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ARTICLE

Cycloaddition of Cyclopropanes for the Elaboration of Medium-sized Carbocycles

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The stereocontrolled formation of medium-sized carbocycles is a major goal in modern organic chemistry due to their widespread occurrence in natural products and pharmaceutically active ingredients. One approach consists in the use of cycloaddition reactions which notably results in high selectivities and atom-economy. To this end, cyclopropanes are ideal substrates since they can provide readily functionalized three- or five-carbon synthons. Herein we report advances made in cycloaddition reactions of cyclopropanes towards the synthesis of medium-sized carbocycles *via* transition metal catalysis or Lewis acid catalysis.

1. Introduction

The cyclopropane unit is a key structural motif in modern organic chemistry.[1] It can be found in many natural products, from simple (+)-trans-chrysanthemic acid or aminocyclopropane carboxylic acid (ACC) to complex terpenoids, steroids or alkaloids.[2] Cyclopropanes are also versatile and valuable building blocks in organic synthesis.[3] Indeed, the highly strained character (ca. 27 kcal.mol^{-1}) of this ring makes it prone to ring-opening, providing highly reactive intermediates granting access to a wide variety of complex molecular structures.

Among the different reactions in which the cyclopropane can be involved, the cycloadditions are undoubtedly the most powerful and widespread. Over the years, the cyclopropane motif has in fact become a privileged partner for the development of new stereocontrolled cycloaddition reactions, toward highly functionalized five- and six-membered rings, as demonstrated by a number of recent reviews,[4] but also for the elaboration of larger carbocycles.

In this review, we describe the important advances in the construction of seven-, eight- and nine-membered carbocycles *via* cycloaddition reactions involving cyclopropanes, with a particular attention to the variety of the mechanisms involved. The different examples are discussed according to the nature of the cyclopropane type: starting from vinylcyclopropanes (VCPs), then alkylidenecyclopropanes (ACPs) and finally donor-acceptor cyclopropanes (DACPs) (Figure 1). Even though seven-membered carbocycles occupy the central part of this review, the last section will be dedicated to the formation of eight- and nine-membered carbocycles.

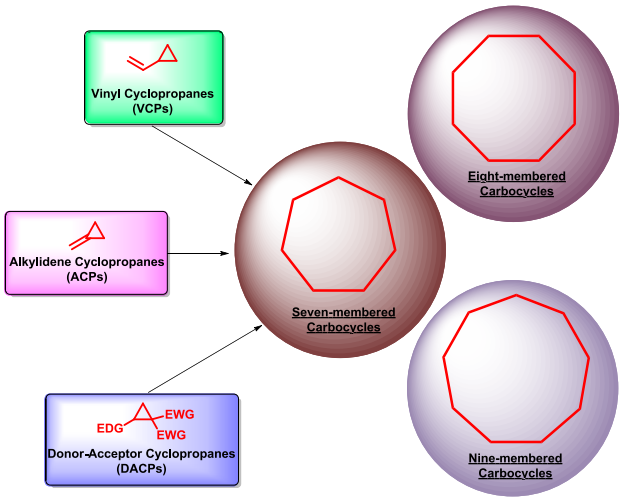

Figure 1. Different types of cyclopropanes engaged in the formation of 7- to 9-membered cycloadducts.

2. Vinylcyclopropanes (VCPs)

Vinylcyclopropanes (VCPs) have a long history as partners in cycloaddition reactions. Usually providing a three-carbon synthon, they typically enable (3+2) cycloadditions leading to five-membered rings.[5] However, it has been shown that the whole five carbon atoms of the VCP motif can also participate in cycloaddition reactions to form larger cycles. In the first part of this section, the use of VCP as a five-carbon synthon in the setup for (5+2) cycloadditions will be discussed. The two main contributors in this domain are Paul A. Wender who focused on rhodium-catalyzed (5+2) cycloadditions and Barry M. Trost who has been exploring the use of ruthenium salts to catalyze these transformations. Research in this area has already received great attention and has been the subject of some reviews.[5,6]

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Finally, a last cycloaddition process constituting a rare (3+3+1) example involving VCPs will be presented. It is important to note that divinyl cyclopropanes are also an excellent scaffold for building seven-membered carbocycles *via* a Cope rearrangement.[7,8] However, since this strategy does not fall in the category of cycloaddition reactions, it will not be covered by this review.

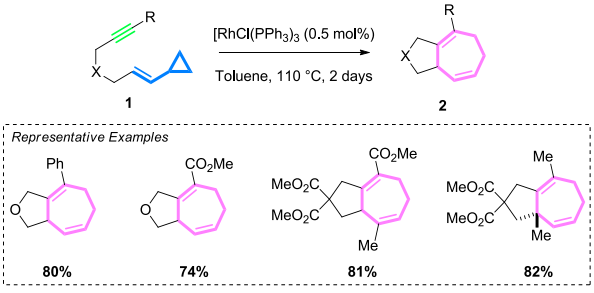
2.1. (5+2) Cycloaddition reactions

2.1.1. Rhodium catalysis

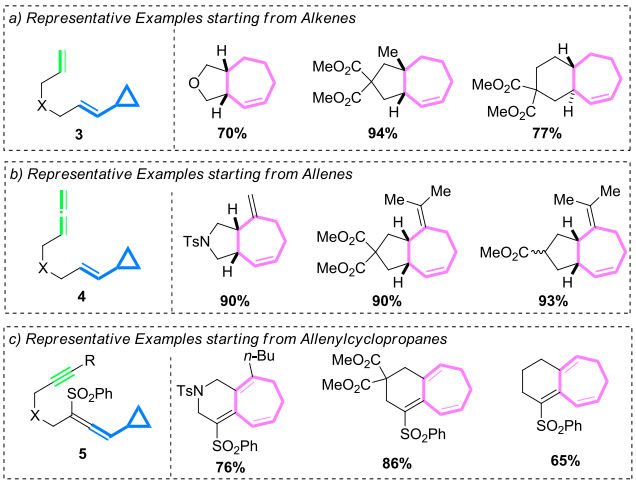
2.1.1.1. Intramolecular version

Wender reported in 1995 the first access to seven-membered rings from VCPs *via* an intramolecular (5+2) cycloaddition strategy.[9] In this seminal report, the formation of a bicyclo [5.2.0] core was accomplished in good yields by intramolecular reaction between a VCP and an alkyne (**1**) upon rhodium catalysis (Scheme 1). However, despite a good activity of the Wilkinson catalyst, it was shown that the addition of the silver salt AgOTf enabled the reduction of the reaction time from two days to only 20 minutes. In general, substitution of the alkene or the alkyne has little impact on the reaction outcome.

Quickly after this discovery, alkenes[10] **3** and allenes[11] **4** were found to be suitable partners, both leading to *cis* compounds (Scheme 2a-b). The reaction also allows the use of four-atom tethers substrates affording [5.4.0] bicycles but now with a *trans* junction. One limitation, however, is that the methodology is restricted to terminal alkenes; reaction of non-terminal alkenes being proved to be unsuccessful. Besides, as compared to alkynes and allenes, alkenes exhibit a fairly lower reactivity and need longer reaction times, typically 24 h instead of a couple of hours. The origin of this feature was unravelled by a computational study showing that it lies in the difficulty, in the case of non-terminal alkenes, to undergo the reductive elimination step.[12] Slightly different [5.4.0] bicycle scaffolds were also obtained from allenylcyclopropanes and alkynes **5** (Scheme 2c).[13] This reaction is actually catalyzed by a different rhodium salt $[RhCl(CO)_2]_2$ that will later prove to be a very efficient catalyst for this kind of transformation (*vide infra*). Other ruthenium complexes were also successfully used as catalysts along with new reaction conditions. The most significant improvements brought by these new catalysts were: 1) the yields, kinetics and temperatures of the reaction with the following complexes $[Rh(DIPHOS)(CH_2Cl_2)_2]SbF_6$,[14]



Scheme 1. Rh-catalyzed (5+2) intramolecular cycloaddition of VCPs with alkynes.

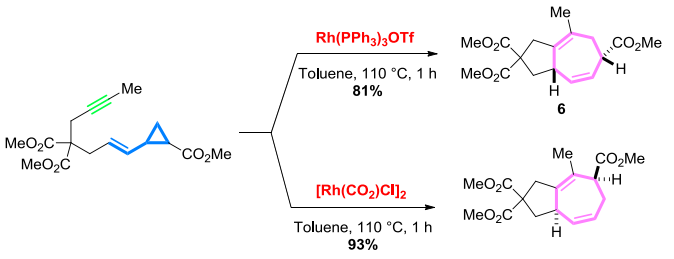


Scheme 2. Rh-catalyzed (5+2) intramolecular cycloaddition of VCPs with a) alkenes, b) allenes and c) alkynes + allenylcyclopropanes.

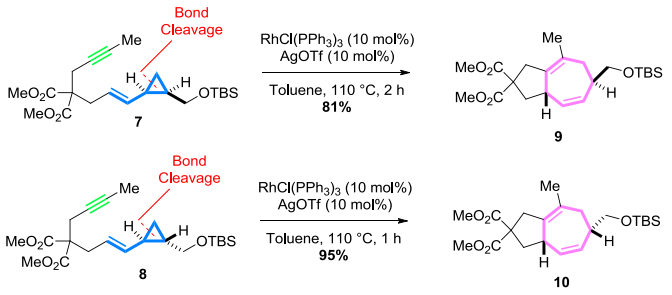
$[Rh(dppb)]SbF_6$,[15] $[(C_{10}H_8)Rh(cod)]SbF_6$,[16] $[Rh(NHC)Cl(cod)]SbF_6$,[17] $[Rh(dncot)(MeCN)_2]SbF_6$,[18] and a NHC-Rh(cod) complex,[19] 2) the use of different solvents such as fluorinated alcohols,[20] or water for a "green" version with $[Rh(nbd)]SBF_6$,[21] and 3) the control and reversal of regioselectivity of 1,2-disubstituted cyclopropanes with $[Rh(CO)_2Cl]_2$.[22]

The influence of a 1,1- and 1,2-disubstitution of the cyclopropane was investigated by the group of Wender.[23] Notably, C^1 disubstitution revealed to be a crucial feature for the intermolecular version (see section 2.1.1.2). With 1,2-disubstitution, interestingly, comes the question of the regiochemistry and the relative stereochemistry. In terms of regioselectivity, only the regioisomer **6** originating from the cleavage of the less substituted bond of the cyclopropane ring is generally obtained. In some cases, it was however shown that regioselectivity can be inverted by changing the nature of the catalyst (Scheme 3). Concerning stereoselectivity, the *cis* or *trans* relationship between the two substituents has a major impact on the stereochemistry of the cycloadduct (Scheme 4). Indeed, the reaction was found to be stereospecific, the *cis* (**7**) and *trans* (**8**) isomers leading to two different diastereomers (respectively **9** and **10**).

Efforts were also devoted to elaborating asymmetric variants of this cycloaddition methodology. Interestingly, the enantioselective version involving alkenes **11** was developed



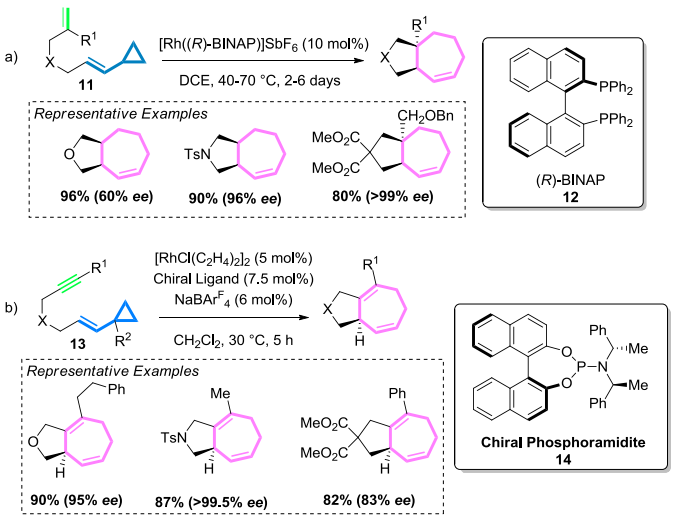
Scheme 3. Regiodivergence in Rh-catalyzed (5+2) cycloadditions of VCPs with alkynes.



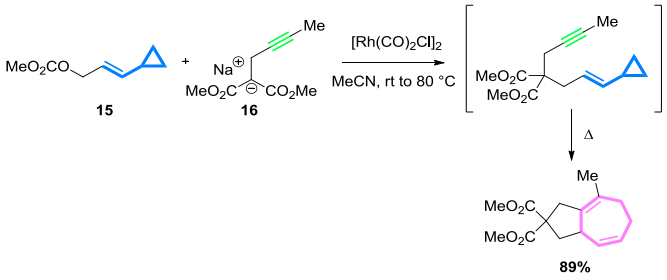
Scheme 4. Stereospecificity with 1,2-disubstituted VCPs in Rh-catalyzed (5+2) cycloadditions of VCPs with alkynes.

prior to alkynes, using (*R*)-BINAP **12** as the chiral ligand (Scheme 5a).[24] The use of this ligand enables high yields and enantioselectivities, even if enantioselective induction was found to depend on the substrate structure. It can also be noted that the observed conversion rate with alkenes was not changed thus leading to several days of reaction before reaching completion. Later, the group of Hayashi and Shintani reported that phosphoramidite **14** are also suitable chiral ligands for the enantioselective (5+2) intramolecular cycloaddition of alkyne and VCPs **13** (Scheme 5b).[25] Obtained *ee* reached up to >99.5% and the robustness of the reaction conditions was further demonstrated with a gram scale reaction yielding identical stereoselectivity.

Another interesting improvement of the reaction was reported by Martin *et al.*[26] It concerns the formation of the substrate: Starting from carbonate **15** and sodiomalonate **16**, a domino reaction involving allylic alkylation followed by (5+2) cycloaddition was made possible in excellent overall yields (Scheme 6). A noticeable feature of this reaction is that the rhodium catalyst $[Rh(CO)_2Cl]_2$ is actually the same for performing both the allylic alkylation and the cycloaddition. This convenient procedure needs only to raise slightly the temperature to promote the carbocyclization, hence being practical and affording simple operating conditions.

