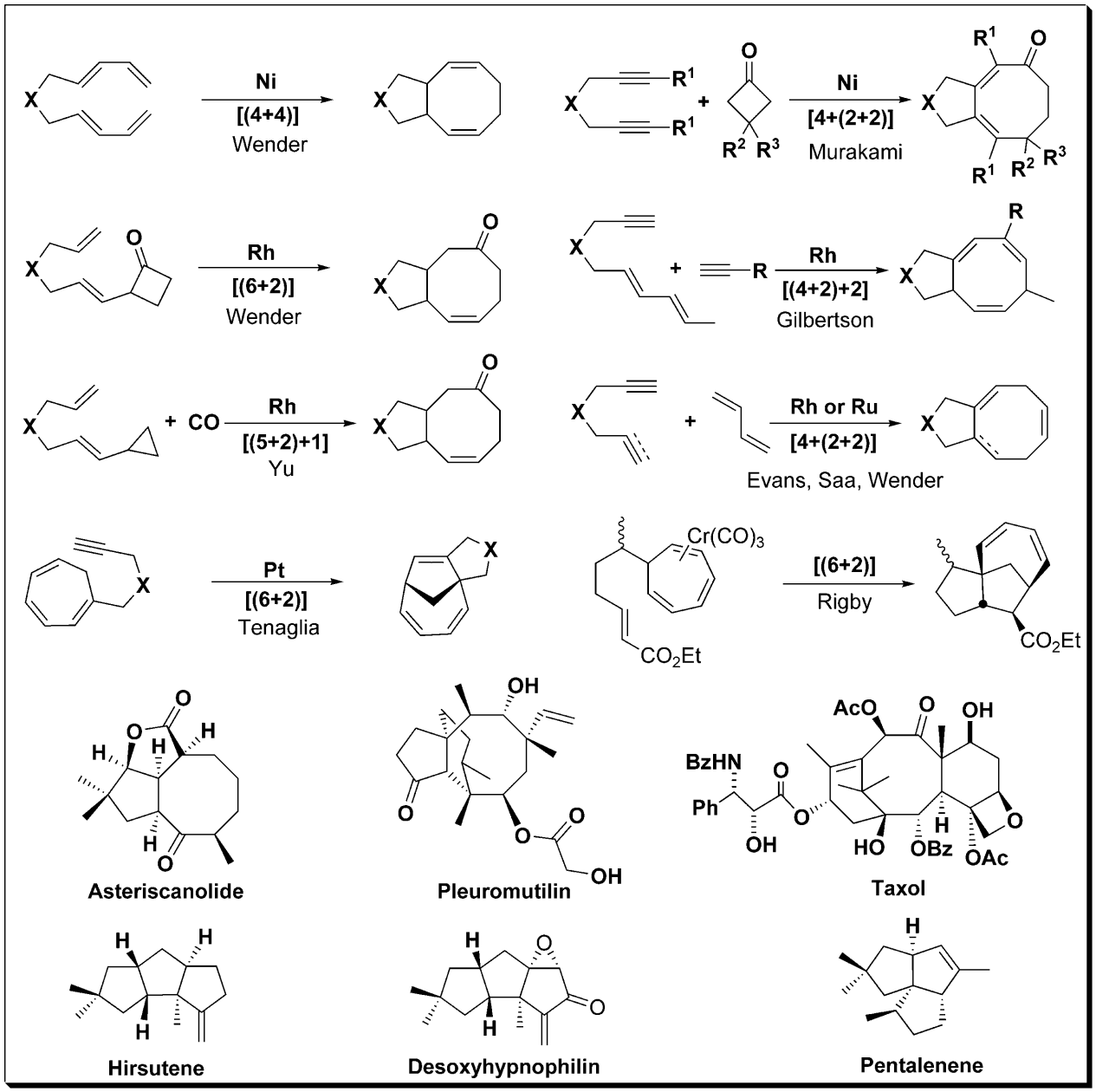
DOI: 10.1002/asia.200900712

Transition-Metal-Catalyzed Cycloadditions for the Synthesis of Eight-Membered Carbocycles

Zhi-Xiang Yu,* Yi Wang, and Yuanyuan Wang[a]

Dedicated to the 100th anniversary of the College of Chemistry, Peking University



Abstract: Eight-membered carbocycles are found in a wide variety of natural products that exhibit a broad range of biological and medicinal activities (cf. the most potent anticancer drug, taxol). However, the synthesis of eight-membered carbocycles is quite challenging as traditional approaches are met with entropic and enthalpic penalties in the ring-forming transition states. These negative effects can be totally or partially avoided with the implementation of transition-metal-catalyzed/mediated cycloadditions. In this Focus Review, examples of elegant and efficient metal-catalyzed and some metal-mediated cycloadditions (including Ni- catalyzed [4+4] and Rh-catalyzed [4+2+2] and [5+2+1] reactions) are presented to illustrate this. Application of these cycloaddition reactions in total synthesis is also presented to show the significance of these reactions in addressing challenges in natural product synthesis.

Keywords: cycloaddition · eight-membered carbocycles · total synthesis · transition metals

Introduction

Carbocycles of various ring sizes are widely found in natural products and often incorporated into drugs. While five- and six-membered carbocycles are most common, seven- and eight-membered or larger carbocycles occupy a significant fraction of these compounds.[1] Figure 1 shows some natural products containing eight-membered carbocycles. Although the number of natural products containing eight-membered carbocycles is limited, these natural products have garnered the attention of synthetic organic and medicinal chemists.[1,2] This interest is a result of the medicinal and biological properties these compounds possess, making them attractive as drugs, drug leads, or biological probes.[3] Taxol, the most well-known natural product in this family, is now among the most potent anticancer drugs in clinical use.[4] In 2008, another member of this family—pleuromutilin—was approved for use as an anitbiotic by the FDA.[5]

Another draw to study eight-membered carbocycles comes from the general challenge of synthesizing medium-sized ring systems (usually 8- to 12-membered rings). Traditional ring-closure strategies are effective for small ring systems, but problematic for medium-sized ring systems owing to entropic and transannular penalties incurred when bringing the two ends of a reactant together.[6]

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To date, several methods to form eight-membered carbocycles have been developed including ring-closing metathesis and Cope rearrangement.[7] Despite these important advances, there is a lack of generality to accommodate many target structures.[2c] Considering the complexity of natural products containing eight-membered carbocycles, new reactions that are both general and robust would be readily welcomed. In recent years, significant progress in this direction

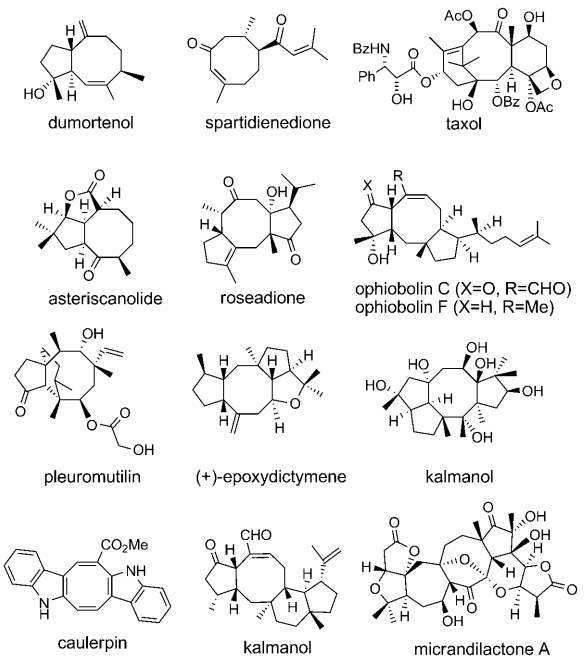

Figure 1. Representative natural products with eight-membered carbocyclic skeletons.

has been made through the development of transition-metal-catalyzed cycloadditions—the focus of this review.

The mechanism of metal-catalyzed cycloadditions allows for efficient ring formation of medium-sized ring compounds. These reactions usually proceed by coordination, oxidative coupling, insertion, and reductive elimination processes, as schematically presented by the three-component transition-metal-catalyzed [*m*+*n*+*o*] cycloaddition shown in Figure 2. Therefore, entropic and enthalpic penalties associated with the traditional ring-closure methods could be circumvented or partially avoided in the metal-catalyzed cycloadditions.

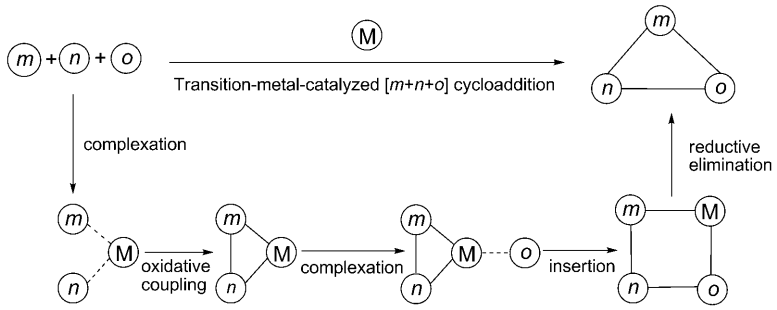

Figure 2. Depiction of the process of transition-metal-catalyzed [*m*+*n*+*o*] cycloaddition.

On the other hand, some two-component cycloadditions such as [4+4] and [6+2] reactions to synthesize eight-membered carbocycles are forbidden according to the Woodward–Hoffmann rules. However, transition-metal-catalyzed cycloadditions can achieve these reactions via the mechanisms shown in Figure 2, providing another impetus to discover metal-catalyzed cycloadditions for the synthesis of eight-membered carbocycles.

In 1996, Lautens and co-workers summarized many metal-catalyzed cycloadditions including metal-catalyzed cycloadditions for eight-membered carbocycle synthesis.[2b] Now 14 years have passed since Lautens' review, and many new results, which will be covered in this Focus Review, have appeared in the literature during this period. To give an overview of all these achievements, several important and representative examples given in Lautens' and others' reviews[2] have also been included here. In the present review, we pay specific attention to metal catalysis; however, several stoichiometric metal-mediated cycloadditions to eight-membered carbocycles have also been described. In addition, we have included the proposed mechanisms of several recently discovered cycloadditions.

