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Review

Mechanistic Studies of Transition-Metal-Catalyzed [2 + 2 + 2] Cycloaddition Reactions

Anna Roglans,* Anna Pla-Quintana,* and Miquel Solà*

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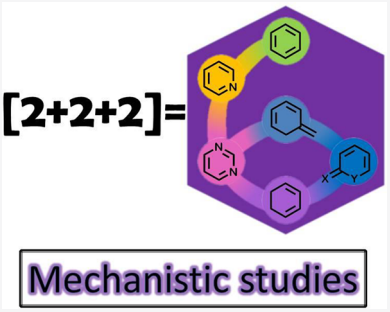
ABSTRACT: The development of catalytic methodologies involving the formation of C−C bonds to enable the generation of cyclic systems constitutes a field of great relevance in synthetic organic chemistry. One paradigmatic process to accomplish this goal efficiently is the transition-metal-catalyzed [2 + 2 + 2] cycloaddition reaction, since it permits the formation of a wide range of highly functionalized 6-membered carbo- and heterocyclic molecules in a single step with high efficiency and perfect atom economy. A key feature of these transformations is the mechanistic pathway that they follow, since a deep knowledge of this mechanism may enable us to understand and improve the efficiency of the reaction. This review covers the mechanistic aspects, studied both from theoretical and experimental points of view, of the transition-metal-catalyzed [2 + 2 + 2] cycloaddition reaction involving all kinds of unsaturated substrates with metals such as Co, Ni, Ru, Rh, Ir, Pd, Zr, Ti, Ta, and Nb. A thorough overview is undertaken, from the seminal studies until the present day, of the key mechanistic aspects that influence the reactivity and selectivity of the reaction, comparing the involvement of different unsaturated substrates as well as the different transition metals used.



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1. INTRODUCTION

The development of chemical processes to enable the construction of ring systems with high structural complexity is an important topic in organic chemistry. One of these processes is the transition-metal-catalyzed [2 + 2 + 2] cycloaddition reaction of three isolated unsaturated moieties to generate a wide range of 6-membered carbo- and heterocyclic derivatives with different functionalities. This process is remarkable in terms of the increase in molecular complexity, the functional group compatibility, and the high atom efficiency. The participation and combination in these cycloadditions of different unsaturations, such as alkynes, alkenes, allenes, nitriles, imines, aldehydes, ketones, isocyanates, and isothiocyanates, opens the door to obtaining a wide range of cyclic compounds which would be difficult to prepare by other methods. It has been found that many metals are capable of mediating or catalyzing such a transformation. The metals that have most often been used are Co, Ni, Ru, Rh, Ir, Pd, Ti, Zr, Nb, and Ta.

Many aspects of this type of process have been studied, including those catalysts that have a high level of activity, types of unsaturated substrates that can participate in the cycloaddition, chemo- and regioselectivity, enantioselectivity, and the applications of these processes especially in the synthesis of natural products. The significance of these [2 + 2 + 2] cycloaddition reactions is clearly seen in the large number of reviews published, particularly in the last 15 years, covering general aspects of the reaction,[1−15] the involvement of different unsaturations other than alkynes,[16−27] stereoselective [2 + 2 + 2] cycloadditions,[28−33] the application of the cycloaddition in the synthesis of relevant organic molecules,[34−38] and the comparison of mononuclear and dinuclear catalysts in alkyne cyclotrimerization.[39] A further particularly important aspect in this field is the elucidation of the mechanisms that govern the cycloaddition, since it aids in the understanding and improvement of the reaction. To our knowledge, only two reviews have been published in the last 15 years covering mechanistic aspects of the [2 + 2 + 2] cycloaddition reactions revealed by computational methods. In the first review,[40] computational results for the [CpRuCl]- and [CpCo]-catalyzed or -mediated cyclotrimerizations of alkynes and alkynes with alkenes are discussed and compared, showing the importance of the nature of the metal, ligands, and substrates in the reaction mechanism (Cp = η^5-C_5H_5). The second review[41] analyzes the reaction mechanisms of the [2 + 2 + 2] cyclotrimerization catalyzed by [CpRu(cod)Cl] (cod = 1,5-cyclooctadiene) of acetylene and the [2 + 2 + 2] cycloaddition of two alkynes and one molecule of ethylene, nitrile derivatives, isocyanates, isothiocyanates, and CX_2 (X = O, S, and Se).

The present review aims to summarize the main developments of mechanistic aspects concerning the transition-metal-catalyzed [2 + 2 + 2] cycloaddition reactions. Both experimental and theoretical studies into the reaction mechanisms will be discussed, since many advances in the mechanistic understanding of organometallic reactions, and, in particular, of these cyclotrimerization reactions, have been achieved by combining experimental and theoretical techniques as a result of close collaboration between computational and experimental chemists.[42−46]

In the following sections, the mechanism of cyclotrimerization reactions involving different unsaturations will be presented. In each section, the discussion will be organized by the metal catalyzing or mediating the process, except for an introductory section in the cycloaddition of three alkynes that summarizes chronologically the initial seminal studies of all transition metals to provide a historical perspective of the topic.

2. [2 + 2 + 2] CYCLOADDITION OF THREE ALKYNES

2.1. General Aspects and Seminal Mechanistic Studies

The uncatalyzed trimerization of acetylene to benzene is an allowed reaction according to the Woodward−Hoffmann rules[47] that is particularly favored from a thermodynamic point of view (by about −140 kcal/mol). Despite this concerted reaction taking place through an aromatic transition state,[48−51] the barrier for the concerted process is high (~40 kcal/mol)[52,53] and the reaction occurs only to a small extent at temperatures above 400 °C.[54,55] The high barrier observed was attributed to the electronic and structural reorganization needed to prepare the reactants for bond reorganization to generate benzene together with the entropy penalty that has to be paid for the simultaneous approach of the three acetylenes.[56−58] Recent calculations indicate that this thermal [2 + 2 + 2] reaction takes place through a cyclobutadiene intermediate formed in a biradical mechanism. From this intermediate, benzene is generated via a Diels−Alder cycloaddition or by biradical processes.[59] Several studies based on transition-metal-free formal [2 + 2 + 2] cycloadditions have been reported in the literature,[60] but the intense development of transition-metal-mediated cycloadditions greatly surpasses the synthetic possibilities of this second methodology in contrast to the first one.

Indeed, the cycloaddition of three alkynes can only proceed smoothly when catalyzed by different transition metals, as was shown for the first time by Reppe and Schweckendiek in 1948.[61] These authors showed that when [$Ni(CO)_2(PPh_3)_2$] was introduced in the [2 + 2 + 2] cycloaddition reaction media, the transformation of three alkynes to a benzene derivative that was hardly feasible under thermal conditions now became very efficient. In the following years, the reaction was further developed by numerous research groups and found to be catalyzed by complexes based on various transition metals. Along with this methodological interest, attention began to be paid to the mechanism that would account for such an efficient transformation.

Seminal mechanistic studies were published in the early 1960s. Hübel et al.[62] studied in 1960 the cyclotrimerization of various acetylenes with metal carbonyls with special emphasis on iron and cobalt complexes. A mechanism involving polar intermediates was ruled out due to the absence of a relationship between the polarity of the solvent and the rate of cyclotrimerization. A radical-based mechanism was also disregarded, since the addition of radical inhibitors did not hamper the reaction. The high preference for the formation of asymmetrically substituted benzene derivatives (i.e., 1,2,4-regioisomer) when asymmetric acetylenes reacted was taken as an indication that a stereospecific bond between the carbon atoms with the same substituents in the alkyne was involved in the mechanism. Hübel and Braye[63] had already described one year earlier the synthesis of ferracyclopentadiene derivatives **1** by reaction of iron dodecacarbonyl and asymmetrically substituted alkynes, observing the preference for such stereospecific bonding (Scheme 1). Isolated bimetallic ferracyclopentadiene **1**, obtained by the reaction of diphenylacetylene, reacted with a *p*,*p*′-dichlorodiphenylacetylene (in a 1:3 ratio) to deliver the two expected trimerization products although in an unexpected

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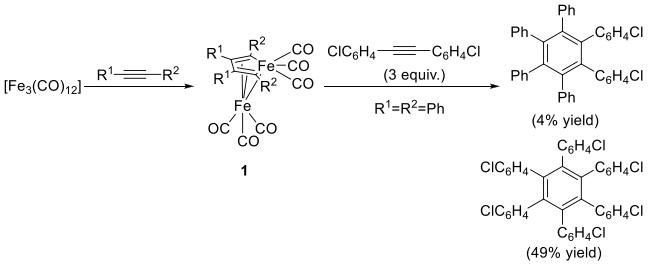
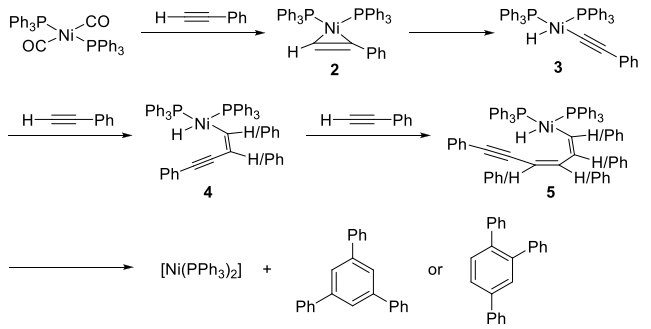
Scheme 1. Hübel[62] Mechanistic Studies of the Cyclotrimerization Catalyzed by Iron Carbonyl Complexes



ratio, allowing the authors to propose that complex **1** was not a reaction intermediate but rather released carbonyl fragments to generate the catalytic species.

In 1962, Kennerly et al.[64] analyzed the $[Ni(CO)_2(PPh_3)_2]$-catalyzed cyclotrimerization and linear polymerization of various acetylenes. A mechanism was postulated based on the analysis of kinetic and deuterium isotope effects together with product structures. Deuterium isotope effects strongly suggested that the rate-determining step in the polymerization of terminal acetylenes involved a hydrogen atom transfer. On the other hand, the deuterium isotope effects observed in the reaction of phenylacetylene, in which both polymerization and cyclotrimerization reactions coexisted, let the authors postulate tentatively that a common step involving hydrogen transfer in both processes took place (Scheme 2). Thus, a mechanism

Scheme 2. Mechanism Proposed by Kennerly et al.[64] for the Cyclotrimerization of Terminal Acetylenes

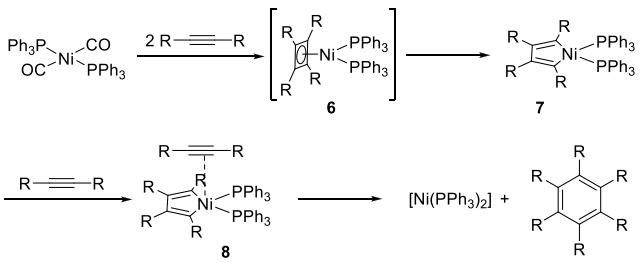


starting with the coordination of the alkyne (**2**) followed by oxidative addition to the C_{sp}–H bond (**3**) was proposed. Sequential insertions[65] of phenylacetylene led to **4** and then **5** from which a concerted hydrogen transfer and ring closure would give the aromatic product.

The same authors also observed the formation of hexasubstituted benzene derivatives from disubstituted acetylenes, a process which could not be explained by a mechanism involving C–H activation. In this case, they proposed the formation of a "*planar complex in which the nickel and two acetylene groups have formed a 5-membered ring*" (**7**) (Scheme 3) and suggested the involvement of an intermediate biphosphine–nickel–cyclobutadiene complex **6**. Coordination of a third acetylene molecule to intermediate **7** with the formation of intermediate **8** was then proposed, which in the words of the authors "*then collapses to the aromatic ring and Ni(PPh$_3$)$_2$*".

The mechanism for the $[PdCl_2(PhCN)_2]$-mediated trimerization of disubstituted acetylenes was also studied by Maitlis et al.[66] in 1962. The palladium complex efficiently mediated the

Scheme 3. Mechanism Proposed by Kennerly et al.[64] for the Cyclotrimerization of Disubstituted Acetylenes



cyclotrimerization of diphenylbenzene to hexaphenylbenzene in non-hydroxylic solvents (benzene, chloroform, and acetone) (Scheme 4, equation a), but when an hydroxylic solvent such as ethanol was added to the reaction media, the stable palladium complex **10** was isolated[67] and then transformed to tetraphenylcyclobutadiene palladium(II) complex **11** upon exposure to dry hydrogen chloride (Scheme 4, equation b). Analogous results were later obtained with di(*p*-chlorophenyl)-acetylene.[67] Complex **11** turned out to be unreactive with phenylacetylene and various acetylenic dienophiles, ruling out a Diels–Alder condensation of cyclobutadiene complex with acetylene as a mechanistic step for the [2 + 2 + 2] cyclotrimerization. The authors speculated that an intermediate of type **9** (Scheme 4), in which the electron localization was not convincingly stated, mediated in the transformation.

The involvement of a 5-membered metallacycle in the cobalt-catalyzed [2 + 2 + 2] cycloaddition reaction was postulated for the first time in 1967 by Yamazaki and Hagihara.[68] Alkyl–cobalt complexes which are known to catalyze the trimerization of acetylene to benzene were generated *in situ* by the reaction of $[CpCo(PPh_3)I_2]$ and Grignard reagents and reacted through the sequential addition of 2 equiv of diphenylacetylene to generate cobaltacyclopentadiene complex **12a**. This was inferred as a reaction intermediate toward the [2 + 2 + 2] cycloaddition of three alkynes since it reacted with another equivalent of diphenylacetylene to give hexaphenylbenzene, although in low yield (Scheme 5).

Collman and Kang[69] reported in 1967 the preparation of rhodium and iridium alkyne complexes with the general formula $[M(PPh_3)_2(CO)Cl(\eta^2\text{-alkyne})]$ (M = Rh, Ir) and their characterization by IR spectroscopy. The intermediacy of a 5-membered metallacyclic ring in the $[Rh(PPh_3)_2(CO)Cl]$-catalyzed cyclotrimerization reaction was also suggested. In a subsequent paper,[70] they reported the synthesis of iridacyclopentadiene **14a** and rhodacyclopentadiene **14b** by oxidative coupling of dimethyl acetylenedicarboxylate to $[Ir(PPh_3)_2(CO)Cl]$ and $[Rh(AsPh_3)_2(CO)Cl]$, respectively (Scheme 6, equation a). Furoyl azide was added to the mixture to displace *in situ* the CO and generate a nitrogen complex which was the one to react with the alkynes. Complexes **14** were shown to catalyze the trimerization of dimethyl acetylenedicarboxylate in boiling toluene or benzene and were thus proposed as intermediates in the cyclotrimerization reaction. In order to unravel the mechanism for the transformation of complexes **14** into the aromatic product, a reaction of **14a** with maleic anhydride was performed. The absence of reactivity suggested the absence of a Diels–Alder reaction. As an alternative, the authors proposed a stepwise ring closure going through a metallacycloheptatriene. An experiment resembling that of Hübel et al.[62] shown in Scheme 1 was then carried out (Scheme

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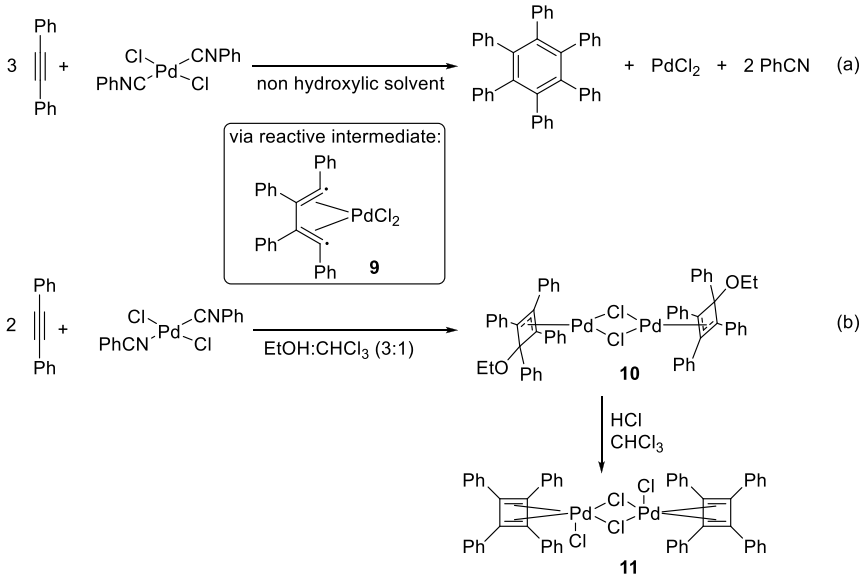
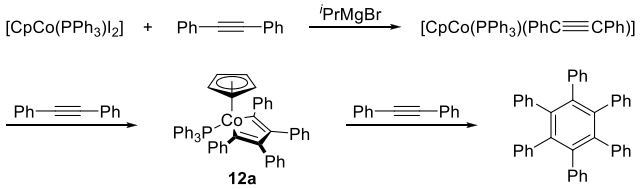
Scheme 4. Palladium Complexes Isolated in the Cyclotrimerization of Diphenylacetylene



Scheme 5. First Cobaltacyclopentadiene Intermediates Isolated by Yamazaki et al.[68]

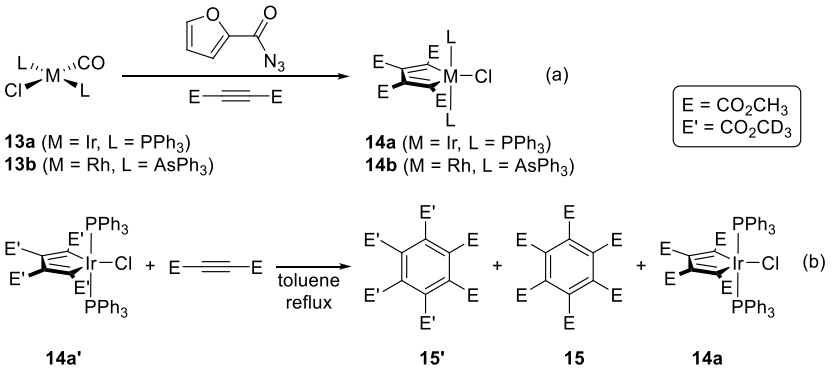


6, equation b). A deuterated analogue of **14a** was prepared, and a reaction with dimethyl acetylenedicarboxylate was performed. The deuterated trimer **15′** was formed in large quantities at early stages of the reaction, but at later stages, the quantity of protio trimer **15** formed increased and **14a** could be detected in the mixture. These results indicated that acetylene fragments react in a stepwise manner and reinforced the assignment of complexes **14** as intermediates in the reaction.

Although most mechanistic works at that time pointed to the involvement of 5-membered metallacyclic rings, other possibilities were also considered. A concerted mechanism was postulated by Schrauzer et al.[71] in 1964. The relationship between the structure of nickel(II) complexes of *N*-alkylsalicylaldimine and their catalytic activity in the synthesis of cyclooctatetraene and benzene was analyzed, and a mechanistic proposal was made for the two processes, which occurred through a concerted mechanism. The authors argued that formation of the π-complex approached the different alkyne substrates and activated the acetylenic carbon atoms, facilitating the formation of a C−C bond. Kennerly et al.[64] had already discussed two years earlier the possibility of a mechanism consisting of direct aromatization from π-complexes but discarded this possibility due to the difficulty in predicting the proportion of 1,2,4- and 1,3,5-trisubstituted benzenes and the difficulties associated with a catalytic version of this transformation. Collman and Kang[69] also disregarded the possibility of a concerted mechanism as proposed by Schrauzer et al.[71] due to the high coordination numbers that would be required.

A controversial point at that time was the involvement of metal-cyclobutadiene in the process. A study by Whitesides and Ehmann[72] in 1969 addressed this point by analyzing the symmetry of the transition-metal intermediates formed upon oxidative coupling in the cyclotrimerization of alkynes. 2-Butyne-1,1,1-d_3 reacted with triphenyltris(tetrahydrofuran)-chromium(III), dimesitylcobalt(II), dicobalt octacarbonyl, bis-(acrylonitrile)nickel(0), titanium tetrachloride-triisobutylaluminum Ziegler catalyst, dichlorobis(benzonitrile)palladium(II), and aluminum chloride and the ratio of the different isomers

Scheme 6. Synthesis and Reactivity of Irida- and Rhodacyclopentadienes Reported by Collman et al.[70]



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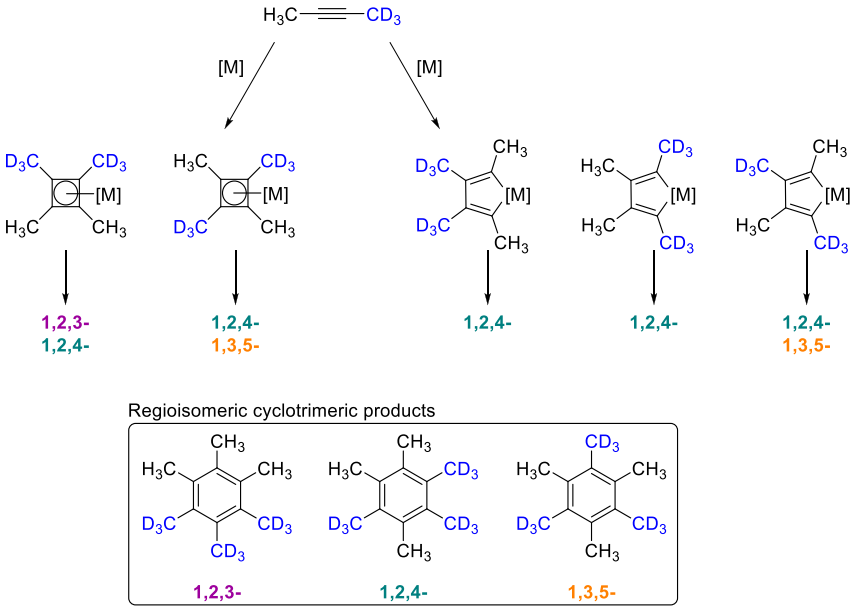
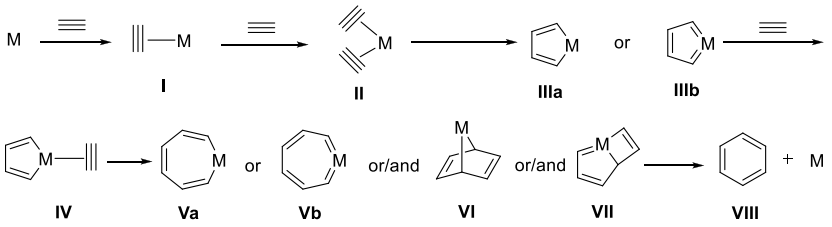
Scheme 7. Product Distribution Based on Cyclobutadiene Intermediates versus Metallacycles



Scheme 8. General Scheme for the Reaction Mechanism of the [2 + 2 + 2] Cycloaddition of Three Alkynes with M = Transition Metal



obtained inferred by analysis of the degradation products of the cyclotrimers. 1,2,3-Trimethyl-4,5,6-tri(methyl-d_3)benzene (**1,2,3-**, Scheme 7) is a possible product of the reaction only if transition-metal-cyclobutadiene intermediates, or intermediates with analogous symmetry, are involved. Thus, the authors concluded that the absence of products derived from the degradation of the 1,2,3-isomer, observed when the catalysts based on chromium, cobalt, nickel, or titanium were used, excluded the generation of reactive cyclobutadiene intermediates in the corresponding cyclotrimerization of alkynes. In contrast, when $AlCl_3$ was used as a catalyst, the ratio of degradation products of the cyclotrimers matched the ratios expected for a mechanism involving tetramethylcyclobutadiene intermediates or intermediates of analogous symmetry. In the case of the cyclotrimerization carried out under catalysis by $[PdCl_2(C_6H_5CN)_2]$, the ratio of degradation products did not match any of the models proposed.

In summary, evidence was already accumulating in the late 1960s that a 5-membered metallacycle was a reaction intermediate in the cyclotrimerization reactions catalyzed by various transition metals. Metallacyclopentadienes[73−75] are powerful intermediates with multireactive sites that are able to evolve through various different reactions, such as transmetalation, hydrolysis, or halogenolysis, a Diels−Alder reaction, or an insertion into the M−C_{sp^2} bond. Evidence was scarcer on the evolution of the 5-membered metallacycles.

Over the years, a consensus has been reached for the general mechanism for cycloaddition of three alkynes catalyzed by transition metals (Scheme 8). Initially, a couple of ligand-alkyne substitutions occur. The two alkyne ligands then generate a metallacyclopentadiene **IIIa** or a metallacyclopentatriene **IIIb** complex through oxidative coupling. After this, the coordination of a third alkyne takes place followed by alkyne insertion. Three different intermediates can then be formed: a planar aromatic metallacycloheptatriene **Va** (formed by the so-called Schore mechanism[4]) or metallacycloheptatetraene **Vb**; a metal-mediated inter- or intramolecular [4 + 2] Diels−Alder cycloaddition to form a 7-metallanorbornadiene complex **VI**; or a [2 + 2] cycloaddition to give a metallabicyclo[3.2.0]-heptatriene **VII**. Some theoretical studies have found that more than one of such intermediates can be sequentially formed in a particular reaction. At this stage, a reductive elimination is produced generating the arene and resulting in the recovery of the catalyst. As will be described in the following sections, different intermediates are found depending on the transition metal and substituents considered. In most cases, the reaction takes place on the singlet potential energy surface (PES). In other cases, however, the triplet state PES is also involved.

2.2. Cobalt Complexes

The octacarbonyl dicobalt complex catalyzes the cyclotrimerization of alkynes. In the 1960s, various groups isolated cobalt complexes upon the reaction of alkynes and $[Co_2(CO)_8]$ and analyzed their involvement in the mechanism of cyclotrimerization. A monoalkyne complex of general formula $[Co_2(CO)_6(alkyne)]$, also known as dicobaltatetrahedrane, was isolated by Krüerke and Hübel[76] under mild conditions

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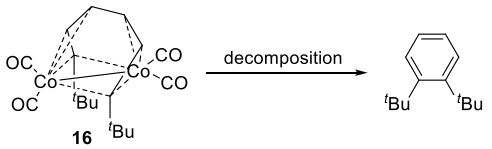
with various alkynes such as diphenylethylene, 3-hexyne, methyl 3-phenylpropiolate, ethynyltrimethylsilane, or acetylene. The monoalkyne complex proved to be catalytically active and thus was inferred to be a reaction intermediate. The same authors also isolated a complex of molecular formula $[Co_2(CO)_4(alkyne)_3]$ that, when decomposed thermally or with bromine, furnished benzene derivatives.[76,77] The spectroscopic study of the complex together with analysis of the decomposition products permitted the authors to propose a nonplanar cobaltacycloheptatriene structure for the compound. In 1964, Mills and Robinson[78] managed to determine the structure of an analogous complex **16** by X-ray diffraction (Scheme 9). Complex **16** has the three alkyne units (two *tert*-

Scheme 9. "Fly-over" Cobalt Complex Isolated by Robinson et al.[78]

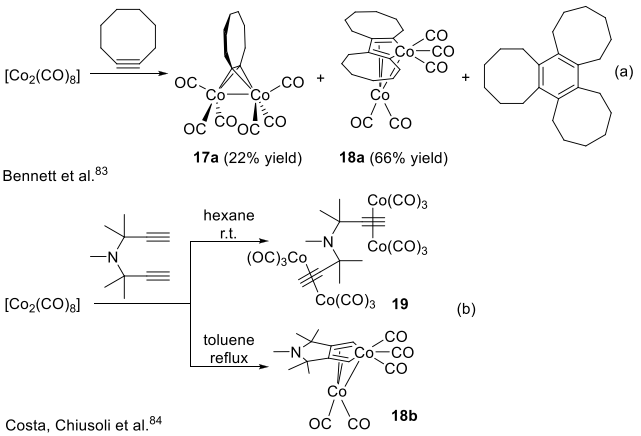


butylacetylenes and one acetylene) oligomerized to form a six-carbon "fly-over" bridge and was described by the authors as a diallyl structure. Analogous complexes were isolated by Dickson et al.,[79−81] and the structure was again confirmed by X-ray diffraction.[82] Although these intermediates may be regarded as possible intermediates in the carbonylcobalt-catalyzed trimerization of alkynes, they were isolated preferentially when the substrates were less prone to cyclotrimerization and, when treated with further equivalents of alkyne, did not catalyze the cyclotrimerization reaction. The authors therefore considered that it was more appropriate to classify these compounds as final products of parallel reactions. It should be noted that, when asymmetrically substituted alkynes were involved in all of these reactions, benzenes with the same substituents in positions 1, 2, and 4 were selectively obtained.

In the previously commented set of studies of the $[Co_2(CO)_8]$-catalyzed cyclotrimerization reaction, only complexes involving one or three alkynes were isolated. Bennet and Donaldson[83] studied the cyclotrimerization of cyclooctyne, which is cyclotrimerized under very mild conditions, with the same catalyst. When the reaction was carried out under nearly stoichiometric conditions, the reaction product was isolated together with monoalkyne complex **17a** and a new organocobalt complex that after X-ray diffraction analysis was assigned as bimetallic cobaltacyclopentadiene complex **18a** (Scheme 10, equation a). The two complexes **17a** and **18a** catalyzed the cyclotrimerization reaction. When monoalkyne complex **17a** was used as the catalyst for the cyclotrimerization of cyclooctyne, cobaltacyclopentadiene complex **18a** was not isolated, an observation that the authors assigned at two independent routes being operative for the $[Co_2(CO)_8]$ cyclotrimerization reaction. Fly-over complexes were not isolated from the reaction mixture but could be obtained upon reaction of **18a** with methyl propiolate.

Costa and Paolo Chiusoli et al.[84] isolated analogous complexes on the reaction of $[Co_2(CO)_8]$ with *N*,*N*-dipropargylmethylamine (Scheme 10, equation b). Under mild reaction conditions, the substrate was coordinated to a hexacarbonyldicobalt fragment at each of its triple bonds in a "saw-horse" geometry, leading to complex **19**, as inferred by X-

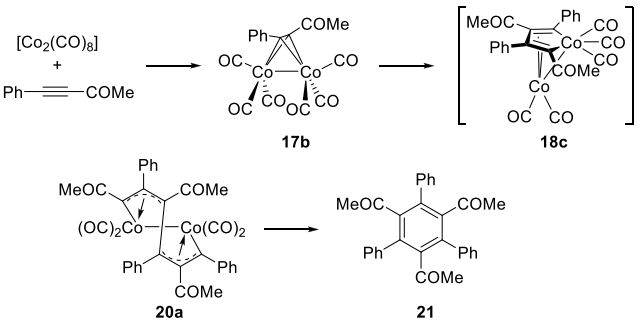
Scheme 10. Cobaltacyclopentadienes Isolated in $[Co_2(CO)_8]$-Mediated Processes



ray diffraction. When the reaction was carried out in refluxing toluene, cobaltacyclopentadiene derivative **18b** was obtained as determined upon X-ray diffraction.[85] The electrons of the double bonds were delocalized over the four-atom system. Complex **18b** was postulated as an intermediate in the reaction of complex **19** with alkynes. Both complexes reacted with alkynes to afford the corresponding benzene derivative.

Sappa et al.[86] in 1993 carried out the reaction of 4-phenylbut-3-yn-2-one in refluxing toluene with $[Co_2(CO)_8]$ and isolated a mixture of the cyclotrimer **21** and two intermediate complexes, a monoalkyne complex **17b** and a fly-over complex **20a** (Scheme 11). In contrast to the previously reported examples that used

Scheme 11. Mechanism Proposed by Sappa et al.[86]



asymmetrically substituted alkynes,[78,82] the symmetrically substituted 1,3,5-triphenyltris(acetyl)benzene **21** was isolated, and also the fly-over complex **20a** was symmetrically substituted. The authors postulated the mechanism shown in Scheme 11, which involved an elusive bimetallic cobaltacyclopentadiene complex **18c**, analogous to the ones isolated earlier,[83,85] formed upon head-to-tail oxidative cyclization from monoalkyne complex **17b**. Upon coordination of a third alkyne, **18c** formed the fly-over complex **20a**, which provides reasonable amounts of the cyclotrimer **21** under relatively mild conditions and short reaction times and was thus postulated as an intermediate in the reaction. Sappa et al.[87] extended the study to other asymmetrically substituted alkynes, reaffirming the proposed mechanism but highlighting the fact that the regioselectivity is highly dependent on the substitution on the triple bond.

Seppelt et al.[88] carried out the reaction of pentafluoro-λ^6-sulfanylacetylene derivatives with $[Co_2(CO)_8]$ and were able to

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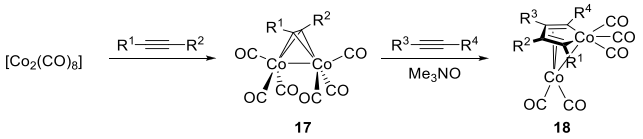
isolate complexes of structure analogous to **17**, **18**, and **20**, although 1,2,4-$(SF_5)_3$-substituted benzenes were only obtained upon bromine degradation from the fly-over complex.

The difficulty in isolating the bimetallic cobaltacyclopentadiene complex led Knox and Spicer et al.[89] to develop an efficient methodology for its synthesis (Scheme 12). The authors

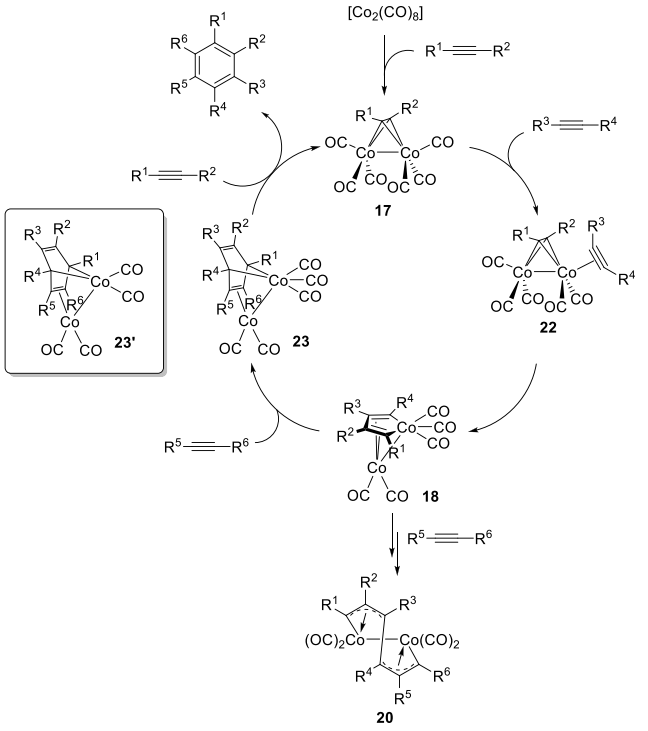
Scheme 12. Synthesis of Bimetallic Cobaltacyclopentadiene Complexes



assumed that it is necessary to remove just one CO ligand from the dicobaltatetrahedranes **17** to achieve alkyne coordination and trigger oxidative cyclization to **18**. A methodology was developed that used amine *N*-oxide to favor CO displacement together with stoichiometric amounts of alkyne under mild reaction conditions. A wide range of cobaltacyclopentadienes **18**, formed by either one or two different alkynes, were synthesized and fully characterized. Key points arose from the study of the complexes: first, the envelope conformation of the Co-containing heterocyclopentadienyl ligand (with the Co disposed above the C_4 plane) suggested that the ring did not have aromaticity; second, the regiochemistry was diverse and not easy to predict; and finally, evidence was obtained that the formation of cobaltacyclopentadienes was reversible.

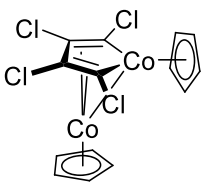
In a back-to-back paper,[90] the same authors analyzed the involvement of fly-over complexes either as intermediates in the [2 + 2 + 2] cycloaddition reaction or as products formed from a competing reaction path, an aspect which had previously been controversial. Thermal or oxidative degradation (using bromine) converted the fly-over complexes into arenes in an efficient and useful manner. However, Knox and Spicer et al.[90] showed that, whereas dicobaltatetrahedranes **17** and cobaltacyclopentadienes **18** catalyzed the formation of arenes with an activity and selectivity paralleling that of $[Co_2(CO)_8]$, the cyclotrimerization of alkynes using fly-over complexes **20** as catalysts yielded only small quantities of the expected arene, presumably resulting from its thermal decomposition without incorporating a free alkyne. Thus, the mechanistic scheme shown in Scheme 13 was proposed. Dicobaltatetrahedrane complex **17** coordinated a second alkyne to generate complex **22** from which cobaltacyclopentadiene **18** is formed by oxidative coupling. This intermediate may evolve through two competing pathways: by formation of the fly-over complex **20** or through a Diels–Alder-like addition of alkyne to the cobaltacyclopentadiene ring to generate bridging bent benzene complex **23**. The authors also took advantage of the possible stepwise preparation of the different intermediates to chemoselectively involve three different alkynes in the process, although facile alkyne exchange processes limited the approach in some cases. Feng and King et al.[91] conducted a computational study at the M06-L/DZP level of theory of the fly-over complex **20**. They discovered a number of isomers of complex **20**, the most stable of which was complex **23′**, which was generated after the release of a CO molecule from the Co with three attached CO ligands in complex **23**. They found that, with bulky substituents at the ends of the six-carbon chain, the experimentally known complex **20** is preferred to complex **23′** by 23.3 kcal/mol (R^n [n = 1−6] = CF_3) or 1.1

Scheme 13. Mechanistic Scheme Proposed by Knox and Spicer et al.[90] for the Cyclotrimerization of Alkynes Catalyzed by an Octacarbonyldicobalt Complex



kcal/mol (R^n [n = 1−6] = ^{t}Bu). On the other hand, for less sterically hindered species, bridging bent benzene ring structure **23′** is favored by 14.3 kcal/mol (R^n [n = 1−6] = H) and 9.8 kcal/mol (R^n [n = 1−6] = CH_3). Therefore, the authors concluded that the stabilization of the fly-over complexes as isolable stable intermediates requires bulky substituents that inhibit cyclization to benzene derivatives.

Sünkel[92] also managed to isolate and characterize by X-ray diffraction cobaltacyclopentadiene **24** (Figure 1) in the



24

Figure 1. CpCo stabilized bimetallic cobaltacyclopentadiene isolated by Sünkel.[92]

cyclotrimerization of dichloroacetylene. The particularity in this case is that the catalyst used is $[CpCo(CO)_2]$; thus, the cobalt releases the two carbon monoxide ligands on treatment with dichloroacetylene and remains coordinated to cyclopentadiene on oxidative cyclization in both cobalt atoms in the intermediate.

The isolation of bimetallic cobaltacyclopentadiene **24** contrasts with most of the cases reported on CpCo-based catalysts, which form monometallic cobaltacyclopentadienes. After Yamazaki and Hagihara[68] isolated cobaltacyclopentadiene complexes **12a** (Scheme 5) that were converted to benzenes

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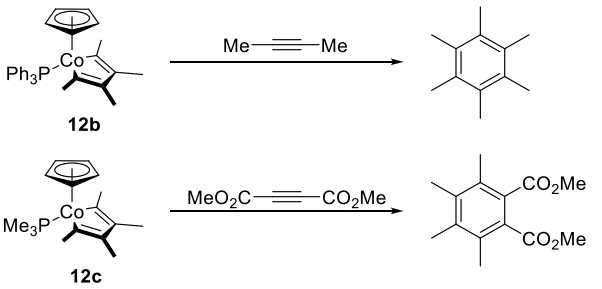
upon reaction with an alkyne, Wakatsuki et al.,[93] in 1974, developed an improved method for the synthesis of **12a** starting from $[CpCo(PPh_3)_2]$. The method was amenable to the synthesis of various cobaltacyclopentadiene derivatives, including compounds formed by the reaction of two different acetylene derivatives. When a reaction of the asymmetrically substituted acetylene compounds was performed, two different isomers were isolated. Reactions of cobaltacyclopentadiene complexes with acetylene derivatives smoothly provided polysubstituted benzenes. In 1977, the same group[94] reported the one-step and stepwise synthesis of cobaltacyclopentadiene complexes from acetylenes, the regioselectivity of which was assessed by spectroscopic techniques as well as by reaction of a third alkyne molecule and the analysis of the substituent positions in the benzene derivative that was formed.

A study by McAlister, Bercaw, and Bergman[95] in 1977 tried to shed light on the second part of the mechanism with the same catalyst. Analysis of the kinetic data of the reaction of **12b** and 2-butyne and **12c** with dimethyl acetylenedicarboxylate (Scheme 14) showed that triphenylphosphine dissociation was necessary

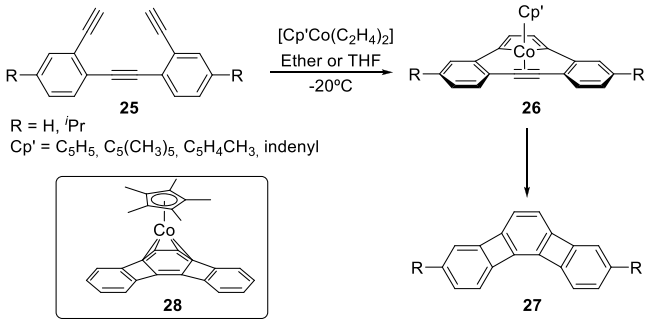
Scheme 14. Reactions Analyzed by McAlister, Bercaw, and Bergman[95] in the Kinetic Study



to allow 2-butyne to enter the coordination sphere of the metal and get involved in the reaction. On the other hand, no dissociation of the phosphine took place in the rate-determining step when dimethyl acetylenedicarboxylate was used. Direct reaction of uncomplexed alkyne to the diene moiety of the metallacycle was postulated as occurring. Thus, different mechanisms, related to different time scales of the kinetics, were observed depending on the electronic nature of the alkyne.

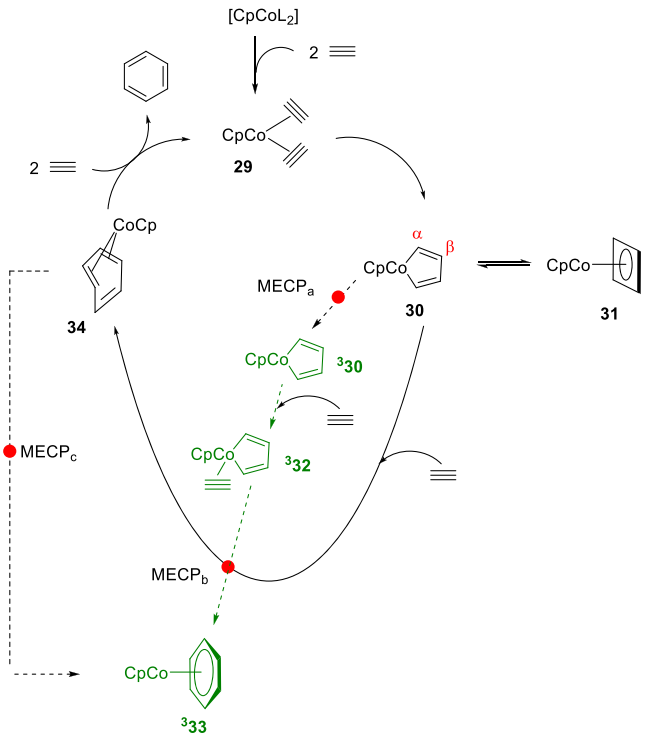
Vollhardt et al.[96] succeeded in isolating a series of cobaltacyclopentadienes **26** bearing a π-bound alkyne ligand, which represented a further step in the mechanistic scheme, by carrying out the reaction of the rigid triyne **25** with $[Cp'Co(C_2H_4)_2]$ at a low temperature (Scheme 15). Characterization was carried out with spectral data and subsequent transformations. Since intermediates **26** were isolated as microcrystalline powders, which were unsuitable for X-ray diffraction, their geometry was calculated at the B3LYP/6-311G* level, revealing a piano-stool topology around cobalt. Some years later, the same group[97] achieved the characterization by X-ray diffraction of an analogue in the synthesis of longer phenylenes. Complexes **26**, which were catalytically active in the cyclotrimerization of **25**, gave the corresponding angular phenylenes **27** in variable yields upon thermal decomposition. A kinetic analysis on the transformation of **26** to **27** showed it to be accelerated in the presence of external ligands that could trap the catalyst and that a first-order rate law, independent of CO pressure, was followed. The authors interpreted the transformation to follow a concerted pathway topologically equivalent to an intermolecular Diels–Alder, which they refer to as a "double vinyl shift". In one of the examples reported (R = H, Cp′ = $C_5(CH_3)_5$), η^4-bound arene intermediate **28** was isolated and characterized by X-ray diffraction and postulated to be an advanced intermediate formed from **26** en route to the final product **27**.

Scheme 15. Intermediates Isolated by Vollhardt et al.[96] in the Cyclotrimerization of a Linear Triyne



The full reaction mechanism of the cyclotrimerization of acetylene to yield benzene catalyzed by $[CpCoL_2]$ (L = CO, PR_3, alkenes) complex has been computationally analyzed in detail by several authors.[98−101] In all cases, the functional chosen was the B3LYP[102,103] using valence double- or triple-ζ basis sets, although, in some cases, QCISD or CCSD(T) single point calculations were performed to certify the reliability of the density functional theory (DFT) results. A summary of the main results obtained can be found in Scheme 16. The initial 18-

Scheme 16. Reaction Mechanism Reported by Koga et al.[107] and Gandon and Aubert et al.[100] for the Cobalt-Catalyzed Cycloaddition of Three Acetylenes[a]



[a]In green are those species that have a triplet ground state. Minimum-energy crossing points (MECPs) are depicted in red.

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electron species [$CpCoL_2$] undergoes a pair of ligand substitution reactions resulting in the formation of the catalytically active bisacetylene complex **29**. For L = PH_3, the conversion of [$CpCo(PH_3)_2$] to [$CpCo(\eta^2\text{-}C_2H_2)_2$] is exothermic by 11.3 kcal/mol according to the computational results of Albright et al.,[98] and, therefore, formation of the catalytically active species is thermodynamically favored. Oxidative coupling of the acetylene ligands in **29** gives a cobaltacyclopentadiene complex **30**. Albright et al.[98] show that this reaction is exothermic by 13.1 kcal/mol and has a relatively small enthalpy barrier of 12.8 kcal/mol. The transformation of **29** to **30** is generally the rate-determining step of the [2 + 2 + 2] cycloaddition reaction and as such has been studied by several authors.[104−107]

There are three aspects that have been discussed in relation to complex **30**, namely, (i) the aromaticity of the 5-membered ring (5-MR), (ii) the regioselectivity of the reaction in the [2 + 2 + 2] cycloaddition of substituted acetylenes, and (iii) the possible transformation of **30** to cobaltacyclobutadiene **31**. Despite a claim in favor of the aromaticity of the 5-MR in the cobaltacyclopentadiene complex,[105] it is widely accepted that complexes **30** are nonaromatic or even antiaromatic species with a clear π-localization with short $C_\alpha-C_\beta$ and long $C_\beta-C_{\beta'}$ bond lengths (see complex **30** in Scheme 16 for labels). An aromaticity analysis in a number of complexes with such a 5-MR concluded that most of these complexes can be catalogued as nonaromatic.[108] In case the reaction takes place with three identical monosubstituted alkynes, the oxidative coupling can occur in either three or four different ways (depending on the symmetry of the catalyst): head-to-head (**30_*α*,*α*′** or **30**_1,4), tail-to-tail (**30_*β*,*β*′** or **30**_2,3), tail-to-head (**30_*α*,*β*′** or **30**_1,3), and head-to-tail (**30_*α*′,*β*** or **30**_2,4). Stockis and Hoffmann[109] found with the extended Hückel method that, if steric effects are unimportant, the oxidative coupling places the C atom with electron-withdrawing groups (EWGs) next to the metal. Thus, from an electronic point of view, the ***α*,*α*′**- and ***β*,*β*′**-couplings should be the most and least favored oxidative couplings, respectively, for acetylenes substituted with EWGs. However, when substituents of terminal alkynes are bulky, the electronic factor becomes unimportant and it is the steric factor that controls the selectivity of the oxidative coupling, favoring the ***α*,*α*′**-coupling.[104] These predictions were computationally confirmed by Dahy and Koga[107] for the oxidative coupling of acetylenes mono- and disubstituted by methyl and methoxycarbonyl groups. In addition, they suggested that the regiochemical preference for ***α***-positions is closely related to the site preference in substituted butadienes. As discussed in the Introduction, the possible involvement of metal-cyclobutadiene species in the reaction mechanism was a hot topic of debate. From a theoretical point of view, transformation of **30** into **31** has been discussed in several works.[98,106] The results from these studies show that, although the generation of **31** from **30** is exothermic by about 30 kcal/mol, it goes through an energy barrier of ca. 20−30 kcal/mol. Since the barriers for the evolution of **30** to **34** are much lower, complex **31** is considered not to play any role in the reaction mechanism. However, the barrier for the **30** → **31** reaction becomes lower for bulky substituents and, consequently, the formation of cyclobutadiene complexes cannot be totally ruled out in these particular cases. It should be mentioned that **30** in the singlet state does not have a perfect C_s structure and that departure of **30** from the C_s symmetry was attributed to a second-order Jahn−Teller distortion.[107] Finally, it is worth noting that Dalla Tiezza, Bickelhaupt, and Orian[110] recently analyzed the group 9 metallacyclopentadienes, [$CpM(\eta^2\text{-}C_2H_2)_2$] (M = Co, Rh, Ir). They found that the oxidative coupling of the two acetylene molecules to generate the metallacyclopentadiene goes with a barrier that increases along CpCo < CpIr < CpRh. They attributed the better performance of the CpCo catalysts to the decrease in the strain energy in the CpCo due to the small size of this metal in comparison to Rh and Ir. Orbital interactions increase when going from CpCo to CpRh to CpIr, but they do not increase sufficiently to compensate the higher steric repulsions of the heaviest metals.

According to the calculations by Albright et al.,[98] coordination of a third acetylene to **30** releases 12.4 kcal/mol. An intramolecular Diels−Alder reaction between the cobaltacyclopentadiene and the coordinated acetylene generates the η^4-benzene complex **34**. This process occurs with a small enthalpy barrier of 0.5 kcal/mol and liberates 81.4 kcal/mol. This high exothermicity is due to the concomitant formation of two new σ-bonds and an aromatic ring. η^4-Coordination is preferred because it leads to an 18-electron species. Interestingly, using a different basis set, Dahy and Koga[107] and Gandon and Aubert et al.[100] found that this transformation of **30** into **34** was a direct intermolecular [4 + 2] cycloaddition that proceeded without an energy barrier. Dahy and Koga[107] analyzed the cobaltacycloheptatriene and cobaltabicyclo[3.2.0]heptatriene intermediates and concluded that, although these complexes exist in the PES, there are no favorable reaction paths through these intermediates. Completion of the catalytic cycle takes place by displacement of the benzene ring with a couple of acetylene molecules to regenerate **29** and releasing 7.4 kcal/mol.

Dahy and Koga[107] in 2005 realized that the triplet state is the ground state for the cobaltacyclopentadiene **30** complex [$CpCo(C_4H_4)$]. They found that the 18-electron cobalt species usually exists as a singlet ground state, whereas its 16-electron counterpart prefers the triplet state as the ground state. Therefore, at many points along the reaction path, the singlet and triplet PES are close in energy. It is likely that, in this situation, one can have a two-state reactivity in which connection between reactants and products occurs through two PESs with different spins (nonadiabatic mechanism).[111] This change from one spin PES to the other takes place at crossing points at which the two spin states differ minimally in structure and energy, the so-called minimum-energy crossing points (MECPs).[112] Both Dahy and Koga[107] and later on Gandon and Aubert et al.[100] revisited the reaction mechanism taking into account the possible two-state reactivity with the B3LYP method. Although it is well-known that this method overestimates the stability of the triplet relative to the singlet, the global picture does not change when using QCISD(T) energies.[101] Dahy and Koga[107] found that the cobaltacyclopentadiene **30** and [$CpCo(\eta^4\text{-}C_6H_6)$] complexes are more stable in the triplet (^{3}**30** and ^{3}**33** green structures in Scheme 16) than in the singlet state. Once the **30** complex is formed in the singlet surface, a surface hopping takes place from the singlet to the triplet state through a crossing point ($MECP_a$ in Scheme 16) located close in energy (at −1.1 kcal/mol) and structure to singlet **30**. From $MECP_a$, the system evolves to the ^{3}**30** complex, which, in contrast to **30**, has C_s symmetry. Coordination of a new alkyne generates complex ^{3}**32** and releases 1.2 kcal/mol. After this, intramolecular Diels−Alder reaction in the triplet state requires an activation energy of 14.1 kcal/mol. However, $MECP_b$ is located at only 7.1 kcal/mol. Therefore, there is a second surface hopping via $MECP_b$ and a direct intramolecular

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[4 + 2] cycloaddition takes place, spontaneously generating complex **34**. The third $MECP_c$, which is only 0.6 kcal/mol higher in energy than **34**, connects **34** in the singlet state with ^{3}**33** in the triplet state. After this, displacement of the benzene ring with a couple of acetylene molecules regenerates **29** and closes the catalytic cycle. As a whole, the most favorable route for the cyclotrimerization of three acetylenes is a two-state reactivity pathway that proceeds in the following way: **29** → **30** → ^{3}**30** → ^{3}**32**→ **34** → ^{3}**33**.

Gandon and Aubert et al.[100] analyzed the possibility that cobaltacyclopentadiene complex **30** could be trapped by a σ-donor ligand L to generate a coordinatively saturated [CpCo(C_4H_4)L] complex. The activation barrier for the intermolecular Diels–Alder cycloaddition to this complex was found to be prohibitively high. Therefore, they concluded that, for reactions in strong σ-donor solvents or with ligands like L = PR_3 or CO, the 18-electron complex [CpCo(C_4H_4)L] could be a relay point, a result that was consistent with experimental results.

It is worth noting that Harris et al.[113] reported an ultrafast study of the photochemistry of [$CpCo(CO)_2$] in neat 1-hexyne. By employing time-resolved infrared (TRIR) spectroscopy together with DFT calculations, the authors concluded that [^{3}CpCo(CO)] coordinated to 1-hexyne without a change of spin state and that the intermediate that was formed subsequently underwent spin crossover to form [^{1}CpCo(CO)-(η^2-1-hexyne)]. The authors suggested that the order of events (coordination prior to spin crossover) can be extrapolated to the other steps in the mechanistic cycle involving coordination of an alkyne to a 16-electron species. This, in fact, is the situation described by Dahy and Koga[107] in the case of $MECP_b$.

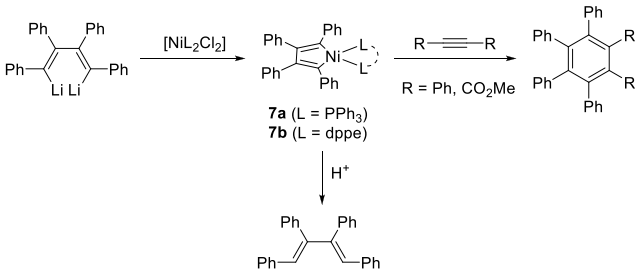
Finally, Kabe et al.[114] recently reported that the CpCo(I)-catalyzed [2 + 2 + 2] cycloaddition of siladiynes and dimethyl acetylenedicarboxylate (DMAD) starts with the oxidative heterocoupling between the siladiyne and DMAD to form a cobaltacyclopentadiene that follows the same two-state reaction mechanism depicted in Scheme 16.

2.3. Nickel Complexes

The intermediacy of nickelacyclopentadiene complexes, also referred to as "nickeloles", in the nickel-catalyzed [2 + 2 + 2] cycloaddition reaction was already postulated by Kennerly et al. in 1962,[64] but it was not until 1975 that Eisch et al.[115] managed to synthesize a nickelacyclopentadiene (although through an independent synthesis) and study its catalytic activity toward alkynes. The reaction of *E,E*-1,4-dilithio-1,2,3,4-tetraphenylbutadiene with [$Ni(PPh_3)_2Cl_2$] or [$Ni(dppe)_2Cl_2$] (dppe = 1,2-bis(diphenylphosphino)ethane) furnished nickelacyclopentadiene complexes **7a** and **7b**, with the latter being highly insoluble, preventing its complete characterization. Reaction of complex **7a** with dimethyl acetylenedicarboxylate yielded the expected aromatic compound (Scheme 17). Furthermore, **7a** efficiently catalyzed the cyclotrimerization of diphenylacetylene. The observed reactivity of nickelacyclopentadiene complexes, together with the detection of *E,E*-1,2,3,4-tetraphenylbutadiene when a cyclotrimerization reaction of diphenylacetylene catalyzed with [$Ni(cod)_2$] was quenched with acid at short reaction times, was taken as strong evidence of the involvement of nickelacyclopentadiene intermediates in the reaction.

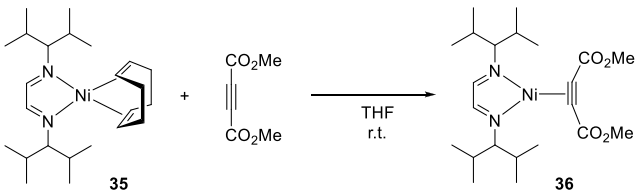
Over 10 years later, the same group[116] further characterized nickelacyclopentadiene complexes **7a** and **7b** and proposed the involvement of a nickelacyclopropene, also referred to as "nickelirene", as a step that was previous to the formation of nickelacyclopentadiene complexes in the cyclotrimerization

Scheme 17. Nickelacyclopentadiene Complexes Synthesized by Eisch et al.[115]



reaction. One of these nickel alkyne complexes had been isolated and characterized by UV–vis, ^{1}H NMR, and IR spectroscopy by Diercks and tom Dieck[117] two years earlier. The cyclotrimerization of various acetylenecarboxylic esters by using diazadiene–nickel(0) complexes was reported. When the reaction of complex **35** with dimethyl acetylenedicarboxylate was carried out stoichiometrically and at room temperature, a green nickel–alkyne complex **36** that was extremely sensitive to oxygen was isolated (Scheme 18). Complex **36** proved to be

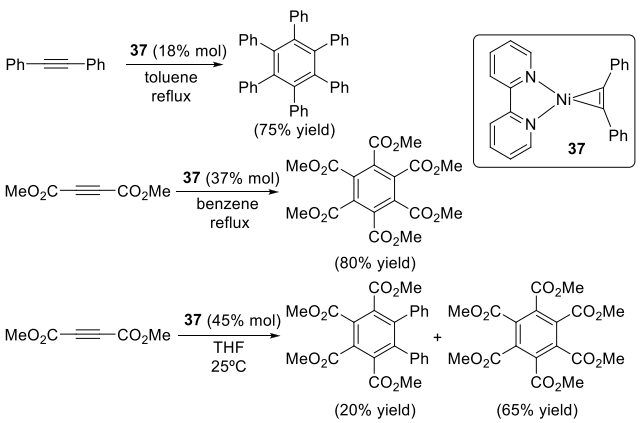
Scheme 18. Nickel/Alkyne Complex Isolated by Diercks and tom Dieck[117]



catalytically active in the cyclotrimerization reaction. Although this was an early intermediate in the catalytic cycle that was expected to evolve through coordination of a second alkyne and oxidative coupling, the authors stated that it was not possible to detect or isolate a nickelacyclopentadiene complex.