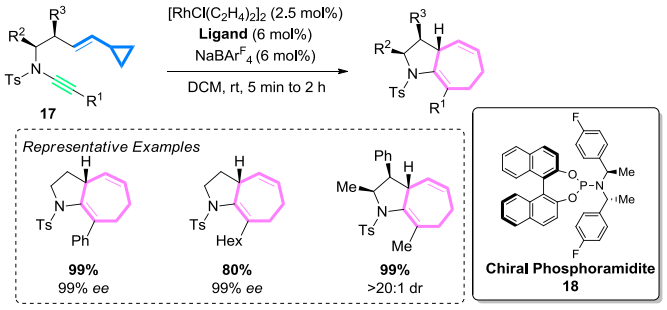


Scheme 5. Asymmetric Rh-mediated (5+2) cycloadditions of VCPs with a) alkenes and b) alkynes.

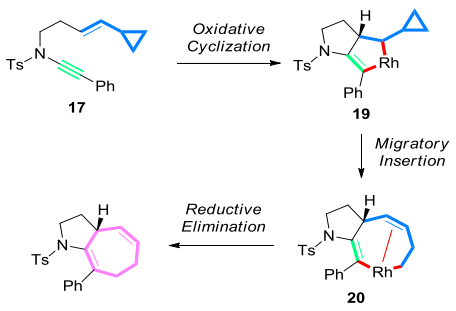


Scheme 6. Rh-catalyzed allylic alkylation/(5+2) cycloaddition domino reaction.

Quite recently, Anderson *et al.* reported the use of ynamide **17** instead of the alkyne partner in a fully detailed study (Scheme 7).[27] [Rh(Naph)(cod)]SbF_6 was found to be the best catalyst for this transformation and excellent yields are obtained at room temperature in 1 hour or even less. The diastereoselectivity is also excellent with the exclusive formation one isomer in most cases. The asymmetric induction was enabled with the chiral phosphoramidite ligand **18** leading to *ee* up to 99.9%. Modelizations were also undertaken to determine the impact of the ynamide function on the reaction mechanism. The vinylcyclopropane pathway, traditionally accepted for this kind of transformation (see section 2.1.1.2), is here not the preferred pathway. Indeed, the metallacyclopentene pathway (intermediate **19**) is favoured by at least 4.9 kcal.mol^{-1} then followed by ring opening of the cyclopropyl unit (**20**) before reductive elimination (Scheme 8). This peculiar behaviour is accounted for by the additional stabilization of the Rh(III) intermediate in the oxidative coupling step by the electron-rich ynamide.



Scheme 7. Rh-catalyzed (5+2) enantioselective cycloaddition of ynamides.

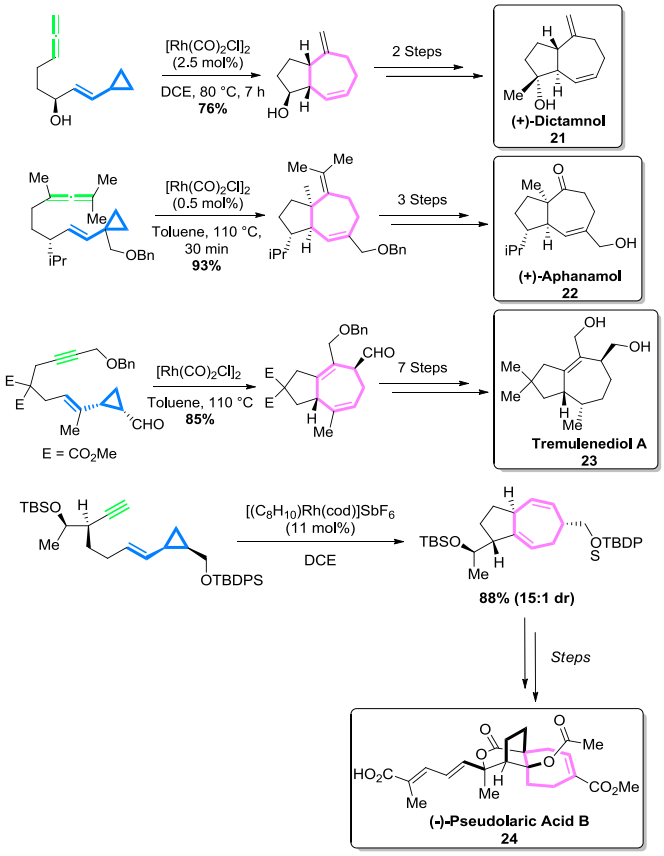


Scheme 8. Mechanism of the Rh-catalyzed (5+2) cycloaddition of ynamides.

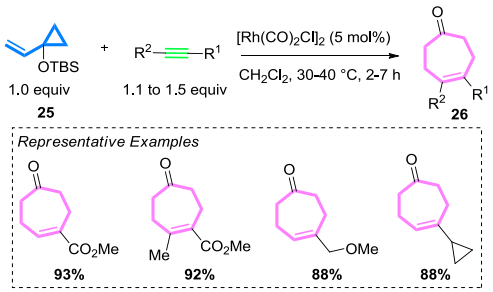
The synthetic utility of these (5+2) cycloaddition reactions was successfully illustrated by their application in the field of natural products total synthesis. For instance, convenient and straightforward accesses to (+)-Dictamnol **21**,[28] (+)-Aphanamol **22**,[29] terpenoids of the tremulene family such as Tremulenediol A (**23**) and (-)-Pseudolaric Acid B (**24**)[30] were reported (Scheme 9).[31] In all cases, the cycloadducts were obtained in excellent regio- and diastereoelectivities along with good to excellent yields emphasizing here a robust access for the expedient elaboration of the [5.3.0] structural core. In most of these transformations, the rhodium catalyst $[Rh(CO)_2Cl]_2$ was found to be the best choice ensuring an optimum reactivity even though extensive heating at reflux of toluene or DCE is necessary.

2.1.1.2. Intermolecular version

Shortly after their seminal paper on intramolecular (5+2) cycloaddition of VCPs,[2] Wender *et al.* reported the first intermolecular variant of this reaction[32] along with an independent example from the de Meijere group.[33] Based on the consistent results obtained previously, alkynes were the first partner to be studied. However, the authors faced numerous failures as the substrates were either not sufficiently reactive or were subjected to undesired cyclotrimerization. The solution derived from an observation made in their intramolecular cycloadditions in which the C^1 substitution of the cyclopropane with an oxygen atom increases the overall reactivity. When applied to the



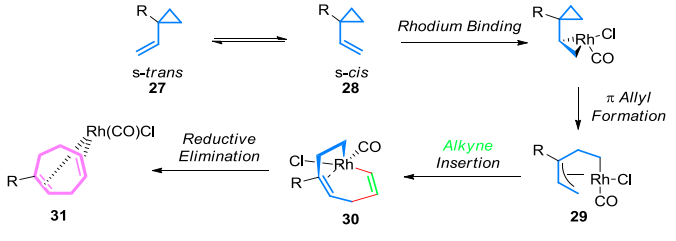
Scheme 9. Example of Rh-catalyzed (5+2) cycloadditions of VCPs in total synthesis.



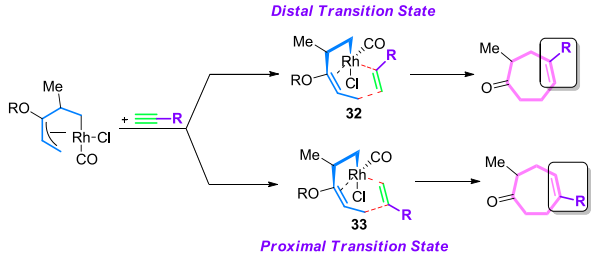
Scheme 10. Rh-mediated (5+2) intermolecular cycloadditions of VCPs with alkynes.

intermolecular reaction, along with the more reactive $[Rh(CO)_2Cl]_2$ catalyst, the expected seven-membered ring is obtained in good to excellent yields (Scheme 10). Acidic workup notably enabled the recovery of the ketone **26** instead of the corresponding silylated enol ether. The reaction proceeds under similar experimental conditions to that of the intramolecular version: identical catalytic load of rhodium, heating reduced but reaction time increased. Interestingly, when the alkyne substrate displays an alkene moiety, only the former function reacts, leaving the alkene unchanged useful for further functionalization. Later, the Wender group showed that C^1 substitution by a bulky alkyl group can also be utilized to achieve the intermolecular (5+2) cycloaddition, even if the reaction is slower than in the case of an oxygen substitutent.[34]

More insights into the reaction mechanism were obtained from theoretical studies.[35] A simplified version of the mechanism is depicted in Scheme 11. The reaction starts by the coordination of the rhodium to the double bond of the VCP. At this stage, the VCP needs to be preorganized into a s-*cis* conformation (**28**) before the insertion of the rhodium into the cyclopropyl C-C bond. However, the ground state of unsubstituted VCPs involves a s-*trans* conformation (**27**). Accordingly, C^1 substitution with a bulky group is necessary to modify the preorganization and favour a s-*cis* conformation (**28**). The insertion of the rhodium catalyst then leads to the formation of an electron-deficient π allyl system (**29**) which is stabilized by electron-donating C^1 substituents such as siloxy or alkoxy groups. The next step, the insertion of the alkyne, is the rate determining step (RDS) of the process forming the rhodacycle **30**. Eventually, after a reductive elimination step, the cycloadduct **31** is released and the catalyst regenerated. The regioselectivity of the alkyne insertion was also deciphered, *via* combined computational and experimental studies.[36a] The regioselectivity is determined at the insertion step; the *distal* and *proximal* transition states leading to



Scheme 11. Mechanism of the Rh-catalyzed (5+2) cycloaddition of VCPs with alkyne.



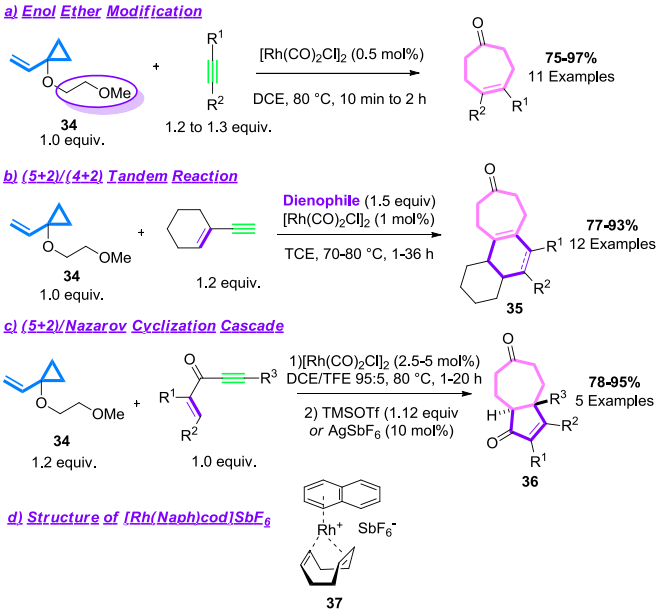
Scheme 12. Illustration of *distal vs proximal* transition states determining regioselectivity in Rh-mediated (5+2) cycloaddition.

regioisomer **32** and **33**, respectively (Scheme 12). It was shown that the structure of the substrate plays a crucial role in determining the regioselectivity: in most cases the most favoured pathway involves a *distal* transition state but if the alkyne is electronically deficient or if the cyclopropane displays a sterically hindered 1,2-disubstitution then the *proximal* pathway is preferred. Further developments with rhodium catalysts $[Rh(dncot)]^+$ and $[Rh(cod)]^+$ showed increased regioselectivity thanks to ligand steric effects.[36b]

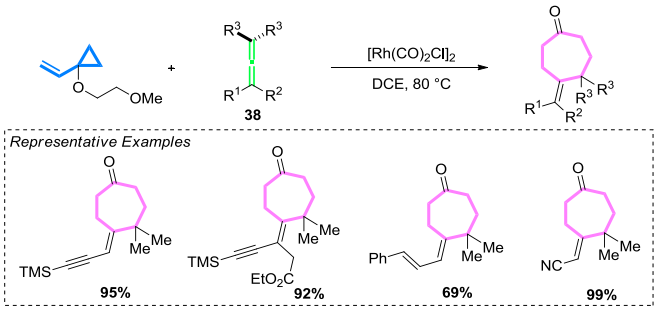
Improvements of the reaction conditions were rapidly undertaken by the group of Wender. A modified version of the enol ether **34** allowed decreasing the catalytic loading of rhodium down to 0.5 mol% as well as reducing the reaction time to usually less than one hour (Scheme 13a).[37] This reagent notably enables cascade reactions such as: (5+2)/(4+2) tandem reactions for the formation of tricyclic compounds **35** or (5+2)/Nazarov cyclization for accessing the [5.3.0] bicyclodecane core **36** (see Scheme 13b-c).[38] In addition, they showed that the cationic rhodium(I) salt $[Rh(Naph)cod]SbF_6$ **37** catalyzes efficiently (5+2) intermolecular cycloadditions at room temperature, within 15 minutes, in high product yields (Scheme 13d).[39] The origin of this peculiar property was deciphered in a subsequent theoretical study,[40] suggesting that the hemilability of the cyclooctadiene ligand allows the catalyst to better accommodate the substrate transition state geometry and electronics.

Substrates other than alkynes were also evaluated. Alkenes lacking of reactivity in the intramolecular version, it was not surprising to observe the absence of reaction with this class of substrates also in the intermolecular version. However, allenes **38** were found to be good partners, even more reactive than alkynes (Scheme 14).[41] Indeed, when the substrate displays both an allene and a conjugated alkyne moiety only the former reacts leaving the alkyne untouched. However, in many cases, the reaction leads to a mixture of diastereomeric alkenes, often hardly separable.

