto esters employing the chiral imidazoline-phosphine ligand **L6** [68, 69] (Fig. 3).

The Tsuji's [3+2] cycloaddition virtually proceeds via dipolar intermediates stabilized both by palladium and the activating groups on the cyclopropane. There had not been an example of unactivated VCPs acting as three-carbon synthons until Yu's group first reported a rhodium-catalyzed intramolecular [3+2] cycloaddition of *trans*-vinylcyclopropane-enes in 2008 [36]. In this reaction, *trans*-2-ene-VCPs underwent an unexpected intramolecular [3+2] cycloaddition (Scheme 8a) rather than a [5+2] cycloaddition (see (15)). This strategy provided an efficient and diastereoselective approach to *cis*-fused bicyclic cyclopentanes (Scheme 8a). Interestingly, the reaction with *cis*-2-ene-VCP substrate gave a [5+2] cycloadduct. The different reaction course of a [3+2] or [5+2] cycloaddition was ascribed to proximity of different carbons in the reductive elimination step for different substrates. α -Ene-vinylcyclopropanes also underwent the similar [3+2] cycloaddition to provide a new approach to bicyclo[4.3.0]nonane and bicyclo [5.3.0]decane skeletons as reported by Yu's group (Scheme 8b) [70].

The 1-substituted-VCPs were also tested to undergo [3+2] cycloaddition by Yu's group, and it worked well with Rh(I)-phosphine complex (Scheme 9a) [71]. Impressively, this strategy was suitable for 1-ene-VCPs, 1-yne-VCPs, as well as 1-allene-VCPs, thus providing access to a wide range of cyclopentane- and cyclopentene-



embedded bicyclic structures with a vinyl-substituted quaternary stereocenter. During the reaction course, the vinyl substituent plays an important role as a "spectator" binding group in facilitating the ring-opening of the cyclopropane through coordination with Rh. DFT study has been conducted to investigate the reaction mechanism [72]. An asymmetric rhodium-catalyzed [3+2] cycloaddition of 1-yne-VCPs, but not 1-ene-VCPs, has also been developed by Yu's group by use of (*R*)-H₈-BINAP as a chiral ligand (Scheme 9b) [73].

2.2.2 Higher Order Cycloadditions

Introducing CO as a reactant to the system of rhodium-catalyzed [3+2] cycloaddition of 1-ene-VCPs and 1-yne-VCPs has led to the corresponding carbonylative [(3+2)+1] cycloaddition, a homologous Pauson–Khand reaction (Scheme 10a)



Scheme 9 Rh(I)-catalyzed [3+2] cycloaddition of 1-substituted-VCPs

[74]. Multifunctional bicyclic cyclohexenone and cyclohexanone products were obtained in good yields with good tolerance of various functional groups and different tethers. Interestingly, for 1-yne-VCPs having an internal alkyne, a competing formal [5+1]/[2+2+1] process arose under some conditions (Scheme 10b) [75]. In the reaction, two carbonyl groups and the entire VCP moiety were incorporated into the products, rendering an unprecedented bicarbonylative cycloaddition mode of 1-yne-VCP. As indicated by its name, the reaction can be viewed as a formal cascade reaction consisting of a [5+1] cycloaddition (between the VCP and CO) and a subsequent intramolecular Pauson–Khand [(2+2)+1] cycloaddition



Scheme 10 Rh(I)-catalyzed (a) [(3+2)+1] cycloaddition and (b) [5+1]/[(2+2)+1] cycloaddition

(between alkyne, in situ generated cyclohexenone, and CO), though both experimental and DFT computational studies suggested an alternative mechanism (Scheme 10b). Optimization of the reaction conditions made the reaction a practical method to synthesize functionalized angular 5/5/6-diones in generally moderate to excellent yields.

In addition, a rhodium-catalyzed [(3+3)+1] cycloaddition of biscyclopropanes with a vinyl substituent was reported by Chung's group [76]. Seven-membered ring products can be obtained from the two different types of vinyl-substituted biscyclopropanes in moderate to good yields (see (32) and (33)).