Eisch et al.[118] achieved in 2001 the characterization by X-ray diffraction of a nickelirene complex, 2,2-bipyridyl(η^2-diphenylacetylene)nickel (**37**, Scheme 19). Complex **37** was formulated as a nickelacyclopropene, instead of its resonance structure where the nickel center only accepts electron density from the

Scheme 19. Nickelacyclopropene Complex Isolated by Eisch et al.[118]



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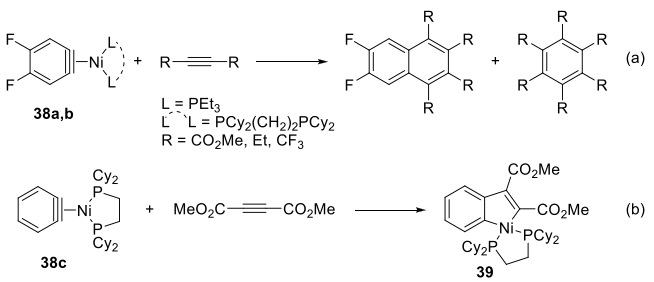
Chem. Rev. XXXX, XXX, XXX–XXX

alkyne, based on its spectroscopic and structural characteristics. Complex **37** catalyzed the cyclotrimerization of phenylacetylene to hexaphenylbenzene and dimethyl acetylenedicarboxylate to hexamethyl mellitate, although in this last example different products were isolated depending on the conditions. When the reaction was carried out in benzene at reflux, only hexamethyl mellitate in an 80% yield was obtained. On the other hand, when the reaction was carried out in THF at 25 °C, apart from the cyclotrimer, 1,2,3,4-tetra(methyloxycarbonyl)-5,6-diphenylbenzene was isolated in a 20% yield. The authors hypothesized that at lower temperatures complex **37** was stable and underwent insertions of dimethyl acetylenedicarboxylate, whereas at higher temperatures **37** decomposed with the transfer of the nickel complex to dimethyl acetylenedicarboxylate. In summary, these results supported the participation of nickelacyclopropenes as crucial intermediates in the cyclotrimerization reaction.

In 1995, Bennett and Wenger[119] reported the reaction of nickel benzyne complexes **38a,b** with alkynes to afford benzene derivatives, by cyclotrimerization of the alkyne, and naphthalene derivatives arising from double insertion of the acetylene into the Ni−benzyne bond and subsequent reductive elimination (Scheme 20, equation a). The structure of an analogous nickel−

Scheme 20. Reactivity of Nickel-Benzyne Complexes with Alkynes

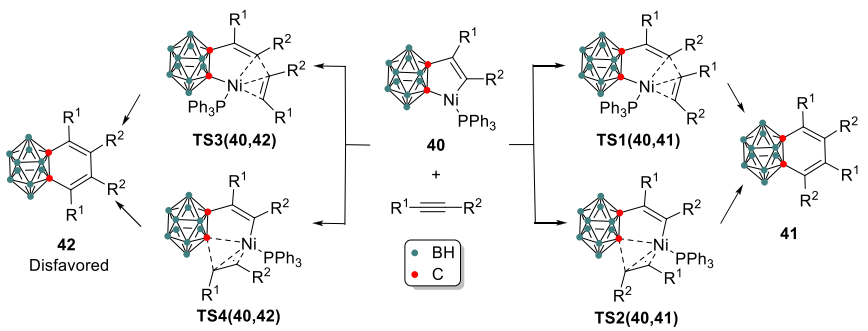


benzyne complex **38c** had been earlier characterized by spectroscopic techniques and X-ray diffraction in the same group[120] and shown to react with dimethyl acetylenedicarboxylate at −10 °C to give an orange complex, which was characterized by spectroscopic techniques as being nickelaindene complex **39** (Scheme 20, equation b). Nickelaindene complexes analogous to **39** could be detected by NMR spectroscopy in the reaction shown in Scheme 20a, although they could not be isolated from the reaction mixture.

Carboryne, $B_{10}C_2H_{10}$, also called 1,2-dehydro-*o*-carborane, is an unstable derivative of *ortho*-carborane ($B_{10}C_2H_{12}$) in which the two H atoms attached to C atoms in *ortho*-carborane have been removed. Carboryne is related to *o*-carborane in a similar way that *o*-benzyne is related to benzene. Carboryne was shown in 2006 by Xie et al.[121] to participate in nickel-catalyzed [2 + 2 + 2] cycloaddition reactions. These Ni-catalyzed reactions showed good regioselectivities, and the yields were higher when the alkynes were substituted with electron-donating groups. The mechanism for the transformation was studied computationally by Mu and Chass et al.[122] in 2015 using the B3LYP method together with a double-ζ basis set and including solvent effects of a THF solution at 363 K. The authors studied the [2 + 2 + 2] cycloaddition of four possible alkynes $R^1C{\equiv}CR^2$ to the carboryne, namely, $R^1 = R^2 =$ Et (reaction **a**), $R^1 = R^2 =$ Ph (reaction **b**), $R^1 =$ Me and $R^2 =$ Ph (reaction **c**), and $R^1 = R^2 =$ ^{t}Bu (reaction **d**). The initial complex was the Ni−carboryne complex $[C_2B_{10}H_{10}Ni(PPh_3)_2]$. The first step corresponds to the loss of PPh_3 followed by the insertion of the alkyne into one of the Ni—C bonds to form **40** (Scheme 21). For reaction **a**, this process has to surmount a barrier of 23.7 kcal/mol and it is exergonic by 16.1 kcal/mol. After this point, another insertion of a new alkyne into the Ni—C bond takes place. Depending on the symmetry of the alkyne, this insertion can occur in two or four different ways (Scheme 21). The most favored route is through **TS1(40,41)** in Scheme 21 with a Gibbs energy barrier of 27.2 kcal/mol for reaction **a**. The alternative insertion via **TS2(40,41)** has a barrier of 49.8 kcal/mol. This insertion of the second alkyne is found to be the rate-determining step for all four [2 + 2 + 2] cycloadditions studied. In all cases, the reaction through **TS1(40,41)** is the most favored. The Gibbs energy barriers for this second insertion are 27.2, 36.6, 31.1, and 60.4 kcal/mol for reactions **a**−**d**, respectively. This computational result concurs with the experimental yields of 67, 44, 54, and 0% obtained for reactions **a**−**d** in this order. In the case of reaction **c**, the barriers through **TS2(40,41)**, **TS3(40,42)**, and **TS4(40,42)** are in the range 44.7−52.6 kcal/mol. The two final steps after the second insertion involve the formation of the benzocarborane product (**41** in Scheme 21) and the release of $NiPPh_3$, which reacts with $Li_2C_2B_{10}H_{10}$ to regenerate the catalyst. The authors warned about the dangers of truncated models of the catalyst, such as $Ni(PMe_3)_2$ or $Ni(PH_3)_2$. They showed that, with these simplified models, the rate-determining step changed from the second to the first alkyne insertion and, therefore, concluded that the real chemical system needs to be employed when modeling this reaction.

A relevant aspect in the nickel-catalyzed [2 + 2 + 2] cycloaddition reaction is the eventual involvement of more than one metal atom in the catalytic cycle. Stone et al.[123] reported in

Scheme 21. Four Different Possible Insertion Reactions in the Nickel-Catalyzed [2 + 2 + 2] Cycloaddition between Carboryne and Alkynes Studied by Mu and Chass et al.[122]



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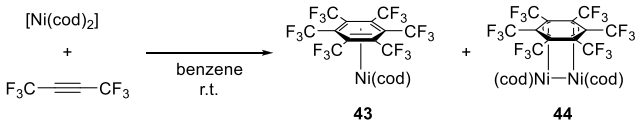
1971 the isolation of two nickel complexes upon reaction of $[Ni(cod)_2]$ and hexafluorobut-2-yne in benzene at room temperature (Scheme 22). Both complexes were characterized

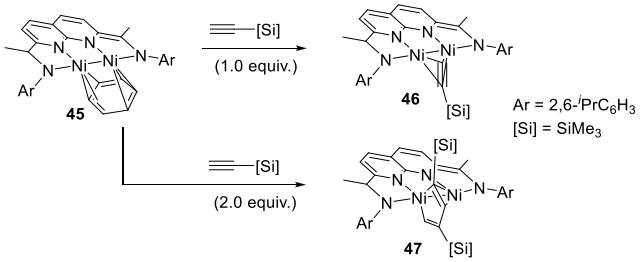
Scheme 22. Nickel Complexes Isolated by Stone et al.[123]



by spectroscopic techniques and elemental analysis, and structures featuring an aromatic ring coordinated to either one, for complex **43**, or two nickel atoms, for complex **44**, were proposed. The authors discussed the coordination geometry for complex **43** and suggested a fluxional behavior between three complexes in which the aromatic ring was η^4 coordinated (to explain the equivalency of the six CF_3 groups).

Pal and Uyeda[124] studied in greater depth the role of nuclearity in the Ni-catalyzed alkyne cyclotrimerization reactions. The catalytic activity of three mononuclear N-chelate nickel complexes was compared to that of dinuclear nickel complex **45** in the cyclotrimerization of terminal alkynes with diverse electronic properties (Scheme 23). The binuclear

Scheme 23. Binuclear Intermediates Isolated by Pal and Uyeda[124]



complex outperformed the others in terms of both activity and selectivity (showing a high preference for trimerization with the formation of the 1,2,4-substituted benzene product). The reaction of complex **45** with terminal alkynes bearing bulky silyl substituents allowed for the isolation of plausible intermediates **46** and **47**, containing one and two reacting alkynes, respectively. In the solid state, monoalkyne complex **46** showed a μ–η^2:η^2 coordination of the alkyne to the two metallic centers, with the alkyne perpendicular to the intermetallic bond vector. Complex **47** features a nickelacyclopentadiene in one of the nickel atoms and an η^2-interaction to the second nickel with a double bond of the diene system providing further stabilization. Selective head-to-tail oxidative coupling is observed, purportedly arising from the steric hindrance imposed by the 2,6-diisopropylphenyl substituents. **47** reacted with methyl propargyl ether (although not with bulky alkynes) to form the corresponding aromatic product. It should be noted that analogous bimetallic stabilized intermediates had previously been reported for cobalt (see section 2.2) and tantalum (see section 2.8). Pal and Uyeda performed additional DFT calculations using the M06/6-31G(d,p) level of theory to rationalize the observed high preference for the formation of the 1,2,4-substituted benzene product. They used a model catalyst with the *i*Pr groups on the aryl substituted by Me. They investigated the different reaction paths described in section 1, i.e., metal-mediated inter- or intramolecular [4 + 2] Diels–Alder cycloaddition to form a 7-metallanorbornadiene complex **VI** and [2 + 2] cycloaddition to give a metallabicyclo[3.2.0]heptatriene **VII** (Scheme 8). Using propyne as a substrate, they only found a transition state for the intermolecular Diels–Alder cycloaddition to generate the final 1,2,4-substituted benzene product with an activation energy of 9.3 kcal/mol. The alternative path leading to the 1,3,5-substituted benzene product was 2.0 kcal/mol higher in energy in agreement with the experimental preference for the 1,2,4-substituted benzene product. They attributed the higher energy of the 1,3,5-transition state to steric effects induced by the presence of the second Ni. In a second related computational work, Ess et al.[125] used the M06L/def2-TZVP//M06L/6-31G(d,p)~LANL2DZ method to study the alkyne cyclotrimerization catalyzed by the homodinuclear nickel complex $[(^{iPr}NDI)Ni_2(C_6H_6)]$ (NDI = naphthyridine-diimine). This complex has a singlet ground state, with the triplet state being only 12.7 kcal/mol higher in energy. This small singlet–triplet energy gap already suggested a possible two-state reactivity mechanism. In fact, substitution of benzene in the initial catalyst $[(^{iPr}NDI)Ni_2(C_6H_6)]$ by two acetylene molecules releases 19.2 kcal/mol and yields a $[(^{iPr}NDI)Ni_2(C_2H_2)_2]$ complex that has a triplet ground state 3.5 kcal/mol more stable than the singlet state. Thus, the catalytic process starts with a surface hopping from the singlet to the triplet PES. The oxidative coupling then takes place on the triplet PES with a Gibbs energy barrier ($\Delta G^{\ddagger}$) of 15.4 kcal/mol. This coupling is exergonic by 32.3 kcal/mol and gives a nickelacyclopentadiene intermediate. For this species, the triplet is the ground state, although the singlet and quintet are within ~2 kcal/mol. An insertion of an additional acetylene molecule to the nickelacyclopentadiene intermediate directly generates the nickelacycloheptatriene complex with $\Delta G^{\ddagger}$ = 15.7 kcal/mol. This process takes place on the triplet-spin-state PES. However, the nickelacycloheptatriene intermediate has a singlet ground state that is more stable than the triplet by less than 1 kcal/mol and a spin-crossing from the triplet-spin surface to the singlet-spin occurs through a MECP with a geometry similar to that of the nickelacycloheptatriene intermediate. The [2 + 2] and the inter- and intramolecular [4 + 2] alternative mechanisms were found to have higher energy barriers. The final reductive elimination step is facile from both the singlet- and triplet-spin surfaces to recover the initial $[(^{iPr}NDI)Ni_2(C_6H_6)]$ complex. The authors also studied the insertion of a new acetylene molecule into the nickelacycloheptatriene intermediate to form a nickelacyclononatetraene species that by reductive elimination yields cyclooctatetraene (COT). The barrier found was 9.2 kcal/mol higher than the barrier for the reductive elimination from the nickelacycloheptatriene intermediate. The authors suggested that the reductive elimination is favored by the *cis* configuration of the Ni–vinyl nonclassical bonds, which are similar to those found in complex **46** in which the acetylene ligand bridges two metal centers.

Lord and Groysman et al.[126] also reported a dinuclear nickel catalyst with a xanthene-bridged bis(iminopyridine) ligand that was active in the cyclotrimerization reaction of terminal alkynes. In contrast to Uyeda's catalyst, there is no nickel–nickel bond in the precatalyst structure, which indeed features a coordination to a triple bond. B3LYP/6-311G(d,p)//B3LYP/6-31G(d,p) calculations by the same authors show that the electronic structure of the initial dinuclear nickel complex coordinated to acetylene is best described as an open-shell singlet with two Ni(I) ions antiferromagnetically coupled to the adjacent Ni

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center and the iminopyridine ligand. In the next step, a second acetylene molecule is coordinated to Ni to generate a diacetylene adduct that is computed to be 23.8 kcal/mol higher in energy than the monoacetylene dinuclear nickel complex. This diacetylene dinuclear nickel complex has a closed-shell electronic structure with no unpaired spins. Subsequent oxidative coupling of the two acetylene molecules coordinated to Ni to form a highly stable nickelacyclopentadiene species has a Gibbs energy barrier of 27.3 kcal/mol with respect to the monoacetylene dinuclear nickel complex. The nickelacyclopentadiene ring is η^4-coordinated to the second Ni atom, which is at variance with the η^2-coordination found in the nickelacyclopentadiene in the Pal and Uyeda dinickel system (Scheme 23).[124] The oxidative coupling reaction is the rate-determining step of the [2 + 2 + 2] cycloaddition studied by Lord and Groysman et al.[126] From the nickelacyclopentadiene complex, the authors explored all possible reaction paths described in section 1 (inter- and intramolecular Diels–Alder and [2 + 2] cycloaddition). Only the transition state for the [2 + 2] cycloaddition that produces the nickelabicyclo[3.2.0]-heptatriene intermediate was located ($\Delta G^{\ddagger}$ = 22.5 kcal/mol). Elongation of the Ni–C bond in this intermediate affords the nickelacycloheptatriene species with a barrier of only 0.4 kcal/mol. Reductive elimination of benzene from the nickelacycloheptatriene intermediate is easy with a barrier of only 1.6 kcal/mol. The authors also explored the origin of the COT formation observed for some alkynes. They were able to optimize a nickelacyclononatetraene intermediate that was only 0.8 kcal/mol less stable than the nickelacycloheptatriene intermediate. However, they were unable to determine the barrier for the [2 + 2] cycloaddition of acetylene to the nickelacycloheptatriene complex.

Finally, Moret et al.[127] recently reported the use of an adaptive diphosphine–benzophenone ligand in the nickel-catalyzed cyclotrimerization of alkynes. Adaptive ligands adapt their coordination mode to the electronic characteristics of the different intermediates. The authors showed that the complex [($^{p\text{-tol}}$**L1**)Ni(BPI)] ($^{p\text{-tol}}$**L1** = 2,2′-bis(di(*para*-tolyl)-phosphino)-benzophenone; BPI = benzophenone imine) was an active catalyst in the [2 + 2 + 2] cyclotrimerization of terminal alkynes, selectively affording the 1,2,4-substituted benzenes. The authors performed B3LYP/6-31G(d,p) geometry optimizations of the nickel alkyne and bisalkyne complexes ([($^{p\text{-tol}}$**L1**)-Ni(C_2H_2)], **48**, and [($^{p\text{-tol}}$**L1**)Ni(C_2H_2)$_2$]) as well as the nickelacyclopentadiene system [($^{p\text{-tol}}$**L1**)Ni(C_4H_4)], **49**. No transition states were located. They found that, in complex **48**, the ketone group was not bound, thus helping the coordination of the second alkyne. On the other hand, in complex **49**, the ketone was η^2-coordinated to the nickel (Figure 2). This interaction favors the oxidative coupling step and the formation of the 2,5-disubstituted nickelacyclopentadiene that leads to the selective formation of the 1,2,4-trisubstituted benzene. Therefore, they concluded that the hemilabile character of the ketone ligand $^{p\text{-tol}}$**L1** favors the high activity and selectivity of the [($^{p\text{-tol}}$**L1**)Ni(BPI)] catalyst in the cyclotrimerization of terminal alkynes.

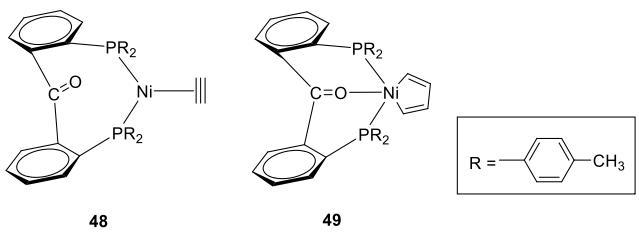

Figure 2. Structures of nickel alkyne complexes described by Moret et al.[127]

2.4. Ruthenium Complexes

Ruthenium is also an active transition metal to promote [2 + 2 + 2] cycloadditions of alkynes. Given its high capacity for multiple metal bonding, the oxidative coupling of ruthenium with two alkynes generates two different types of metallacycles: ruthenacyclopentadienes or ruthenacyclopentatrienes with a biscarbene structure. It is important to note that the kind of metallacycle generated is basically determined by the X-ray analysis, and depending on the Ru–C and C–C bond distances, some of the intermediates are represented as highly delocalized structures, suggesting the contribution of the two metallacycles.

Singleton et al.[128] were the first to isolate and characterize a metallacyclopentatriene complex. When Ru complex **50a** reacted with 4 equiv of phenylacetylene in dichloromethane at 0 °C, ruthenacyclopentatriene **51a** was obtained as green crystals (Scheme 24, equation a). **51a** was characterized by NMR spectroscopy and X-ray diffraction analysis. The bond lengths within the metallacycle suggest a largely delocalized metallacyclopentatriene structure. The treatment of complex **51a** with donor ligands such as morpholine, trimethyl phosphite, or dimethylphenylphosphine triggered the formation of a metallacyclopentadiene **52a**, given that the pair of electrons of the ligand makes it unnecessary for the triene structure to form a saturated 18-electron complex. A similar study was performed by Kirchner et al.[129] in which they analyzed the substitution chemistry of [Cp*Ru(tmeda)Cl] complex **53** with terminal acetylenes R–C≡CH (Scheme 24, equation b). Depending on the nature of the R, three different ruthenium complexes were obtained: ruthenacyclopentatriene **51b**, cyclobutadiene complex **54**, or the binuclear complex **55**. A third study by Yi et al.[130] described the synthesis of ruthenacyclopentadiene complex **52b** from the reaction of **56** with an excess of acetylene (Scheme 24, equation c). Complex **52b** was described as a ruthenacyclopentadiene with a slight contribution from the metallacyclopentatriene resonance structure. From these studies, it seems that the formation of a cyclopentatriene or a cyclopentadiene structure depends not only on the nature of the ligands but also on the nature of the alkyne used. Neither Singleton nor Kirchner studied the catalytic ability of these ruthenium complexes as catalysts in the [2 + 2 + 2] cycloaddition reaction, limiting themselves to purely structural studies. In the case of Yi, complex **52b** catalyzed the linear coupling of acetylene and acrylonitrile but no cyclic products from [2 + 2 + 2] cycloaddition were detected.

An interesting study involving ruthenium in [2 + 2 + 2] cycloaddition in which a ruthenium intermediate was isolated was undertaken by Lindler et al.[131] The initial ruthenium precatalyst was the carbonyl olefin complex **57**, which reacted with activated alkynes such as dimethyl and diethyl acetylenedicarboxylates to give tricyclic compounds **58a** and **58b**, respectively. Full characterization of these dimeric complexes by NMR spectroscopy and X-ray diffraction analysis showed that the geometry of each ruthenium atom is roughly octahedral and that the 8-membered ring has a chair conformation. Complexes **58** were found to be good catalysts for the cycloaddition of dialkyl acetylenedicarboxylates to afford

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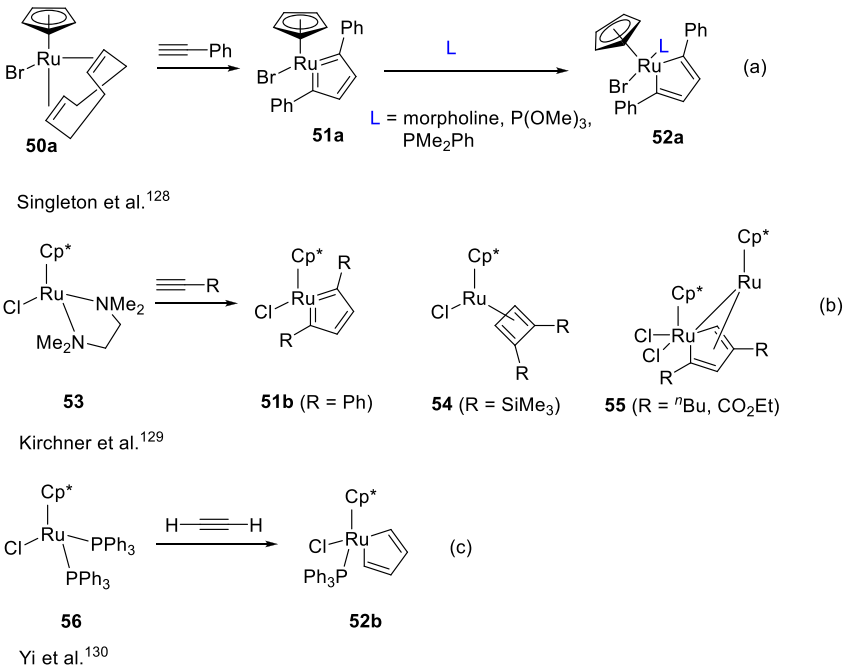
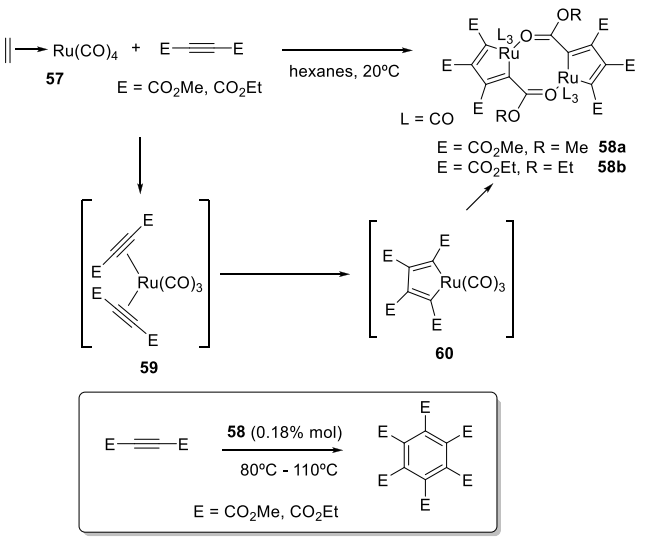
Scheme 24. Structure of Ruthenacycles Generated from Oxidative Coupling of a Ruthenium Complex with Two Alkynes



a quantitative yield of hexaalkyl mellitate derivatives (Scheme 25).

Scheme 25. Catalytic Activity of Bisruthenacyclopentadienes 58 in Cyclotrimerization Reactions



The authors postulated that complex **57** lost the ethylene ligand together with one carbonyl group to give the dialkyne coordinated complex **59** that evolved into a nonstable ruthenacyclopentadiene **60**, which finally generated dimer **58**. Although intermediate **60** cannot be isolated from the structure of dimer **58**, the authors postulated a metallacyclopentadiene in **60**.

In 2004, Yamamoto et al.[132] described the synthesis of a dinuclear ruthenium complex **62** generated when $[Ru_3(CO)_{12}]$ reacted with 1.5 equiv of oxygen-tethered diyne **61a** under 5 atm of CO in CH_3CN at 120 °C for 12 h (Scheme 26). Depending on the equivalents of the diyne **61a** used, ruthenacyclopentadiene **63** was also obtained. Once isolated, **63** was treated with $[Ru_3(CO)_{12}]$ under the same optimized reaction conditions. **62** was then obtained with a 78% yield, demonstrating that **63** was a precursor of **62**. Both complexes **62** and **63** were characterized by NMR and IR spectroscopy and X-ray diffraction analysis (Scheme 26, equation a). Ruthenabicycle **62** was then converted into the corresponding monotrimethylamine complex **64** when treated with Me_3NO, by the substitution of one of the CO ligands. The authors then studied the reactivity of complex **64** with alkynes. A similar dinuclear cobaltacyclopentadiene **18b** (see, for instance, Scheme 10) described by Costa et al.[84] afforded fused benzene derivatives when reacted with alkynes. When **64** was treated with an excess of dimethyl acetylenedicarboxylate (DMAD), a new dinuclear complex **65**, characterized by X-ray diffraction analysis, was formed by the oxidative addition of the alkyne to **64** and only traces of the [2 + 2 + 2] cycloadduct were obtained. In contrast, when using diphenylacetylene as the alkyne, the benzene derivative was obtained with a 44% yield (Scheme 26, equation b). This study demonstrates that the dinuclear species were less active as a catalyst in [2 + 2 + 2] cycloaddition reactions than in other studies by Yamamoto's group that used mononuclear ruthenium complexes (see in later sections).

Studies were also performed to investigate the role of a metallacyclopentatriene derivative as an intermediate in cycloaddition reactions. In 1999, Dinjus et al.[133] reported the synthesis and characterization by X-ray diffraction analysis of the ruthenacyclopentatriene **51b** and the stable cationic sandwich complex **66**, which were obtained, respectively, when phenylacetylene reacted with [Cp*Ru(cod)Cl] **50b** under different reaction conditions (Scheme 27). The authors compared the intermediates generated with those isolated in the case of the CpCo fragment published by Vollhardt et al.[96] (see, for instance, Scheme 15) in which intermediate **28** is an η^4-bound arene derivative. The authors interpreted complexes **51b** and **66** as being intermediates in the cyclotrimerization of alkynes.

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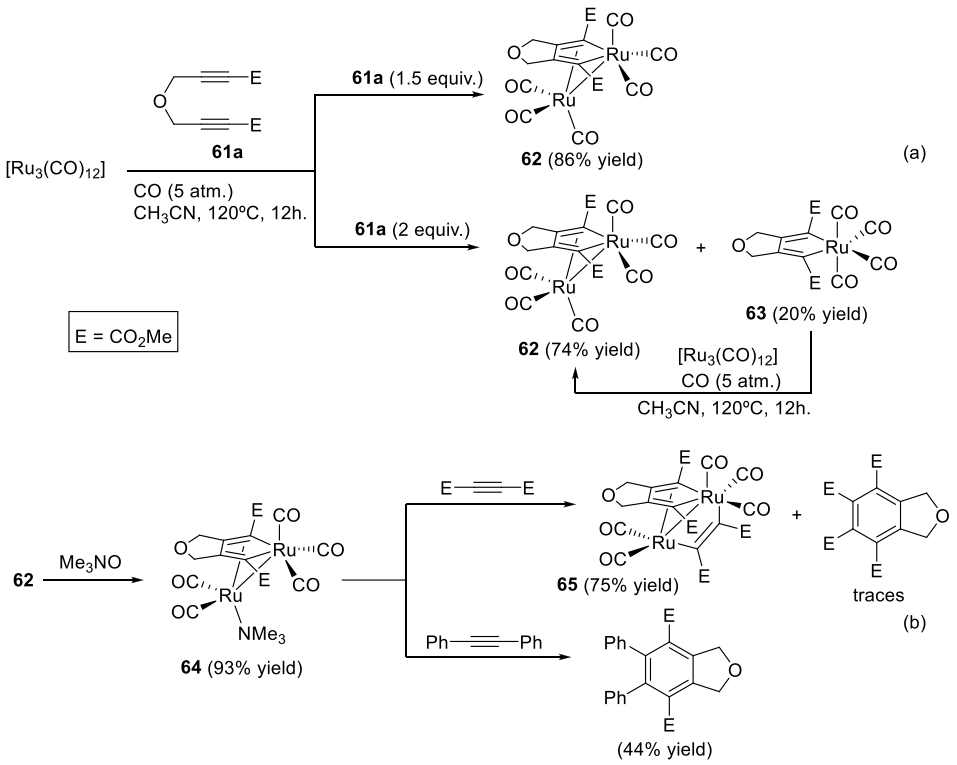
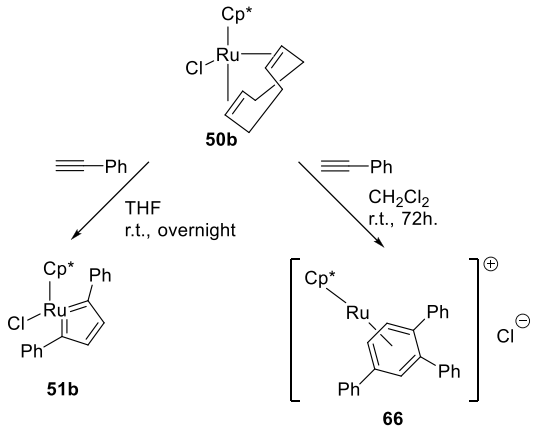
Scheme 26. Synthesis and Reactivity of Dinuclear Ruthenabicyclic Complexes 62 and 64



Scheme 27. Reaction of [Cp*Ru(cod)Cl] with Phenylacetylene



From a computational point of view, Kirchner and Calhorda et al.[134] studied the formation of the ruthenacyclopentatriene from the model catalyst $[CpRu(NCH)_2(PH_3)]^+$ and two acetylene molecules at the B3LYP/6-31G(d,p)~SDD level of theory. Substitution of hydrogen cyanide molecules by acetylene ligands occurs via a dissociative mechanism, as was found experimentally. Oxidative coupling of the two acetylene molecules leads to the formation of a ruthenacyclopentatriene complex $[CpRu(C_4H_4)(PH_3)]^+$. In this complex, the RuC_4 cycle is essentially planar with alternating C−C bond distances of 1.432 and 1.382 Å for the C_α−C_β and C_β−$C_{\beta'}$ bonds, respectively. The generation of the ruthenacyclopentatriene complex from the initial catalyst and the two acetylene molecules releases 22.1 kcal/mol after surmounting a barrier of 18.0 kcal/mol. In two subsequent works,[135,136] the nature of the $[CpRu(C_4H_4)Cl]$ complex was also described as a ruthenacyclopentatriene complex. However, in that case, the C_α−C_β and C_β−$C_{\beta'}$ bonds have almost the same bond length and, therefore, it is probably better described as a resonance hybrid with equal contributions from the ruthenacyclopentadiene and ruthenacyclopentatriene resonance structures. It is worth noting that, despite that the $[CpRu(PH_3)]^+$, CpRuCl, and CpCo are isolobal fragments, the electronic structure of the metallacycle can be defined as a metallacyclopentatriene, metallacyclopentadiene, or a combination of both depending on the catalyst.

Yamamoto et al.[137−139] published many studies into the cycloaddition reaction using ruthenium(II) as a catalyst from experimental and theoretical points of view. They studied the use of [Cp*Ru(cod)Cl] **50b** as a catalyst and tested the cycloaddition of 1,2-bis(propiolyl)benzenes with monoalkynes to afford anthraquinone derivatives[138] and the cycloaddition of 1,6-diynes with monoalkynes to generate bicyclic benzene derivatives[139] (Scheme 28). In the case of the cycloaddition of 1,2-bis(propiolyl)benzenes, when the diyne had two terminal phenyl groups (**67**), the cycloaddition did not work with either diphenyl acetylene or acetylene. In fact, when they tested the reaction of diyne **67** with **50b** in dichloroethane at room temperature, the ruthenacycle intermediate **68** was isolated and characterized, but it was not active as a [2 + 2 + 2] cycloaddition catalyst upon exposure with acetylene, diphenylacetylene, and dimethyl acetylenedicarboxylate (Scheme 28, equation a). On the other hand, the reaction of O-tethered-diyne **61b** that has also phenyl terminal groups with stoichiometric amounts of ruthenium complex **50b** afforded the corresponding ruthenacyclopentatriene **70**, which was heated at 40 °C after isolation in the presence of acetylene to give the terphenyl derivative **71** with a 32% yield. Therefore, in this case, the authors demonstrated

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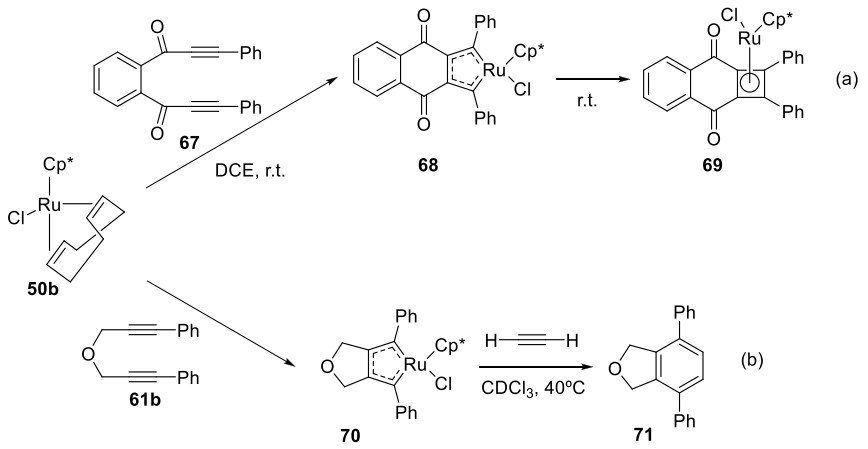
Scheme 28. Reaction of [Cp*Ru(cod)Cl] with Diynes Studied by Yamamoto et al.[138−140]



that the ruthenacyclopentatriene **70** is an intermediate in the cycloaddition reaction (Scheme 28, equation b).

After an NMR study and comparing the data of the X-ray analysis with the previous cases described (Singleton,[128] Yi,[130] and Dinjus[133]), the authors confirmed that the ruthenacycle in complexes **68** and **70** have a highly delocalized structure.

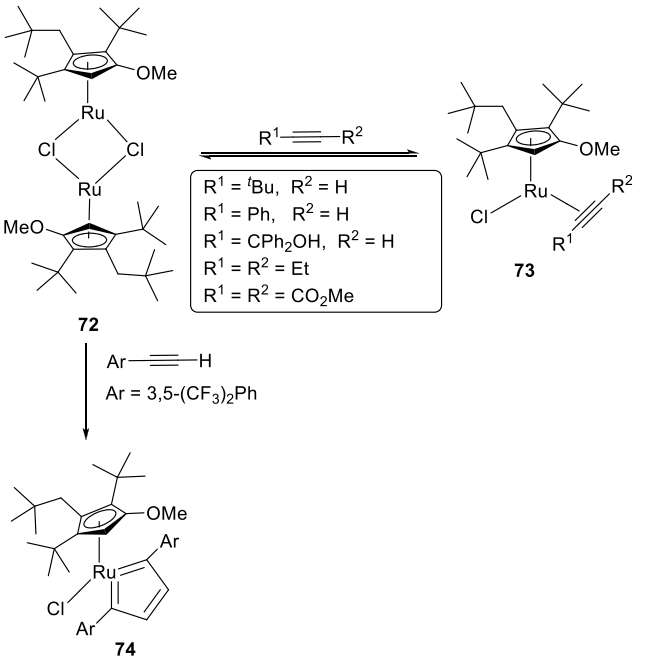
Shortly afterward, the same research group[140] took a further step in the reactivity of complex **68**, finding that it converted into cyclobutadiene complex **69** after being stirred for 3 days at room temperature. At the time the mechanism for this isomerization process was unknown but the authors discarded a simple reductive elimination step. As found in previous studies,[134] DFT calculations indicate the cyclobutadiene complex **69** is somewhat more stable than the ruthenacyclopentatriene **68**, although the reaction mechanism of this isomerization was not unraveled.

From the previous results, the authors postulated that the lack of reactivity of complex **68** toward [2 + 2 + 2] cycloaddition reactions is the result of two factors: first, the high stability of complex **68** due to the two phenyl terminal groups and, second, the steric hindrance around the ruthenium atom that prevents the insertion of the third alkyne. However, in the case of complex **70**, which was active as a catalyst in the cycloaddition, the intermediate also has the two phenyl terminal groups and comparison of the X-ray analyses of the two complexes showed that the steric crowding around the ruthenium center is similar. Therefore, it would seem likely that another factor perhaps derived from the nature of the tether governs the different reactivity of the two ruthenacyclopentatrienes.

Until now, the intermediates isolated, detected, or calculated in the ruthenium-catalyzed [2 + 2 + 2] cycloaddition reaction were those resulting from the oxidative coupling of the starting Ru complex with two alkyne molecules. However, the previous intermediates, such as the coordination of the ruthenium with one or two alkynes before oxidative coupling, had never been isolated or characterized. Severin el al.[141] have particularly focused on this aspect, synthesizing a ruthenium dimeric complex **72** containing a sterically demanding Cp^ ligand (Cp^:η^5-1-methoxy-2,4-*tert*-butyl-3-neopentylcyclopentadienyl). With this ligand, the authors postulated that it could be possible to electronically stabilize unsaturated 16-electron complexes and, therefore, isolate the mono(η^2-alkyne) adducts (**73**), which are the first intermediates postulated in the generation of oxidative coupling derivatives (Scheme 29).

The stability and further evolution of complexes **73** depend on the nature of the alkyne. Violet crystals of complexes **73** were

Scheme 29. Catalytic Intermediates in the Early Stages of Ru-Catalyzed Cycloadditions



obtained in all cases, although, for terminal alkynes, monoadducts **73** were highly labile and solid material decomposed easily. Although a large excess of alkyne was used in the synthesis of **73**, alkyne cyclotrimerization was only observed when they used dimethyl acetylenedicarboxylate, an activated alkyne to afford the corresponding hexasubstituted benzene derivative. The characterization of all complexes **73** was done by X-ray diffraction analysis, and all of them showed a "piano-stool" geometry. For terminal alkynes, it could be seen that the R group pointed away from the Cp ligand. Further characterization of complex **73a** (R^1 = ^{t}Bu, R^2 = H) was performed by ^{13}C CP-MAS NMR spectroscopy. In the particular case of 3,5-bis(trifluoromethyl)phenylacetylene, the violet solution was stored at −20 °C for 2 days and the most advanced ruthenacyclopentatriene intermediate **74** was obtained as red crystals (Scheme 29). DFT calculations were performed with the M06/6-31G(d)~LANL2DZ method to rationalize the different behavior of the alkynes and to understand the effect of the bulky Cp^

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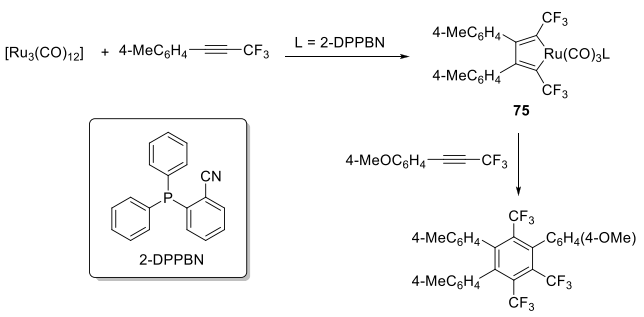
ligand on the ruthenium complex. Solvent effects of a dichloromethane solution were also included in the calculations. In particular, the authors analyzed the reaction of complexes **73a** (R^1 = ^{t}Bu, R^2 = H) [(Cp^)RuCl(η^2-HC≡CC(CH_3)$_3$)], **73b** (R^1 = R^2 = CO_2Me) [(Cp^)RuCl(η^2-MeO_2CC≡CCO_2Me)], and complex **73a′** (R^1 = ^{t}Bu, R^2 = H) [CpRuCl(η^2-HC≡CC(CH_3)$_3$)] with a second molecule of the corresponding alkyne. Their results show that the oxidative coupling reaction with **73a** to form **74a** is the least exergonic (6.5 kcal/mol) and has the highest Gibbs energy barrier (25.2 kcal/mol) relative to **73a** + HC≡CC(CH_3)$_3$. Changing the Cp^ ligand by a Cp group has an enormous influence on the Gibbs energy barrier that is reduced by more than 10 kcal/mol. This reduction was attributed to unfavorable steric repulsions between the Cp^ ligand and the *tert*-butyl groups of the alkyne. Finally, the change of HC≡CC(CH_3)$_3$ by the more activated alkyne MeO_2CC≡CCO_2Me also reduces the Gibbs energy barrier but to a lower extent (by 6.7 kcal/mol). The transformation of **73b** to **74b** was found to be the most exergonic of the three processes studied computationally.

Kawatsura and Itoh et al.[142] demonstrated the catalytic activity of [$Ru_3(CO)_{12}$] with 2-(diphenylphosphino)-benzonitrile as the ligand (L = 2-DPPBN) for the cyclotrimerization of trifluoromethylated internal alkynes (Scheme 30). After analyzing the optimal reaction conditions and

Scheme 30. Cyclotrimerization of Trifluoromethylacetylenes Catalyzed by [$Ru_3(CO)_{12}$]



studying the scope of the process, the authors further tried to isolate some reaction intermediates. Therefore, the reaction of [$Ru_3(CO)_{12}$]/L with 1-tolyl-3,3,3-trifluoropropyne afforded a 54% yield of ruthenacyclopentadiene **75** characterized by X-ray analysis, demonstrating that the 2-DPPBN acted as a phosphine monodentate ligand and that the nitrile group was not coordinated to the metal. The reaction of **75** with stoichiometric amounts of 1-(4-methoxyphenyl)-3,3,3-trifluoropropyne afforded the hexasubstituted benzene derivative in a regioselective manner. In addition, ruthenium complex **75** was an active catalyst for the cycloaddition reaction of several trifluoromethyl alkynes. All of these experiments demonstrate once again that the metallacyclopentadiene **75** is a reaction intermediate in the cycloaddition process.

At the same time, Berry et al.[143] studied the behavior of a low-valent ruthenium complex **70** with alkynes (Scheme 31). Ru(0) complex **76** acted as an active catalyst for the cyclotrimerization of acetylene. However, treatment of **76** with a slight excess of acetylene afforded complex **77**, coordinated with only one alkyne, which further reacted with an excess of acetylene at room temperature to give benzene as a result of the cyclotrimerization reaction. Although η^6-benzene complexes may be intermediate species during the cyclotrimerization, complex **77** seems to be the resting state of the catalyst. B3LYP/6-31G(d,p)~SDD calculations indicate that this complex **77** has a singlet ground state with Ru in the neutral formal oxidation state (Ru(0)). Complex **76** also catalyzed the cyclotrimerization of propyne, while the homologous complex **77** could not be isolated. When complex **76** was treated with an excess of diphenylacetylene, the oxidative coupling took place, giving a 93% yield of the corresponding ruthenacyclopentadiene **78a**. The coordinated homologous complex **77** was not detected. X-ray diffraction analysis demonstrated that the structure was a metallacyclopentadiene rather than a metallacyclopentatriene. The reaction of **78a** with diphenylacetylene did not produce the cyclotrimerization product, presumably due to the considerable hindrance of ruthenacyclopentadiene **78a** that avoided the insertion of a third unsaturation. On the other hand, **77** reacted with diphenylacetylene to generate the corresponding benzene derivatives via ruthenacyclopentadiene **78b**, a less hindered intermediate than **78a** that allowed the insertion of a second molecule of diphenylacetylene. B3LYP/6-31G(d,p)~SDD calculations support the ruthenacyclopentadiene description instead of the ruthenacyclopentatriene structure reported in previous studies.[134]

Another type of ruthenium complexes that have been demonstrated to be active in [2 + 2 + 2] cycloaddition reactions are ruthenium carbene complexes such as Grubbs' metathesis catalysts. The initial studies by Peters and Blechert[144] and Das and Roy[145] described the cycloaddition of triynes and the cyclotrimerization of alkynes, respectively, using the first generation Grubbs' catalyst, [PhCH═Ru(PCy_3)$_2$$Cl_2$]. In both cases, the authors proposed a cascade of metathesis catalytic cycles (Scheme 32) starting with a regioselective addition of the ruthenium carbene complex to the less hindered site of the triple bond, instead of the mechanism based on the initial generation of a ruthenacyclopentadiene/ruthenacyclopentatriene intermediate as in the previous cases detailed in this section. The new mechanistic proposal for these cases was studied in depth by DFT calculations. BP86-D2/6-31+G(d,p)//BP86/6-31G(d) calculations including the effect of the solvent (dichloromethane) by Remya and Suresh[146] analyzed the reaction mechanism depicted in Scheme 32 catalyzed by [MeCH═Ru(PCy_3)$_2$$Cl_2$]. The metathesis reaction path starts with the dissociation of a phosphine ligand from the initial catalyst and the coordination of an acetylene molecule. This initial process is endergonic by 21.7 kcal/mol. Subsequent [2 + 2] cycloaddition with a Gibbs energy barrier of 9.5 kcal/mol gives the ruthenacyclobutene complex characterized by short (1.39 Å) and long (1.49 Å) C_α—C_β bonds as well as a relatively short Ru—C_β bond, indicating an η^3 interaction of the metal with the carbon unit. Next, the ruthenacyclobutene complex opens up in an electrocyclic ring opening reaction with almost no barrier. This process is repeated twice with attainable barriers for the two [2 + 2] cycloadditions (3.9 and 13.2 kcal/mol, in this order). Once we have a chain of seven unsaturated carbon atoms, a 6-membered ring-closing metathesis (RCM) releasing benzene can take place. This RCM has to compete with a possible subsequent metathesis step that will expand the carbon chain. The Gibbs energy barrier for the RCM was calculated to be 30.0 kcal/mol as compared with the 11.5 kcal/mol barrier for the chain expansion. Therefore, although the barrier for the RCM process could be attained by increasing the temperature of the reaction, the conclusion of the authors was that the cyclotrimerization reaction did not proceed through the metathesis

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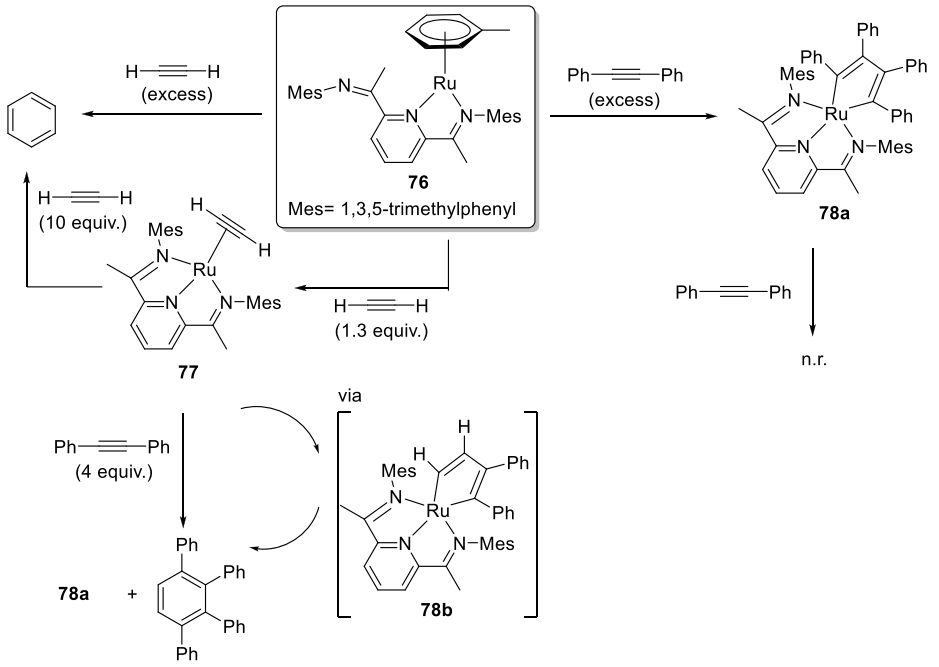
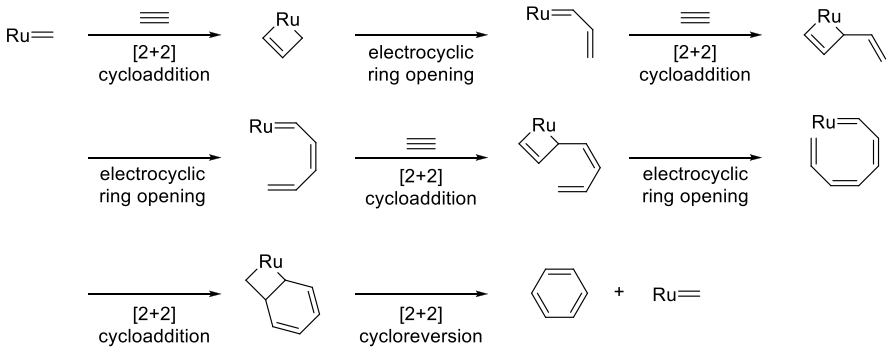
Scheme 31. Structural Studies and Reactivity of Ruthenium Complex 76



Scheme 32. Cascade of Metathesis Reactions Suggested for the Alkyne Cyclotrimerization in the Presence of Grubbs Catalysts



pathway but rather via the usual [2 + 2 + 2] cycloaddition reaction pathway through a ruthenacyclopentadiene or ruthenacyclopentatriene complex. For this [2 + 2 + 2] cycloaddition, the active species was considered to be the [MeCH═$Ru(PCy_3)Cl_2$] complex. Similarly, the cyclotrimerization of terminal arylalkynes catalyzed by the third-generation Grubbs catalyst [PhCH═$Ru(3\text{-}Br\text{-}py)_2(H_2IMes)Cl_2$] ($H_2IMes$ = 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene) was analyzed computationally by Czeluśniak et al.[147,148] and was found to proceed not via a metathesis pathway but rather through the classical [2 + 2 + 2] cycloaddition reaction mechanism thanks to the degradation of the Grubbs catalyst that generates the [$Ru(H_2IMes)Cl_2$] catalytically active species for this [2 + 2 + 2] cycloaddition.

The reaction pathway of the [2 + 2 + 2] cycloaddition of three acetylene molecules through a ruthenacyclopentadiene or ruthenacyclopentatriene complex has been studied computationally by many authors. Basically, two active species have been considered: CpRuCl and $CpRu^+$. The computational study of the trimerization of acetylene catalyzed by CpRuCl was performed in two almost simultaneous works by Kirchner and Calhorda et al.[135] and Yamamoto et al.[136] using the B3LYP method in conjunction with a double-ζ basis set. These two works have been described in two previous reviews.[40,41] Since the conclusions of the works by Calhorda et al. and Yamamoto et al. are basically the same, we will focus our attention on the work by Kirchner and Calhorda et al.[135] that was performed at the B3LYP/6-31G(d,p)~SDD level of theory (Scheme 33). Starting from a labile precursor such as [CpRu(cod)Cl], the first step corresponds to the dissociation of the cod ligand and substitution by two alkyne molecules to yield complex **79**. Oxidative coupling of the two acetylenes leads to the formation of the ruthenacyclopentatriene complex **80**. As said before, this complex has almost identical C_α–C_β and C_β–$C_{\beta'}$ bond lengths, so it is probably best described by a combination of cyclopentatriene and cyclopentadiene resonant structures. Indeed, Yamamoto et al.[136] describe **80** as a 5-membered aromatic compound rather than a ruthenacyclopentatriene. With a Gibbs energy barrier of 13.2 kcal/mol, this step is the rate-determining step of the reaction that proceeds under mild conditions (at room temperature or even below). Complex **80** adds another acetylene that coordinates in an η^2-fashion to provide complex **81** that contains a ruthenacyclopentadiene. An almost barrierless [2 + 2] cycloaddition (or [5 + 2] cycloaddition according to Yamamoto et al.[136]) provides the ruthenabicyclo[3.2.0]heptatriene complex **82** that rearranges to

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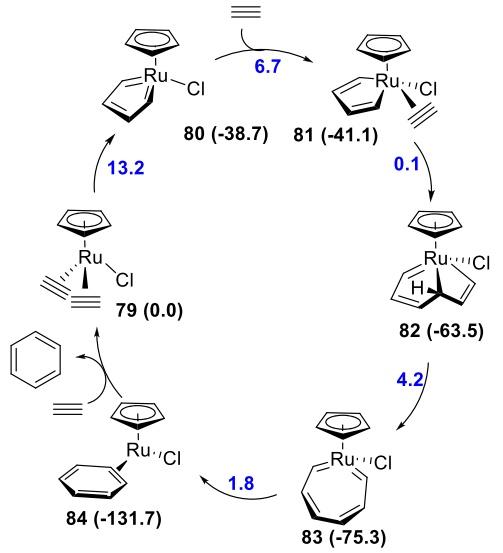
Scheme 33. Catalytic Cycle of the [2 + 2 + 2] Cycloaddition of Three Acetylenes Catalyzed by [CpRuCl] Described by Kirchner and Calhorda et al.[135,a]



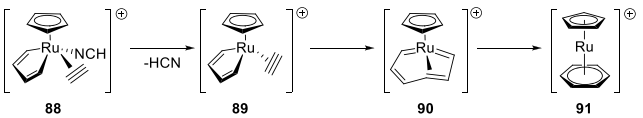
[a]Relative Gibbs energies referred to complex **79** are in kcal/mol. Gibbs energy barriers (in kcal/mol) for each step are given in blue.

an unusual ruthenacycloheptatetraene complex **83**. In this complex, the Cp ring is coordinated to the Ru with a hapticity between η^3 and η^5 as a consequence of ring slippage. Due to the bond length equalization in this ruthenacycloheptatetraene complex **83**, Yamamoto et al.[136] classify this metallacycle as aromatic. **83** evolves via reductive elimination to give complex **84** with the benzene molecule η^2 bonded to Ru (rather than η^4, as expected from the 18-electron rule). Completion of the cycle is reached by an exothermic displacement (21.4 kcal/mol) of the benzene ring by two acetylene molecules to recover complex **79**. The authors searched for alternative intermediates, such as the ruthenanorbornadiene intermediate, but they were unable to locate them in the PES. The same reaction mechanism was computationally proposed by Kabe et al.[114] for the [CpRuCl]-catalyzed [2 + 2 + 2] cycloaddition of siladiynes and DMAD. The oxidative homocoupling of the siladiyne is preferred over the oxidative heterocoupling of a siladyine and DMAD, contrary to what is found for the [CpCo]-catalyzed process.

The effect of the substitution in the Cp ligand by one to five methyl groups of ruthenium complexes of type [(η^5-$C_5Me_nH_{5-n}$)Ru(cod)Cl] has been studied by Yamamoto et al.[149] in the cycloaddition of diynes and alkynes. The complex bearing the 1,2,4-Me_3Cp ligand gave the best results in terms of turnover number in the cycloaddition of diiododiyne with acetylene. Cyclic voltammetry (CV) and kinetic studies led the authors to conclude that the steric accessibility to the ruthenium center—balanced with a high electron richness—was responsible for the rate enhancement for the 1,2,4-Me_3Cp containing complex. The authors then analyzed the effect that Cp ligand steric shielding of the metal center had on the regioselectivity of the [2 + 2 + 2] cycloaddition of an unsymmetrical diyne. Whereas high regioselectivity (96:4) was achieved with the bulkier Cp*, Me_4Cp and 1,2,4-Me_3-Cp gave only slightly higher regioselectivity (about 80:20) than the one achieved with the remaining ligands (about 75:25), including Cp. The two regioisomers are obtained by the approach of the alkyne to either of the two sides of the ruthenacyclopentatriene intermediate of type **80** (Scheme 33). The steric shielding between the Cp substituents and the terminal substituent of the diyne in ruthenabicyclo[3.2.0]heptatriene of type **82** (Scheme 33) when the alkyne approaches the more hindered face explains the experimental data obtained. The steric shielding is maximal in Cp* but can be relaxed in its less substituted analogues by properly rotating the Cp ligand.

