Organic & Biomolecular Chemistry

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REVIEW

Beyond Geminal Diesters: Increasing the Scope of Metal-Mediated Vinylcyclopropane Annulations while Decreasing Pre-Activation

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The utilization of unactivated substrates in annulation reactions provides access to complex products without the need for subsequent removal of the activating group. Vinylcyclopropanes (VCPs) occur naturally in several monoterpene natural products, are an important building block for organic chemistry, and can be activated by electron withdrawing substituents directly on the cyclopropane to facilitate ring opening reactions. However, many VCPs that lack these activated groups remain reactive with several group 8, 9 and 10 transition metals, by alternative modes of activation, forming metallacycles. These useful intermediates produce annulation products in reactions with unsaturated π-units, providing rapid access to new carbocycles. Several formal cycloadditions that incorporate unactivated VCPs as substrates have been developed, including [5+2], [5+2+1], [5+1+2+1], [3+2], [3+2+1], [5+1], and others, using Rh, Ni, Ru, Ir, Fe and Co based catalysts. Mono- and polycyclic ring systems have been made using these methods with their utility demonstrated through the synthesis of complex natural products. This review will summarize the annulations of VCPs that lack geminal diesters, but retain reactivity via transition metal catalysts.

1. Introduction

Annulations are an important class of reactions due to the ubiquity of cyclic systems from materials to natural products and the development of new annulation reactions remains an active area in synthetic research. Concerted cycloadditions, such as the classic Diels-Alder reaction, are pericyclic reactions, and can be mediated by Lewis acids, heat, or light.[1] Transition metal catalysts are also used to catalyze formal cycloadditions by coordinating to unsaturated moieties such as alkenes or alkynes and accessing catalytic pathways not available to concerted processes.[1] An important building block for formal cycloadditions are vinylcyclopropanes (VCPs). VCPs can act as either 3 or 5 carbon synthons in annulations depending if the alkene moiety participates in the formation of the new ring. VCP reactivity originates from the large ring strain of the cyclopropanes (29.0 kcal/mol for unsubstituted cyclopropane) which facilitates ring opening.[2] Despite the large strain energy, cyclopropanes tend not to react under typical reaction conditions without additional activating groups to further enhance reactivity. At the same time the pendant alkene in VCPs readily coordinates to transition metal centers, which brings the metal within proximity of the cyclopropane, facilitating ring cleavage.[3, 4] VCPs have been well-studied
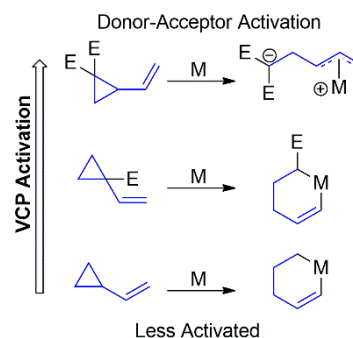

Fig. 1 Multiple types of VCP reactivity are possible depending on additional functionality.

building blocks with early examples demonstrating the ability to readily isomerize to cyclopentene, as well as coordinate with transition metals.[5-7] Depending on the additional functionality around the VCP, multiple types of reactivity are accessible for ring opening (Fig. 1).

VCPs with several strong electron withdrawing groups (EWGs) attached to the cyclopropane are considered donor-acceptor VCPs, or Tsuji-type VCPs due to Tsuji's pioneering work in this area.[3, 8, 9] Donor-acceptor VCPs have a vinyl group which acts as an electron donating group (donor), and typically geminal diesters as EWGs (acceptors).[8] Donor-acceptor VCPs typically behave like 1,3-dipoles as the EWG can stabilize a negative charge, while the vinyl group delocalizes the positive charge (Fig. 1). These VCPs are readily activated via transition metals such as palladium, or Lewis acids to form 1,3-dipoles capable of

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annulation or substitution reactions.[3, 4, 8-10] This review will focus on VCPs that are either unactivated, or have reduced activation with respect to geminal diester cyclopropanes, as this class of compounds offers tremendous potential in complex molecule synthesis.[3, 4, 11-17] As well, the unique reactivity of these VCPs will be demonstrated and current examples of their transition metal mediated formal cycloadditions with be provided.

Due to the lack of strong EWGs, unactivated VCPs generally do not form 1,3-dipoles in the presence of catalysts, such as palladium. Instead, in the presence of several other metals, VCPs undergo oxidative addition, forming a metallacycle which may initiate a subsequent formal cycloaddition.[18, 19] As stoichiometric activating groups are generally not required after the reaction and require subsequent removal, transformations that avoid prefunctionalization are ideal as additional tools to access complex molecular scaffolds.[20] As well, their differing reactivities provide alternate pathways to form carbocycles not accessible from donor-acceptor VCPs, such as the ability to utilize VCPs as 5 carbon synthons.

VCPs are known to participate in annulation reactions in the presence of transition metal catalysts. Donor-acceptor VCPs tend to undergo formal cycloadditions as 3 carbon synthons leaving the tethered alkene intact, usually with Pd or Ni catalysts.[8] Unactivated VCPs can be used as either 3 or 5 carbon synthons in Rh catalyzed annulations, and 5 carbon synthons for annulations with other metals such as Ru, Ir, Fe, Co and Ni.[21-25] Using these transition metal catalysts, unactivated VCPs have been demonstrated to undergo a variety of formal cycloadditions with alkenes, allenes, alkynes, and multicomponent reactions with CO. Pioneered by the Wender group, Rh catalysts have been the most developed catalysts for VCP annulations and new reaction and catalyst developments are frequently compared to their initial investigations of rhodium complexes. While other metals are currently less explored for VCP annulations, they provide complementary and alternative synthetic routes. New catalyst development for unactivated VCP annulations is still an important task to move away from rare and expensive metals such as Rh, ideally utilizing abundant first row transition metals.

1.1 Examples and synthesis of VCPs

VCPs exist in a variety of natural products, including monoterpenes such as 2-carene, thujene (α and β), and sabinene (Fig. 2). The synthesis of VCPs commonly relies on established reactions such as Simmons-Smith cyclopropanation, and the Wurtz reaction, such as VCPs **7**, **10** and **13** which were utilized by Wender for several VCP syntheses
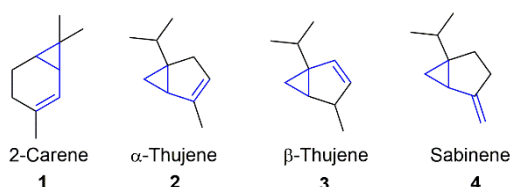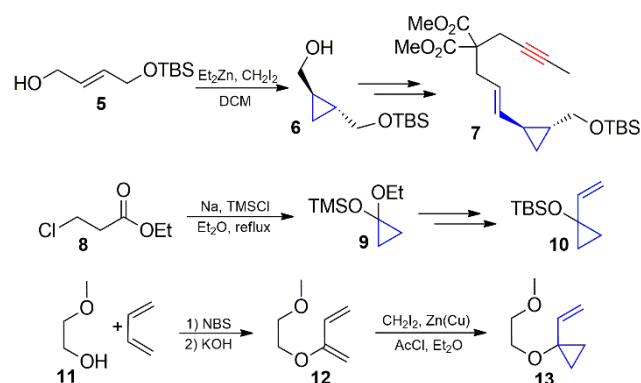
Fig. 2 VCP containing monoterpene natural products.

Scheme 1 Common strategies to access VCP substrates.

(Scheme 1).[26] Development of cyclopropanation reactions which lead to useful VCP moieties continue to be important as this functionality is present in natural products, and can be further reacted in complex molecule synthesis.[12, 27] Rearrangement-based cyclopropanation reactions developed in our lab have been used to produce VCPs intermediates in the synthesis of several sesquiterpenoid scaffolds.[28] This has led to our group's interest in VCPs as building blocks for complex frameworks. While important to the development of new VCP reactions, the synthesis of these building blocks have been summarized elsewhere.[12]

2. Rhodium Catalyzed VCP Annulations

2.1 [5+2] annulations

Generally, both the inter-and intramolecular [5+2] **annulations** follow the general mechanism shown in Fig. 3, with varying rate limiting steps, depending on the 2π-unit used. [18,19, 29]

2.1.1 Intramolecular [5+2] annulations. A seminal example of a [5+2] formal cycloaddition was reported by Wender and coworkers in 1995 (Scheme 2).[30] This was an intramolecular
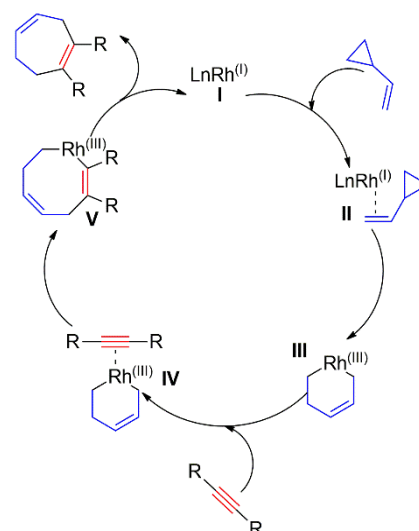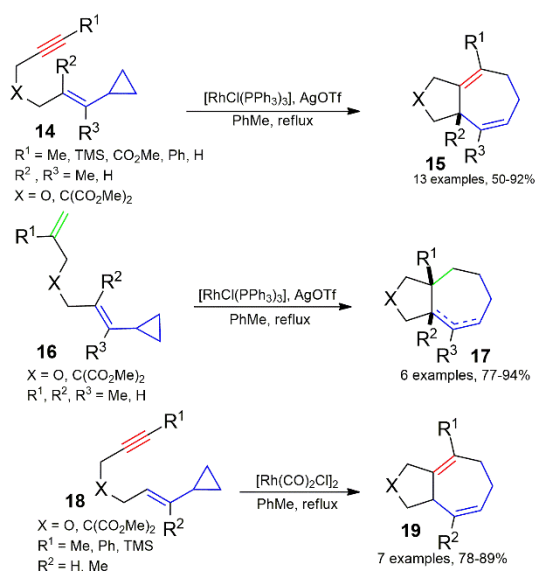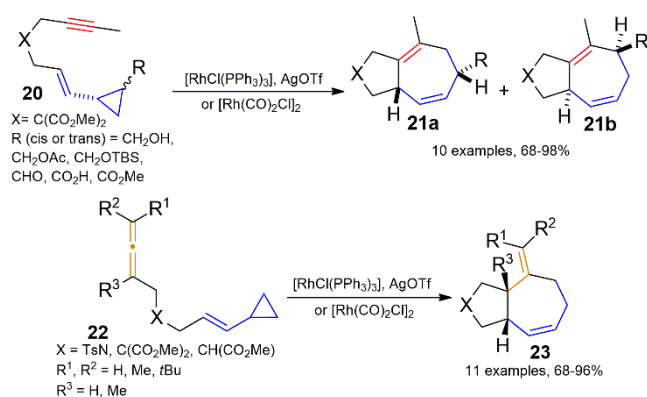
Fig. 3 General mechanism for the rhodium catalyzed [5+2] annulation, shown using an alkyne as a 2π-unit
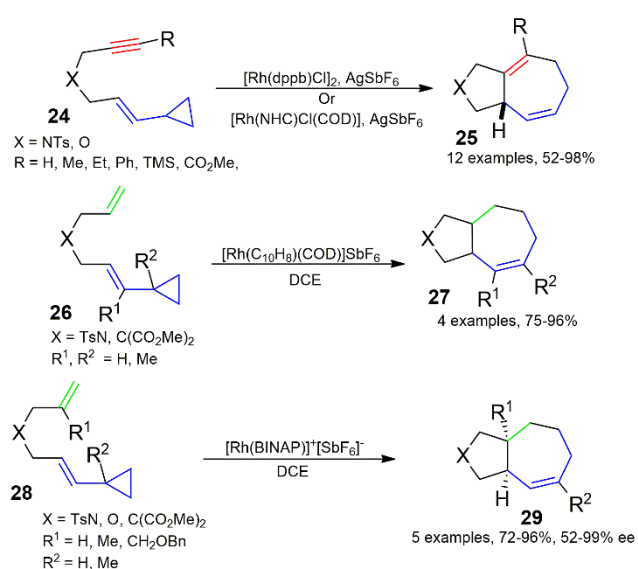
Scheme 2 Initial development of the intramolecular [5+2] VCP annulation.