Furthermore, it was found that, counterintuitively, non-substituted terminal allenes provide lower cycloadduct yields than their more sterically encumbered internal analogues, or were even in some cases unreactive. Also, all the (5+2) cycloadditions proceeded exclusively at the terminal double bond of the allene, if the substrate displayed a dialkyl substitution, but never on the internal double bond of the

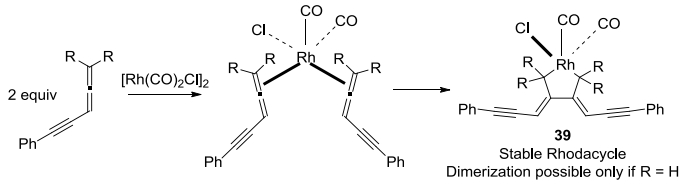


Scheme 13. Improvements of Rh-catalyzed (5+2) intramolecular cycloadditions.



Scheme 14. Rh-mediated (5+2) intermolecular cycloadditions of VCPs with allenes.

allene. These observations prompted Wender and Houk to undertake additional combined experimental and DFT studies, which pointed out the deleterious effect of terminal unsubstituted allenes as rhodium catalyst poisons.[42] Calculations showed that the observed low yields for terminally unsubstituted allenes can be accounted for by a competing allene dimerization in these cases. In addition, the rhodacycle **39** was found to be particularly stable, hence preventing the rhodium catalyst from being available to catalyze further (5+2) cycloadditions (Scheme 15). With terminally substituted allenes, the dimerization is strongly disfavoured, due to steric repulsion, while the barrier to (5+2) cycloaddition is not significantly affected. Finally, the authors were able to elucidate the origin of chemoselectivity. They showed that the insertion of the terminal double bond is favoured due to a stronger d-π* backdonation. On the other hand, conjugation of the internal double bond to the alkyne and steric repulsion around the alkyne prevent the insertion of rhodium on these two π-bonds.

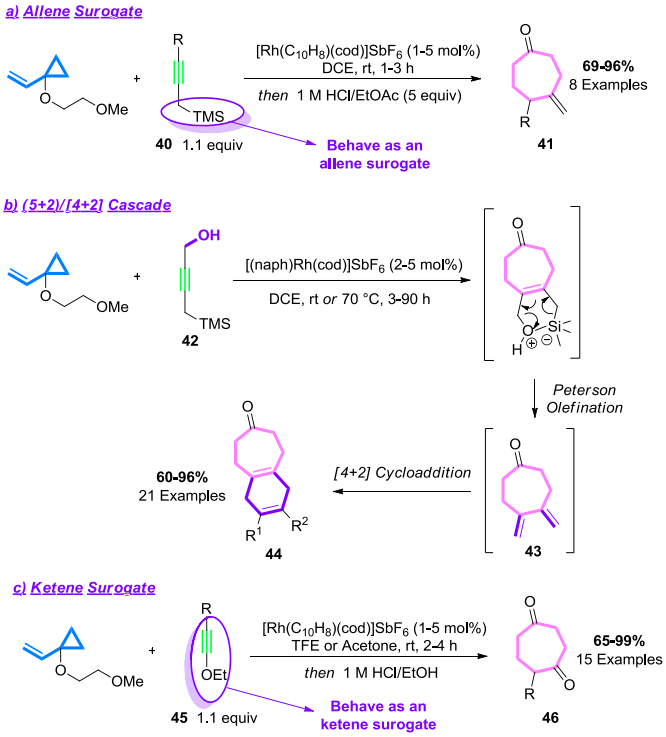


Scheme 15. Dimerization of the allene substrate and formation of the deleterious rhodacycle **39**.

An allene surrogate was next developed by Wender *et al.*, consisting in propargyltrimethylsilane derivatives **40** (Scheme 16a).[43] In conjunction with $[Rh(C_{10}H_8(cod)]SbF_6$ and after a Brønsted acid-mediated protodesilylation step, seven-membered rings bearing an exocyclic double bond (**41**) were formed, in an identical fashion to that of allenes but without the trouble of handling quasi-gaseous and more toxic substrates. It is interesting to note that the (5+2) cycloaddition can be performed at room temperature in a short reaction time (15 min to 3 h). Remarkably, with an appropriate hydroxymethyl substitution (see **42**), the formation of an exocyclic 1,3-diene **43** was observed, through Peterson olefination, hence opening access to a subsequent [4+2] cycloaddition reactions for the elaboration of [5.4.0] bicyclic compounds **44** in one synthetic step (Scheme 16b).[44]

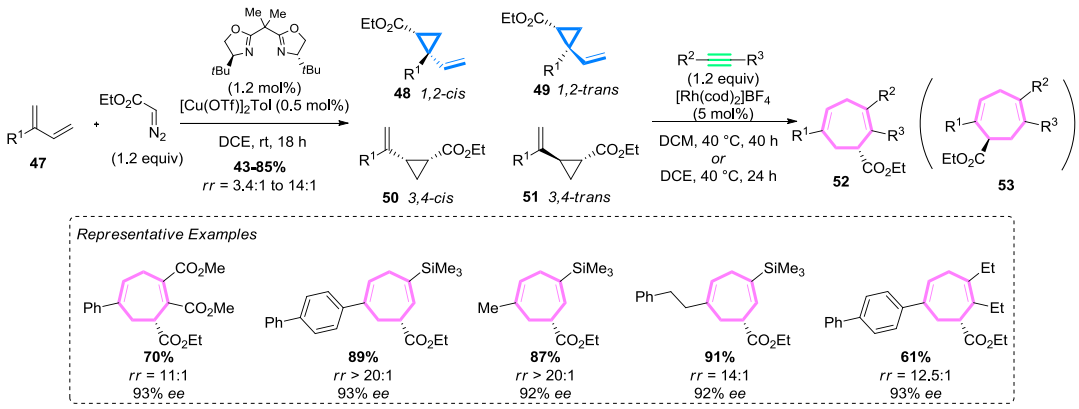
Wender *et al.* reported also the use of ynol ethers **45** as ketene surrogate.[45] This study was prompted by the fact that ketene derivatives would furnish good substrates but their electron-poor nature is limiting as well as their propensity of undergoing unwanted side reactions such as dimerization. Alkyl and aryl ynol ethers **45**, readily accessible in one step from commercial ethoxyethyne, react smoothly in the reaction conditions of the intermolecular (5+2) cycloaddition leading to the cyclohepta-1,4-dione core **46** in excellent yields after a few hours (Scheme 16c). The rhodium catalyst $[Rh(naph)(cod)]SbF_6$ is typically used for these transformations with 5 mol% catalyst loading (in some cases 3 mol% catalytic loading is sufficient). Noteworthy, halogenated TFE solvent can be efficiently replaced by acetone for this reaction.

Very recently, the group of Mazet proposed an unexplored stereoconvergent approach to intermolecular (5+2)



Scheme 16. Allene surrogate and cascade reaction in (5+2) intermolecular Rh-catalyzed cycloadditions.

cycloadditions based on a two-step sequence.[46] The first step consists in an asymmetric copper-catalyzed cyclopropanation of a 1,3-diene substrate **47** (Scheme 17). A BOX ligand ensures satisfactory *ee*'s, usually around 90%, and the cyclopropanation proceeds regioselectively on the most substituted olefin with a modest diastereoselectivity. Four isomeric VCPs are formed at this stage and their subsequent transformation *via* (5+2) cycloaddition is achieved using the cationic catalyst $[Rh(cod)_2]BF_4$; attempts with common rhodium catalysts for this kind of transformation were unsuccessful. The stereoconvergent strategy demonstrates here its powerfulness since only the trisubstituted VCPs **48** and **49** react leaving the disubstituted VCPs **50** and **51** unaffected upon reaction conditions. This result highlights the absolute



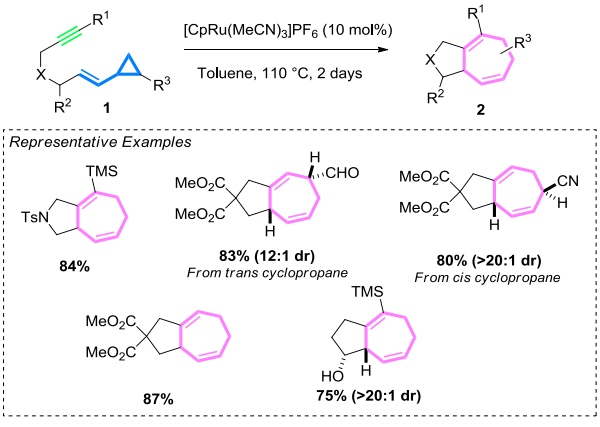
Scheme 17. Enantioconvergent Rh-catalyzed intermolecular (5+2) cycloaddition with stereoretention.

necessity of a quaternary centre in the VCP partner for undergoing intermolecular (5+2) transformation. In addition, the cycloaddition is enantiospecific with the stereochemistry of the monosubstituted cyclopropane carbon determining the configuration of the seven-membered ring: the 1,2-*cis*-VCP **48** leads exclusively to enantiomer **52** with a total regioselectivity for the addition of the alkyne while the 1,2-*trans*-VCP **49** provides the same enantiomer (**52**) but in a mixture with its regioisomer **53**. However, since the 1,2-*cis*-VCP **48** is the main product of the cyclopropanation step, the overall process eventually affords stereocontrolled seven-membered rings **52** in good to excellent yields, typically ranging from 70% to 90%.

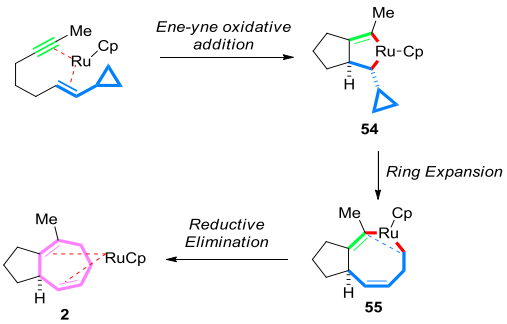
2.1.2. Ruthenium catalysis

Five years after the discovery of the rhodium-catalyzed (5+2) cycloaddition of VCPs and alkynes by Wender *et al.*, the group of Trost proposed another transition-metal catalysis system based on the ruthenium.[47] Indeed, they showed that the treatment of the same ene-yne substrates **1** with a 10 mol% loading of a cationic ruthenium catalyst in acetone affords corresponding cycloadducts **2** in good yields (Scheme 18). As compared to rhodium catalysis, the use of ruthenium resulted in improved kinetics; the vast majority of the cycloadditions being completed after one or two hours, sometimes less, at room temperature. When the cyclopropane is 1,2-disusbtituted, the regioselectivity is substrate-controlled. Indeed, in the case of *trans* cyclopropanes, that is the bond between the two substituents which is preferentially cleaved while for *cis* isomers a total regioselectivity of the cleavage of the less substituted bond is observed (excepted with CHO substitution), thus allowing access to complementary products. The stereochemistry of the double bond also has a determinant impact on the reaction outcome as (*Z*)-VCP predominantly leads to ene reactions. The products derived from the ene reaction are sometimes observed with (*E*)-VCP substrates too but in much lower ratio. Contrary to rhodium-catalyzed reactions, in this case, changing the alkyne for an alkene does not lead to the expected cycloadduct but, instead, to a cyclodecadienyl ruthenium complex.[48]The ruthenium-catalyzed (5+2) cycloaddition was investigated by computational (DFT) means, allowing to decipher key features of the reaction mechanism.[49] This study showed that this latter is different than in the case of rhodium catalysis. With ruthenium, the difference in free energy barrier between the 2π insertion and the ene-yne oxidative addition is only 2.2 kcal.mol^{-1} in favour of the latter pathway (Scheme 19). Accordingly, the ene-yne oxidative addition leads first to the formation of a ruthenacyclopentene **54** which then undergoes ring expansion to provide a cyclooctadiene **55** whose reductive elimination finally delivers the cycloadduct **2**. One has also to note that the overall free energy barrier is significantly lower with ruthenium than in the case of rhodium catalysis, explaining the observed shorter reaction times in the former case. This higher reactivity is accounted for by the difference in redox potentials of the two transition-metals.

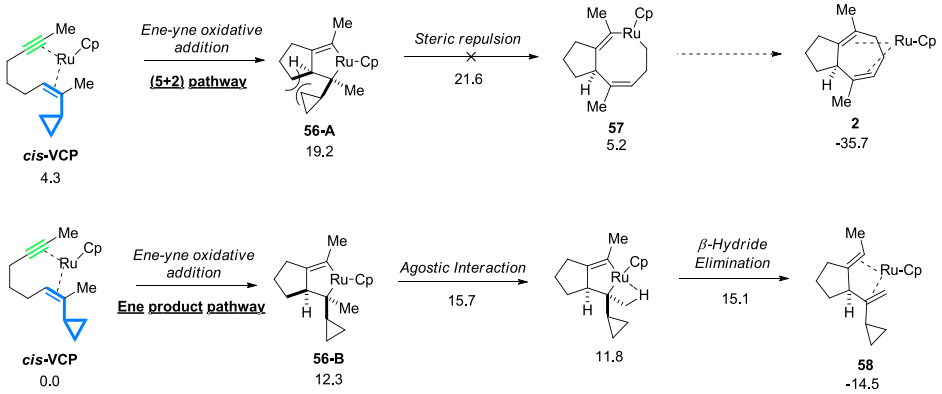
The competition between (5+2) cycloaddition and ene reaction was also investigated. The selectivity is determined at the level of the ruthenacyclopentene intermediate **56** which can undergo either a cyclopropane ring-opening leading to the seven-membered ring **2** or a β-hydride elimination *via* an agostic interaction allowing the formation of the ene product **58**. For the *trans*-VCP, calculations show that the ring cleavage pathway is intrinsically favoured (by 2.9 kcal.mol^{-1}) thus predicting the formation of the more stable (5+2) cycloadduct **2**, in good agreement with experiments. In the case of the *cis*-VCP, that is the β-hydride elimination pathway which is favoured (by 5.9 kcal.mol^{-1}) even though the ene product **58** is computed to be less stable than the (5+2) cycloadduct **2** (Scheme 20). This is attributed to the fact that, in this case, the intermediate **56-A** has to adopt an unfavourable conformation, involving a steric clash between the cyclopropyl unit and the formed five-membered ring, in order to react and form the *cis*-double bond in the cyclooctaadiene **57**.