In what follows, we can see that cycloadditions take place in either an intramolecular or an intermolecular fashion. They could be two-component, three-component, or multi-component. All these cycloadditions are traditionally named as [*m*+*n*], [*m*+*n*+*o*], [*m*+*n*+*o*+*x*] cycloadditions. Here *m*, *n*, *o*, and *x* are the numbers of carbon units which are incorporated in the eight-membered carbocycles. Here we wish to introduce a new nomenclature for these cycloaddition reactions. If a reaction is a two-, three-, or four-component reaction, this reaction is called an [*m*+*n*], [*m*+*n*+*o*], or [*m*+*n*+*o*+*p*] reaction. In this case, *m*, *n*, *o*, and *p* components come from different molecules. If a reaction is written as a [(*m*+*n*+*o*)] reaction, this implies that it is an intramolecular reaction, where *m*, *n*, and *o* units come from one molecule. In a similar way, an [(*m*+*n*)+*o*] reaction means that it is a two-component intermolecular reaction, where *m* and *n* units come from one molecule, but the *o* unit comes from another molecule. Compared to the traditional nomenclature, the present nomenclature is not easy, but can pro-

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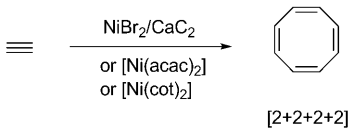
vide more information to the referred reactions. For example, this nomenclature can tell us how a reaction really happens and where these carbon units come from. We prefer to use this new nomenclature for every discussed cycloaddition reaction below. When we collect similar reactions together for a subtitle in this review, we will still use the traditional nomenclature of metal-catalyzed cycloadditions.

1. [2+2+2+2] Cycloadditions

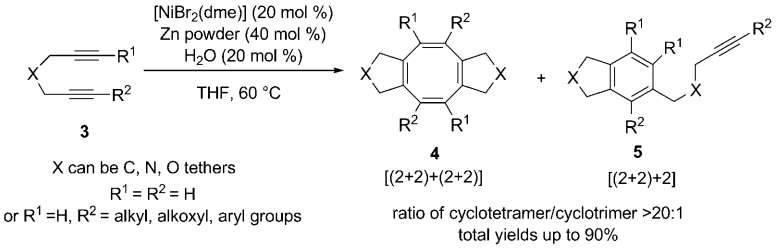
The first [2+2+2+2] cycloaddition of acetylene to form cyclooctatetraene (COT) was discovered by Reppe in the late 1940s. The originally reported tetramerization of acetylene was catalyzed by $NiBr_2$/CaC_2 (Scheme 1). Later on it was found that [Ni(acac)$_2$] or [Ni(cot)$_2$] can also catalyze this reaction. This [2+2+2+2] reaction has now been applied in the synthesis of COT in industry.[8]



Scheme 1.

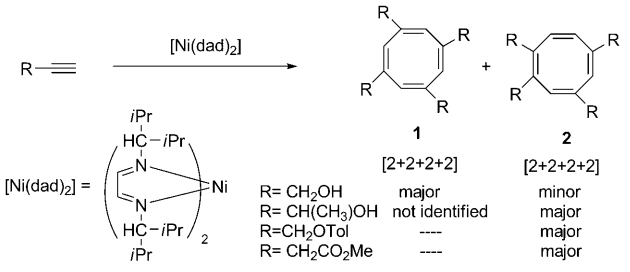
The above [2+2+2+2] reaction led to a mixture of various substituted COT compounds when substituted alkynes were used. To overcome this shortcoming, tom Dieck[9] developed a regioselective [2+2+2+2] cycloaddition of monosubstituted alkynes to generate 1,3,5,7- or 1,2,4,6-tetrasubstituted cyclooctatetraenes (Scheme 2). The catalyst used by his group was a 1,4-diazadiene nickel complex, a Ni catalyst with two bulkyl ligands.

A solution to control the regioselectivity of alkyne tetramerization was to use diyne substrates, which can undergo two-component [(2+2)+(2+2)] cycloaddition to give COT in the presence of Ni catalysts. However, this tetramerization reaction often suffers from a competitive (and dominant in most cases) [(2+2)+2] cyclotrimerization reaction, leading to substituted benzenes. In 2007, Wender[10,11a] and co-workers found that the two-component [(2+2)+(2+2)] cycloaddition reaction of diynes with various tethers became favored dramatically over the cyclotrimerization by using [$NiBr_2$(dme)] and zinc dust in THF at 60 °C (Scheme 3). The catalytic species was believed to be Ni^0, in situ generated by the reduction of [$NiBr_2$(dme)] with zinc. It was found that the efficiency and selectivity of the [(2+2)+(2+2)] reaction was affected by the catalyst loading and catalyst concentration. Increasing the catalyst loading from 20 to 40 mol% improved the selectivity of COT over arene from 6.9:1 to 52:1. The Ni-catalyzed [(2+2)+(2+2)] reaction was scalable to obtain the COT compounds on a gram scale and can be extended to synthesize unsymmetrical COTs if two different diynes were used. In 2009, Wender and co-workers further demonstrated that the [(2+2)+(2+2)] reaction can be carried out by using mixed diynes, with both internal and terminal yne units, providing hexa- and octasubstituted COTs in good yields (Scheme 3).[11b] When aromatic or heteroaromatic diynes were used as substrates, the ratio of COT/benzene derivatives was as high as 20:1. Recently, Okamoto and coworkers extended Wender's [(2+2)+(2+2)] reaction protocol by using ionic liquid supported nickel complexes in an ionic liquid/toluene biphasic system.[11c]

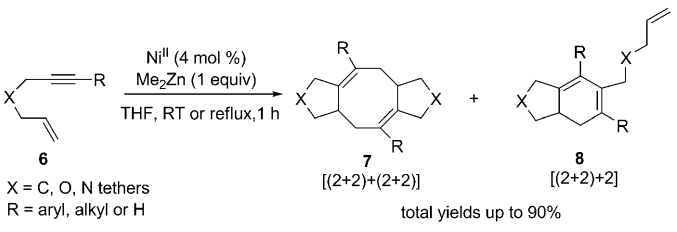


Scheme 3.

One drawback of the above mentioned Ni-catalyzed [(2+2)+(2+2)] cycloaddition with diynes was that a large amount of the Ni catalyst (20–40 mol%) had to be used. In 2009, Zhao and co-workers found that 1,6-enynes can also undergo the [(2+2)+(2+2)] cycloaddition to give 1,5-cyclooctadienes together with some [(2+2)+2] products when lower loading of Ni/R_2Zn (4 mol%) was used as the catalyst (Scheme 4).[12] It is interesting to note that the choice of a



Scheme 2.

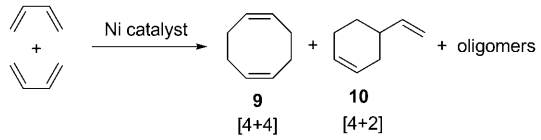


Scheme 4.

combination of different Ni complexes and R_2Zn had a dramatic influence on the reaction of 1,6-enynes. When a [Ni(acac)$_2$]/Me_2Zn combination was employed, high total yields with poor selectivities ([(2+2)+(2+2)]/[(2+2)+2] = 1:1) were observed for carbon-tethered aryl enynes (here R = Ar in Scheme 4). Unidentifiable polymeric products or a complex reaction mixture were obtained using *N*-tosyl and *N*-benzyl enynes as substrates under these catalytic conditions. However, for the [$NiCl_2(PCy_3)_2$]/Me_2Zn combination, these substrates invariably favored the formation of the [(2+2)+2] products in moderate yields with ratios of [(2+2)+2] cycloadducts over [(2+2)+(2+2)] cycloadducts ranging from 4:1 to 7:1. In contrast, when Et_2Zn instead of Me_2Zn, or only 0.6 equivalents of Et_2Zn, was used as the reducing reagent under the same reaction conditions, reductive eneyne cyclization products were exclusively formed.

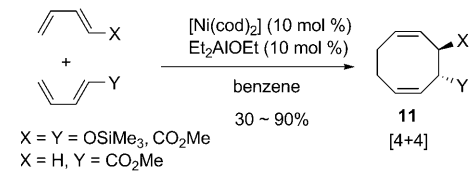
2. [4+4] Cycloadditions

In the early 1950s, Ziegler and Reed discovered that butadiene can dimerize and oligomerize with a metal catalyst (Scheme 5).[13] The dimerization reactions led to two products, cyclooctadiene (via a [4+4] reaction), and 4-vinyl cyclohexene (via a [4+2] reaction). After optimization of the reaction conditions, Wilke and Heimbach discovered that the reaction yield of the [4+4] cycloaddition to give cyclooctadiene (COD) can reach 95% when a phosphine ligand was introduced to the Ni reaction system.[14] The yield was found to be dependent on both the ligands and the ratio of catalyst to ligand. When a bis(π-allyl) nickel complex was used, cyclooctadiene **9** was formed in preference to other products such as vinylcyclohexene (VCH) **10**, divinylcylobutane, and cyclic trimers of butadiene.

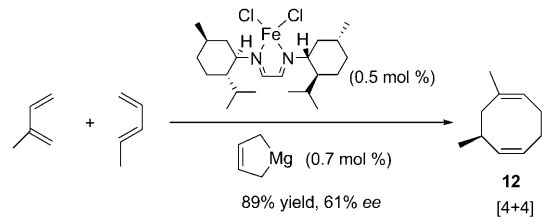


Scheme 5.