Scheme 3 Further substrate development of the intramolecular [5+2] VCP formal cycloaddition.

Scheme 4 Further catalyst development of the intramolecular [5+2] VCP annulation.

reaction between a VCP and a tethered alkyne (**14**), generating a fused 5,7-bicyclic system (**15**) via the general mechanism highlighted in Fig. 3. This early example utilized [Rh(PPh$_3$)$_3$Cl] (Wilkinson's catalyst) and silver triflate to initiate this reaction. This example inspired developments in rhodium catalysis for VCP **annulations** that are still being investigated. The substrate scope was quickly expanded to include tethered alkenes such as **16** using the same conditions.[31]

The [5+2] formal cycloaddition was further improved by utilizing [Rh(CO)$_2$Cl]$_2$ (Scheme 2),[32] as this catalyst proved to work in milder conditions, combined with shorter reaction times and greater yields than Wilkinson's catalyst, as well as reacting with a greater variety of substrates without the need for silver activation. The improved reactivity for this catalyst is believed to be due to the lower ligand count, and reduced steric hindrance compared to Wilkinson's catalyst, both of which improve the catalyst's ability to cleave the cyclopropane ring, initiating the annulation.[32] Using DFT calculations the mechanism of an yne-VCP formal cycloaddition with [Rh(CO)$_2$Cl]$_2$ as a catalyst was investigated.[18] The Wender group continued to expand the substrate scope by investigating the

effects of cyclopropyl substituents on **20**, probing the regioselectivity using *cis* and *trans* VCPs, and exploring allenes as 2π-units (Scheme 3).[33-35]
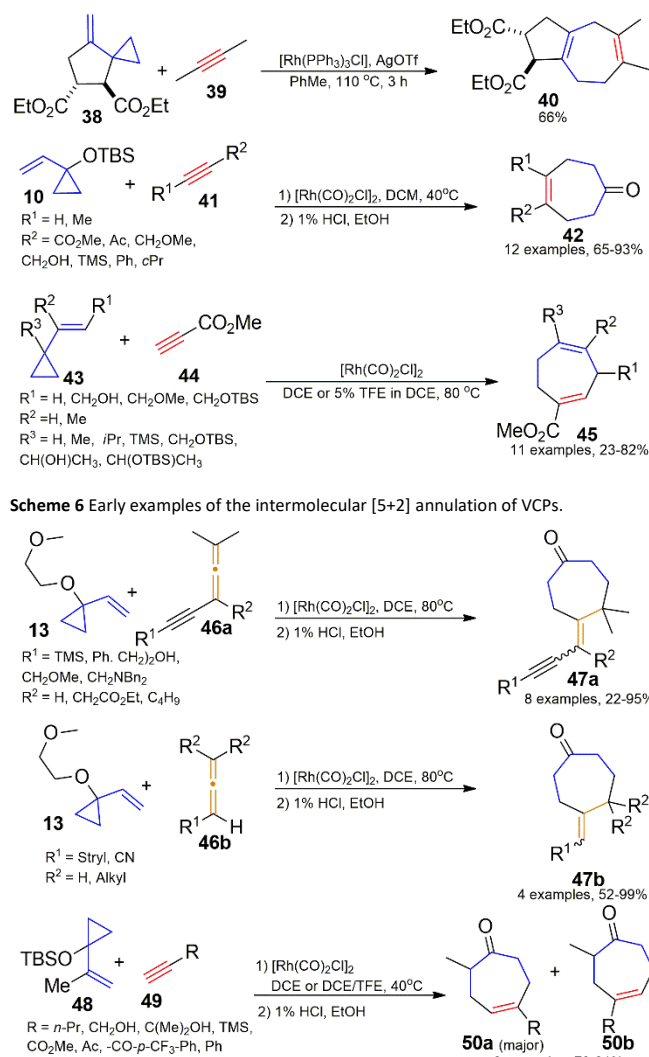
The Zhang group demonstrated a rhodium catalyst based on bisphosphine ligands which worked efficiently with tethered substrates such as **24**, allowing the reaction to occur at room temperature.[36] Other groups soon demonstrated additional catalysts which also proved to work at milder conditions, offering a wide variety of rhodium reagents capable of catalyzing this transformation (Schemes 4 and 5).[37-39] Complexes with chiral phosphine ligands were also examined for their ability to induce enantioselectivity for **28** which proved successful.[40, 41]

Recent developments of the intramolecular [5+2] formal cycloaddition have included expanding the scope of allene-VCP interactions (Scheme 5). Allenylcyclopropanes have similar reactivity as VCPs.[42, 43] The intramolecular [5+2] annulation between allenylcyclopropane **34** and its tethered alkyne resulted in **35** using either [Rh(CO)$_2$Cl]$_2$ or [Rh(CO)(dppp)Cl]$_2$ catalysts. Most allenylcyclopropanes contained allenyl-phenylsulfonyl moieties at the R^1 position, with one example containing a methyl group instead (Scheme 5).[42] Good yields were still obtained with the alkyl group, demonstrating that a sulfonyl group is not always required.[42] Recently, control of the VCP-allene annulation has been demonstrated where the cyclization of **36** yields **37**, a bridged decane skeleton, over the expected fused 5,7-bicycle, bringing additional diversity to this reaction.[44]
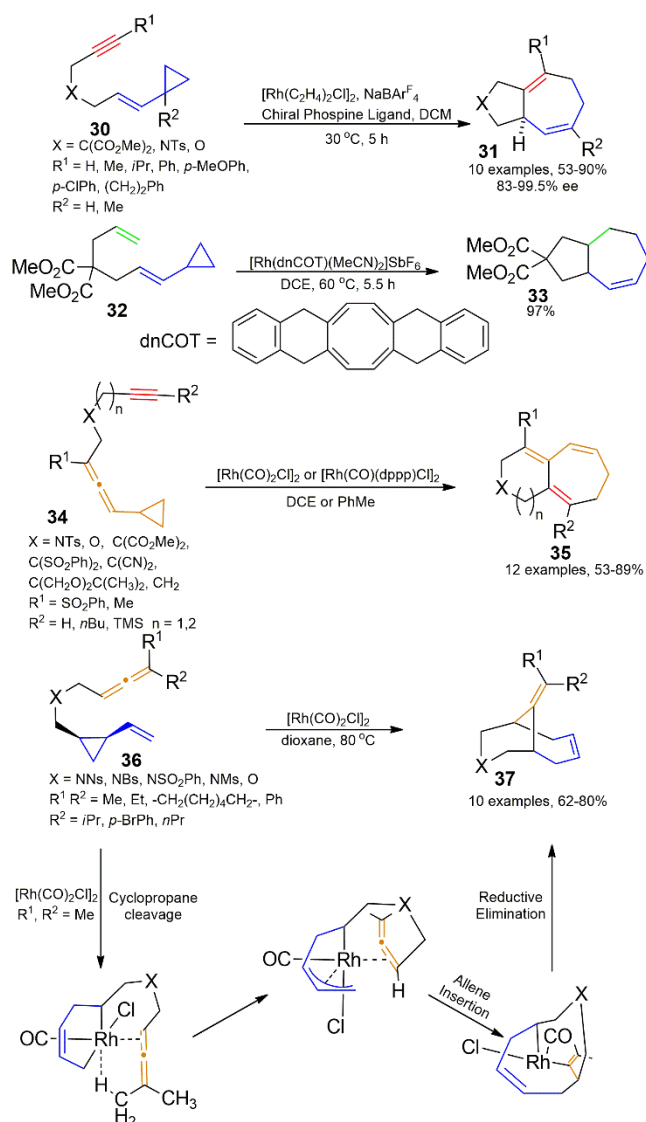
Scheme 5 Continued advancements in catalyst development and substrate scope for the intramolecular [5+2] annulation.

Scheme 6 Early examples of the intermolecular [5+2] annulation of VCPs.

Scheme 7 Inclusion of allenes in the intermolecular [5+2] substrate scope (top), and effect of alkenyl substituents on regioselectivity (bottom).