Scheme 18. Ru-catalyzed (5+2) intramolecular cycloadditions of VCPs with alkynes.



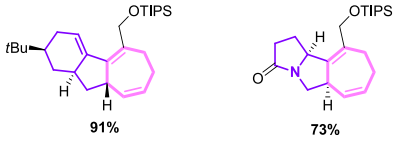
Scheme 19. Mechanism of the Ru-mediated (5+2) intramolecular cycloadditions of VCPs with alkynes.



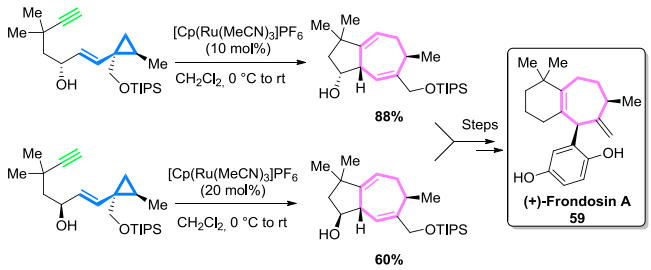
Scheme 20. Mechanism of the formation of the undesired ene product. Free energy in kcal.mol^{-1} relative to *cis*-VCP.

In contrast to the rhodium-catalyzed methodology, there is to date no report on an intermolecular version nor on the successful use of other substrates than alkynes. The (5+2) ruthenium-catalyzed cycloaddition methodology was however extended to the synthesis of tricyclic compounds, notably with substrates derived from norcarane (Scheme 21).[50]

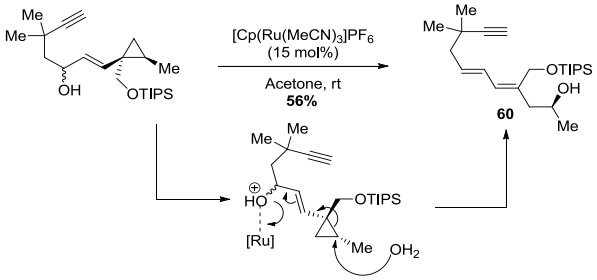
The methodology was also applied to the synthesis of natural product (+)-Frondosin A (**59**) (Scheme 22).[51] Optimization of the reaction conditions were needed to render the (5+2) ruthenium-catalyzed cycloaddition effective. Indeed, under standard reaction conditions, only the unexpected diene **60** is formed, as a single enantiomer though (Scheme 23). Its formation was rationalized by the presence of trace amount of water responsible of a solvolysis process, the VCP being activated due to the binding of the oxygen with the transition metal. Interestingly, the author observed a significant difference in kinetics between the two starting diastereoisomers, resulting in two different yields: 88% for the faster one *vs* 60% for the slower one.



Scheme 21. Examples of tricyclic compounds obtained *via* Ru-catalyzed (5+2) cycloadditions between VCPs and alkynes.



Scheme 22. Formation of the seven-membered carbocycles in the course of (+)-Frondosin A total synthesis.



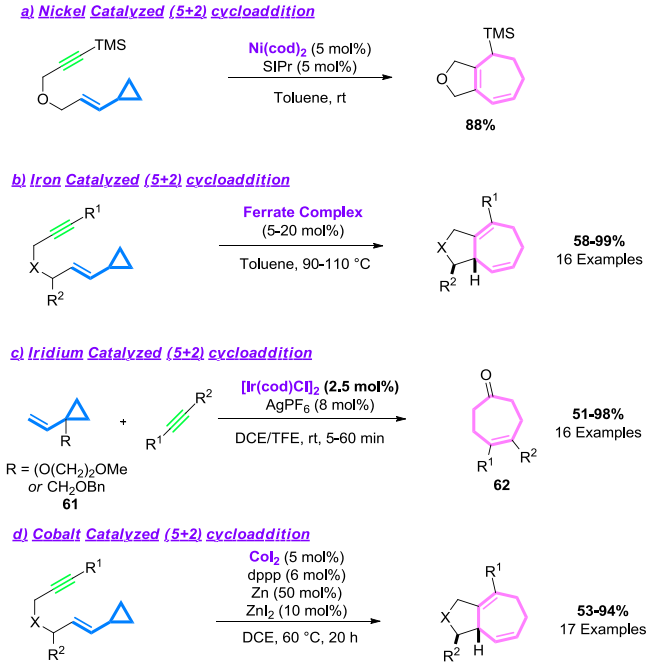
Scheme 23. Mechanism of the formation of undesired diene **60**.

2.1.3. Other transition-metal catalysts

Apart from rhodium and ruthenium catalysis, few reports on other transition-metal catalysts were published in the field of (5+2) cycloaddition between VCPs and alkynes.

In 2005, the group of Louie reported the use of Ni(cod)$_2$ and NHC ligand SIPr to catalyze the *intramolecular* (5+2) cycloaddition of VCP with alkynes (Scheme 24a).[52] Three different products arise from this study: the (5+2) cycloadduct along with an isomer and the homo-ene product. The latter constituted, in fact, the major product, excepted when the alkyne is substituted by bulky groups. Some years later, the mechanism of this reaction was investigated computationally by Houk.[53] This study showed that the reaction mechanism starts following the same trend as in the case of ruthenium catalysis, with the preferred formation of the five-membered metallacycle, through ene-yne oxidative cyclization, over cyclopropane cleavage and alkyne insertion. However, in the case of nickel, the β-hydride elimination process prevails (by 2.3 kcal.mol^{-1}) over the cyclization, hence furnishing the homo-ene product. The β-hydride elimination transition state can be nonetheless destabilized by steric repulsions if the alkyne displays a bulky substituent or if the size of the NHC ligand increases (such as SIPr ligand) to favour the formation of the (5+2) cycloadduct.

The use of two ferrate complexes, diethylene- and cod-containing ferrates, was also reported by the Fürstner group (Scheme 24b).[54] The cod-containing ferrate complex was found to be the most efficient to trigger the (5+2) cycloaddition in the absence of allylic substitution. The observed diastereoselectivity is in favour of the *trans* isomer. A wide



Scheme 24. (5+2) cycloaddition of VCPs and alkynes under various transition-metal catalysis.

variety of chemical diversity at the alkyne substitution is tolerated without noticeable change in reactivity. However, trisubstitution at the VCP double bond resulted in a complete loss of reactivity, constituting a limitation of the method.

In 2015, Strand *et al.* proposed a new variation of both *intramolecular* and *intermolecular* (5+2) cycloaddition of VCPs and alkynes based on iridium catalysis (Scheme 24c).[55] Alkoxy substituted VCPs **61** were reported to be the ideal substrates, corroborating the work of Wender on rhodium catalysis. In the presence of the additive $AgPF_6$, $[Ir(cod)Cl_2]$ was found to be the best catalyst for the reaction, affording the heptanone **62** product in high yields. The most interesting feature here is the fast reaction kinetic as compared to rhodium catalysis (completion reached within one hour, sometimes within 10 min, at room temperature). A computational study indicated that this behaviour can be attributed to an easy alkyne insertion step. Finally, this methodology was successfully applied to the *intramolecular* (5+2) cycloaddition, maintaining goods yields and short reaction times.

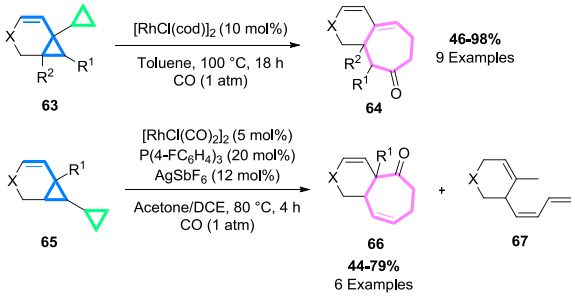
Quite recently, Yoshikai reported the first successful use of cobalt for *intramolecular* (5+2) cycloaddition of VCPs and alkynes (Scheme 24d).[56] Here the reaction outcome is highly solvent-dependant furnishing either the (5+2) cycloadduct in DCE or the homo-ene product in acetonitrile. For ensuring the formation of the seven-membered ring, the catalytic system involves a CoI_2 precatalyst alongside ZnI_2 as an additive to accelerate the reaction at lower temperature. Zn dust is the reducing agent and the dppp ligand was found to play an important role since other phosphine ligand did not provide the expected product. If good to excellent yields are usually obtained it is worth noting that terminal alkynes were not suitable partners and failed to deliver the cycloadduct. A glimpse into the reaction mechanism was undertaken by means of DFT calculations. Obtained results indicate that oxidative cyclization would deliver the cobaltacyclooctadiene intermediate with an activation free energy of 12.1 kcal.mol^{-1}. From this common intermediate the (5+2) cycloaddition pathway is favoured over the homo-ene pathway by an overall 3.3 kcal.mol^{-1} difference in free energy barrier. The *cis*-olefin in the cobaltacyclooctadiene plays a significant role as a π-acceptor in order to help the reductive elimination process.

2.2. (3+3+1) Cycloaddition reactions

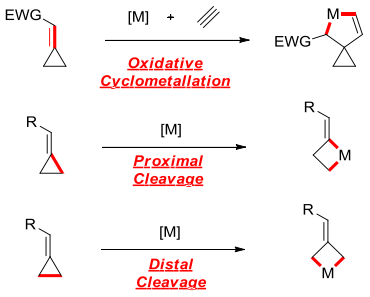
To date, the only example of (3+3+1) cycloaddition involving VCPs was described in 2008 by Chung *et al.*[57] In this report, the authors describe the behaviour of unusual VCP substrates **63** decorated with an additional cyclopropane as C^1 substitution (biscyclopropane) in carbonylative rhodium-catalyzed reaction (Scheme 25). Only three carbon atoms of the VCP actually participate in the elaboration of the seven-membered ring **64**. The reaction proceeds in good to excellent yields but is unexpectedly not working when the R^2 substitution is a phenyl group. Swapping the position of the external cyclopropane and the R^1 substitution (see **65**) results in a mixture of two products: the expected bicycle **66** and the monocyclic triene **67**. The latter comes from the easy ring opening of the two cyclopropane units before any carbonylation could occur.

3. Alkylidene cyclopropanes (ACPs)

Alkylidene cyclopropanes (ACPs) attracted also great attention as building blocks for the elaboration of complex structures. In contrast to VCPs, ACPs count only as three carbon synthons in cycloaddition reactions. Therefore, in order to furnish seven-membered cycles, cycloadditions involving ACPs rely either on a (3+2+2) process, with two alkynes and/or alkenes partners, or on (4+3) cycloadditions if 1,3-dienes are used as partners. In this field, advances were achieved mostly from the efforts of Mascareñas, Saito and Evans groups; a series of recent reviews reflect the growing interest in this research field.[58] Different activation modes can be encountered when discussing the reactivity of ACPs and especially the cleavage of their cyclopropane ring. These modes differ by the first step undertaken by the transition-metal catalyst and can be summarized as follow: 1) oxidative addition prior to cyclopropane cleavage, 2) proximal cleavage then alkene insertion and 3) distal cleavage then alkene insertion (Scheme 26).



Scheme 25. Rh-catalyzed (3+3+1) cycloadditions of VCPs with cyclopropane.

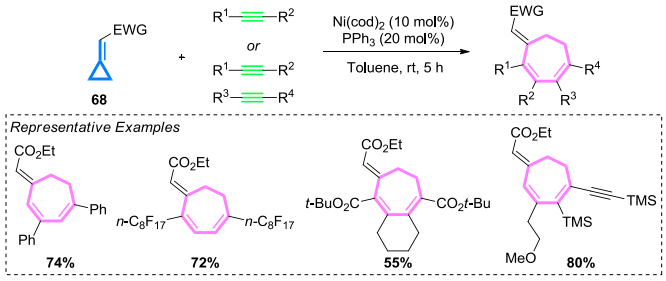


Scheme 26. Possible ring-opening mechanisms encountered with ACPs.

3.1. (3+2+2) Cycloaddition starting by oxidative addition

The nickel-mediated (3+2+2) cycloaddition of electron-deficient ACPs **68** with alkynes has been developed by the group of Saito. In 2004, they reported that upon $Ni(cod)_2$ catalysis, diversely substituted alkynes and ACPs **68** undergo a (3+2+2) cycloaddition at room temperature in toluene in moderate to good yields (Scheme 27).[59] Satisfactorily, when two different alkynes are used, the reaction yields predominantly one isomer; the opposite (minor) regioisomer is observed only in the case of electron-deficient alkynes, typically perfluorinated alkyl chain. Reactions with ketones as EWG resulted in mixtures of several products and thus are not recommended for performing (3+2+2) cycloadditions. Application to diynes was successfully undertaken, granting access to bicyclic compounds and polyconjugated systems.