Stimulated by the seminal studies shown in Scheme 5, Waegell and co-workers developed a regioselective [4+4] cycloaddition of monosubstituted butadienes in 1985 (Scheme 6).[15] The final cycloadducts were generated by a head-to-head cycloaddition mode, and the substituents in the final product have a *trans* configuration. tom Dieck[16] found that an iron complex can also catalyze this reaction and they demonstrated that the asymmetric version of this reaction can be achieved if a chiral catalyst is used (Scheme 7). In 1995, Itoh and co-workers found that



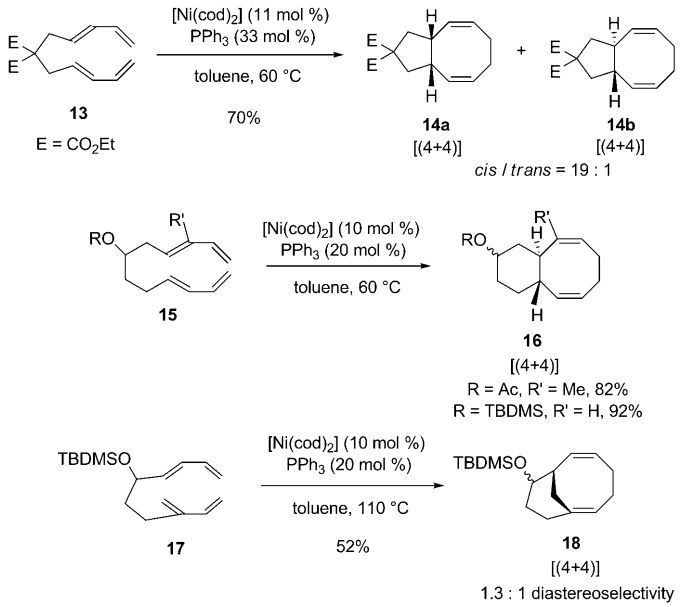
Scheme 6.



Scheme 7.

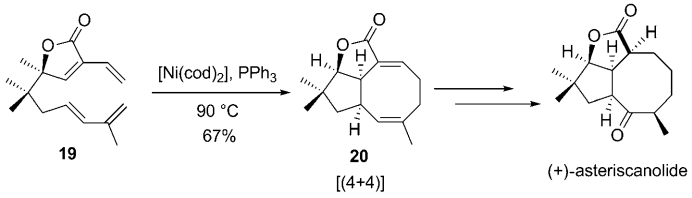
$[(C_5R_5)Ru(diene)]^+$ can catalyze/mediate dimerization of conjugated dienes via a [4+4] cycloaddition.[17] However, preliminary results showed that the regioselectivity of Itoh's [4+4] cycloaddition was not satisfactory.

Considering the common existence of eight-membered carbocycles fused with other rings in natural products, Wender[18] and co-workers sought to explore an intramolecular [(4+4)] reaction that could have application in natural product synthesis. They succeeded in developing [(4+4)] cycloadditions to synthesize 5/8 and 6/8 bicyclic COD (Scheme 8). In the 5/8 system, when **13** was treated in toluene at 60 °C with 11 mol% [Ni(cod)$_2$] and 33 mol% PPh_3, the major product is *cis*-fused, whereas for the 6/8 system, *trans* products dominate (**15** to **16**). A type-II Ni-catalyzed [(4+4)] reaction was also developed by Wender's group to synthesize bridge-fused bicyclic cyclooctadienes (**17** to **18**).[19]

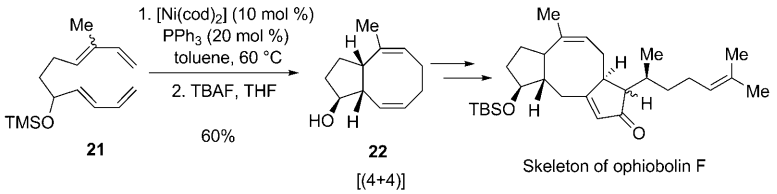


Scheme 8.

A total synthesis of the naturally occurring sesquiterpene asteriscanolide using Ni-catalyzed intramolecular [(4+4)] cycloaddition was achieved by Wender.[20] The eight-membered ring-forming transformation of **19** to **20**, the key step of this total synthesis, was accomplished in 67% yield and gave a single diastereomer (Scheme 9).[20a] Wender also utilized this [(4+4)] reaction to construct the 5/8/5 skeleton of ophiobolin F (Scheme 10).[20b] The key cycloaddition was accomplished by treatment of bis-diene **21** with 10 mol% [Ni(cod)$_2$] and 20 mol% triphenylphosphine in toluene at 60°C, followed by desilylation, affording bicyclic cyclooctadiene **22** in 60% yield. After further elaborations from **22**, the core structure of ophiobolin F was constructed.



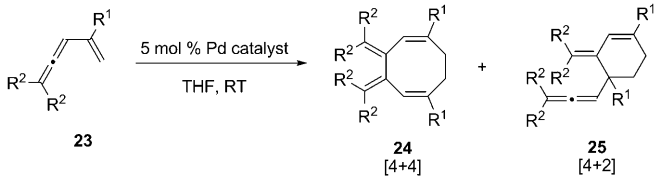
Scheme 9.



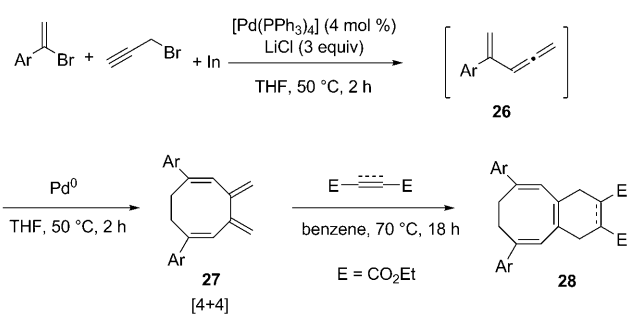
Scheme 10.

In 1999, Murakami and Ito reported a palladium-catalyzed [4+4] cycloaddition reaction of vinylallenes to construct eight-membered carbocyclic rings (Scheme 11).[21] They found that the R^1 group in **23** must be either a phenyl or vinyl group for this [4+4] reaction. Otherwise, only [4+2] cycloadditions took place. In some cases, the [4+4] reactions are competitive with the intermolecular [4+2] cycloadditions of vinylallenes.

The above Pd-catalyzed [4+4] cycloaddition was further developed by Lee and co-workers.[22] In 2006, they reported a Pd-catalyzed intermolecular [4+4] cycloaddition reaction of vinylallenes, generated in situ from α-bromovinyl arenes and propargyl bromides (Scheme 12). The formed [4+4] cycloadduct **27** can act as a diene to further react with various dienophiles to give a 6/8 bicyclic skeleton (for example, compound **28** in Scheme 12), allowing rapid synthesis of eight-membered carbocycles with excellent yields. More importantly, they found that this reaction could be accomplished in one pot to achieve high synthetic efficiency.

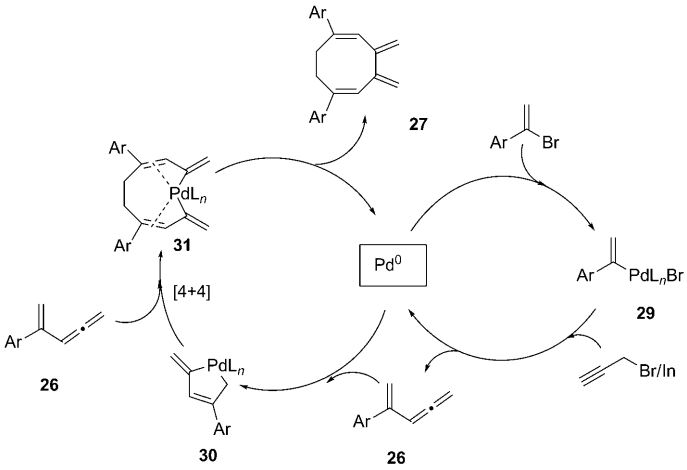


Scheme 11.



Scheme 12.

A possible reaction pathway for the reaction in Scheme 12 is described as follows (Scheme 13). Oxidative addition of a Pd^0 catalyst to the vinyl bromide gives **29**. Then transmetalation between **29** and propagyl bromide/indium complex, followed by reductive elimination, leads to vinylallene **26**. Oxidative cyclometallation of **26** to Pd affords intermediate **30**, which subsequently reacts with another molecule of vinylallene at the internal double bond of the allene to give a bis(σ-allyl)palladium intermediate **31**. Subsequent reductive elimination

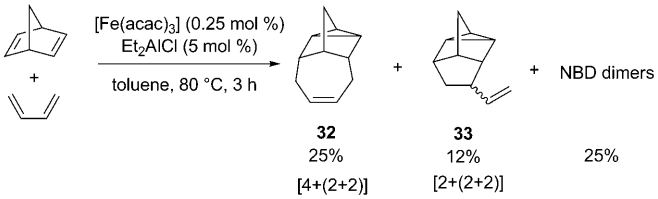


Scheme 13.

from **31** gives rise to eight-membered carbocycle **27**. This Pd-catalyzed [4+4] catalytic cycle of vinylallenes was originally proposed by Murakami and Ito for the reaction shown in Scheme 11.

3. [4+2+2] Cycloadditions

The first [4+(2+2)] reaction was reported in 1970 by Carbonaro,[23a] who discovered that [Fe(acac)$_3$] can catalyze the reaction between 1,3-butadiene and norbornadiene (NBD) to give [4+(2+2)] cycloaddition product **32** in 25% yield and [2+(2+2)] adduct **33** in 12% yield, together with some NBD dimers (Scheme 14). Later on Carbonaro, Inukai, and



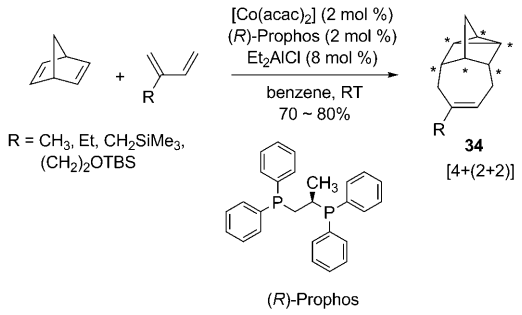
Scheme 14.

Lyons found that cobalt complexes can catalyze the [4+(2+2)] cycloadditions of NBD with dienes also, usually with better yields compared to those obtained by iron catalysts.[23b–d]

Lautens[24] and co-workers reported the asymmetric induction of this [4+(2+2)] cycloaddition employing cobalt catalysts in the presence of a chiral phosphine ligand and Et$_2$AlCl (as a reducing agent). [Co(acac)$_2$] and [Co(acac)$_3$] were both effective as precatalysts and gave similar levels of asymmetric induction. Of the various chiral phosphines tested, (*R*)-Prophos gave the highest enantiomeric excess of 70% (Scheme 15).