2.1.2 Intermolecular [5+2] Annulations. Homologous to the Diels-Alder reaction, intermolecular [5+2] formal cycloadditions are a powerful tool to form new rings from simple substrates. An early report of the transition metal catalyzed intermolecular [5+2] annulation of unactivated VCPs was a single example reported by the Meijere group (Scheme 6).[45] They used Wilkinson's catalyst with silver triflate, similar to Wender's intramolecular [5+2] formal cycloaddition, to induce a reaction between spirocyclic VCP **38** and alkyne **39**. Soon after, Wender reported the first general method for this reaction between **10** and **41**.[46] Emphasis was placed on the importance of the [Rh(CO)$_2$Cl]$_2$ catalyst for the annulation to occur, as well as the use of a siloxy substituted VCP which greatly enhanced the rate of the reaction. The mechanism of this transformation was investigated using DFT calculations and found that the active catalyst is Rh(CO)Cl and that the rate limiting step was the migratory insertion of the alkyne, similar to the intramolecular [5+2] annulation.[18]

Expansion of the scope of the VCP were made with the use of aliphatic substitutions on the cyclopropane ring (Scheme 6). [26, 47] Most early examples of VCPs for this reaction included heteroatom substituents at the 1-position of the VCP, such as alkoxy or siloxy groups (eg. **13** Scheme 1, 7, etc.). However, it was later found that bulky alkyl groups at the same position were also tolerated such as those seen in VCPs **43**.[47] It was determined that these substituents influenced the correct conformation of the required transition state.[19] Through hyperconjugation or resonance, bulky aliphatic and heteroatom substituents reduce the energetic barrier of the alkyne migratory insertion.

Attempts to expand the substrate scope of the intermolecular [5+2] formal cycloaddition succeeded with the use of allenes (eg. **46**) which were specifically prepared with additional coordinating groups (Scheme 7).[48] It was found that the allene must have a pendant ligand, such as an alkyne, styrl, or cyano group to avoid coordination of the allene to the rhodium center. As well, methyl substituted allenes opposite of the coordinating group had much greater yields than those without. A

computational study later found that without the added methyl groups on allenes **46** (Scheme 7), the allene dimerizes with the rhodium catalyst in a competing pathway with the [5+2] product, forming a stable rhodium complex, effectively poisoning the catalyst.[49] The addition of the methyl groups to the allene made this undesirable pathway much more energetically demanding, while the [5+2] pathway remained mostly unaffected.

The difference of reactivities between allenes, alkynes, and alkenes in [5+2] **annulation**s with VCPs were investigated using DFT calculations.[29] This study helped confirm the experimental observation that alkenes are the least reactive of these π-systems, for both intra- and intermolecular [5+2] formal cycloadditions using $[Rh(CO)_2Cl]_2$ as a catalyst. The difference originates from the increased energetic barriers for the reductive elimination step (Fig. 3, step **V**) which was calculated to be 29.3 kcal/mol for ethylene, compared to 14.5 kcal/mol and 20.0 kcal/mol for acetylene and allene, respectively. This changes the rate limiting step from migratory insertion (Fig. 3, step **IV**) for alkynes to reductive elimination for alkenes (Fig. 3, step **V**). The authors hypothesized that the difference of energies in this step arises from ethylene's lack of a residual π-bond after migratory insertion to stabilize the reductive elimination transition state. Allenes and alkynes can undergo migratory reductive elimination, while the alkene is forced to undergo a more demanding reductive elimination which is not stabilized by a π-system and an energetically costlier $C(sp^3)$-$C(sp^3)$ bond is formed. Despite this difference of reactivity, intramolecular **annulation**s between tethered alkenes and VCPs using rhodium complexes have been well studied in both [5+2] and [3+2] reactions under more forcing conditions. However, an intermolecular [5+2] **annulation** between an unactivated VCP and alkene has yet to be reported, likely due to the high energetic cost associated with this transformation.

Regioselectivity of the intermolecular [5+2] **annulation** of VCPs was further explored by investigating the effects of substituents on the alkene (Scheme 7).[50] It was found that the preference for the formation of the distal products **50a** could be reduced by adding substituents to the internal position of the alkene (**48**), while substituents at the terminal position favoured only the distal product.[50] A new application for the reaction was found in the preparation of vinyl ketone **52** for a Nazarov cyclization, creating a new strategy for the formation of polycyclic frameworks (Scheme 8).[51] New catalysts were also developed to work in milder conditions, with greater control over regioselectivity.[39, 52, 53] Several catalysts have recently been investigated in a computational study to compare their differences in efficiencies for the [5+2] formal cycloaddition.[54] The transition states of the reaction were all found to be similar, despite different catalysts being used, and an induced fit model was applied to rationalize this result. The model suggested that the catalysts which could conform themselves around the rigid transition state of the VCP is the most efficient, providing a model to enhance future catalyst performance.
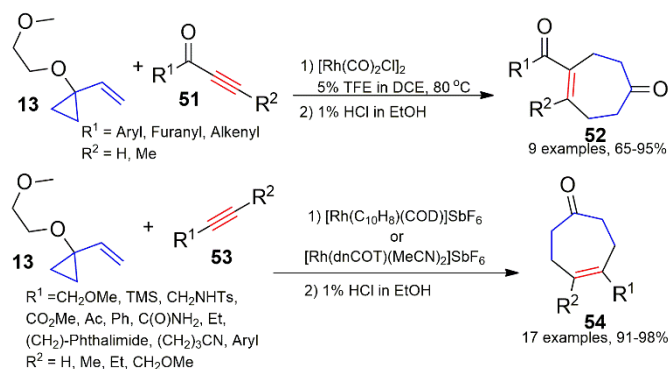
Scheme 8 Utilization of the [5+2] annulation for the preparation of vinyl ketones for Nazarov cyclizations (top), and further improvements in catalyst development (bottom).
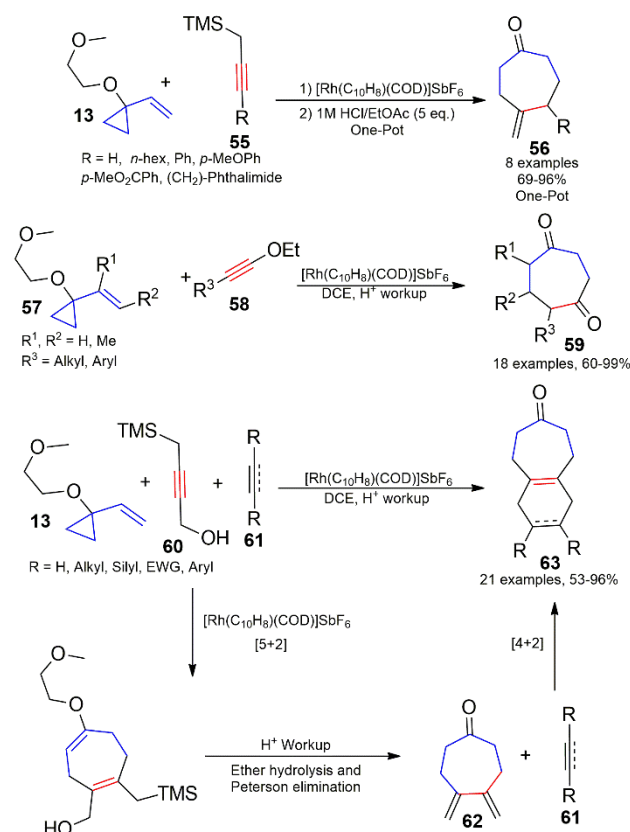
Scheme 9 Substrate improvement for the intermolecular [5+2] annulation via chemical equivalency of allenes, ketenes, and butatrienes.

Expansion of the substrate scope has recently been established by the Wender group. Using several strategies, they have been able to use synthetic equivalents of substrates such as allenes, for the intermolecular [5+2] **annulation** (Scheme 9).[55] One of the strategies relies on propargyltrimethylsilanes (**55**) which act as allene equivalents, but are much more convenient to use since they are liquids at room temperature, and do not require additional coordinating groups. *In situ* removal of the TMS group gives the synthetically equivalent allene product.

Recently, the Wender group has shown that ynol ether **58** can act as a ketene equivalent, affording enedione **59** (Scheme 9). [56a] The regioselectivity of this reaction was also explored by
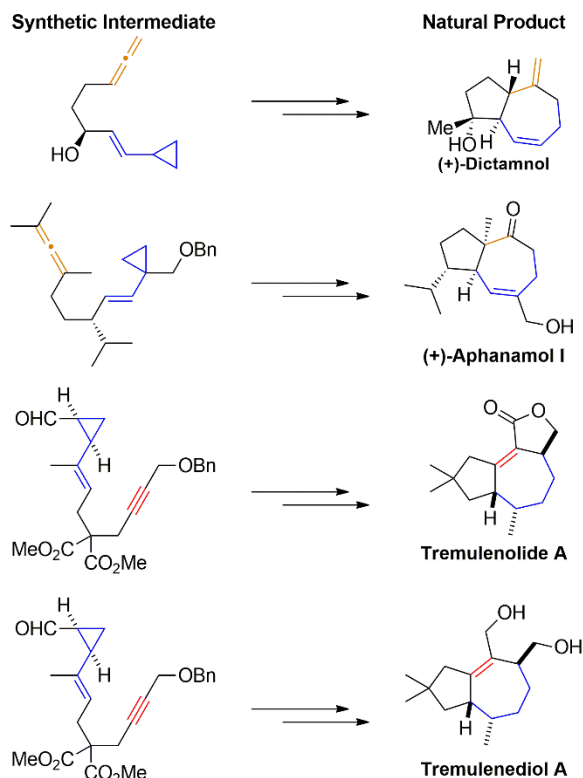
Fig. 4 Natural product syntheses using the rhodium catalyzed [5+2] formal cycloaddition of VCPs.

determining the effect of methylsubstituents on VCP **57**. Another strategy is the use of alkyne **60** as a butatriene equivalent.[56b] **60** undergoes the expected [5+2] formal cycloaddition with **13**, and then 1,4-Peterson elimination rapidly occurs giving intermediate diene **62**. This compound can then react with either an alkyne or alkene, giving **63** promoted
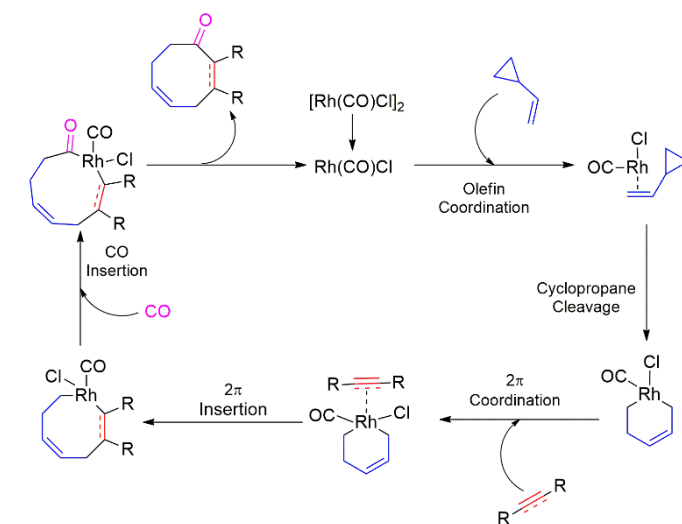