The reaction mechanism of the Ni(0)-catalyzed (3+2+2) cycloaddition of ACPs **68** has been elucidated using DFT methods.[60] Computations showed that, in all cases, the



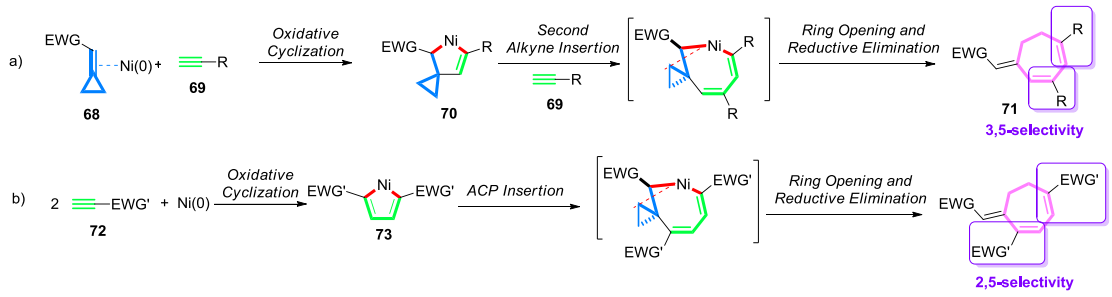
Scheme 27. Ni-catalyzed (3+2+2) cycloadditions of ACPs with alkynes.

oxidative cyclization is the rate determining step of the process but, according to the nature of the alkyne, the reaction pathway involves different intermediates. In the case of non-activated alkynes **69**, the initial π-complexation of the nickel catalyst does not proceed with the alkyne but with the ACP **68** due to more favourable electron-accepting ability of the ACP (Scheme 28a). Then, oxidative addition takes place with one equivalent of alkyne furnishing nickelacyclopentene intermediates **70**. Next, this latter undergoes the insertion of a second equivalent of alkyne through a low free energy barrier (3.1 $kcal.mol^{-1}$) followed by cyclopropane ring opening and reductive elimination. The strong exergonicity of the cyclopropane ring opening constitutes the driving force of the reaction. When strongly electro-deficient alkynes **72** are used, the mechanism is different. In these cases, it involves the more common oxidative cyclization between the two alkynes first and then insertion of the ACP (Scheme 28b).

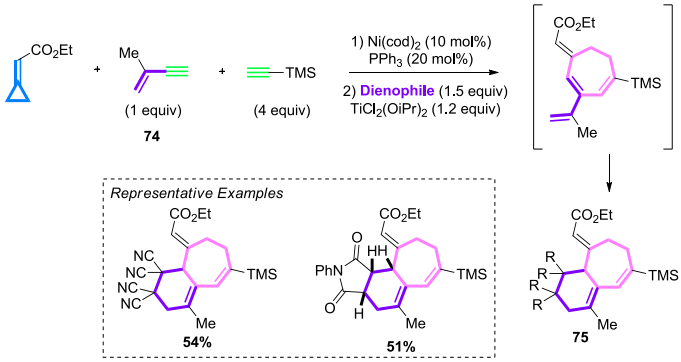
The origin of the regioselectivity was also explained. During the course of the second alkyne insertion, steric factors direct the approach to a head-to-tail addition, hence producing 3,5-disubstituted regioisomers **71**. With strongly electron-deficient alkynes **72**, the regioselectivity is a consequence of the oxidative cyclization rate determining step as it will force the nickelacycle **73** to preferentially adopt a 2,5-disubstitution pattern for electronic reasons.

Starting from this convenient operational procedure, cascade (3+2+2)/(4+2) reactions were also developed by using well-chosen ene-yne substrates **74** (Scheme 29).[61] The subsequent Diels-Alder reaction resulted in the predominant or exclusive formation of the *endo* adduct. This work constitutes an expedient route for the elaboration of seven-membered containing polycyclic derivatives **75**.

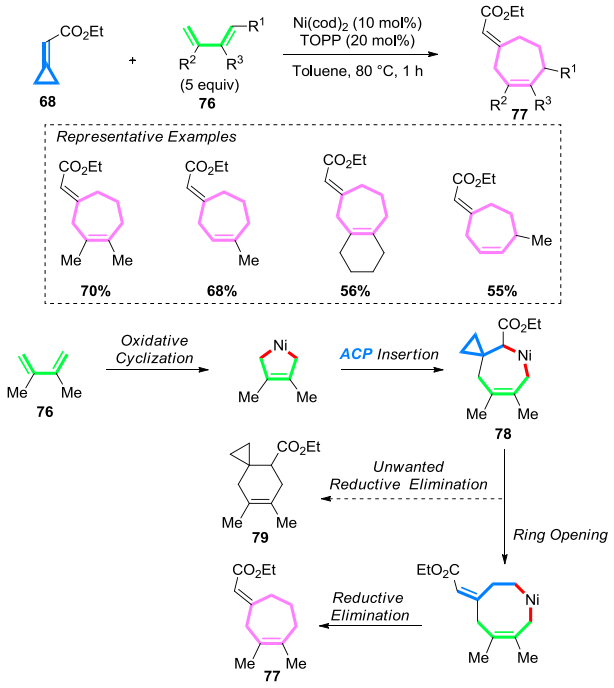
The group of Saito has also contributed to the field of (4+3) cycloadditions with an extension of their previous work on the (3+2+2) cycloaddition adapted to 1,3-dienes **76**.[62] Indeed, upon nickel catalysis, a mixture of electro-deficient ACP **68** and 1,3-dienes **76** results in the formation of seven-membered rings **77** in moderate yields (Scheme 30). It is interesting to note that optimization was needed to prevent the ACP substrate **68** from dimerizing. The reactivity was finally tamed by the help of bulky phosphite ligand TOPP. The observed formation of an undesired six-membered ring (**79**) prompted the author to propose a different mechanism than for their nickel-catalyzed (3+2+2) cycloadditions. Here, the 1,3-diene **76**



Scheme 28. Mechanisms of the Ni(0)-catalyzed (3+2+2) cycloaddition of ACPs and alkynes.



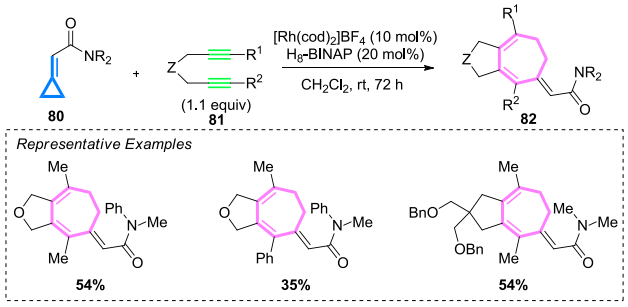
Scheme 29. Cascade (3+2+2) cycloaddition / Diels-Alder reaction.



Scheme 30. Ni-catalyzed (4+3) cycloadditions of ACPs with dienes.

first undergoes a facile oxidative cyclization with the nickel catalyst followed by the insertion of the double bond of the ACP. At this stage, the resulting seven-membered nickelacycle **78** proceeds to a cyclopropane ring opening (preferred pathway) providing the seven-membered ring **77** or can undergo an undesired reductive elimination leading to the cyclohexene **79** (less favoured pathway).

(3+2+2) Cycloadditions involving ACPs by oxidative addition are not limited to nickel catalysis as attested by the work of Tanaka *et al.* based on rhodium catalysis.[63] Upon reaction between acrylamide derivatives **80**, diyne substrates **81** and the cationic rhodium catalyst $[Rh(cod)_2]BF_4$, the seven-membered cycloadducts **82** are obtained in modest yields (Scheme 31). The reaction can be conducted at room temperature but suffer from long reaction times reaching typically 72 h and the necessity of a fairly high catalyst loading of 10 mol%. A competitive reaction leading to a six-membered cycloadduct was observed but could hopefully be suppressed thanks to the dedicated H_8-binap ligand. Terminal alkynes led to complex mixtures but unsymmetrical diynes provide the

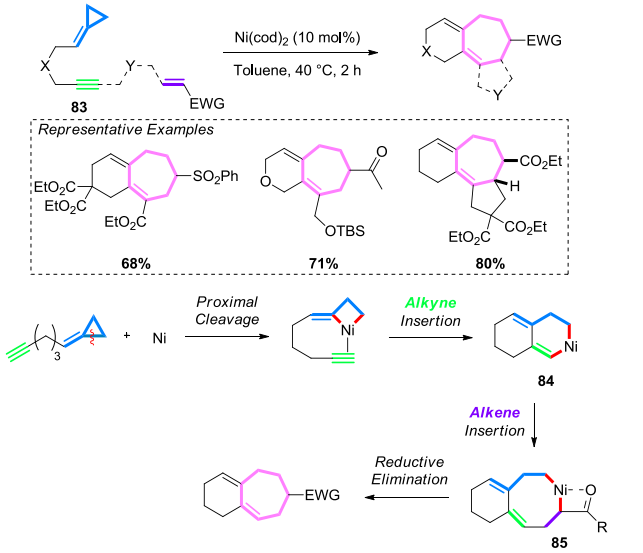


Scheme 31. Rh-catalyzed (3+2+2) cycloaddition of ACPs with diynes.

expected adduct as a single regioisomer. The exact mechanism remains unsolved, but the authors proposed the formation of a rhodacycle from the rhodium catalyst and the two alkynes prior to alkene insertion from the ACP **80**. At this stage, the resulting rhodacycloheptene can undergo a reductive elimination furnishing the spirocycle. Alternatively, β-carbon elimination followed by subsequent reductive elimination provides the expected seven-membered ring **82**.

3.2. (3+2+2) cycloaddition starting by proximal cleavage

In 2010, the Mascareñas group reported a nickel-catalyzed (3+2+2) cycloaddition between activated alkenes and yne-ACP partners **83** (Scheme 32).[64] Notably, alkene partner needs to be activated by an electron-withdrawing group, unactivated alkenes being no reactive. A full *intramolecular* version was also developed by the same group to access [6-7-5] tricyclic systems.[65] Unlike in reactions described in section 3.1, ACP substrates here are not ester-substituted and this structural feature has an influence on the reaction mechanism. Indeed, the preferred pathway does not start by the oxidative cyclization but with the *proximal* bond cleavage of the cyclopropane ring. Alkyne insertion then leads to the corresponding nickelacyclohexene intermediate **84**. At this point, the author emphasized that different pathways can be



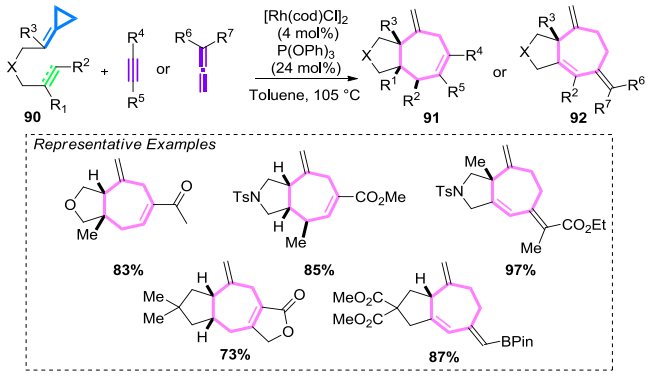
Scheme 32. Ni-catalyzed intramolecular (3+2+2) cycloadditions of ACPs, alkyne and alkene by proximal cleavage.

considered. Nonetheless, the preferred one involves coordination of the alkene prior to insertion, which is regioselective due to a Ni-O interaction in **85**. The alkene insertion was found to be the rate-determining step with a free energy barrier of 26.2 kcal.mol^{-1}. The product is eventually obtained after a reductive elimination step.

Interestingly, this process of *proximal* bond cleavage can also be applied to bicyclopropylidene (BCP, **86**) in an *intermolecular* fashion, as demonstrated by de Meijere *et al.* (Scheme 33).[66] Under the standard reaction conditions and with one equivalent of each reagent, only the surprising tricyclopropanated compound **88** is formed from two units of BCP instead of the expected cycloadduct **89**. It must be noted that the double bond of the ene-yne substrate **87** is not affected by the reaction outlining here a significant difference in reactivity between standard alkenes and the internal alkene of BCP (**86**). The mechanism is not yet fully understood; the two main pathways described in nickel-catalyzed (3+2+2) cycloadditions can be envisaged (oxidative cyclization or *proximal* cleavage). However, in light of the work of Mascareñas, it is likely that the reaction predominantly involves *proximal* cleavage, especially since the alkene does not show an electron-withdrawing group substitution.

3.3. (3+2+2) cycloaddition starting by distal cleavage

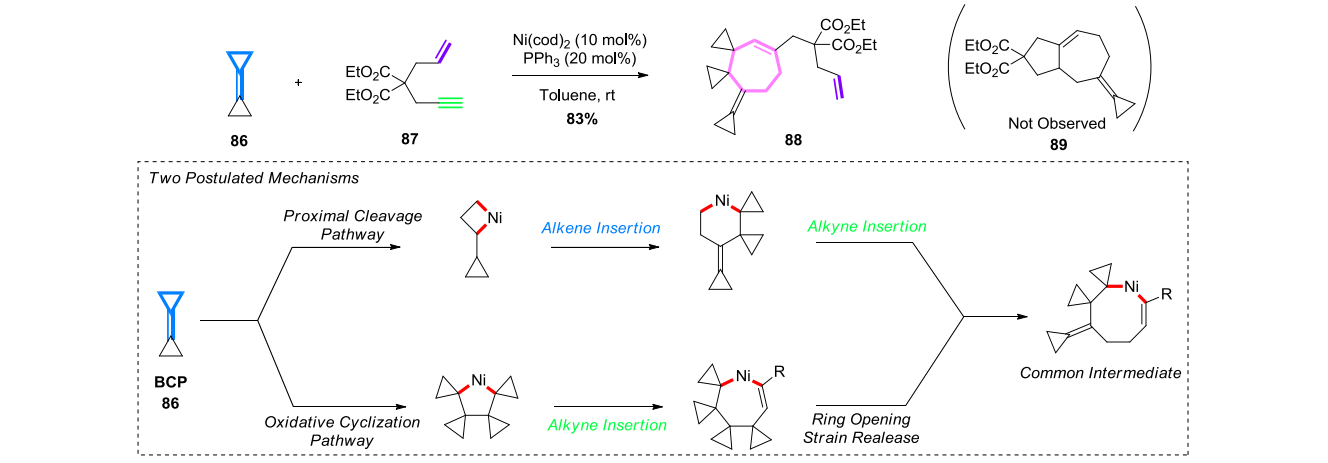
Rhodium-mediated *intermolecular* (3+2+2) cycloaditions were first reported by Evans in 2008.[67] Upon heating, the reaction between an ene-ACP substrate **90** and an external alkyne affords [5.3.0] bicyclic compounds **91** (Scheme 34). The regioselectivity issue was solved by using a bulky phosphite ligand, $P(OPh)_3$, in excess with respect to the rhodium catalyst. The diastereoselectivity is in favour of the *cis* isomer in all cases. This convenient procedure served as a basis for the expedient three-step synthesis of Pyrovellerolactone (overall yield of 48%).[68] Extension of this methodology to allenes (with replacement of ene-ACP by yne-ACP) produces corresponding cycloadducts **92** displaying two exocyclic double bonds, opening access to many possibilities of post-