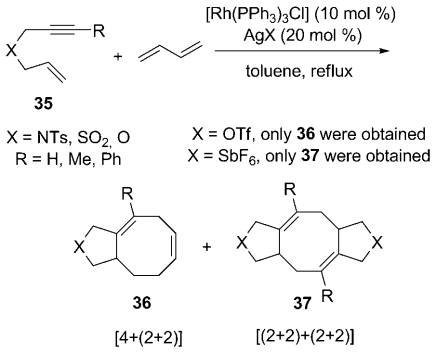
Even though the above [4+2+2] reactions above suffered from low reaction yields and produced excess NBD dimers, they provided inspirations for further development of [4+2+2] reactions to synthesize eight-membered carbocycles.

In 2002, Evans[25] and co-workers discovered a Rh-catalyzed two-component [4+(2+2)] reaction of butadiene and



Scheme 15.

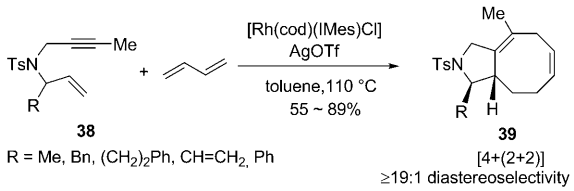
heteroatom-tethered enyne derivatives to synthesize eight-membered carbocycles (Scheme 16). The tethers can be nitrogen, sulfur, or oxygen atoms. The silver salt was critical to the success of Evans' [4+(2+2)] reaction. If AgOTf was



Scheme 16.

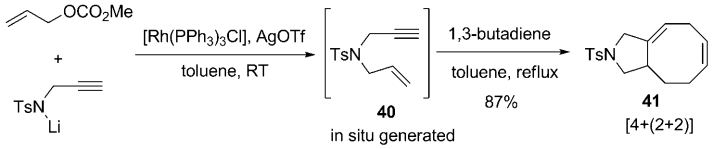
used to generate a cationic Rh catalyst from Wilkinson catalyst, high yields of the [4+(2+2)] reaction can be achieved. However, if AgSbF$_6$ was used, the dominant products were the homodimers generated via a Rh-catalyzed [(2+2)+(2+2)] reaction of the enynes. Evans found that in the latter case, butadiene underwent oligomerization and could not take part in the [4+(2+2)] reaction. Consequently, the remaining enyne in the reaction system would undergo homodimerization. This [(2+2)+(2+2)] reaction of enynes catalyzed by Rh complements the same reaction catalyzed by Ni in the Zhao group (see Scheme 4).[10]

Evans and co-workers found that when utilizing a rhodium N-heterocyclic carbene (NHC) complex, [Rh(COD)(IMes)Cl], as the catalyst, it was very efficient to achieve high diastereoselectivities in the [4+(2+2)] reaction of substituted enynes **38** and butadiene (Scheme 17).[26] This was the first example of a rhodium-NHC complex catalyzed [*m*+*n*+*o*]-type cyclization to give eight-membered carbocycles with high diastereoselectivity.



Scheme 17.

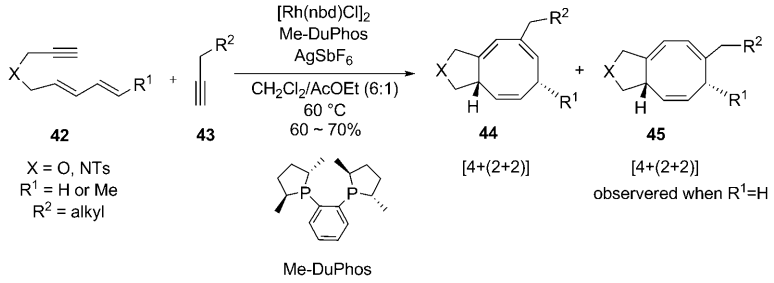
A sequential three-component allylic amination/[4+(2+2)] reaction can be realized to synthesize bicyclic cyclooctadienes (Scheme 18).[26] Treatment of allylcarbonate with the lithium salt of *N*-tosylpropargylamine in the presence of Wilkinson's catalyst, modified with silver triflate, gave enyne **40**, which was not isolated but directly subjected to heat at reflux for 12 h under an atmosphere of 1,3-buta-



Scheme 18.

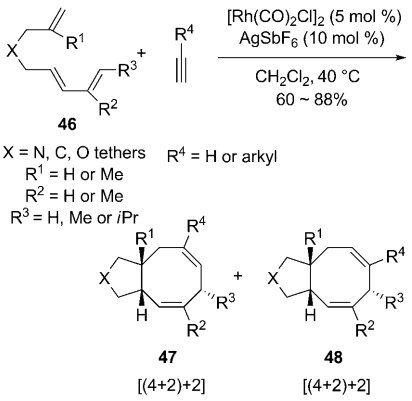
diene. In this case, the tandem reaction afforded the cycloaddition adduct in 87% yield.

In 2002, Gilbertson[27] explored a new Rh-catalyzed [(4+2)+2] cycloadditon of dienynes and terminal alkynes (Scheme 19). They found that the cycloaddition reaction catalyzed by $[Rh(nbd)Cl]_2$ and $AgSbF_6$ in the presence of Me-DuPhos at 60 °C gave the final cycloadducts in good to excellent yields. The alkyne portion of the dienynes was a terminal alkyne. If the R^1 group in dienynes **42** was hydrogen, the [(4+2)+2] cycloadditions with terminal alkynes gave a mixture of two regioisomers **44** and **45**, owing to the two different insertion modes of the terminal alkyne to the Rh–C bond. However, if the R^1 group was methyl, only one regioisomer **44** was generated. Gilbertson found that in **44**, the R^1 group and the bridgehead hydrogen had a *trans* configuration (see Scheme 19). Simple acetylene can also take part in the [(4+2)+2] reaction with dienynes. It is interesting to note that, although a chiral ligand was used in Gilberson's reaction, no enantioselectivity was observed. Only one [(4+2)+2] reaction examined had an *ee* value of 41%. This was different from the Rh-catalyzed intramolecular [(4+2)] reaction of dienynes, wherein a high-chirality transfer from the ligand to the products was observed by Gilbertson.[28] If no external alkyne was added, dienynes underwent [(4+2)+2] reactions between two dienynes, where one dienyne provided the diene (four-carbon component) and yne (two-carbon component) parts, and the other dienyne used its yne part (two-carbon component).



Scheme 19.

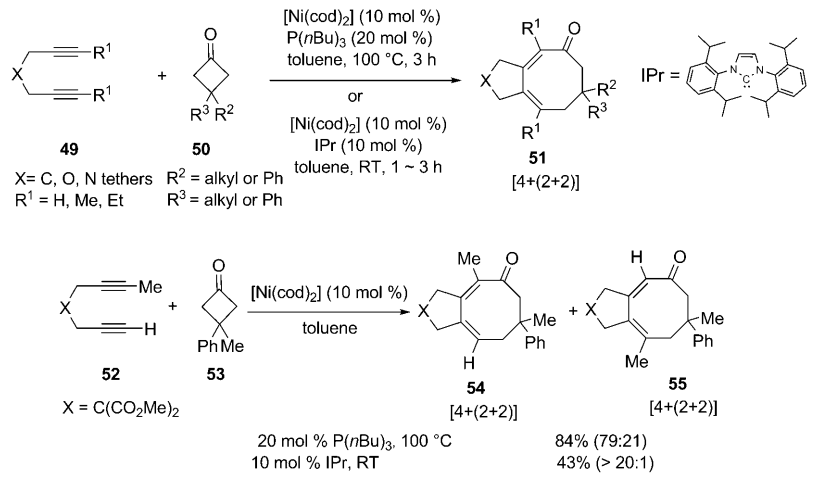
Even though Evans and Gilbertson's reactions can generate eight-membered carbocycles, their reactions cannot tolerate substrates with carbon tethers (with the exception of carbon tethers in the form of an aromatic ring). In 2006, Wender and co-workers reported a new [(4+2)+2] reaction between ene-dienes and terminal alkynes catalyzed by $[Rh(CO)_2Cl]_2$ and $AgSbF_6$ in dichloroethane solvent (Scheme 20).[29] One of the significant features of Wender's [(4+2)+2] reaction was that carbon, nitrogen, and oxygen tethers can all be incorporated. Usually the Wender [(4+2)+2] cycloaddition gave a mixture of two regioisomers using the terminal alkynes as two-carbon synthons. It was found that the regioselectivity of the alkyne insertion was influenced by both steric and electronic features of the alkyne. Wender and his co-workers further extended this two-component reaction into a three-component [4+2+2] reaction by using 2,3-dimethyl-1,3-butadiene, norbornene, and methyl propargyl ether as substrates.



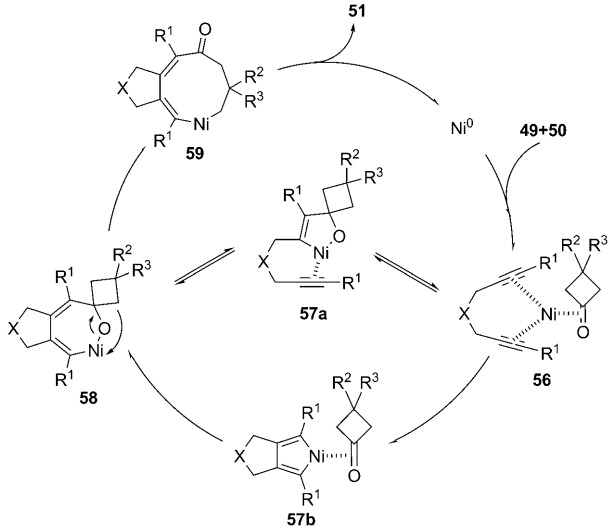
Scheme 20.

In 2006, Murakami[30] reported a nickel-catalyzed intermolecular [4+(2+2)] annulation reaction of cyclobutanones with diynes that furnished bicyclic eight-membered cyclic ketones (Scheme 21). They found that the N-heterocyclic carbene ligand IPr improved the activity of the nickel catalyst compared to the phosphine ligand, making the reaction occur at room temperature and have excellent reaction yields. When unsymmetrical diynes were used, a 4:1 mixture of regiosomers **54** and **55** was obtained with $P(n\mathrm{Bu})_3$ as the ligand, whereas only **54** was obtained when the sterically bulkier IPr ligand was used. The use of unsymmetrical 2-substituted cyclobutanones was also examined, showing a high regioselectivity (>20:1) under Ni-IPr catalysis.