Fig. 5 A generic mechanism of the [5+2+1] formal cycloaddition of VCPs.

by either a Diels-Alder or rhodium catalyzed formal cycloaddition. This strategy gave tricyclic products which could be further functionalized via oxidative aromatization. Demonstrating the importance of the [5+2] VCP **annulation**, various natural products have been synthesized using this reaction as a key step (Fig. 4).[11, 57-59]

2.2 Multicomponent [5+2+n] annulations

Under an atmosphere of CO, a multicomponent **annulation** can occur during the [5+2] VCP formal cycloaddition, where CO can insert into the reaction intermediate providing either a 3- or 4-component product (Fig. 5).[48, 60, 61] Initial studies found [Rh(CO)$_2$Cl]$_2$ to be a suitable catalyst for the intermolecular multicomponent reaction, of alkynes **64** or **70** and allene **68**
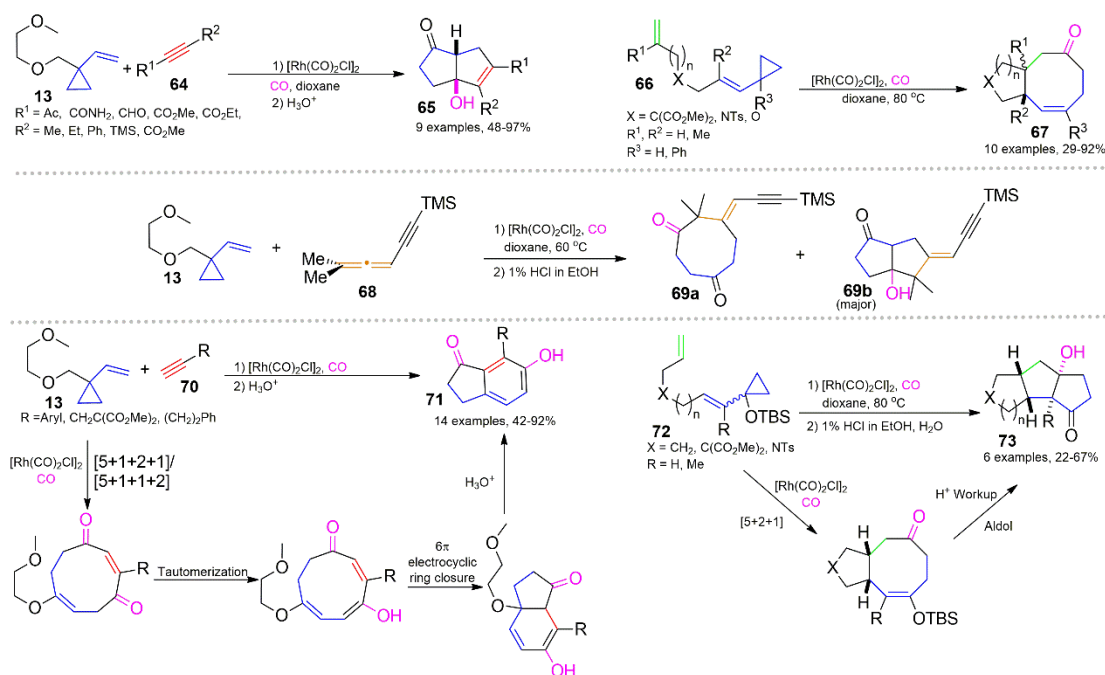
Scheme 10 Rhodium catalyzed multicomponent [5+2+n] annulations of VCPs.

Fig. 6 Natural product syntheses using the [5+2+1] formal cycloaddition of VCPs.
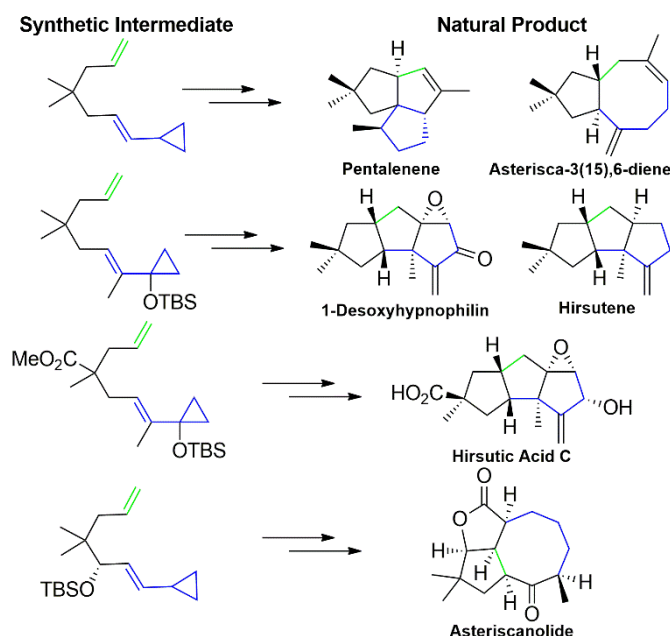
with VCP **13** (Scheme 10).[48, 60, 61] Self cyclization of these rings readily occurred providing bicyclic systems **65**, **71**, **69b** as the major products. The mechanism of the intermolecular 4-component **annulation** was recently investigated by the Ylijoki group.[62] Using DFT calculations, evidence for two different mechanistic pathways, [5+1+1+2] and [5+1+2+1], were identified. These pathways differed only by 2 kcal/mol, and both resulted in **71** where the original [5+1+2+1] pathway proposed by Wender was slightly energetically preferred.

The Yu group began to investigate the intramolecular [5+2+1] reaction using tethered alkenes **66** and **72** as the unsaturated π-unit (Scheme 10).[63] They further studied substituent effects, tether lengths, and the formation of tricyclic systems through self cyclization or placement of the cyclopropane group on another ring prior to the cyclization reaction.[63-66] Interestingly, the addition of CO to the [5+2] formal cycloaddition makes it energetically more favourable for alkenes since CO inserts between the alkene and Rh center. This allows for reductive elimination to readily occur due to the preferential formation of an energetically favourable $C(sp^2)$-$C(sp^3)$ bond over a $C(sp^3)$-$C(sp^3)$ bond.[66] Using their elegant strategy for the formation of 8 member rings and tricyclic systems, the Yu group demonstrated the usefulness of these reactions by undertaking several formal and total syntheses of natural products (Fig. 6).[66]

2.3 [3+2] annulations

The specific placement of the tethered 2π-unit on a VCP can force conditions to favour a [3+2] formal cycloaddition as the tethered unit must approach the VCP on the opposite face of the vinyl group, preventing the formation of a bond between the 2π-unit and the VCP alkene (Fig. 7).[67-69] The Yu group were the first to report a [3+2] formal cycloaddition of an unactivated
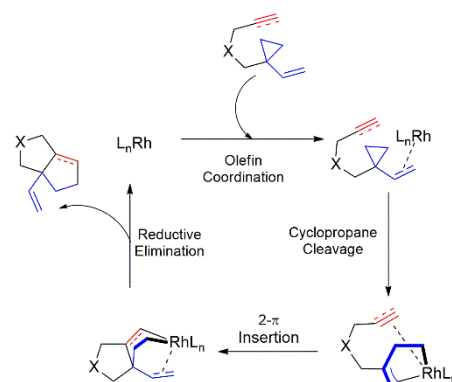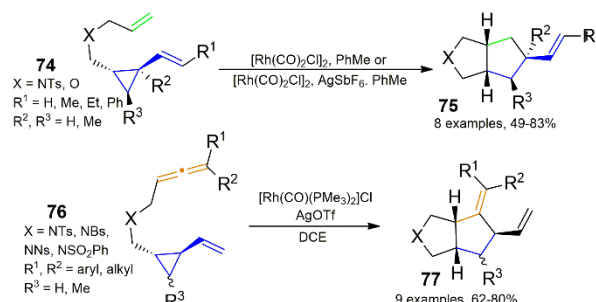

Fig. 7 General mechanism of the rhodium catalyzed [3+2] annulation of VCPs, using a 1-ene/yne-VCP as an example.

Scheme 11 Intramolecular [3+2] formal cycloadditions with trans-2-ene/allene-VCPs.
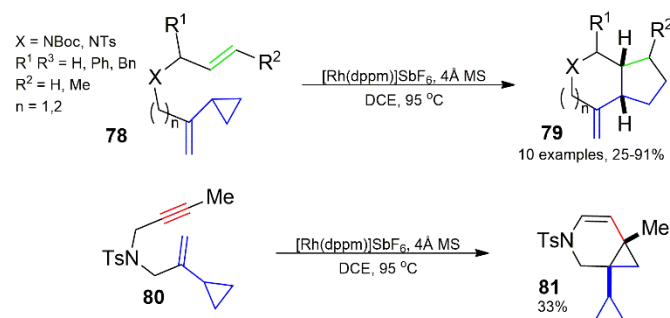
Scheme 12 Intramolecular [3+2] annulations with α-ene-VCPs.

VCP (Scheme 11).[67a] Their example was an intramolecular **annulation** with an alkene producing a bicyclic system, which left the vinyl tether intact. The strategic difference between the intramolecular [5+2] and [3+2] **annulation**s was the placement of the tethered 2π-unit with respect to the VCP. For example, if a tethered alkene is placed in a trans-2-ene-VCP (**74** and **76**, Scheme 11), α-ene-VCP (**78** and **80**, Scheme 12), or 1-ene-VCP (**82**, **84**, **86** and **88**, Scheme 13) position a [3+2] formal cycloaddition can occur, while if the alkene placed in a β-ene-VCP, or cis-2-ene-VCP configuration a [5+2] can take place. The [3+2] **annulation** was found to works with several substitution patterns, and asymmetric and multicomponent versions were also reported.[67, 69-72]

Initially, the Yu group screened [Rh(CO)₂Cl]₂ and Wilkinson's catalyst under various conditions for the [3+2] formal cycloaddition of trans-2-ene-VCP **74**, and found [Rh(CO)₂Cl]₂ to efficiently catalyze this reaction (Scheme 11).[67a] This
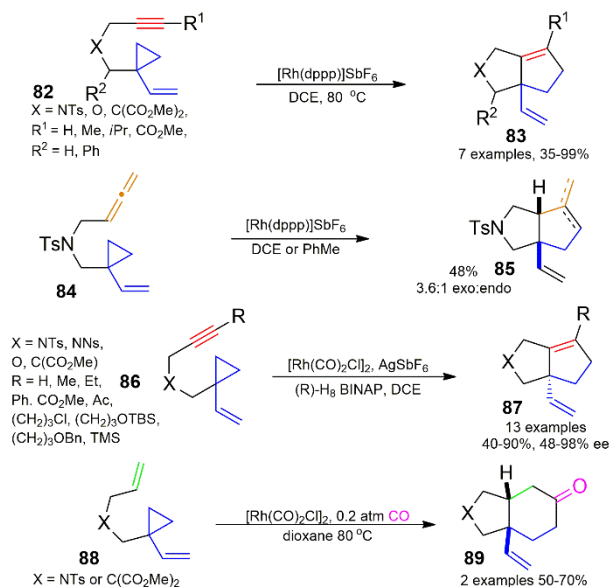
Scheme 13 Intramolecular [3+2] and [3+2+1] annulations using 1-ene/yne/allene-VCPs.