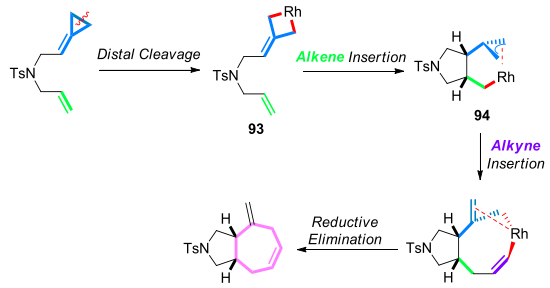
Scheme 34. Rh-catalyzed (3+2+2) cycloadditions of ACPs with alkynes or allenes *via* distal cleavage.

functionalization.[69]

Mechanistic studies revealed a different behaviour of ACPs when treated with a rhodium salt (Scheme 35).[70] Unlike in the case of nickel catalysis, the reaction starts here by a rhodium insertion by *distal* cleavage of the cyclopropane unit. From the obtained rhodacyclobutane **93**, two different pathways can be considered depending on the order of insertion of the two partners: alkene prior to alkyne or the opposite. Calculations predict that the pathway involving first the alkene insertion and then alkyne carbometalation is the most favoured one. According to this pathway, the alkyne insertion is the rate-determining step of the process closely followed by reductive elimination. On the other hand, the pathway involving alkyne insertion prior to alkene carbometalation is predicted to involve a high free energy barrier of 41.7 kcal.mol^{-1} for the reductive elimination step thus preventing the reaction from following this mechanism. This difference Is accounted for by the higher stability of the rhodium complex in the former mechanism (formally between 14*e* and 16*e* instead of 12*e* to 14*e*). The recent isolation and characterization of the rhodacycle intermediate **94** resulting from *distal* cleavage and alkene insertion provided support to the predicted model.[71]



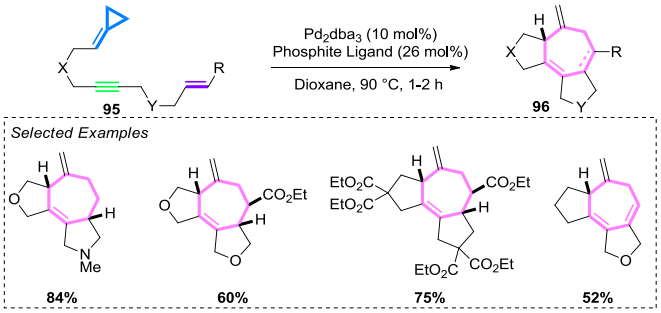
Scheme 33. Ni-catalyzed (3+2+2) cycloaddition with BCP and alkynes.



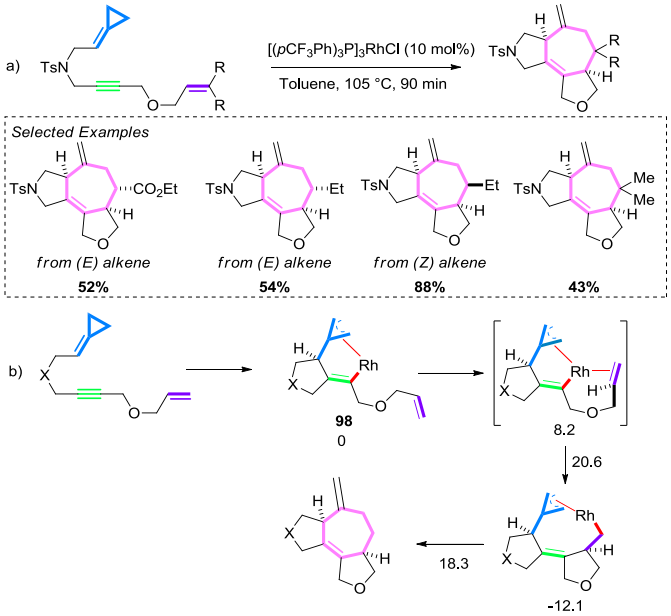
Scheme 35. Mechanism of the Rh-catalyzed (3+2+2) cycloadditions of ACPs with alkynes *via* distal cleavage.

Mascareñas *et al.* reported in 2010 an *intramolecular* palladium-mediated (3+2+2) cycloaddition involving ACPs.[72] Reaction of diyne or ene-yne substrates **95** similar to those used in their nickel-catalyzed cycloadditions (see section 3.2.) resulted in the formation of tricyclic [5-7-5] systems **96** in moderate to good yields with an exclusive all-*cis* diasteroselectivity (Scheme 36). It is important to point that the choice of the palladium ligand was shown to be crucial as only bulky phosphite ligands enable preferred formation of the seven-membered adduct over other cyclization products. Unfortunately, the exact nature of the mechanism remains unsolved to date. However, the same group reported the palladium-catalyzed (4+3) cycloaddition of ACP for which the supported mechanism involves the *distal* cleavage of the cyclopropyl unit (*vide infra*). Their mechanistic hypothesis for the (3+2+2) cycloaddition follows that same pathway, which is different from the *proximal* cleavage observed in nickel catalysis but is coherent with rhodium catalysis.

A few years later, Mascareñas *et al.* improved the reaction outcome of the (3+2+2) cycloaddition by using a dedicated rhodium catalyst [(pCF$_3$Ph$_3$P]$_3$RhCl (Scheme 37a).[73] In comparison to palladium catalysis, rhodium-mediated (3+2+2) transformation allows the use of trisubstituted alkenes **97** with excellent diastereoselectivities depending on the nature of the alkene. Yields are moderate to good and no compound derived from the (3+2) cycloaddition was observed. A theoretical study provided insights into the origin of the *syn* diastereoselectivity and the absence of (3+2) cycloadduct (Scheme 37b). Upon rhodium catalysis, the rhodacycle **98** is first formed by oxidative cyclometallation between the alkene of the ACP and the alkyne partner involving a distal cleavage of the cyclopropyl unit. From this intermediate (**98**), alkene insertion



Scheme 36. Pd-catalyzed (3+2+2) intramolecular cycloaddition of ACPs with alkynes and alkenes.

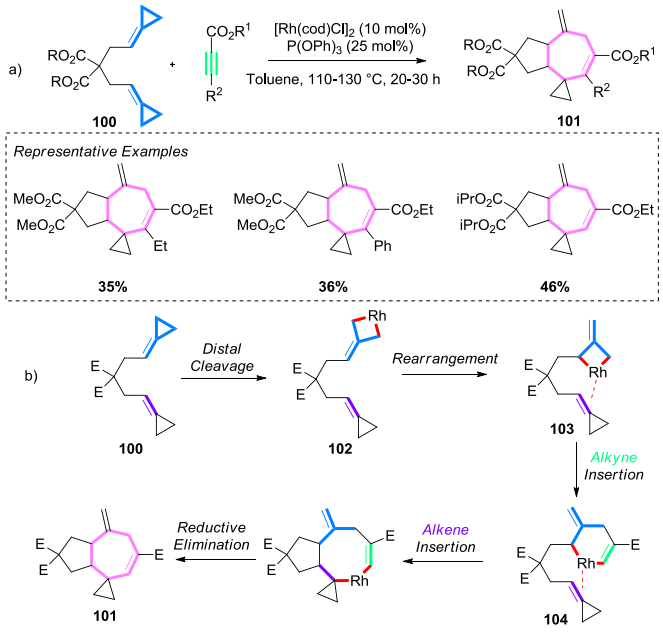


Scheme 37. Rh-catalyzed intramolecular (3+2+2) cycloaddition of ACPs with alkynes and alkenes. Free energies are given in kcal.mol^{-1} relative to **98**.

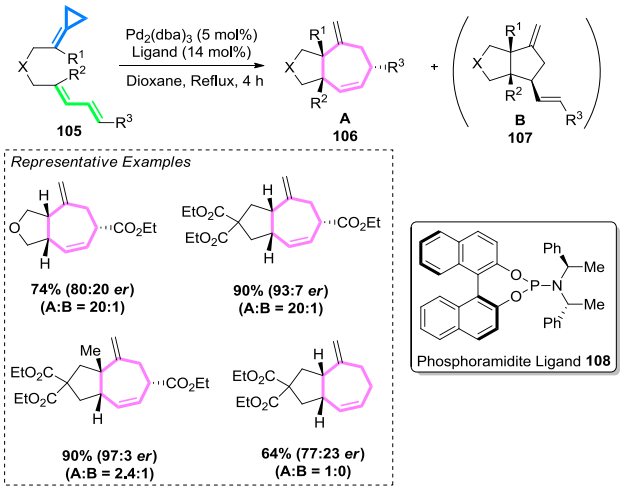
and subsequent reductive elimination (with a quite high energetic barrier of 30.4 kcal.mol^{-1}) lead to *cis* cycloadduct. The absence of *trans* cycloadduct and (3+2) cycloadduct lies in a significantly higher free energy barrier for the reductive elimination step (38.3 kcal.mol^{-1} and 44.4 kcal.mol^{-1} respectively), thus justifying the need of heating. In comparison, palladium catalysis involves lower energetic barriers, especially between the (3+2+2) and (3+2) cycloadducts resulting in the presence of undesired (3+2) compounds with this catalyst.

Recently, the formation of 5-7-3 spirocyclic carbocycles **101** was achieved starting from bis(methylenecyclopropanes) **100** in an intermolecular fashion upon rhodium catalysis.[74] The reaction grants access to an original motif featuring a spiro center but somehow suffers from a relatively high catalyst loading of 10 mol% along with low to moderate yields (Scheme 38a). Only electron-deficient alkyne are however suitable substrates. Despite elevated temperatures and long reaction times, the reaction proved to be highly regioselective. The authors postulated a mechanism involving an initial distal cleavage of the cyclopropyl unit (Scheme 38b). Once the rhodacyclobutane **102** is formed, a rearrangement into **103** would enable a potential alkyne insertion forming the rhodacyclohexene **104**. This intermediate would evolve *via* alkene insertion and then reductive elimination would furnish the spiro cycloadduct **101**.

In 2007, the Mascareñas group described the palladium-catalyzed *intramolecular* cyclization between ACPs and dienes **105** as component of a (4+3) cycloaddition.[75] The reaction yields [5.3.0] bicycloadducts **106** displaying an exocyclic alkene and a *cis* relationship at the cycle junction (Scheme 39). The formation of a [3.3.0] bicycle **107** was also observed and the use of phosphoramidite ligands greatly favoured the formation of the seven-membered product over the five-membered one.



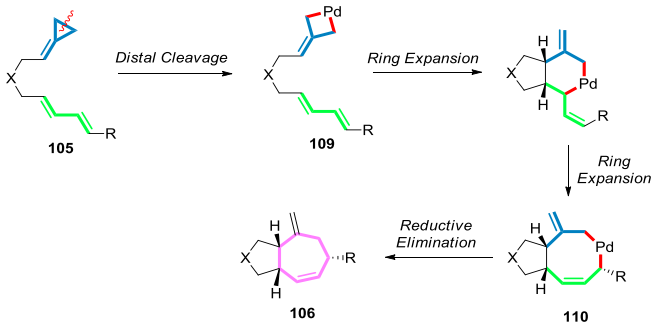
Scheme 38. Rh-catalyzed (3+2+2) cycloaddition between bis(methylenecyclopropanes) and alkynes.



Scheme 39. Pd-catalyzed (4+3) intramolecular cycloaddition of ACPs with dienes.

An asymmetric variant of this reaction was reported recently by the same group using chiral phosphoramidite ligand **108**.[76]

The mechanism postulated by the authors proceeds as follows: First, the *distal* bond of the cyclopropane ring is cleaved by the palladium complex affording the corresponding palladocyclobutane intermediate **109** (Scheme 40). Then, successive ring expansion, *via* (3+2) cycloaddition, and [1,3] shift of the palladium delivers the palladocyclooctane **110**. Finally, the reductive elimination step closes the catalytic cycle to provide the [5.3.0] bicycloadduct **106**.



Scheme 40. Mechanism of the Pd-mediated (4+3) cycloaddition.

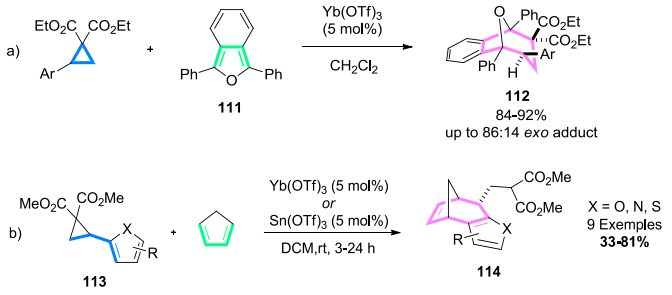
4. Donor-acceptor cyclopropanes (DACP)

Donor-acceptor cyclopropanes (DACP) can be used as a three-carbon unit in many cycloaddition reactions.[77] Indeed, the donor and acceptor substituents of DACP favour the heterolytic ring-opening of the cycle generating a reactive 1,3-zwitterion intermediate which can then react in a variety of cycloaddition reactions. When the partner is a 1,3-dienes, it results in a (4+3) cycloaddition. In this field, the group of Ivanova has made significant advances.[78] They showed that, upon Lewis acid catalysis, typically $Yb(OTf)_3$, excellent yields in (4+3) cycloadducts **112** are obtained using isobenzofuran **111** as the diene partner (Scheme 41a). Although mixtures of *endo* and *exo* adducts are observed, the *exo* approach is favoured. This methodology was also successfully applied to anthracenes by the group of Ivanova.[80]

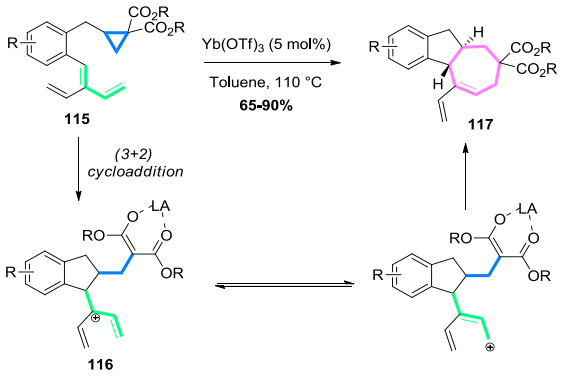
Recently, Werz *et al.* evaluated the relationship between the specific rate constant and the nature of the substitution of the cyclopropane and has shown that the reaction is significantly accelerated with electron-donnor substituents.[79] Even though this study was originally devoted to the (3+2) cycloaddition, the authors demonstrated that the same trends could be obtained for the (4+3) cycloaddition.