The authors postulated the following mechanism (Scheme 22). The diyne and cyclobutanone initially bind on nickel(0) to give complex **56**. Then intermediate **57a** or **57b**, or both, is obtained through oxidative cyclometalation of the two alkyne moieties to nickel(0), or through hetero-type oxidative cyclization of the carbonyl group. Subsequent incorporation of the third unsaturated functionality into the Ni–C bond of the five-membered nickelacycles leads to the formation of oxanickelacycloheptadiene **58**. Then the four-



Scheme 21.

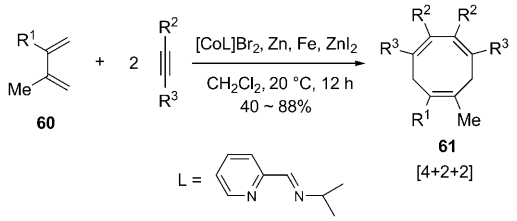


Scheme 22.

membered ring of this spiro nickelacycle is opened by β-carbon elimination to expand the seven-membered nickelacycle. Finally, reductive elimination gives the eight-membered product and regenerates the catalyst of nickel(0).

In contrast to the nickel-catalyzed cyclotetramerization of alkynes (see Scheme 1), cobalt-catalyzed reactions of alkynes mainly lead to [2+2+2] cyclotrimerizations to form benzene derivatives. In 2008, Hilt[31] et.al successfully coupled two alkynes with 1,3-dienes to generate eight-membered ring systems in an unprecedented three-component [4+2+2] fashion (Scheme 23). In this reaction, they utilized a cobalt catalyst in the presence of Zn, Fe, and ZnI_2. The [4+2+2] products were formed regioselectively with the two substituents from the alkynes in a 1,2-relation. The addition of iron powder reduced the amount of side products and increased the yield of the eight-membered ring products. When acceptor-substituted terminal alkynes reacted with electron-rich 1,3-dienes, the corresponding cyclooctadienones could be obtained in excellent yields (up to 90%).

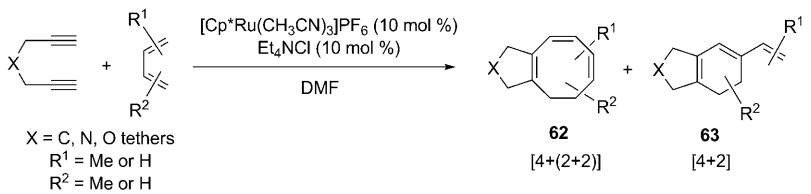
Saa[32] and co-workers reported a Ru-catalyzed [4+(2+2)] cycloaddition between diynes and 1,3-butadienes in 2003 (Scheme 24). They found that under the catalysis of 10% Ru complex and 10% Et_4NCl in DMF, diynes and 1,4-substituted dienes gave [4+(2+2)] cycloadducts of 1,3,5-cyclooctatrienes and 1-vinyl-1,3-cyclohexadienes. This formal [4+(2+2)] cycloaddition



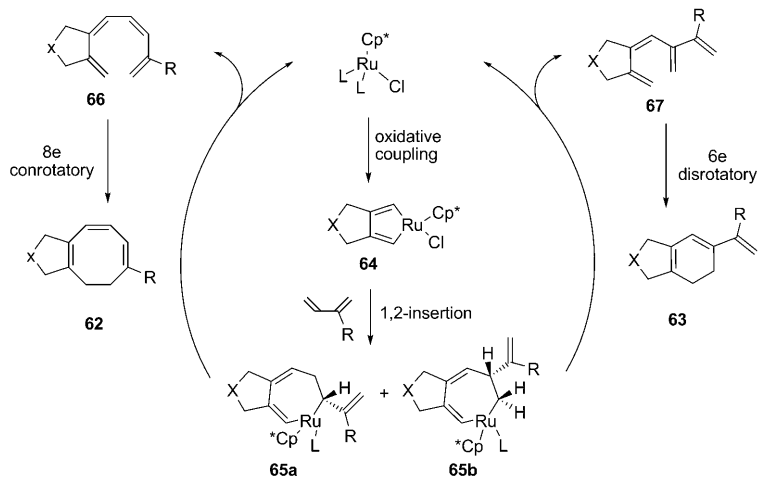
Scheme 23.

was a tandem process and required addition of Et_4NCl to the reaction system. The purpose of the addition of Et_4NCl was to neutralize the positively charged moiety in $[Cp^*Ru(CH_3CN)_3]PF_6$, generating a neutral complex of $[Cp^*Ru^{II}(CH_3CN)_2Cl]$ in situ as the catalyst.

Saa proposed the following reaction mechanism to explain their experimental results (Scheme 25). Firstly, oxidative addition of 1,6-diyne to the Ru catalyst gives a ruthenium cyclic species **64**. Then diene insertion into the Ru–C bond in **64** gives rise to two seven-membered intermediates **65a** and **65b**. The ratio of **65a/65b** was dependent on the substitution pattern in the butadiene component, and was deter-



Scheme 24.

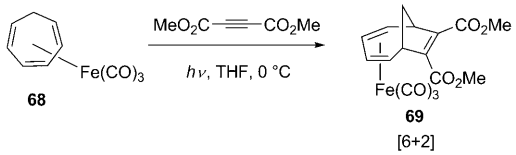


Scheme 25.

mined by the steric and electronic nature of the diene insertion transition states. **65a** and **65b** then undergo β-hydride elimination and reductive elimination to give **66** and **67**, respectively, together with regeneration of the catalyst. Finally, intermediate **66** undergoes 8π electrocyclization to furnish the [4+(2+2)] product of **62**, whereas intermediate **67** undergoes 6π electrocyclization to give vinylcyclohexadiene **63**.

4. [6+2] Cycloadditions

The first metal-catalyzed [6+2] cycloaddition was reported by Pettit,[33] who showed that cycloheptatriene-iron tricarbonyl complex **68** and dimethyl acetylenedicarbornate under photolysis gave an iron-diene complex (Scheme 26). The

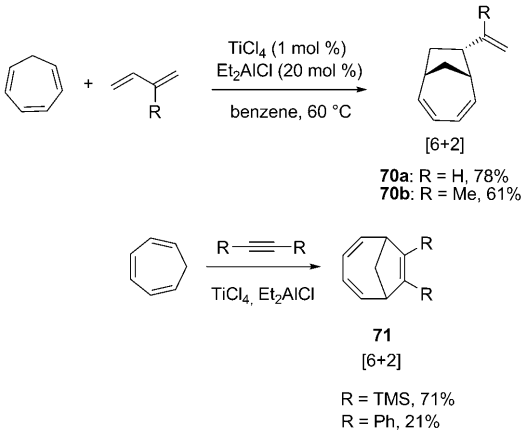


Scheme 26.

photolysis here aimed to release a CO molecule from cycloheptatriene-iron tricarbonyl complex to generate an active cycloheptatriene-iron dicarbonyl complex, which then underwent [6+2] reaction with electron deficient acetylene. Finally CO complexation gave the tricarbonyl complex **69**. Even though this [6+2] reaction had low reaction yield, this original discovery inspired further research in metal-mediated/-catalyzed [6+2] cycloadditions.

In 1983, Mach[34] and co-workers reported a metal-catalyzed [6+2] cycloaddition for accessing eight-membered rings. The cycloaddition reaction between cycloheptatriene (CHT) and butadiene in the presence of 1 mol% $TiCl_4$ and 20 mol% Et_2AlCl led to the cycloadduct **70** bearing an eight-membered ring with a bicyclo[4.2.1] nonane framework (Scheme 27). Under the optimized conditions, adduct **70a** was obtained in 78% yield. When butadiene was replaced by isoprene, cycloaddition occurred exclusively on the less substituted olefin, providing **70b** in 61% yield. CHT could also react with alkynes to give [6+2] cycloadducts **71**.

Recently, Schmidt[35] reported a molybdenum complex catalyzed [6+2] addition between

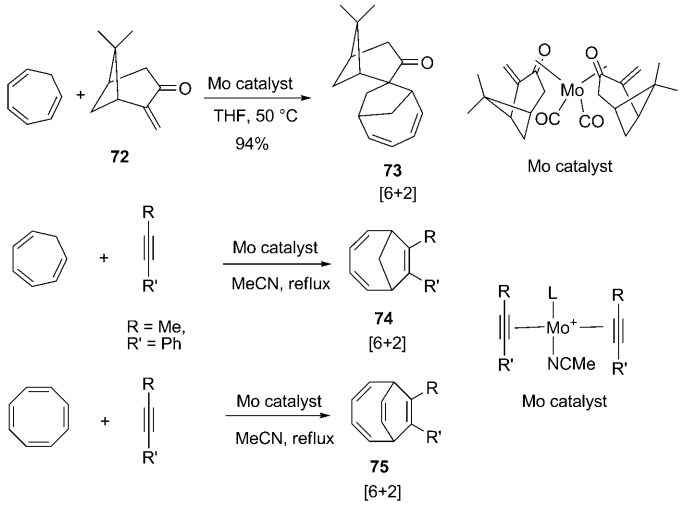


Scheme 27.

pinocarvone and cycloheptatriene to give an eight-membered cycloadduct in excellent yield (Scheme 28). Using molybdenum η^4-oxadiene complexes as the catalysts, the [6+2]cycloaddition reactions proceeded smoothly at 50 °C or below. But analogous tungsten complexes exhibited a slightly lower catalytic activity toward the [6+2] reaction. Green[36] also reported [6+2] additions of CHT and COT with disubstituted acetylenes catalyzed by molybdenum η^4-oxadiene complexes to give the corresponding cycloadducts **74** and **75**, respectively.

Kreiter[37] and co-workers reported their first study of the [6+2] reaction of $[(cht)Cr(CO)_3]$ complexes with various dienes under photochemical conditions. They observed that [6+2] and [6+4] cycloadditions could occur, depending on the structure of the dienes. But further study of the origins of the different regioselectivities and of how to control the regioselectivity has not been reported.