configuration has recently been expanded to include *trans*-2-allene-VCPs (**76**) using [Rh(CO)(PMe$_3$)$_2$]Cl as a catalyst.[67b]

Optimization of the [3+2] **annulation** of α-ene-VCPs **78** and **80** (Scheme 12) found [Rh(dppm)]SbF$_6$ to be the most effective catalyst.[71] However, only α-ene-VCPs underwent the [3+2] formal cycloaddition and when yne-VCP **80** was reacted under identical conditions only the cyclization product **81** was formed. [Rh(dppp)]SbF$_6$ was an exceptionally good catalyst for 1-ene-VCPs, 1-yne-VCPs, and 1-allene-VCPs (Scheme 13).[71, 72] A DFT study found that [Rh(dppp)]SbF$_6$ inhibited the β-hydride elimination product loss pathway, to only give the [3+2] **annulation** product, making it more efficient than other rhodium catalysts.[68] The Yu group then developed the first asymmetric [3+2] **annulation** of 1-yne-VCPs using chiral diphosphine ligands in the presence of [Rh(CO)$_2$Cl]$_2$ and AgSbF$_6$ to generate a chiral rhodium(I)-phosphine catalyst, which gave product **87** with enantioselectivites ranging from 48-98%.[69]

A multicomponent [3+2+1] formal cycloaddition was developed with [Rh(CO)$_2$Cl]$_2$ as a catalyst (Scheme 13).[70] Using 1-ene-VCP **88**, the fused bicycles **89** was effectively synthesized under an atmosphere of CO, and examples also exist for 1-yne-VCPs. A testament to this reaction's utility, several natural product syntheses have been completed using this **annulation** (Fig. 8).[11, 70, 73, 74] Thus far there are no examples of intermolecular [3+2] formal cycloaddition reactions using unactivated VCPs as substrates with transition metal catalysts. This is likely due to the mechanism of the [3+2] **annulation** which requires the tethered 2π-unit to be opposite of the π-allyl intermediate. [67] This configuration prevents formation of C-C bonds between the VCP alkene and tethered 2π-unit. Therefore, without a tethered π-unit which forces the required intermediate geometry, a [5+2] **annulation** will occur preferentially. In contrast to the lack of intermolecular [3+2] **annulation**s of unactivated VCPs, many examples exist in the literature for donor-acceptor type VCPs which undergo a 1,3-dipole
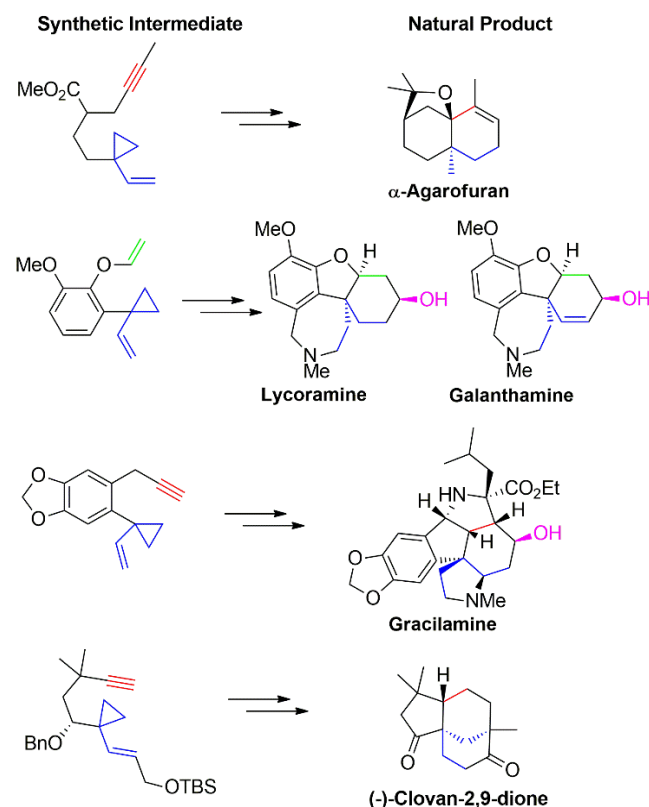
Fig. 8 Natural product syntheses using the [3+2+1] annulation of VCPs
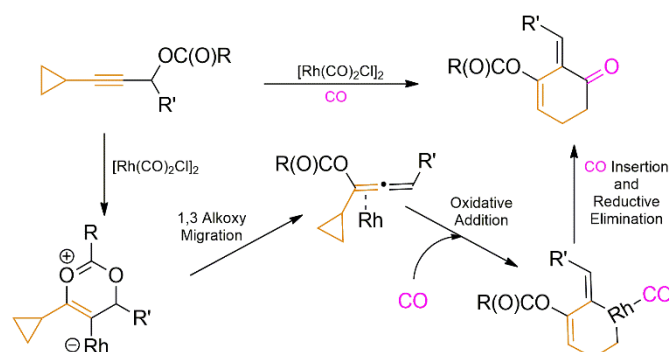
Fig. 9 General mechanism of the [5+1] annulation of *in situ* generated allenylcyclopropanes from alkynylcyclopropanes via a 1,3 alkoxy migration.
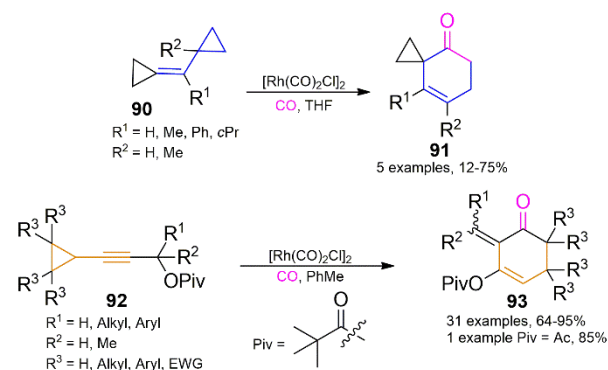
Scheme 14 Early development of the rhodium catalyzed [5+1] formal cycloaddition of VCPs and *in situ* generated allenylcyclopropanes from alkynylcyclopropanes.

intermediate, favouring the [3+2] formal cycloaddition with palladium-based catalysts.[3, 4, 9, 12]

2.4 [5+1] and [7+1] annulations
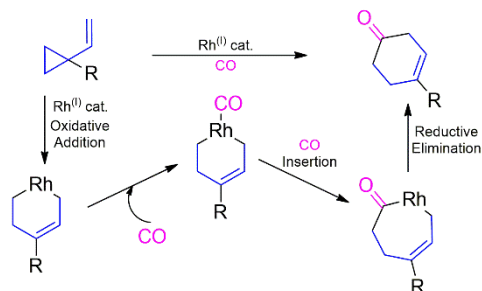
Fig. 10 General mechanism of the rhodium catalyzed [5+1] annulation of VCPs.
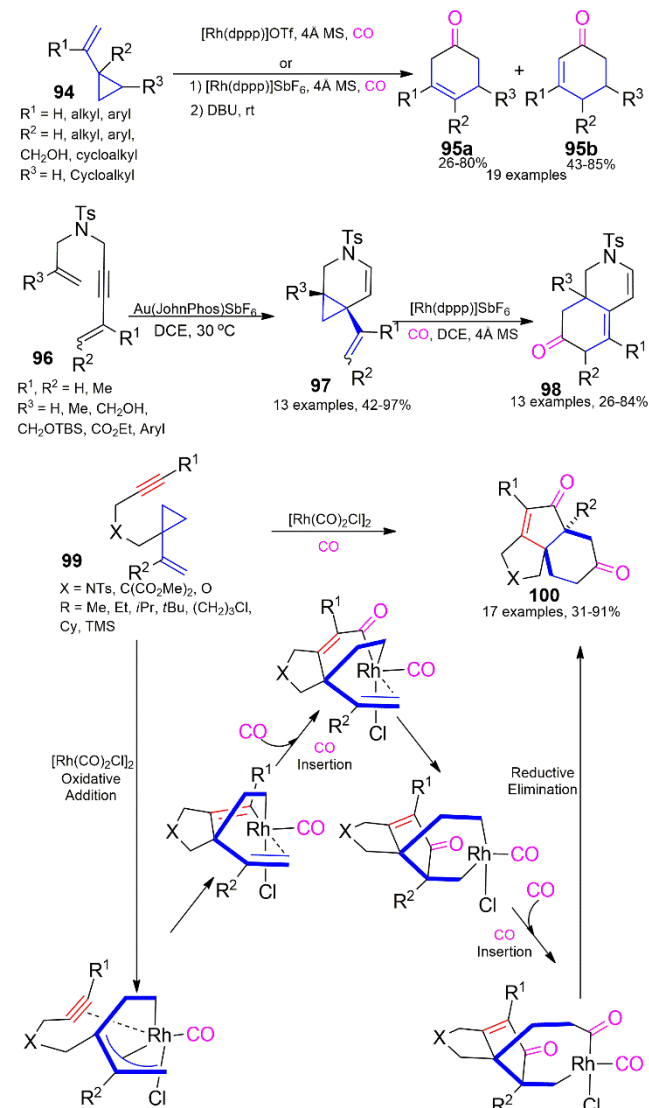
Scheme 15 The direct rhodium catalyzed [5+1] and the [5+1]/[2+2+1] annulation of VCPs.