3 MCP Chemistry in Transition Metal-Catalyzed Cycloadditions

Methylenecyclopropanes (MCPs) are another type of important versatile building blocks bearing cyclopropane rings in organic synthesis. The unique structure confers rich reactivities to MCPs and the chemistry of MCPs has been profoundly investigated by numerous groups since the 1970s [77, 78]. The chemistry of MCPs includes reactions originating from reactivities of the double bond alone, reactions involving the cyclopropane ring opening leading to open chain compounds, as well as the cycloadditions of MCPs as three-carbon synthons. In this review we will focus on transition metal-catalyzed cycloadditions of MCPs as three-carbon synthons via carbon-carbon bond activation mechanism for synthesis of carbocycles. Generally, transition metal-catalyzed cycloadditions of MCPs and other unsaturated components can proceed with cyclopropyl ring cleavage via three different reaction pathways leading to regioisomeric products (Scheme 11, as illustrated in the case of intramolecular [3+2] cycloadditions). The oxidative addition of the transition metal into the distal C-C bond leads to the formation of the metallacyclobutane species followed by insertion of the multiple bond (pathway **a**). On the other hand, a proximal bond cleavage proceeds through either oxidative addition of the transition metal into the proximal C-C bond or formation of a metallacyclopentane with the multiple bond followed by cyclopropylmethylbutenyl rearrangement (pathway b). In addition, MCPs could go through the formation of reactive metal-TMM intermediate (pathway c). The different reaction course is influenced by many factors, including different metals (Ni or Pd mostly), the type and number of the ligands bonded to the metal, the type, number, and position of substituents on the methylenecyclopropanes, and the electronic properties of the olefin subunit. Due to the multiple factors that may operate, it is usually difficult to predict the accurate reaction course.

3.1 [3+2] Cycloadditions

Since Noyori reported the first example of intermolecular [3+2] cycloaddition between MCP and olefins using a nickel catalyst (see (34)) [79, 80], the intermolecular [3+2] cycloaddition of MCP with different reaction partners has evolved into a powerful method to synthesize cyclopentanoid skeletons due to the

a distal bond cleavage



Scheme 11 Pathways of transition metal-catalyzed cycloadditions of MCPs

extensive efforts from the groups of Noyori ([79, 80] and see reviews: [77, 78, 84]), Binger (see reviews: [77, 78, 84]), Trost (see reviews: [77, 78, 84]), and others (see reviews: [77, 78, 84]).

$$\downarrow + _ COOR \xrightarrow{Ni(cod)_2} \xrightarrow{Ni(cod)_2} \xrightarrow{OOR} (34)$$

The [3+2] cycloaddition is mostly catalyzed by Ni or Pd catalysts. The MCPs can have substituents on the olefin or cyclopropane, and the two-atom partners can be electron neutral or deficient alkenes, alkynes, and carbon–heteroatom multiple bonds. Since there are different reaction courses of MCP in cycloaddition, introducing substituents on either MCP or the two-atom reaction partners complicates the reaction even more, considering the associated selectivity issues. Consequently, cycloaddition with multi-substituted substrates often gives mixtures though sometimes good selectivity can be achieved by adjusting reaction conditions and substituents. The intramolecular version of [3+2] cycloaddition, mainly developed by Motherwell [81], Nakamura [82], Lautens [83], and Mascareñas [87–91], may address the issues of selectivity to some extent, and leads to polycyclic structure meanwhile. All these have been summarized by several excellent reviews [1, 84–86] and herein we will only update the [3+2] cycloaddition of MCP for synthesis of carbocycles with some recent representative examples.

After Mascareñas reported the first intramolecular [3+2] MCP-alkyne cycloaddition catalyzed by either $Pd_2(dba)_3$ [87] or the first-generation Grubbs ruthenium carbene complex [88], Mascareñas' group found that the protocol can be applied to cycloaddition of MCPs with alkenes (see (35)) [89] as well as MCPs with allenes (see (36)) [90]. The authors also conducted DFT study about the mechanism of these transformations [89, 91]. Buono reported an impressive intermolecular [2+1]/ [3+2] cycloaddition sequence of norbornadiene with several alkynes catalyzed by secondary phosphine oxide-based platinum complexes (see (37)) [92]. MCPs were demonstrated to be the intermediate participating in the [3+2] cycloaddition which, however, is limited to alkynes bearing a heteroatom substituent on the propargylic carbon atom. Zhang's group disclosed a Ni-catalyzed intramolecular [3+2] cycloaddition of MCPs to arylalkynes via proximal bond cleavage to prepare cyclopenta [*a*]indene derivatives (see (38)) [93].





