The Diene Effect: The Design, Development, and Mechanistic Investigation of Metal-Catalyzed Diene-yne, Diene-ene, and Diene-allene [2+2+1] Cycloaddition Reactions

By: Mitchell P. Croatt and Paul A. Wender

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Abstract:
Metal-catalyzed diene-yne, diene-ene, and diene-allene [2+2+1] cycloaddition reactions provide new methods for the facile construction of highly functionalized five-membered rings. These reactions can be conducted with a variety of substrate substitution patterns and functional groups and often in the absence of solvent. The special reactivity of dienes, a key to enabling or enhancing the effectiveness of the [2+2+1] and other reactions, is significantly different from that of alkynes, alkenes, or allenes. For example, the [2+2+1] reaction of a diene-yne is accelerated compared to that of the corresponding ene-yne. An even more dramatic "diene effect" is found with diene-enes and diene-allenes. While bis-enes and ene-allenes are not reported to yield [2+2+1] cycloadducts, the related diene-enes and diene-allenes undergo efficient [2+2+1] cycloadditions, providing new routes to cyclopentanones and alkylidenecyclopentanones. Mechanistic studies suggest that the unique reactivity observed with dienes arises from their participation in the putative rate-determining reductive elimination step by providing an additional energy-lowering coordination site for the transition metal catalyst.
Keywords: Cycloaddition / Pauson–Khand reaction / Rhodium / Heterogeneous catalysis / Allenes

Article:
1. Introduction
The design and discovery of new reactions are of unique importance to the advancement of synthesis. New reactions not only offer enhanced process efficiencies and selectivities, they also serve as the starting point for the introduction of new synthetic strategies and the resultant realization of greater step economy.[1] All of these factors are of critical importance to green chemistry and the ideal synthesis.[1] To appreciate this point, one need only consider the first synthesis of cyclooctatetraene by Willstätter in 1911, which was ten steps,[2] and the subsequent one-step synthesis reported by Reppe in 1948[3] based on a then new reaction, the [2+2+2+2] cyclotetramerization of acetylene. In addition to step savings and efficiency and selectivity advantages, new reactions often provide greener[4] options for route, reagent,[5] and starting material selection and frequently allow for reduction of waste stream (steps add solvent from reactions and purifications),[6] development time, and cost, collectively contributing to greater productivity (i.e., human economy). Prompted by these considerations, our group has directed attention to the design and development of new or novel reactions for the synthesis of commonly encountered ring systems based on metal-catalyzed 2-, 3-, and 4-component processes (i.e., [$m+n$], [$m+n+o$], [$m+n+o+p$] cycloadditions wherein m, n, o, and p are the number of atoms in each component joined in forming a new ring). A conceptual theme in many of these studies has been to use a catalyst to convert a commonly available starting functionality (e.g., alkene, alkyne, allene, or diene, the last a focus of this review) to a reactive intermediate that could then be trapped by one or more commonly available 1-, 2-, 3-, 4-, or 5-atom systems to produce a multicomponent product, a form of controlled oligomerization.[7] For example, our design of metal-catalyzed [5+2] reactions[8] was based on reports that vinylcyclopropanes react with transition metals to produce acyclic dienes and cyclopentene.[9] It was hypothesized that this process proceeded through a reactive metallacyclohexene intermediate that might be trapped by a 2-atom π-component

to produce a metallacyclooctene, which upon reductive elimination would give a seven-membered ring, overall representing a new [5+2] cycloaddition reaction, a homolog of the Diels—Alder [4+2] cycloaddition.[10] This process has now been shown to succeed intra- and intermolecularly.[8] It also inspired the design of an analogous [6+2] reaction of vinylcyclobutanones with π-systems,[11] related studies on the [6+1] reactions of allenylcyclobutanes and carbon monoxide (CO),[12] and the [3+2] reactions of cyclopropenones and alkynes.[13]