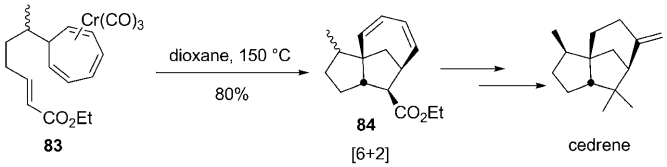
Later on, Rigby[38] and co-workers examined in detail the cycloaddition of Cr complexes with various types of alkenes with regard to selectivity and synthetic potential. High diastereoselectivity was observed in the reaction of **76a** with



Scheme 28.

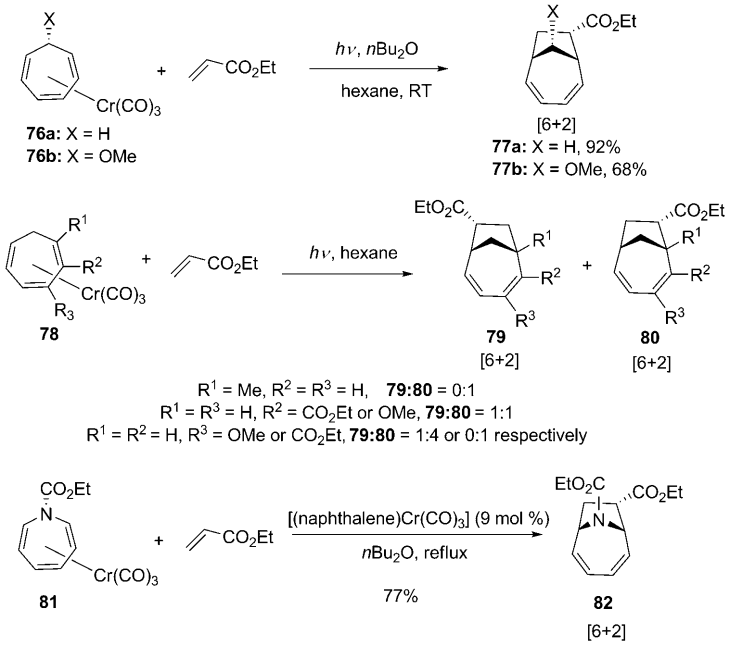
ethyl acrylate to give **77a** in 92% yield as a single diastereomer (Scheme 29). Reaction of a stereochemically homogeneous chromium complex **76b** revealed that complexation of the alkene to the metal occurred prior to carbon–carbon bond formation, in accord with Pettit's results obtained from the iron complexes. The position of the substituent on the cht complexes was critical to the regioselectivity of this cycloaddition. For example, single regiosomers were observed with 1-substituted cht ligands. However, when 2-substituted cht was used, no selectivity was observed, irrespective of the electronic nature of the substituents on the cht ligands. Surprisingly, the level of selectivity with 3-substituted cht was excellent with respect to an electron-poor cht, and modest with respect to an electron-rich cht. A catalytic amount of a naphthalenechromiun tricarbonyl complex can induce cycloaddition when azepines participate as the triene partners in this reaction. This catalytic [6+2] reaction gave **82** (Scheme 29) with a reaction yield of 77% and a catalyst turnover number of larger than 8. The [6+2] reactions of cht-Cr complex with allenes were developed by Rigby in 2008.[38h] Interestingly, Rigby and co-workers developed a resin-based chromium catalyst that can perform [6+2] cycloadditions of a variety of cht derivatives and α,β-unsaturated esters at 150 °C.[38g]

Rigby designed a concise approach to synthesize cedrene by using the chromium-mediated [6+2] reaction (Scheme 30).[39] The [6+2] cycloaddition of **83** was conducted at 150 °C, furnishing tricyclic ester **84** in 80% yield. After further elaboration, cedrene was synthesized successfully from **84**.

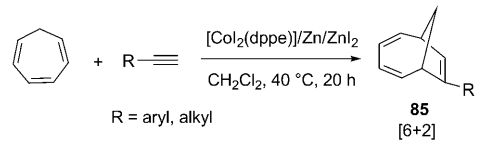


Scheme 30.

$[(cht)Cr(CO)_3]$ complexes can react with alkenes to give [6+2] products; however, they fail to react with alkynes. Buono[40a] found that the $[CoI_2(dppe)]/Zn/ZnI_2$ system effectively catalyzed the [6+2] cycloaddition of CHT and terminal alkynes without irradiation (Scheme 31). When a chiral ligand binol phosphoramidite was used, the enantioselective cycloaddition of CHT and phenylacetylene afforded the cycloadduct in up to 91% yield and 74% *ee*. Importantly, the catalyst system could tolerate a wide range of functional groups such as ketone, sulfone, ester, alcohol, imide, and nitrile. In 2008, Buono developed this Co-catalyzed [6+2] reaction to its asymmetric version by introducing chiral phosphoramidites as ligands (up to 92% *ee* was achieved).[40b] In 2005, Buono and co-workers found that both cyclooctatetraene and 1,3,5-cyclooctatriene react with terminal alkynes to give [6+2] cycloadducts under the colbalt catalysis.[40c] In 2009, Hilt and co-workers made further advance in this field, showing that CHT reacted with both internal al-



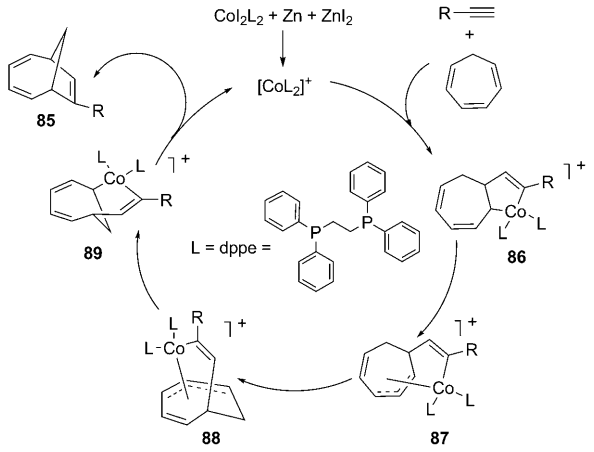
Scheme 29.



Scheme 31.

kynes and terminal alkenes to give [6+2] cycloadducts in the presence of catalytic amounts of cobalt dibromide [bis-(triisopropylphosphite) comlexes.[40d]

Buono and co-workers proposed the following mechanism for the Cr-catalyzed [6+2] reaction (Scheme 32). Firstly

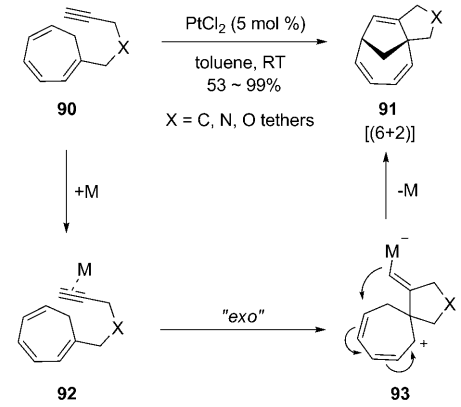


Scheme 32.

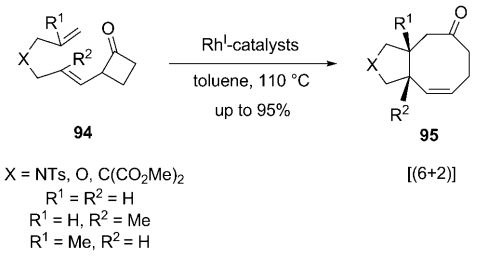
$[CoL_2I_2]$ is reduced by zinc metal and ZnI_2 to a cationic $[CoL_2]^+$ complex. Then coordination of the alkyne and cycloheptatriene to the metal center, followed by oxidative cyclization, lead to the generation of cobaltacyclopentene **86**. A series of 1,5-migrations of the $C(sp^3)$–Co bond happen through consecutive σ,π-allyl complexes **87, 88**, and **89**. Finally reductive elimination from **89** generates the [6+2] cycloadduct **85** and the catalyst.

An intramolecular [(6+2)] cycloaddition between CHT and an alkyne to afford cycloheptatrienes was developed recently by Tenaglia[41] and co-workers using $PtCl_2$ as the catalyst (Scheme 33). Complex heterocyclic compounds were obtained when this reaction was applied to substrates containing a heteroatom (O or N) in the tether. A proposed mechanism accounting for the [(6+2)] cycloaddition is given in Scheme 33.

Wender[42] reported a Rh-catalyzed [(6+2)] cycloaddition between vinylcyclobutanones and alkenes in 2000 (Scheme 34). This reaction proceeded in good to excellent yields for substrates with N, C, and O tethers. High stereoselectivity was found in this reaction in most cases, where *cis*-fused products were formed exclusively or preferentially. Quaternary carbon centers can be installed at the bridgehead carbon atoms of the final [(6+2)] cycloadducts. In addition, this [(6+2)] reaction can be extended to an intramo-



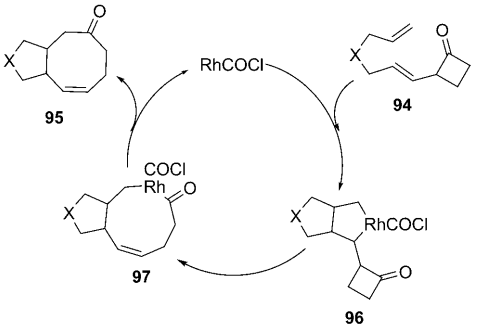
Scheme 33.



Scheme 34.

lecular [(6+2)] reaction between vinylcyclobutanones and allenes.

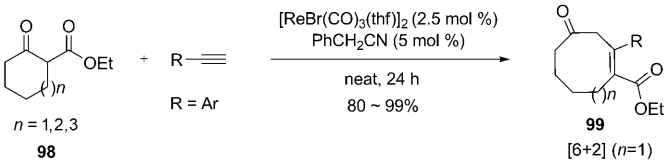
Rodríguez-Otero[43] studied the mechanism of the Wender [(6+2)] cycloaddition using density functional theory calculations in 2008 (Scheme 35). It was proposed that this reac-



Scheme 35.

tion starts with oxidative addition of **94** to the catalytic species of [Rh(CO)Cl],[44] giving metallacyclopentane intermediate **96**. Then β-carbon elimination leads to a nine-membered-ring rhodacycle **97**. Finally reductive elimination furnishes the [(6+2)] cycloadduct **95** and regenerates the catalyst.