3.2 Other Types of Cycloadditions

de Meijere's group reported an example of cobalt-catalyzed [3+1] cycloaddition of MCPs. The reaction afforded cyclobutanones arising from proximal CO insertion of the cyclopropane ring in moderate to high yields (see (39)) [94, 95].



de Meijere's group also reported a novel [4+1] cycloaddition of Fischer carbenes and MCPs in which MCPs acted as a four-carbon synthon [95]. The process of the reaction was believed to involve a [2+2] cycloaddition of the MCP to the Fischer carbene, followed by a cyclopropylmethylmetal to homoallylmetal rearrangement, CO insertion, and reductive elimination (Scheme 12).

Kamikawa developed a nickel-catalyzed [3+1+1] cycloaddition of MCPs with Fischer carbenes to produce methylenecyclopentanones (see (40)) [96].



A combined theoretical and experimental development of a rhodium-catalyzed [(3+2)+1] cycloaddition of ene-MCPs and CO was described by Evans' group in 2012 [97]. The reaction proceeded well in good to excellent yields with high diastereoselectivity to give *cis*-fused bicyclohexenones (see (41)). The first highly enantioselective reaction, according to the authors, involving an MCP employing a chiral P,N-ligand was also described (see (42)).



Scheme 12 [4+1] Cycloaddition of Fisher carbenes



In 2010, Ohashi and Ogoshi found an interesting nickel-catalyzed [3+3] cyclodimerization of ester-substituted MCPs giving six- and five-membered ring derivatives (see (43)) [98].



Moreover, MCPs have been used as three-carbon components participating in [3+2+2] or [4+3] cycloadditions to build seven-membered rings. Early in the 1980s, Binger reported some examples of [3+2+2] and [4+3] cycloadditions: a multicomponent [3+2+2] cycloaddition of MCP and two units of allenes catalyzed by Pd(0) [99], a mono-component [3+2+2] cycloaddition of three units of MCPs catalyzed by Ni(0) [100], and a [4+3] cycloaddition of MCPs and dienes catalyzed by Pd(0) [78] (Scheme 13). Saito and co-workers have made some impressive contributions in this area. They developed a series of Ni(0)-catalyzed [3+2+2] and



Scheme 13 Multicomponent intermolecular cycloadditions of MCPs by Binger or Saito

[4+3] cycloadditions, including [3+2+2] cycloadditions of MCPs with two units of alkynes [101–106], and [4+3] cycloadditions of MCPs with dienes [107] (Scheme 13). A DFT study of the mechanism of nickel-catalyzed [3+2+2] cyclo-addition has been carried out recently [108]. They also developed a Ni(0)-catalyzed [4+3+2] cycloaddition of MCPs and diene-ynes to synthesize nine-membered carbocycles [109, 110] (Scheme 13). Evans also reported an example of Rh(I)-catalyzed [3+2+2] cycloaddition (see (44)) [111]. In this reaction, ene-MCPs and electron-deficient alkynes were chosen to build bicyclo[5.3.0]decane compounds at high temperature. Mascareñas reported the Ni(0)-catalyzed intermolecular [3+2+2] cycloaddition of yne-MCPs and alkenes to build bicyclo[5.4.0]undecane systems (see (45)) [112], the Pd(0)-catalyzed intramolecular [3+2+2] cycloaddition of ene-yne-MCPs to produce the tricyclic products (see (46)) [113], and the Pd(0)-catalyzed intramolecular [4+3] cycloaddition of diene-MCPs to build bicyclo[5.3.0] decane systems (see (47)) [114].



4 Other Types of Cyclopropanes

Carbonyl-activated or imino-activated cyclopropanes can undergo Ni-catalyzed dimerization, or [3+2] cycloaddition with α , β -unsaturated ketones, generally at a much slower rate, to give five-membered carbocycles. This topic was tactfully investigated by Ogoshi [115–117] and Montgomery [118, 119] (Scheme 14).