While there is precedent for the [5+1] **annulation** between VCPs and CO with either Fe(CO)$_5$ and Co$_2$(CO)$_8$ in catalytic or stoichiometric amounts, this reaction has only been recently developed to work with rhodium complexes.[6, 15, 75, 76] An early example of this formal cycloaddition was reported by Meijere, who utilized either [Rh(CO)$_2$Cl]$_2$ or Co$_2$(CO)$_8$ under a CO atmosphere. However, the alkylidene cyclopropane-VCP **90** was

required for the rhodium catalyst to work (Scheme 14).[77] Other
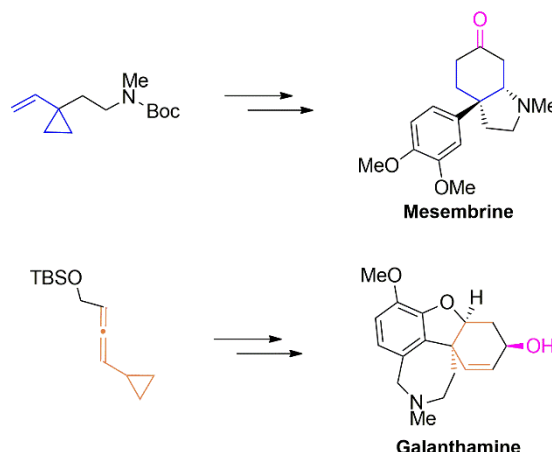
Fig. 11 Natural product syntheses using the rhodium catalyzed [5+1] annulation of VCPs.
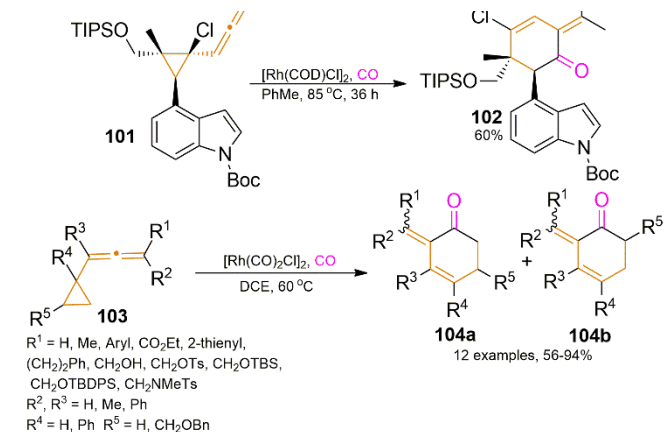
Scheme 16 Direct rhodium catalyzed [5+1] annulation of allenylcyclopropanes.

developments from the Tang group utilized the *in situ* formation of allenylcyclopropanes from alkynylcyclopropane **92** (Scheme 14), which then cyclized with CO to form the corresponding 6-member rings (Fig. 9).[78, 79] A general method was soon developed by the Yu group for the direct [5+1] **annulation** of VCPs which used [Rh(dppp)]SbF$_6$ or [Rh(dppp)]OTf as catalysts, (Fig. 10).[80] This method proved to tolerate less functionalized VCPs such as **94**, and provided a direct route to cyclohexanones **95** (Scheme 15). The regioselectivity of this method was also explored through VCP **94** which yielded a mixture of products with limited regioselective control.[80] This reaction was then utilized for the total synthesis of (±)-mesembrine, in only 4 steps from the N-Boc protected VCP, with a total yield of 18% (Fig. 11).[81] A two-step strategy to form tetrahydroisoquinolinones using a [5+1] annulation has recently been reported.[82] A gold catalyzed cycloisomerization of enyne-ene **96** was used to afford the requisite bicyclic-VCP **97**, followed by the rhodium catalyzed [5+1] formal cycloaddition under a partial atmosphere of CO, to give the desired tetrahydroisoquinolinone framework **98** with a quaternary center at the R^3 position (Scheme 15).

A [5+1]/[2+2+1] formal cycloaddition of VCPs producing angular tricyclic products was also developed by the Yu group,
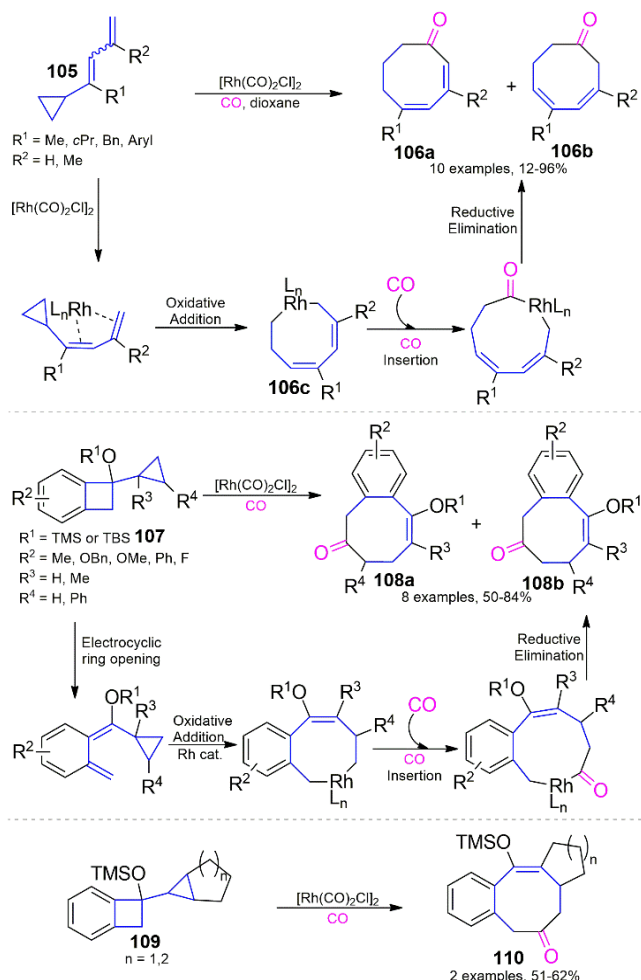
Scheme 17 The rhodium catalyzed [7+1] formal cycloaddition of diene-VCPs.

with [Rh(CO)₂Cl]₂ as a catalyst (Scheme 15).[83] The [3+2+1] annulation was a competing pathway for this reaction, and substituents on the VCP alkene resulted in a higher yield for the [3+2+1] products. A variety of substituents on the tethered alkyne were tolerated, and when sterically bulkier substituents were used at this position the formation of tricycle product **100** was favoured. As opposed to methods which rely on the *in situ* formation of an allenylcyclopropane, several studies have examined the direct [5+1] annulation of allenylcyclopropanes (Scheme 16). The first example was reported by Tang, where the highly functionalized core of **102** was produced from its resulting allenylcyclopropane, **101**, using [Rh(COD)Cl]₂.[84] A general method using allenylcyclopropanes was then reported by the Yu group, with [Rh(CO)₂Cl]₂ as a catalyst, which was used in the formal synthesis of (-)-galanthamine (Fig. 11).[85] They reported good functional group tolerance, and the ability to control configuration of the resulting substituted alkene **104** to favour the *E*-conformation when aryl groups were attached to allene **103**.

[7+1] annulations of diene-VCPs can be considered to have similar reactivity as [5+1] annulations.[86] The [7+1] formal cycloaddition requires an additional vinyl group, forming a diene on the cyclopropane moiety. This entire functionality can then act as a 7-carbon synthon in the annulation, forming an 8-member carbocycle (Scheme 17). While the self cyclization of

the 7-carbon building block is possible, the formation of the resulting C(sp³)-C(sp³) bond (derived from reductive elimination of **106c**) is energetically demanding.[86] Therefore the migratory insertion of a CO unit is preferred leading to the reductive elimination and formation of the less demanding C(sp²)-C(sp³) bond, forming an 8-membered ring. Initial studies of this reaction resulted in a general method for the formation of 8-member rings **106a** and **106b**.[86] To achieve good to moderate yields the substituents on the internal vinyl group were restricted to aryl groups. A recent study used cyclopropyl-benzocyclobutene **107** as a starting material which undergoes a thermally allowed electrocyclic ring opening to give an intermediate diene-VCP.[87] In turn, this diene-VCP then undergoes a [7+1] annulation with CO, to give **108**, and when R³ has a substituent **108a** is slightly favoured over **108b**. This method was applied to fused 3,5- and 3,6-bicycles **109** to form tricyclic product **110**. Unfortunately, this method did not allow for substitution on the cyclobutene ring, which the authors hypothesized was due to unfavourable sterics. Both examples of [7+1] annulations relied on [Rh(CO)₂Cl]₂ as a catalyst.

2.5 Additional annulations and cyclizations

Several additional rhodium catalyzed formal cycloadditions for unactivated VCPs exist which are unique and do not fit into the categories listed *vide supra*. The first of these reactions is the [3+3+1] annulation,[88] which involves bisvinylcyclopropanes **111** and **113**, where the two cyclopropanes units act as 3-carbon synthons, and CO acts as a one carbon unit (Scheme 18). Using [Rh(COD)Cl]₂ under an atmosphere of CO, the reaction tolerated several heterocyclic substituents in the 6-member ring, and a few minor substitutions on the fused cyclopropane ring. Another interesting transformation is the cycloisomerization of allenylcyclopropanes with alkenes from the Mukai group (Scheme 19).[44] The expected [5+2] product is not formed when tethered alkenes are used, and instead the fused 5,6-bicyclic compound **116** is produced which is decorated with two methyl groups and has three contiguous stereocenters that are all *cis* to each other. An additional unique
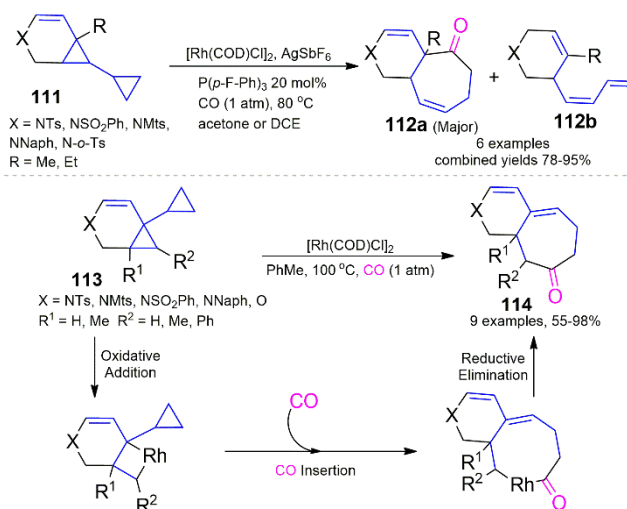
Scheme 18 The rhodium catalyzed [3+3+1] formal cycloaddition of bis-VCPs.