Some authors have analyzed the [2 + 2 + 2] cycloaddition catalyzed by a $CpRu^+$ or $CpRuL^+$ catalyst.[150,151] Kirchner et al.[150] analyzed the reaction described in Scheme 34. They found that, with terminal alkynes HC≡C^{n}Bu, HC≡CCH_2Ph, and HC≡CCO_2Et, isomeric mixtures of benzenes derivatives in a 3:1 ratio are isolated in low to medium yields. They also obtained with the same 3:1 ratio arene complexes **86** and **87**. With HC≡CPh and HC≡CC_6H_9, no cyclotrimerization products were found. To rationalize these experimental results, they performed B3LYP/6-31G(d,p)~SDD calculations for the reaction of **85** with three acetylene units. They found the same reaction path as that for CpRuCl (Scheme 33). Substitution of Cl by $NCCH_3$ did not bring major changes. Oxidative coupling was again the rate-determining step with a barrier of 10.0 kcal/mol. Interestingly, calculations showed that the ruthenacyclopentadiene complex **88** in Scheme 35 can release HCN to form

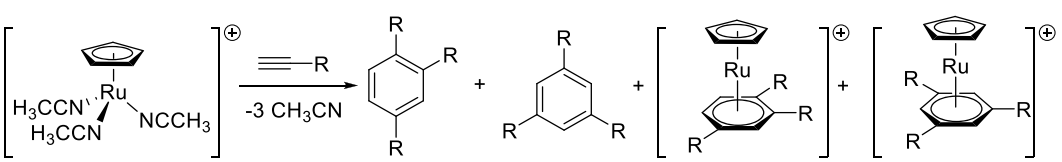
Scheme 35. One of the Possible Routes for the Formation of Arene Complexes in the Cyclotrimerization of Terminal Alkynes by [CpRu(CH_3CN)$_3$]$^+$



89 that easily ($\Delta G^{\ddagger}$ = 3.0 kcal/mol) rearranges to cyclic biscarbene **90**. Reductive elimination through a small barrier of 1.5 kcal/mol yielded species **91**. This complex **91** can also be generated by the release of HCN ligand from the analogues of complex **84** in which the Cl ligand is substituted by a HCN molecule. Both routes are active according to the calculations of Kirchner et al.,[150] explaining the formation of arene complexes **86** and **87**.

In 2008, Kirchner[151] analyzed theoretically the cyclotrimerization catalyzed by the cationic complexes [CpRu-

Scheme 34. Cyclotrimerization of Terminal Alkynes by [CpRu(CH_3CN)$_3$]$^+$



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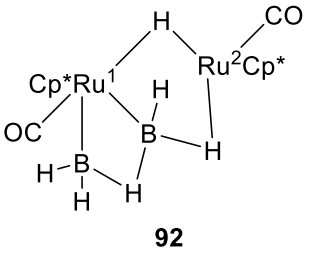
$(CH_3CN)_2L]^+$ with L = PR_3 or *N*-heterocyclic carbene (NHC). The author found that these complexes were inactive for the cyclotrimerization of alkynes and led to the ruthenacyclopentatriene complex by the common oxidative coupling of two alkynes. However, addition of a third alkyne to afford a benzene ring did not occur and instead the PR_3 or NHC ligands migrated from the Ru metal and inserted into Ru═C of the electrophilic ruthenacyclopentatriene complex to generate a stable allyl carbene species.

Finally, Holthausen and Ghosh et al.[152] reported in 2012 an interesting example of a [2 + 2 + 2] alkyne cyclotrimerization catalyzed by a dinuclear *arachno*-$[(Cp^*RuCO)_2B_2H_6]$ complex **92** (Figure 3). They found that complex **92** was catalytically



92

Figure 3. Structure of the dinuclear *arachno*-$[(Cp^*RuCO)_2B_2H_6]$ complex.

inactive toward acetylene cyclotrimerization. On the other hand, this complex catalyzed the cyclotrimerization of a number of terminal alkynes, giving a mixture of 1,3,5- and 1,2,4-regioisomers with ratios of 1:1 to 1:6 in favor of the 1,2,4-regioisomer. They also observed that EWG in the alkynes increased their reactivity. The authors performed DFT calculations for the cyclotrimerization of $HC{\equiv}CCO_2Et$ with the B3LYP-D/def2-SVP~def2-ECP//PBEPBE/def2-SVP~def2-ECP method using a model catalyst in which Cp* was replaced by Cp. The reaction mechanism described by the authors is much more complicated than the usual reaction pathway shown in Scheme 33 given that it involves multiple rearrangements of the ligands leading to many intermediates, some of which have one or two μ_2-CO bridges between Ru metals and with the B_2H_6 fragment changing from bridging ligand to terminal. In addition, some parts of the common reaction mechanism change. CO dissociation in complex **92** is thermodynamically unfavorable. Therefore, coordination of the alkyne to Ru^2 (Figure 3) of complex **92** is an associative process that has to surmount a barrier of 28.8 kcal/mol and is the rate-determining step. The complex resulting from the coordination of the first alkyne evolves to generate a vinyl ligand that interacts with the second alkyne via a C—C coupling to afford a butadienyl ligand that finally rearranges to the ruthenacyclopentadiene complex. As a result, the formation of the ruthenacyclopentadiene on Ru^2 did not take place by the usual oxidative coupling. Interestingly, the B_2H_6 fragment acted as a hydrogen-atom buffer by first transferring a hydrogen atom to afford the butadienyl ligand and then recovering it when the ruthenacyclopentadiene complex was formed. Moreover, the insertion of the third alkyne took place through a [4 + 2] cycloaddition (and not the usual [2 + 2] cycloaddition found in CpRuCl catalyst), yielding an η^2-coordinated benzene adduct directly.

2.5. Rhodium Complexes

As we can see in the preliminary section, metallacyclopentadiene complexes generated by the oxidative coupling of two alkynes and/or diynes are considered as key intermediates in the [2 + 2 + 2] cycloaddition reaction. Some metallacyclopentadienes have been isolated and characterized, and their role as intermediates in the cycloaddition process has been demonstrated. In the particular case of rhodacyclopentadienes, many examples have been described in the literature.[153−156] Müller[157,158] in a review paper brings together a set of studies in which a series of 1,5- and 1,6-diynes reacted with the Wilkinson catalyst $[Rh(PPh_3)_3Cl]$ to afford the corresponding rhodacyclopentadiene derivatives

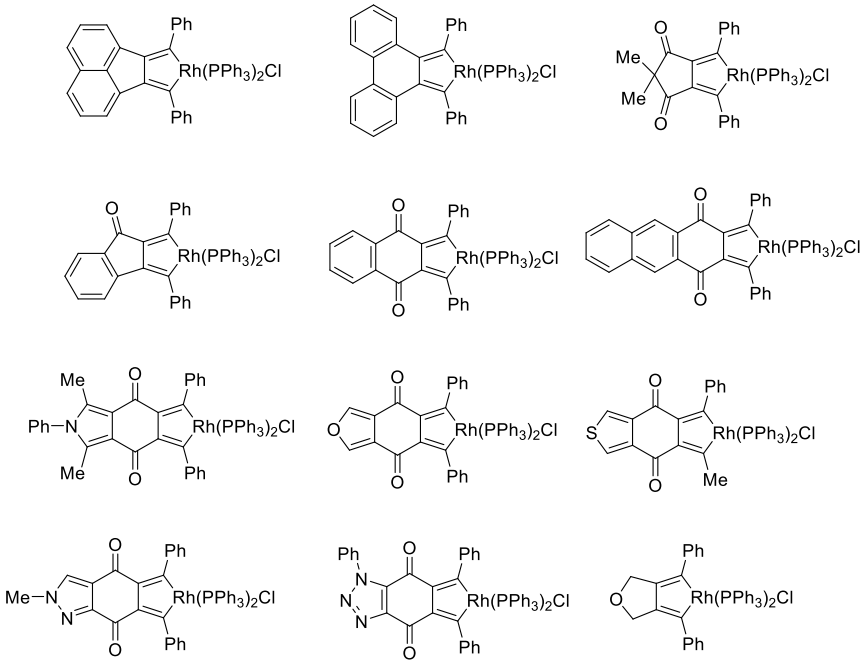


Figure 4. Structure of isolated rhodacyclopentadiene derivatives.

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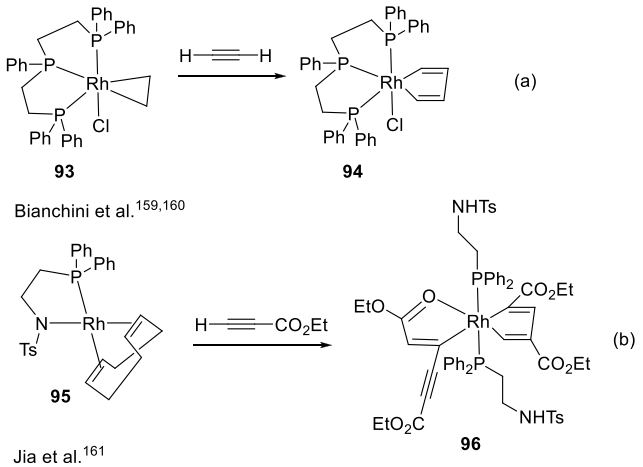
(Figure 4). Further reaction of these rhodium complexes with a wide range of alkynes afforded the aromatic scaffolds, generated from a [2 + 2 + 2] cycloaddition reaction, showing themselves to be intermediates in the process. Due to the age of the studies, little spectroscopic data and X-ray analysis was performed.

More recently, isolated rhodacyclopentadienes and their application as catalysts in [2 + 2 + 2] cycloaddition reaction, confirming their role as intermediates in this process, have also been described. Rhodacyclopentadienes containing tridentate ligands have been described by the group of Bianchini.[159,160] The authors synthesized the rhodacyclopentadiene **94** containing a tripodal phosphine ligand (triphos = bis(diphenylphosphinoethyl)phenylphosphine) from Rh complex **93** under an acetylene atmosphere (Scheme 36, equation a).

Scheme 36. Rhodacyclopentadienes Described by Bianchini et al.[159,160] and Jia et al.[161]



Complex **94** was an active catalyst in the cyclotrimerization of acetylene at room temperature with a turnover number of 6, demonstrating its role as an intermediate in the cyclization process. Jia et al.[161] prepared rhodium complex **95** with a bidentate phosphinosulfonamido ligand that was active in the cyclotrimerization of methyl and ethyl propiolate. In addition, in the same reaction with ethyl propiolate, rhodacyclopentadiene **96** was isolated and characterized by X-ray analysis, which revealed that four molecules of ethyl propiolate were incorporated into the rhodium center, two forming a rhodacyclopentadiene ring and two coupling to form a ligand that also chelated to rhodium. In addition, the structure of **96** containing two phosphine ligands led the authors to conclude that other species should be generated in the formation of **96** but none were found. Complex **96** was also active in the cyclotrimerization of ethyl propiolate, affording a mixture of the two trisubstituted benzene regioisomers: 1,2,4- and 1,3,5- in a 1:1 ratio (Scheme 36, equation b).

Nishiyama et al.[162,163] described the synthesis, characterization, and catalytic activity of rhodacyclopentadienes **97a,b** and **98**, containing tridentate ligands such as *N,N,N*-type ligand (pybox: 2,6-bis(2-oxazoline)pyridine) and xanthene-based *N,O,N*-type ligand (Xabox: 4,5-bis(2-oxazolinyl)xanthene). The authors first isolated a 68% yield of rhodacyclopentadiene **97a** when a 1:2 mixture of $[Rh(coe)_2Cl]_2$ (coe = cyclooctene) and pybox ligand reacted with diyne **61a** in THF at 25−30 °C. The complex was characterized by NMR spectroscopy and X-ray diffraction analysis, which determined that the structure was a cyclopentadiene with an octahedral configuration around the rhodium atom. The new complex **97a** acted as a good catalyst in the cycloaddition of diyne **61a** with several alkynes such as phenylacetylene, 1-hexyne, and (trimethylsilyl)acetylene. Rhodacyclopentadiene **97b** was also tested as a catalyst in the cycloaddition of nonsymmetrical diyne **61c** with phenylacetylene, affording a mixture of regioisomers in a 51:49 ratio. Five years later, the same authors synthesized the homologous rhodacyclopentadiene **98** with the Xabox ligand, which was also characterized by X-ray analysis. In Scheme 37, the catalytic activity of the three Rh complexes is given in order to compare their efficiency using phenylacetylene as the alkyne. In all cases, heating at 80 °C was necessary and the yields obtained were similar.

The first computational study of the reaction mechanism of a [2 + 2 + 2] cyclotrimerization of acetylene to generate benzene catalyzed by Rh was performed at the ZORA-BLYP/TZ2P level of theory by Orian, van Stralen, and Bickelhaupt in 2007.[164] The catalyst considered was [CpRh] generated from $[CpRhL_2]$ (L = CO, C_2H_4; L_2 = cod). In 2009, our group published the results of the same [2 + 2 + 2] cyclotrimerization catalyzed by the Wilkinson catalyst, $[RhCl(PPh_3)_3]$, using the B3LYP/cc-pVDZ-PP method.[165] More recently, we recomputed the same reaction mechanism using the somewhat more sophisticated M06L-D3/cc-pVTZ-PP//B3LYP-D3/cc-pVDZ-PP method that takes into consideration dispersion effects and we also included the solvent effects of a toluene solution.[166] Since, the results of these three studies are similar, we focus here on the results reported in the last work. Scheme 38 depicts the intermediates found in the catalytic cycle. We analyzed all possible reaction intermediates with $RhCl(PPh_3)_2$, $RhCl(PPh_3)$, and RhCl as possible catalysts. The lowest reaction path in terms of energy followed in the catalytic cycle takes place, keeping two phosphine ligands coordinated to Rh. As shown in Scheme 38, there is a preactivation of the catalysts before entering the catalytic cycle as the 16-electron species **99**. Complex **99** is reached when the initial Wilkinson catalyst coordinates an incoming acetylene molecule and loses a phosphine in a process that is endergonic by 15.0 kcal/mol. As found experimentally,[167] the easiest dissociation corresponds to the PPh_3 located in the equatorial site *cis* to Cl and *trans* to another PPh_3. The geometry of complex **99** is pseudotetrahedral. **99** adds an acetylene molecule to generate the 18-electron species **100** in which the two PPh_3 ligands occupy axial positions of the trigonal bipyramid. This process is exergonic by only 2.2 kcal/mol. Oxidative coupling from **100** with two equatorial acetylene ligands has a large Gibbs energy barrier of 37.5 kcal/mol. Thus, this oxidative coupling takes place through its less stable isomer **101**, in which the acetylene ligands occupy axial and equatorial positions, with an energy barrier of 14.3 kcal/mol to generate the rhodacyclopentadiene complex **102**. This is the highest energy barrier throughout the catalytic cycle, and therefore, it is the rate-determining step (rds). Species **102** adds an acetylene molecule to form the distorted octahedral complex **103** and releases 22.8 kcal/mol. Intramolecular [4 + 2] cycloaddition of the coordinated acetylene to the rhodacyclopentadiene affords complex **104**. The Gibbs energy barrier for this process is small (2.1 kcal/mol), and the exergonicity is high (72.7 kcal/mol). In **104**, the generated benzene molecule is η^4-coordinated to Rh. The uncoordinated part of the benzene molecule has a significant hinge angle[168] and bond length alternation (BLA), indicating that the aromaticity of benzene in **104** is partially lost. Ring slippage in **104** leads to **105**, releasing 5.5 kcal/mol. In **105**,

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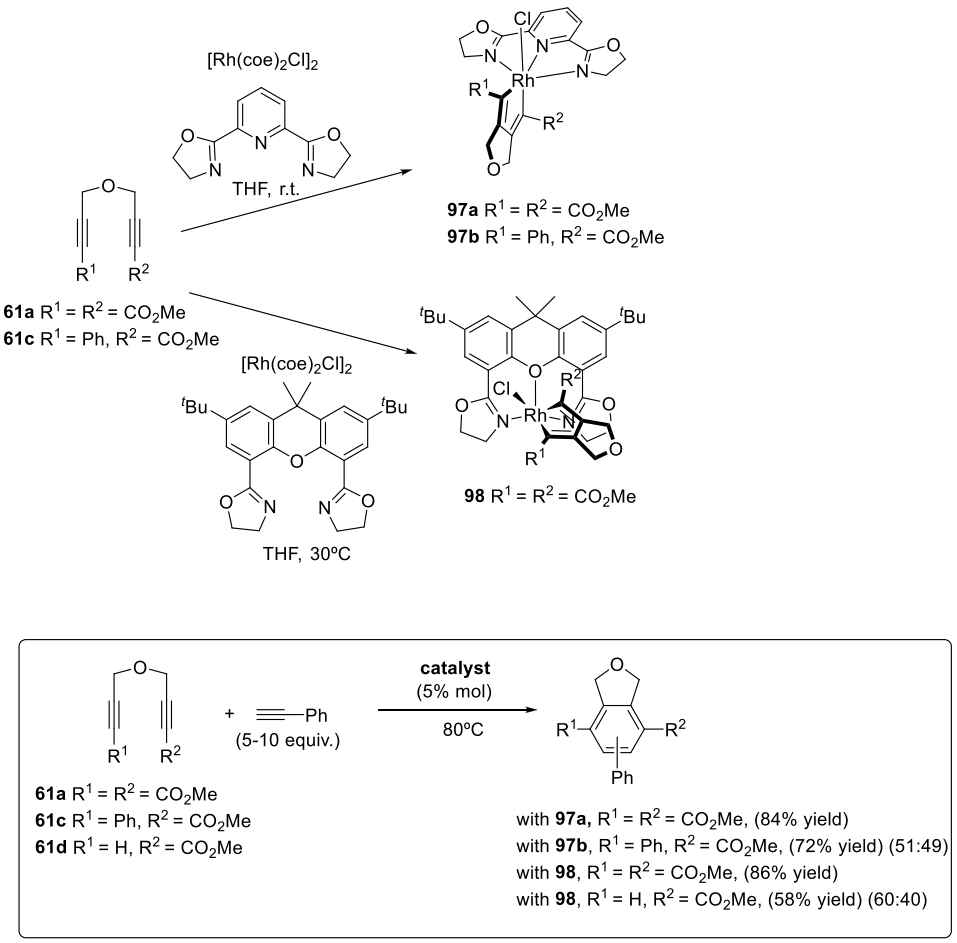
Scheme 37. Catalytic Activity of Rhodacyclopentadienes with Tridentate Ligands



the benzene ring is more planar and suffers less BLA. Addition of an incoming acetylene to **105** is exergonic by 20.3 kcal/mol and generates species **106**, from which the release of benzene takes place by surmounting a barrier of 5.6 kcal/mol to close the cycle and recover the original active catalyst **99**. There is an alternative mechanism that goes through the rhodabicyclo[3.2.0]-heptatriene and rhodacycloheptatriene complexes that is somewhat higher in energy. Finally, as expected from the absence of strong polar species in the reaction mechanism, solvent effects have little influence on the energetics of the whole process.

The use of a model of the Wilkinson catalyst, $[RhCl(PH_3)_3]$, in which PPh_3 ligands have been substituted by PH_3 groups was analyzed by our group.[165] In general, modeling PPh_3 by PH_3 results in minor changes in the thermodynamics and kinetics of the reaction mechanism. However, the Gibbs energy barrier of the rate-determining step is higher by about 5 kcal/mol in the model catalyst.

The energy profile described for the cyclotrimerization of acetylene catalyzed by [CpRh] evolves in a similar manner to that described above for the Wilkinson catalyst.[164] The two main differences are as follows: (1) The associative mechanism in the preactivation of the catalysts is possible if a haptotropic shift of the Cp ring from η^5 to η^3 or less occurs to open a new coordination site in the metal. (2) The rhodacyclopentadiene ring is tilted by 32° from the axis defined by the metal and the center of the Cp ring. In the same study,[164] the authors analyze the reaction mechanism when the Cp group in CpRh is substituted by an indenyl ligand to generate the IndRh catalyst. The energy profile of the cyclotrimerization of acetylene catalyzed by IndRh is very close to that of CpRh. However, the barrier for the oxidative coupling of two acetylenes, which is the rate-determining step in the catalytic cycle, is found to be 2.5 kcal/mol higher in IndRh. The authors attributed the poorer performance of IndRh as compared to CpRh to higher steric hindrance and less efficient donation of IndRh and referred to this lower reactivity as a reverse indenyl effect (the indenyl effect is seen experimentally when the cyclotrimerization proceeds faster when Cp is replaced by Ind).[169] Due to the discrepancy between theory and experiment, the authors decided to revisit the reaction mechanism of the [2 + 2 + 2] cyclotrimerization of acetylene catalyzed by CpRh and IndRh.[170] Given that Booth et al.[169] found that there is an effect of ancillary ligands, the authors took CO as an ancillary ligand and analyzed the reaction mechanism of [CpRh(CO)] and [IndRh(CO)]. The results of this second study show that the rate-determining step is not the oxidative coupling but the coordination of the third acetylene to the rhodacyclopentadiene complex. This step is accompanied by a hapticity change from η^5 to η^1 and ring slippage, which occurs more easily for Ind than for Cp metal fragments. Interestingly, the reaction mechanism in [CpRh(CO)] and [IndRh(CO)] proceeds through rhodabicyclo[3.2.0]heptatriene and rhodacycloheptatriene intermediates (Schore's mechanism) instead of via intramolecular [4 + 2] cycloaddition of the coordinated acetylene.

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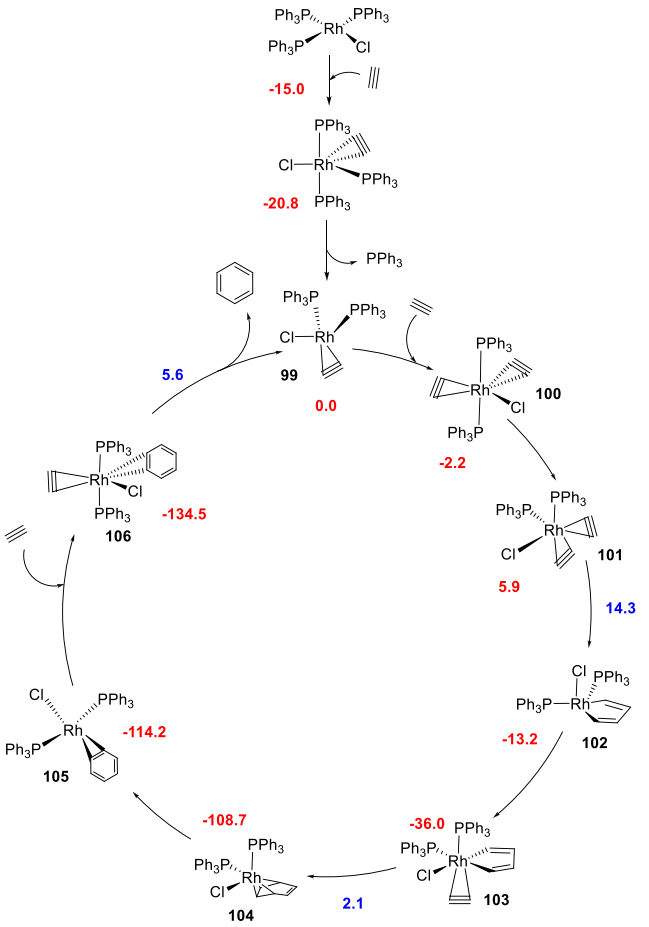
Scheme 38. Catalytic Cycle of the [2 + 2 + 2] Cycloaddition of Three Acetylenes Catalyzed by $[RhCl(PPh_3)_3]$[a]



[a]Relative Gibbs energies are given in red. Gibbs energy barriers for each step are given in blue. All energies are referred to complex **99** and are in kcal/mol. Adapted with permission from ref 166. Copyright 2017 Wiley.

Finally, Orian and Bickelhaupt et al.[171,172] analyzed in two papers the effect of changing a C−C unit to a B−N fragment in Cp and Ind to generate the 1,2-azaboryl (Ab) and 3a,7a-azaborindenyl (Abi) ligands. In the latter ligand, the C−C bond substituted is that of the ring junction between the 5- and 6-membered rings. The authors observed a loss of performance for the Ab and Abi ligands as compared to Cp and Ind. They introduced a parameter to measure the slippage, the so-called label-independent slippage parameter (LISP), and they observed an inverse trend between the LISP and the turnover frequency of the catalysis. It was found that the highest performance of the catalysts is linked to the smallest slippage variation along the catalytic cycle. The indenyl effect is only seen when an ancillary ligand remains bonded to Rh along the whole catalytic cycle. When this is not the case, an inverse indenyl effect is observed.

In our research group,[173] we developed a project aimed at synthesizing polyacetylenic azamacrocycles and testing them in the rhodium-catalyzed cycloisomerization to afford highly functionalized fused polycyclic systems (Scheme 39). The Wilkinson complex was the catalyst of choice. When 15- and 25-membered azamacrocycles **107** and **108** with different aryl units (Ar = *p*-tolyl, 2,4,6-triisopropylphenyl) were tested, cycloisomerization was effective. In the case of the 25-membered ring, compound **111** derived from the cycloaddition between three consecutive triple bonds was obtained instead of cycloadduct **112** from nonconsecutive triple bonds. In contrast, 20-membered azamacrocycle **109** was treated with the Wilkinson complex in refluxing toluene and only starting material or decomposition products were obtained. A stoichiometric amount of $[CpCo(CO)_2]$ was also tested, but no cycloadduct **113** could be obtained. We performed a computational study at the B3LYP/cc-pVDZ-PP level of theory of the intramolecular [2 + 2 + 2] cycloadditions in macrocycles **107**, **108**, and **109** using a model catalyst, $[RhCl(PH_3)_3]$. The $ArSO_2$ groups in the macrocyles were also substituted by H atoms in the simulations to reduce the computational effort. The overall transformation of **107** to **110**, of **108** to **111**, of **108** to **112**, and of **109** to **113** is highly exergonic by 128.4, 121.6, 98.8, and 122.0 kcal/mol, respectively. Hence, the reason for the lack of reactivity of **109** had to be kinetic. Moreover, the greater stability of **111** as compared to **112** (22.8 kcal/mol) was attributed to the formation of two 10-membered rings with a triple bond that are particularly strained. In fact, in **108**, we found that reaction pathways involving the addition of three contiguous triple bonds were favored because they avoid the formation of 10-membered rings with triple bonds. Focusing on the kinetics, we found that the Gibbs energy barriers of the oxidative coupling, which is the rate-determining step, for macrocycles **107**, **108**, and **109** were 21.9, 12.3, and 33.1 kcal/mol, respectively. These results were in agreement with the experimental observation that macrocycle **109** does not react. Analysis of these energy barriers indicated that the deformation energy, i.e., the energy required to deform the reactants to the geometry they have in the transition state, is not responsible for the higher energy barrier found for macrocycle **109**. We proposed two factors that contributed to the lack of reactivity of **109**: first, a more stable and delocalized HOMO orbital, as compared to **107** and **108**, which interacts less favorably with the LUMO of the catalyst, and, second, the formation of a strained 10-membered ring containing a triple bond. Finally, it is worth mentioning that the process that inserts an additional alkyne into the rhodacyclopentadiene intermediate was found to be an intramolecular [4 + 2] Diels−Alder reaction in macrocyle **107**. However, in **108** and **109**, it was an insertion leading to a nonplanar rhodacycloheptatriene intermediate.

In addition to our theoretical studies in $[RhCl(PPh_3)_3]$-catalyzed [2 + 2 + 2] cycloaddition reactions, a kinetic study by electrochemical techniques as well as NMR spectroscopy and electrospray ionization mass spectrometry (ESI-MS) of the cycloaddition of three alkynes were performed.[174] A partially intramolecular cycloaddition between diynes **114** and 2-butyn-1,4-diol catalyzed by the Wilkinson complex was chosen as a model reaction (Scheme 40).

The two main steps of the catalytic cycle were studied. The reactions of diynes **114a** and **114b** with $[RhCl(PPh_3)_3]$ were followed by cyclic voltammetry, ^{31}P NMR spectroscopy, and ESI-MS, and the rhodacyclopentadienes formed (**116a** and **116b**) were also characterized by the same techniques (Scheme 41).

From the values of the half-reaction times $t_{A1/2}$ and $t_{B1/2}$ of steps **A** and **B**, respectively, it was found that step **A**, resulting from coordination of the two triple bonds of **114a** followed by oxidative coupling, was rate-determining for the cycloaddition of the bulky diyne **114a**. In contrast, step **B**, the reaction of **116b** with 2-butyn-1,4-diol with subsequent recovery of the Wilkinson

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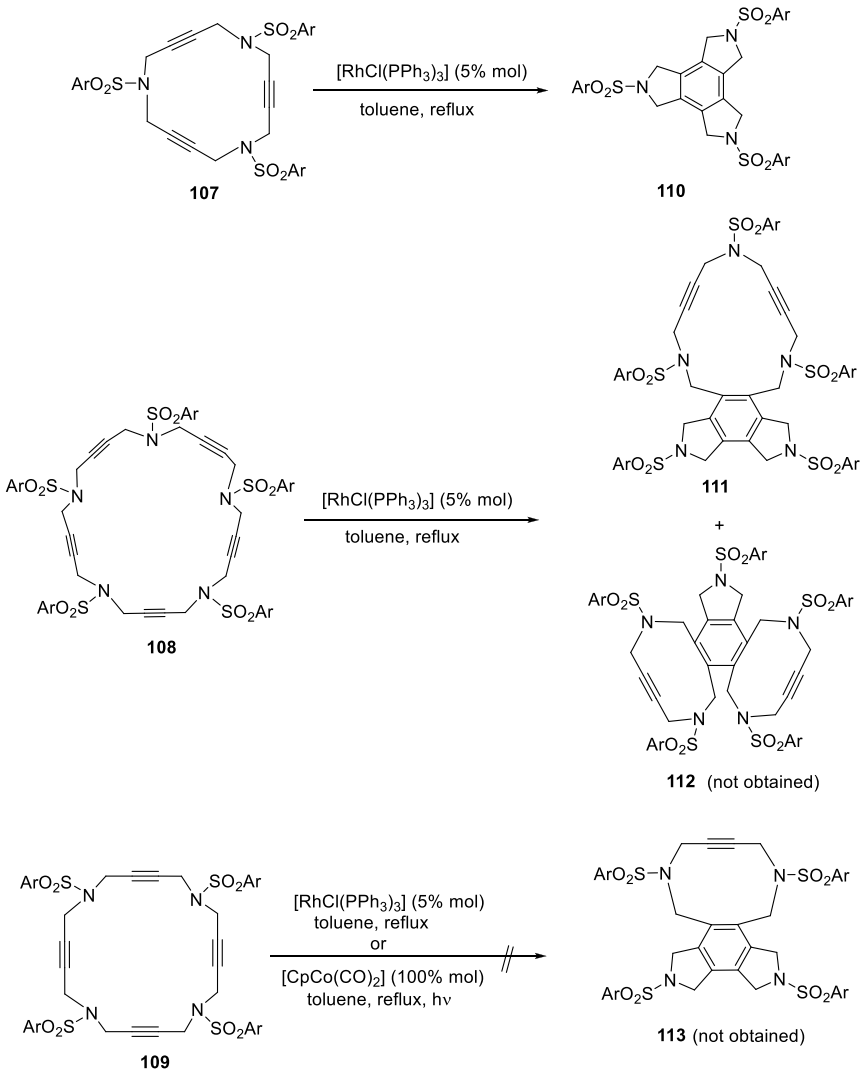
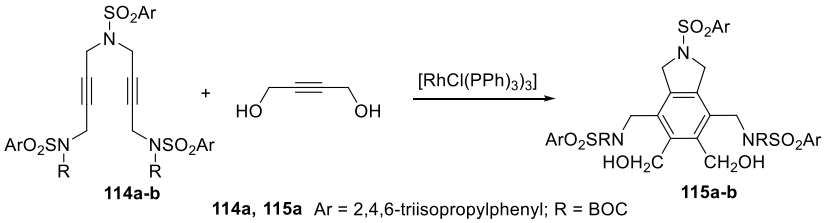
Scheme 39. Studies of Cycloisomerization Reactions of 15-, 20-, and 25-Membered Acetylenic Azamacrocycles



Scheme 40. Wilkinson-Complex-Catalyzed [2 + 2 + 2] Cycloaddition Reactions between Diynes 114 and 2-Butyn-1,4-diol



114a, 115a Ar = 2,4,6-triisopropylphenyl; R = BOC
114b, 115b Ar = 2,4,6-triisopropylphenyl, R = H

catalyst, was rate-determining. The results of these kinetic studies indicate that the rate-determining step depends on the structure of the starting reagents.

Metallacyclopentadienes or metallacyclopentatrienes generated from the oxidative coupling of two alkynes had been identified as the intermediates in the first step of the catalytic cycle of the [2 + 2 + 2] cycloaddition reaction. A large range of these metallacycles has been isolated and fully characterized, confirming their role as intermediates in the cycloaddition process. However, even though more advanced intermediates in the catalytic cycle, derived from the insertion of the third alkyne into the metallapentacycle, have been postulated or calculated in theoretical studies by DFT as previously seen, little experimental data had been reported.

The detection or isolation of intermediates of the rhodium-catalyzed [2 + 2 + 2] cycloaddition reaction was studied by our group[175] and the group of Paneque[176] from an experimental point of view. Electrospray ionization mass spectrometry (ESI-MS) was used to obtain detailed data by trapping and identifying short-lived intermediates in the cycloaddition reaction. The very mild ionization conditions in the ESI mass spectrometer permit data to be acquired directly from solutions where reactions are taking place. The rhodium-catalyzed [2 + 2 + 2] cycloaddition of diyne **117** and *p*-methylphenylacetylene was studied by this

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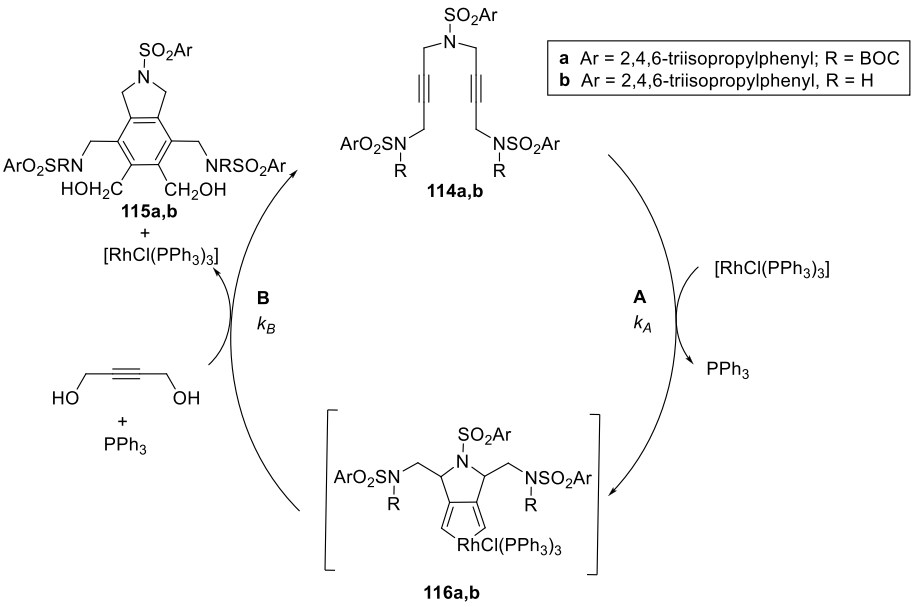
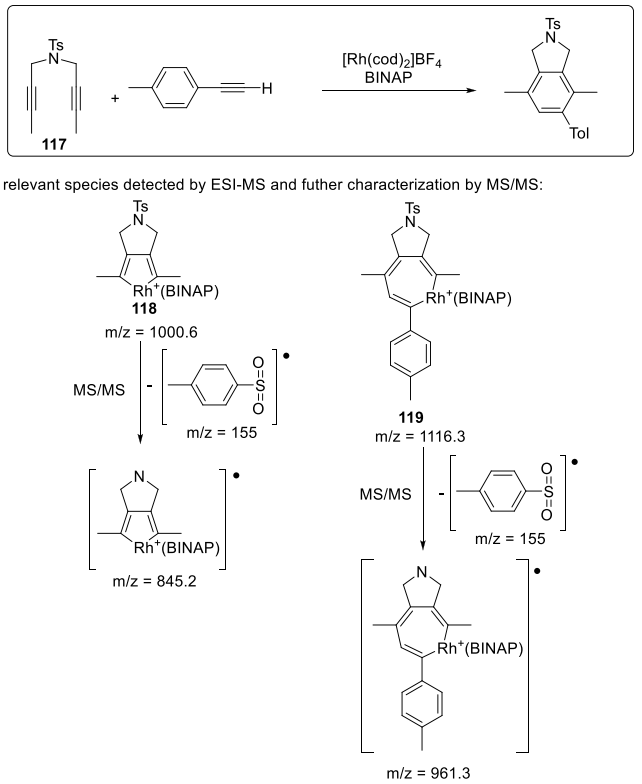
Scheme 41. Cycloaddition Reactions Studied by CV, ^{31}P NMR, and ESI-MS



technique (Scheme 42). A cationic catalytic system based on a mixture of $[Rh(cod)_2]BF_4$ and BINAP was used to generate cationic intermediates that were easily detectable in the mass spectrometry compared with neutral reactants and reaction products. A mixture of diyne **117**, $[Rh(cod)_2]BF_4$/BINAP catalyst, and *p*-methylphenylacetylene in dichloromethane was injected into the mass spectrometer at certain time intervals.

Scheme 42. Species Detected by ESI-MS in the [2 + 2 + 2] Cycloaddition between Diyne 117 and *p*-Methylphenylacetylene



Rhodacyclopentadiene **118** was detected in the mass spectrum at m/z = 1000.6 Da and further characterized by MS/MS analysis. The MS/MS showed a fragment at m/z = 845.2, corresponding to the loss of the tosyl group through S−N bond fragmentation, in which homolytic cleavage led to the loss of radical Ts and the detection of a cationic radical fragment. This fragmentation pattern suggested that the intermediate corresponded to rhodacyclopentadiene intermediate **118**. In the spectra, another cluster at m/z = 1116.3 was detected although at a very low intensity. The peak corresponded to intermediate **119**, the formal addition of *p*-methylphenylacetylene to the rhodacyclopentadiene intermediate **118**. When this peak was submitted to MS/MS, the loss of a tosyl group was also observed, demonstrating the detection of the addition intermediate **119** rather than a coordination intermediate. The same pattern of behavior and the detection of homologous clusters were observed when the ESI-MS study was conducted varying the diyne (a malonate-tethered diyne) and the alkyne (Ar = *p*-OMePh, Ph, *p*-^{t}BuPh, *p*-FPh, *p*-BrPh) and using different biphosphines (H_8−BINAP, BIPHEP), confirming the nature of all of the intermediates that were observed and characterized. ESI-MS did not allow the structure of the intermediate to be unequivocally determined. DFT calculations were therefore performed using the B3LYP/cc-pVDZ-PP method. To reduce the computational effort, the BINAP ligand was substituted by a BIPHEP and the aryl groups of the tosyl units were substituted by CH_3 fragments. Our simulations excluded as a possible structure for intermediate **119** the 7-rhodanorbornadiene intermediate formed by [4 + 2] intra- or intermolecular cycloaddition, since this intermediate could not be located in the potential energy surface. Instead, we could locate as possible intermediates a rhodabicyclo[3.2.0]-heptatriene and a rhodacycloheptatriene. The former evolves to the latter with a Gibbs energy barrier of only 1.7 kcal/mol, whereas the latter progresses to the final product through a Gibbs energy barrier of 2.2 kcal/mol. These results favor the assignment of intermediate **119** to a rhodacycloheptatriene species because it is kinetically somewhat more stable than the rhodabicyclo[3.2.0]heptatriene complex. However, the small

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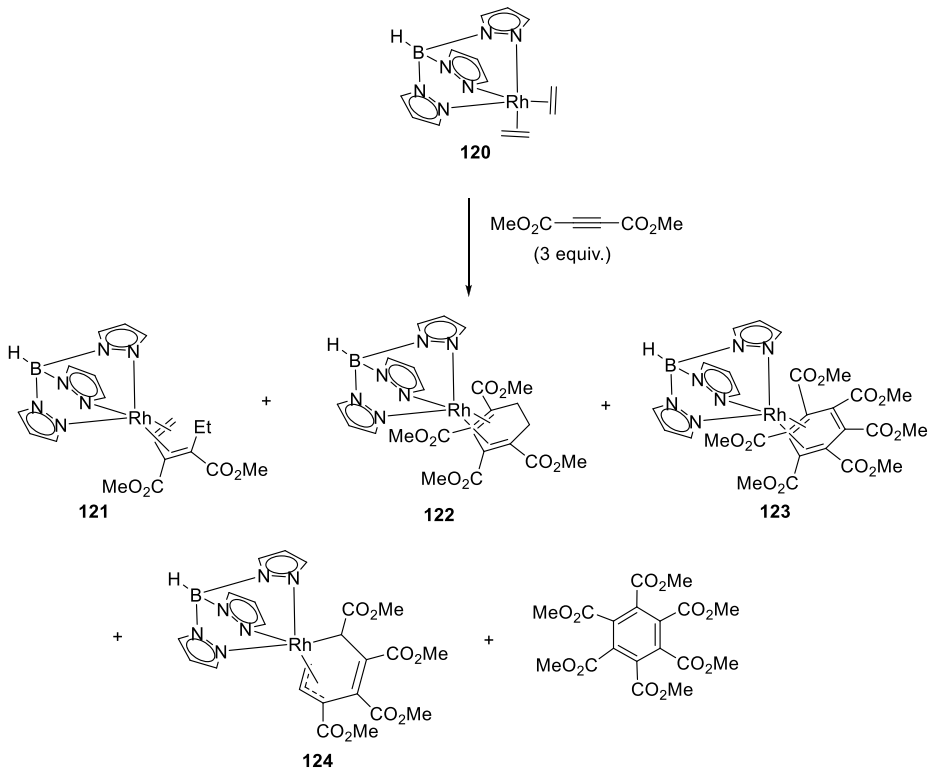
Scheme 43. Organometallic Species Generated by Reaction of Complex 120 with 3 equiv of Dimethyl Acetylenedicarboxylate



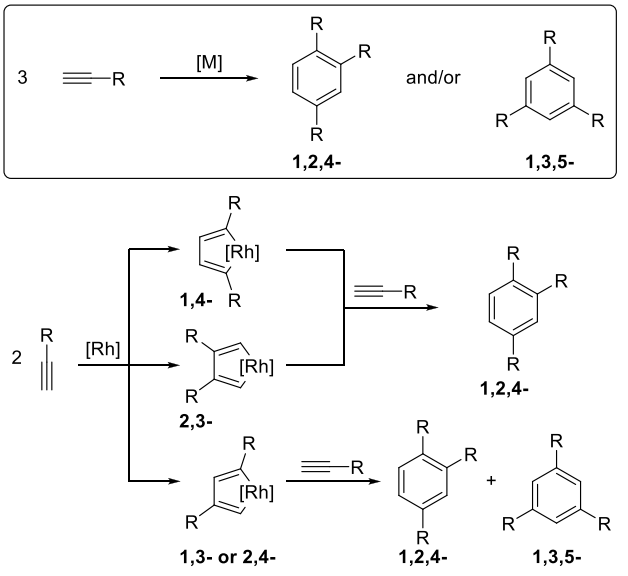
energy difference between the two Gibbs energy barriers prevented a definitive conclusion about the nature of intermediate **119**.

The group of Paneque has published extensively on the chemistry of iridacycles containing the TpIr moiety, their preparation, and their reactivity (see complete details in section 2.6). The difficulty of these TpIr(III) complexes to give reductive elimination, resulting from their poor ability to eliminate the aromatic compound from the metallacycle, makes it possible to isolate these complexes that have been postulated as playing a role as intermediates in [2 + 2 + 2] cycloadditions but which, on the other hand, do not evolve toward the cycloaddition products. The same group[176] has described the synthesis and reactivity of the homologous $[TpRh(C_2H_4)_2]$ **120** with dimethyl acetylenedicarboxylate in an attempt to identify intermediates of the [2 + 2 + 2] cyclotrimerization of alkynes. Given that the TpRh(III) has a higher tendency to undergo reductive elimination to Rh(I) compared to iridium, a detailed study was performed. The isolated organometallic species **121**−**124** and hexamethyl mellitate generated from the reaction of Rh complex **120** with 3 equiv of dimethyl acetylenedicarboxylate are shown in Scheme 43.

The reaction of complex **120** with dimethyl acetylenedicarboxylate generated three Rh(I) species, **121**, **122**, and **123**, that differ in the coordinated η^4-diene unit which incorporated one, two, or three dimethyl acetylenedicarboxylate units, respectively. It also generated allyl Rh(III) derivative **124**. Hexamethyl mellitate, resulting from the [2 + 2 + 2] cyclotrimerization of dimethyl acetylenedicarboxylate, was also detected in the reaction mixture. However, even when an excess of dimethyl acetylenedicarboxylate was used, a small amount of this compound was obtained, demonstrating the poor catalytic activity of rhodium complex **120**. Furthermore, the high thermal stability of compound **123** resulted in it being a poor catalyst for the cyclotrimerization reaction.

Another aspect that is important in the [2 + 2 + 2] cyclotrimerization of three identical monosubstituted alkynes is the control of the regioselectivity. As indicated in Scheme 44, two possible regiosiomers can be formed, namely, the 1,2,4- and 1,3,5-trisubstituted benzene rings. The regioselectivity is

Scheme 44. Two Possible Regioisomers That Can Be Formed in the [2 + 2 + 2] Cyclotrimerization of Identical Monosubstituted Alkynes and the Mechanism of Formation[a]



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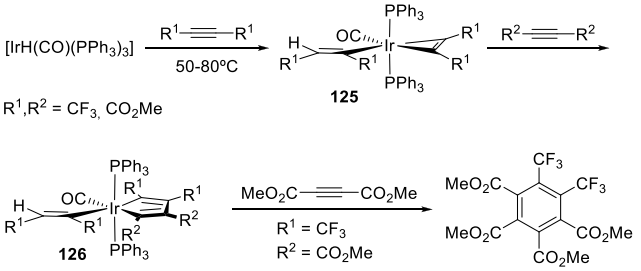
determined by two steps: the oxidative coupling and the insertion of the third alkyne. As for the oxidative coupling, it can occur in four different ways: head-to-head, tail-to-tail, tail-to-head, and head-to-tail to yield the 1,4-, 2,3-, 1,3-, and 2,4-rhodacyclopentadienes. Depending on the symmetry of the catalyst, the two latter may be the same intermediate. After insertion of the third alkyne, 1,4- and 2,3-rhodacyclopentadienes afford exclusively the 1,2,4-trisubstituted benzene, whereas the 1,3-, and 2,4-rhodacyclopentadienes give a mixture of 1,2,4- and 1,3,5-trisubstituted benzene rings.

In our group,[177] we performed a combined computational and experimental study of the [2 + 2 + 2] cyclotrimerization catalyzed by $[Rh(BIPHEP)]^+$ of a series of *p*-X-substituted phenylacetylenes (X = H, NO_2, and NH_2 for the computational study and X = H, NO_2, NMe_2, F, Me, ^{t}Bu, and OMe in experiments). The aim was to analyze the effect of the electronic character of the phenyl substituents in the regioselectivity. Our B3LYP-D3/aug-cc-pVTZ-PP//B3LYP-D3/cc-pVDZ-PP calculations including solvent effects indicated that *p*-nitrophenylacetylene, which has the most electron-withdrawing substituent, produces exclusively the 1,2,4-regioisomer, since the oxidative coupling leading to the 1,4-di-*p*-nitrophenylrhodacyclopentadiene has both the lowest energy barrier and the highest stability among the different transition states for the oxidative coupling. In all cases, we considered both the reaction path with the lowest energy barrier and the reaction path through the most stable transition state (Curtin–Hammett principle).[178] The predictions of the latter path were found to be in better agreement with the experimental results than those of the reaction path with the lowest energy barrier. Experimentally, for the *p*-dimethylaminophenylacetylene, the cyclotrimerization yielded a mixture of the two regioisomers in a 59:41 ratio (in favor of the 1,2,4-regioisomer), whereas computationally we predicted a ratio of 54:46 for the *p*-aminophenylacetylene. The calculated ratio was obtained using the rate constants from transition state theory and the Gibbs energy barriers of the different possible reaction pathways. For X = H, we obtained a 96:4 experimental ratio and computationally we calculated a 99:1 ratio. Finally, we observed a fairly good correlation between the electronic nature of the substituents measured with the Hammett σ_{para} constant[179] and the regioisomeric ratios experimentally obtained and computationally predicted.

2.6. Iridium Complexes

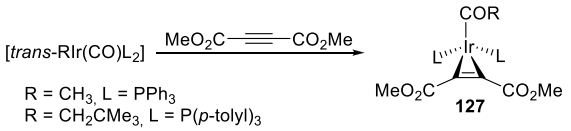
Baddley and Tupper[180] reported the formation of σ-alkenyl-π-acetylene complex **125** upon reactions of alkynes with electron-withdrawing substituents with $[IrH(CO)(PPh_3)_3]$. Characterization by X-ray diffraction of an analogous complex obtained by the reaction of dicyanoacetylene had earlier been reported by Ibers and Kirchner.[181] Complex **125** reacted further with disubstituted acetylenes to give iridacyclopentadiene **126**, as determined by spectroscopic techniques. By using different acetylenes in the two sequential steps, asymmetrically substituted metallocycles could be obtained (Scheme 45). Stoichiometric reaction of **126** with dimethyl acetylenedicarboxylate furnished the expected aromatic compound, suggesting that iridacyclopentadiene complex **125**, and not a decomposition product, was involved in arene formation. Furthermore, complexes **126** were efficient catalysts for the cyclotrimerization reaction of dimethyl acetylenedicarboxylate. Comparison of the catalytic activity of **126** with the chloro derivative reported by Collman et al.[70] showed that it is enhanced when an alkenyl group is an auxiliary ligand rather than the chloride ion.

Scheme 45. Isolation of Alkenyliridium Complexes Reported by Baddley et al.[180]



The formation of stable monoacetylene complexes seems to be a characteristic feature in the reaction of iridium complexes and alkynes. Atwood et al.[182] reported the isolation and characterization by X-ray diffraction of monoacetylene complex **127** (for R = CH_2CMe_3, L = $P(p\text{-tolyl})_3$) and justified the increased reactivity of alkyl complexes of iridium as compared to the chloro analogues, due to the facile opening of a coordination position by migration of the alkyl to the CO and formation of quasitetrahedral complex **127**. Complexes **127** were active catalysts in the cyclotrimerization of dimethyl acetylenedicarboxylate and thus were postulated as intermediates in such a transformation (Scheme 46).

Scheme 46. Quasitetrahedral Monoalkyne Iridum Complexes Isolated by Atwood et al.[182]



Bianchini, Caulton, and Eisenstein et al.[160,183] studied the structure, bonding, and reactivity of iridium–triphos complexes with acetylene (triphos = $MeC(CH_2PPh_2)_3$) (Scheme 47). Iridium–triphos bis- (**129**) or monoalkene (**130**) complexes reacted under a flow of acetylene at room temperature in THF to efficiently generate benzene complex **132a**. The same complex was obtained in an almost quantitative yield by the reaction of iridacyclopentadiene complex **131a** (which was also fully characterized by NMR studies), under analogous conditions. It is noteworthy that the reaction only proceeded for cationic complexes in which the chloride (if present) had been abstracted by the action of a scavenger. Complex **132a** was fully characterized by a detailed NMR study and X-ray diffraction. The structural study indicated that iridium is bound in an η^4 fashion to the benzene leading to a nonplanar ring, showing fluxional behavior, like the Ni complexes isolated by Stone et al.[123] Complex **132a** catalyzed the cyclotrimerization of acetylene to furnish benzene with great efficiency, in a process that again was stopped by the addition of chloride and restarted when a chloride scavenger was added. Bianchini and Caulton et al.[184] showed that (ethene)dihydro complex **128** could also serve as the starting product for the preparation of **132a**, in a process in which a π-acetylene complex $[(triphos)Ir(\pi\text{-}C_2H_2)]BPh_4$ could be detected by NMR. The authors of these studies[160,183] performed some preliminary extended Hückel calculations (EHT). Results from a correlation diagram indicated that the oxidative coupling that generated iridacyclopentadiene complex $[(PR_3)_3Ir(C_4H_4)]^+$ was allowed when the

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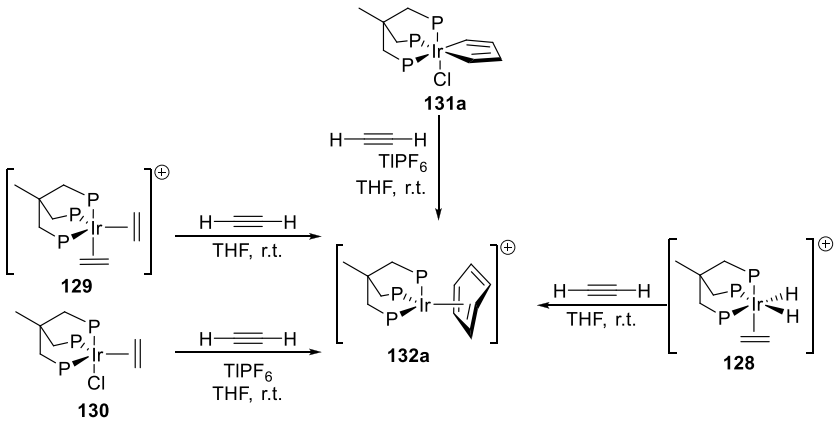
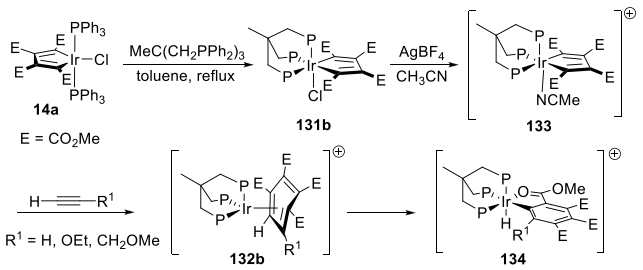
Scheme 47. Triphos Iridium Complexes Isolated by Bianchini et al.[160,183,184]



three phosphine ligands had a pyramidal P_3Ir^+ structure (*fac* geometry) and was forbidden with a planar P_3Ir^+ structure (*mer* geometry). It is worth noting that the transformation between the *fac* and *mer* structures was found relatively easily in the $[(PPh_3)_3Ir(CF_3)]$ complex.[185] In the addition of the third alkyne to the iridacyclopentadiene complex, the four alkyne orbitals ($\pi_{\parallel}$, $\pi^*_{\parallel}$, $\pi_{\perp}$, $\pi^*_{\perp}$) were ideally suited to interact with the frontier orbitals of the iridacyclopentadiene complex to form the $[P_3Ir(\eta^4\text{-}C_6H_6)]^+$ species (complex **132a**). The addition of the alkyne to the iridacyclopentadiene complex proceeded in a concerted manner and should be classified as a *metal-assisted Diels–Alder reaction*. Interestingly, variable temperature ^{31}P and ^1H NMR spectra in $CDCl_3$ showed that all six benzene carbons and the three phosphines were time-average equivalent, indicating that complex **132a** was fluxional. EHT calculations demonstrated that the fluxionality was achieved by the movement of the metal over the ring and the rotation of the P_3Ir^+ group. $[P_3Ir(\eta^4\text{-}C_6H_6)]^+$ species were found to be high in energy, and therefore, it was concluded that they could not be formed. The insertion of an acetylene molecule to complex **131a** generated the $[P_3Ir(\eta^2\text{-}C_6H_6)]^+$ species that, in a subsequent step, incorporated another acetylene molecule and released benzene to form $[P_3Ir(\eta^2\text{-}C_2H_2)]^+$.

O'Connor et al.[186] also managed to characterize reaction intermediates in [2 + 2 + 2] cycloaddition reactions mediated by Ir–triphos complexes. Starting from the iridacyclopentadiene complex **14a** reported by Collman et al.,[70] triphenylphosphine ligands were exchanged to triphos to obtain iridacyclopentadiene complex **131b**, which could be easily converted to the cation **133** by treatment with $AgBF_4$ (Scheme 48). Treatment of complex **133** with certain terminal alkynes (acetylene, ethyl ethynyl ether, and methyl propargyl ether) led to the isolation of iridium(III) aryl-hydride complexes **134**. The authors postulated the formation of η^4-benzene intermediate **132b**, analogous to that reported by Bianchini et al.,[183] which subsequently suffered an intramolecular insertion of iridium into the carbon–hydrogen bond, a process which was facilitated by the *ortho* effect of the carbomethoxy group. It should be noted that the same authors had earlier reported the preparation of fulvenes through [2 + 2 + 1] cycloaddition with terminal alkynes of different electronic and steric nature with the same iridium complexes.[187]

Scheme 48. Triphos Iridium Complexes Isolated by O'Connor et al.[186]



Paneque et al.[188] reported the preparation and characterization by X-ray diffraction of iridacycloheptatriene complex **136a**, formed by the reaction of iridium(I) butadiene derivative **135** with 3 equiv of dimethyl acetylenedicarboxylate (Scheme 49). No intermediates in the process could be detected by NMR monitoring. Similarly, the reaction of $[Tp^{Me2}Ir(C_6H_5)_2(N_2)]$ **137** with dimethyl acetylenedicarboxylate led to the isolation of complexes **138** and **139** in a 1:2 ratio, both containing a benzannelated iridacycloheptatriene linkage, resulting from the formal cycloaddition of one benzyne and two dimethyl acetylenedicarboxylate units (although mechanistically the authors postulate the insertion of DMAD into an Ir–Ph bond followed by *o*-metalation).[189] All of these complexes had an adventitious water molecule that completed the metal coordination that could be easily replaced by other Lewis bases. Whereas complex **136a** was reluctant to eliminate reductively the iridium to furnish the hexamethyl mellitate, complexes **138** and **139**, after water exchange to PMe_3, gave rise to 1,2,3,4-tetra(carbomethyl)naphthalene under very drastic oxidation conditions.