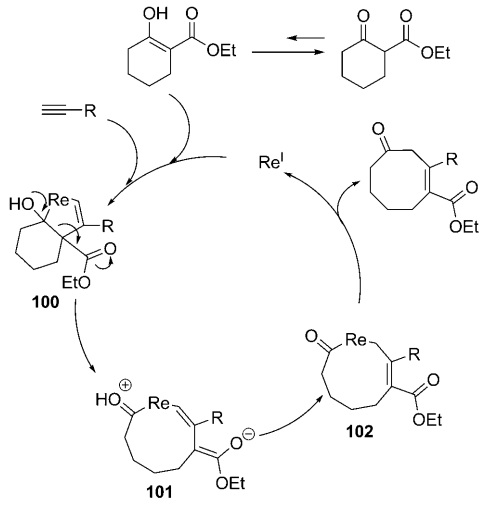
In 2006, Kuninobu and Takai[45a] reported a rhenium-catalyzed two-component [*m*+2]-like reaction between 1,3-keto esters and alkynes, where *m* can be 5, 6, 7, or 8 (Scheme 36).



Scheme 36.

This is an especially efficient [6+2] reaction for synthesizing eight-membered rings. The formation of **99** proceeded efficiently in toluene at 50 °C for 24 h by using 5 mol % $[ReBr(CO)_5]$ as the catalyst and 5 mol % benzyl isocyanide as the addiditive. Treatment of **98** with arylacetylenes bearing substituents such as electron-donating methoxy and methyl groups and electron-withdrawing trifluoromethyl and bromo groups afforded the corresponding eight-membered cyclic compounds in 86–97 % yields. In 2009, they found that the reaction system can be promoted by the addition of 4 Å molecular sieves instead of a catalytic amount of phenylacetonitrile.[45b]

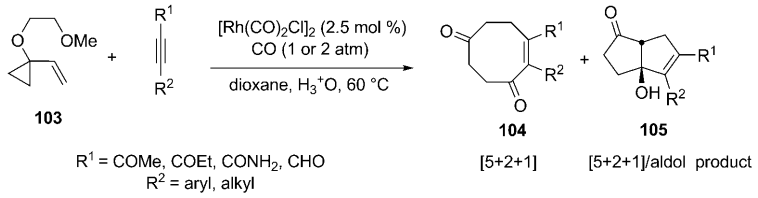
This Re-catalyzed addition was proposed to start with oxidative addition of the enol ether tautomer and the terminal acetylene (Scheme 37). Then a sequence of reactions involving ring opening, retro-aldol reaction, isomerization and reductive elimination give the final [*m*+2] products.



Scheme 37.

5. [5+2+1] Cycloadditions

In 2001, Wender[46] and co-workers reported the first transition-metal-catalyzed intermolecular [5+2+1] cycloaddition reactions of activated alkynes, CO, and vinylcyclopropanes (VCPs), leading to eight-membered rings (Scheme 38). The final products obtained from Wender's [5+2+1] reaction were bicyclo[3.3.0]octenones **105**, which were generated, during the hydrolytic workup, through the intramolecular aldol reaction of the in situ generated [5+2+1] cycloadducts **104**. In some cases, a small amount of [5+2+1] reaction products **104** was obtained. The alkynes used in Wender's [5+2+1] reaction were carbonyl activated. Very high regioselectivities could be realized when unsymmetric activated alkynes were used, showing that the R^2 group, not the carbonyl groups (R^1 groups), preferred to be adjacent to the inserted CO group in the final products.

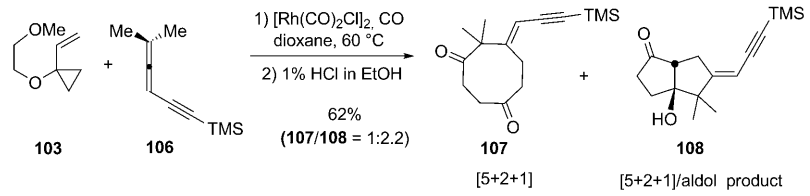


Scheme 38.

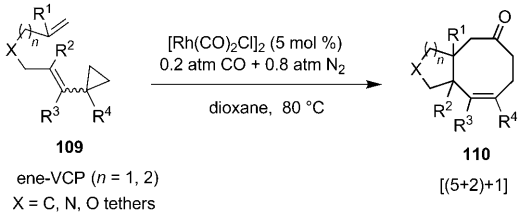
Wender[47] and co-workers found that allene can also act as the two-carbon unit to take part in the three-component [5+2+1] reaction (Scheme 39). Under standard reaction conditions (1 mol % $[Rh(CO)_2Cl]_2$, dioxane as solvent, one atmosphere of CO gas), cyclooctanedione **107** and its transannular aldol product hydroxybicyclo[3.3.0] octanone **108** were obtained in 88 % yield in only 1 h. Increasing the CO pressure from 1 atm to 2 atm improved the total yield to 94 % and modestly changed the ratio of **107**/**108** from 1:2.2 to 1:1.3, but required a longer reaction time of 15 h. Both products were obtained as single *E* isomers. Here the used allene was not carbonyl substituted, suggesting that allene is more reactive than alkyne in this [5+2+1] reaction.

In 2007, Yu[48] and co-workers reported a two-component [(5+2)+1] reaction of ene-vinylcyclopropanes (ene-VCPs) and CO to give bicyclic cyclooctenones **110** (Scheme 40). This reaction was efficient with low CO pressure and the substrates can have carbon, nitrogen, and oxygen tethers. The [(5+2)+1] reaction gave only cis-5/8 bicyclic cyclooctenones when R^3 was hydrogen. However, when R^3 was a methyl group, the formed 5/8 bicyclic cyclooctenones can be in a *cis* (when *cis* ene-VCPs were used) or *trans* (when *trans* ene-VCPs were used) configuration. The [(5+2)+1] reaction can also be used to synthesize 6/8 bicyclic compounds, in which *trans*-fused 6/8 compounds were dominant.

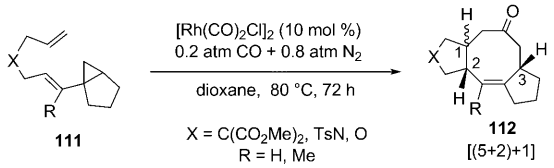
This [(5+2)+1] reaction was also effective to reach 5/8/5 systems if the cyclopropane ring of the ene-VCP was fused by a five-membered carbocycle (Scheme 41).[49] It was found that, in the final products, the bridgehead C2 and C3 hydrogen atoms always had a *cis* configuration. The configuration of the bridgehead C1 was also *cis* with respect to C2 and C3 when R was hydrogen. However, when R was a methyl group, the final 5/8/5 compounds were a mixture of both *cis* and *trans* configurations at the C1 atom (with respect to the C2 atom, see numbering of the carbon atoms in Scheme 41).



Scheme 39.



Scheme 40.

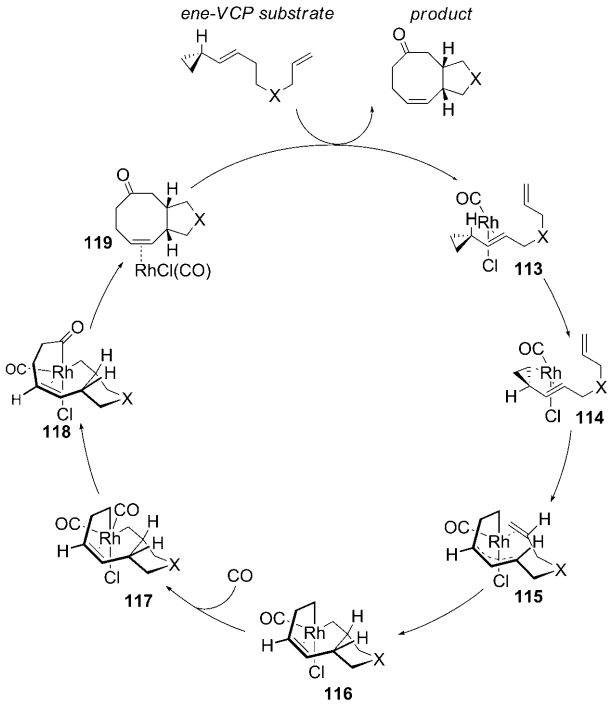


Scheme 41.

The proposed mechanism for the [(5+2)+1] reaction is shown in Scheme 42. The catalytic cycle starts with the ligand exchange of the product-catalyst complex, 5/8-ring-fused cyclooctenone-Rh(CO)Cl complex **119**, with the ene-VCP substrate, followed by VCP coordination and opening of the cyclopropyl group, giving **115**. Then coordination and insertion of the alkene leads to rhodabicyclooctene **116**. CO coordination and insertion affords rhodabicyclononenone **118**, which subsequently undergoes a migratory reductive elimination to give the [(5+2)+1] cycloadduct and completes the [(5+2)+1] catalytic cycle.

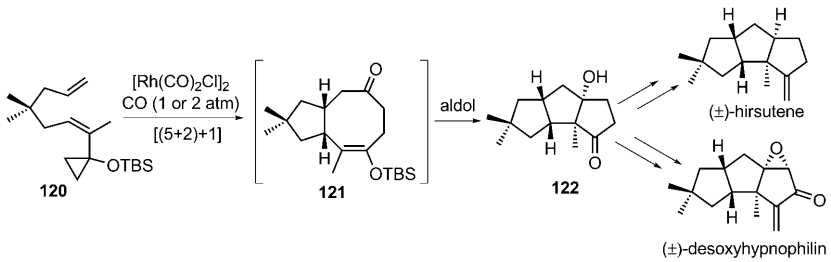
Application of this [(5+2)+1] cycloaddition to the syntheses of natural products containing eight-membered carbocyclic skeletons and linear and branched triquinane skeletons was demonstrated by Yu and co-workers.[50a] A very efficient tandem Rh^{I}-catalyzed [(5+2)+1]/aldol cycloaddition process was developed to construct the triquinane skeleton and this strategy was successfully applied to the total syntheses of (±)-hirsutene and (±)-desoxyhypnophilin with high step economy (Scheme 43).