A significant characteristic of the above [*m+n*] reactions is that they convert relatively simple starting materials into products of increased molecular complexity and, therefore, often added value. Obviously, additional value could be realized if more components could be incorporated into the overall cycloaddition process. Like most cycloadditions, the previously described [*m+n*] processes allow for the formation of, at most, two new bonds from two components (*m* and *n*) through capture of an organometallic intermediate. Additional bonds, and therefore value, could be created by "recycling" intermediates, i.e., using the organometallic intermediate involved in the coupling of the first two components to incorporate additional components, thereby forming subsequent organometallic intermediates and ultimately a multicomponent product. For example, the [5+2] cycloaddition has been used to incorporate one or two equivalents of CO leading to the first [5+2+1][14] and [5+1+2+1][15] cycloaddition reactions. A related series of studies in our group started with investigations on the first intramolecular [4+4] cycloadditions of bis-dienes[16] and led to the first metal-catalyzed intramolecular [4+2] cycloadditions,[17] which in turn prompted studies on the interception of organometallic intermediates in the latter reaction with CO.[18] This resulted in the first [4+2+1] and [2+2+1][19] reactions of dienes, π-systems, and CO, the topic of this microreview. Our treatment is organized into sections dealing with the design of the reactions (Section 2), reactions of dienes, CO, and alkynes (Section 3), alkenes (Section 4), and allenes (Section 5), mechanistic investigations (Section 6), and concluding remarks (Section 7).

2. Design of the [4+2+1] and [2+2+1] Reactions of Dienes Tethered to π-Systems

Similar to our trapping of intermediates in the [5+2] reaction with CO to produce a [5+2+1] reaction, it was proposed that organometallic intermediates in the metal-catalyzed [4+2] reaction could incorporate a molecule of CO to produce either a [2+2+1] or [4+2+1] reaction (Figure 1), the former being an unexplored variant of the Pauson—Khand reaction[20] and the latter an entirely new process.[21] Experimentally, this notion received encouraging support when the treatment of diene-yne 7 with a rhodium(I) catalyst under an atmosphere of CO yielded compounds resulting from the [4+2] cycloaddition and the new [2+2+1] and [4+2+1] reaction pathways (Scheme 1).[19a,22]
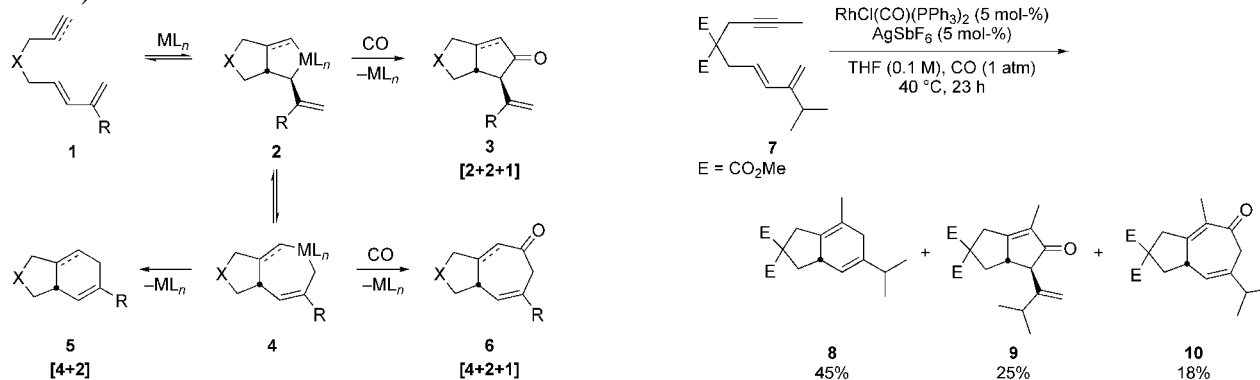

Figure 1. New reaction design: proposed trapping of intermediates in the [4+2] reaction with CO.

Scheme 1. Preliminary trapping studies: diversion of the [4+2] cycloaddition leads to new [2+2+1] and [4+2+1] reactions.
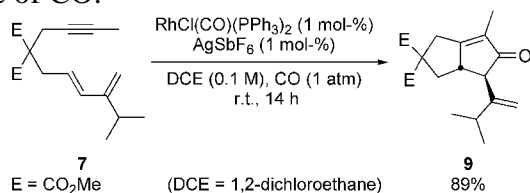
3. The Dienyl-Pauson—Khand Reaction

3.1 The Intramolecular Dienyl-Pauson—Khand Reaction[19a]

3.1.1 Reaction Optimization

By variation of the reaction conditions that concomitantly produced the [4+2] product 8, [2+2+1] reaction product 9 (dienyl-Pauson—Khand reaction), and [4+2+1] reaction product 10 (Scheme 1), conditions were found that selectively and efficiently produced cyclopentenone 9 (Scheme 2). Important observations from the optimization study were that the [4+2] reaction product 8 was essentially eliminated by lowering the reaction

temperature from 40 °C to ambient temperature and that the [2+2+1] reaction was not significantly affected by increasing or decreasing the pressure of CO.