In a subsequent paper, Paneque et al.[190] found that the presence of water in the reaction mixture had a key role in the outcome of the reaction and led to the isolation of different reaction intermediates. When the reaction of complex **135** with DMAD was carried out in the presence of 10 equiv of water, iridacyclopentadiene complex **140** was isolated. This complex could be reacted with 2-butyne to give a mixture of complexes **136b** and **141**, which were present in a proportion that depended on the amount of water present in the media (Scheme 50).[191] Although none of these complexes evolve to the aromatic cyclotrimerization product, their isolation is relevant given that they are models of the intermediates proposed by theoretical calculations in the [2 + 2 + 2] cycloaddition reaction of three alkynes. Complex **136b** is an iridacycloheptatriene complex similar to that computationally found by Ess et al.[125] in the alkyne cyclotrimerization catalyzed by the homodinuclear nickel

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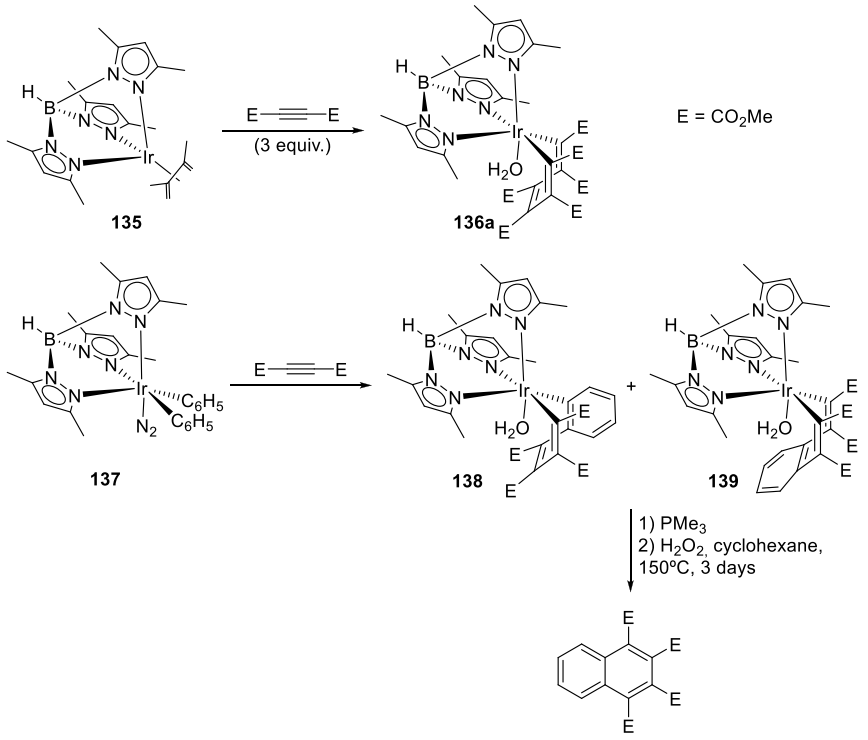
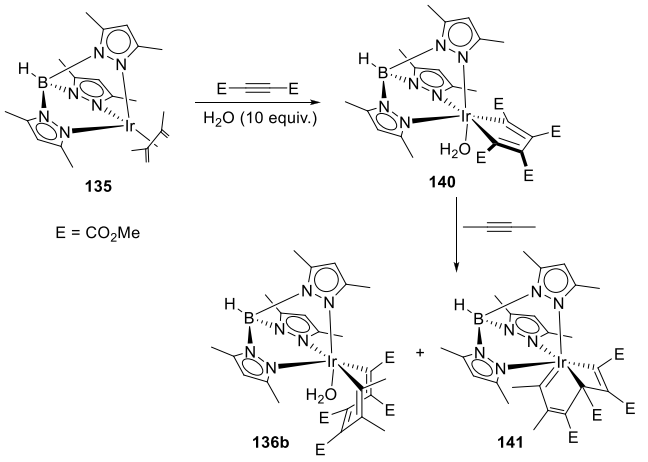
Scheme 49. Iridacycloheptatrienes Isolated by Paneque et al.[188,189]



Scheme 50. Iridacyclopentadiene and Iridacycloheptatrienes Isolated by Paneque et al.[190,191]



complex [($^{i\text{-Pr}}$NDI)Ni$_2$(C_6H_6)] (NDI = naphthyridine-diimine) or by our own group[175] in the Rh(BIPHEP)$^+$-catalyzed [2 + 2 + 2] cycloaddition of diyne **117** and *p*-methylphenylacetylene (see, for instance, Scheme 42). On the other hand, complex **141** is an iridabicyclo[3.2.0]heptatriene analogous to that found in the theoretical study by Lord and Groysman et al.[126] of the cyclotrimerization reaction of terminal alkynes catalyzed by a dinuclear nickel complex with a xanthene-bridged bis(iminopyridine) ligand or that found in the computational studies of the trimerization of acetylene catalyzed by [CpRuCl] performed by Kirchner and Calhorda et al.[135] and Yamamoto et al.[136] As we have already discussed,[170] the cyclotrimerization of acetylene by [CpRh(CO)] and [IndRh(CO)] also proceeds through rhodabicyclo[3.2.0]heptatriene and rhodacycloheptatriene intermediates.

Wu and Jiao et al.[192] studied the acetylene cyclotrimerization catalyzed by the [CpIr] complex using the B3LYP/6-311+G(d,p)~LANL2DZ method. As usual, the first step, which was the oxidative coupling of two acetylene molecules to form the iridacyclopentadiene complex, was found to be the rate-determining step with a Gibbs energy barrier of 14.8 kcal/mol. The addition of an acetylene molecule to the iridacyclopentadiene complex was a barrierless process. The [CpIr(C_4H_4)(η^2-C_2H_2)] complex formed has the triple bond oriented perpendicular to the axis formed by the Ir atom and the center of the Cp unit to maximize back-donation, as predicted by Hoffmann et al.[193] This complex evolves to the final [CpIr(η^6-C_6H_6)] complex via an intramolecular [4 + 2] Diels−Alder reaction with a Gibbs energy barrier of 8.2 kcal/mol. Alternatively, an acetylene molecule is intermolecularly inserted into the iridacyclopentadiene complex to form an iridabicyclo[3.2.0] complex with a barrier of 8.6 kcal/mol. Given the small energy difference between the two Gibbs energy barriers, both pathways should in principle be operative. The formation of an iridacycloheptatriene intermediate is thermodynamically highly favored but kinetically strongly disfavored. However, at high temperatures, this iridacycloheptatriene complex could be a trap in the catalytic cycle. These results are qualitatively close to those of the already discussed cyclotrimerization of acetylene by CpRh catalyst.[110]

The mechanism of the TpIr (Tp = hydrotris(pyrazolyl)borate)-catalyzed cyclotrimerization was studied by Dahy and Koga.[194] These authors used the B3LYP and M06 functionals obtaining similar results. We will refer here only to the B3LYP/6-311G(d,p)~LANL08(f)//B3LYP/6-31G(d)~LANL2DZ+f calculations. The authors considered the possibility that intermediates or transition states in their triplet states were involved in the reaction mechanism, but as in the case of Rh-catalyzed cyclotrimerizations, triplet states were found to be less stable than singlet ones in all cases. They started their study from

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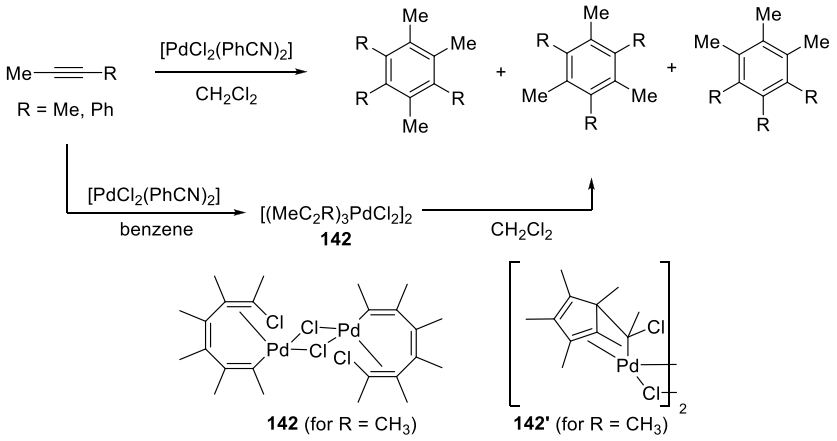
Scheme 51. Palladium Intermediates Isolated by Maitlis et al.[195,196]



complex $[TpIr(\eta^2\text{-}C_2H_2)_2]$ in which, unexpectedly, one of the acetylene ligands was more strongly coordinated than the other. Oxidative coupling was exothermic by 32.5 kcal/mol and had an activation barrier of only 7.5 kcal/mol. The iridacyclopentadiene intermediate formed was distorted from the C_s symmetry because of a second-order Jahn−Teller distortion similar to that found in a previously studied cobaltacyclopentadiene.[107] The addition of the incoming acetylene molecule took place via a symmetry-allowed intramolecular [4 + 2] cycloaddition mechanism with an activation energy of 9.3 kcal/mol and an energy release of 42.5 kcal/mol to give the $TpIr(\eta^4\text{-}C_6H_6)$ complex. This was the rate-determining step in this particular cyclotrimerization of acetylene. The authors found an alternative path for the formation of the benzene Ir complex through a [2 + 2] insertion of the acetylene to the iridacyclopentadiene intermediate to yield the iridabicyclo[3.2.0]heptatriene intermediate that evolved to the iridacycloheptatriene complex (Schore's mechanism) before affording the benzene Ir complex. The iridabicyclo[3.2.0]-heptatriene complex **141** isolated by Paneque et al.[188] had a similar geometry to that located computationally. As in the previous study, the iridacycloheptatriene complex was very stable and could represent a trap on the catalytic process. In the gas phase, this alternative path had slightly higher energy barriers. Moreover, when solvent effects of a cyclohexane solution were included in the calculation, the Schore mechanism no longer existed. Solvent effects in [2 + 2 + 2] cyclotrimerization reactions are minor due to the absence of polar species, but in this particular case, solvent effects induced an important change in the PES. Similarly, when the authors studied the cyclotrimerization of substituted acetylenes ($H_3CC{\equiv}CCH_3$ and $CH_3O_2CC{\equiv}CCO_2CH_3$), they found that the reaction could proceed only via the Schore mechanism because of the effect of the substituents. In this case, the direct transformation of the iridabicyclo[3.2.0]heptatriene intermediate to the $TpIr(\eta^4\text{-}C_6H_6)$ complex was the rate-determining step of the mechanism. This study showed that small changes in the reaction conditions can generate important changes in the PES and, therefore, in the reaction mechanism. Thus, a change in the ligands from CpIr to TpIr modified the rate-determining step from oxidative coupling to intramolecular Diels−Alder addition of the third alkyne or a change from unsubstituted to substituted acetylenes changes the intramolecular Diels−Alder addition of the third alkyne by a [2 + 2] insertion or inclusion of a solvent made the Schore mechanism unavailable in the cyclotrimerization of acetylene by TpIr.

2.7. Palladium Complexes

Initial studies into the mechanism of palladium-catalyzed [2 + 2 + 2] cyclotrimerization reactions were carried out in the group of Maitlis, who observed different trends depending on the oxidation state of the metal. With regard to palladium(II), the study into the cyclotrimerization of diphenylacetylene referred to in section 2.1[66] was followed by a detailed study on the trimerization of 2-butyne and 1-phenyl-1-propyne.[195] Both alkynes were efficiently cyclotrimerized by the reaction of bis(benzonitrile)palladium chloride in halogenated solvents (Scheme 51). For 1-phenyl-1-propyne, apart from 1,2,4-trimethyl-3,5,6-triphenylbenzene and 1,3,5-trimethyl-2,4,6-triphenylbenzene, small amounts (3%) of 1,2,3-trimethyl-4,5,6-triphenylbenzene were obtained (in line with the results obtained by Ehmann et al.[72]). When the reaction was carried out in benzene at 5 °C, an intermediate of molecular formula $[(MeC_2R)_3PdCl_2]_2$ (**142**) was isolated. No crystals suitable for X-ray diffraction could be obtained; thus, the complex was characterized by NMR, IR, and decomposition reactions.[196] The dimeric structure **142** shown in Scheme 51 for R = Me was proposed. Its formation entailed a chlorine migration from palladium to an acetylenic carbon. The authors hypothesized that scrambling of substituents to afford the 1,2,3-substituted benzene could occur during the decomposition of **142** to the aromatic ring, although this hypothesis relied only on limited experimental evidence.

Further support of the formation of intermediates where a chloride migrated to the acetylene was gained by the same research group[197] three years later. Dimethyl acetylenedicarboxylate reacted with bis(benzonitrile)palladium chloride to form dimeric palladium complex **142″**, which, upon treatment with thallium acetylacetonate, generated monomeric palladium complex **143** that could be characterized by X-ray diffraction (Scheme 52). Complex **142″** gave benzenoid hexamethyl mellitate on heating. These results permitted Maitlis et al. to postulate **142′** as an alternative structure for the intermediate isolated in their previous study[198] (Scheme 51).

This series of studies allowed the authors to postulate a stepwise mechanism (Scheme 53),[198] involving a series of *cis* insertions of coordinated acetylenes. The Cl migration takes place in Cl−Pd of palladium chloride, giving σ-vinyl intermediate **144**; subsequent insertion of two additional

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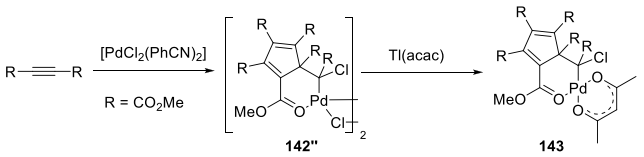
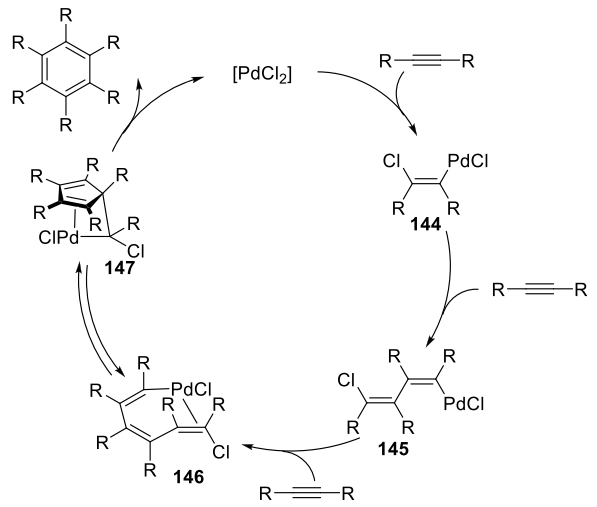
Scheme 52. Palladium Complexes Isolated by Maitlis et al.[197]



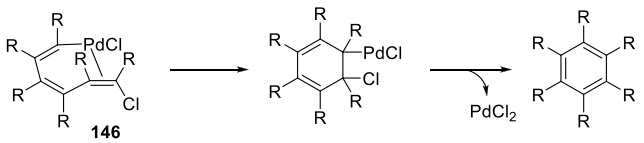
Scheme 53. Stepwise Mechanism Proposed for $PdCl_2$-Catalyzed Cyclotrimerization Reactions by Maitlis et al.[198]



alkynes generated the cyclopentadiene−Pd complex **147**. The mode by which **147** generates the benzene was not clear, but the authors postulated that it probably involved a bicycle[3.1.0]-hexenyl complex that would explain the scrambling of substituents observed. The rate of the different steps and, therefore, the outcome of the reaction was found to be critically dependent on the bulkiness of the acetylenic substituents.

Jiang et al.[199] reported the cyclotrimerization of 4-octyne, 1-heptyne, 3,3-dimethyl-1-butyne, 1-phenyl-1-propyne, and 1-ethynyl-1-methylbenzene under catalysis by $PdCl_2$ in the presence of $CuCl_2$. The asymmetrically substituted alkynes regioselectively gave the 1,3,5-substituted isomer except for 1-ethynyl-1-methylbenzene that gave the 1,2,4-substituted derivative. The mechanism postulated is analogous to that proposed by Maitlis et al. in the first part of the catalytic cycle s54 but differs in the last step, as shown in Scheme 54.

Scheme 54. Ring-Closing Sequence Proposed by Jiang et al.[199]



In the case of palladium(0), Moseley and Maitlis[200,201] reported the cyclotrimerization reaction of dimethyl acetylenedicarboxylate catalyzed by [Pd(dba)$_2$] (dba = dibenzylideneacetone). The reaction proceeded through palladacyclopentadiene complex **148**, which was isolated and characterized in its polymeric form but could be easily depolymerized by treatment s55 with complexing ligands (Scheme 55). Palladacyclopentadiene **148** reacted with dimethyl acetylenedicarboxylate or diphenylacetylene on warming to give the aromatic compound and was also shown to catalyze the cyclotrimerization reaction.

Formation of palladacyclopentadienes was also reported by tom Dieck et al.[202] although stabilized by diazadiene ligands, which had earlier been shown to form nickelacyclopentadienes.[117] The reaction of *N*-aryldiazadienes with bis(dibenzylideneacetone)palladium and acetylenedicarboxylic acid esters at room temperature afforded palladacyclopentadiene complexes **149** (Scheme 56). Thermal reaction of **149** s56 with 1 equiv of an ester of acetylenedicarboxylic acid gave the corresponding aromatic compounds in a stoichiometric process. The reaction could also be run catalytically. Complex **149** readily catalyzed the cyclotrimerization of esters of acetylenedicarboxylic acid but also the co-cyclotrimerization of 2 mol of the diester with various alkynes.

Itoh and Yamamoto et al.[203,204] reported the cycloaddition of a diyne diester with dialkyl acetylenedicarboxylates catalyzed by [Pd_2(dba)$_3$] (a process which required electron-withdrawing ester substituents for all of the alkyne components to proceed efficiently). The cycloaddition required the addition of PPh_3, which presumably prevented the formation of palladacyclopentadiene oligomer complexes. These are not particularly soluble in common solvents and activated the Pd−C bond at its *trans* position for further additions. When the oxygen-tethered diyne diester **61a** was treated with the palladium complex in acetone under milder conditions, palladacyclopentadiene oligomer **150** was isolated as a green powder which could not be characterized due to its low solubility but could be converted into the monomeric bispyridine complex **151**, whose structure was unequivocally determined by X-ray diffraction (Scheme 57). s57 Treatment of **151** with dimethyl acetylenedicarboxylate, even at room temperature, led to the formation of the aromatic product. For this last step, the authors postulated two possible mechanisms: an insertion/reductive elimination sequence through a palladacycloheptatriene intermediate or an indirect [4 + 2] cycloaddition mechanism involving a palladacyclopentadiene(alkyne) complex intermediate.

The same authors extended the study to the cyclization of triynes.[203] Under the same reaction conditions, the cycloaddition efficiently afforded tricyclic derivatives, in a process that was even efficient in the absence of added phosphines. The authors expected the formation of a palladacyclopentadiene intermediate with the palladium coordinated to the unreacted alkyne, by analogy to the results obtained by Vollhardt et al.,[96] but instead obtained triyne complex **152** (Scheme 58). s58 Heating or addition of triphenylphosphine efficiently promoted the cyclotrimerization reaction. Furthermore, **152** was shown to catalyze the cyclotrimerization of 1,6,11-triyne in the absence of added phosphines. Since it was not possible to detect any further intermediate in the reaction, the authors proceeded to determine the relative thermodynamic stability of the plausible palladacyclopentadiene(alkyne) intermediate complexes **153** and **154**. Calculations at the B3LYP/6-31G(d)∼SDD(2f+g) level of theory indicated that **153** is more stable than **154** by 12 kcal/mol. They attributed the lower stability of **154** to the fact that the triple bond in **154** is not coordinated to Pd due to unfavorable chain strain generating an unsaturated palladacyclopentadiene. Consequently, the authors concluded that the transformation of **152** to the arene product had taken place via complex **153** rather than **154**.

Canovese et al.[205] reported the oxidative coupling of dimethyl acetylenedicarboxylate with palladium(0) olefin complexes bearing a pyridylthioether ancillary ligand. Reaction of the

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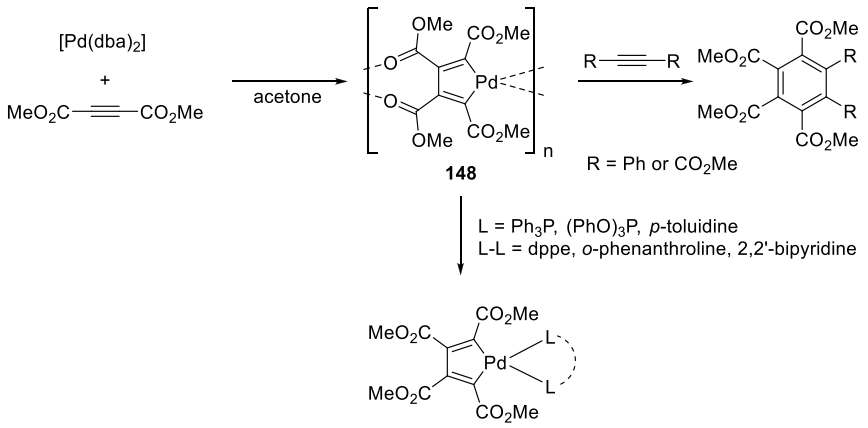
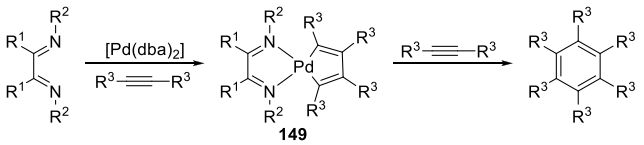
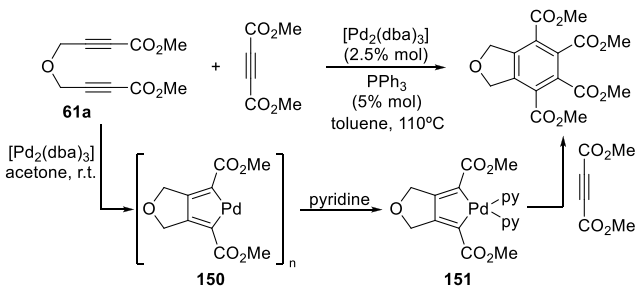
Scheme 55. Polymeric Palladacyclopentadiene Intermediate Isolated by Maitlis et al.[200,201]



Scheme 56. Palladacyclopentadiene−Diazadiene Complexes Isolated by tom Dieck et al.[202]



Scheme 57. Palladacyclopentadiene Intermediate Isolated by Yamamoto et al.[203,204]

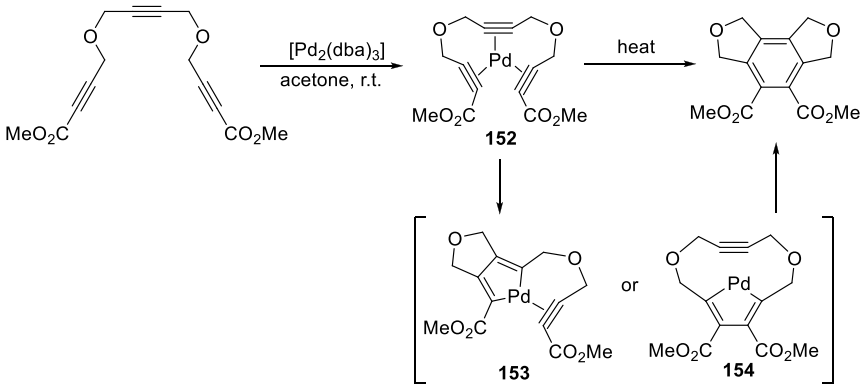


alkyne and the palladium complex gave palladacyclopentadiene complex as the main product together with some amounts of the palladium−alkyne complex and hexamethyl mellitate. The amount of hexamethyl mellitate being formed depended on the alkyne/palladium complex ratio (at high ratios, its formation decreased) and the nature of the complex itself. Reaction of the free alkyne with the palladacyclopentadiene complex did not provide hexamethyl mellitate under mild conditions; thus, the authors postulated that hexamethyl mellitate was being formed by the reaction of palladacyclopentadiene complex with palladium−alkyne complex. Canovese and Elsevier et al.[206] reported a detailed kinetic study on the formation of palladacyclopentadienes in analogous reactions where the palladium was stabilized by bipyridine ligands.

2.8. Other Complexes of Zirconium, Titanium, Tantalum, and Niobium

The metals of group 4[207] have also proved to be active in [2 + 2 + 2] cycloaddition reactions. Zirconacyclopentadienes and titanacyclopentadienes with two Cp ligands [Cp_2M] are easily prepared and isolated from the oxidative coupling of two alkynes with a low-valent Zr or Ti precursor.[73,208,209] With these metals, it is possible to selectively synthesize asymmetrical zirconacyclopentadienes and titanacyclopentadienes by controlling the steric and electronic nature of the substituents.[210] One of the advantages of selectively having available asymmetrical metallacyclopentadienes is that if they react with a third alkyne they can generate in a highly selective manner polysubstituted benzene derivatives through [2 + 2 + 2] cyclotrimerization. The transition-metal-catalyzed cycloaddition of three different alkynes is a major challenge, since this totally intermolecular version is difficult to control and usually generates a mixture of different benzene derivatives, which is an important drawback for this process. It is important to note that with these metals

Scheme 58. Palladium−Triyne Complex Isolated by Itoh et al.[203]



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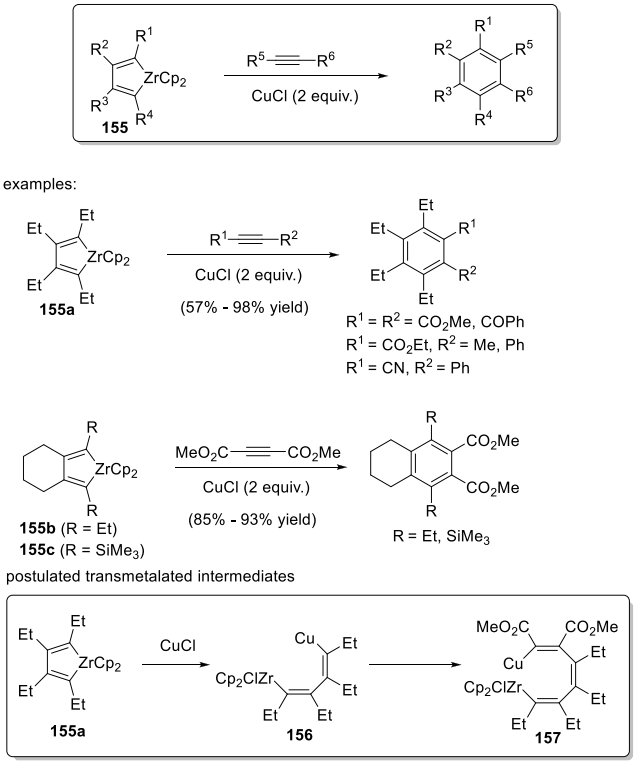
stoichiometric quantities are usually required to perform the cycloaddition.

Takahashi et al.[211] studied the regioselective synthesis of zirconacyclopentadienes from the oxidative coupling of two different alkynes with a low-valent zirconocene precursor. However, due to the low nucleophilicity of the zirconacyclopentadiene, a third unsaturation was not able to insert itself in the Zr−C bond and, therefore, no benzene derivative was generated. In order to afford the cycloaddition of the zirconacyclopentadiene with a third alkyne, the presence of stoichiometric quantities of other metals[212,213] such as copper[214,215] or nickel[216] was required. These metals provoke the transmetalation from zirconium to the metal, and the new metal intermediate can incorporate the third alkyne. In the first studies, zirconacyclopentadiene **155**, which was selectively prepared from two identical or different alkynes, was treated with an alkyne in the presence of stoichiometric quantities of CuCl to afford benzene derivatives in excellent yields. However, the third alkyne needs to have an electron-withdrawing group and be nonterminal (see specific examples **155a**, **155b**, and **155c** in Scheme 59). Given that zirconacyclopentadiene **155a** did not

Scheme 59. Cycloaddition of Zirconacyclopentadienes to Alkynes Using Copper Salts



react with dimethyl acetylenedicarboxylate in the absence of CuCl, the authors postulated that a transmetalation step from zirconium to copper may occur and that structures **156** and **157** were possible intermediates. Michael-type addition of dienylcopper intermediate **156** to dimethyl acetylenedicarboxylate justified the third alkyne having an electron-withdrawing group (Scheme 59).

In addition, the authors also established a one-pot procedure starting from $[Cp_2ZrCl_2]$ that gave good yields of the corresponding benzene derivatives. The asymmetrical zirconacyclopentadiene **155** was prepared by stepwise addition of two different alkynes. The path proposed for this process is shown in Scheme 60. First of all, a zirconacyclopentane **158** was formed in the presence of ethylene. The two alkynes then reacted gradually with **158**, affording zirconacyclopentadiene **155**, which finally, with the third alkyne and in the presence of CuCl, gave the cycloaddition reaction that generated the benzene derivative in good yields (Scheme 60).

The reaction of different zirconacyclopentadienes with alkynes bearing at least one electron-withdrawing group attached to the triple bond to afford [2 + 2 + 2] cycloaddition reactions in the presence of CuCl has been studied by the same and other research groups. Haloterphenyl derivatives,[217] haloterphenyl compounds with chiral backbones,[218] polyacenes,[219] highly substituted phenylferrocenes,[220] and sterically hindered biaryls[221] were prepared using this process.

In order to overcome the problem that only electron-deficient and nonterminal alkynes were active in the reaction with zirconacyclopentadienes, Takahashi et al.[216] optimized the selective synthesis of benzene derivatives using a metal known to efficiently catalyze the [2 + 2 + 2] cycloaddition such as nickel instead of copper. Using stoichiometric quantities of $[NiBr_2(PPh_3)_2]$, the reaction of zirconacyclopentadienes **155** with a wide range of alkynes (alkyl-, aryl-, and trimethylsilylalkynes, alkynes with electron-withdrawing and electron-donating groups, and also terminal alkynes) selectively afforded excellent yields of the benzene compounds. It is important to note that no homocyclotrimerization of the third alkyne took place in any case. In order to deepen the understanding of the mechanism of the process, tetraphenylzirconacyclopentadiene **155d** was treated with $[NiCl_2(dppe)]$ in THF at reflux, giving a 78% yield of the corresponding nickelacyclopentadiene **7b** as a red solid. The reaction of **7b** with 4-octyne afforded benzene derivative in a 54% yield. This result proved that the two Zr−C bonds in zirconacyclopentadiene **155d** simultaneously transmetalated to give **7b**, suggesting its role as an intermediate in the [2 + 2 + 2] cycloaddition (Scheme 61).

Kotora et al. also used $[NiX_2(PPh_3)_2]$ (X = Cl or Br) for the cycloaddition of zirconacyclopentadienes with alkynes such as ethynylferrocenes[220] and arylpropionates.[221] In the case of ferrocenyl derivatives, no electron-withdrawing group was required in the third alkyne to make the process efficient.

More recently, Xie et al.[222] reported the cycloaddition of zirconacyclopentenes **159** incorporating a carboranyl moiety with alkynes in the presence of nickel complexes to afford highly substituted benzocarboranes in good yields (Scheme 62). The reaction also worked efficiently using catalytic quantities of $[NiCl_2(PMe_3)_3]$ in the presence of an excess of $FeCl_3$. The role of $FeCl_3$ is to oxidize Ni(0) to Ni(II), which is the active catalytic species. The reaction of **159** ($R^1 = R^2 = Ph$) with $[NiCl_2(dppe)]$ in refluxing toluene afforded the corresponding nickelacyclopentene **160**, which they identified as a key intermediate in the cycloaddition. The structure of **160** was confirmed by NMR spectroscopy and X-ray diffraction studies.

Although the zirconacyclopentadiene derivatives mentioned above were considered as being inert with regard to the insertion of a third alkyne, Gambarotta et al.[223] prepared and characterized by IR and NMR spectroscopy and X-ray diffraction analysis three different zirconacyclopentadienes **161a−c**, with **161c** regiospecifically generated via a head-to-tail dimerization process, which were able to promote cyclotrimerization reactions with nonbulky alkynes without the presence of copper or nickel. The dmpe bisphosphine ligand (dmpe = 1,2-bis(dimethylphosphino)ethane) can easily dis-

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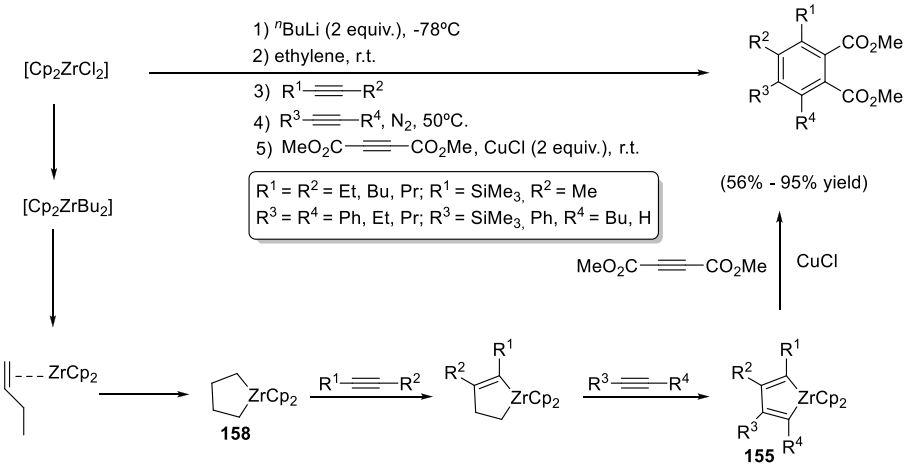
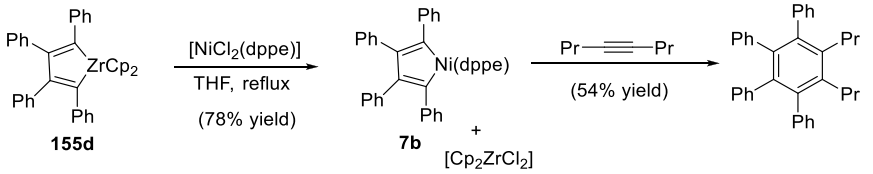
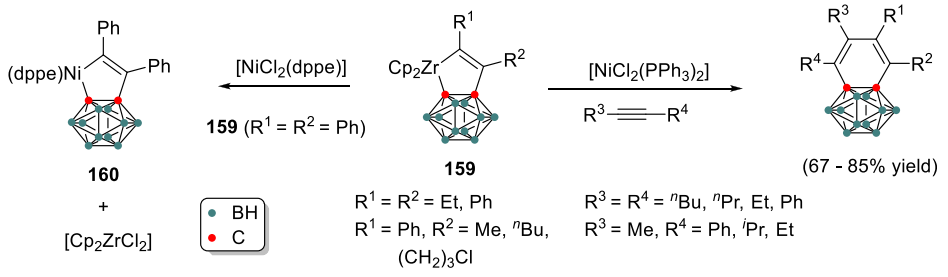
Scheme 60. Synthesis of Benzene Derivatives by One-Pot Reaction



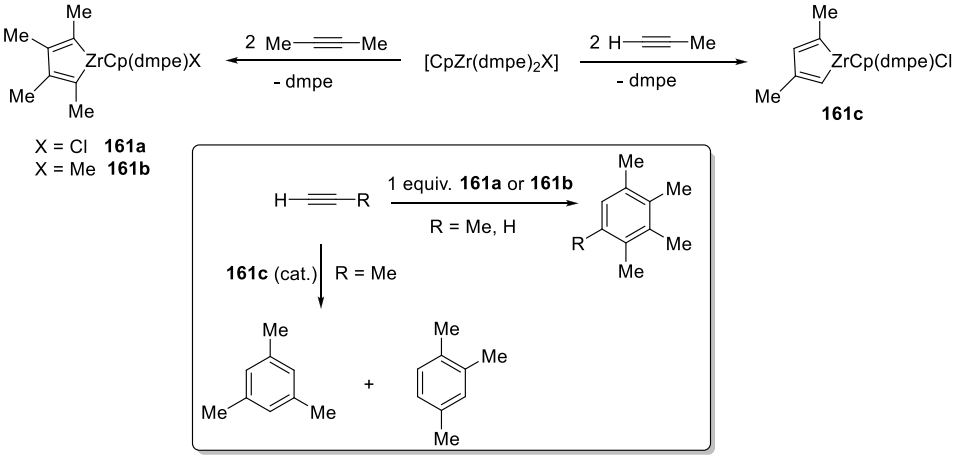
Scheme 61. Synthesis of Benzene Derivatives from Zirconacyclopentadiene 155d in the Presence of Nickel



Scheme 62. Cycloaddition of Zirconacyclopentene Containing a Carborane Unit with Alkynes in the Presence of Nickel



Scheme 63. Cyclotrimerization of Alkynes Promoted by Zirconacyclopentadienes 161



sociate from the zirconium and be substituted by alkyne ligands. The X-ray analysis of the three structures showed the apical position of the Cp ring, with the metallacycle occupying two equatorial positions and the biphosphine occupying one equatorial and one axial site in the complex. When complex **161c** was used as a catalyst, an equimolar mixture of 1,3,5- and 1,2,4-mesitylene was obtained (Scheme 63).

As stated in the above studies, the electronic and steric properties of an ancillary ligand may have an important effect on the reactivity of a transition metal complex. In this direction and

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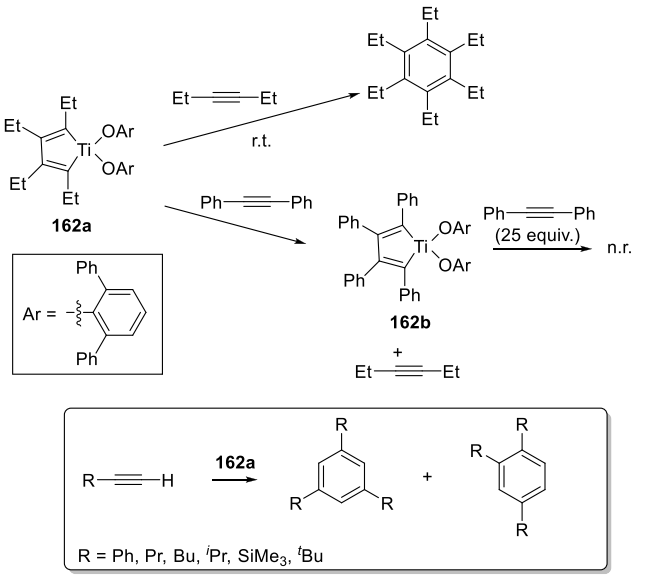
with regard to titanium, Rothwell et al.[224,225] described the synthesis of titanacyclopentadiene derivatives bearing ancillary bulky aryloxide ligands [$(ArO)_2M$]. Therefore, in contrast to [Cp_2Zr]-cyclopentadienes, which did not have a further reaction with a third alkyne, the aryloxide-containing titanacyclopentadiene **162a** reacted with an excess of 3-hexyne to afford hexaethylbenzene. However, when **162a** reacted with a bulkier alkyne such as diphenylacetylene, new titanacyclopentadiene **162b** was generated and its reaction with an excess of diphenylacetylene did not occur. Therefore, the reaction of **162a** with a third alkyne to obtain a benzene derivative is dependent on the steric hindrance of alkyne substituents. In addition, complex **162a** is an efficient catalyst for the cyclotrimerization of terminal alkynes, affording the corresponding benzene derivatives in good yields (Scheme 64). The regioselectivity toward 1,3,5- or 1,2,4-trisubstituted benzene derivatives was found to be dependent on the bulkiness of R (from 7:93 to 95:5).

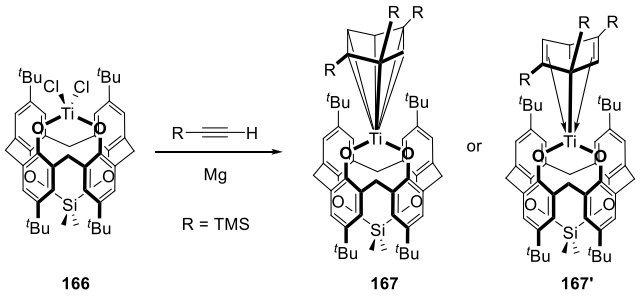
Scheme 64. Catalytic Activity of Titanacyclopentadiene 162a with Phenylphenoxide Ligands



Sato et al.[226] optimized what they called a metalative Reppe reaction based on the synthesis of a dialkoxytitanacyclopentadiene **163** from two different alkynes. Further reaction with ethynyl tolyl sulfone afforded aryltitanium derivative **164**, which after treatment with H^+ as an electrophile resulted in the regioselective formation of 1,2,4-trisubstituted benzene derivative in moderate yields (Scheme 65). The SO_2Tol group in the third alkyne had an important role in the cyclotrimerization, since after insertion of ethynyl tolyl sulfone in the titanacyclopentadiene **163**, by formation of either postulated intermediates **165a** or **165b**, the final step consisted of the elimination of the sulfonyl group rather than the reductive elimination of the metal that is seen in the common mechanistic proposal for this process.

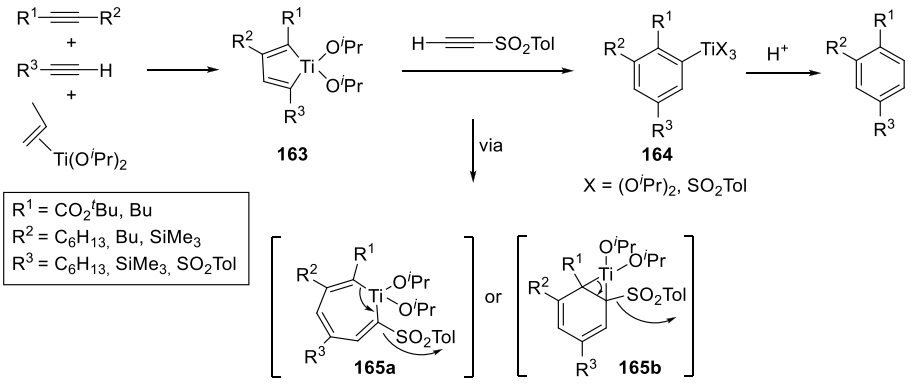
Ladipo et al.[227−229] described the highly regioselective cyclotrimerization of three terminal alkynes using titanium as the transition metal (Scheme 66). In their studies, titanium

Scheme 66. Synthesis of Arene Complexes of Titanium Described by Ladipo et al.[227−229]



complex **166** was supported by a 1,2-alternate dimethylsilyl-bridged *p*-tert-butylcalix[4]arene (DMSC) bis(aryloxide) ligand. Due to the steric environment imposed on titanium by the calixarene cavity, the cycloaddition resulted in being highly regioselective. When **166** reacted with an excess of trimethylsilylacetylene in the presence of activated magnesium, a Ti−arene complex was obtained and fully characterized by NMR spectroscopy and X-ray diffraction analysis. The complex can be described either as Ti(II)−η^6-arene complex **167** or 7-titananorbornadiene Ti(IV) complex **167′**. The geometrical parameters determined by X-ray diffraction (especially the folding of the arene ring) suggested that the latter (**167′**) better described the complex being obtained. However, complex **167′** was not obtained when **166** was treated with magnesium in the presence of 1,2,4-$C_6H_3(SiMe_3)_3$, demonstrating that arene complex **167′** was involved in the cyclotrimerization process. Complex **167′** is an effective catalyst for the cyclotrimerization

Scheme 65. Metalative Reppe Reaction Described by Sato et al.[226]



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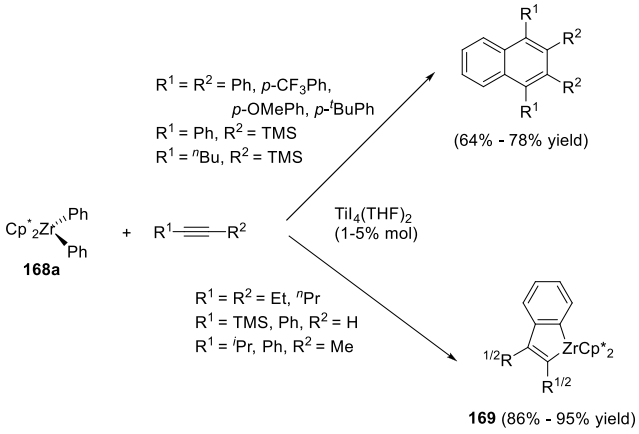
of terminal alkynes affording excellent yields of 1,2,4-trisubstituted benzene derivatives with high regioselectivity. Complex **167′** was the resting state of the catalyst in the [2 + 2 + 2] cyclotrimerization of $Me_3SiC{\equiv}CH$. Kinetic studies following the reaction at several time intervals by ^1H NMR spectroscopy were performed adding an excess of trimethylsilylacetylene to complex **167′**. Given that the reaction showed first-order on [**167′**] and [alkyne], the authors concluded that the rate-determining step was the displacement of the 1,2,4-trimethylsilylbenzene. The failure of the bulky or nonterminal alkynes to react with **167′** was postulated as being due to their inability to displace the arene ligand. After this study, the authors concluded that the arene species were involved in the rate-determining step of the [2 + 2 + 2] cyclotrimerization of alkynes.

In a recent paper by Reiner and Tonks,[230] diarylmetallocenes of type $[Cp_2MAr_2]$ (M = Zr, Ti) **168** were used as aryne precursors for titanium-catalyzed [2 + 2 + 2] cycloaddition of arynes with alkynes (Scheme 67). Only alkynes with bulky

Scheme 67. Diphenylzirconacene 168a as a Benzyne Precursor for Ti-Catalyzed [2 + 2 + 2] Cycloaddition Described by Reiner and Tonk[230]s



substituents afforded naphthalene derivatives in high yields. With less hindered alkynes, zirconaindene **169** was isolated as the major product. When **169** was heated with more alkyne, no naphthalene derivative was obtained.

As a plausible mechanism, the authors proposed an initial oxidative coupling of Ti(II) species to two molecules of alkyne to afford titanacyclopentadiene **170**. Further reaction of **170** with a Zr−benzyne adduct **171** generated **172**, either by a transmetalation process or by a [4 + 2] cycloaddition reaction, to give naphthalene derivative after a reductive elimination process. Confirmation of Cp^*_2Zr−benzyne adduct as an intermediate was achieved by performing an experiment starting with $[Cp_2Zr(p\text{-tolyl})_2]$ **168b** that gave isomeric naphthalene derivatives (Scheme 68). The formation of the two regioisomeric naphthalene derivatives only can be explained via an isomerization process of an aryne intermediate.

Nb[231] and Ta as group 5 metals have also promoted [2 + 2 + 2] cycloaddition reactions. Wigley et al.[232−234] described the synthesis of tantallacyclopentadiene complexes containing alkoxide ligands **173a** that did not react with an excess of *tert*-butylacetylene. However, on heating **173a** at 90 °C, an isomerization process took place affording the less congested tantallacyclopentadiene **173b**. Kinetic studies to shed light on this isomerization process indicated that the formation of a bis(alkyne) complex did not take place but rather **173a** lost a *tert*-butylacetylene, generating a metallacyclopropene intermediate. Further reaction of **173b** with *tert*-butylacetylene generated the η^6-arene complex **174**. When **174** was treated with an excess of the same alkyne, 1,3,5-tris-*tert*-butylbenzene cycloadduct was obtained together with the regenerated **173a**, demonstrating the role of **173b** and **174** as intermediates in the process (Scheme 69).

Takai, Yamada, and Utimoto[235] described a tantallacyclopropene generated from an internal acetylene and a low-valent tantalum ($TaCl_5$/Zn) as the first intermediate in the cycloaddition of alkynes and diynes. The tantallacycle was prepared *in situ* and was not isolated.

Dinuclear tantalum complexes are also active in [2 + 2 + 2] cycloaddition reactions. Yamamoto, Tsurugi, and Mashima[236] synthesized several ditantallacyclopentadiene complexes bridging two tantalum atoms (Scheme 70). These dinuclear complexes were active as catalysts in the cyclotrimerization of internal alkynes. In this study, in order to detect some intermediates in the cycloaddition reaction, ditantalum complex **175** was prepared and treated with two alkynes: 2-butyne, an internal acetylene, and 1-hexyne, a terminal acetylene. In the first case, arene complex **176** was obtained and further heating of **176** at 80 °C induced rotation by 60° of the $C_6Et_4Me_2$ ligand and afforded complex **176′**, which is thermodynamically more stable than **176**. Complex **177** was obtained at −78 °C and after being warmed to room temperature **177′** was generated due to the rotation of the arene. Based on these experimental results, the authors postulated that the reaction proceeded through an intermolecular [4 + 2] cycloaddition instead of an insertion and further cyclization pathway. This is due to the restricted rotation of the arene ligands on the tantalum center.

The arene dinuclear complexes **176** and **177** were not active as catalysts in the cycloaddition of alkynes. The authors postulated that this is due to the nonlability of the arene ligand. However, these complexes can be considered a model for the most advanced intermediate in the catalytic cycle of a [2 + 2 + 2] cycloaddition process.

In the case of niobium complexes, niobacyclopropene complex **178** generated by the reduction of $[CpNbCl_4]$ with Mg in the presence of phenylacetylene was postulated as a first intermediate in the cycloaddition of terminal alkynes by the group of Livinghouse.[237] The isolation and characterization of **178** were not successful,[238,239] but evidence of its formation was corroborated by its capture by PhNCO to afford a cinnamide derivative (Scheme 71).

Fujihara et al.[240] described the catalytic activity of a dinuclear niobium(III) complex **179** in the cycloaddition of a wide range of alkynes, finding that those that had electron-withdrawing groups were more easily cyclotrimerized (Scheme 72).

When niobium complex **179** reacted with 6 equiv of 3-hexyne, apart from the hexaethylbenzene generated, niobacyclopentadiene **180** was also obtained, which was characterized by NMR and mass spectrometry (Scheme 73). The reaction of **179** with 2-hexyne was monitored by NMR and dinuclear Nb(V) complex **181** was identified and postulated as the first intermediate formed in the catalytic cycle. In addition, when the reaction of 2-hexyne and 0.5 equiv of **179** was monitored, signals assigned to benzene derivative and tetrahydrothiophene ligand were observed. All of these experiments suggested that the rate-determining step of the catalytic process was the insertion of the second alkyne to intermediate **181**. In any of these experiments, niobacyclopentadiene **180** was detected,

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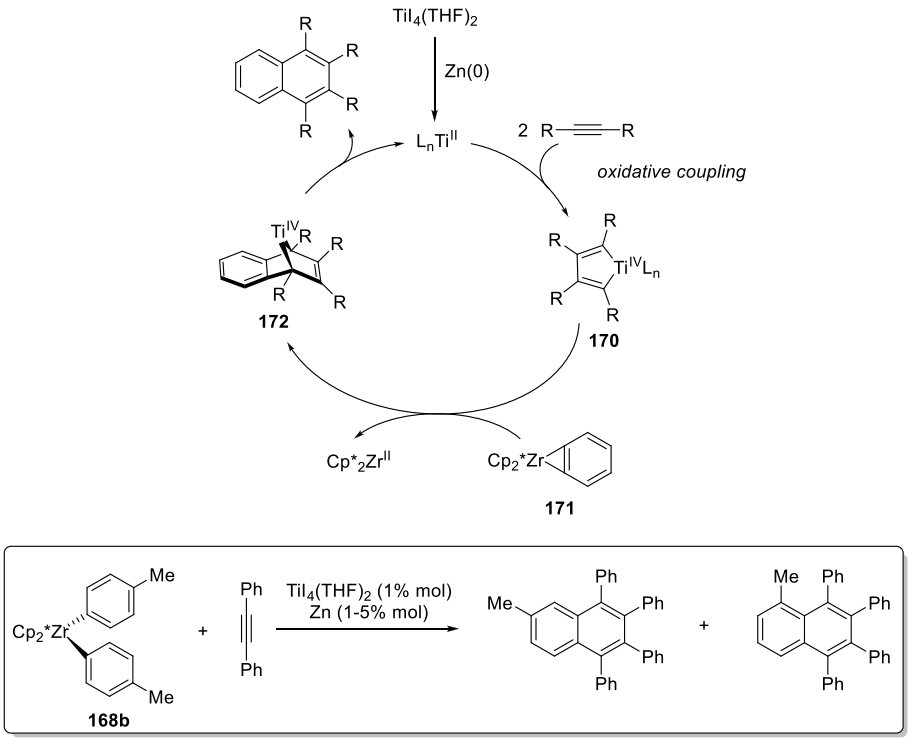
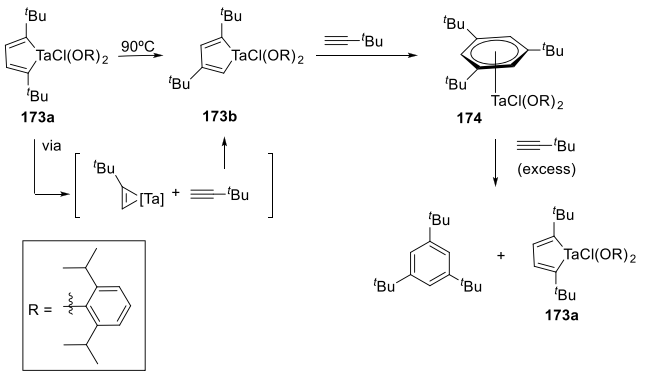
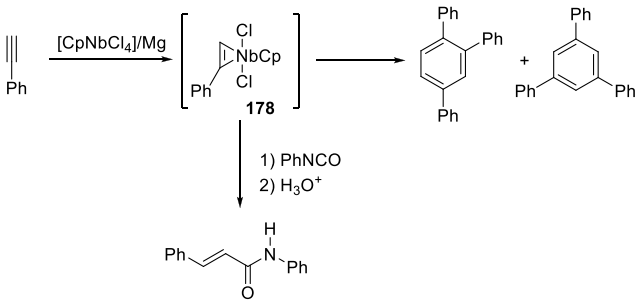
Scheme 68. Postulated Mechanism for Cycloaddition of Scheme 67



Scheme 69. Conversion of Tantallacyclopentadiene 173a to η^6-Arene Ta Complex 174 Described by Wigley et al.[232−234]

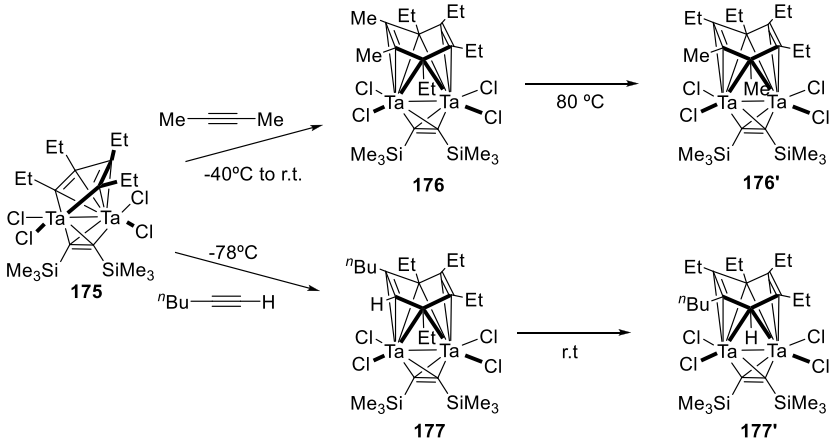


Scheme 71. Niobacyclopropene 178 as an Intermediate of the Cyclotrimerization of Alkynes



suggesting that it was formed by degradation of a dinuclear complex **182**, which is supposed to be one of the relevant

Scheme 70. Synthesis of Dinuclear η^6-Arene Tantalum Complexes by Yamamoto, Tsurugi, and Mashima[236]



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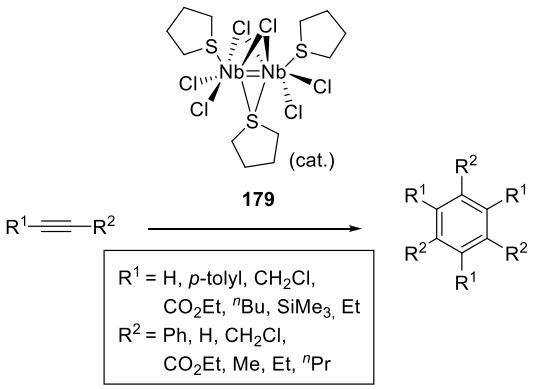
Scheme 72. Dinuclear Niobium Complexes as Catalysts for the Cyclotrimerization of Alkynes



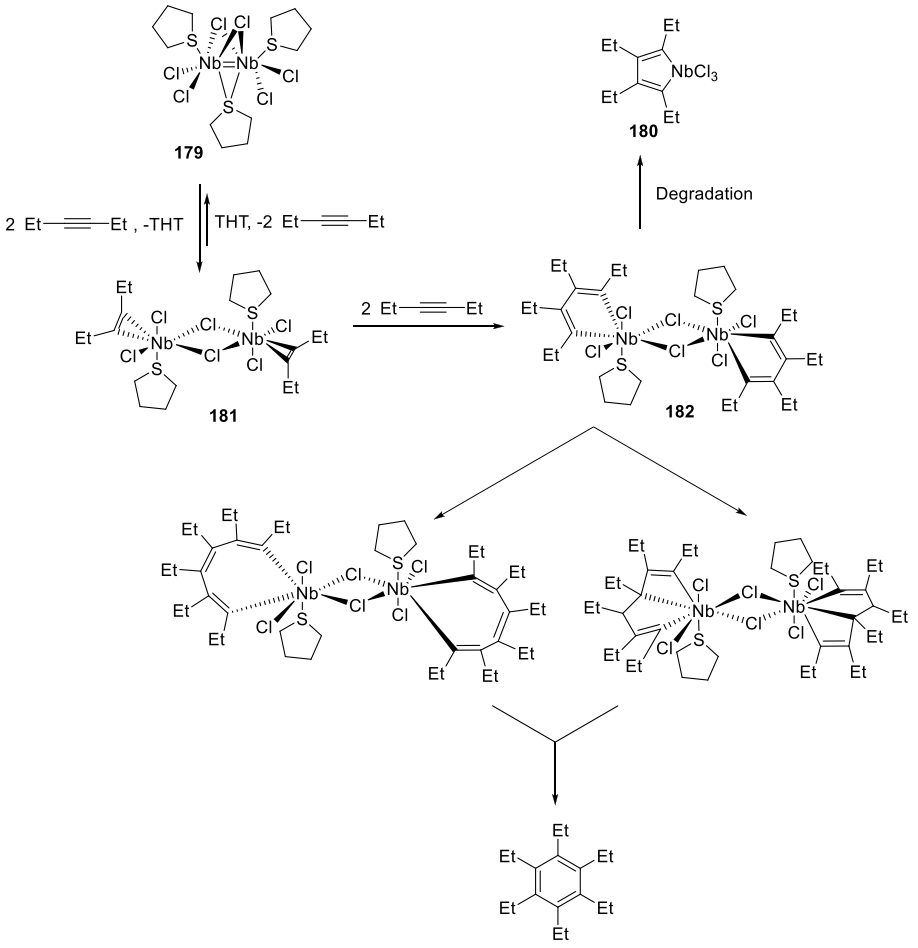
intermediates in the catalytic cycle. Unfortunately, no more advanced intermediates involving the third alkyne were observed, although it was postulated that all intermediates had a dinuclear structure. In a subsequent paper, Fujihara et al.[241] performed SVWN/6-31+G(2d)~SDD calculations to prove that the catalytically active species has a dinuclear structure. They found that dissociation of the dinuclear $[\{NbCl_2(Me_2S)(\eta^2\text{-}CH_3C{=}CCH_3)\}_2(\mu\text{-}Cl)_2]$ complex into two mononuclear $[NbCl_3(Me_2S)(\eta^2\text{-}CH_3C{=}CCH_3)]$ species with distorted bipyramidal structure has an energetic cost of 35.4 kcal/mol and, therefore, mononuclear complexes cannot be formed from dinuclear species at the operating room temperature.