In the case of furan-, pyrrole- or thiophen-substituted DACP **113**, the reactivity changes drastically since this kind of DACP acts as a VCP (Scheme 41b). Accordingly, two of the three carbons of the initial cyclopropane ring are not part of the seven-membered final product **114**.[81]

Unfortunately, simple non-cyclic 1,3-dienes failed to provide the expected seven-membered cycloadduct with the exclusive formation of a vinylcyclopentane derivative, originating from a (3+2) cycloaddition process.[82] An elegant



Scheme 41. (4+3) cycloaddition of DACPs with isobenzoxazole derivative.



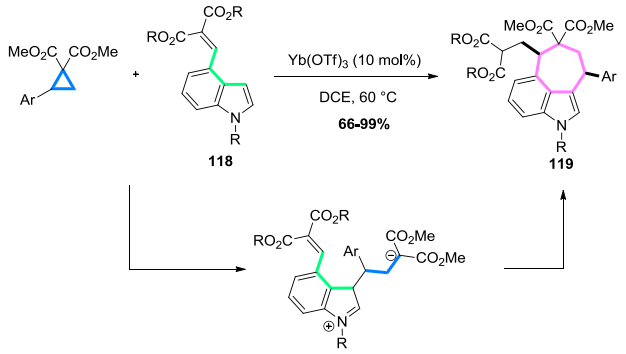
Scheme 42. (4+3) cycloaddition of DACPs with trienes.

solution to this problem was brought by the group of Wang, relying on the use of the triene **115** exhibiting a double geminal vinyl substitution (Scheme 42).[83] Indeed, after the first C-C bond formation, the triene structure leads to a stable divinyl-substituted carbocation **116**. The trapping of this species eventually provides the desired overall (4+3) cycloadduct **117** showing a conjugated diene motif. This procedure is however restrained to intramolecular processes.

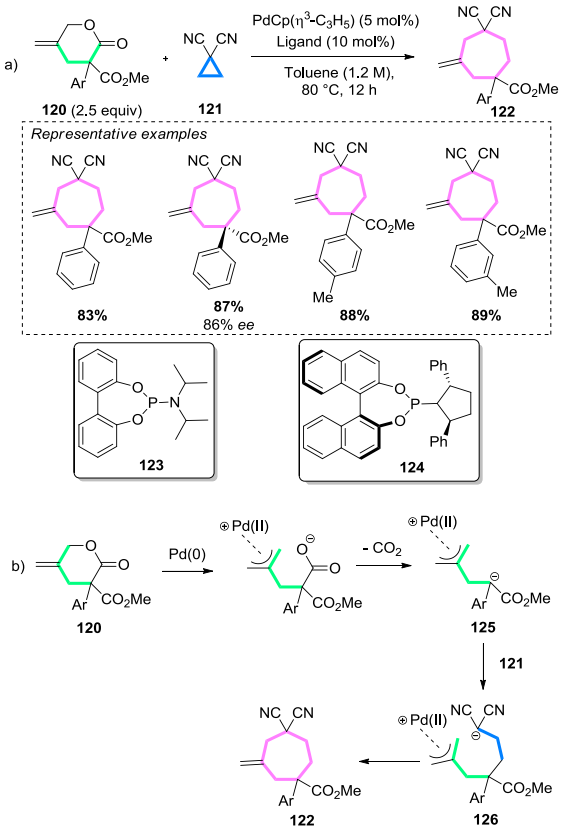
Recently, indoles **118** substituted in C^4 position by a Michael acceptor motif were also explored as potential partners with DACP.[84] Upon Lewis acid catalysis, a cascade reaction consisting of a Friedel-Craft alkylation followed by a Michael addition is made possible (Scheme 43). The observed diastereoselectivity is excellent, ranging from 9:1 to >20:1. The cycloadduct **119** exhibits an uncommon polycyclic core connecting seven-, six- and five-membered rings.

Decarboxylative mechanism can also be used upon palladium catalysis as attested by Shintani and Hayashi's work.[85] In this example, the cyclopropane **121** is only acceptor and the four-atom partner is an allylic lactone (**120**, Scheme 44a).

The achiral phosphoramidite ligand **123** revealed to be mandatory, in a quite concentrated media, to observe good yields. In a dedicated chiral version using **124**, good *ee* were obtained. In terms of mechanism, oxidative addition on the allyl moiety of **120** leads to decarboxylation and the corresponding stabilized carbanion **125** reacts by ring-opening of the cyclopropyl unit. Then, the ring closure occurs after addition on the π-allylpalladium of **126** to deliver the seven-



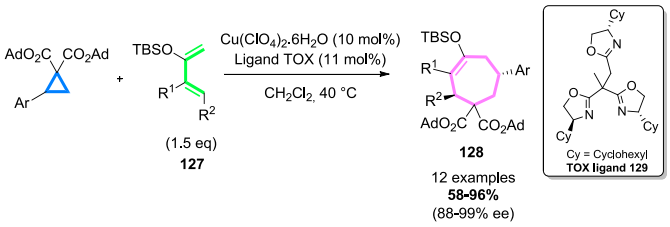
Scheme 43. Cascade reaction between ACPs and C4-substituted indoles **118**.



Scheme 44. Pd-catalyzed (4+3) cycloaddition of allyliclactone with 1,1-dicyanocyclopropane.

membered rings **122** in good to excellent yields (Scheme 44b). Interestingly, the reactivity can be completely switched to (6+3) cycloaddition by changing the lactone substituents, hence avoiding the decarboxylative step if alkyl substituents are used instead of aryl substituents.

A nice example of asymmetric annulation of DACP with 1,3-dienes was reported by Tang (Scheme 45).[86] The reaction features a dienolsilyl ether **127** as the diene partner and an uncommon copper catalysis in the field of DACP. Regarding the enantiocontrol, the BOX ligands enabled a good stereoselectivity reaching up to 92% *ee* but with moderate yields. These low yields can be attributed to competition between (4+3) and (3+2) cycloaddition processes. With the help of TOX (TrisOXazoline) ligand (**129**), both *ee*'s and yields are excellent, with the exclusive formation of the seven-membered cycle **128**. This report constitutes a rare example of asymmetric catalysis with DACP for the elaboration of seven-membered rings.



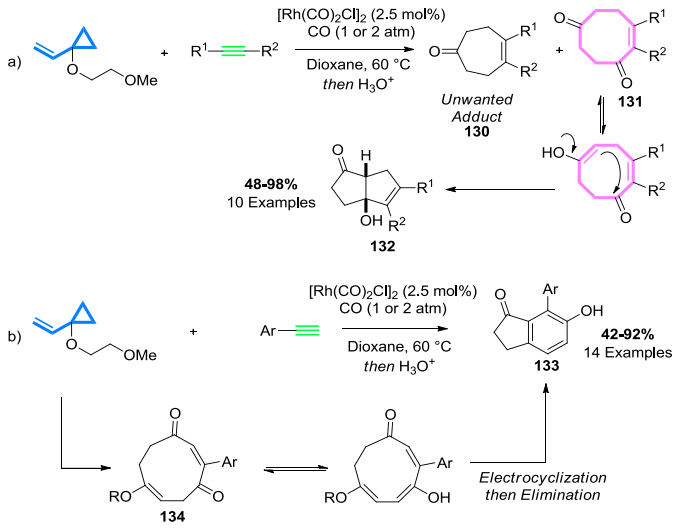
Scheme 45. Asymmetric (4+3) cycloaddition between DACPs and conjugated enol ethers.

5. Eight and nine-membered carbocycles

The synthesis of eight-membered carbocycles from cyclopropanes relies essentially on the transition metal-catalyzed (5+2) cycloaddition reaction of VCP but performed under CO atmosphere in order to provide the extra carbon atom. Accordingly, these methodologies are frequently labelled as (5+2+1) cycloaddition reactions or even (7+1) if the VCP and the alkyne/alkene partner are parts of the same molecule. In this field the groups of Wender and Yu made significant contributions.[33,87] More occasional synthetic strategies toward eight-membered carbocycles from cyclopropanes involve Lewis acid catalysis. Finally, the synthesis of nine-membered carbocycles will be briefly discussed illustrating the (4+3+2) cycloaddition process.

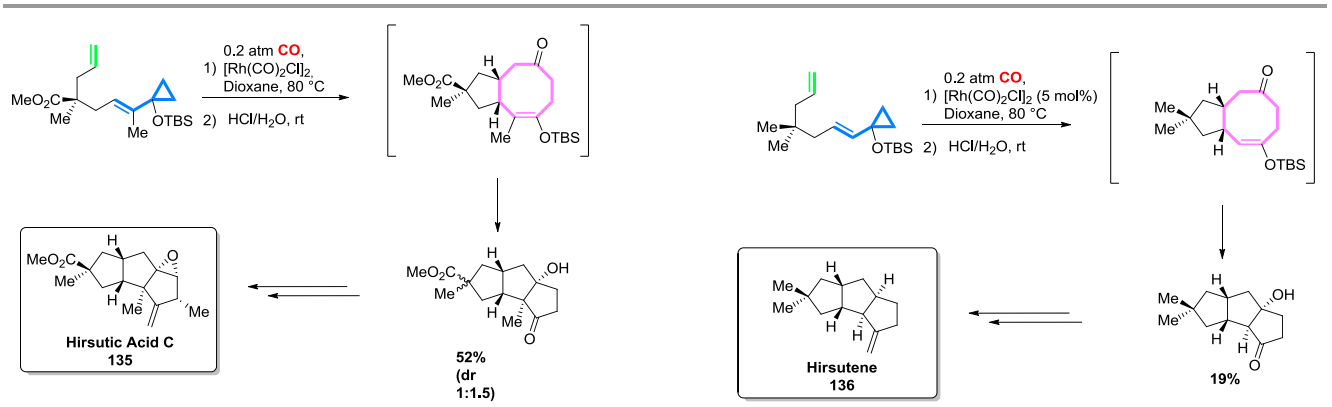
5.1 (5+2+1) / (7+1) cycloaddition

The possibility of performing a homologous version of the rhodium-mediated (5+2) cycloaddition process under CO atmosphere was investigated by the Wender group as early as in 2002.[88] However, initial attempts provided only minor amounts of the desired eight-membered ring **131** along with undesired seven-membered ring **130** and, as the main product, an unexpected [3.3.0] bicyclic compound **132** (Scheme 46a). This low proportion of the expected cycloadduct can be explained by the fact that it undergoes in situ a subsequent transannular cyclization leading to **132**. It is important to note that the alkyne partner was systematically substituted by an electron-withdrawing group, typically an ester or a ketone, to ensure a suitable reaction outcome. Indeed, in the absence of this substitution pattern, the reactivity is in favour of a (5+1+2+1) four-component process that eventually furnishes indenone derivatives **133**, the eight-membered cycle being observed only in very low proportion (< 16%) (Scheme 46b).[89] Formation of indenones **133** in these cases is due to a second CO insertion leading to the formation of a nine-membered carbocycle **134** that undergoes an electrocyclization followed by an elimination, driven by aromatization. Thus, this methodology does not grant access to eight-membered rings but constitutes an expedient access to the [3.3.0] bicycle scaffold **132** as illustrated by the total synthesis of Hirsutic Acid C[90] **135** and Hirsutene[91] **136** (Scheme 47). Concerning the synthesis of Hirsutene **136**, the authors described the (5+2+1) process for seven different substrates, reaching yields up to 67%. Sadly, the dedicated substrate was the worst to perform. Interestingly, in one of those examples, no further contraction was observed and an eight-membered cycloadduct was finally obtained in 50% yield, as a single diastereomer.



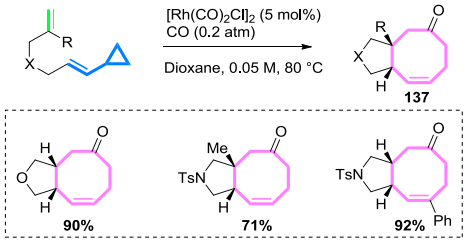
Scheme 46. Rh-catalyzed (5+2+1) cycloadditions between VCPs and alkynes and their subsequent transannular cyclization.