annulation is the intramolecular [5+2-2] formal cycloaddition of
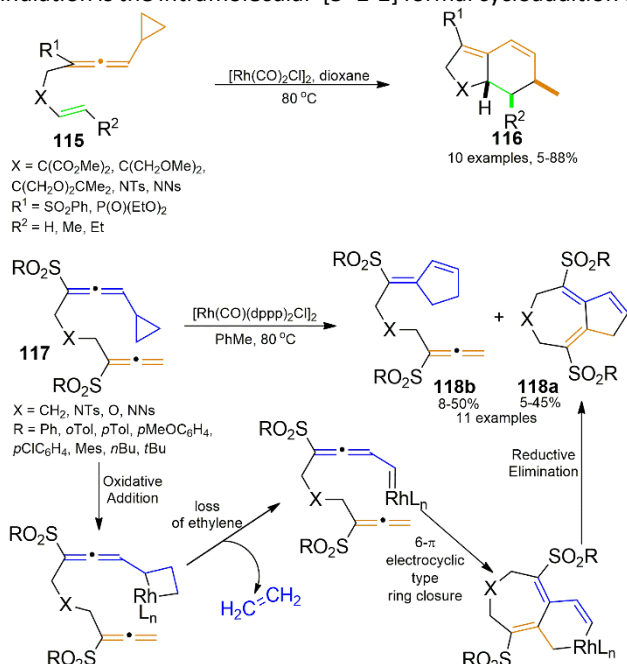
Scheme 19 Rhodium catalyzed cyclizations and [5+2-2] annulations of allenylcyclopropanes.

allenylcyclopropanes with tethered allenes which forms a fused 7,5-ring system **118a**, in which the heteroatom substituent is in the 7-member ring, opposite of what is normally observed for [5+2] formal cycloadditions of VCPs (Scheme 19).[89] Precursors with deuterium labelling on the cyclopropane ring helped provide evidence that the cyclopropane group forms ethylene and leaves during the formal cycloaddition, as the annulation products were found to have no deuterium, while the self-cyclization products **118b** remained deuterated, following the proposed mechanism shown in Scheme 19. Sulfonyl or phosphonate groups were required on the internal position of at least one of the allenes during this reaction to achieve good yields, limiting the substrate scope of this reaction.

3. Other Metals Used for Annulations

3.1 Palladium

Thus far there are no literature examples that show unactivated VCPs undergoing annulations with palladium based catalysts.
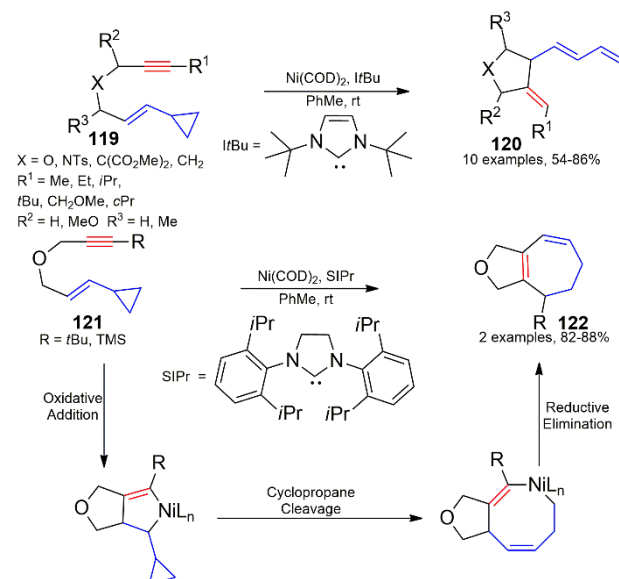
Scheme 20 Nickel catalyzed cyclization or formal cycloaddition of VCPs.

There are extensive examples of activated, donor-acceptor VCPs undergoing formal cycloadditions (and other reactions) with palladium catalysts, since this metal is known to stabilize the π-allyl intermediate of the 1,3-dipole for donor-acceptor VCPs.[3, 8] Despite this, palladium is known to react with unactivated VCPs in other reactions such as hydrogenation, hydrochlorination and isomerization reactions.[90, 91]

3.2 Nickel

Nickel catalysts have been demonstrated to be effective for formal cycloadditions of Tsuji-type VCPs,[3] however, their use as catalysts for unactivated VCPs remains limited to only a few examples (Scheme 20).[25] The Louie group demonstrated the ability of nickel catalysts to promote a formal cycloaddition of unactivated VCPs. The [5+2] annulation product **122** was controlled for when slightly bulkier N-heterocyclic carbene (NHC) ligands were utilized, over less sterically demanding NHCs which promoted the formation of cycloisomerization product **120**. The mechanism of this reaction was later studied computationally by the Houk group,[92] which provided evidence that the nickel catalyst energetically preferred the formation of a metallacycle with the alkyne and alkene of the VCP as the first step in the mechanism followed by cyclopropane cleavage

Fig. 12 General mechanism of the ruthenium catalyzed [5+2] annulation of VCPs.

affording an 8-member metallacycle (Scheme 20). This is unique compared to the mechanism for rhodium [5+2] annulations (Fig. 3), and similar to the mechanism employed by ruthenium catalysts (Fig. 12).[93] The competition between β-hydride elimination and reductive elimination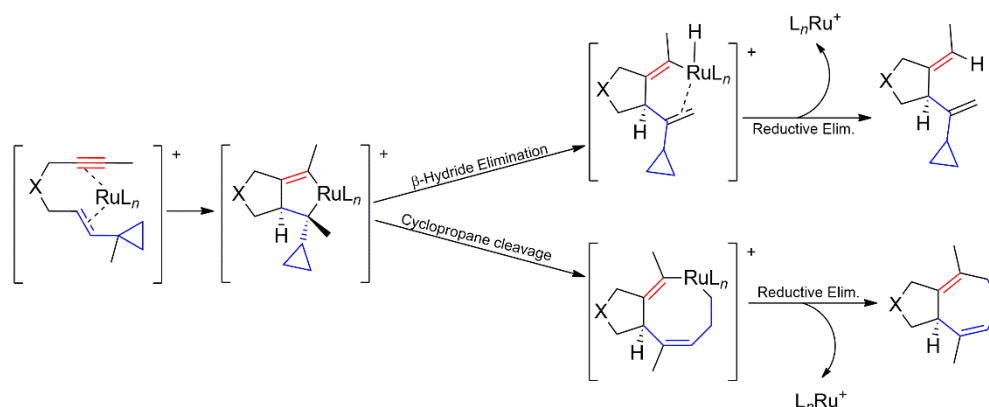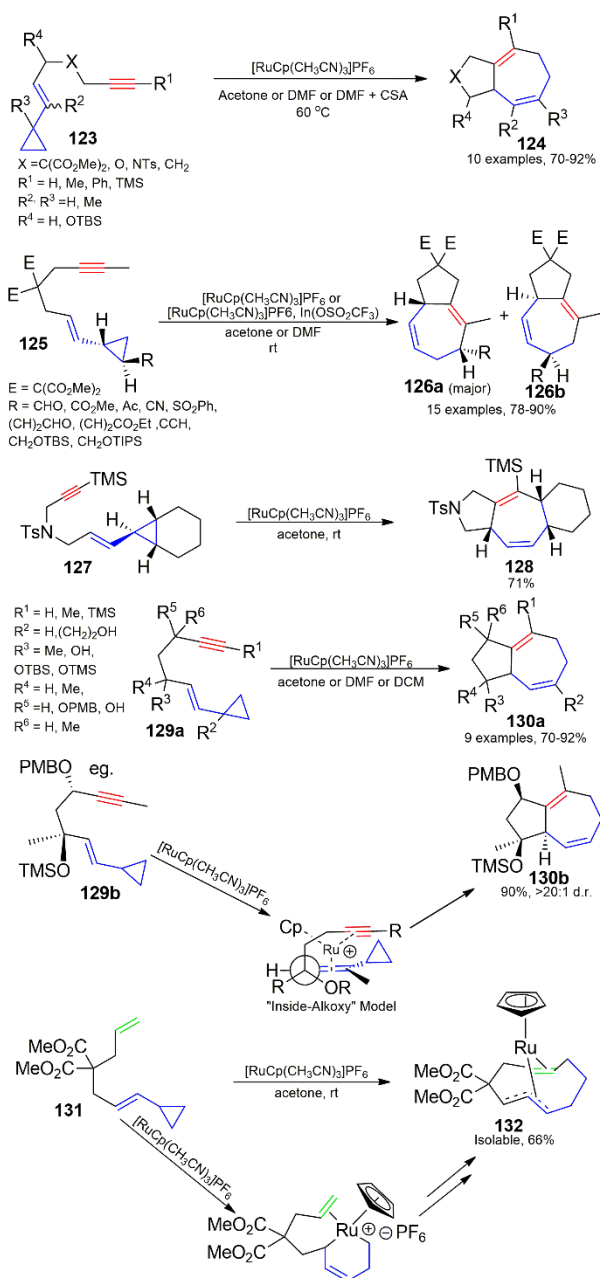 of the resulting intermediate determined whether **120** or **122** was formed. The difference in NHC ligand reactivity was rationalized by the slightly differing steric environments created by the ligands.

3.3 Ruthenium

The Trost group reported the first use of a ruthenium catalyst capable of initiating an intramolecular [5+2] formal cycloaddition between unactivated VCPs and alkynes (Scheme

21).[94] The catalyst used was [RuCp(CH3CN)3]PF6, which proved to work under mild conditions with good yields. Investigation of the regioselectivity of the cyclopropyl opening was performed, and the majority of the substituents on the cyclopropyl ring were found to favour product **126a** except for those with bulky silyl groups which favoured **126b**.[95] This regioselectivity was opposite to that observed by the Wender group with [Rh(CO)2Cl]2 as a catalyst, demonstrating that the ruthenium catalyzed annulation is complementary to rhodium reactivity. A reaction that demonstrated the utility of the ruthenium catalyzed formal cycloaddition was the construction of several tricyclic cores, such as the conversion of **127** to **128**.[96]

Another study by the Trost group examined the diastereoselectivity of the ruthenium [5+2] annulation (Scheme 21).[97] Asymmetric yne-VCPs **129** were prepared, and in all cases high diastereoselectivity from the existing stereogenic centers and the newly installed chiral center at the bridgehead hydrogen was observed, and greater diastereoselectivity was achieved when bulky substituents were placed on the substrate. Interestingly, the favoured diastereomer consistently contained a bridgehead hydrogen atom *trans* to the hydroxyl group. This was rationalized mechanistically by the inside-alkoxy model which describes the antibonding orbital of the alkoxy group destabilizes the transition state, while the antibonding orbitals of the C-H or C-R bond are stabilizing, and thus the *trans* relationship is observed.[97]

Attempts to expand the substrate scope beyond alkynes to other π-systems have not been reported in the literature. The Trost group reported the isolation of a novel ruthenium complex from the attempted intramolecular formal cycloaddition of an alkene with a VCP in the presence of their [RuCp(CH3CN)3]PF6 catalyst.[98] Complex **132** helped shed light on the difference of reactivity between ruthenium and rhodium annulations. While intramolecular formal cycloadditions between alkenes and VCPs are possible with rhodium catalysis, the ruthenium catalyst has poor coordination with alkenes, and a ruthenacyclohexene intermediate forms instead of the ruthenacyclopentene required for the annulation to proceed

Scheme 21 Ruthenium catalyzed [5+2] annulations of VCPs.