3. [2 + 2 + 2] CYCLOADDITION OF TWO ALKYNES AND CN MULTIPLE BONDS

The transition-metal-catalyzed [2 + 2 + 2] cycloaddition of two alkynes and a nitrile molecule has received considerable attention as a straightforward way to obtain substituted pyridines, especially due to their atom-economical, environmentally benign, and convergent synthetic nature.[16−19]

Following the general postulated mechanism for the [2 + 2 + 2] cycloaddition reaction (Scheme 8), when the third unsaturation is different from an alkyne such as a nitrile, there are two possible initial steps in the process. One is that there is an oxidative coupling taking place between the two acetylenes and further insertion of the nitrile to the metallacyclopentadiene **IIIa** or metallacyclopentatriene **IIIb** (Scheme 74, equation a). The second possibility is that the oxidative coupling takes place between an alkyne and a nitrile, affording an initial azametallacycle (**IIIc**) before the insertion of the second alkyne (Scheme 74, equation b). Several theoretical studies have addressed these two possibilities. Although many metallacyclopentadienes generated from oxidative coupling of two alkynes have been isolated, characterized, and identified as reaction intermediates in the cycloaddition processes, isolated azametallacyclopentadienes are scarcer.

Scheme 73. Postulated Mechanism for the Cyclotrimerization of Alkynes by Dinuclear Niobium Complex 179



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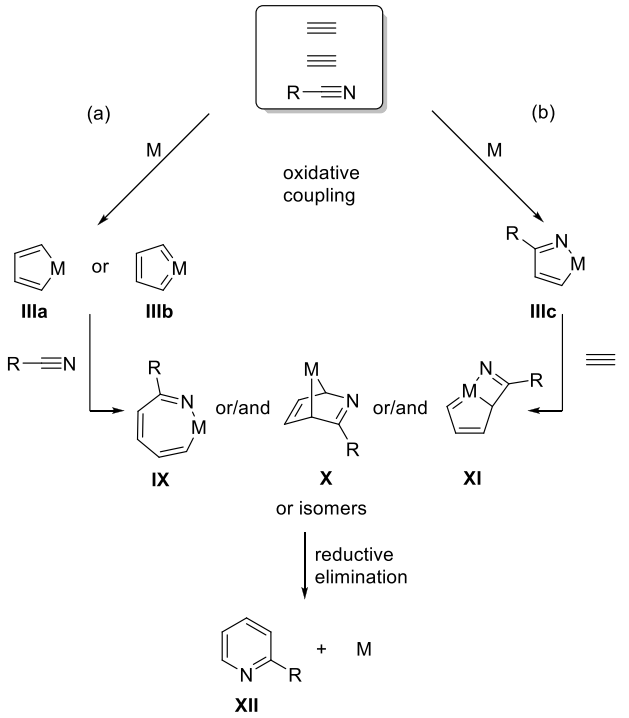
Scheme 74. Two Possible Pathways for Alkyne and Nitrile Cycloaddition

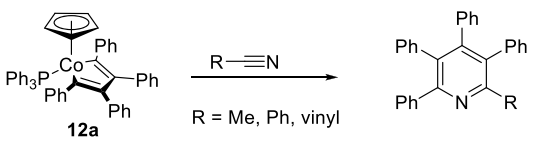


In all reported azametallacyclopentadiene, azametallacycloheptatriene, and azametallabicyclo[3.2.0]heptatriene intermediates, the N is located in the α-position with respect to the metal. Calculations by Koga et al.[242] found that, for the CpCo catalyst, the azacobaltacycloheptatriene with the N in the α-position is more stable than that in the β position by 2.6 kcal/mol. In the case of the azacobaltabicyclo[3.2.0]heptatriene, the difference is even larger (9.7 kcal/mol). Similarly, for the $[OsCl_2(SNC_2H_3)(PH_3)_2]$ azaosmathiophenes, the most stable isomer is the one having the N in the α-position.[243] To our knowledge, no study discussing the reasons for the preference of the α-position of the N atom in these intermediates has been reported yet. However, it is likely that the σ-donor properties of N through its lone pair and the shape of the LUMO orbital with the largest lobe in the C atom favor coupling or insertion with N in the α-position.

3.1. Cobalt Complexes

One of the first studies to prepare pyridines by the reaction of an isolated cobaltacyclopentadiene with 1 equiv of a nitrile was performed by Wakatsuki and Yamazaki.[244,245] The same cobaltacycle intermediate **12a** that was used by the authors in the reaction with alkynes to afford benzene derivatives (Scheme 5) has also been used by them with nitriles to obtain moderate to good yields of pyridine derivatives (Scheme 75). In addition, Co complex **12a** was shown to catalyze the cycloaddition of 2 mol of acetylene and 1 mol of nitrile to afford the corresponding pyridine derivative. As a drawback, mixtures of regioisomers were obtained when alkynes were not symmetrical, although sometimes the regioselectivity could be controlled by the substituents of the alkynes. Therefore, oxidative coupling of the two alkynes before inserting the nitrile scaffold was shown to be a plausible mechanistic pathway in Co-catalyzed cycloaddition of alkynes and nitriles.

Scheme 75. Synthesis of Pyridines from Co Complex 12a and Nitriles



Saá et al.[246,247] found that the [2 + 2 + 2] cycloaddition of 5-hexynenitrile and 1,4-bis(trimethylsilyl)-1,3-butadiyne catalyzed by $[CpCo(CO)_2]$ (R = TMS in Scheme 76) produced a 77% yield of pyridine **184a**, whereas pyridine **184b** was not observed. This high regioselectivity was explained through theoretical calculations at the B3LYP/LANL2DZ level of theory of species in Scheme 76 with R = SiH_3 (a simplified model of TMS) and R = H. The authors calculated the energy of the cobaltacyclopentadiene complexes **183a** and **183b** and found that **183a** was more stable than **183b** by 4.3 (R = SiH_3) and 5.8 (R = H) kcal/mol. In the case of an electron-donating group such as the SiH_3, the LUMO orbital of the butadiyne derivative has the largest lobe in the substituted C atom, and therefore, **183a** should be the preferred isomer according to the Stockis and Hoffmann[109] findings indicating that the C atom with the biggest LUMO lobe in the oxidative coupling process of two alkynes is located β to the metal. Taking into account that both electronic and steric effects are relevant in R = SiH_3 and only steric factors are important in R = H and that electronic and steric factors have opposite regioselective preferences, the authors concluded that the electronic factors are responsible for the formation of **183a** that leads exclusively to **184a**.

The first DFT study of a cobalt-catalyzed formation of pyridine from two acetylenes and a hydrogen cyanide was carried out by Kirchner et al.[248] in 2006 with the B3LYP/6-31G(d,p)~SDD method using a cyclopentadienylcobalt catalyst (Scheme 77). As in the case of the cyclotrimerization of acetylene, the first step corresponded to the oxidative coupling of the two acetylene molecules that formed the cobaltacyclopentadiene intermediate **30** with a Gibbs energy barrier of 12.5 kcal/mol. The alternative oxidative coupling between an acetylene and a hydrogen cyanide to form an azacobaltacyclopentadiene intermediate with the N atom in the α-position with respect to the Co had a higher energy barrier (16.5 kcal/mol). Hydrogen cyanide coordinated to the cobaltacyclopentadiene intermediate in an η^2 fashion and inserted to give an azacobaltabicyclo[3.2.0]heptatriene intermediate **186** in which the N atom occupied an α-position. By reductive elimination, this intermediate led to an η^4-pyridine complex **187** that released pyridine after complexation of two acetylene molecules. This insertion pathway was favored over the intramolecular [4 + 2] cycloaddition of the hydrogen cyanide to the cobaltacyclopentadiene intermediate. This study was performed exclusively in the singlet state potential energy surface. However, as discussed in section 2.2, whereas 18-electron cobalt complexes have a singlet ground state, the 16-electron cobalt species have a triplet ground state. Therefore, the [2 + 2 + 2] cycloaddition of two acetylenes and a hydrogen cyanide is expected to be a two-state reactivity process.

Three years later, Koga et al.[242] studied the same [2 + 2 + 2] cycloaddition with acetonitrile instead of hydrogen cyanide and now considering both the singlet and triplet potential energy surfaces. The investigation was performed at the B3LYP/6-31G(d,p) level of theory, and some conclusions differ from the study of Kirchner et al.[248] As in the previous study by the same

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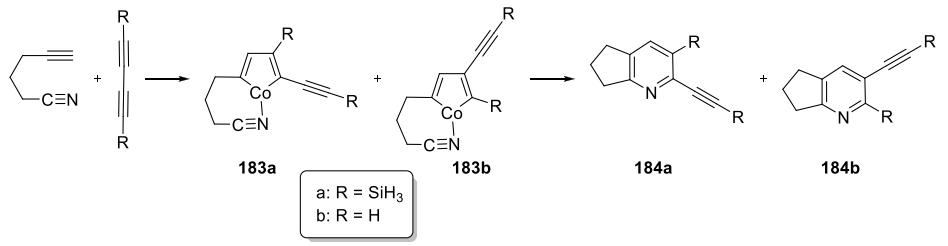
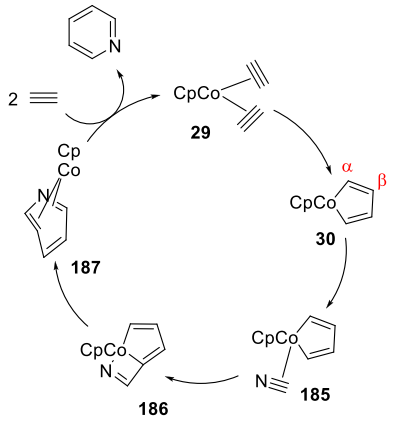
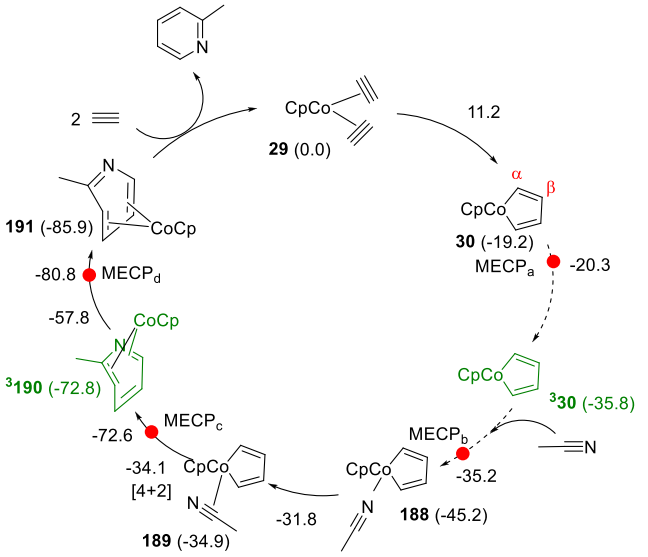
Scheme 76. [CpCo(CO)$_2$]-Catalyzed [2 + 2 + 2] Cycloaddition of 5-Hexynenitrile and 1,3-Butadiyne Derivatives



Scheme 77. Reaction Mechanism Reported by Kirchner et al.[248] for the Cobalt-Catalyzed Cycloaddition of Two Acetylenes and Hydrogen Cyanide



Scheme 78. Reaction Mechanism Reported by Koga et al.[242] for the Cobalt-Catalyzed Cycloaddition of Two Acetylenes and an Acetonitrile[a]



[a]In green are the species that have a triplet ground state. MECPs, depicted in red, are minimum-energy crossing points. All relative energies are ZPE corrected and are given in kcal/mol.

group of the [2 + 2 + 2] cyclotrimerization of three acetylenes,[107] the first step corresponded to the oxidative coupling of two acetylenes, leading to the cobaltacyclopentadiene **30** after surmounting a Gibbs energy barrier of 11.2 kcal/mol. There is then a surface hopping from the singlet to the s78 triplet state through a crossing point (MECP$_a$ in Scheme 78) located close in energy (at −1.1 kcal/mol) and structure to singlet **30** to form ^{3}**30**. This latter intermediate interacts with the acetonitrile to give the singlet η^1 complex **188** with a Co−N bond length of 1.833 Å. The end-on (σ-coordination) complex **188** rearranges to the side-on (π-coordination) intermediate **189** that undergoes an intramolecular [4 + 2] cycloaddition through an early transition state with a small activation energy of 0.8 kcal/mol to yield the ^{3}**190** with a triplet ground state that transforms first to ^{3}**191**, surmounting a barrier of 15.0 kcal/mol and then moving through a crossing point (MECP$_d$ in Scheme 78) to the final **191** complex in the singlet state. This latter complex adds two acetylenes and releases the final product to regenerate the active intermediate **29**. The authors compared this mechanism via intramolecular [4 + 2] cycloaddition and the mechanisms through an intermolecular [4 + 2] cycloaddition and found the former to be more favorable. Schore's mechanism involving the azacobaltabicyclo[3.2.0]heptatriene and the azacobaltacycloheptatriene intermediates was ruled out because it was not possible to connect **30** with any of the two azacobaltabicyclo[3.2.0]heptatriene intermediates located. Therefore, the whole [2 + 2 + 2] cycloaddition of two acetylenes and an acetonitrile was found to be a two-state reactivity process similar to that described in Scheme 16 for the cyclotrimerization of three acetylenes. The main difference is that complex ^{3}**30** in Scheme 16 suffers a surface hopping and a subsequent direct intramolecular [4 + 2] cycloaddition to generate the final benzene molecule coordinated to [CpCo] spontaneously.

In a subsequent study, Dahy and Koga[249] analyzed the same [2 + 2 + 2] cycloaddition reaction but now with HCN and F_3CCN instead of H_3CCN. They found that for HCN and F_3CCN the C≡N bond inserts into the Co—C bond in the singlet state to form an azacobaltacycloheptatriene intermediate instead of the intramolecular [4 + 2] cycloaddition operative for acetonitrile. By reductive elimination, the azacobaltacycloheptatriene intermediate yielded the pyridine ring. The difference found in the reaction mechanism was rationalized in terms of the energies of the frontier orbitals, so that an electron-donating group such as the methyl group destabilizes the HOMO and prefers a [4 + 2] cycloaddition and an electron-withdrawing group such as the trifluoromethyl lowers the LUMO and favors insertion.

Malacria, Aubert, and Gandon et al.[250] studied computationally at the B3LYP/6-31G(d,p) level the formation of aminopyridines through CpCo-catalyzed [2 + 2 + 2] cycloaddition of *N*-ethynylpent-4-ynamine and acetonitrile. Calculations suggested that 3-aminopyridines are formed by formal intramolecular [4 + 2] cycloaddition between the nitrile and the intermediate cobaltacyclopentadiene. On the other hand, 4-aminopyridines are obtained from the insertion pathway via a cobaltacycloheptatriene complex. Calculated Gibbs energy

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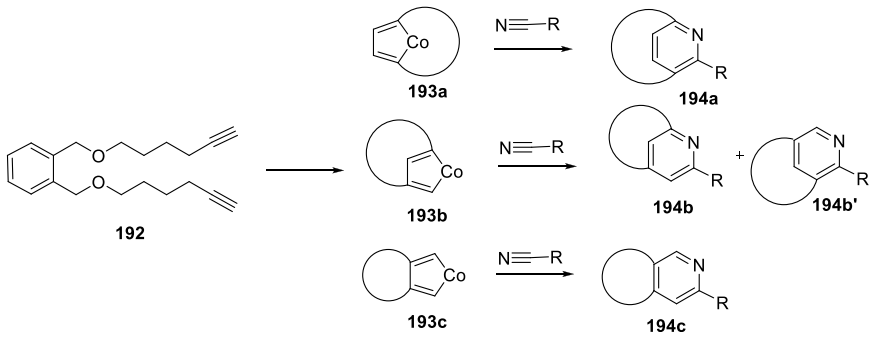
Scheme 79. [$CpCo(CO)_2$]-Catalyzed [2 + 2 + 2] Cycloaddition of Several α,ω-Diynes with Possible Cobaltacyclopentadiene Intermediates and Products Formed



barriers favor the insertion ($\Delta G^{\ddagger}$ = 11.8 kcal/mol) over the intramolecular [4 + 2] cycloaddition ($\Delta G^{\ddagger}$ = 13.9 kcal/mol), which is in agreement with the experimental result that 4-aminopyridines are the major product when ynamides bear no substituent on the terminal alkyne. Although previous work by Dahy and Koga[249] indicated that electron-rich acetonitrile reacts with cobaltacyclopentadienes via a [4 + 2] cycloaddition, Malacria, Aubert, and Gandon et al.[250] found that the presence of the amino group in the cobaltacyclopentadiene intermediate makes the insertion pathway more favorable. As discussed before, subtle balances determine the reaction pathway followed in [2 + 2 + 2] cycloadditions.

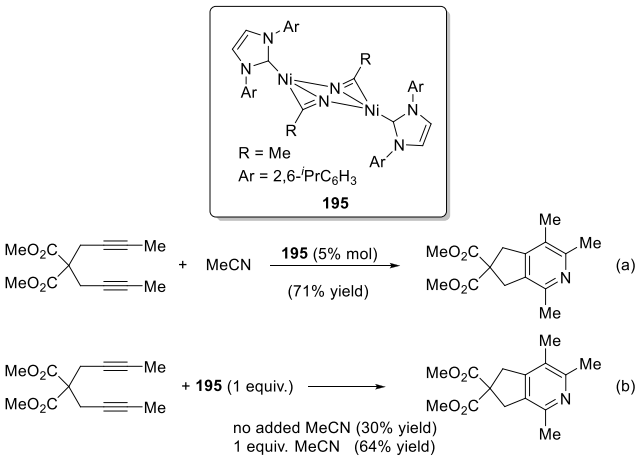
B3LYP/6-31G(d) calculations including solvent effects of a toluene solution were performed by Prieto and García et al.[251] for the [2 + 2 + 2] cycloaddition of *N*-methyldipropargylamine and benzonitrile. Starting from [$CpCo(CO)_2$], displacement of two CO molecules by *N*-methyldipropargylamine had a cost of 28.4 kcal/mol. Formation of this first intermediate is a slow process that took place during the induction period. The [$CpCo$(*N*-methyldipropargylamine)] underwent easy oxidative coupling ($\Delta G^{\ddagger}$ = 7.3 kcal/mol) to generate the cobaltacyclopentadiene intermediate that relaxed to the triplet state and, in the next step, benzontrile enters the coordination sphere of Co to generate a singlet intermediate with benzonitrile η^2 coordinated to the cobaltacyclopentadiene intermediate. Intramolecular metal-assisted [4 + 2] cycloaddition in this intermediate yielded a [$CpCo(\eta^4$-azaarene)] complex overcoming a barrier of 11.9 kcal/mol. Although other reaction pathways were analyzed, they were ruled out, since intramolecular [4 + 2] cycloaddition was the kinetically most favorable reaction path.

The synthesis of macrocycles from [2 + 2 + 2] cycloadditions of α,ω-diynes with nitriles in the presence of [$CpCo(CO)_2$] was studied by Maryanoff et al.[252] Scheme 79 depicts one of the α,ω-diynes used in the cycloadditions and the possible cobaltacyclopentadiene intermediates that could be formed as well as the resulting products. B3LYP/6-31G~LACVP calculations indicated that, in the case of 1,17-diyne **192**, the α,α'-substituted cobaltacycle intermediate **193a** (head-to-head coupling) was 0.5 kcal/mol more stable than the α,β-substituted cobaltacyclopentadiene intermediate **193b** (head-to-tail and tail-to-head) and 7.5 kcal/mol more stable than the β,β'-substituted cobaltacycle intermediate **193c** (tail-to-tail). This thermodynamic result was in agreement with the fact that experimentally cycloaddition of **192** with different nitriles yielded a mixture of regioisomeric products **194a** and **194b**, **194b'** in a ratio close to 1:1. Similar calculations assuming that energy barriers for the oxidative couplings follow the same trends as the reaction energies were used to justify the outcomes of several α,ω-diynes.

3.2. Nickel Complexes

Louie et al.[253] have attempted to decipher the mechanism of the cycloaddition involving nitriles under catalysis by nickel. In 2012, they described the synthesis and characterization of a dimeric NHC−Ni complex [$Ni(NHC)RCN]_2$ **195** and its use as a catalyst for the cycloaddition of diynes and nitriles to afford pyridines (Scheme 80, equation a). Nickel derivative **195** shows

Scheme 80. Catalytic Activity of Dimer Nickel Complex 195 Described by Louie et al.[253]



each nitrile to be complexed via the nitrogen lone pair (η^1-nitrile) by one of the nickel atoms and through the C≡N π-orbital (η^2-nitrile) by the other. In this study, the authors carried out an interesting mechanistic study trying to shed light on which intermediates were involved in the cycloaddition reaction when nitriles participate as unsaturations as well as on the role of this dimeric complex. Kinetic analysis of the cycloaddition represented in Scheme 80 performed using ^{1}H NMR spectroscopy showed that the reaction had first-order dependence only with regard to the nickel dimer complex **195**. In addition, stoichiometric competitive studies were performed observing that the addition of the free nitrile to the reaction mixture increased the yields of the cycloadduct (from 30 to 64% yield, Scheme 80, equation b). After additional dimer crossover and ligand exchange experiments, the mechanistic proposal shown in Scheme 81 was postulated.

The process starts with a partial nickel dimer opening, by breaking of one of the η^1-nitrile coordination, which is

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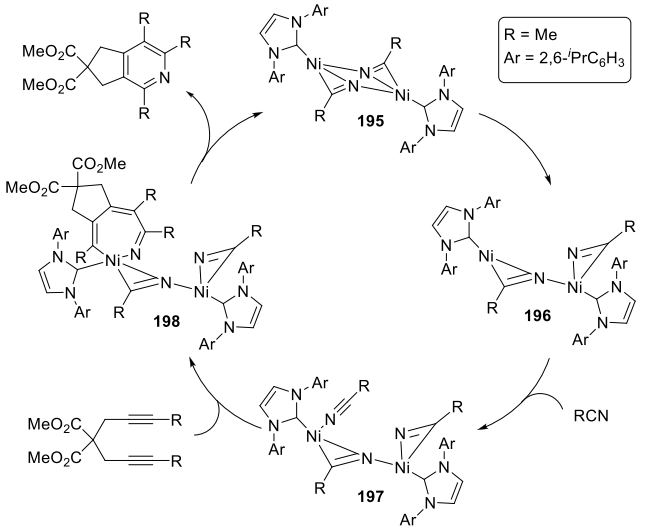
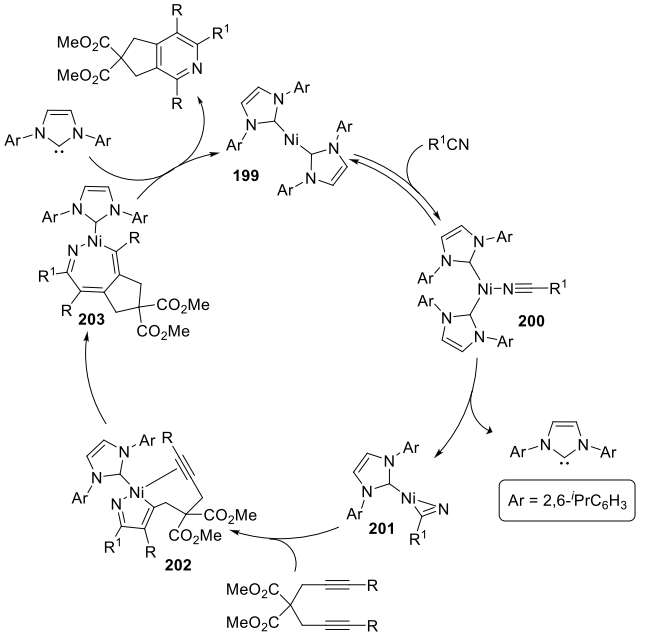
Scheme 81. Proposed Mechanism for the Cycloaddition of Diynes and Nitriles Catalyzed by Nickel Complex 195



postulated as being the rate-determining step, to afford intermediate **196**. In the next step, an exogenous nitrile coordinates at the less saturated Ni atom and subsequent oxidative heterocoupling takes place with the diyne. A competing pathway must also be operative to account for the incorporation of the nitrile initially contained in the dimer. After a reductive elimination step, pyridine was formed. With this proposal, the authors concluded that the catalyst maintains a bimetallic structure in the catalytic cycle.

The following year, Louie et al.[254] made a further mechanistic study of the same cycloaddition reaction but this time using a nickel monomeric complex $[Ni(NHC)_2]$ **199** as the catalyst. In contrast to the Ni−NHC dimer, when $[Ni(NHC)_2]$ was used, the kinetic studies showed a strong dependence of the reaction rate on the nature of the nitrile used as well as the steric bulk and electronic effects of the carbene ligands. In addition, the study of stoichiometric transmetalation reactions and the regioselectivity of the cycloaddition allowed the authors to propose the mechanistic scenario shown in Scheme 82.

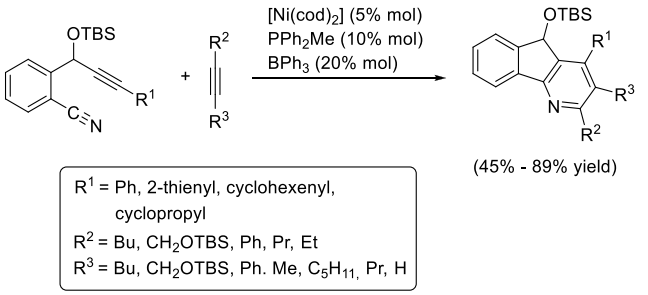
Scheme 82. Proposed Mechanism for the Cycloaddition of Diynes and Nitriles Catalyzed by Nickel Complex 199



The catalytic cycle begins with an η^1-coordination of the nitrile to the nickel complex. Depending on the steric and electronic nature of the nitrile, the rate-determining step could be either the coordination of the nitrile (for example, for isobutyronitrile) or the ligand loss and an $\eta^1-\eta^2$ hapticity shift (for acetonitrile) to form azanickelacyclopropene **201**. An oxidative heterocoupling then takes place between one of the triple bonds of the diyne and Ni complex **201**, affording the azanickelacyclopentadiene **202** which, after insertion of the second alkyne of the diyne, generates the azanickelacycloheptatriene **203**. Further reductive elimination affords pyridine derivative and recovers $[Ni(NHC)_2]$ catalyst.

Liu et al.[255] also studied the [2 + 2 + 2] cycloaddition to generate pyridines, but instead of a diyne, the alkyne and the nitrile scaffolds are in the same molecule (Scheme 83). $[Ni(cod)_2]$ was the complex used, and several phosphines were tested as ligands. In addition, the presence of a Lewis acid as a cocatalyst had a relevant effect in the efficiency of the reaction. The optimal reaction conditions, as well as some examples, are shown in Scheme 83.

Scheme 83. Cycloaddition of Alkynes and Nitriles under Nickel Catalysis and Assisted by Lewis Acids Described by Liu et al.[255]



The authors postulated an initial nickel−alkyne complex **204** in which the cyano group was coordinated to the Lewis acid. Oxidative heterocoupling then took place to form intermediate **205**, which further evolved to pyridine after the insertion of the external alkyne. Intermediate **205** was favored via enhancement of the electrophilicity of the cyano group due to the effect of the Lewis acid together with the entropic effect (Scheme 84).

Several experiments helped to confirm the intermediates proposed. The reaction of cyanoalkyne derivative with 1 equiv of $[Ni(cod)_2]$ and 2 equiv of PPh_2Me afforded an 85% yield of nickel complex **206**, characterized by X-ray diffraction analysis, showing that the Ni atom is coordinated to the alkyne. Complex **206** reacted with 1 equiv of 3-hexyne and 1 equiv of BPh_3 to afford the corresponding pyridine derivative. In the absence of the Lewis acid, the reaction did not proceed. Therefore, the authors concluded that the Lewis acid assisted in the oxidative coupling by coordination with the cyano group (intermediate **204**).

The first study in which a 5-membered azanickelacycle complex was isolated and characterized was undertaken by Ogoshi et al.[256,257] when they studied the cycloaddition of imines and two alkynes to generate 1,2-dihydropyridines **210** (Scheme 85). The cycloaddition between benzaldimine **207a** and diphenylacetylene in the presence of $[Ni(cod)_2]$ and PCy_3

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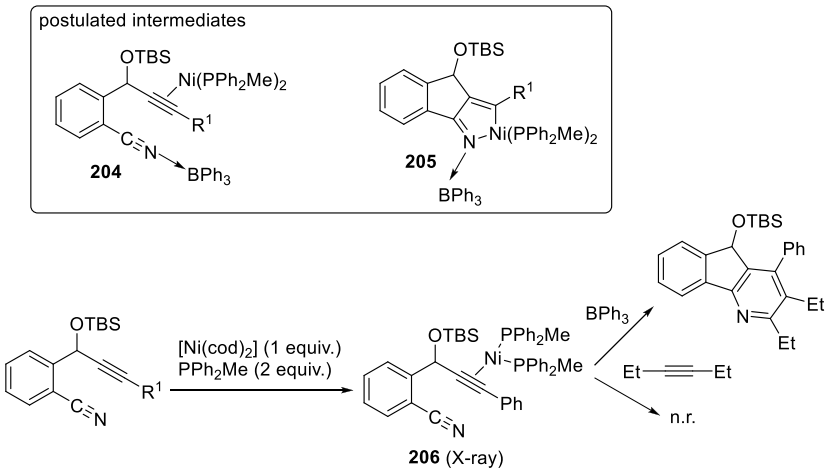
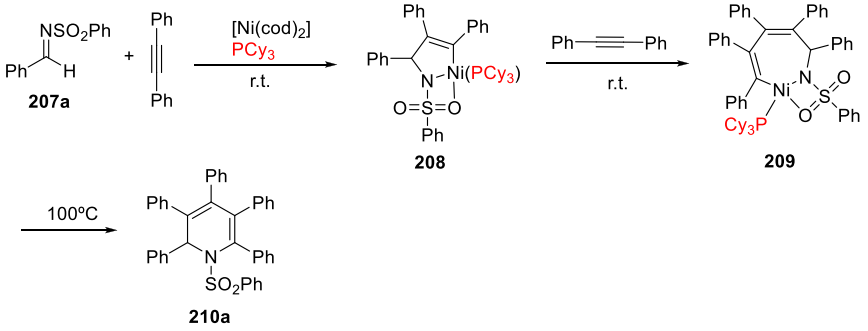
Scheme 84. Mechanistic Studies of the Cycloaddition of Alkynes and Nitriles under Nickel Catalysis and Assisted by Lewis Acids



Scheme 85. Formation of Azanickelacycles 208 and 209 by Reaction of Imines and Alkynes

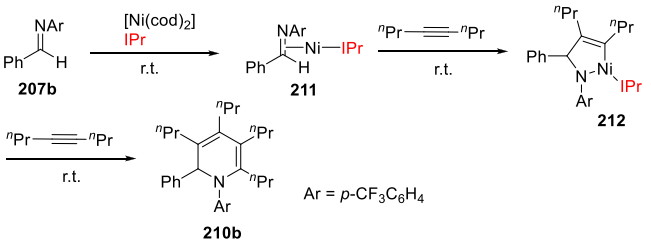


as ligand generated the nickelapyrroline **208**, where the coordination of one of the oxygen atoms of the sulfonyl group to nickel stabilizes the intermediate (*vide infra*), favoring the oxidative heterocoupling. The treatment of **208** with a second equivalent of diphenylacetylene gave the corresponding nickeladihydroazepine derivative **209** due to the insertion of the alkyne to complex **208**. X-ray diffraction analysis of **209** demonstrated the coordination of the oxygen atom to the nickel metal. Further heating of **209** at 100 °C promoted reductive elimination, affording final product **210a**, in what the authors postulated was the rate-limiting step.

Yoshikai et al.,[258] based on the previous Ogoshi results, studied the cycloaddition of aldimines bearing a 3-methyl-2-pyridyl group with the aim of stabilizing the azanickelacycle of type **208** by coordination of the nitrogen atom of the pyridine to nickel. To gain insight into the reaction mechanism, the authors performed B3LYP/6-31G(d)~LANL2DZ calculations on a model reaction. They considered the $[Ni(PMe_3)_2]$ complex as the catalysts and 2-butyne and an imine derived from acetaldehyde and 2-pyridylamine as the reactants. The initial complex in the catalytic cycle corresponded to the $[Ni(PMe_3)_2(PyN{=}CMeH)]$ (Py = pyridyl) in which the imine was π-coordinated to the Ni atom. The reaction started with the reversible exchange of a PMe_3 ligand by 2-butyne. Oxidative coupling took place with an activation energy of 20.8 kcal/mol to give an azanickelapentene complex that was stabilized by internal coordination of the pyridyl group. Coordination of 2-butyne to the azanickelacyclopentene intermediate was followed by alkyne insertion ($\Delta G^{\ddagger}$ = 9.0 kcal/mol) to generate an azanickelacycloheptadiene intermediate. Reductive elimination to yield the final 1,2-dihydropyridine derivative had to surmount a barrier of 26.5 kcal/mol, and therefore, this process was the rate-determining step of this [2 + 2 + 2] cycloaddition.

In 2014, Ogoshi's group[259] tried to expand the scope of imines in the cycloaddition with alkynes. Their aim was to use N-aryl benzaldimines **207b** (Scheme 86) instead of N-sulfonyl benzaldimines **207a**. To this end and with a view to stabilizing the azanickelacycle intermediates of type **208** (Scheme 85), they used a stronger electron-donating and more sterically demanding ligand, such as an NHC ligand (IPr) instead of PCy_3 for the nickel catalyst. In this way, it was possible to avoid the presence of a sulfonyl group in the nitrogen atom of the imine (Scheme 86).

Scheme 86. Formation of Azanickelacycle 212 by Reaction of N-Arylimines and Alkynes Catalyzed by the Ni(IPr) Complex



The reaction of imine **207b** with stoichiometric quantities of nickel complex afforded intermediate **211**, whose structure was confirmed by X-ray diffraction analysis. The sterically bulky NHC ligand may stabilize the highly reactive 14-electron nickel

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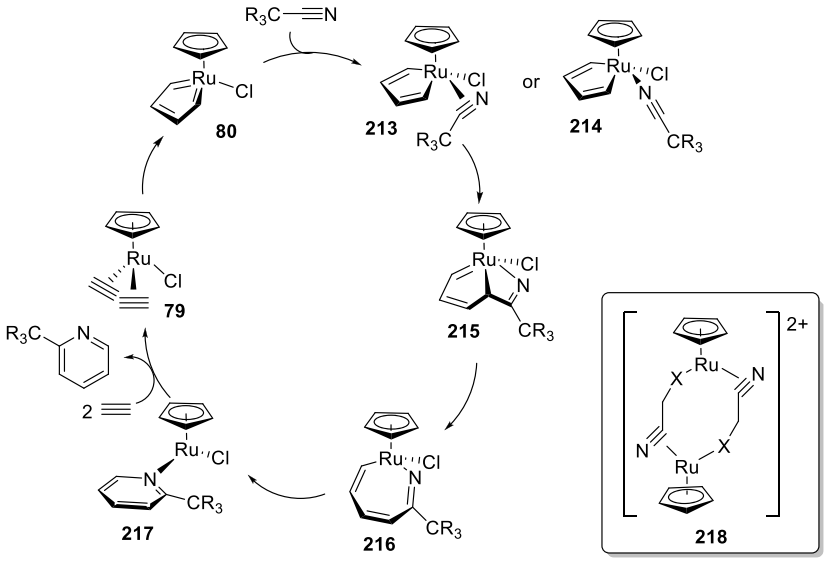
Scheme 87. Catalytic Cycle of the [2 + 2 + 2] Cycloaddition of Two Acetylenes and an Acetonitrile (R = H) or a Trifluoroacetonitrile (R = F) Catalyzed by [CpRuCl]



complex **211**. Further reaction of **211** with 4-octyne at room temperature gave the azanickelapentacycle **212** (the homologous complex obtained from **211** and 2-butyne was isolated, and its structure was confirmed by X-ray analysis). Finally, the treatment of **212** with an excess of 4-octyne directly afforded the corresponding 1,2-dihydropyridine **210b** without generating the homologous azanickelacycloheptadiene **209** (Scheme 85), indicating that in this case the rate-determining step is the insertion of the second alkyne to **212** rather than the reductive elimination step. In addition, catalytic cycloaddition of N-aryl imines with alkynes was carried out using 2% mol of $[Ni(cod)_2]$/NHC to afford good yields of the corresponding dihydropyridines.

Therefore, in the case of nickel catalysts, there is experimental evidence that unlike other metals the oxidative coupling takes place between an alkyne and a nitrile or imine, affording a 5-membered azanickelacycle intermediate.

3.3. Ruthenium Complexes

Three computational groups have studied the intermolecular or intramolecular ruthenium-catalyzed [2 + 2 + 2] cycloaddition of two alkynes and a nitrile to form pyridine rings. Yamamoto et al.[260] analyzed with the B3LYP/6-311++G(d,p)~SDD//B3LYP/6-31g(d)~LANL2DZ method the intermolecular cycloaddition of two acetylene molecules and an electron-deficient nitrile such as trifluoroacetonitrile catalyzed by [CpRuCl]. An electron-deficient nitrile was considered because the [2 + 2 + 2] cycloaddition catalyzed by Ru works better with this type of nitriles. In fact, they compared the reaction mechanism obtained with trifluoroacetonitrile with that of acetonitrile. The overall mechanism of the intermolecular [2 + 2 + 2] cycloaddition of two acetylenes and trifluoroacetonitrile or acetonitrile catalyzed by [CpRuCl] is similar to that discussed for the cyclotrimerization of acetylene mediated by the same catalyst (section 2.4) (Scheme 87). The reaction started with the displacement of 1,5-cyclooctadiene (cod) from [CpRu(cod)Cl] by coordination of two acetylene molecules. Oxidative coupling led to the ruthenacyclopentatriene intermediate **80** with the three C−C bond lengths similar to those of benzene, suggesting a highly delocalized structure. The activation barrier of this step, which was the rate-determining step, was 16.0 kcal/mol. Alternatively, one acetylene molecule and one nitrile molecule may displace the cod and form an azaruthenacyclopentadiene intermediate by oxidative coupling. This alternative process had an activation energy of 25.3 kcal/mol and, consequently, cannot compete with the oxidative coupling of the two acetylenes. The incoming trifluoroacetonitrile coordinated to the ruthenacyclopentatriene intermediate in end-on or side-on modes. The former was 7.1 kcal/mol more stable, but only the latter allowed the cycloaddition process to continue. By coordination of the nitrile, the structure of the 5-membered ring changed from the delocalized ruthenacyclopentatriene to a ruthenacyclopentadiene intermediate with $C_\alpha-C_\beta$ localized double bonds. The [2 + 2] cycloaddition of trifluoroacetonitrile was an almost barrierless process yielding an azaruthenabicyclo[3.2.0]-heptatriene complex **215** that evolved to the azaruthenacycloheptatriene intermediate **216** ($\Delta G^{\ddagger}$ = 9.8 kcal/mol) that after reductive elimination gave an η^1-pyridine complex **217**. The main difference between the reaction mechanism involving trifluoroacetonitrile or acetonitrile was that in the latter the insertion of the nitrile to the $Ru-C_\alpha$ bond of the ruthenacyclopentadiene was less favorable both kinetically and thermodynamically. This result was attributed to the electron-accepting character of the CF_3 group that lowers the LUMO of trifluoroacetonitrile as compared to that of acetonitrile. It is worth noting that Yamomoto et al.[261] found that nitriles with a coordinating group such as dicyanides and α-halonitriles (XCH_2CN, X = CN, Cl, F, Br, OMe, SMe) also efficiently participated in the Ru-catalyzed cycloaddition with 1,6-diynes. B3LYP/6-31G(d)~LANL2DZ calculations performed by the authors suggested the active species to be a symmetrical dinuclear ruthenium complex with two bridging η^2-nitrile ligands (see structure **218** in Scheme 87). This side-on coordination of the cyano group was considered to be beneficial to cyclocotrimerization, leading to bicyclic pyridines.

The second DFT study was performed by Kirchner et al.[248] using the B3LYP/6-31G(d,p)~SDD method for the [CpRuCl]-catalyzed formation of pyridine from two acetylenes and an $RC\equiv N$ (R = H, Me, Cl, CO_2Me) nitrile. The reaction mechanism found in this work is the same as that in the previous

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study by Yamamoto et al.[260] The main difference found was in the rate-determining step. While according to Yamamoto the rate-determining step is the oxidative coupling of the two acetylenes to form the ruthenacyclopentatriene, for Kirchner et al.,[248] oxidative coupling is the rate-determining step only for R = Cl. For R = H, Me, and CO_2Me, the rate-determining step corresponded to the transformation of the azaruthenabicyclo[3.2.0]heptatriene complex to the azaruthenacycloheptatriene intermediate. For instance, for R = H, the oxidative coupling had a barrier of 11.4 kcal/mol, whereas the activation barrier for the opening of the azaruthenabicyclo[3.2.0]heptatriene was 6.2 kcal/mol higher in energy. Interestingly, the authors reported that for R = H, Cl, and CO_2Me the side-on insertion of nitriles was kinetically more favored than acetylene insertion and, therefore, pyridine formation was favored in comparison to benzene generation, as was found experimentally. However, for R = Cl, the addition of a third alkyne to the ruthenacyclopentatriene had a lower activation energy than the addition of ClC≡N.

The third DFT study[262] BP86-D2/6-31G+(d,p)~LANL2DZ +f//BP86/6-31G(d)~LANL2DZ including solvent effects of a dichloromethane solution) analyzed the [2 + 2 + 2] cycloaddition of diynes and acetonitrile catalyzed by Grubbs-type Ru catalysts. Experimentally, this reaction was successfully carried out by Pérez-Castells et al.[263] Two reaction pathways were studied for this cycloaddition, i.e., the metathesis and non-metathesis ones. The metathesis path consists of a series of four metathesis steps following the mechanism described in Scheme 32, with the last addition being not that of acetylene but that of acetonitrile. The first intermediate of this reaction mechanism is a ruthenacyclobutene complex. The non-metathesis path is the traditional path depicted in Scheme 74, with the first intermediate being the ruthenacyclopentatriene species. Four catalyst models were considered, namely, Hoveyda−Grubbs catalyst (**219**) and Grubbs second generation catalyst (**220**) of Figure 5 and two simplified versions of these two catalysts.

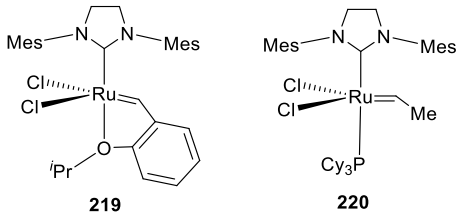


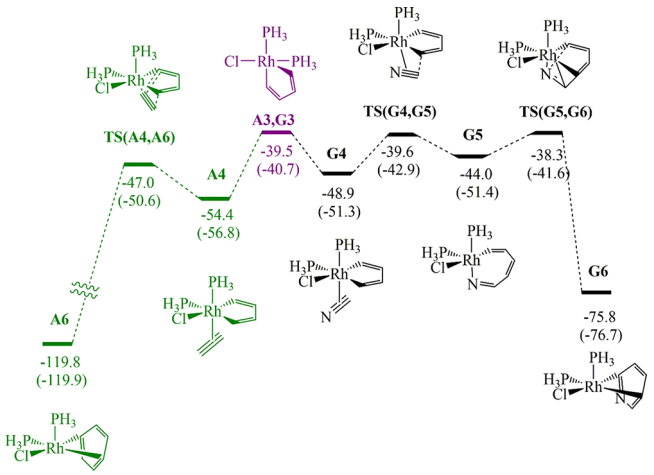
Figure 5. Catalysts used in the study by Remya and Suresh.[262]

As to the metathesis pathway, the authors found that the third metathesis involving the CN bond coupling was the rate-determining step with a Gibbs energy barrier slightly higher than 30 kcal/mol. The [2 + 2 + 2] cycloaddition was also studied following the traditional reaction mechanism. The authors found that the initial migration of a chloro ligand from the metal to the C of the carbene required an active catalyst to be generated for the traditional [2 + 2 + 2] cycloaddition and had a Gibbs energy barrier higher than 40 kcal/mol, and therefore, this possible route was ruled out, except if the catalyst decomposes. If the catalyst does not decompose, the metathesis pathway is preferred over the traditional reaction mechanism. The authors considered that, under experimental conditions,[263] the more facile formation of benzene via the metathesis pathway is suppressed by the presence of an excess of nitriles.

3.4. Rhodium Complexes

To date, the intermolecular [2 + 2 + 2] cycloaddition of two alkynes and a nitrile to form substituted pyridine rings catalyzed by Rh complexes has been studied computationally by three groups. Kirchner et al.[248] and Orian, van Stralen, and Bickelhaupt[164] performed the mechanistic analysis considering the [CpRh] catalyst, whereas our group[264] performed the study with a model of the Wilkinson catalyst, the $[RhCl(PH_3)_3]$ complex. We shall focus on the latter study carried out at the B3LYP-D2/aug-cc-pVTZ-PP//B3LYP/cc-pVDZ-PP level of theory (solvent effects of a toluene solution were also added), but we shall refer to the other two studies in the steps of the reaction mechanism in which significant differences between the two mechanisms appear. In our study,[264] we discussed all possible substitutions of one or two phosphine ligands (whether axial or equatorial) by two acetylenes or an acetylene and a hydrogen cyanide and subsequent oxidative coupling. The most favorable oxidative coupling took place after the release of a phosphine ligand and the coordination of two acetylene molecules in equatorial positions. The Gibbs energy barrier for this oxidative coupling that generates a rhodacyclopentadiene intermediate was 22.2 kcal/mol. Any other possible oxidative coupling process had a Gibbs energy barrier that was at least 15 kcal/mol larger. This oxidative coupling was the rate-determining step. It is worth mentioning that the oxidative coupling by [CpRh] had a lower Gibbs energy barrier (12.7 kcal/mol).[164] Once the rhodacyclopentadiene **A3** or **G3** was formed, it could add either acetylene or hydrogen cyanide (see Scheme 88 left and right, respectively). In the case of the addition of hydrogen cyanide, the axial vacant position in the coordination sphere was occupied by an end-on HCN releasing 17.1 kcal/mol. Side-on coordination of HCN released only 9.4 kcal/mol, but this was the only species that could evolve to the final pyridine ring formation. The Gibbs energy barrier that had to be surmounted to transform the end-on to side-on coordination was of 11.0 kcal/mol. Similar results for the end-on to side-on transformation have been reported by Orian, van

Scheme 88. Gibbs Energy Profile at 298 K (Electronic Energies in Parentheses) for the Insertion of an Acetylene (Left, Green) and Hydrogen Cyanide (Right, Black) Molecules into the Rhodacyclopentadiene Intermediate[a]



[a]All energies in kcal/mol. Please note that the two paths have a common intermediate labeled A3,G3. Reprinted with permission from ref 264. Copyright 2014 Elsevier.

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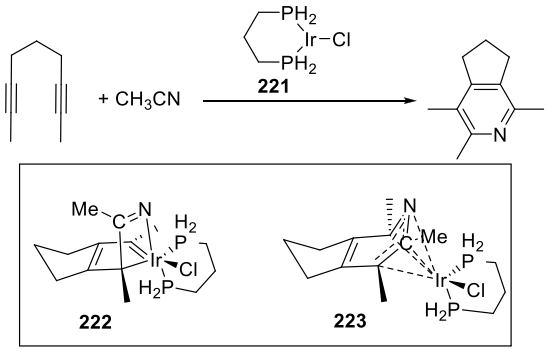
Zeist, and Bickelhaupt for a series of nitriles.[265] Insertion of the HCN to the Rh−C bond of the rhodacyclopentadiene took place through a Gibbs energy barrier of 9.3 kcal/mol with respect to the side-on complex, generating a rhodacycloheptatriene complex **G5**. All possible insertion processes were analyzed, and the barrier for the insertion that formed two new Rh−N and C−C bonds was found to be 1.0 kcal/mol lower than the one that resulted in new Rh−C and C−N bonds. Such a rhodacycloheptatriene complex was not found when the catalyst was [CpRh]. Instead, Orian, van Stralen, and Bickelhaupt[164] observed the formation of an azarhodabicyclo[3.2.0]heptatriene complex. Reductive elimination from the rhodacycloheptatriene complex yielded complex **G6**, in which the pyridine was η^4-coordinated to Rh(I). Alternatively, the rhodacyclopentadiene **A3** or **G3** may insert an acetylene molecule. In this case, it directly generated the $[RhCl(PH_3)_2(\eta^4\text{-}C_6H_6)]$ complex. The release of pyridine or benzene and regeneration of the catalyst occurred by stepwise addition of two acetylene molecules. The insertion of acetylene into the rhodacyclopentadiene intermediate was somewhat more favorable than the insertion of HCN, and therefore, the pyridine ring will only be formed in the presence of an excess of nitrile. We also analyzed[264] the [2 + 2 + 2] cycloaddition of two acetylenes and an acetyl cyanide. As in the case of the Ru-catalyzed process (Section 3.3), the presence of an electron-withdrawing group such as the acetyl group favored the incorporation of the nitrile. In addition, it improves the ratio of pyridine vs benzene obtained.

3.5. Iridium Complexes

Takeuchi et al.[266] studied computationally the reaction mechanism of the [2 + 2 + 2] cycloaddition of 1,6-diynes and acetonitrile to form a substituted pyridine ring catalyzed by the Ir complex **221** (Scheme 89), a model of the real catalyst

Scheme 89. Model Reaction Studied by Takeuchi et al.[266] Together with Some Relevant Intermediates

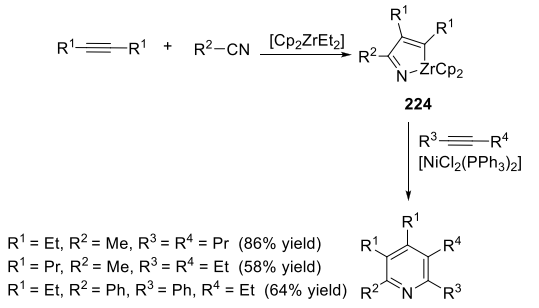


that, subsequently, was transformed to an η^2-pyridine complex that dissociated to release the final product and to recover the catalyst **221**. Reductive elimination was the rate-determining step of this process. In a second work by the same group,[267] the authors explain why cyanamide is more reactive than acetonitrile in the Ir-catalyzed [2 + 2 + 2] cycloaddition with 1,6-diynes. They followed the same approach using the same method, but in this second work, they used the full [Ir(DPPE)Cl] catalyst. They found that the Gibbs energy barriers for the insertion process of cyanamide and acetonitrile were comparable, but for reductive elimination, the Gibbs energy barrier for cyanamide was 5.7 kcal/mol lower than that of acetonitrile in agreement with experimental findings. They attributed this difference to the higher π-nucleophilicity (higher HOMO orbital) of the cyano group in Me_2NCN than in MeCN.

3.6. Other Complexes of Zirconium, Titanium, Tantalum, and Niobium

Zirconium can easily generate azazirconacyclopentadienes by oxidatively coupling of an alkyne and a nitrile in an analogous manner to nickel but in contrast to Co, Rh, Ru, and Ir. Several azazirconacyclopentadienes have been synthesized and characterized, and their reactivity has been studied. As in the case of zirconacyclopentadienes, which have been demonstrated to be intermediates in the selective preparation of substituted benzenes by cyclotrimerization of three different alkynes (see, for instance, Scheme 60), the control of the selectivity of the intermolecular cycloaddition of two different alkynes and one nitrile could be possible by the selective formation of azazirconacyclopentadiene derivatives. Takahashi et al.[268] described the coupling reaction between azazirconacyclopentadiene **224** and several alkynes in the presence of an equivalent of nickel complex to afford good yields of the corresponding pyridine derivatives as single isomers (Scheme 90). As in the

Scheme 90. Regioselective Synthesis of Pyridines Starting with Azanickelacyclopentadiene 224



case of the cyclotrimerization of three alkynes (Scheme 61 and Scheme 62), nickel metal was necessary for the transmetalation reaction of the azazirconacyclopentadiene **224** to afford the pyridine compound. As has been commented before, nickel is one of the few metals that can oxidatively couple with an alkyne and a nitrile. Takahashi et al. also tried the transmetalation with CuCl, but it was unsuccessful.

The introduction of two different alkynes in a different order allowed the different isomers to be obtained with complete selectivity. In addition, when an asymmetrical alkyne was used (R^3 = Ph, R^4 = Et) as a second alkyne, a high regioselective reaction also took place (Scheme 90). One-pot synthesis of pyridine derivatives was also performed as a highly regioselective

experimentally used by the same authors in which phenyl groups were replaced by H atoms. Their calculations were performed with the B3LYP/6-31G(d)~LANL2DZ method. Initial complexation of the diyne to **221** was exergonic by 5.9 kcal/mol. Consequent oxidative coupling had a Gibbs energy barrier of only 5.6 kcal/mol and led to the formation of an iridacyclopentadiene intermediate. End-on coordination of acetonitrile to this intermediate released 5.4 kcal/mol. No side-on complex was found in this study. The nitrile insertion proceeded via an asynchronous addition into the Ir−C bond to form the azairidabicyclo[3.2.0]heptatriene complex **222** surmounting a Gibbs energy barrier of 19.2 kcal/mol. Reductive elimination had to overcome an overall Gibbs energy barrier of 23.7 kcal/mol to generate the η^4-pyridine Ir(I) complex **223**

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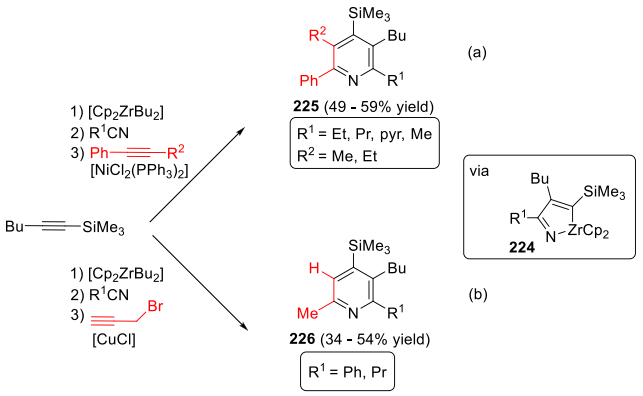
process. In this case, the formation of intermediate **224** was not observed.

An extension of this work two years later by the same authors[269] set up the regioselective synthesis of different pentasubstituted pyridines **225**. The authors selected a first alkyne with a trialkylsilyl group and the second alkyne with a phenyl group (Scheme 91, equation a). In these cases, the order

Scheme 91. Regioselective Synthesis of Pyridines via Azazirconacyclopentadiene Intermediate 224



of the addition of the two alkynes as well as the nature of the functional groups in the alkynes governed the regioselectivity of the process. In addition, when the second alkyne was propargyl bromide, CuCl allowed the transmetalation step to afford pyridine derivatives **226** (Scheme 91, equation b).

Agapie et al.[270] have recently described a bisphenoxide zirconium(IV) complex with pendant anthracene **227** and its catalytic activity in the cycloaddition of alkynes and nitriles. In this particular case, optimal reaction conditions were found to generate pyrimidines instead of pyridines (Scheme 92). In order to demonstrate the role of azazirconacyclopentadiene **228** as an intermediate in the cycloaddition reaction, 1 equiv of **227**, 1 equiv of phenylacetylene, and 2 equiv of benzonitrile were mixed to afford **228**, which was isolated and characterized by XRD analysis. This intermediate preferred the insertion of a second molecule of a nitrile instead of a second alkyne to generate the corresponding pyrimidines. The authors postulated that the particular reactivity of zirconium complex **227** was due to the nature of the anthracene scaffold, which promotes redox chemistry and product dissociation.

The groups of Liu[271,272] and Rosenthal[273,274] independently described the synthesis of pyrimidines by reaction of zirconacycles with nitriles (Scheme 93). Zirconacycles **229** and **230**, which were prepared from 1,3-butadiynes, were in equilibrium in the reaction mixture. Complex **229** seems to be the most reactive, and 5-membered zirconacyclocumulene **230** was isolated and characterized by NMR and X-ray diffraction analysis. The authors proposed the subsequent insertion of two molecules of nitriles to afford the corresponding pyrimidines, although no further intermediate was isolated or characterized.

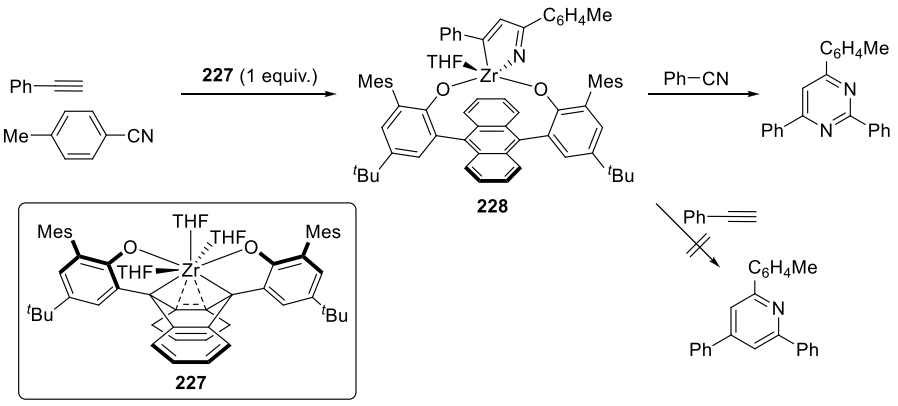
Rosenthal prepared the 7-membered zirconacyclocumulene **231**, which the authors proposed to be in equilibrium with species of type **229** and **230**, on heating at 100 °C, by eliminating one butadiyne molecule. The reaction of **231** with acetonitrile at 100 °C afforded dimer **232**, regarding which the authors postulate that an azazirconacyclopentadiene is an intermediate before the insertion of the second molecule of nitrile. When benzonitrile was used, the corresponding dimer **232** was not isolated and the pyrimidine derivative was formed. In addition, zirconacomplex **231** acted as a catalyst in the cycloaddion of 1,4-butadiynes and benzonitrile.