In 1999, Narasaka reported an example of intramolecular [(3+2)+1] cycloaddition of unactivated yne-CPs with carbon monoxide catalyzed by Rh(I) at 160°C to give the corresponding bicyclic products in low to moderate yields (Scheme 15) [120].

A novel rhodium-catalyzed carbonylation of spiropentanes leading to cyclopentenones was uncovered by Murakami in 2007 (Scheme 16) [121]. The reaction was proposed to proceed by the following pathway: oxidative addition of C–C σ -bond of the unsubstituted cyclopropane affords a spirocyclic rhodacyclobutane



Scheme 14 Ni-catalyzed [3+2] cycloaddition of activated CPs



Scheme 15 Rh-catalyzed [(3+2)+1] cycloaddition of unactivated yne-CPs

species, which undergoes CO insertion to give a rhodacyclopentanone intermediate. β -Carbon elimination converts the rhodacyclopentanone into a six-membered rhodacycle. Finally, reductive elimination followed by alkene isomerization leads to the cyclopentenone product.

Shi and co-workers reported a Pauson–Khand type [3+2+1] cycloaddition reaction of ene-vinylidenecyclopropanes and CO in the presence of rhodium(I) catalyst [122]. Both cyclic and noncyclic substituent could be tolerated (see (48)). Shi also reported a tandem process that converted 1,4-enynes tethered by cyclopropyl group



Scheme 16 Rhodium-catalyzed carbonylation of spiropentanes

to phenol bicyclic derivatives with rhodium catalyst (see (49)) [123]. A plausible mechanism was proposed by the authors (Scheme 17). Initially, a Pauson–Khand cycloaddition induced by Rh(I) involving the alkyl group, alkenyl group, and a unit of CO gave the tricyclic spiro intermediate. The following step was analogous to the transformation reported by Murakami [121]. The ring expansion of the [2.2]spiro intermediate was promoted by Rh(I) followed by carbon monoxide insertion. Then reductive elimination and isomerization completed the catalytic cycle and afforded the desired product.



Bower reported a directing group enhanced rhodium-catalyzed [(3+2)+1] cycloaddition reaction of nitrogen-tethered yne-CPs and CO (see (50)) [124]. The authors used the urea as the directing group to induce the oxidative addition at the proximal bond of the amino-cyclopropanes.



Scheme 17 Mechanism of Rh(I)-catalyzed [3+2+1] cycloaddition



Yu's group reported the first Rh-catalyzed [7+1] cycloaddition of buta-1,3dienylcyclopropanes and CO for the synthesis of cyclooctadienones (see (51)) [125]. This reaction showed good compatibility with different functional groups, providing an efficient entry to the eight-membered carbocyclic rings.









Fig. 4 Applications in natural products synthesis

5 Applications in Natural Products Synthesis

Transition metal-catalyzed cyclopropane-based cycloadditions provide efficient strategies for the construction of (poly)cyclic structures. More importantly, the cycloadditions feature atom- and step-economy, good regio- and stereoselectivity, and excellent functional group tolerance. More and more total syntheses of natural products benefit from the rich cycloaddition chemistry of VCPs and MCPs. To date, numerous total syntheses of natural products have been accomplished utilizing these methodologies as key steps. Listed in Fig. 4 are some selected examples.

6 Conclusion

During the past several decades, with the aid of transition metals, cyclopropanes have been incorporated into cycloadditions via C–C bond cleavage and have led to many desirable types of transformations, mainly involving vinylcyclopropanes (VCPs) and methylenecyclopropanes (MCPs) [140]. These methods are complementary to traditional cycloaddition reactions. In particular, the VCP- or MCP-involved cycloadditions can provide efficient accesses to different sized

ring structures of considerable complexity which are otherwise difficult to prepare by traditional approaches. The methodologies of VCPs and MCPs cycloadditions have also found many applications in total synthesis of natural products. Further advancement can be expected that include developing new synthons of cyclopropanes and combinations of different reaction partners leading to potentially new types of cycloadditions. More mechanistic studies and applications in total synthesis of the VCP- and MCP-cycloadditions are also highly desirable.

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