Later on, a stepwise strategy to synthesize hirsutene was realized by the Yu group. In this strategy, the [(5+2)+1] cycloadduct **123** was transformed to symmetric diketone **124**. Then a sequence of aldol reaction, dehydration, alkylation, and olefination converted **124** to hirsutene (Scheme 44).[50b] This tandem approach to hirsutene can be modified to an asymmetric version when the aldol reaction used a chiral catalyst.[50b] The cycloadduct **123** can also be transformed to unsymmetric diketone **125**, which then can be further elaborated to the synthesis of pentalenene and asterisca-3(15)-diene (Scheme 44).[50c]

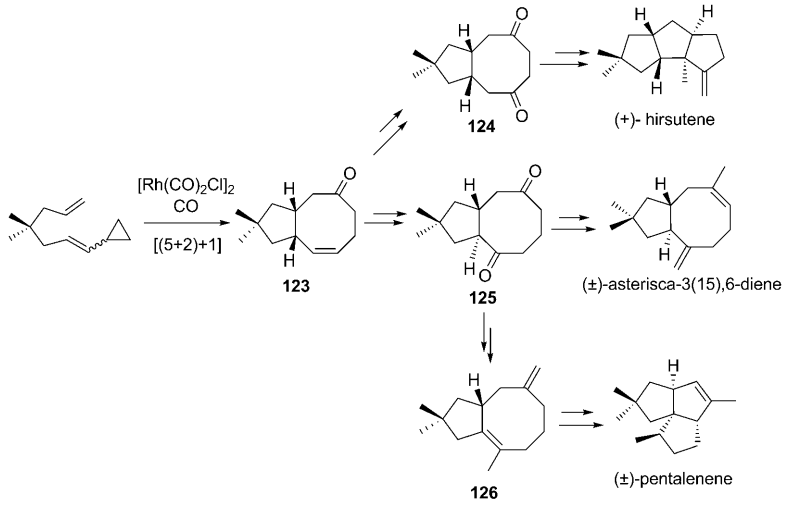


Scheme 42.

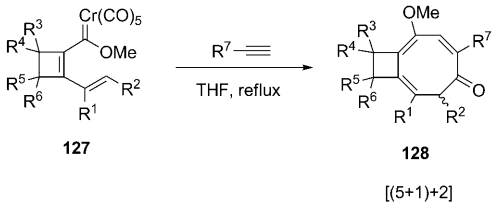
Barluenga[51] reported the first Dotz-like reaction between conjugated dienyl carbene chromium complexes and terminal alkynes to afford eight-membered carbocycles (Scheme 45). This reaction can be named as a [(5+1)+2] reaction since the five-carbon synthon and CO come from **127**, and the external alkyne acts as a two-carbon synthon.



Scheme 43.



Scheme 44.



Scheme 45.

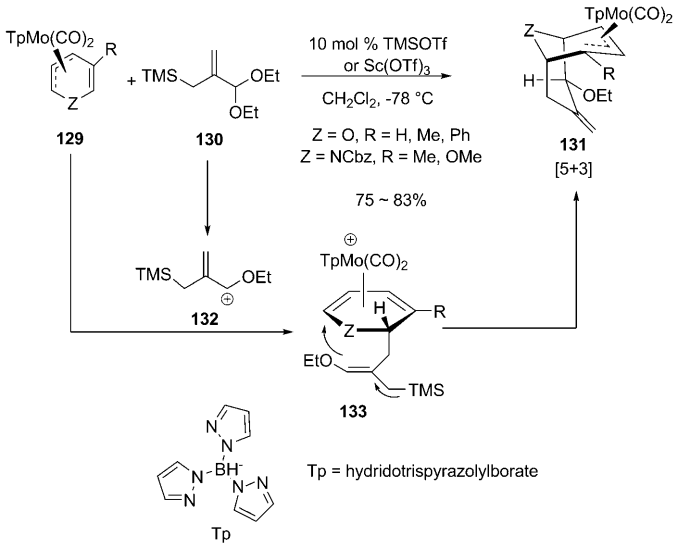
This reaction provides an elegant way to synthesize 4/8 bicyclic ring compounds, which are challenging to all above-mentioned metal-catalyzed/mediated cycloadditions. Barluenga found that this [(5+1)+2] reaction can also be performed photochemically with similar reaction yields compared to those obtained under thermal reaction conditions.

6. [5+3] Cycloadditions

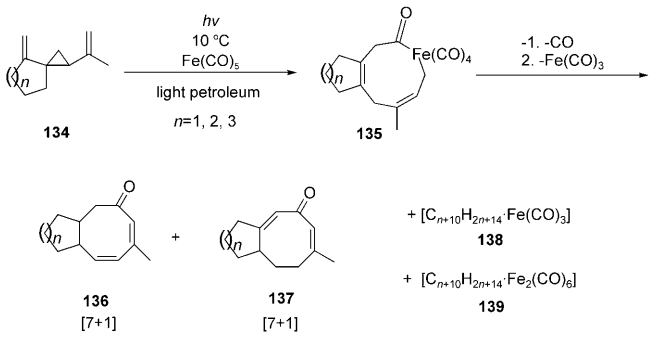
Liebeskind and co-workers developed η^3-pyranyl and η^3-pyridinyl molybdenum π-complexes **129** as five-carbon synthons in cycloadditions (Scheme 46).[52] In 2003, they discovered that, under catalysis of TMSOTf or $Sc(OTf)_3$, **129** reacted with oxyallyl cation **132**, in situ generated from **130**, to give oxa- and aza[3.3.1]bicycles **131** via a [5+3] reaction. They found such a [5+3] reaction produced enantiocontrolled complexes **131** when enantiopure complexes **129** were used. The [5+3] reaction was proposed to occur via a stepwise process starting from the attack of the in situ generated cation **132** toward **129**, giving rise to a cationic intermediate **133**. Then intramolecular ring-closure gives the final [5+3] products **131** with exclusive *endo* selectivity. Complexes **131** can be transformed to various functionalized hetero-bicyclic eight-membered carbocycles via demetalations (such as using strong acids, ceric ammonium nitrate (CAN) with or without Et_3N, or pyridinium dichromate). Liebeskind found that in some cases, the reaction gave [3+2]cycloadducts as by-products.

7. [7+1] Cycloadditions

Sarel and Langbeheim found an $Fe(CO)_5$ mediated [7+1] reaction between divinylcyclopropanes and $Fe(CO)_5$ under photolysis conditions (Scheme 47).[53] This reaction was proposed to occur via the intermediate of ferra-cyclononadiene **135**, which, upon loss of CO and $Fe(CO)_3$, gave cyclo-octadienones **136** and **137**. This [7+1] reaction also gave organometallic complexes **138** and **139** as the byproducts.



Scheme 46.



Scheme 47.

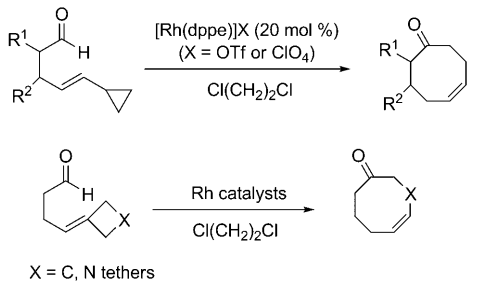
Conclusions and Perspectives

In this Focus Review, we present the recent progresses in metal-catalyzed cycloadditions to synthesize eight-membered carbocycles, which are core structures of many natural products of biological and medicinal significance. The advantages of these metal-catalyzed cycloadditions are: usually the reactions use easily accessed starting materials; the reaction conditions are mild; moderate to high reaction yields can be achieved in most cases. These metal-catalyzed reactions have great impact on the synthesis of natural products with eight-membered carbocycle skeletons or skeletons formed from eight-membered carbocycles, as demonstrated in the synthesis of astericanolide and the skeleton of ophiobolin F by Wender via Ni-catalyzed [(4+4)] reaction,[20] of cedrene by Rigby via Cr-mediated [6+2] reaction,[39] of hirsutene, desoxyhypnophiline, pentalenene, and asterisca-3(15)-diene by Yu via Rh-catalyzed [(5+2)+1] cycloaddition.[50]

Despite the above successes, continuous endeavors are required for further advances. One such required endeavor is to develop asymmetric versions of these cycloadditions so that the asymmetric synthesis of eight-membered carbocyles can also be easily fulfilled. The second effort in this line is to reduce the catalyst loading so that these reactions could be used on a large scale in the chemical or pharmaceutical industry. Thirdly, more applications of these reactions to the synthesis of complex natural products should be pursued to better understand the scope of these reactions, and to address challenges in natural product synthesis.

Fourthly, investigating the mechanisms of these metal-catalyzed cycloaddition reactions is critical, not only for understanding these reactions and providing in-depth information for the substrate scope expansion and reaction optimization, but also for guiding discovery and development of new reactions and catalysts. Two examples of eight-membered cyclooctenone synthesis inspired by Wender's [(5+2)] and [(6+2)] reactions and Murakami's [4+(2+2)] reaction are given in Scheme 48, where Shair developed a hydroacylation/cyclopropane cleavage strategy, and Aissa developed a hydroacylation/cyclobutane cleavage strategy to synthesize eight-membered carbocycles.[54]

Fifthly, it is very important to test whether these metal-catalyzed reactions can be extended to the synthesis of eight-membered heterocycles, which are also important motifs in natural products. Two very recent examples in this regard are Rovis's N-heterocyclic [4+2+2] reaction[55] and Woerpel's heterocyclic [6+2] reaction of vinyl silaoxetanes (obtained from silylenes and vinyl epoxides) and aldehydes.[56,57] Finally, discovering and developing more new metal-catalyzed cycloadditions that can complement or surpass the above-mentioned cycloadditions for the synthesis of eight-membered carbocycles is still highly demanded, considering the various substitution patterns in natural products and pharmaceuticals.



Scheme 48.

Acknowledgements

We are indebted to generous financial support from a new faculty grant from the 985 Program for Excellent Researches in Peking University, the National Natural Science Foundation of China (20825205-National Science Fund for Distinguished Young Scholars, 20772007 and 20672005), and the National Basic Research Program of China-973 Program (2010CB833203).

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Received: December 14, 2009