We shall now turn to the case of titanium. Rothwell et al.[224] extended the study of the reactivity of bisaryloxy titanacyclopentadiene **162a** (Scheme 64) with nitriles (Scheme 94). Insertion of acetonitrile as well as benzonitrile into **162a** afforded the corresponding pentasubstituted pyridine derivatives.

Following the study of a metalative Reppe reaction described by Sato et al.[226] in the cyclotrimerization of three alkynes mediated by titanium complexes (see, for instance, Scheme 65), the same research group makes an important contribution to the study of the cycloaddition of two different alkynes with nitriles to afford metalated pyridines in a highly regioselective manner (Scheme 95). The authors focus on two strategies of synthesis: (i) the regioselective generation of a titanacyclopentadiene **163** by oxidative coupling of two different alkynes and the further insertion of the nitrile to afford pyridine derivatives **237** after hydrolysis of metalated pyridines **233**–**236**[275,276] (Scheme 95, equations a) and (ii) the regioselective generation of azatitanacyclopentadiene **238** and the further insertion of the second alkyne to afford the corresponding pyridine derivative (Scheme 95, equation b).[277]

In the first study (Scheme 95, equation a), the reaction took a different course, giving four different metalated pyridines **233**–**236** depending on the nature of the substituents in the two

Scheme 92. Synthesis of Pyrimidines via Azazirconacyclopentadiene Intermediate 228



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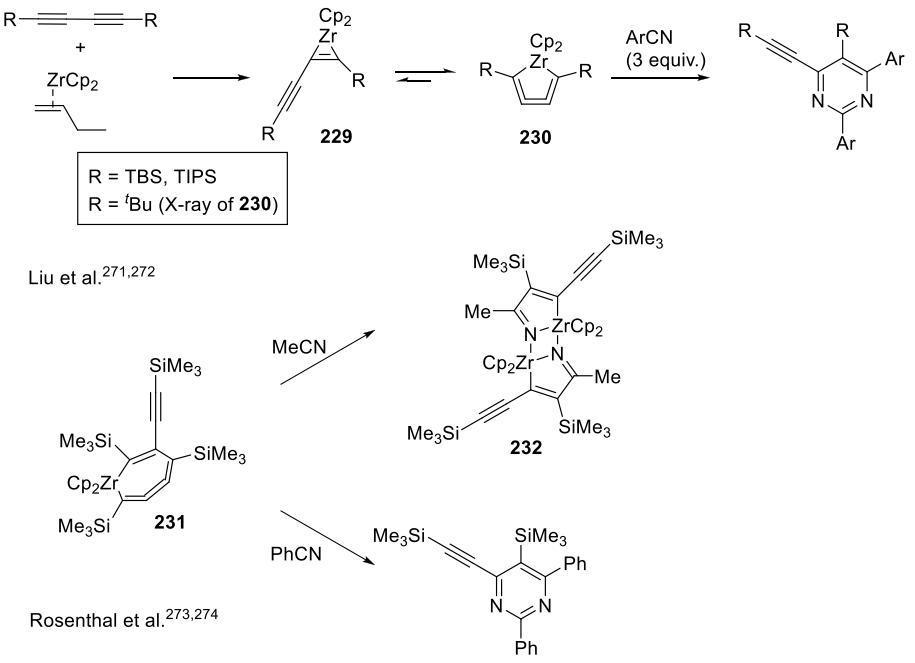
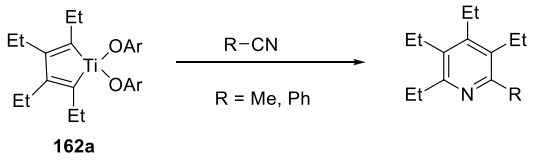
Scheme 93. Synthesis of Pyrimidines via Zirconacycles



Scheme 94. Synthesis of Pyridines via Titanacyclopentadiene 162a



alkynes as well as the substitution in the nitrile counterpart. The results allowed the efficient synthesis of a vast array of polysubstituted pyridines in a regioselective manner. Although the titanacyclopentadiene intermediate **163** was isolated and characterized, a more advanced intermediate referring to the nitrile insertion was postulated but not identified by the authors. In the second study (Scheme 95, equation b), oxidative heterocoupling of one alkyne and an α-heterofunctionalized nitrile to the titanium complex afforded the azatitanacyclopentadiene **238**, which was explored as an intermediate of the cycloaddition for the first time. As before, this intermediate was isolated but further intermediates involving the insertion of the second alkyne were only postulated by the authors. The evidence of these studies suggests that titanium can generate azatitanacyclopentadienes under certain circumstances.

Tilley et al.[278] recently described the first example of a titanium-mediated [2 + 2 + 2] cycloaddition of two nitriles and one alkyne to afford pyrazine derivatives (Scheme 96). When the biphenyldicarbonitrile derivative reacted with titanium complex **239**, diazatitanacyclopentadiene **240** was obtained and characterized by X-ray diffraction analysis. Further reaction with an electron-deficient alkyne produced the corresponding pyrazine derivatives in good yields together with titanacyclopentadiene **241** obtained as a byproduct. The authors postulate that the role of the alkyne was also to favor the extrusion of Cp_2Ti fragment from **240**.

In the field of tantalum chemistry, Wigley et al.[233,234] started from the same metallacyclopentadiene **173a** (see, for instance, Scheme 69) and after isomerizing to **173b** and further reaction with *tert*-butyl cyanide afforded η^1-nitrile complex **242**, which can only be isolated at low temperatures. At room temperature, **242** evolved to pyridine complex **243.** After an X-ray diffraction analysis, **243** was characterized by an η^2 coordination mode of the pyridine in contrast with tantalum complex **174**, which had an η^6 coordination mode with the benzene ring. Chemical oxidation of **243** afforded 2,4,6-tris-*tert*-butylpyridine isolated by sublimation. The authors claimed that complex **243** is a particular intermediate in [2 + 2 + 2] cycloaddition reactions (Scheme 97).

In a study by Satoh and Obora,[279] niobium complexes catalyzed the cycloaddition of *tert*-butylacetylene and several arylnitriles to form polysubstituted pyridine derivatives (Scheme 98). The authors proposed as a mechanism the formation of a niobacyclopentadiene **244** as a first intermediate rather than an azaniobacyclopentadiene **245**. Further insertion of the second equivalent of the alkyne to **244** afforded an azaniobacycloheptatriene, which after reductive elimination generated the pyridine. Neither intermediate **244** nor azaniobacycloheptatriene could be isolated and characterized, probably due to their instability. However, the experimental evidence led the authors to hypothesize the formation of **244** given that the hydrolysis of the compound generated by the reaction of a stoichiometric mixture of *tert*-butylacetylene and benzonitrile only gave diene **246**, the formation of which can only be derived from intermediate **244**.

4. [2 + 2 + 2] CYCLOADDITION OF TWO ALKYNES AND ONE ALKENE

Involvement of one alkene in the [2 + 2 + 2] cycloaddition reaction leads to the formation of 1,3-cyclohexadienes,[27,29,32] key building blocks in the construction of a wide range of important organic frameworks, and ideal substrates for the [4 + 2] Diels−Alder reactions in a view to access higher substituted polycyclic structures. A relevant feature, as compared to the use

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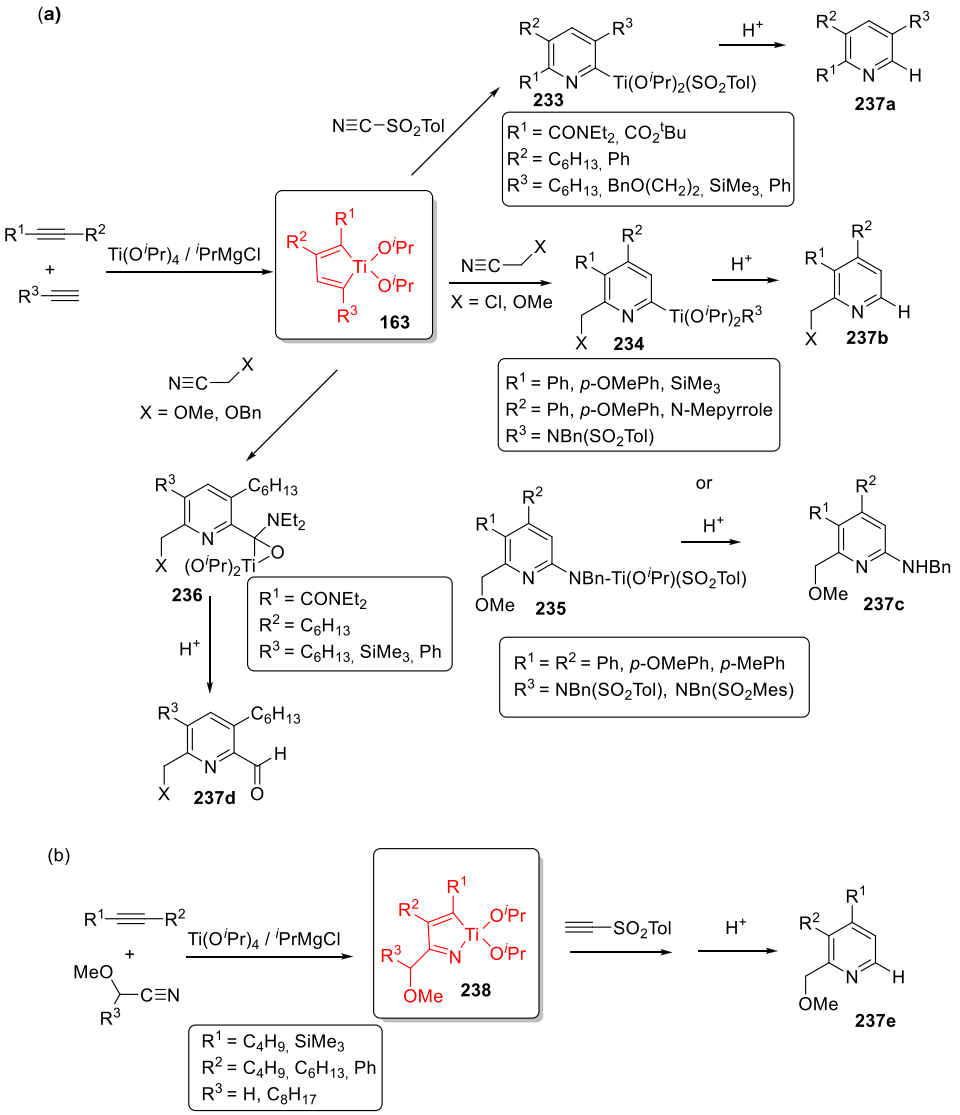
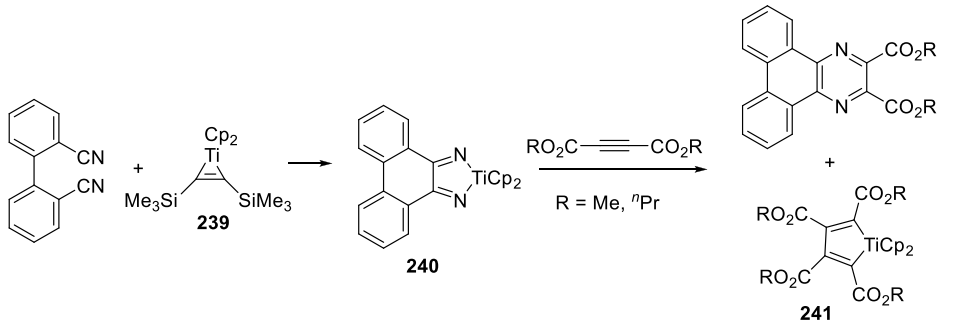
Scheme 95. Synthesis of Metalated Pyridines via Titanacycles 163 and 238



Scheme 96. Synthesis of Pyridazines via Diazatitanacyclopentadiene 240



of alkynes and nitriles, is the possibility of accessing compounds containing stereogenic centers.

Regarding the mechanism, some particularities are especially worth attention. The alkene can be introduced either in the oxidative coupling step or in the addition to the 5-membered metallacyclic ring. Furthermore, the decreased reactivity of alkenes as compared to alkynes in the [2 + 2 + 2] cycloaddition reaction poses a challenge in controlling the chemoselectivity of the process.

4.1. Cobalt Complexes

Wakatsuki et al.[280,281] disclosed that the reaction of cobalt complex [CpCo(PPh$_3$)(RC≡CCO$_2$Me)] (R = Ph or CO$_2$Me) **247** with disubstituted olefins such as dimethyl maleate, dimethyl fumarate, fumaronitrile, and crotononitrile at room

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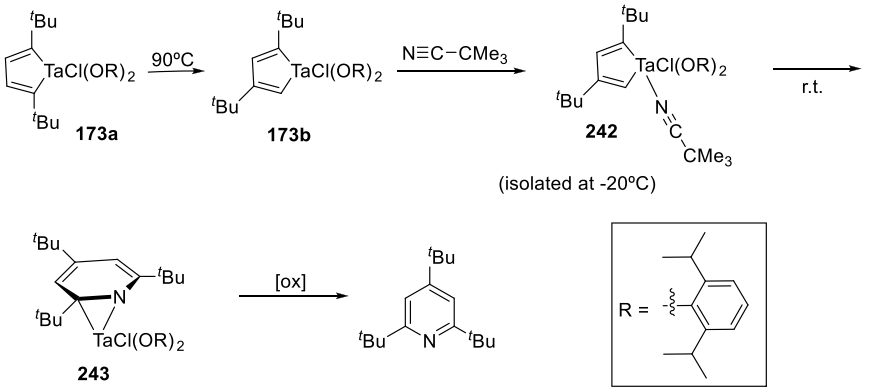
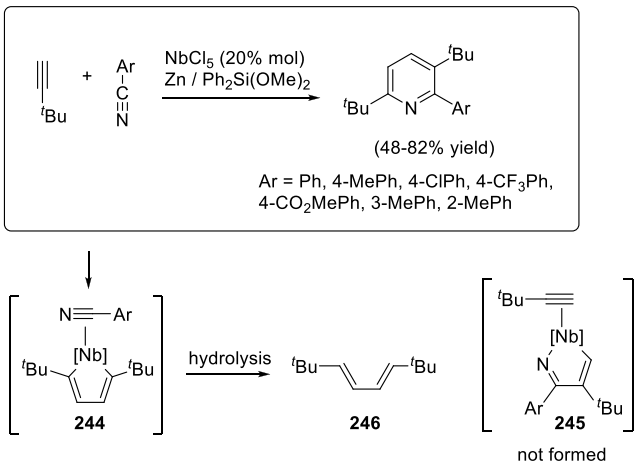
Scheme 97. Synthesis of Pyridines via Tantallacyclopentadiene 173

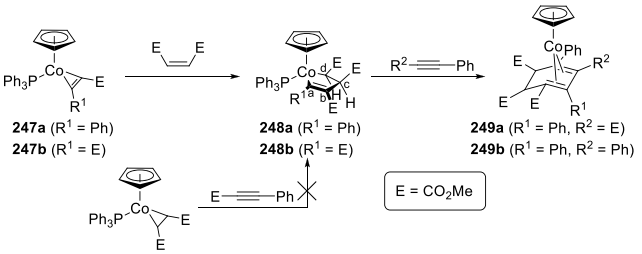


Scheme 98. Synthesis of Pyridines Catalyzed by Nb Complexes



temperature gave red products, which could be assigned to cobaltacyclopentene complexes **248** by spectroscopic methods. The stereospecificity of the reaction needs to be taken into account in reactions of sp^2 hybridized unsaturations. Oxidative coupling (as well as insertion of an unsaturation into the 5-membered metallacyclic rings, *vide infra*) is an elemental step that occurs in a stereospecific manner for sp^2 hybridized unsaturations. *Cis* disubstituted olefin dimethylmaleate yielded only one of the two possible *syn* cobaltacyclopentene products (due to the lack of symmetry of the ligands around the metal atom). As could be confirmed by X-ray diffraction of the isolated diastereoisomer of **248a**, the two ester groups of the former olefin were pointing toward the Cp ring (Scheme 99). Taking a closer look at the structure, it could be determined that the

Scheme 99. Synthesis and Reactivity of Cobaltacyclopentene Complexes Reported by Wakatsuki et al.[280,281]



cobalt atom and three of the carbons (carbons a, b, and c, as labeled in the structure) laid in the same plane, whereas carbon d was bent from the plane by 34.2°. *Trans* disubstituted olefins were coupled stereospecifically but gave a mixture of the two possible isomeric cobaltacyclopentenes (again as a result of the lack of symmetry of the ligands around the cobalt). Even for the asymmetrically substituted olefin crotonitrile, only two isomers were isolated, showing that the oxidative coupling had taken place with high regioselectivity.

A kinetic study was then undertaken to unravel the mechanism for the formation of **248**. The reaction with and without the addition of PPh_3 was monitored by NMR, and the observed reaction rate was consistent with a three-step transformation comprising as a first step PPh_3 to alkene ligand exchange, followed by oxidative cyclization and subsequent recoordination of phosphine ligand. It is worth mentioning that compound **248a** could not be obtained by a reaction in which the alkyne and alkene counterparts have exchanged roles, suggesting that displacement of the phosphine by acetylene in the olefin complex does not occur under reaction conditions.

Next, the reactivity of **248** toward alkynes and alkenes was studied. The reaction with acrylonitrile leads to the formation of open-chain oligomeric complexes. On the other hand, reaction of **248a** with diphenylacetylene or methyl 3-phenylpropiolate afforded cyclohexadiene cobalt complexes **249**. 1,3-Cyclohexadienes are good ligands for transition metals, including cobalt, which hampered their use in these transformations in catalytic quantities. Kinetic studies showed that added triphenylphosphine markedly hindered the reaction. Thus, a mechanistic scheme was postulated that involved replacement of the phosphine by the alkyne followed by the insertion of the alkyne to form a 7-membered cobalt metallocycle. The authors explained the difference in reactivity based on the different relative coordination abilities of alkenes and alkynes.

Complexes **249** can also be obtained by reaction of isolated cobaltacyclopentadienes **12** with olefins, as the same group[93,282] had also reported. The reaction was run in benzene or toluene at high temperature to give cyclohexadienes and/or intermediate cyclohexadiene cobalt complexes (which could be decomposed to cyclohexadienes by treatment with Ce^{4+} in benzene/ethanol solution) (Scheme 100). Since the reaction was retarded by the addition of triphenylphosphine and inhibited by use of more tightly bound phosphines, the authors postulated again that the first step was the displacement of the phosphine by the olefin. The second step of the reaction was regarded as a formal Diels–Alder reaction within the coordination sphere of the transition

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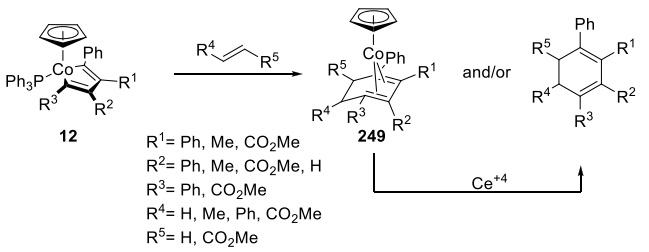
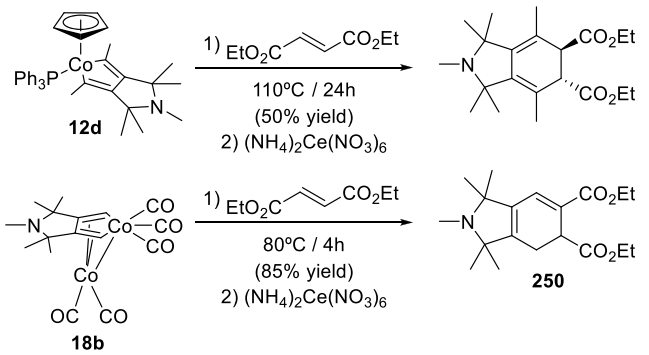
Scheme 100. Reaction of Cobaltacyclopentadienes with Alkenes Reported by Wakatsuki et al.[93,282]



metal, and as such, the *endo*−*exo* stereochemistry was analyzed when dimethyl maleate was used as a dienophile. The endo rule was only obeyed when $R^1 = R^4 = Ph$.

Chiusoli and Costa et al.[283] compared the reactivity of isolated cobalt complexes **12d** and **18b** toward diethyl fumarate. Cobaltacyclopentadiene complex **12d** needed higher temperature (110 °C vs 80 °C) and longer reaction time (24 h vs 4 h) than bimetallic complex **18b** to insert the alkene and still did it with lower efficiency (Scheme 101). Cyclohexadiene cobalt

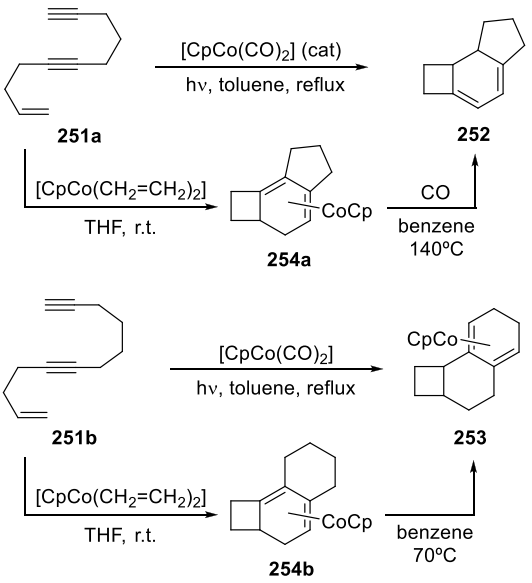
Scheme 101. Comparative Reactivity of Isolated Cobaltacyclopentadienes Reported by Costa and Chiusoli et al.[283]



complexes were obtained, which were decomposed by treatment with a solution of cerium ammonium nitrate. The authors proposed that the results can be interpreted in terms of different abilities to undergo coordination of unsaturated substrates, although it would have been necessary to consider the different substitution on the acetylene termini of the substrates. No justification was provided either for the isolation of the double bond isomerized cycloadduct **250** when the bimetallic cobalt catalyst **18b** was used.

The possibility of isomerization processes had earlier been studied by Gadek and Vollhardt[284] when reporting the $[CpCo(CO)_2]$-catalyzed cycloaddition of enediyne substrates. Stoichiometric reactions using $[CpCo(CO)_2]$, which were the vast majority at the time, led to the isolation of the cycloadduct as a [CoCp] complex. This was postulated to prevent the rearrangement of the diene unit. Vollhardt et al.[285] reported the cycloaddition of **251a**, both under stoichiometric and catalytic conditions, to afford free cycloadduct **252** in which the double bonds were shifted from their expected positions (Scheme 102). Reaction of analogue **251b** proceeded only under stoichiometric conditions to give CpCo-complexed cycloadduct **253** where the double bonds were again shifted from their expected positions. The process was studied by deuterium-labeling experiments,

Scheme 102. $[CpCo(L)_2]$-Catalyzed [2 + 2 + 2] Cycloaddition Reaction of Enediynes Reported by Vollhardt et al.[285]



which were in agreement with a cobalt-mediated α-hydride migration through η^3-allyl hydrides. When the same substrates were treated with the Jonas catalyst $[CpCo(CH_2{=}CH_2)_2]$, a much more active source of CpCo, at room temperature, the strained expected cycloadducts **254a** and **254b** were isolated.[286] The ease of isomerization was rationalized based on the strain in the initially formed tricyclic diene systems.

In section 2.2, we have shown that the cobalt-mediated [2 + 2 + 2] cyclotrimerization of three alkynes is a two-state reaction. The first DFT study of the [2 + 2 + 2] cobalt-catalyzed cycloaddition of two alkynes and one alkene to give cyclohexadienes was performed by Gandon and Aubert et al. in 2006[287] with the B3LYP/6-311+G(2d,2p)~LANL2DZ//B3LYP/6-31G(d,p)~LANL2DZ method. They found that this cycloaddition also displays two-state reactivity. A summary of their main results obtained is displayed in Scheme 103. There are two possible oxidative couplings for this reaction. The coupling between two acetylenes has a Gibbs energy barrier of 11.9 kcal/mol and is exergonic by 21.2 kcal/mol, whereas the oxidative coupling between an acetylene and an ethene to form a cobaltacyclopentene has to surmount a barrier of 20.4 kcal/mol. Therefore, the active coupling is the one that transforms **29** into cobaltacyclopentadiene **30**. This complex evolves through a crossing point, $MECP_a$, lying just 0.1 kcal/mol above singlet **30**, to its triplet state, ^{3}**30**, which is the ground state for such a 16-electron species. Coordination of the ethene to ^{3}**30** is barrierless and generates complex **255** in its singlet state, releasing 2.2 kcal/mol. The $MECP_b$ is only 1.8 kcal/mol higher in energy than ^{3}**30** + ethene. The next step corresponds to the insertion of the ethene in the Co—C σ-bond rather than intramolecular [4 + 2] cycloaddition (as found for the cyclotrimerization of three alkynes) to yield the cobaltacycloheptadiene complex **256**, that evolves to its triplet ground state through a spin crossing point, $MECP_c$ (1.9 kcal/mol higher in energy than complex **256**), releasing 9.8 kcal/mol. A reductive elimination in the triplet state with a Gibbs energy barrier of 9.6 kcal/mol leads to the CpCo(η^2-cyclohexadiene) complex ^{3}**257**. The $MECP_d$ lies 6.3 kcal/mol above ^{3}**257** and results in the formation of **258**. Final

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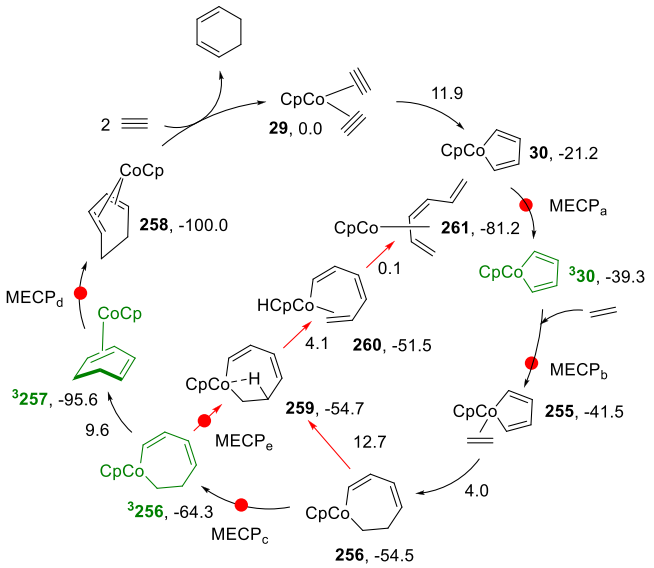
Scheme 103. Reaction Mechanism Reported by Gandon and Aubert et al.[287] for the Cobalt-Catalyzed Cycloaddition of Two Acetylenes and One Ethene[a]



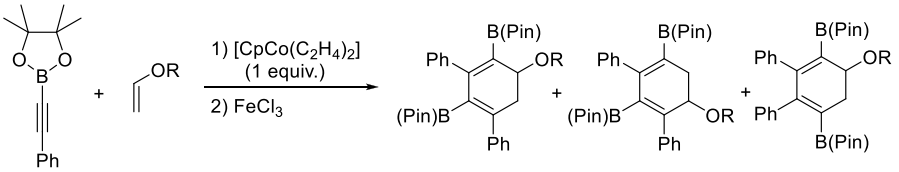
[a]In green are those species that have a triplet ground state. MECPs are minimum-energy crossing points depicted in red. Energies are in kcal/mol.

replacement of cyclohexadiene by two acetylenes recovers the original active catalyst **29**. Alternatively, the cobaltacycloheptadiene complex **256** can also evolve to form open-chained hexatriene complexes that have been occasionally observed in experiments. Starting from **256**, a conformational change ($\Delta G^{\ddagger}$ = 12.7 kcal/mol) results in complex **259** stabilized by a $^{\beta}$H agostic interaction. β-Hydride elimination transforms **259** into **260** through a Gibbs energy barrier of only 4.1 kcal/mol. Facile and exergonic reductive elimination ($\Delta G^{\ddagger}$ = 0.1 kcal/mol, ΔG = −29.7 kcal/mol) leads to the CpCo(η^4-hexatriene) complex **261**. This C—H activation route is clearly disfavored for ethene, as shown in Scheme 103. However, for C=C bonds of aromatic systems, the two options become competitive. For the particular case of benzene, this C—H activation pathway is preferred over the [2 + 2 + 2] cycloaddition by 7.5 kcal/mol.

After the complete theoretical DFT study discussed above, Vollhardt, Gandon, and Aubert et al.[288] studied the particularities for the mechanism for the [2 + 2 + 2] cycloaddition reaction involving alkynyl boronates and alkenes. The chemoselectivity of the reaction (cyclotrimerization of the alkynyl boronate leading to benzene derivatives vs alkyne−alkene co-cyclotrimerization leading to cyclohexadiene derivatives vs alkynylboronate dimerization leading to metalated cyclobutadienes) was experimentally found to be dependent on the sterics of the alkynyl boronate. However, the alkene used in the reaction was found to have a crucial impact on the regioselectivity of the co-cyclotrimerization, leading again to cyclohexadiene cobalt complexes, which were oxidatively demetalated with iron(III) chloride (Scheme 104). The general mechanism reported before, entailing formation of a cobaltacyclopentadiene by oxidative coupling of two alkynes, should not manifest an influence of the alkene on the regioselectivity of the reaction. Therefore, the precise mechanism for this transformation was studied by means of DFT computations at the same B3LYP/6-311+G(2d,2p)~LANL2DZ//B3LYP/6-31G(d,p)~LANL2DZ level of theory as the previous study. The reaction mechanism followed is the one shown in Scheme 103. As for the oxidative coupling, it can occur in three different ways: head-to-head, tail-to-tail, and tail-to-head or head-to-tail (the two latter are equivalent) to yield 1,4-, 2,3-, and 1,3-cobaltacyclopentadienes. For steric reasons, the 2,3-coupling with the two boryl substituents in C$_\beta$ atoms is not possible. For relatively large substituents, the 1,3-coupling with the boryl substituents in alternated C atoms is preferred over the 1,4-coupling. For instance, for R = Ph, the barrier for the 1,3-oxidative coupling is 4.0 kcal/mol lower than that of the 1,4-coupling. On the other hand, for smaller substituents like R = Me, this preference disappears. These results are in agreement with the observed experimental regiochemistry. The next step corresponds to the insertion of the alkene. In the case of 1,4-cobaltacyclopentadienes, the insertion and subsequent reductive elimination yield exclusively species like compound **263c** in Scheme 104. For the interaction of unsymmetrical alkenes with 1,3-cobaltacyclopentadienes, there are four possible different insertions that result in the formation of species like compounds **263a** and **263b**. It is found that the most stable complex between the alkene and the 1,3-cobaltacyclopentadiene is the one that has also a lower Gibbs activation barrier for the insertion. Interestingly, the charges in free alkenes can be used to anticipate the best arrangement and the major regioisomer of the reaction. It is found that the carbon atom of the alkene which bears the strongest negative charge binds Co and that the positive charge at the other alkene carbon interacts with the most negative C$_\alpha$ of the 1,3-cobaltacyclopentadiene intermediate. In this way, it is possible to rationalize the regiochemistry observed for different substituted ethenes.

The same group disclosed the experimental[289] and theoretical[290] study of the reaction of pyridine-2-one and pyrazinone derivatives toward alkynes mediated by [CpCo(C$_2$H$_4$)$_2$]. For the theoretical study, they used the same method employed in previous studies, i.e., the B3LYP/6-311+G-

Scheme 104. Alkene Dependent Regioselectivity on the Co-cyclotrimerization of Alkenes and Alkynyl Boronates



262 **263a** **263b** **263c**

R = O^{t}Bu (65% yield, 1:0:0 (**263a**:**263b**:**263c**) ratio)
R = OSiMe$_3$ (35% yield, 1:1.6:0 (**263a**:**263b**:**263c**) ratio)
R = OEt (30% yield, 0:0:1 (**263a**:**263b**:**263c**) ratio)

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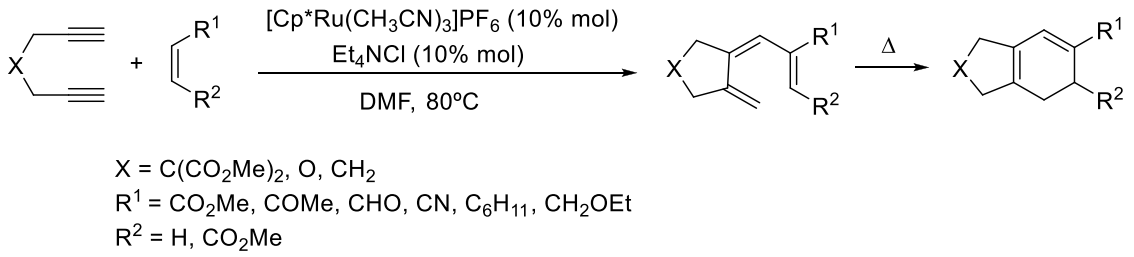
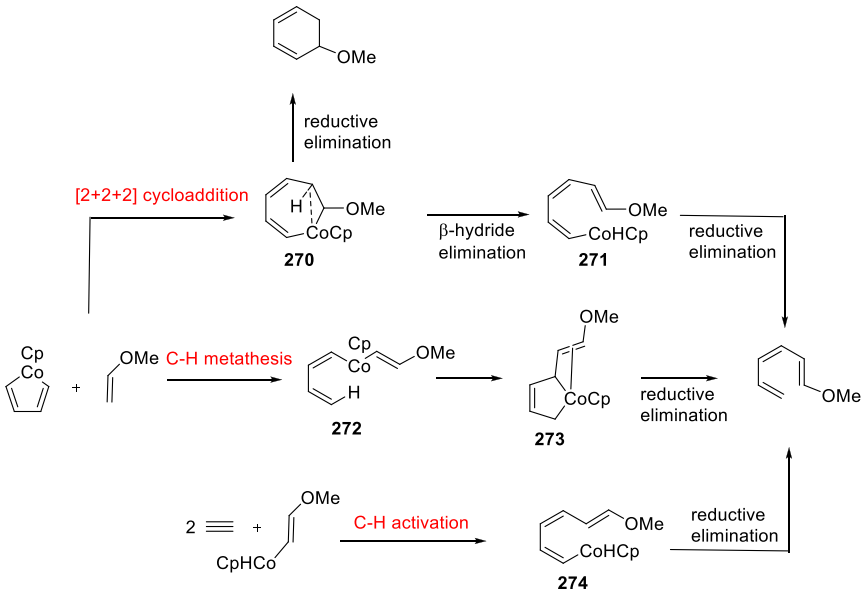
Scheme 105. Three Possible Pathways for the Reaction of Pyridine-2-ones and Cobaltacyclopentadiene[a]



[a]Enthalpy barriers for each step are given in kcal/mol.

Scheme 106. Three Possible Mechanistic Pathways Studied for the Reaction of Methoxyethene and Two Acetylene Molecules Catalyzed by CpCo



(2d,2p)~LANL2DZ//B3LYP/6-31G(d,p)~LANL2DZ method, and analyzed only the singlet potential energy surface. As shown in Scheme 105, the reaction of pyridine-2-one with the cobaltacyclopentadiene intermediate can follow three different paths, namely, C−H activation, N−H activation, and [2 + 2 + 2] cycloaddition. They started the study by studying all possible structures that can be formed by coordination of pyridine-2-one to the cobaltacyclopentadiene intermediate. They found 10 possible structures (5 *exo* and 5 *endo* within an energy range of 8.7 kcal/mol) that are expected to be in equilibrium. The structure with the lowest in energy pathway for C−H activation and [2 + 2 + 2] cycloaddition is the *exo* complex **264**, whereas that with the lowest in energy pathway for N−H activation is the *exo* species **265**. **264** is more stable than **265** by 1.4 kcal/mol. Calculations showed that the most favorable C−H activation corresponds to the H of the C adjacent to the nitrogen. From the analysis of the enthalpy barriers at 298 K for each step shown in Scheme 105, the authors concluded that the N−H activation is more facile than the C−H activation. The [2 + 2 + 2] cycloaddition involves the formation of the cobaltacycloheptadiene intermediate **266**, that isomerizes to a cobaltanorbornene **267** stabilized by the nitrogen atom. Reductive elimination leads to the final bicyclic product. The rate-determining step for the [2 + 2 + 2] cycloaddition, which is the isomerization from cobaltacycloheptadiene to cobaltanorbornene, has an energy barrier that is 3.2 kcal/mol higher than that of the rate-determining step of the N−H activation corresponding to the reductive elimination from **268** to **269**. When the H of the NH group in pyridine-2-one derivatives is substituted by another group, the N−H activation is blocked and then the C−H activation and the [2 + 2 + 2] cycloaddition proceed with energetically close-lying trajectories.

After the study reported above, Aubert and Gandon et al.[291] studied the reaction pathways of the cobalt-mediated co-oligomerization of alkynes with alkoxylated alkenes to give 1-alkoxy-1,3,5-trienes. On the contrary, reaction with alkenes yields 1,3-cyclohexadienes. The three possible reaction paths studied for the reaction of alkynes with alkoxylated alkenes are drawn in Scheme 106. In the standard [2 + 2 + 2] cycloaddition mechanism, insertion of the alkoxylated alkene to cobaltacyclopentadiene gives the cobaltacycloheptadiene intermediate **270** that generates the corresponding 1,3-cyclohexadiene by reductive elimination. Alternatively, *β*-hydride elimination followed by reductive elimination furnishes alkoxy-1,3,5-triene (see also **256** → **261** in Scheme 103). Another alternative is metathesis of the C−H bond of the alkene moiety generating the cobaltacyclopentene complex **273** that by reductive elimination generates alkoxy-1,3,5-triene. This path is the preferred one for pyridines[290] and aromatic molecules such as benzene, thiophene, and furan.[287] Finally, one can consider early C−H activation of the alkene followed by two carbometalations of the triple bonds to generate **274**. After reductive elimination, alkoxy-

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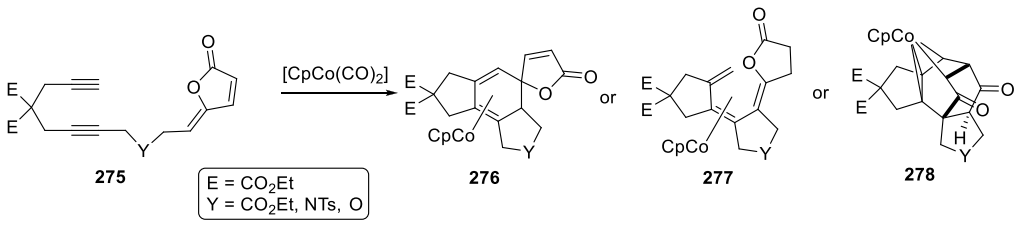
Scheme 107. Possible Outcomes of the Co(I)-Mediated Reaction with Enediyne 275



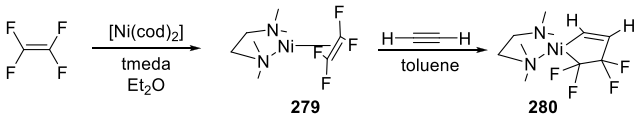
1,3,5-triene was obtained. Calculations at the B3LYP/6-311+G(2d,2p)~LANL2DZ//B3LYP/6-31G(d,p)~LANL2DZ level of theory show that activation of any C−H bond of the methoxyethene to give a cobalt hydride **274** requires a prohibitive enthalpy barrier above 30 kcal/mol. This makes this pathway very unlikely and indicates that the first step of the reaction is the alkyne oxidative coupling to form the cobaltacyclopentadiene intermediate. Enthalpy barriers for the oxidative hydrogen migration to dienyl vinylcobalt intermediate **272** and subsequent metathesis to the cobaltacyclopentene complex **273** were quite high, indicating that this route is not competitive. On the other hand, insertion of the methoxyethene to the cobaltacyclopentadiene complex to form **270** was found to be facile ($\Delta G^{\ddagger}$ = 3.8 kcal/mol). From **270**, two possible reaction routes are possible. First, isomerization of **270** to a cobaltanorbornene structure yields 1,3-cyclohexadiene derivative by reductive elimination. Second, β-hydride elimination forms **271** and reductive elimination occurs to generate the corresponding triene. Both processes go through relatively low-lying transition states, and therefore, it is likely that both pathways are operative, as observed experimentally.

Amatore, Nava, and Commeiras et al.[292] reported a cobalt-catalyzed cycloaddition of an enediyne **275** bearing an alkylidenebutenolide moiety (Scheme 107) that did not lead to the expected cycloadduct. The [2 + 2 + 2] cycloaddition in this species should result in the formation of complex **276**. As discussed above, alkoxylated alkenes give 1-alkoxy-1,3,5-trienes, and therefore, one could also expect formation of species **277**. However, unexpectedly, the product observed is the bicyclo[3.3.1]non-3-en-2-one species **278**. BP86-D3/def2-TZVP calculations found a feasible reaction path that transforms **275** into **278** through a 7-membered oxo-ketene intermediate. Formation of this intermediate is the rate-determining step with a Gibbs energy barrier of 19.5 kcal/mol at 110 °C. The reaction mechanisms leading to **276** and **277** were not determined.

4.2. Nickel Complexes

Pörschke et al.[293] described the reaction of [Ni(cod)$_2$] with tmeda (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) and the highly electrophilic olefin tetrafluoroethylene to synthesize the 16-electron nickel−olefin complex [(tmeda)Ni(C_2F_4)] **279**, which was fully characterized including X-ray diffraction analysis. The trigonal-planar (or pseudo-square-planar) complex reacted with acetylene to afford nickelacyclopentene **280** (Scheme 108),

Scheme 108. Nickelacyclopentene Complex Described by Pörschke et al.[293]



which was spectroscopically characterized. The reaction was very slow at atmospheric pressure but could be substantially accelerated at higher pressure (8−20 bar), although the quantity of polyacetylenic byproducts obtained also increased. The authors did not describe the formation of cyclohexadiene scaffolds and disclosed that no further reaction of **280** with C_2F_4 could be achieved.

An inverted oxidative cyclization strategy toward the synthesis of fluorinated nickelacyclopentenes was described by Bennett et al.[294] involving the reaction of tetrafluoroethylene and 2,3-naphthalyne complex of nickel(0) **281**, synthesized by alkali-metal reduction of the corresponding (2-halogenoaryl)nickel-(II) complexes (Scheme 109, equation a). The structure of naphthalene-fused nickelacyclopentene **282** was confirmed by single crystal X-ray structural analysis. Dimethyl acetylenedicarboxylate reacted with **282** to give the 7-membered nickelacycle **283**. The four fluorine atoms in **283** were inequivalent in the ^{19}F NMR spectrum, suggesting that the chelate ring was not planar, a suggestion that was confirmed by X-ray crystallography, which showed a boat-shaped 7-membered nickelacycle. Reductive elimination products were not observed in the reaction in contrast to the results previously reported by Carmona et al.[295] on a similar nickelacyclopentene **284** (which was not formed by oxidative cyclization) (Scheme 109, equation b). The authors suggested that the monodentate versus bidentate nature of the phosphine ligands present in the two complexes accounts for their difference in reactivity. The presence of 1,2-bis(dicyclohexylphosphino)ethane in **283**, a bidentate phosphine ligand, reduces the rate of the reductive elimination step in such a degree that complex **283** is a very stable complex (it is isolated upon insertion of dimethyl acetylenedicarboxylate in refluxing tetrahydrofuran, and no organic products arising from reductive elimination are detected). On the contrary, Carmona et al. complex **284**, where the nickel is stabilized by monodentate PMe_3 or PPh_3, experiences such a fast reductive elimination that prevents the isolation and even detection by NMR of the 7-membered intermediate.

Ichikawa et al.[296] also studied the mechanism of a nickel-catalyzed [2 + 2 + 2] cycloaddition reaction of fluorinated olefins. A procedure developed for the synthesis of tetrasubstituted fluoroarenes involved the [2 + 2 + 2] cycloaddition of two molecules of alkyne and one molecule of 1,1-difluoroethylene followed by aromatization (Scheme 110). A kinetic study revealed a first-order dependence on the concentration of 1,1-difluoroethylene, alkyne, and nickel(0) complex, which was taken as an indication that the initial rate-limiting oxidative cyclization proceeded with the involvement of these three species to form a nickelacyclopentene. Thus, the mechanism postulated for the process entailed the formation of nickelacyclopentene **285**, to which a second alkyne was inserted to give **286** that subsequently suffered α-fluorine elimination to

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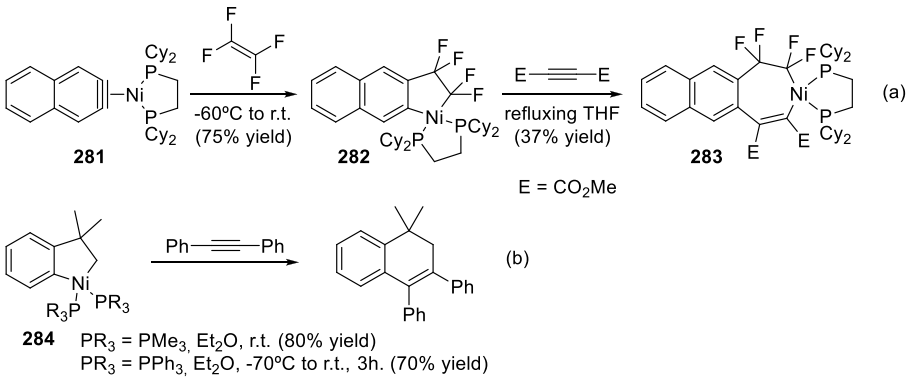
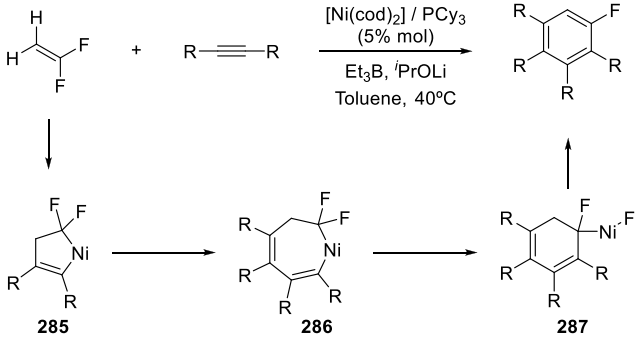
Scheme 109. Nickelacyclopentene Formation and Reaction with Alkynes



281 282 283 284

Scheme 110. Mechanism for the [2 + 2 + 2] Cycloaddiiton of Alkynes and 1,1-Difluoroethylene Reported by Ichikawa et al.[296]



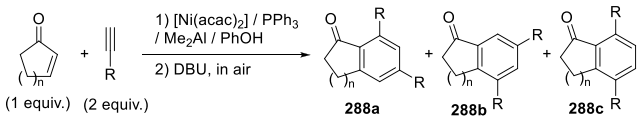
285 286 287

give cyclohexadienylnickel(II) fluoride **287**. Aromatization through β-hydrogen elimination furnishes fluorobenzene derivative. Nickel(0) catalyst is recovered through transmetalation with Et_3B activated with ^{i}PrOLi and reductive elimination.

Nickel complexes have also been shown to be really good catalysts for the cycloaddition reaction of alkynes and enones. Some authors have studied the mechanism of such a transformation. Ikeda et al.[297] reported the regioselective cyclotrimerization of enones with two molecules of alkynes in the presence of a nickel(0) and aluminum catalytic system. The reaction afforded cyclohexadienes that were subsequently oxidized to benzene derivatives (**288a**–**288c**) to facilitate the determination of the regioselectivity of the reaction (Scheme 111). To assess if the reaction proceeded through nickelacyclopentadiene or nickelacyclopentene intermediates, stoichiometric experiments were carried out and monitored by NMR. No intermediate could be detected, but when a control reaction was carried out under acidic conditions, small amounts of diene, presumably arising from nickelacyclopentadiene, were isolated, thus pointing to the involvement of this metallacycle as a key intermediate. The regioselectivity of the reaction was then explained by considering the reaction via nickelacyclopentadienes and Stockis and Hoffmann[109] rules that dictate how electronic and steric factors interplay in their regioselective formation. The electron-donating character of Me_3Si favors the formation of 1,4-disubstituted nickelacyclopentadiene by locating the large lobes of the polarized π^* of the starting substrates facing each other in the β-position of the metallacycle. On the other hand, with alkyl-substituted alkynes, both 1,3- and 1,4-substituted nickelacyclopentadienes are formed but the 1,3-disubstituted one reacts faster with the enone through the less-hindered (unsubstituted) α-carbon. The trends observed were used to optimize a selective [2 + 2 + 2] cycloaddition involving an enone and two different alkynes.

Ogoshi et al.[298] studied the cycloaddition of two enones and one alkyne, resulting in the highly chemo- and regioselective synthesis of cyclohexene scaffolds **289** (Scheme 112). When unsymmetrically substituted alkynes reacted, the regioselectivity depended on the type of substituent in the alkyne. When benzylic or allylic alkynes were used, good regioselectivities (above 90:10 and 80:20, respectively) were obtained, whereas alkyl-substituted alkynes gave only moderate selectivities (ranging from 68:32 to 65:35). The authors postulate that η^3-

Scheme 111. Regioselective Cyclotrimerization of Two Alkynes and One Enone Reported by Ikeda et al.[297]

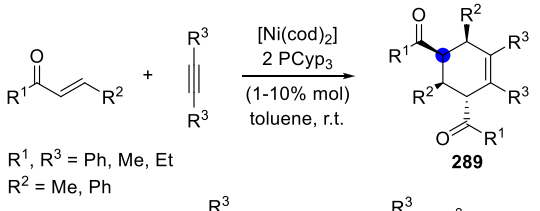


288a 288b 288c

n = 1-3
R = Bu, ^{t}BuMe$_2$SiO(CH$_2$), Me, ^{t}Bu, Me$_3$Si

Selected **288a**:**288b**:**288c** ratios:
(0:0:>99) for n = 1, R = Me$_3$Si
(82:4:14) for n = 1, R = Bu
(>99:0:0) for n = 1, R = ^{t}BuMe$_2$SiO(CH$_2$)

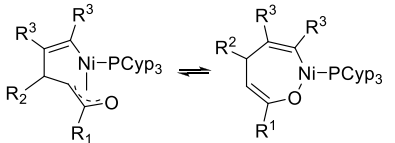
Scheme 112. Regioselective Cyclotrimerization of One Alkyne and Two Enones Reported by Ogoshi et al.[298]



289

R^1, R^3 = Ph, Me, Et
R^2 = Me, Ph

Intermediates:



290a 290b

Isolated and characterized by XRD for R^1 = R^2 = R^3 = Ph

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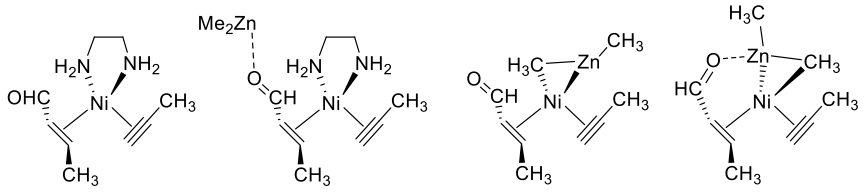
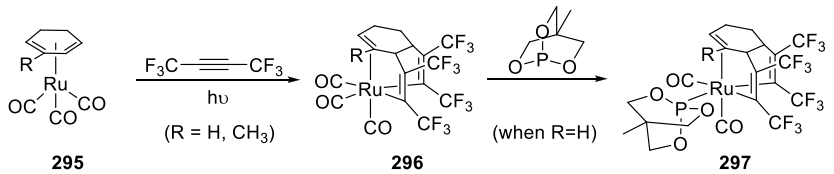


Figure 6. Different oxidative couplings studied by Schlegel and Montgomery et al.[302]

Scheme 113. Synthesis and Characterization of Ruthenacycloheptadiene Complexes by Green and Woodward et al.[303]



benzyl or η^3-allyl interactions in the reaction intermediates might account for the improved regioselectivities. In order to learn more about the reaction mechanism, the stoichiometric reaction of (*E*)-chalcone (R^1 = R^2 = Ph, Scheme 112) and diphenylacetylene with [Ni(cod)$_2$] and tricyclopentylphosphine ($PCyp_3$) was carried out, leading to the isolation in 95% yield of η^3-oxallylnickelacyclopentene **290a**, as revealed by X-ray crystallography. Intermediate **290** reacted with further enone to give the expected cyclohexene derivative. A reversible oxidative cyclization was postulated based on the observation of scrambled products when an enone different to (*E*)-chalcone reacted with **290**. Thus, the mechanism for the reaction was postulated to involve reversible oxidative cyclization of an enone and an alkyne with nickel(0) to generate an η^3-oxallylnickelacyclopentene **290a**, which might be in equilibrium with isomeric 7-membered η^1-*O*-nickelenolate **290b**. 7-Membered η^1-*O*-nickelenolate structures had been earlier characterized as intermediates in enyne cyclizations of alkynyl enal substrates by Montgomery et al.[299] A second enone could then enter the catalytic cycle to generate a 7-membered nickelacycle intermediate that upon reductive elimination furnishes **289** and regenerates the nickel(0) catalytic species. The authors justify the inversion of the stereochemistry (*trans* arrangement of the groups, which were in *trans* in the olefin would be expected) of the carbon marked with a blue spot in product **289** by the involvement of η^1-*O*-nickelenolate **290b**, as previously disclosed by the same group in 6-membered oxa-nickelacycles.[300,301]

Schlegel and Montgomery et al.[302] studied the mechanism of nickel-catalyzed couplings of an enone, alkyne, and organozinc species. They focused their B3LYP/6-31G(d) computational study on the oxidative coupling between the enone and the alkyne and in the role played by dimethylzinc in the process. They considered the four possible oxidative couplings represented (Figure 6). The first corresponds to the usual oxidative coupling in [2 + 2 + 2] cycloaddition reactions (**291**). In this particular case, the barrier is 30.8 kcal/mol. When dimethylzinc acts as a Lewis acid activating the enal carbonyl (**292**), the barrier is reduced by 4.5 kcal/mol. Lewis basic activation via Zn−C agostic interaction (**293**) reduces the Gibbs energy barrier to 10.4 kcal/mol. Finally, combination of the Lewis acid and basic activation (**294**) results in the most favorable oxidative coupling ($\Delta G^{\ddagger}$ = 8.7 kcal/mol). This study demonstrated that organozinc compounds play a key role in the nickel-catalyzed oxidative coupling of an enone and alkyne and that they may be relevant in many cross-coupling processes.

4.3. Ruthenium Complexes

In 1977, Green and Woodward et al.[303] reported the isolation and characterization by X-ray diffraction of ruthenacyclohepta-2,6-diene complex **297** (Scheme 113). Tricarbonyl(cyclohexa-1,3-diene)ruthenium complexes **295** were treated with an excess of hexafluorobut-2-yne under UV light irradiation to generate the coordination sites. Colorless crystalline complexes of **296** were isolated that were shown by mass spectrometry and elemental analysis to have added two alkyne molecules. Replacement of one terminal bonded carbon monoxide by 4-methyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane allowed for the formation of complex **297** that could be characterized by X-ray diffraction. The structure showed that only one of the double bonds (with complete selectivity for the unsubstituted ones) in the original cyclohexa-1,3-diene system in **295** had participated in the processes. Each of the two hexafluorobut-2-yne molecules was formally inserted between the ruthenium atom and one of the carbon atoms of the olefin. The other olefinic bond remained bonded to the ruthenium atom. No reductive elimination was observed in contrast to analogous studies with rhodium (*vide infra*).

As discussed in section 2.4, Kirchner and Calhorda et al.[135] studied the reaction mechanism of the [2 + 2 + 2] cycloaddition of three acetylene molecules catalyzed by [CpRuCl] at the B3LYP/6-31G(d,p)∼SDD level of theory. In the same work, the authors also discussed the [2 + 2 + 2] cycloaddition between ethylene and two acetylene molecules to form cyclohexadiene. They started from the interaction of ruthenacyclopentatriene complex **80** (see, for instance, Scheme 33) with ethylene that coordinates in an η^2-fashion to provide complex [CpRuCl-(C_4H_4)(C_2H_4)] that contains a ruthenacyclopentadiene moiety. Insertion of ethylene into the Ru−C bond is kinetically and thermodynamically less favorable as compared to the acetylene insertion ($\Delta G^{\ddagger}$ = 7.7 vs 0.1 kcal/mol and ΔG_r = −4.6 vs −22.4 kcal/mol, respectively) and results in the formation of a ruthenabicyclo[3.2.0]heptadiene complex. In the rate-determining step, this complex evolves to a ruthenanorbornene complex that is stabilized by an agostic Ru···C−H interaction with one of the two CH_2 groups ($\Delta G^{\ddagger}$ = 24.1 kcal/mol). A subsequent reductive elimination yields an η^4-cyclohexadiene coordinated to [CpRuCl]. The exchange of the cyclohexadiene by two

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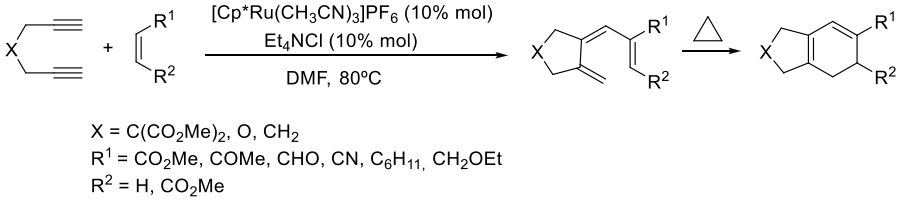
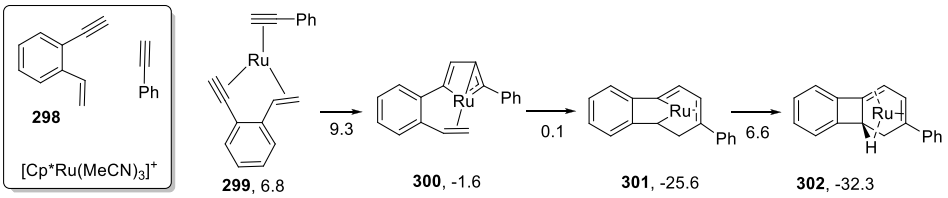
Scheme 114. Formation of Functionalized Bicyclic 1,3-Cyclohexadienes by the Ru-Catalyzed Coupling of Acyclic Alkenes to 1,6-Diynes



Scheme 115. Reaction Mechanism for the [2 + 2 + 2] Cycloaddition of 298 and Phenylacetylene Catalyzed by [Cp*Ru(CH$_3$CN)$_3$] Proposed by Wang et al.[115,a]



[a]Gibbs energies of all intermediates referred to [Cp*Ru(**298**)CH$_3$CN]$^+$ and Gibbs barriers for each step are given in kcal/mol. Ru = [Cp*Ru$^+$].

acetylene molecules allows the catalyst to be recovered and the cycle be reinitiated. As a whole, the barriers involved in the [2 + 2 + 2] cycloaddition of ethylene and two acetylenes catalyzed by [CpRuCl] are higher and the reaction is less exothermic by 4.2 kcal/mol than the corresponding cyclotrimerization of acetylene. Similar results were reported in a following work by Yamamoto et al.[136] that analyzed the [2 + 2 + 2] cycloaddition of two acetylenes and norbornene catalyzed by [CpRuCl]. The main difference was that the ruthenabicyclo[3.2.0]heptadiene complex evolves by ring expansion to a ruthenacycloheptadiene intermediate instead of a ruthenanorbornene complex. The authors studied a competitive cyclopropanation starting from the ruthenabicyclo[3.2.0]heptadiene complex, but the barrier involved in this alternative process was found higher than those corresponding to the [2 + 2 + 2] cycloaddition. Unfortunately, this result was inconsistent with experimental results for unknown reasons.