Fig. 13 Natural product syntheses utilizing or attempted to utilize the ruthenium catalyzed VCP annulation.

(Fig. 12).[18] The ruthenacyclohexene can then lead to compound **132**, trapping the ruthenium center, preventing any potential formal cycloaddition pathways from occurring. DFT calculations were later performed to study the mechanism of the ruthenium based [5+2] reaction.[93] Further evidence for the formation of a 5-member metallacycle from the oxidative cyclization between the alkyne and alkene of the VCP was provided. Once the metallacycle intermediate is formed, competing pathways between the β-hydride elimination product and the [5+2] formal cycloadditions decide the fate of the mechanism (Fig. 12). This reaction has been applied to the synthesis of Frondosin A, and was attempted in the synthesis of Pseudolaric Acid B, although a rhodium catalyzed [5+2] annulation proved to be more efficient (Fig. 13).[99, 100]

3.4 Iridium

The Strand group has recently reported the first iridium based intra- and intermolecular [5+2] annulations of unactivated VCPs (Scheme 22).[22] [Ir(COD)Cl]$_2$ was found to be the optimal catalyst for the intermolecular [5+2] annulation between **133** and **134** while [Ir(dbCOT)Cl]$_2$ worked best with **136** for the intramolecular annulation. In both reactions, silver salts were added to activate the catalyst. DFT calculations provided insight into the mechanism of the intermolecular formal cycloaddition which was demonstrated to proceed through similar transition states as rhodium catalysis. The iridium mechanism was shown to have lower energetic barriers, allowing for very mild reaction conditions compared to the rhodium counterpart. Despite this, the substrate scope of this reaction has been limited to alkynes for both reactions.

Iridium has also been used for the [5+1] annulation of allenylcyclopropane **138**.[101] Vaska's complex (IrCl(CO)(PPh$_3$)$_2$) was used under 5 atm of CO to produce the resulting 6-member ring **139**. A [5+1] formal cycloaddition of a VCP was attempted

Scheme 22 Iridium catalyzed [5+2] and [5+1] formal cycloadditions of VCPs.

using the same reaction conditions, however, no reaction was observed. This suggests that allenylcyclopropanes are required when using Vaska's complex for a [5+1] annulation, and different iridium catalysts should be explored for the direct carbonylation of VCPs.

3.5 Iron

Iron has been known to interact with VCPs for several decades.[6,]

Fig. 14 General mechanism of the photolytic [5+1] iron mediated annulation of VCPs.

[75] Early work by Sarel demonstrated the ability of Fe(CO)$_5$ under

Scheme 23 Early developments of the iron mediated [5+1] formal cycloaddition of

Scheme 24 Multicyclic examples of the photolytic [5+1] iron mediated formal cycloaddition.

photochemical conditions to add a CO unit to VCP **140**, forming **141** (Scheme 23).[7] The mechanism requires the photolytic dissociation of $Fe(CO)_5$ to $Fe(CO)_3$ which acts as the active catalyst, coordinating to the olefin of the VCP (Fig. 14).[102, 103] Once coordinated, cyclopropyl cleavage occurs followed by CO insertion, reductive elimination to form the 6-member ring, and regeneration of the active $Fe(CO)_3$ catalyst can occur if the reaction is done under a CO atmosphere.[104] The Taber group further explored the regioselectivity of this reaction, and developed a general method for the preparation of optically activate substituted cyclohexenones (Scheme 23).[76, 102] This reaction was then utilized in a method for the preparation of multicyclic ring systems, where $Fe(CO)_5$ mediated the synthesis of a cyclohexenone (Scheme 24).[103] Several natural products were also synthesized by the Taber group using this methodology (Fig. 15).[105-107] The Yu group has recently developed a variant of this reaction utilizing $Fe_2(CO)_9$, a safer alternative compared to the volatile $Fe(CO)_5$, also avoiding photochemical conditions (Scheme 25).[108]

Iron based catalysts have also been used for an intramolecular [5+2] annulation of unactivated VCPs **156** (Scheme 25).[23] Ferrate complexes **157a** and **157b** were demonstrated to catalyze the [5+2] annulation between a tethered alkyne and a VCP. This reaction tolerated a variety of substitutions on the
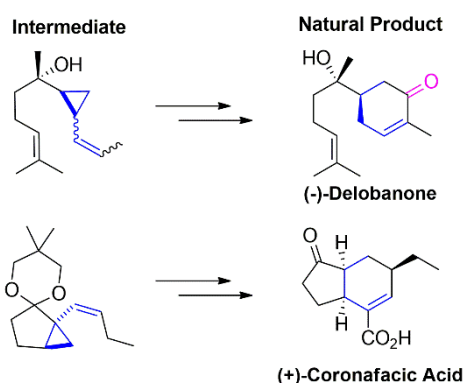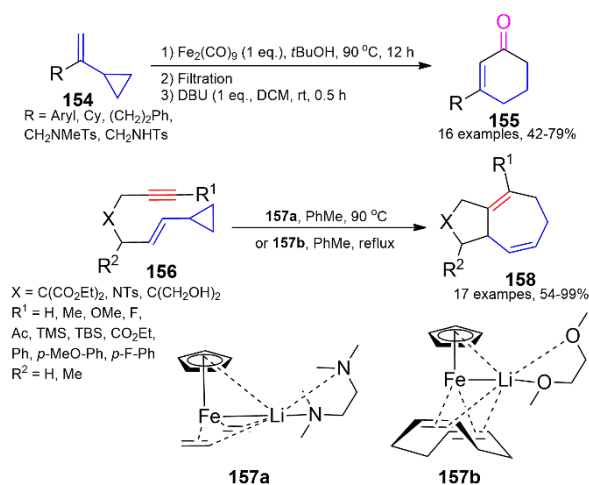

**Fig. 15** Natural product syntheses using iron mediated [5+1] formal cycloadditions.

Scheme 25 The non-photolytic iron mediated [5+1] and iron catalyzed [5+2] formal cycloadditions of VCPs.

alkyne, and has so far proved to be analogous to rhodium catalysts, potentially providing a more economical catalyst.

3.6 Cobalt

Cobalt has been utilized for [5+1] formal cycloadditions of VCPs (Scheme 26). Initial development of the cobalt mediated [5+1] annulation required stochiometric amounts of $Co_2(CO)_8$, even under an atmosphere of CO, however, unlike iron mediated carbonylations, there was no need for photochemical conditions.[24] This study used allenylcyclopropane **159**, which worked well under very mild conditions and underwent aromatization to produce **160**. Meijere then reported the use of $Co_2(CO)_8$ to mediate the [5+1] annulation of unactivated VCPs **161**, and **163** either stoichiometrically, or catalytically under an atmosphere of CO.[77] While this study relied on elevated temperatures, catalytic amounts of the cobalt source were competent catalysts when CO was present.
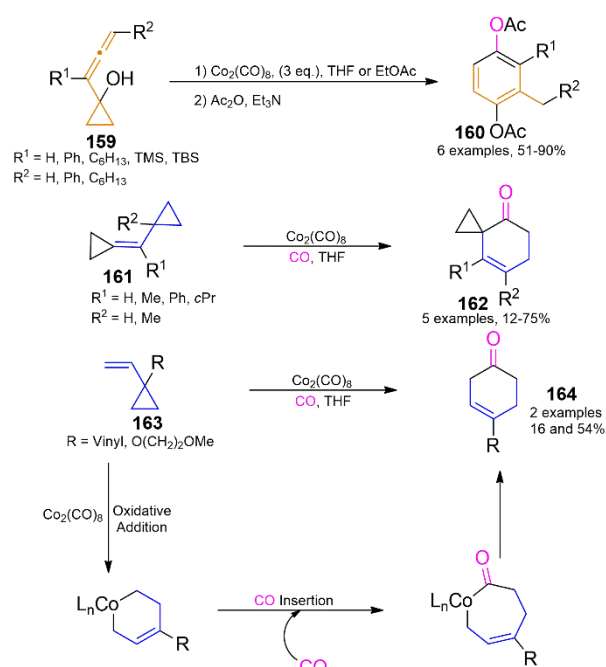
Scheme 26 Examples of the cobalt mediated [5+1] annulation of VCPs.

4. Conclusion

The ability to activate C-C bonds to facilitate annulations is an ongoing challenge for unactivated VCPs. Although extensive efforts have been committed to donor-acceptor type VCP reactions, research on substrates lacking activating groups has proven to be an independently challenging task due to different mechanistic pathways. We have summarized the efforts in the recent literature in utilizing transition metals, particularly Rh, Ru, and Ir to induce formal cycloaddition reactivity. Recent progress with Fe, Ni, and Co also show promise in using common first-row metals but there is considerable scope

remaining with these reaction catalysts. The utility of unactivated VCPs in complex natural product synthesis has demonstrated the potential of catalysis to access reactivity with challenging substrates. We anticipate that reactions of complex VCPs will continue to provide a fertile area for investigation, particularly as chemists turn toward abundant first-row transition-metals to mediate difficult reactions.[109]

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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Graphical Abstract (Max 30 words, one sentence):
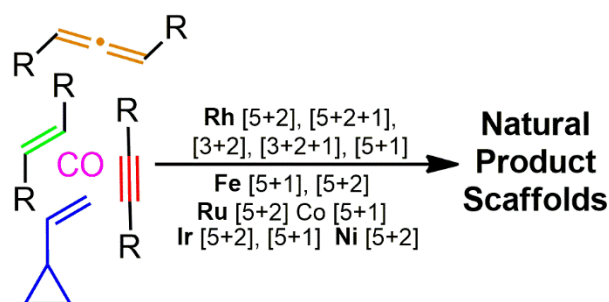
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This review covers the transition metal mediated annulation chemistry of vinylcyclopropanes with an emphasis on non-donor-acceptor examples, and where pertinent, examples of natural product syntheses are shown.

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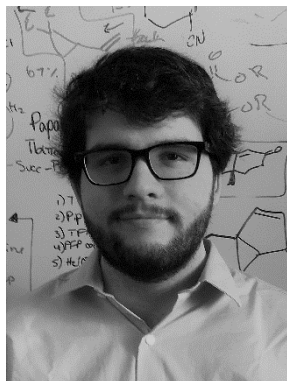
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