The first successful report of a (5+2+1) process without subsequent transannular cyclization was reported by Wender and Yu in 2007 with the intramolecular reaction of VCP and alkenes (Scheme 48).[92] This work was prompted by the fact that $[Rh(CO)_2Cl]_2$ is unable to promote the (5+2) cycloaddition of VCP with alkenes, due to a difficult reductive elimination to form a $C(sp^3)$-$C(sp^3)$ bond. The authors reasoned that insertion of CO would lead to a $C(sp^2)$-Rh-$C(sp^3)$ intermediate for which migratory reductive elimination (MRE) to a (5+2+1)

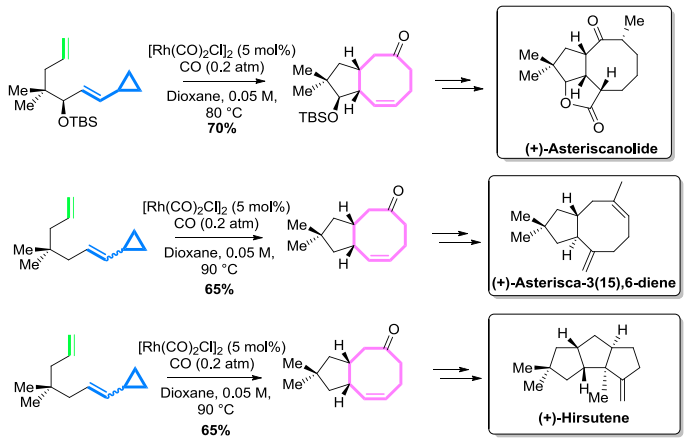


Scheme 47. Rh-catalyzed (5+2+1) cycloadditions in natural product total synthesis.

cycloadduct would be favoured by the formation of a C(sp^2)-Csp^3) bond. In practice, under 0.2 atmosphere of CO, the expected [6.3.0] bicycles **137** were effectively obtained as single *cis* isomers and in excellent yields. It can be noted however that reactions were undertaken in dilute solutions and needed a temperature of 80 °C. The application of this methodology was quickly illustrated by the synthesis of Asterisca-3(15),6-diene,[93] Hirsutene[94] and (+)-Asteriscanolide (Scheme 49).[95]

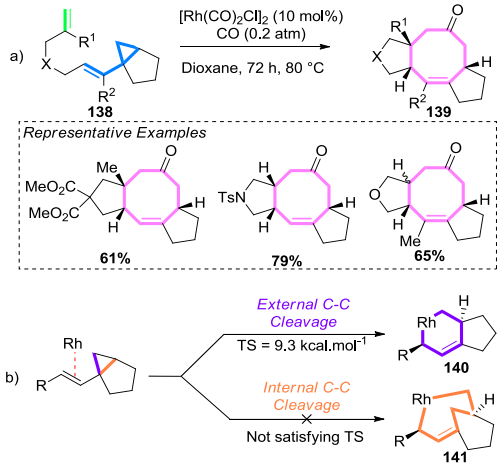


Scheme 48. Rh-mediated (5+2+1) cycloadditions between VCPs and alkenes

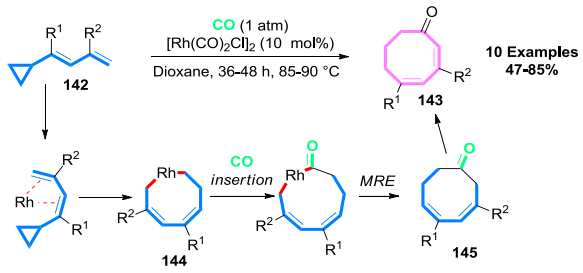


Scheme 49. Application of the Rh-catalyzed (5+2+1) methodology in total synthesis.

Extension of this methodology to a fused VCP substrate **138** was reported three years later.[96] With this kind of substrate, the (5+2+1) cycloaddition yields [5-8-5] tricyclic compounds **139** (Scheme 50a). With substituted VCPs the diastereoselectivity is low, ranging from 1:1.3 to 1:1.6 and the reaction still requires a long reaction time of 72 h. Calculations suggest that the cyclopropane cleavage involves a free energy barrier of 9.3 kcal.mol^{-1} to form the rhodacyclohexene **140** (Scheme 50b). The possibility of a cleavage of the internal C-C bond was also evaluated but no satisfying TS could be obtained.



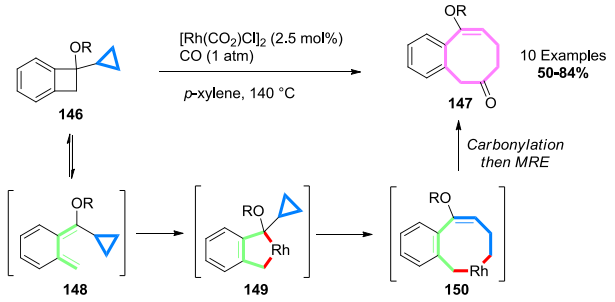
Scheme 50. Rh-catalyzed (5+2+1) cycloaddition with fused VCPs.



Scheme 51. Rh-catalyzed (7+1) cycloaddition with buta-1,3-dienylcyclopropanes.

Besides the (5+3+1) cycloaddition, access to eight-membered carbocycles from cyclopropanes was also described *via* a (7+1) process by the group of Yu in 2011. Starting from buta-1,3-dienylcyclopropanes **142**, upon rhodium catalysis and a CO atmosphere, the corresponding cycloadducts **143** were obtained in moderate to good yields (Scheme 51).[97] The reaction suffers from long reaction times typically comprised between 36 and 46 h with extensive heating in dioxane. According to the authors, the mechanism would involve the formation of a rhodacyclooctadiene **144** *via* complexation of the rhodium catalyst to the double bonds of the substrate. At this stage, the reductive elimination is considered difficult between two sp^3 carbon. However, when the carbonylation occurs, the migratory reductive elimination proceeds with much more efficiency and eventually affords the cycloadduct **145**. An isomerisation step finally delivers the fully conjugated compound **143**.

More recently, the group of Yu reported also the use of benzocyclobutenes **146** as the polyene partner in a formal (7+1) cycloaddition process (Scheme 52).[98] In conjunction with a rhodium catalyst and under a CO atmosphere the corresponding eight-membered rings **147** are obtained in good yields. According to the authors, the mechanism would start by the ring-opening of the cyclobutene enabling the formation of the key conjugated diene **148**. Then, oxidative addition of the rhodium catalyst would form the rhodacyclopentene **149**

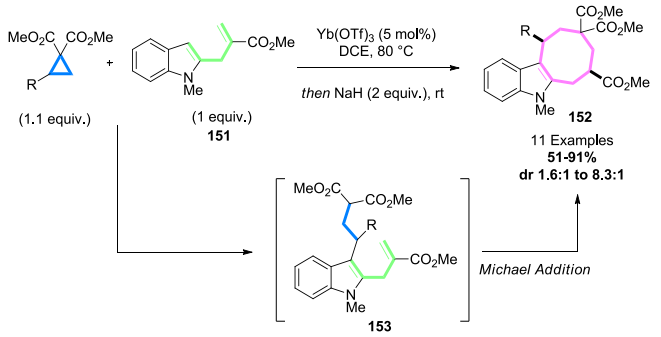


Scheme 52. Rh-catalyzed (7+1) cycloaddition of benzocyclobutenes.

which would evolve into the corresponding rhodacyclooctadiene **150** after ring-opening of the cyclopropane unit. The carbonylation step would occur at this stage, therefore furnishing the expected cycloadduct due to a facile migratory reductive elimination process. In order, for this process, to be efficient, it is required to protect the alcohol function by a silyl group. Otherwise, the formation of the corresponding cyclopropyl ketone is observed.

5.2 Miscellaneous methods

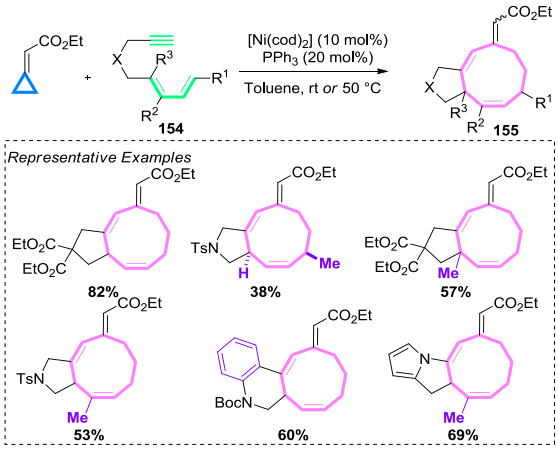
Besides the (5+2+1) and (7+1) cycloaddition strategies, a few reports contribute to the synthesis of eight-membered rings from cyclopropanes. In 2019, the group of Harada and Nishida reported a (5+3) annulation strategy involving DACP and indole derivatives **151** (scheme 53).[99] This tandem reaction features first a ring-opening of the cyclopropane unit, triggered by the nucleophilic addition of the indole moiety, followed by an intramolecular Michael addition to afford the corresponding eight-membered carbocycle **152**. Although this reaction can be performed in a one-pot manner, it is possible to isolate the intermediate **153**. Here, $Yb(OTf)_3$ was found to be the best Lewis acid to activate the cyclopropane. The diastereoselectivity is in favour of the *cis* isomer but selectivity is low (usually from 1:2 to 1:5). When an optically pure DACP is used, the reaction proved to be stereospecific since the cycloadduct **152** shares an unmodified enantiomeric excess.



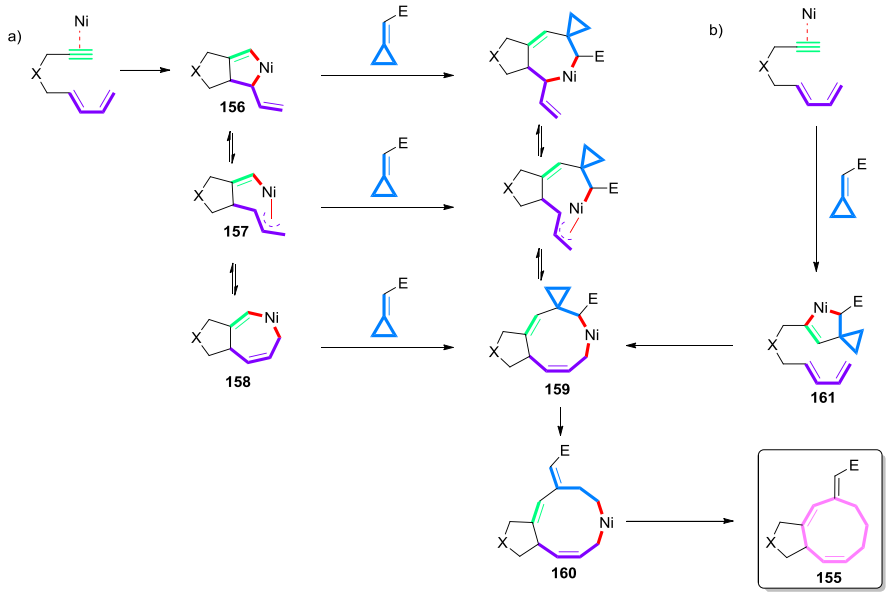
Scheme 53. (5+3) cycloadditions between DACPs and 2-substituted indoles **151**.

5.3 Nine-Membered Carbocycles

To date, the only example of the synthesis of nine-membered carbocycle from cyclopropane has been reported by the Saito group.[100] Their methodology relies on nickel-mediated (4+3+2) cycloaddition between an ester-substituted ACP and a diene-yne substrate **154** (Scheme 54). The reaction proceeds at room temperature or 50 °C in toluene and requires a slow addition of a mixture of substrates on the nickel catalyst. The main cycloadducts **155** always display a *E* stereochemistry of the exocyclic double bond but the separation from the *Z* isomer is reported to be tedious in several cases. The nature of the substituents on **154** proved to be determinant for the reactivity: in the case of terminal alkene substitution, the reaction takes place successfully for the *E* isomer whereas the reaction of the *Z* and *ipso* isomers results in the absence of the expected cycloadduct **155**. The substitution of the internal alkene has, on the contrary, no impact on the reaction outcome. Its stereochemistry is however crucial since the reaction works only for the *E* isomer, the *Z* alkene providing complex mixtures. Concerning the alkyne moiety, it must be terminal; substitution resulting in no cycloadduct. Lastly, several linkers were evaluated with success such as a *o*-ethynylbenzene core or pyrrole derivatives.



Scheme 54. Ni-catalyzed (4+3+2) cycloaddition between electron-poor ACP and diene-yne.



Scheme 55. Possible reaction pathways for the Ni-mediated (4+3+2) cycloaddition.

The exact mechanism of this (4+3+2) cycloaddition process remains unsolved. However, two pathways involving nickelacycle intermediates have been proposed by the authors. The coordination of the alkyne to the nickel catalyst is very facile and thus constitutes the common starting point of both mechanisms. The first pathway involves the formation of a nickelacyclopentene **156** from the alkyne and the internal alkene of the diene-yne substrate **154** (Scheme 55a). This intermediate would then equilibrate with a nickelacycloheptadiene **158**, through a π-complex **157**. For each of these putative intermediates it is possible to consider the insertion of the alkene from ACP. Eventually, after ring-opening of the cyclopropyl unit, all these intermediates would converge to a ten-membered nickelacycle **160** from which the expected cycloadduct **155** is obtained after reductive elimination. The other postulated pathway involves the formation of a nickelacyclopentene **161** from the alkyne and the ACP's alkene (Scheme 55b). Insertion of the diene moiety would then furnish the corresponding nine-membered nickelacycle **159**, already encountered in the first proposed pathway. From there, the rest of the mechanism is identical, *i.e*. cyclopropane cleavage and reductive elimination.

Conclusions

For more than 25 years, the cyclopropyl unit has been a key building block for the development of synthetic methodologies toward medium-sized carbocycles. The different patterns of the cyclopropane core (VCPs, ACPs or DACPs) allow for a diverse array of cycloaddition reaction profiles such as (5+2), (3+3+1), (3+2+2) or (4+3) for seven-membered carbocycles and (5+2+1), (7+1) and (4+3+2) for eight- and nine-membered respectively. A series of transition metals have been described to catalyze such transformations, the most prevalent metals being Rh, Ru, Ir as well as the more earth-abundant Cu, Fe and Co. Lewis acids proved also to be efficient catalysts to trigger the ring-opening and cycloaddition of DACPs. The classic mechanism behind most of the transition metal-catalyzed transformations involves the formation of a metallacycle *via* oxidative cyclization and cyclopropane ring-opening. The reactivity of these metallacycles has been studied by computational means in order to get a better understanding of the reactivity and selectivity in the cycloaddition processes. The interest of cyclopropanes in the synthesis of medium-sized carbocycles has been demonstrated by their application in the stereoselective preparation of many complex molecules including natural products and pharmaceuticals. In the future, the development of new catalytic systems should enable to increase further the reactivity in these cycloadditions (temperature being an issue) and the substrate scope. The use of more sustainable catalysts, maybe involving other modes of activation, is another space for further developments.

Author Contributions

All authors contributed equally to the elaboration of this work.

Conflicts of interest

There are no conflicts to declare.

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