The Ru-catalyzed [2 + 2 + 2] cycloaddition of 1,6-diynes with alkenes was originally reported by Itoh et al.[304,305] Later, Saá et al.[306,307] reported a study of the Ru(II)-catalyzed cycloaddition of 1,6-diynes and alkenes in which the authors found that, when cyclic alkenes were used, the expected [2 + 2 + 2] cycloadduct was obtained. However, when acyclic olefins reacted, a bicyclic cyclohexadiene in which the double bonds "migrated" from their expected positions was isolated (Scheme 114).

Similar to what was found by Gandon and Aubert et al.[291] in the cobalt-mediated co-oligomerization of alkynes with alkoxylated alkenes (see, for instance, Scheme 106), the reaction of 1,6-diynes and linear alkenes produced 1,3,5-trienes, which after a thermal disrotatory 6e$^-$ π-electrocyclization led to the final 1,3-cyclohexadiene. Therefore, the course of this reaction varies with the nature of the alkene. To characterize the reaction mechanisms of the cyclic and acyclic alkenes, the authors performed B3LYP/6-31G(d)~LANL2DZ calculations with the [Cp*RuCl] catalyst. As a model of cyclic and acyclic alkenes, the authors studied cyclopentene and propene. The most likely reaction mechanism for cyclopentene and propene shares the same steps as those discussed in the previous examples of the Ru(II)-catalyzed [2 + 2 + 2] cycloadditions involving alkenes until the formation of the ruthenacycloheptadiene intermediate. From this intermediate, two different paths can be envisaged, namely, reductive elimination to afford the cyclohexadiene derivative η^2-coordinated to [Cp*RuCl] or β-hydride elimination followed by a reductive elimination to form the 1,3,5-hexatriene derivative η^4-coordinated to [Cp*RuCl]. In the case of propene, the *endo* insertion of the cyclopentene to the ruthenacyclopentadiene intermediate is favored over the *exo* one ($\Delta G^{\ddagger}$ = 6.1 vs 6.9 kcal/mol), generating a ruthenabicyclo[3.2.0]heptatriene and a subsequent ruthenacycloheptadiene stabilized by a C$_\beta$–H agostic interaction. In the next step, the reductive elimination to yield cyclohexadiene has a Gibbs energy barrier of 10.8 kcal/mol, whereas that of the β-hydride elimination to generate the 1,3,5-hexatriene derivative is much lower ($\Delta G^{\ddagger}$ = 1.7 kcal/mol). Both pathways are thermodynamically favored, but the β-hydride elimination is kinetically preferred. This result concurs with the experimental finding that monosubstituted acyclic alkenes give exclusively open 1,3,5-hexatrienes that undergo a thermal disrotatory 6e$^-$ π-electrocyclization to the final observed 1,3-cyclohexadienes. On the other hand, for the cyclopentene, the *exo* insertion of the cyclopentene to the ruthenacyclopentadiene intermediate is more favorable than the *endo* one ($\Delta G^{\ddagger}$ = 8.2 vs 10.9 kcal/mol). In the *exo* ruthenabicyclo[3.2.0]heptatriene and in the *exo* ruthenacycloheptadiene formed by subsequent electrocyclic opening, the H atoms of the initial double bond in the cyclopentene point away from the metal and cannot form a stabilizing C$_\beta$–H agostic interaction with the Ru. Therefore, for cyclopentene, the only possible route is the reductive elimination to yield the cyclohexadiene derivative η^2-coordinated to [Cp*RuCl], explaining the experimental observations.

In 2014, Wang et al.[308] analyzed computationally the formation of dihydrophenylenes from the Ru(II)-catalyzed [2 + 2 + 2] cycloaddition of *o*-alkenylarylacetylene **298** and phenyacetylene (Scheme 115). This reaction was developed experimentally by Saá et al.[309] who also carried out deuterium-labeling experiments that showed no scrambling and thus ruled out the formation of ruthenium-hydride species followed by sequential insertions. The study of Wang et al. was performed with the M06/6-311++G(d,p)~SDD//M06/6-31G(d)~SDD method including the solvent effects of a methanol solution with

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the SMD solvent model. The authors studied first the substitution of two acetonitrile ligands from $[Cp^*Ru(CH_3CN)_3]^+$ by **298**. This process is exergonic by 9.7 kcal/mol and generates the active catalyst $[Cp^*Ru(\mathbf{298})CH_3CN]^+$. Replacement of the acetonitrile in this complex by phenyacetylene is also an exergonic substitution by 6.8 kcal/mol. Three possible oxidative couplings can occur in **299**, i.e., intermolecular alkyne−alkyne, intermolecular alkyne−alkene, and intramolecular alkyne−alkene. The Gibbs energy barriers for these couplings are 9.3, 12.8, and 37.8 kcal/mol, respectively. The authors concluded that the intermolecular alkyne−alkyne is the most efficient, although the intramolecular alkyne−alkene should be favored entropically. This alkyne−alkyne coupling can be head-to-head and head-to-tail. The head-to-tail has a barrier 4.1 kcal/mol higher than the head-to-head coupling that is the preferred and leads to the formation of complex **300**. From the C−C bond distances of the 5-membered ring, the authors concluded that complex **300** does not have a bis(carbene) structure. In the next step, the insertion of the alkene on the Ru−C bond can be a *distal* or *proximal* insertion. The alkene *distal* insertion, which gives rise to **301**, has a very low Gibbs energy barrier of only 0.1 kcal/mol, much lower than that of the *proximal* insertion ($\Delta G^{\ddagger}$ = 53.6 kcal/mol). The higher barrier of the latter is attributed to the formation of a strained 4-membered ring. The reductive elimination from **301** with a Gibbs barrier of 6.6 kcal/mol is exergonic by 6.7 kcal/mol. It generates complex **302** with an η^4-coordination of the dihydrophenylene to $[Cp^*Ru^+]$ and a C−H agostic bond that further stabilizes this complex. The authors also compared the cocyclization of **298** and phenylacetylene with the dimerization of two *o*-alkenylarylacetylenes **298**. The reaction mechanism followed exactly the same steps, but the barriers were lower for the cocyclization of **298** and phenylacetylene. In particular, the Gibbs barrier of the rate-determining step corresponding to the oxidative coupling is 1.5 kcal/mol lower for the cocyclization than for the dimerization.

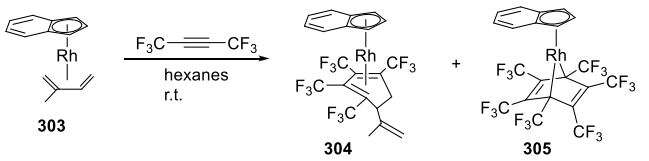
With regard to the work by Saá et al.,[309] Yamamoto et al.[310] reported in 2017 the Cp*RuCl-catalyzed cycloisomerization of 1,5,10-enediynes bearing a styryl terminal to afford exocyclic 1,3-dienes with an indenylidene group. On the basis of M06-DFT calculations and deuterium labeling experiments, the authors also found that the most favorable alkene insertion mode in the cycloisomerization is the one that avoids the formation of a strained 4-membered ring moiety.

4.4. Rhodium Complexes

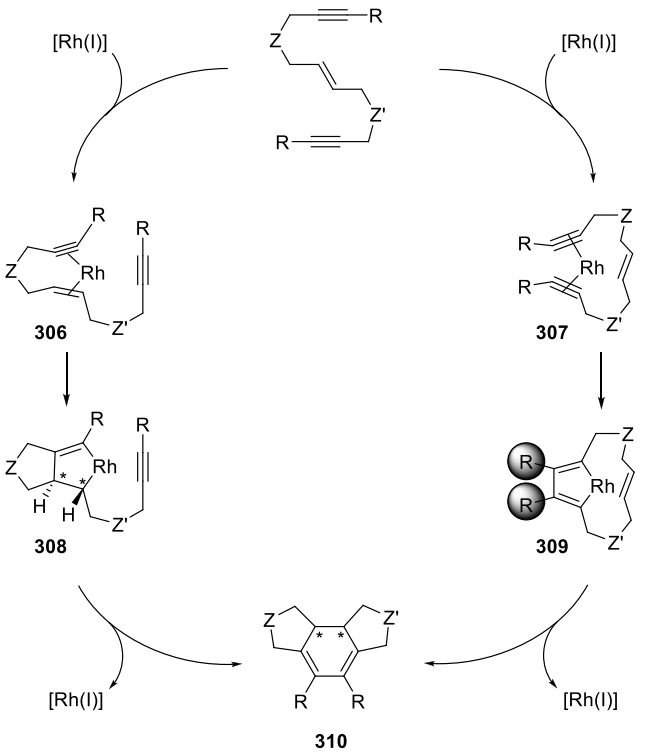
Green et al.[311] studied the reaction of η^4-1,3-diene(η^5-indenyl) rhodium complexes **303** with hexafluorobut-2-yne (Scheme 116), in a continuation of the study previously undertaken with ruthenium.[303] The reaction was fast in hexanes at room temperature and led to a crystalline product **304** that upon characterization by X-ray diffraction was shown to feature a propenylcyclohexa-1,3-diene ring η^4-attached to the rhodium atom. Thus, a cyclotrimerization of one of the alkenes in the diene and two alkynes had taken place. The reaction was also efficient using *trans*-penta-1,3-diene or ethylene as an olefinic component and 3,3-dimethylbut-1-yne as an alkyne, although, in these cases, the product could only be determined by spectroscopic techniques. A second isolated product **305** was assigned by means of spectroscopic techniques to η^5-indenyl-[hexakis(trifluoromethyl)benzene]rhodium, by analogy with isostructural η^5-cyclopentadienylrhodium species, characterized by X-ray diffraction.[312,313] **305** and its cyclopentadienyl analogue are examples of isolated and characterized 7-rhodanorbornadiene complexes, which are postulated as intermediates in the [2 + 2 + 2] cycloaddition of three alkynes. However, no evolution to the benzene derivative was reported.

In 2011, our group studied computationally the oxidative coupling in enediynes catalyzed by the Wilkinson catalyst.[314] As shown in Scheme 117, there are two possible intramolecular

Scheme 116. Intermediates Isolated upon Reaction of Indenyl Rhodium Complexes and Hexafluorobut-2-yne



Scheme 117. Possible Routes for the Oxidative Addition and [2 + 2 + 2] Cycloaddition Process in Enediynes[a]



[a]Reprinted with permission from ref 314. Copyright 2011 ACS.

oxidative couplings: alkene−alkyne through rhodacyclopentene **308** and alkyne−alkyne via rhodacyclopentadiene **309**. In the alkene−alkyne coupling, one must also consider the two different faces of the alkene. Shibata et al.[315] suggested that the enantiomeric excess observed in the final product **310** (Scheme 117) should be greater if the alkene−alkyne coupling is the active oxidative coupling route. Given that the oxidative coupling is the rate-determining step, the barrier of this step should be relatively high and the energy difference between the transition states leading to the two different diastereoisomers could be relatively large, resulting in higher enantiomeric excesses. Our study performed at the B3LYP/cc-pVDZ-PP level of theory considered the oxidative coupling processes for Z and Z′ = O, NH, CH_2, CH_3SO_2N, and $C(CO_2CH_3)_2$, R = H and

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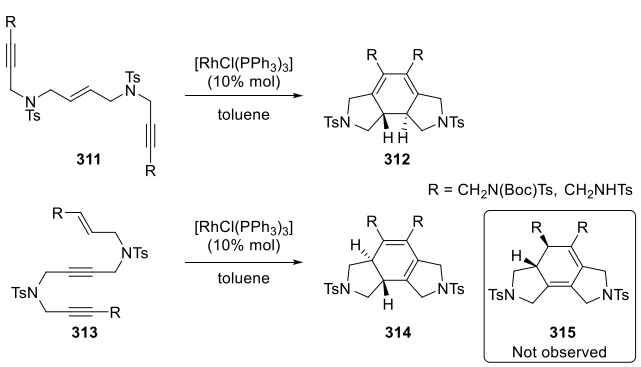
CH_3, and $[RhClPH_3]$ and $[RhCl(PH_3)_2]$ as possible catalysts. Although the $[RhClPH_3]$ catalyst is more efficient for the oxidative coupling step, the $[RhCl(PH_3)_2]$ catalyst was taken as a model for the active catalytic species bearing biphosphine ligands. As a preliminary result, we compared the barriers obtained with the model catalyst $[RhClPH_3]$ with those of the real $[RhClPPh_3]$ species for Z = Z′ = O and R = H and CH_3. The conclusion was that substitution of PPh_3 by PH_3 increases the Gibbs barriers of the oxidative coupling by 15−20 kcal/mol, but the qualitative conclusions are the same; i.e., the lower barriers correspond to the coupling of the two alkynes if the alkynes are terminal, whereas, in the case of R = CH_3, the two oxidative couplings have similar Gibbs energy barriers. By moving from R = H to CH_3, the barriers for the alkyne−alkyne coupling increase by ca. 10 kcal/mol and those of the alkyne−alkene coupling by 2 kcal/mol, in agreement with the observed reduction of reactivity when changing R = H by R = CH_3.[316] The same qualitative results were obtained for the rest of the tethers considered. Deformation energies of the enediynes and the active catalyst led to the conclusion that the alkyne−alkyne coupling in methyl-substituted alkynes is less favored because it requires a higher enediyne deformation energy in the transition state due to the steric repulsion between the two methyl groups (see species **309** in Scheme 117). Moreover, the oxidative coupling for R = H is favored as compared to R = CH_3 due to the lower reactivity of the internal alkynes. On the other hand, although the effect of the tether is minor, the barrier for the oxidative coupling increases somewhat in the order Z = O < NH < CH_2, being lower for more electronegative tethers. Bulkier tethers like CH_3SO_2N or $C(CO_2CH_3)_2$ favor alkyne−alkyne coupling irrespective of the R substituent. We concluded that higher enantiomeric excesses are expected for bulky R terminal substituents and chiral Rh(I) catalysts with biphosphine ligands.

Our group[317] studied also the effect that the order of the unsaturations in linear endiyne substrates had on the products being formed and justified it mechanistically. Enediyne substrates **311**, with the double bond in the central position of the chain, gave the expected tricyclic cyclohexadiene compounds **312** upon treatment with the Wilkinson catalyst in toluene at 100 °C. On the contrary, the reaction of enediynes **313**, that had the two alkynes in contiguous positions, afforded cycloadduct **314** with the double bonds shifted from their expected positions (Scheme 118). The reason for the different behavior of enedyines **311** and **313** was analyzed by performing B3LYP/cc-pVDZ-PP calculations. To reduce the computational effort, the SO_2Ar moieties and the phenyl groups of the Wilkinson catalyst were substituted by a H atom. Moreover, in our models of **311** and **313** with R = CH_2NH_2, we considered both $[RhClPH_3]$ and $[RhCl(PH_3)_2]$ as possible active catalysts. According to our calculations, the two catalysts were similarly efficient to catalyze the [2 + 2 + 2] cycloaddition of **311-A** (our model of **311**) following the traditional Rh(I)-catalyzed [2 + 2 + 2] steps, namely, alkyne−alkyne coupling that is the rate-determining step, alkene insertion to yield the rhodacycloheptadiene intermediate, and final reductive elimination. It is worth noting that the rhodacycloheptadiene intermediate has no hydrogen atoms at the β position that can interact with rhodium (the closest H_β is at 3.4 Å). Therefore, β-hydride elimination is not possible for the enediyne substrate **311-A**. On the other hand, the reaction mechanism for enediyne **313-A** is shown in Scheme 119. The reaction starts with the alkyne−alkyne coupling, which is the most favored among all possible oxidative couplings, to give rhodacyclopentadiene **316**. There are several options for the insertion of the alkene to **316**; the insertion having the lowest Gibbs energy barrier is the one that forms rhodabicyclic complex **317**. There are two possible pathways from complex **317**: first, C−C bond formation assisted by a H_β agostic interaction to yield **318** ($\Delta G^{\ddagger}$ = 14.5 kcal/mol), and second, electrocyclic opening to give a rhodacycloheptadiene with a Gibbs barrier of 7.2 kcal/mol. Although the latter path is kinetically favored, it cannot continue because reductive elimination from the rhodacycloheptadiene has a high barrier of 24.5 kcal/mol. This transformation from **317** to the rhodacycloheptadiene is reversible, and then, **317** can evolve to **318** that is easily transformed into **319** by a β-hydride elimination. As said before, the β-hydride elimination is a quite common process in CpCo- and Cp*RuCl-catalyzed cycloadditions involving alkenes. Reductive elimination ($\Delta G^{\ddagger}$ = 16.8 kcal/mol) generates product **314-A** η^2-coordinated to $[RhClPH_3]$. And final exchange of ligands closes the catalytic cycle.

Evans et al.[318,319] reported in 2010 that the regioisomer obtained in the [2 + 2 + 2] cycloaddition between 1,6-enynes and alkylsubstituted propiolates could be efficiently controlled by the use of different ancillary ligands on the metal center (Scheme 120). Five years later, the results were rationalized by means of B3LYP-D3/cc-pVTZ(-f)~LACV3P//B3LYP-D3/6-31G(d,p)~LACVP calculations including solvent effects in a collaboration with Baik et al.[320] In their computational study, Evans and Baik et al. considered $[Rh(PH_3)_2]^+$ and [Rh(S)-xyl-BINAP]$^+$ as active catalysts and as reactant **321** with X = O and R = CH_3. In the case of $[Rh(PH_3)_2]^+$, the authors found that the most favorable oxidative coupling is the intramolecular alkyne−alkene coupling of the 1,6-enyne leading to a rhodacyclopentene intermediate ($\Delta G^{\ddagger}$ = 11.5 kcal/mol). The catalytic cycle continues with the binding of the methyl-substituted propiolate and subsequent insertion into the Rh−C(alkenyl) or Rh−C(alkyl) bonds of the rhodacyclopentene complex. The stronger interaction of the p_π orbital of the alkenyl carbon with the alkyne substrate favors the insertion into the Rh−C(alkenyl) bond. The orientation of the methyl-substituted propiolate during the insertion determines the regioselectivity of the reaction. As shown in Figure 7, the p_π orbital of the alkenyl carbon in the rhodacyclopentene intermediate overlaps more efficiently with the π^* of the alkyne in the insertion that finally leads to product **322a** than that in the route to **322b**, which translates into a lower barrier for the former ($\Delta G^{\ddagger}$ = 13.0 vs 16.5 kcal/mol). The insertion, which is the rate-determining step, generates a rhodacycloheptadiene intermediate. Reductive elimination and

Scheme 118. Diverse Outcomes on the Reaction of Linear Enediynes and the Wilkinson Catalyst



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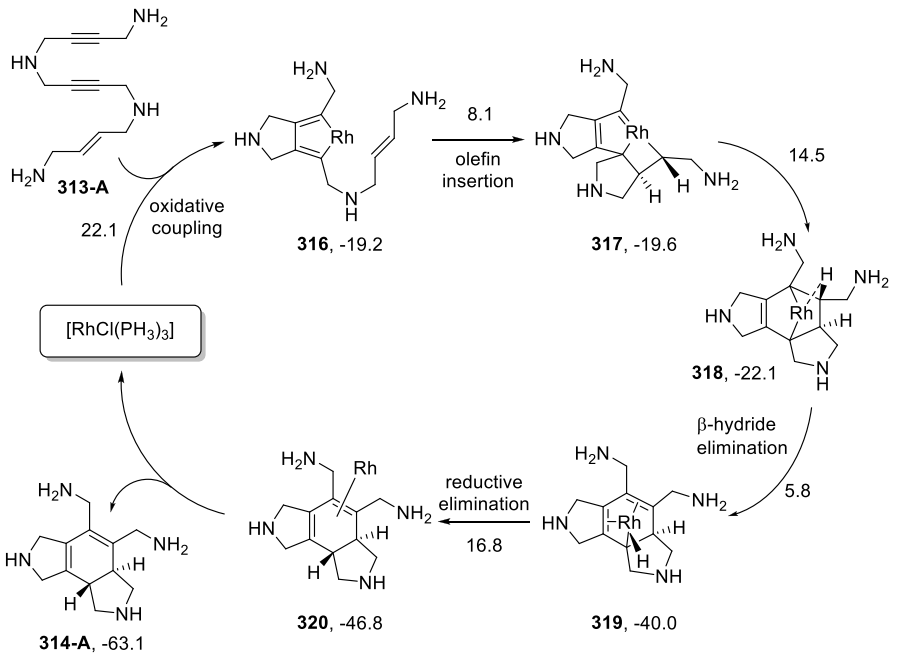
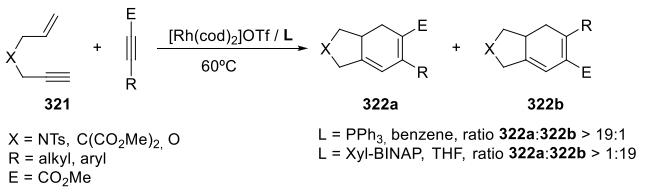
Scheme 119. Reaction Mechanism for the [2 + 2 + 2] Cycloaddition of 313-A Catalyzed by $[RhCl(PH_3)_3]$ from ref 317[a]



[a]Gibbs energies of all intermediates referred to **313-A** and the Wilkinson catalyst and Gibbs barriers for each step. All energies are given in kcal/mol. Rh = $[RhCl(PH_3)_2]$, except for **319** and **320** for which Rh = $[RhClPH_3]$.

Scheme 120. Ancilliary Ligand Controlled Regioselectivity in the Cycloaddition of Enynes and Propiolates



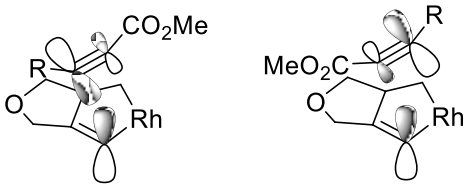


Figure 7. Main orbital interaction in the insertion of substituted methyl propiolate into the Rh−C(alkenyl) bond of the rhodacyclopentene intermediate.

ligand substitution afford the bicyclohexadiene product **322a** and reinitiate the catalytic cycle. Therefore, the outcome of the $[Rh(PH_3)_2]^+$-catalyzed [2 + 2 + 2] cycloaddition between 1,6-enynes and alkylsubstituted propiolates is electronically controlled. In the case of the $[Rh(S)$-xyl-BINAP$]^+$ catalyst, the bulkier xyl-BINAP ligand produces a steric clash between one of the xylyl groups and the ester group forcing the insertion in the orientation that yields product **322b**. This insertion has now a lower Gibbs energy barrier than that leading to **322a** ($\Delta G^{\ddagger}$ = 18.5 vs 21.8 kcal/mol) in agreement with the experimental observed outcomes.

Fullerene C_{60} is a specific type of olefin that our group has been able to involve in rhodium-catalyzed [2 + 2 + 2] cycloaddition reactions and unravel the peculiarities of the reaction mechanism by making use of DFT calculations. In a first paper,[166] we computationally studied the mechanism of the intermolecular [2 + 2 + 2] cycloaddition of acetylene and C_{60} catalyzed by $[RhCl(PPh_3)_3]$ with the M06-L-D3/cc-pVTZ-PP//B3LYP-D3/cc-pVDZ-PP method. We included energy corrections for dispersion (the D3 correction by Grimme) because dispersion corrections are essential in the study of the reactivity of fullerenes.[321] We analyzed all potential reaction paths (in particular, alkyne−alkyne vs alkyne−C_{60} oxidative coupling and insertion of the [6,6] and [5,6] bonds of C_{60} into the rhodacyclopentadiene intermediate) and concluded that, first, alkyne−alkyne oxidative coupling is favored; second, the [6,6] bonds of C_{60} are more reactive than the [5,6] ones; and, third, the reaction is kinetically and thermodynamically feasible. These preliminary results also indicated that, to avoid benzene formation from the cyclotrimerization of acetylene, it is convenient to work with an excess of C_{60}. We also suggested to use diynes instead of acetylene molecules to entropically reduce the energy barriers.

Once the feasibility of the reaction was proven, the reaction was tested in the laboratory. We were able to show that the reaction, when catalyzed by $[Rh(cod)_2]BF_4$ and Tol-BINAP, not only worked with great efficiency but also allowed for the direct preparation of open-cage fullerenes **323** (Scheme 121).[322] We completed our experimental work by performing a computational study with the M06-L-D3/cc-pVTZ-PP//B3LYP-D3/cc-pVDZ-PP method of the reaction mechanism of the intermolecular [2 + 2 + 2] cycloaddition of the 1,6-diyne of Scheme 121 and C_{60} catalyzed by $[RhBINAP]^+$. To reduce the computational cost, the tosyl group of the 1,6-diyne was substituted by a mesyl group and, in the catalyst ligand, the tolyl groups were replaced by methyl groups and the binaphthyl was replaced by a biphenyl (see **P9** in Scheme 122). We focused our attention in the last steps of the reaction corresponding to the opening of the fullerenic cage. The steps of the initial part of the

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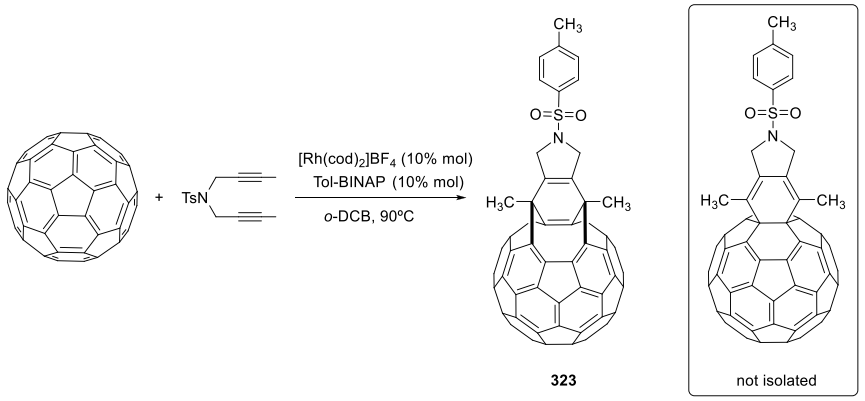
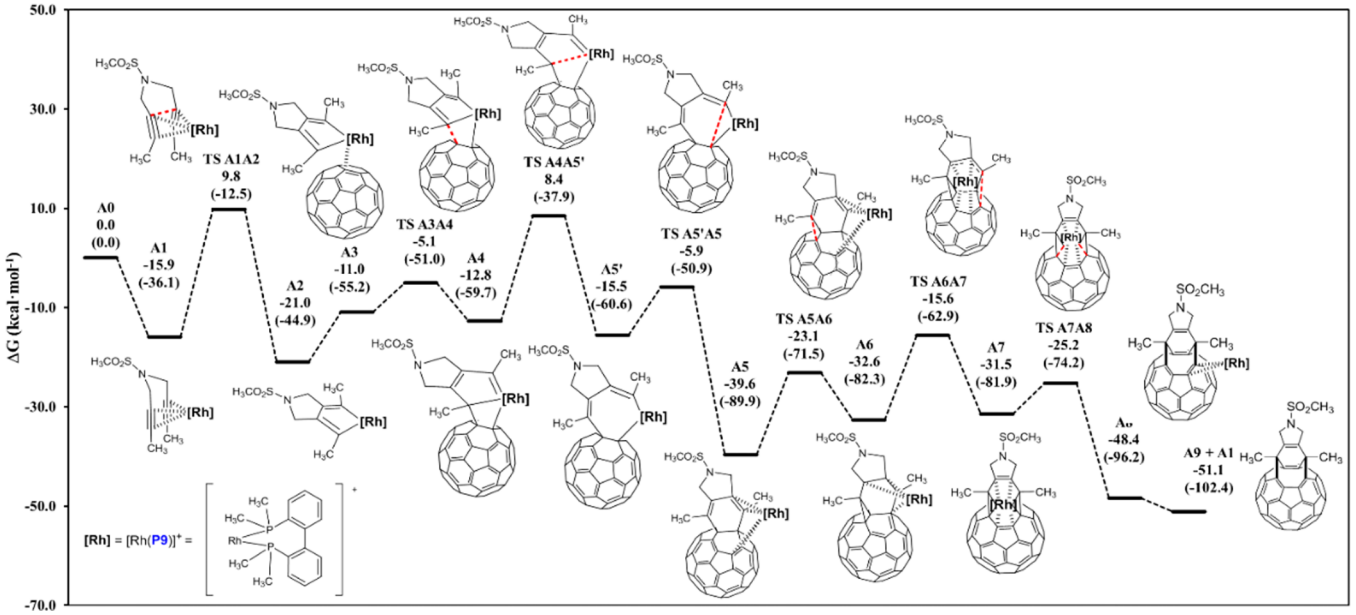
Scheme 121. Direct Formation of Open-Cage C_{60} Fullerenes by Rhodium-Catalyzed [2 + 2 + 2] Cycloaddition of 1,6-Diynes and Fullerene C_{60}



Scheme 122. M06-L-D3/cc-pVTZ-PP//B3LYP-D3/cc-pVDZ-PP Gibbs Energy Profile at 363.15 K Including Solvent Effects of the [2 + 2 + 2] Cycloaddition Reaction of C_{60} and a Nonterminal Tethered Diyne to Yield the Cyclohexadiene-Fused C_{60} Derivative A5 Followed by Fullerene Cage Opening to Form A9[a]



[a]Energies in parentheses are electronic energies. All relative energies in kcal/mol are given relative to **A0** (C_{60} + catalyst + nonterminal tethered diyne). Reprinted with permission from ref 322. Copyright 2018 Wiley.

reaction (**A0** → **A5**) are typical for a metal-catalyzed [2 + 2 + 2] cycloaddition, i.e., intramolecular oxidative alkyne−alkyne coupling, insertion of a [6,6] bond of C_{60} to the rhodacyclopentadiene intermediate to form a rhodabicyclo[3.2.0]heptadiene complex, and reductive elimination to form **A5** in which the Rh is coordinated to both the C_{60} and cyclohexadiene moieties. The oxidative coupling with a Gibbs energy barrier of 25.7 kcal/mol is the rate-determining step of this process. Release of the cyclohexadiene-fused C_{60} product and substitution by 1,6-diyne to recover **A1** is exergonic by 8.9 kcal/mol. However, transformation from free cyclohexadiene-fused C_{60} product to the final bis(fulleroid) product requires photoexcitation either through a combination of [4 + 4] and retro-[2 + 2 + 2] cycloaddition or via stepwise di-π-methane rearrangement, because the [4 + 4] and the di-π-methane rearrangement processes are thermally forbidden. Given that our system was not irradiated, the formation of the bis(fulleroid) product could be justified only thanks to the presence of the catalyst. As shown in Scheme 122, in the presence of the catalyst, **A5** can be transformed into the [5,6] (bis)methanofullerene η^4-coordinated to Rh **A7** by a stepwise di-π-methane rearrangement with an overall Gibbs energy barrier of 24.0 kcal/mol. Opening the two fullerene C−C bonds of the cyclopropane moieties via an allowed retro-[2 + 2 + 2] cycloaddition in **A7** easily generates complex **A8** containing the final bis(fulleroid) coordinated to [Rh(**P9**)]$^+$. Final release of **A9** product exchanged by a 1,6-diyne reactant is slightly exergonic (ΔG_r = −2.8 kcal/mol) and allows the catalytic cycle to be reinitiated.

4.5. Iridium Complexes

Paneque and Poveda et al.[323] have studied the reaction of iridium(I) bis(ethylene) complex **324** with alkynes in dichloromethane (Scheme 123). The reaction with 2 equiv of alkyne at room temperature afforded compound **327**. Compound **327** was transformed into **328** slowly when it was kept at room

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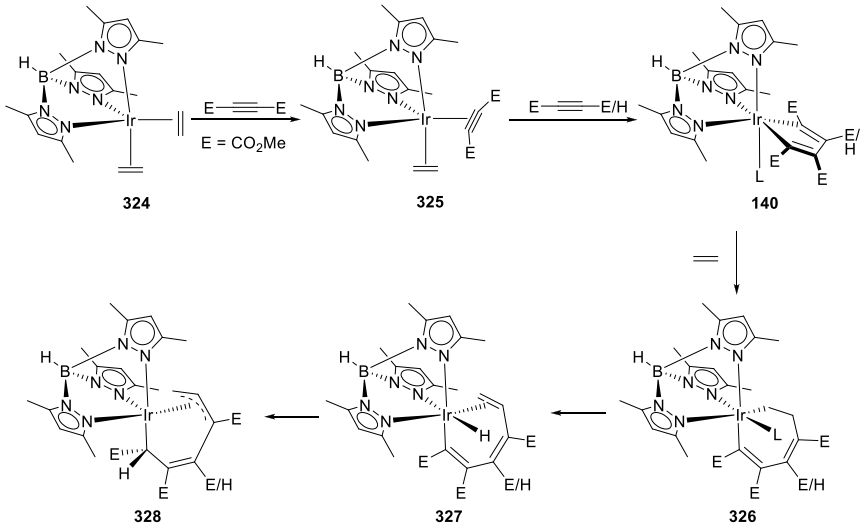
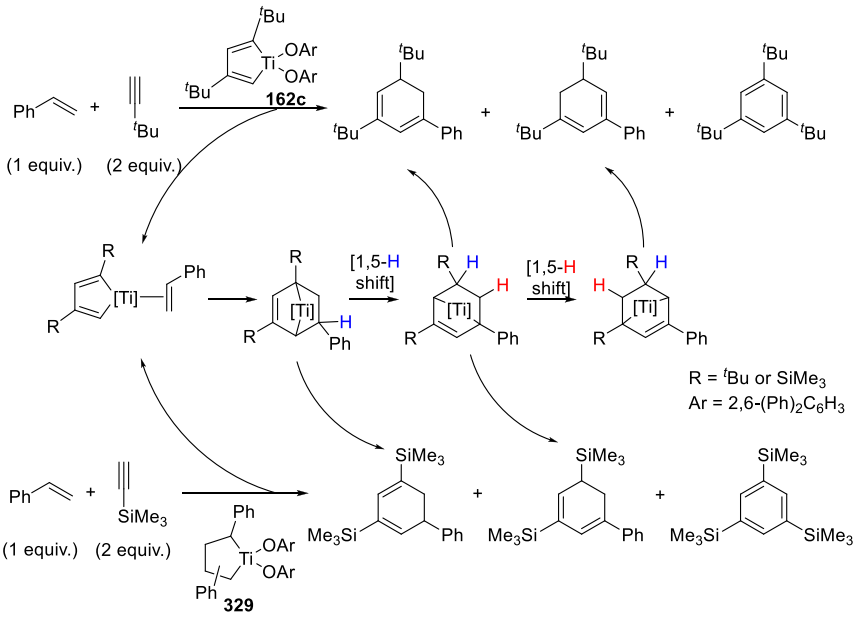
Scheme 123. Iridium Intermediates Detected and Characterized by Paneque and Poveda et al.[323]



Scheme 124. Titanium-Catalyzed [2 + 2 + 2] Cycloaddition of Alkynes and Alkenes



temperature but cleanly and faster upon heating at 60 °C. Intermediate **325**, corresponding to the substitution (by an associative mechanism) of one of the ethylene ligands by a molecule of alkyne, could be detected when monitoring the reaction at low temperature by NMR. Detection and characterization of **140** (L = H_2O) were made possible by the use of water as a trapping agent, as previously reported by the same authors[191] (see, for instance, Scheme 50). Reaction of **140** (L = H_2O) toward ethylene was monitored by NMR at room temperature. Formation of **326**, which again evolved into **328** upon heating, was detected. Complex **326** results, presumably, from initial coordination of ethylene to iridium and subsequent insertion into the Ir−C bond. Characterization of complex **326** was accomplished by X-ray crystallography when an 18-electron complex was formed by reaction with acetonitrile. Reductive elimination from **326** was not observed. When two different alkynes—methyl propiolate and dimethyl acetylenedicarboxylate—reacted with **324**, formation of the iridacyclopentadiene **140** and the subsequent ethylene insertion took place in a regio- and stereoselective manner. As in the analogous study with alkynes, none of the complexes evolve to the [2 + 2 + 2] cycloaddition product. Still, the characterization of these complexes supports the structures proposed for the addition of alkenes to metallacyclopentadienes.

4.6. Palladium Complexes

One of the main difficulties in achieving, in a completely intermolecular setup, selective [2 + 2 + 2] cyclotrimerizations of two alkynes and one alkene is to avoid the competitive cycloaddition of three alkynes, purportedly running through the same metallacyclopentadiene intermediate. In 1976, Itoh and Ibers et al.[324] made use of the electron-biasing of the unsaturated reagents to report a selective co-cycloaddition of two alkynes and one alkene. Tetrakis(methoxycarbonyl)-palladacyclopentadiene in its oligomeric form, generated by reaction of dimethyl acetylenedicarboxylate with $[Pd_2(dba)_3]$ as

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already reported in 1974 by Moseley and Maitlis,[201] was found to form stable adducts with cyclooctadiene and norbornadiene. These complexes with electron-rich olefins could be isolated and characterized (including X-ray diffraction for the norbornadiene one) in contrast to the electron-poor dimethyl acetylenedicarboxylate adduct, which could not be isolated. Advantage was taken of the preferential formation of the adduct with the electron-rich olefins to achieve the selective cyclotrimerization of two DMAD molecules and one electron-rich olefin, such as norbornene or norbornadiene, using tetrakis(methoxycarbonyl)palladacyclopentadiene as catalyst.

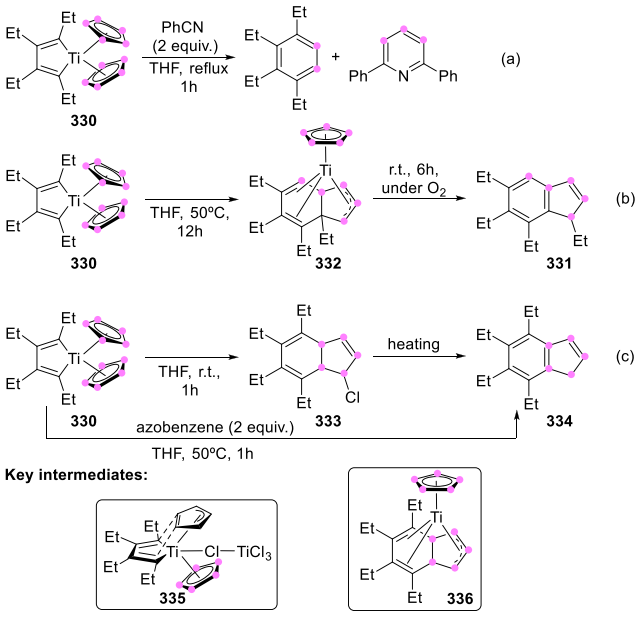
4.7. Titanium Complexes

Rothwell et al.[325,326] reported the selective synthesis of 1,3-cyclohexadiene scaffolds by reaction of two alkynes and one olefin under catalysis by titanacyclopentadiene (**162c**) or titanacyclopentane (**329**) aryloxide complexes (Scheme 124). Even when starting from titanacyclopentane **329**, the reaction was postulated to involve titanacyclopentadiene complexes as key intermediates, as supported by NMR studies. The preferential interaction of titanacyclopentadienes with alkene over alkyne explains the selective formation of cyclohexadiene scaffolds over benzene compounds, which are generally obtained as minor byproducts. A prominent feature of the methodology developed is the isomerization observed leading to regioisomeric 1,3-cyclohexadienes where the double bonds are shifted from their expected positions. Kinetic studies pointed out a rate-determining attack of the olefin on the titanacyclopentadiene to produce a metal-bound 1,3-cyclohexadiene. A concerted formation of the two C−C bonds forming a titananorbornene structure seemed more plausible based on the known reactivity of organometallic species of titanium (i.e., the known easy β-hydrogen abstraction/elimination process in 7-membered titanacyclic rings to form 1,3,5-trienes[327]). The titananorbornene complex could also account for the isomerization process via intermediate cyclohexadienyl hydride complexes, leading to overall 1,5-hydrogen shifts, as supported by deuterium labeling experiments.

Six years later, Cha et al.[328] reported that the use of homoallylic alcohols in reactions analogous to the ones reported by Rothwell et al.[325,326] prevented the isomerization of the 1,3-cyclohexadiene by metal-mediated 1,5-hydrogen shift. Cha et al.[328] postulated that homoallylic alcohol in situ exchanged with an alkoxide on the titanium. Thus, insertion of the alkene into the titanacyclopentadiene generated a strained 6-membered titanate, which favored reductive elimination over 1,5-hydrogen shift.

Although the Cp ligand was considered inert for a long time, the group of Takahashi described a series of unusual reactions of titanacyclopentadiene complexes with Cp ligands and revealed that Cp is not always as innocent as it may seem. In 2003, a first paper was published, which described the reaction of titanacyclopentadiene **330** with 2 equiv of benzonitrile in refluxing THF to afford 1,2,3,4-tetraethylbenzene and 2,6-diphenylpyridine, in 60 and 52% yield, respectively (Scheme 125, equation a).[329] The authors postulated an unprecedented cleavage of the Cp ligand with two of its carbon atoms ending up in the benzene derivative and the remaining three in the pyridine, as evidenced by deuterium and ^{13}C labeling studies. When the reaction was carried out excluding the nitrile, indene derivative **331** (Scheme 125, equation b), in which one of the Et groups had unexpectedly migrated onto the 5-membered ring, could be isolated.[330] The reaction yield was highly dependent on the reaction workup, being optimal when the reaction mixture was stirred in the presence of oxygen once the reaction was completed. The precise placement in the product of the carbon atoms coming from the Cp was established by ^{13}C-labeling experiments, which indicated that the cyclopentadienyl ligand had been cleaved. The authors showed that the transformation proceeded via a reaction complex **332**, already described in 1996 by Rosenthal et al.,[331] in which the alkyl group had not migrated yet. Oxidation of the Ti(II) to Ti(IV) in **332** triggers aromatization by elimination of a hydrogen atom with concomitant alkyl migration. In a subsequent paper, the authors could establish that Cp breakage was avoided by carrying out the reaction with an excess of $TiCl_4$.[332] Formation of 1-chloro-4,5,6,7-tetraalkyldihydroindene **333** was postulated to take place through Cp ring slippage (from η^5- to η^3-) triggered by $TiCl_4$ coordination, followed by Diels−Alder (see key intermediate **335** in Scheme 125) or stepwise reaction of the slipped Cp ring and the titanacyclopentadiene. Heating in toluene at reflux efficiently transformed dihydroindene **333** to indene **334** (Scheme 125, equation c). The mechanism for the formation of indenyl derivatives from **330**, including the unusual rearrangement of the cyclic five carbons of the Cp ring to linearly aligned carbons in **331** and **332**, was unraveled in a subsequent paper.[333] A kinetic study revealed that the reaction rates for the formation of **332** from **330** and **334** from **330** (with an improved experimental methodology that used azobenzene as a reducing agent) were almost the same, leading the authors to postulate a common intermediate **336**. The reorganization of the Cp carbons from **336** to **332** is explained by metathesis-type carbon−carbon bond cleavage in titanacyclobutane intermediates. This process has recently been exploited by the same group to make the 5-membered ring in titanadihydroindene complexes to travel all around the 6-membered ring.[334] Finally, the same group disclosed that, when **330** was treated with PMe_3 and azobenzene, 4,5,6-trisubstituted indene derivatives were obtained with the loss of one substituent and linear rearrangement of the Cp ligand carbons.[335]

Scheme 125. Unusual Reactions of Titanacyclopentadienes with Cp Ligands



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5. [2 + 2 + 2] CYCLOADDITION OF CUMULATED SYSTEMS

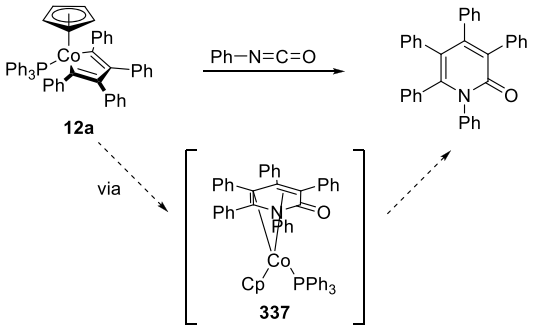
The transition-metal-catalyzed [2 + 2 + 2] cycloaddition of alkynes and cumulated systems such as isocyanates, isothiocyanates, ketenes, allenes, carbodiimides, carbon dioxide, and carbon disulfide is a straightforward and excellent method to obtain different carbo- and heterocyclic compounds.[21,23,25,26]

When this kind of unsaturation is involved in the cycloaddition, two aspects have to be considered from the point of view of the mechanism: at which step the cumulated system enters the catalytic cycle and which of the two double bonds of the unsaturation participates in the cycloaddition. In the case of isocyanates, experimental results demonstrated that the cycloaddition involves only the N=C bond instead of the C=O bond, generating pyridine-2-one derivatives. When isothiocyanates are participating, the cycloaddition takes place on their C=S bond to afford thiopyranimines. In the case of ketenes, substrates that have been poorly used in cycloadditions, the C=C bond is involved in the cycloaddition, affording the corresponding cyclohexadienones. In contrast, when allenes participate in the cycloaddition, the chemoselectivity with regard to which of its two C=C double bonds reacts need to be controlled. In this case, the number of possible chemo- and regioisomers is increased.

5.1. Cobalt Complexes

Hong and Yamazaki[336] studied the reaction of isolated cobaltacyclopentadiene **12a** with isocyanates to afford 2-oxo-1,2-dihydropyridines (Scheme 126). The same authors had

Scheme 126. Synthesis of Pyridine-2-ones from Co Complex 12a and Isocyanates

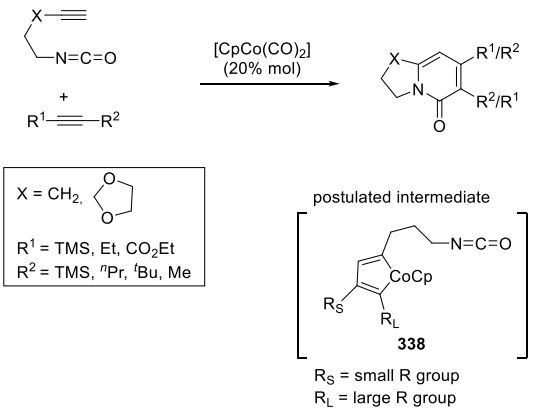


previously done analogous reactions with alkynes to afford benzene derivatives (Scheme 5), with nitriles to obtain pyridines (Scheme 75) and with olefins to obtain 1,3-cyclohexadienes (Scheme 100). The reaction took place with the N=C bond of the isocyanate. When complex **12a** reacted with phenylisocyanate, a crystalline solid was isolated. Further oxidation with ceric ammonium nitrate and thermolysis afforded pyridine-2-one derivative. The authors postulated a pyridone–cobalt complex **337** in which the cobalt was coordinated to the diene part, concluding that it may be an intermediate in the formation of pyridine-2-ones.

Cobalt complex **12a** also reacted with carbon disulfide and methyl isothiocyanate to afford the corresponding dithiopyrone and (2*H*)-thiopyran-2-imine in 50 and 10% yields, respectively.[244,337]

Vollhardt and Earl[338] set up a cobalt-catalyzed [2 + 2 + 2] cycloaddition reaction of 5-isocyanatopentynes with monoalkynes to be applied in the synthetic approach to the antitumor alkaloid camptothecin (Scheme 127). The regioselectivity observed in the process studied allowed the authors to postulate

Scheme 127. Synthesis of Pyridine-2-one Derivatives from 5-Isocyanatopentynes and Monoalkynes



an initial oxidative coupling between the two alkynes in which the large group of the external alkyne was situated in the α-position of the cobalt metal (intermediate **338**) and, therefore, next to the pyridone carbonyl group in the final product. The regioselectivity observed in the formation of cobaltacyclopentadiene from unsymmetrical alkynes, with the bulkier group preferentially occupying the position α to cobalt, is in agreement with calculations of Wakatsuki et al.,[104] showing that the regioisomeric distribution in the oxidative coupling of unsymmetrical alkynes depends primarily upon the steric requirements of the substituents. The intramolecular oxidative coupling between the alkyne and the isocyano group was discarded.

In 2013, Lv et al.[339] carried out the first computational study using the B3LYP/6-311+G(d)~SDD method of the two-state reaction mechanism for the reaction catalyzed by CpCo of two acetylenes with hydrogen isocyanate (HN=C=O, isoelectronic with CO_2) to yield pyridine-2-one. As discussed in section 2.2 (Scheme 16), they also found that first the cobaltacyclopentadiene $CpCo(C_4H_4)$ intermediate is generated in the singlet state but rapidly evolved to its triplet ground state through a MECP located at 1.3 kcal/mol from the singlet complex. During the end-on coordination of hydrogen isocyanate to triplet cobaltacyclopentadiene, a crossing and spin inversion to the singlet state took place with an intersystem crossing barrier of only 8.4 kcal/mol. The magnitude of the spin–orbit coupling (SOC) of 393.37 cm^{-1} for such intersystem crossing, calculated with a CASSCF method using the second-order configuration interaction procedure, indicated that the spin crossing was quite feasible. Facile hydrogen isocyanate insertion ($\Delta G^{\ddagger}$ = 2.5 kcal/mol) generated the azacobaltabicyclo[3.2.0]heptadienone intermediate in which the N is located at the α-site with respect to the metal. Interestingly, the same insertion with the carbon atom α to the metal had an energy barrier of 43.7 kcal/mol, and consequently, this alternative insertion can be ruled out. The authors attributed the more favorable N attack to form the N—Co bond to the good overlap of the HOMO of HN=C=O (π-molecular orbital with the largest lobes in N and O) with the Co empty d LUMO orbitals. The generated azacobaltabicyclo[3.2.0]-heptadienone intermediate evolved through a barrierless process to pyridine-2-one η^4-coordinated to CpCo. In this intermediate, the C and N atoms of the hydrogen isocyanate were involved in

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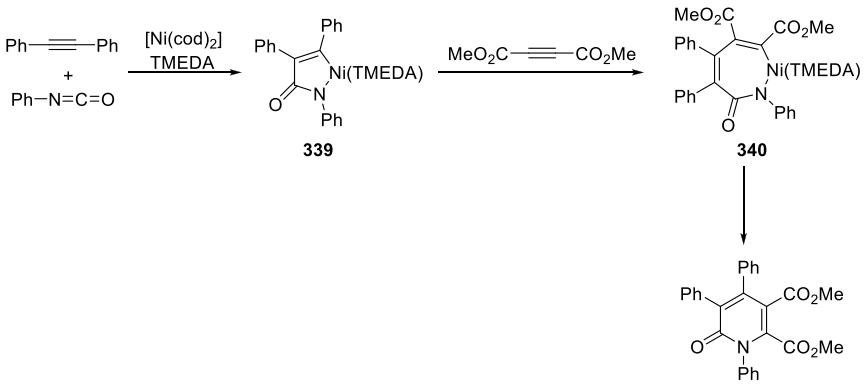
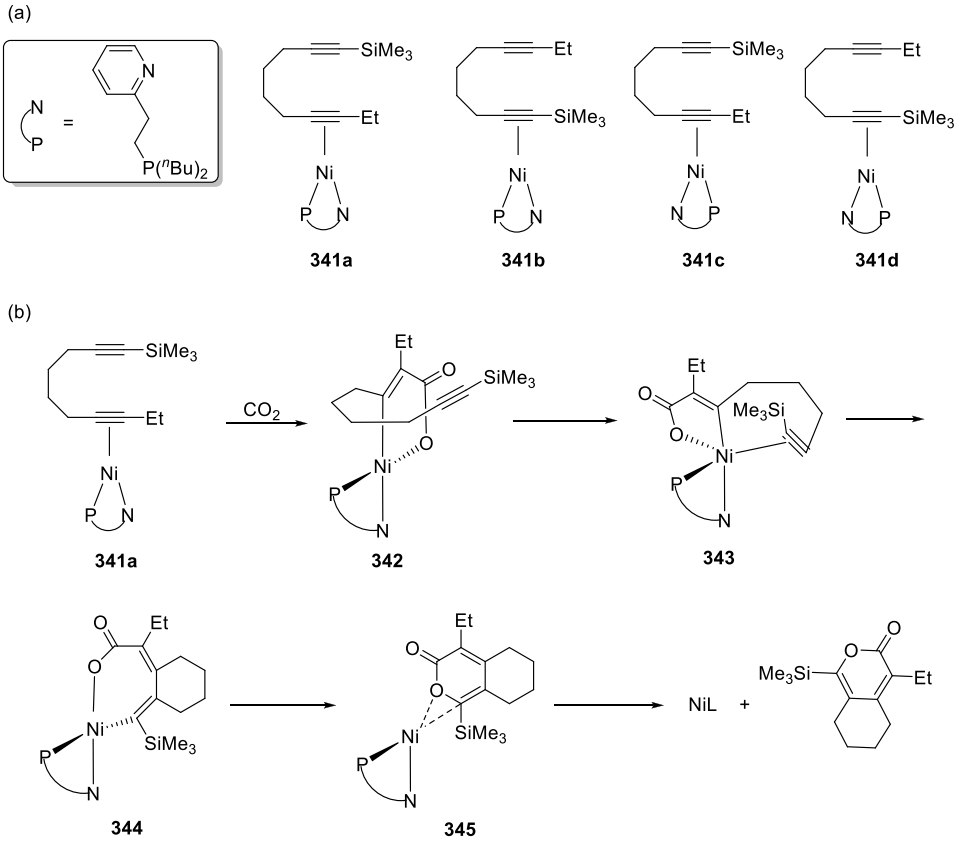
Scheme 128. Ni-Catalyzed [2 + 2 + 2] Cycloaddition of Alkynes with Phenylisocyanate



Scheme 129. NiL-Catalyzed [2 + 2 + 2] Cycloaddition of Unsymmetric Diynes with CO_2, (a) Initial Complex; (b) Reaction Mechanism



the η^4-coordination. This intermediate rearranged to a pyridine-2-one η^4-coordinated to CpCo through the four C atoms of the heterocycle releasing 25.8 kcal/mol. A second crossing point located at 2.5 kcal/mol transformed efficiently the singlet to the more stable triplet (SOC = 225.3 cm^{-1}). In this final product, the unpaired electrons were mainly located in the Co atom and the pyridine-2-one was η^2-coordinated to CpCo.

One year later, Dahy and Koga[340] performed B3LYP/6-31G(d,p) calculations of the reaction mechanisms for the reactions of cobaltacyclopentadiene with hydrogen isocyanate and hydrogen isothiocyanate in the singlet and triplet states catalyzed by CpCo. The possible organic products of these reactions are pyridin-2-one and pyran-2-imine for the reaction of HN═C═O and pyridine-2-thione and thiopyran-2-imine for the reaction of HN═C═S. Pyridin-2-one and pyridine-2-thione were 22−26 kcal/mol more stable than pyran-2-imine and thiopyran-2-imine. The authors attributed the higher stabilization of pyridin-2-one and pyridine-2-thione to better aromatic stabilization energies. In the case of the [2 + 2 + 2] cycloaddition of hydrogen isocyanate, the main differences between the study of Dahy and Koga[340] and that of Lv et al.[339] was that the HN═C═O insertion to (HNCO)CpCo(C_4H_4) complex in the singlet state generated an azacobaltacycloheptadienone complex (instead of the azacobaltabicyclo[3.2.0]heptadienone complex) with an activation barrier of only 0.4 kcal/mol. This intermediate evolved to its triplet ground state through a MECP located at 2.0 kcal/mol from the singlet complex. Reductive elimination with a barrier of 18.0 kcal/mol

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formed a pyridine-2-one η^2-coordinated to CpCo in the triplet state. This step was the rate-determining step. Because the pyridine-2-one was more stable in the singlet than in the triplet state, a change in the spin took place in the last step to yield the pyridine-2-one η^4-coordinated to CpCo by the four carbon atoms of the heterocycle in the singlet state. Dahy and Koga attributed the differences observed in the two studies to the fact that the azacobaltabicyclo[3.2.0]heptadienone intermediate located by Lv et al.[339] was not a stationary point. Finally, the reaction mechanism for the reaction with hydrogen isothiocyanate to form pyridine-2-thione was essentially the same as that found for the reaction with hydrogen isocyanate. The most important difference was that, in the reaction with NH═C═S, the authors were able to locate an azacobaltabicyclo[3.2.0]-heptadienthione intermediate that transformed to the azacobaltacycloheptadienthione complex, both in the singlet state.

Let us conclude by noting that none of the two previous studies analyzed the possible involvement of the C═O double bond in the cycloaddition process, although knowing that [2 + 2 + 2] cycloaddition involving CO_2 requires harsher conditions, it is likely that insertion of the C═O bond is not competitive with the insertion of the C═N bond. Moreover, Dahy and Koga attributed the observed pyridin-2-one and pyridine-2-thione formation rather than pyran-2-imine and thiopyran-2-imine to the higher stability of the formers.

5.2. Nickel Complexes

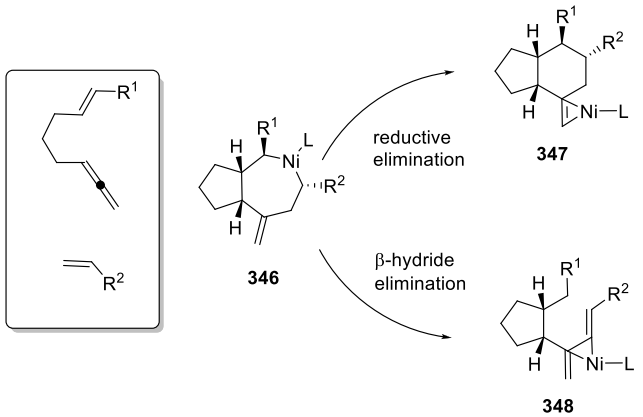
In contrast to the cobalt cases commented above, Hoberg et al.[341,342] isolated an azanickelapentacycle complex **339** in the nickel-catalyzed [2 + 2 + 2] cycloaddition of diphenylacetylene and phenylisocyanate (Scheme 128). Complex **339** further reacted with an activated alkyne to afford azanickelaheptacycle derivative **340**, which could also be isolated. In this case, the oxidative coupling took place between the alkyne and the isocyanate with the nitrogen atom being placed next to the nickel. The insertion of a second molecule of an activated alkyne to intermediate **339** took place in the nickel−carbon bond rather than the nickel−nitrogen bond, affording **340**, which gave the corresponding pyridine-2-one after reductive elimination.

Louie and Duong[343] in 2006 in a study based on the cycloaddition of one alkyne and two isocyanates in order to obtain pyrimidinedione derivatives also proposed an initial oxidative coupling between the alkyne and the isocyanate to afford an azanickelapentacycle complex homologous to **339** described by Hoberg. Product distribution resulting from competition experiments (the reaction of 1-trimethylsilyl-1-propyne with two different isocyanates) helped the authors to confirm the initial formation of an azanickelapentacycle intermediate in the catalytic cycle.

Liu and Bi et al.[344] studied at the B3LYP/6-31G-(d,p)~LANL2DZ level the reaction mechanism of the NiL-catalyzed (L = 1-(2′-pyridyl)-2-(di-*n*-butyl-phosphine)ethane) [2 + 2 + 2] cycloaddition of unsymmetrical 1,7-diynes and CO_2 in tetrahydrofuran (THF) to generate pyrones (Scheme 129). The P—N catalyst investigated by these authors was employed in the experimental nickel(0)-catalyzed cycloaddition of silyl diynes with carbon dioxide reported by Tsuda and Saegusa et al.[345] The initial coordination of the diyne to the catalyst NiL generated species **341a−341d** (Scheme 129, equation a). All reaction paths starting from any of these complexes were studied, together with the possibility that oxidative coupling occurs between the coordinated C≡C bond and CO_2 or with the coordinated and uncoordinated C≡C bonds. Given that one expects equilibrium between species **341a−341d**, the Curtin−Hammett principle[178] holds, and, therefore, the major nickelafuranone intermediate should be the one coming from the oxidative coupling with the lowest in energy transition state among the eight possible reaction paths. The most favorable path was the one that started from complex **341a** in Scheme 129. First, a CO_2 molecule oxidatively coupled with the coordinated RC≡CEt bond to afford a 5-membered nickelafuranone intermediate **342** with a Gibbs energy barrier of 20.3 kcal/mol. Alkyne−alkyne coupling requires a much higher energy barrier ($\Delta G^{\ddagger}$ = 47.2 kcal/mol). The fact that the oxidative coupling between CO_2 and alkyne was preferred over the alkyne−alkyne coupling in Ni-catalyzed [2 + 2 + 2] cycloadditions was previously experimentally reported.[346−348] Then, the nickelafuranone intermediate **342** isomerized through a series of C—C single bond rotations to place the RC≡CSiMe$_3$ triple bond coordinating to Ni (**343**). This process costs 16.1 kcal/mol. Next, the C≡C coordinated triple bond inserted into the Ni—C bond to generate a 7-membered nickelaheterocycle **344**. The Gibbs energy barrier for this process was 33.1 kcal/mol, and therefore, C≡C insertion was the rate-determining step of this [2 + 2 + 2] cycloaddition. The final reductive elimination to generate the pyrone and recover the catalyst had to surmount a barrier of 19.9 kcal/mol. All other reaction paths involved higher energy barriers.

Yang and Ehara[349] studied computationally the cycloaddition of 1,6-ene-allenes and alkenes with the M06/6-311++G-(2d,2p)~SDD//B3LYP/6-31G(d,p)~LANL2DZ method including the solvent effects of a benzene solution with the SMD solvation model. Their aim was to provide clues to understand the fact that, experimentally, the nickel shows strong ligand control in the preference for the reductive elimination or the β-hydride elimination in the final step of the [2 + 2 + 2] cycloaddition between 1,6-ene-allenes and alkenes (Scheme 130). The Ni with the P(*o*-tol)$_3$ ligand always suffers reductive elimination from the nickelacycloheptane intermediate **346** delivering a *cis*-hydrinane **347**, whereas with the PBu$_3$ ligand the nickelacycloheptane intermediate undergoes β-hydride elimination to produce *trans* diene **348**. The reaction mechanism of this [2 + 2 + 2] cycloaddition was studied taking into account the 1,6-ene-allene with R^1 = H and the alkene with R^2 = H in Scheme 130 and NiPMe$_3$ as the catalyst. The oxidative coupling can be an intermolecular process involving the allene and the alkene of

Scheme 130. Final Steps of the Ni-Catalyzed [2 + 2 + 2] Cycloaddition of 1,6-Ene-allenes and Alkenes



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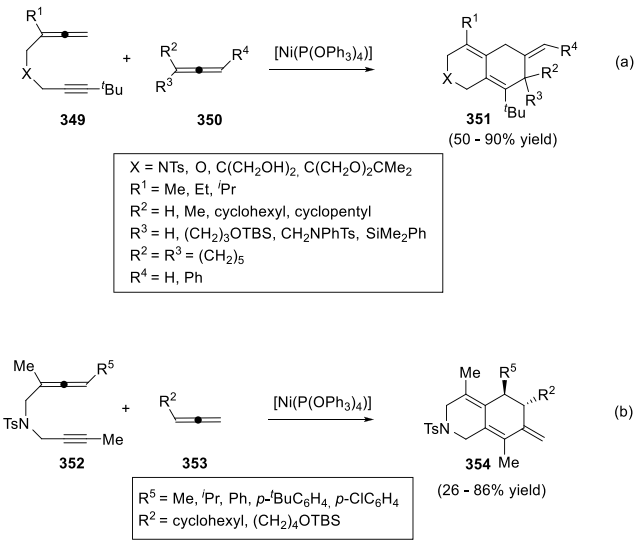
the 1,6-ene-allene or the allene and the external alkene. The latter coupling with a Gibbs energy barrier of 27.3 kcal/mol had a lower barrier than the former by 7.6 kcal/mol. Subsequent alkene insertion to yield the nickelacycloheptane **346** was also more favorable for the nickelacyclopentane formed with the allene of the 1,6-ene-allene and the external alkene. The nickelacycloheptane intermediate has four stereocenters, with the transition state leading to stereoisomer **346** being the most stable by at least 2.5 kcal/mol. For this catalyst, the final reductive elimination from the nickelacycloheptane intermediate had a Gibbs energy barrier of only 3.4 kcal/mol as compared to the barrier for the β-hydride elimination of 11.2 kcal/mol. Therefore, the cyclohexane product was kinetically and thermodynamically favored. Further calculations with the experimental P(*o*-tol)$_3$ and PBu$_3$ ligands confirmed that the reductive elimination was preferred over the hydride elimination, irrespective of the ligand considered. However, for L = PBu$_3$, the presence of bulky R^1 groups in the 1,6-ene-allene such as CO$_2$Me or CO$_2$Et destabilized the reductive elimination process and the alkenylative cyclization became the preferred reaction path for the last step of the cycloaddition. In the particular case of R^1 = CO$_2$Et and R^2 = CO$_2$^{t}Bu, the transition state for the hydride elimination was found to be more stable than that of the reductive elimination by 4.2 kcal/mol. The authors attributed the different chemoselectivity found for the P(*o*-tol)$_3$ and PBu$_3$ ligands in the [2 + 2 + 2] cycloaddition of alkenes and 1,6-ene-allenes with bulky R^1 substituents to the capability of the PBu$_3$ ligand to reduce the substrate−ligand repulsion in the transition state of the β-hydride elimination by adjusting its configuration from C_{3v} to C_{2v}.

Whereas the theoretical study of Yang and Ehara focused on the cycloaddition of 1,6-ene-allenes and alkenes, recently, Arai et al.[350] performed an experimental and theoretical study based on the [2 + 2 + 2] cycloaddition of 1,6-yne-allenes **349** and **352** and allenes **350** and **353** (Scheme 131). In all cases, the cycloaddition was chemoselective, taking place between the terminal double bond of the yne-allene and with the more substituted double bond of the external allene. Therefore, two fused 6-membered ring systems were formed selectively. The steric bulk of R^1 and the terminal ^{t}butyl group in **349** directed the regioselectivity of the process, generating only regioisomer **351** (Scheme 131, equation a). On the other hand, the presence of an R^5 terminal group in the yne-allene **352** when reacting with monoallenes **353** afforded the other regioisomer **354** with a *trans* configuration (Scheme 131, equation b).

Scheme 131. Ni-Catalyzed [2 + 2 + 2] Cycloaddition of 1,6-Yne-allenes and Allenes



To reveal the reaction mechanism of this process and especially the origin of the regioselectivity, M06/6-31G(d)∼LANL2DZ calculations were run for a model of the reaction in equation a in Scheme 131 in which X = NMs instead of NTs for **349**, the catalyst was [Ni(P(OMe)$_3$)$_4$], and R^1 = R^2 = R^3 = Me and R^4 = H. The reaction starts with the formation of a π-complex between [Ni(POMe$_3$)] and **349**. Oxidative coupling between the C≡C coordinated triple bond and the terminal double bond of the allene takes place ($\Delta G^{\ddagger}$ = 15.7 kcal/mol). The alternative coupling with the internal double bond of the allene was not considered. Next, the external allene **350** coordinates to nickelacyclopentene and inserts into the nickelacyclopentene. All eight possible insertions resulting from the substituted vs unsubstituted double bond of the allene, insertion into Ni—C(sp^3) vs Ni—C(sp^2) bonds, and the two possible orientations of the external allene (either substituted or unsubstituted double bond close to the ^{t}Bu substituent) were analyzed. It was found that the most favorable insertion corresponds to the insertion of the unsubstituted double bond of the allene into the Ni—C(sp^3) bond of the nickelacyclopentene overcoming a barrier of 27.7 kcal/mol. This insertion took advantage of minimizing the steric repulsion between ^{t}Bu and dimethyl groups and led to the final observed product **351** after facile reductive elimination. The rest of the insertions had higher energy barriers by 3−30 kcal/mol.

5.3. Ruthenium Complexes

Schmid and Kirchner[351] studied with the B3LYP/6-31G(d,p)∼SDD method the [2 + 2 + 2] cycloaddition catalyzed by CpRuCl of two acetylenes with isocyanate (HN═C═O) to produce pyridine-2-one or pyrane-2-imines and with isothiocyanate (HN═C═S) to yield pyridine-2-thione or thiopyrane-2-imines. As discussed in section 2.4 in Scheme 33, the first step corresponded to the coordination of the two acetylene molecules to yield complex **79**. Oxidative coupling of the two acetylenes leads to the formation of the ruthenacyclopentatriene complex **80** ($\Delta G^{\ddagger}$ = 13.7 kcal/mol). The key step was the intermolecular insertion of a double bond into the ruthenacyclopentatriene intermediate in a concerted fashion, affording a bicycle carbene intermediate. In the case of the isocyanate, the most favorable insertion corresponded to the N═C bond, with the N directly attached to Ru in the final bicycle carbene intermediate. In addition, for unsymmetrical ruthenacyclopentatrienes, the insertion took place in the Ru—C$_\alpha$ bond of the most electronegative α-carbon.[260] The insertion of the N═C bond of isocyanate into the ruthenacyclopentatriene intermediate, which was responsible for the chemoselectivity of the reaction, had a Gibbs energy barrier of only 2.9 kcal/mol, 15.1 kcal/mol lower than the insertion of the C═O bond. Subsequent rearrangement to an azaruthenanorbornenone was the rate-determining step ($\Delta G^{\ddagger}$ = 23.5 kcal/mol). Then, reductive elimination generated the final pyridine-2-one η^4-coordinated to CpRuCl. The cycle was completed by an exothermic displacement of pyridine-2-one by two acetylene molecules. The main difference with isothiocyanate was that the most favorable insertion corresponded to the C═S bond, with the S directly attached to Ru in the final bicycle carbene intermediate. This insertion had a Gibbs energy barrier of 6.1

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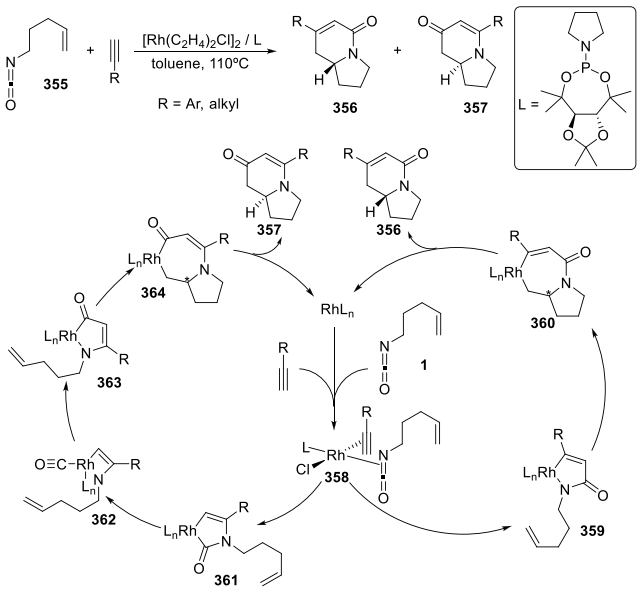
kcal/mol as compared to the 13.0 kcal/mol of the insertion of the N═C bond, and the final product was a thiopyrane-2-imine molecule. As before, the rate-determining step corresponded to the rearrangement of the bicyclic carbene intermediate ($\Delta G^{\ddagger}$ = 23.7 kcal/mol). The change of chemoselectivity from pyridine-2-one to thiopyrane-2-imine when moving from isocyanate to isothiocyanate was in line with experimental observations.[352,353]

In a subsequent paper, Kirchner et al.[354] studied with the same method the [2 + 2 + 2] cycloaddition of two acetylenes and a CX_2 (X = O, S, Se) molecule catalyzed by CpRuCl to yield pyrane-2-one, thiopyrane-2-thione, and selenopyrane-2-selenone. For CO_2, the intermediates involved in the reaction mechanism were the same as those in the case of isocyanate and isothiocyanate, although the rate-determining step had a Gibbs energy barrier of 34.7 kcal/mol, notably higher than those of isocyanate and isothiocyanate. For CS_2 and CSe_2, the reaction mechanism followed the same steps but now the rate-determining step was the final reductive elimination with Gibbs energy barriers of 31.6 kcal/mol for CS_2 and of 34.1 kcal/mol for CSe_2. Therefore, the most favorable [2 + 2 + 2] cycloaddition among CX_2 (X = O, S, Se) took place for CS_2. The results for the cycloaddition of two acetylenes and CS_2 were already discussed in a previous paper by the same authors.[135]

5.4. Rhodium Complexes

Rovis et al.[355] developed an asymmetric rhodium-catalyzed [2 + 2 + 2] cycloaddition of terminal alkynes and alkenyl isocyanates **355**, leading to the formation of two different products, lactam **356** and vinylogous amide **357** (Scheme 132, top). The selectivity depended not only on the structure and electronics of the ligand used but also on the steric and electronic effects of the alkyne substrate.

Scheme 132. Rhodium-Phosphoramidite-Catalyzed Cycloaddition of Alkenyl Isocyanates and Alkynes



Based on the product ratios and competitive reactions, the authors postulated a reaction mechanism (Scheme 132, bottom) involving oxidative cyclization of the alkyne and the isocyanate to form two different regioisomeric intermediates **359** and **361**, in which the relative orientation of the two unsaturations is surprisingly switched. Whereas intermediate **359** easily inserted the alkene into the Rh−N bond to afford intermediate **360**, insertion of the alkene in **361** was presumably impeded by the strain in the bicyclic intermediate to be formed and thus CO migration through intermediate **362** operated. Intramolecular oxidative cyclization of alkenylisocyanate **355** was disregarded basically as a result of the competitive experiments involving alkenes with different steric shielding that led to equimolar amounts of the corresponding products and the formation of opposite major enantiomers of **356** and **357** with the same ligand.

The remarkable regioselectivity obtained in the reaction was justified by the steric environment created by the monodentate C_2-symmetric phosphoramidite ligands used. Analysis of the X-ray crystal structures of various rhodium(I)(cod)chloride/phosphoramidite complexes showed that the phosphoramidite ligands biased the coordination of the alkyne and isocyanate substrates with their smaller substituents in the same hemisphere of the square-planar complex by sterically hindering the other face (see intermediate **358** in Scheme 132). The authors suggested that both products **356** and **357** were formed from this complex with orthogonally coordinated π-components. Intermediate **359** that leads to lactam product **356** was formed by bending the CO of the isocyanate and the terminal C−H of the alkyne away from the Rh center and toward each other. On the other hand, intermediate **361**, en route to product **357**, was obtained when the *N*-alkyl group of the isocyanate and the internal carbon of the alkyne bend away from the Rh center. Neither the Wakatsuki−Yamazaki steric nor Stockis−Hoffman stereoelectronic models adequately explain the regioselectivity obtained. Thus, the authors postulated that a complex interplay of steric and electronic effects controls the selectivity of the reactions. Finally, the authors focused their attention on the rationalization of the stereochemistry observed. With regard to the formation of lactam products **356**, it was suggested that the enantioinduction which takes place in the *syn*-coplanar intermediate preceding alkene insertion was controlled both by facial selectivity of the alkene (dictated by the geometry of the tether) and facial selectivity at the rhodium. The lack of DFT or experimental data on the rhodium(III) intermediates involved in the enantioselective formation of the vinylogous amide **357**, comprising migration of the CO, impeded a conclusive enantioinduction rationalization.

Our research group[356,357] has studied the involvement of allenes as cumulated unsaturated compounds in rhodium-catalyzed [2 + 2 + 2] cycloaddition reactions. In a first study,[356] linear allene-ene-allene substrates **365** and allene-yne-allene substrates **366** were treated with the Wilkinson complex, affording tricyclic structures **367** and **368**, respectively. These compounds were obtained as single diastereoisomers, and both feature an exocyclic diene. In addition to this highly stereoselective process, the reaction was also regioselective with cycloaddition taking place only with the inner double bond of the two allenes (Scheme 133).

In order to go further in the mechanism of the cycloaddition of these substrates, DFT calculations were performed at the M06-2X/cc-pVTZ//B3LYP/cc-pVDZ level of theory on the substrate **365b** of Scheme 133. As suggested by previous results,[165] the [$RhCl(PPh_3)$] complex derived from the Wilkinson catalyst was considered the active catalytic species. The goal was first to analyze which of the three unsaturations initially gave the oxidative coupling to generate the rhodacyclopentane intermediate, second, to understand why it was that the inner double bond of the allene participated in the cyclo-

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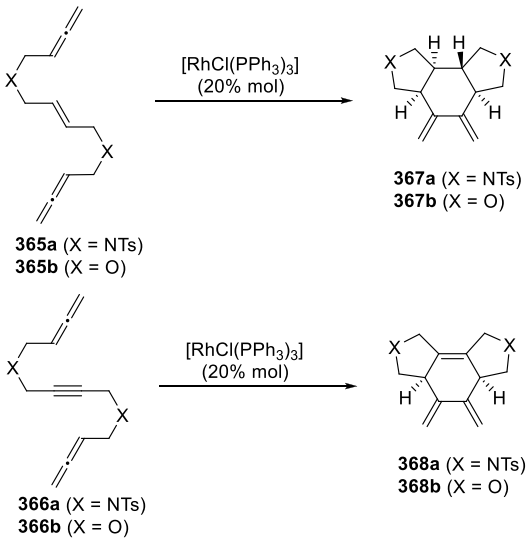
Scheme 133. Rh-Catalyzed [2 + 2 + 2] Cycloaddition of Allene-ene/Yne-allene Substrates 365 and 366



addition, and, finally, to discover why the reaction was diastereoselective. To reach the first goal, we studied the possible oxidative couplings shown in Figure 8. Only some of

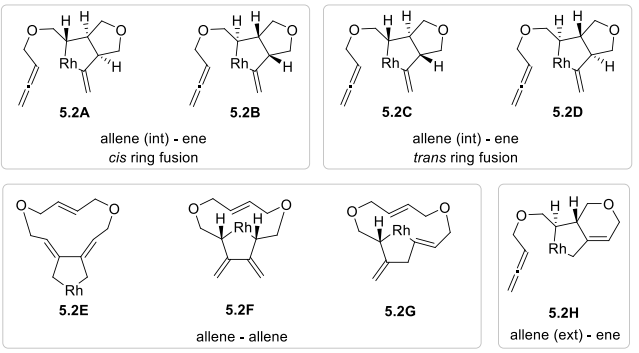


Figure 8. Structure of the different rhodacyclopentadienes obtained from the different oxidative couplings studied. [Rh] = [RhCl(PPh$_3$)]. Reprinted with permission from ref 356. Copyright 2014 Wiley-VCH.

them lead to the experimentally observed product (**5.2A-D** and **5.2F**). The oxidative couplings between the ene and the internal double bond of the allenes **A**–**D** differ either in the relative position of the phosphine ligand (A and B) or in the face of the double bond, resulting in the four possible *cis* **A** and **B** and *trans* **C** and **D** attacks. The most favored oxidative coupling with a Gibbs energy barrier of 18.7 kcal/mol was the one that generated the rhodacyclopentane **5.2A** with a *cis* ring fusion. The larger reactivity of the internal double bond of the allene was attributed to the fact that the occupied π-molecular orbital of the internal double bond was 0.4 eV destabilized as compared to that of the terminal double bond. However, it is worth noting that there are examples of oxidative couplings in which the external double bond of the allene is more reactive than the internal one.[358]

The next step was the insertion or the Diels–Alder addition of the allene to generate a rhodacycloheptane, a rhodabicyclo[3.2.0]heptane, or a rhodanorbornane intermediate. For this step, only the internal double bond of the unreacted allene was taken into account given that this insertion is the only one that leads to the experimentally observed products. Figure 9 draws the four possible insertions and the two intramolecular

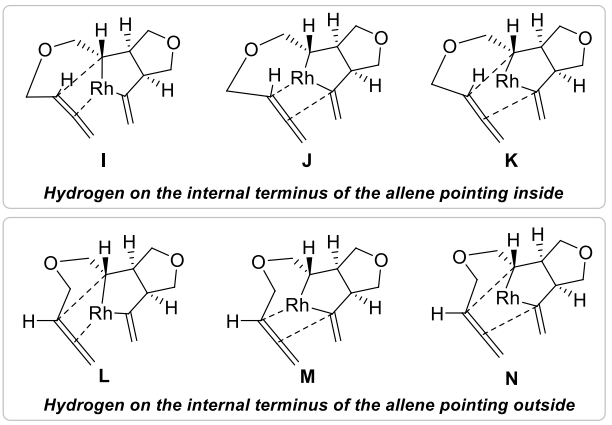


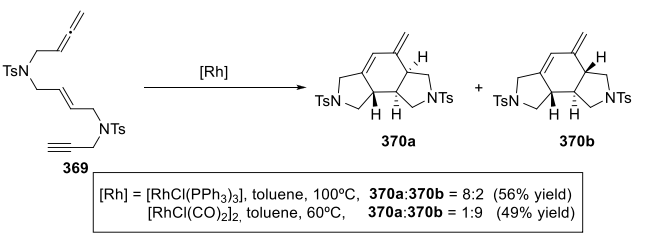
Figure 9. Structure of the different approximation analyzed for the insertion of the internal double bond of the unreacted allene to the rhodacyclopentane **5.2A**. [Rh] = [RhCl(PPh$_3$)]. Reprinted with permission from ref 356. Copyright 2014 Wiley-VCH.

Diels–Alder additions studied. All approaches of the unreacted allene occurred in one of the faces of the rhodium, since the other was hindered by the presence of the phosphine and the chloride. We were unable to locate the rhodanorbornane intermediates corresponding to attacks **K** and **N** in Figure 9. Consequently, a possible intramolecular Diels–Alder addition was discarded. Among the different allene insertions, we found that attack **I** is the most favorable with a Gibbs energy barrier of 24.0 kcal/mol. This step is the rate-determining step of this process and leads to a rhodacycloheptane intermediate. Subsequent reductive elimination ($\Delta G^{\ddagger}$ = 12.5 kcal/mol) yielded product **367b** η^2-coordinated to Rh. **367b** was finally released by substitution with **365b**. As a whole, the transformation of **365b** to **367b** was exergonic by 80.4 kcal/mol.

We then extended the previous study to rhodium-catalyzed cycloaddition of linear allene-ene-yne substrates **369**.[357] In this case, the inner double bond of the terminal allene was also the bond that was involved in the cycloaddition, affording tricyclic derivatives **370**, featuring an exocyclic double bond. Two diastereoisomers **370a** and **370b** were obtained, and it was possible to modulate the ratio using different rhodium catalytic systems (Scheme 134).

In our previous study, we had demonstrated by DFT calculations that the initial oxidative coupling took place between one allene unit and the contiguous unsaturation. Given that in substrates **369** the oxidative coupling of the allene with the alkyne is not geometrically favored, we were interested

Scheme 134. Rh-Catalyzed [2 + 2 + 2] Cycloaddition of Allene-ene-yne Substrates 369



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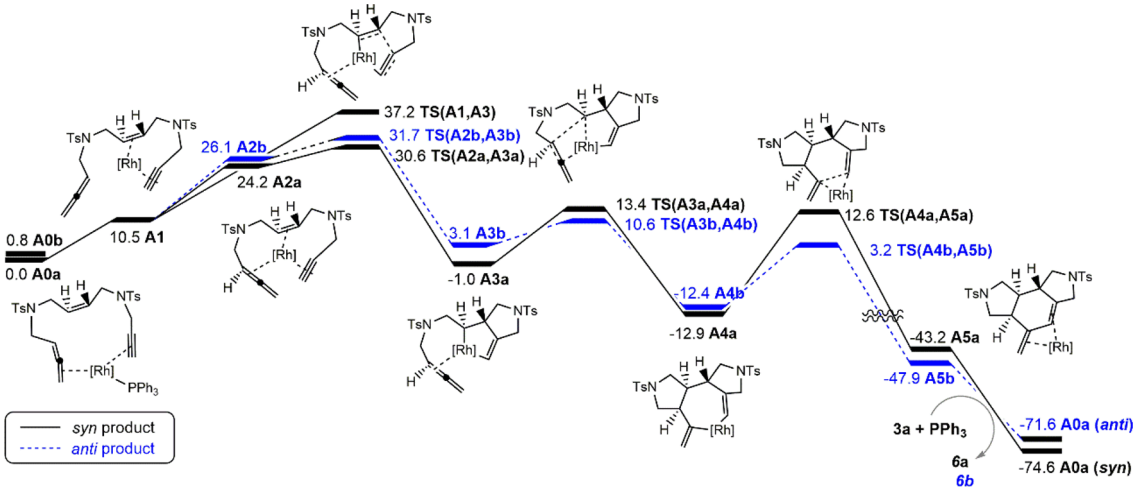
Scheme 135. Gibbs Energy Profile for the Most Favorable Route of the $[RhCl(PPh_3)_3]$−Catalyzed [2 + 2 + 2] Cycloaddition of Allene-ene-yne 369 Leading to 370a and 370b[a]



[a]Energies are relative to complex **A0a**. Only the schematic drawings of the structures for the *syn* path to **370a** are depicted. [Rh] = RhCl. Adapted with permission from ref 357. Copyright 2017 Wiley-VCH.

in finding out the order in which the three unsaturations participate in the catalytic cycle. In addition, DFT calculations at the B3LYP-D3/cc-PVDZ-PP level of theory helped to understand the difference in selectivity obtained using the two catalytic systems, $[RhCl(PPh)_3]_3$ and $[RhCl(CO)_2]_2$. Scheme 135 summarizes the main results of the [2 + 2 + 2] cycloaddition of allene-ene-yne substrate **369** mediated by the Wilkinson catalyst. Initially, two phosphine ligands were exchanged by substrate **369** to yield complex **A0a** in which the rhodium atom was coordinated to the alkyne and the external double bond of the allene. Direct oxidative coupling of the alkyne and the external double bond of the allene did not explain the experimental outcome of the reaction. To explain the formation of **370a** and **370b** required rearrangement of **A0** to **A1** in which the Rh was coordinated to the alkyne and the alkene. Direct oxidative coupling from **A1** had a Gibbs energy barrier too high ($\Delta G^{\ddagger}$ = 37.2 kcal/mol) to be surmountable. A more affordable route involved release of the phosphine ligand and coordination of the Rh to the alkyne, alkene, and the internal double bond of the allene to generate **A2**. Oxidative coupling between the alkyne and alkene in **A2** occurred with Gibbs energy barriers of about 31 kcal/mol, with the barrier for the *syn* rhodacyclopentene intermediate in route to product **370a** being 1.1 kcal/mol lower than that of the *anti* intermediate that will form **370b**. Next, the insertion of the internal double bond of the allene occurred preferentially on the Rh−C(sp^3) bond to form a rhodacyclopheptene intermediate followed by reductive elimination to afford the final product **370**. The overall [2 + 2 + 2] cycloaddition of allene-ene-yne substrate **369** catalyzed by $[RhCl(PPh)_3]_3$ was exergonic by 71.6−74.6 kcal/mol, and the overall Gibbs energy barrier for the path leading to **370a** was lower by 1.1 kcal/mol than that of the route to **370b**. For the $[RhCl(CO)_2]_2$ catalyst, we considered the monomeric form, i.e., $[RhCl(CO)_2]$, based on our ESI-MS results and previous studies.[359,360] In this case, the reaction started with the $[RhCl(CO)_2]$ coordinated to the alkene and alkyne to generate the rhodacyclopentene by oxidative coupling with a Gibbs energy barrier of 15.1 kcal/mol. All other possible combinations for different oxidative couplings were found to have higher Gibbs energy barriers. In the rhodacyclopentene formed by oxidative coupling, the allene can coordinate the Rh with the H atom oriented *syn* in the route to **370a** or *anti* in the path to **370b**. For the *syn* rhodacyclopentene, the insertion of the internal double bond of the allene took place in the Rh−C(sp^3) bond to yield a rhodacyclopheptene intermediate with a *cis*-ring fusion. On the other hand, in the *anti* rhodacyclopentene, the insertion of the internal double bond of the allene took place in the Rh−C(sp^2) bond. The reductive elimination for the rhodacyclopheptene intermediate with a *cis*-ring fusion had to overcome a barrier of 16.2 kcal/mol, whereas the Gibbs energy barrier for the reductive elimination in the rhodacyclopheptene intermediate with a *trans*-ring fusion was 11.0 kcal/mol. The rate-determining step for the *anti* pathway turned out to be the oxidative coupling with a Gibbs energy barrier of 15.1 kcal/mol, whereas that of the *syn* pathway was the reductive elimination with a barrier of 16.2 kcal/mol. Therefore, for the $[RhCl(CO)_2]_2$ catalysts, the *anti* pathway was preferred over the *syn* path by 1.1 kcal/mol, in agreement with experimental results showing that the diastereoselectivity of the process was catalyst-dependent.

5.5. Zirconium Complexes

Zirconacyclopentadienes **155a** and **155b** (see, for instance, Scheme 59) prepared by Takahashi[216] also reacted with allenes mediated by $[NiBr_2(PPh_3)_2]$ to afford benzene derivatives. The reaction was not chemoselective, as the two double bonds of the allene were involved in the cycloaddition, affording two different regioisomers. In addition, further isomerization processes of the initial cyclohexadienes took place to afford the corresponding benzene derivatives (Scheme 136).

The same research group tested the formation of pyridine-2-ones **371** and iminopyridines **372** involving two different alkynes and isocyanates or carbodiimides, respectively (Scheme 137).[269] Using the same strategy based on the one-pot synthesis that they used in the pyridine synthesis (see, for instance, Scheme 91), selective formation of pyridine-2-ones **371** and iminopyridines **372** was achieved.

The authors postulated intermediates **373** and **374** in the case of isocyanates (Scheme 138, equation a) and intermediates **375** and **376** in the case of carbodiimides (Scheme 138, equation b). None of these intermediates were isolated and characterized.

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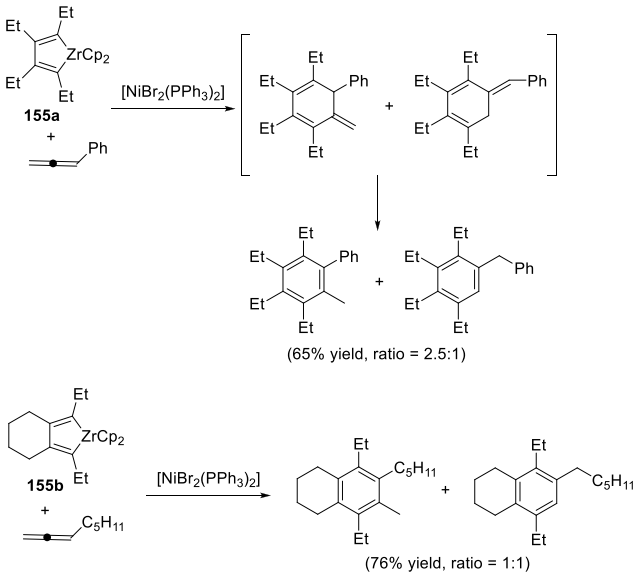
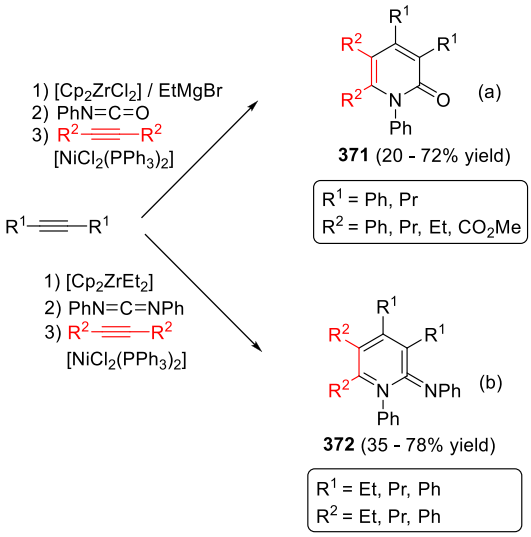
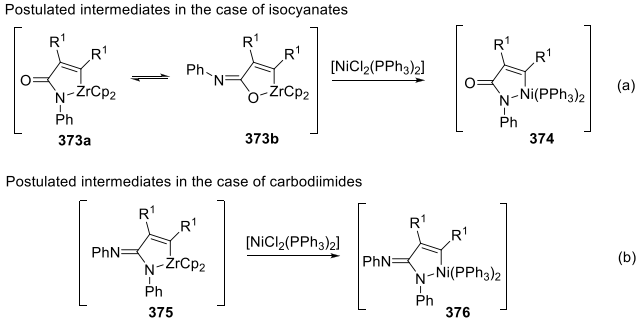
Scheme 136. Reaction of Zirconacyclopentadienes 155 with Allenes Mediated by $[NiBr_2(PPh_3)_2]$



Scheme 137. Synthesis of Pyridine-2-ones 371 and Iminopyridines 372



Scheme 138. Postulated Zirconacycle and Nickelacycle Intermediates in the Cycloaddition Involving Isocyanates and Carbodiimides



However, monitoring the reaction of $[Cp_2ZrEt_2]$, alkyne, and isocyanate by NMR spectroscopy, it could be seen that only one of the two zirconacycles **373** was generated, either the azazirconacycle **373a** or the oxazirconacycle **373b**, although they were not able to establish the definitive structure (Scheme 138).[361]

It is important to note that an experimental result that supported the formation of the azametallacycles shown in Scheme 138 as intermediates in the [2 + 2 + 2] cycloaddition reaction was the unsuccessful reaction between a zirconacyclopentadiene of type **150** and butylisocyanate. The presence of equimolar quantities of CuCl or $[NiCl_2(PPh_3)_2]$ provoked the consumption of the zirconium complex, but no identified products were formed.[362]

6. [2 + 2 + 2] CYCLOADDITION OF TWO ALKYNES AND A C═O BOND

Another of the unsaturations that has been studied in [2 + 2 + 2] cycloaddition reactions is the CO carbonyl function, which opens the door to the direct synthesis of 2*H*-pyran derivatives. However, this cycloaddition has not been studied to the same extent as those commented on in the sections before. This is probably due to several factors such as the weak coordination ability of a carbonyl group to a metal as compared, for example, to nitrogen-containing heterounsaturations, and the energetically demanding reductive elimination for the formation of the C−O bond of the pyran derivatives.[363] From the mechanistic point of view, it is important to determine the sequence with which the three unsaturations enter the catalytic cycle, in other words, at what stage the carbonyl moiety is incorporated and bonded to the metal. A trend of the most reported cases of these [2 + 2 + 2] cycloaddition reactions is for the pyran derivatives that are generated to suffer a thermal electrocyclic ring opening process that finally gives dienone compounds.

Pioneering studies of the cycloaddition of alkynes and aldehydes and ketones using cobalt[364,365] and nickel[366] complexes were reported in or around 1989. More recently, important contributions to this type of cycloaddition were made by the group of Louie,[367,368] using nickel/NHC catalytic systems, and the groups of Shibata[369] and Tanaka,[370] using rhodium complexes. In the case of ruthenium, it was Itoh et al.[371] in 2002 who performed the ruthenium-catalyzed [2 + 2 + 2] cycloaddition of a tricarbonyl compound, specifically the diethyl 2-oxomalonate **378**, with 1,6-diynes **377**. The bicyclic pyran derivatives **379** initially formed could not be isolated because they suffered a further electrocyclic ring opening affording dienylketone compounds **380** (Scheme 139, equation a). The two electron-withdrawing groups in the ketone substrate seemed to be crucial for the efficiency of the process.

In this report,[371] the authors proposed an initial oxidative coupling between one of the triple bonds of the 1,6-diyne and the carbonyl group, affording an oxaruthenacyclopentene intermediate **381**. Subsequent insertion of the second alkyne unit generated oxaruthenacycloheptadiene intermediate **382**, which after reductive elimination afforded the 2*H*-pyran derivative. However, DFT calculations carried out later by Rodríguez-Otero et al.[372,373] showed that an alternative mechanism in which the initial coupling takes place between the two alkyne groups is much more likely. The authors studied the [Cp*RuCl]-catalyzed [2 + 2 + 2] cycloaddition represented in Scheme 139a (when X = O, R = H, and CO_2Et groups in the tricarbonyl compound are replaced by COH) using the B3LYP/6-31G(d)~LANL2DZ method (Scheme 140). The catalytic

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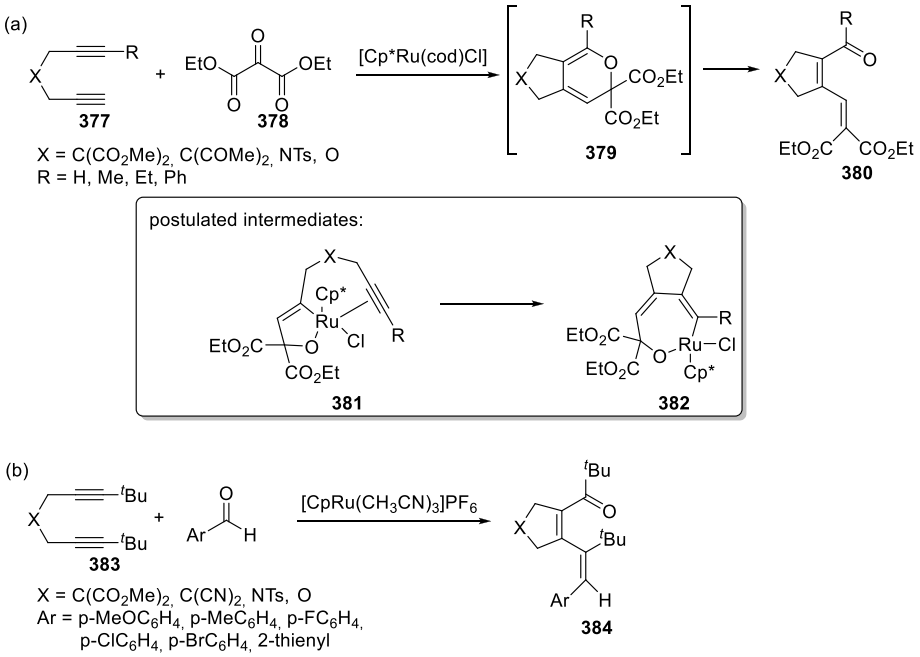
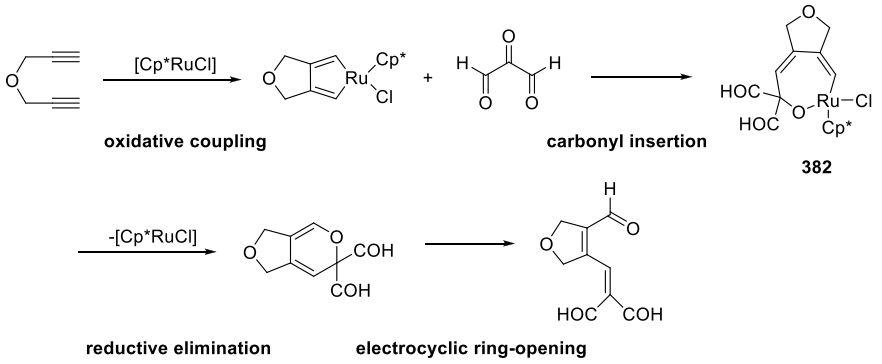
Scheme 139. Ru(II)-Catalyzed Cycloaddition of 1,6-Diynes with Ketones and Aldehydes



Scheme 140. Proposed Reaction Mechanism for the Ruthenium-Catalyzed [2 + 2 + 2] Cycloaddition of 1,6-Diynes with Diformyl Ketone



cycle begins with an oxidative coupling of the 1,6-diyne to the Ru catalyst with a Gibbs energy barrier of 9.0 kcal/mol. The alternative coupling between the alkyne and the carbonyl group has to surmount a much higher energy barrier and, consequently, the presence of intermediate **381** in the reaction mechanism was ruled out. This oxidative coupling is followed by an insertion of the central carbonyl group of the tricarbonyl compound ($\Delta G^{\ddagger}$ = 18.2 kcal/mol) that generates a 7-membered ruthenacycle complex (intermediate **382**). The subsequent reductive elimination with a Gibbs energy barrier of 26.0 kcal/mol is the rate-determining step of the process. Finally, the 2*H*-pyran ring formed suffers a disrotatory electrocyclic ring-opening through a concerted transition state with a Gibbs energy barrier of 15.3 kcal/mol. The pathway corresponding to the dimerization of 1,6-diynes that generates a minor product of the reaction was found to be competitive with the [2 + 2 + 2] cycloaddition of 1,6-diynes and tricarbonyl compounds.

Very recently, Yamamoto et al.[374] found that aldehydes could also give a [2 + 2 + 2] cycloaddition reaction to afford the corresponding dienones in good yields (Scheme 139, equation b). In this study, the ruthenium complex used was the cationic $[Cp^*Ru(CH_3CN)_3]PF_6$ complex. Interestingly, they found exclusive formation of the (*Z*)-stereoisomer of dienyl ketones. The authors studied, with the M06-L/6-311++G(d,p)~SDD//B3LYP/6-31G(d)~LANL2DZ method including the effect of a THF solution, the reaction mechanism of the [2 + 2 + 2] cycloaddition shown in Scheme 139b substituting the ^{t}Bu groups by methyls and considering X = O and R = Ph. The reported reaction mechanism is qualitatively the same as that reported by Rodríguez-Otero et al. (Scheme 140), except in the fact that Yamamoto et al. found that CO insertion (or CO [2 + 2] addition) to the ruthenacyclopentadiene ring leads first to a oxaruthenabicylo[3.2.0]cycloheptadiene complex that in a next step evolves to the oxaruthenacycloheptadiene complex (intermediate **382**). It is worth noting that the [2 + 2] addition of benzaldehyde can take place with the Ph group *endo* or *exo* with respect to the ruthenacyclopentadiene ring. The authors reported that the Gibbs energy barrier of the *exo* addition that leads to the final (*Z*)-dienyl ketones is about 3.5 kcal/mol lower than that of the *endo* addition. This result explains the stereochemistry of the process that affords the exclusive formation of the (*Z*)-dienyl ketones. The (*E*)-dienyl ketone is

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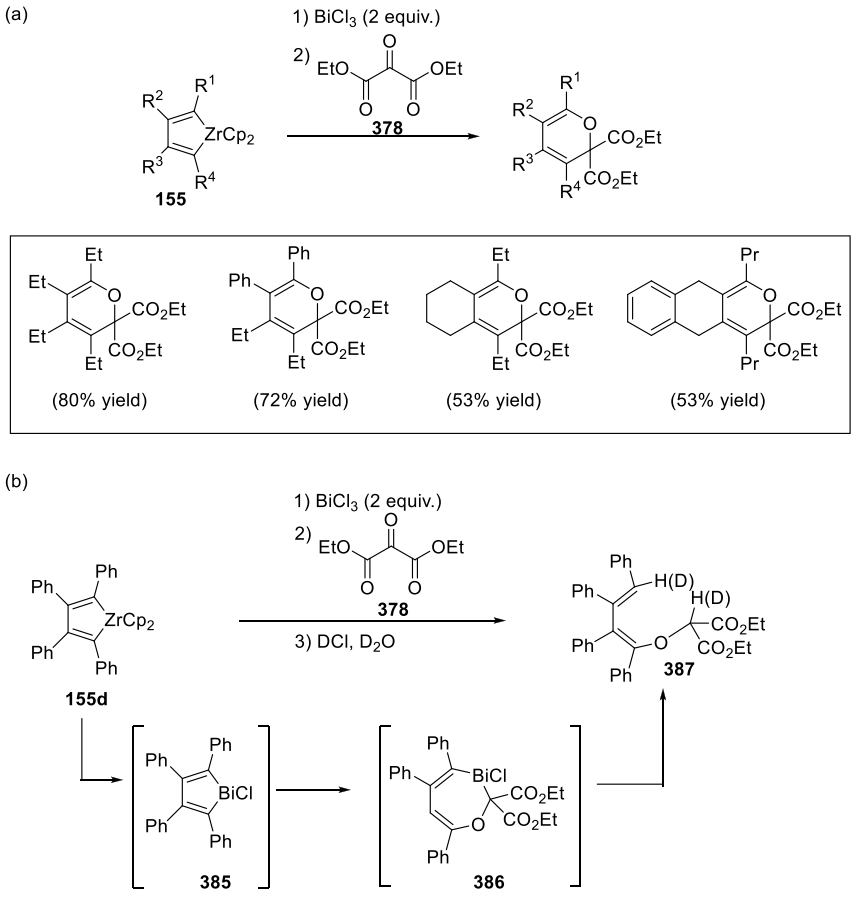
Scheme 141. Reactions of Zirconacyclopentadienes 155 with Diethyl 2-Oxomalonate 378



experimentally not observed, despite that the authors found that it is thermodynamically preferred as compared to (*Z*)-dienyl ketone by 2.0 kcal/mol.

Zirconacyclopentadienes of type **155** synthesized by Takahashi et al.[375] have also been demonstrated to react with diethyl 2-oxomalonate **378** to give α-pyrans but in the presence of $BiCl_3$ (Scheme 141, equation a). The authors tried other metal salts as in the reaction of zirconacyclopentadienes with alkynes and nitriles such as CuCl or $[NiCl_2(PPh_3)_2]$ (see, for instance, sections 2.8 and 3.6), but the only one that gave high yields of the corresponding pyran derivative was $BiCl_3$. When 2,3,4,5-tetraphenylzirconacyclopentadiene **155d** was treated with $BiCl_3$ and **378** followed by deuteriolysis with 20% DCl in D_2O, a 53% yield of dienolic ether **387** was obtained. In view of these results, the authors suggested the initial formation of a chlorobismole **385**, followed by the insertion of the carbonyl group to generate a 7-membered oxabismacycle **386**, as intermediates in the cycloaddition reaction. The formation of **387**, characterized by X-ray diffraction analysis, was indicative that the carbon atom of the CO group was inserted next to Bi instead of the oxygen atom (Scheme 141, equation b). The formation and characterization of chlorobismoles of type **385** from zirconacyclopentadienes and $BiCl_3$ has been previously reported.[376]

7. SOME FINAL CONSIDERATIONS ON COMPUTATIONAL ASPECTS

In the present review, we have seen that the number of computational studies on transition-metal-catalyzed [2 + 2 + 2] cycloadditions has increased significantly over the last two decades. The combined use of experimental and theoretical techniques to explore the different reaction paths is the most successful approach to unravel reaction mechanisms.[377−379] The theoretical studies discussed here have used various methods to obtain information on the different reaction pathways. Except for a few studies performed at the QCSID or CCSD(T) level to certify the reliability of the DFT calculations, all calculations reported in this review have been performed with the DFT method.[380,381] The vast majority, more than 75%, were carried out with the B3LYP functional,[102,103] about 20% with the Minnesota functionals (M06, M06-L, and M06-2X)[382,383] and the rest with the BP86 or BLYP functionals.[103,384−386] The popularity of these functionals is due to their good performance and their implementation in widely used commercial programs.

There are several limitations to the DFT calculations[387,388] that make computational chemists cautious about the results that are obtained. The main problem is that even though DFT is a formally exact reformulation of the Schrödinger equation, in the current state of the theory, approximations are required for the exchange-correlation energy functional. Furthermore, if the exchange-correlation potential used does not give the expected results, there is no systematic way to improve them. Another drawback of DFT is that many functionals overstabilize systems with highly delocalized densities over localized alternatives. Such an imbalance can lead to erroneous predictions in, for instance, the calculations of reaction barriers of chemical reactions that are commonly underestimated,[389−391] the charge transfer excitation energies,[392] the electronic states and molecular structure of the ground state of some transition

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metal complexes,[393] and the quantification of aromaticity.[394,395] A third problem of DFT is the poor treatment of long-range noncovalent interactions. Many functionals give incorrect results for $\pi\cdots\pi$ stacking,[396] weak hydrogen bonds, and van der Waals interactions.[397] To solve this problem, damped atom-pairwise dispersion corrections of the form $C6{\cdot}R^{-6}$ have been introduced by Grimme et al.[398,399] In some cases, recent functionals such as the Minnesota family of Truhlar et al. have been specifically designed to be able to describe noncovalent interactions correctly. Most recent calculations on transition-metal-catalyzed [2 + 2 + 2] cycloadditions already incorporate dispersion corrections in the functionals. Lack of inclusion of these dispersion corrections in some cases can have a detrimental effect on the calculated energy barriers.[321] Despite these limitations, experience shows that, in general, DFT methods provide excellent results outperforming MP2 (or even CASSCF in some cases) while requiring much less computer time.

When initiating the study with a DFT method of a new reaction mechanism, it is a good practice to perform benchmark calculations with high level ab initio methods, such as CCSD(T), QCISD(T), or CASPT2 of a simple model of the reaction studied, to detect possible errors of the DFT functionals. Clark et al.[101] performed a study of the full reaction mechanism in the singlet and triplet states of the cyclotrimerization of acetylene to yield benzene catalyzed by [CpCo] with the B3LYP and QCISD(T) methods. They found that, although B3LYP overestimates the stability of the triplet state relative to the singlet state, the overall picture produced by B3LYP does not change when using QCISD(T). This result provided confidence in the use of the B3LYP method in the study of transition-metal-catalyzed [2 + 2 + 2] cycloadditions. On the other hand, the oxidative coupling is the rate-determining step in most transition-metal-catalyzed [2 + 2 + 2] cycloadditions. Bickelhaupt et al.[400] propose an ab initio benchmark of the oxidative addition of the ethane C−C bond to Pd to test the reliability of different DFT functionals. The authors reported that the BLYP functional slightly underestimates (by only 0.9 kcal/mol) the overall barrier of the process, whereas B3LYP overestimates it by 5.8 kcal/mol. The addition of a percentage of Hartree−Fock exchange in hybrid functionals, such as B3LYP, partially corrects the usual underestimation of reaction barriers by DFT. Similar results were reported for the oxidative addition of the methane C−H bond to Pd.[401]

Two further parameters determine the quality of the DFT calculations, namely, the size of the basis set used and the treatment of relativistic effects. With regard to the basis set, most of the works discussed here were performed using a double-ζ basis set with polarization functions for the geometry optimizations and a triple-ζ basis set with polarization functions for final single point energy calculations. Works by Bickelhaupt et al.[400,402] have highlighted the importance of adding sufficient higher angular momentum polarization functions for correctly describing metal−d-electron correlation in oxidative coupling processes. On the other hand, the calculation of relativistic effects is required to achieve good accuracy for compounds of the second and third transition metal rows. Relativistic effects lead to a contraction of the s and p shells and decontraction of the d and f shells. These can be included in DFT calculations in two ways: first, using all-electron basis sets and solving the four-component Dirac equation or with approximate treatments, such as the zero-order regular approximation (ZORA),[403] and second, by using quasi-relativistic pseudopotentials or effective core potentials (ECPs) that are optimized to reproduce relativistic all-electron calculations of the atoms. One important point is the size of the ECP that replaces the inner core electrons. Although small-core ECPs are more computationally demanding than large-core ECPS, they are more accurate and should be preferred. The use of ECPs for metals of the second and third transition metal rows has been the preferred option in the calculations presented in this review.

8. CONCLUSIONS AND OUTLOOK

The transition-metal-catalyzed [2 + 2 + 2] cycloaddition reaction is a powerful tool for the assembly of 6-membered rings, that has found broad application in synthetic organic chemistry. Regarding its reaction mechanism, it is a quite unique case due to the fact that the three unsaturated units that are assembled can exchange roles in the reaction sequence. This scenario opens up a broad range of mechanistic possibilities that need to be specifically analyzed in every example due to their influence in the chemo- and regioselectivity of the reaction. The point in which each unsaturation enters the mechanistic scheme—as well as the specific orientation—depends on an intricate interplay of the different reactivity of the unsaturated component (influenced by its chemical entity, its electronic effects and its bulkiness) but also on the existence of linkages between the unsaturated units. On the other hand, the reaction can be catalyzed by a wide range of transition metals, each one with its particularities, that also greatly influence the mechanism followed. Thus, the PES and the mechanism are substantially affected by the substrates, the catalyst, and even the reaction conditions. Far from being a problem, this wealth of mechanistic pathways contributes to the enormous synthetic potential of the reaction. And the only way to fully exploit its potential is to analyze the mechanistic details of every example. Kinetic studies, spectroscopic and spectrometric techniques, the isolation of intermediates, and computational methods have been efficiently used in the past to gather mechanistic information. The combination of different tools, especially when combining experimental and modeling data, is and will be the key to develop the full potential of the transformation. A special effort is to be made in the future to decipher the mechanistic aspects that control the stereoselectivity of the reaction and to develop predictive models for the chemo- and regioselectivity control in the different variants of the reaction.

AUTHOR INFORMATION

Corresponding Authors

Anna Roglans − *Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Universitat de Girona, E-17003 Girona, Catalonia, Spain;* orcid.org/0000-0002-7943-5706; Email: anna.roglans@udg.edu

Anna Pla-Quintana − *Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Universitat de Girona, E-17003 Girona, Catalonia, Spain;* orcid.org/0000-0003-2545-9048; Email: anna.plaq@udg.edu

Miquel Solà − *Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Universitat de Girona, E-17003 Girona, Catalonia, Spain;* orcid.org/0000-0002-1917-7450; Email: miquel.sola@udg.edu

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.chemrev.0c00062

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Notes

The authors declare no competing financial interest.

Biographies

Anna Roglans (1964, Palafrugell) obtained her PhD in chemistry from the Autonomous University of Barcelona (UAB) in 1994 under the supervision of Prof. M. Moreno-Mañas, before joining the group of Prof. V. Snieckus at the University of Waterloo (Canada) for postdoctoral studies. She returned to the UAB with a postdoctoral contract and in 1998 obtained a position as a lecturer at the University of Girona (UdG). In 2010, she was promoted to full professor in chemistry. She currently leads the Transition Metals in Organic Synthesis Group, and her research interests involve the study of transition metal catalysis, organometallic chemistry, and the elucidation of reaction mechanisms.

Anna Pla-Quintana (1978, Banyoles) obtained her PhD in chemistry from the University of Girona (UdG) in 2004. After postdoctoral studies under the supervision of Dr. Jean-Pierre Majoral at the Laboratoire de Chimie de Coordination (LCC) Toulouse (2005−2007), she was promoted to lecturer in chemistry in 2010. Her research focuses on the development of transition-metal-catalyzed processes and the study of the mechanisms involved.

Miquel Solà (1964, Fonteta) obtained his PhD at the UAB in 1991 with academic honors under the supervision of Profs. J. Bertran and A. Lledós. In 1993, he moved to the University of Girona (UdG) as assistant researcher. In 1994, he did postdoctoral research in Amsterdam with Prof. Baerends and in 1995 in Calgary with Prof. Ziegler. He was appointed assistant professor of the UdG in 1997. In 2001, he got the Catalan Distinction for the Promotion of University Research. Since 2003, he is full professor at the UdG. He was awarded with the ICREA Academia Prize twice, in 2009 and 2014. In 2013, he got the Physical Chemistry prize awarded by the Spanish Royal Society of Chemistry. In 2019, he received the recognition of Honorary member of the Polish Chemical Society. His research focuses on the analysis of reaction mechanisms of organic and organometallic systems and the study of chemical bonding, electron delocalization, and aromaticity.

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