Scheme 2. The optimized dienyl-Pauson–Khand reaction.

3.1.2 Substrate Scope

Using conditions similar to those of Scheme 2, dieneynes with various substitutions were examined, and excellent yields of the dienyl-Pauson–Khand products resulted (Scheme 3). Many substrates with terminal alkynes (e.g., 13) produced only modest yields of cycloadducts; however, substrates with silyl-substituted alkynes (e.g., 15), which can be used as surrogates for terminal alkynes, reacted much more efficiently. Significantly, *spiro*-fused ring system 18, incorporating a quaternary center, can be formed diastereoselectively in excellent yield.
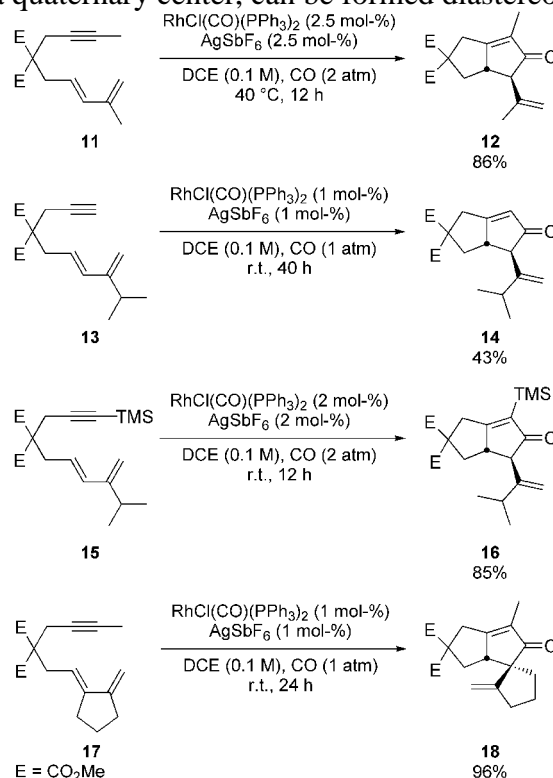
Scheme 3. Representative dienyl-Pauson–Khand reactions.

3.1.3 Diene and Alkene Comparison

To explore the relative reactivities of dienes, alkenes, and styrenes as 2-carbon components in the [2+2+1] process, the reactions of ene-ynes 21 and 23 were compared with that of diene-yne 19 under similar conditions (Scheme 4). Significantly, ene-ynes 21 and 23 required higher catalyst loadings, increased temperatures, and extended reaction times when compared to the reaction of diene-yne 19. These reactions illustrate that the additional unsaturation of a diene and its nature (ene vs. arene) significantly influence the rate of these cycloadditions.

3.2 The Intermolecular Dienyl-Pauson—Khand Reaction[19b]

The Pauson–Khand reaction is a powerful process for assembling five-membered rings, but in most cases the two π-systems must be tethered. The intermolecular Pauson–Khand reaction has potential to yield products of significantly increased molecular complexity since it combines three separate, simple components. However, systems that work well intramolecularly with a five-atom tether often do not succeed with longer tethers or when conducted inter-molecularly. To achieve an intermolecular Pauson-Khand reaction, some additional

reactivity is required in the form of strain, [23] chelation assistance,[24] or both. [23b] In fact, Narasaka noted in the first report of a rhodium(I)-catalyzed intermolecular Pauson–Khand reaction, "the use of more reactive alkenes is essential' for the reaction with his best yield (69%) obtained with norbornene.[25] Based on the increase in reactivity observed with dienes relative to alkenes in the intramolecular dienyl-Pauson–Khand reaction, it was hypothesized that a diene could be used as a more reactive n-system in the intermolecular Pauson–Khand reaction.
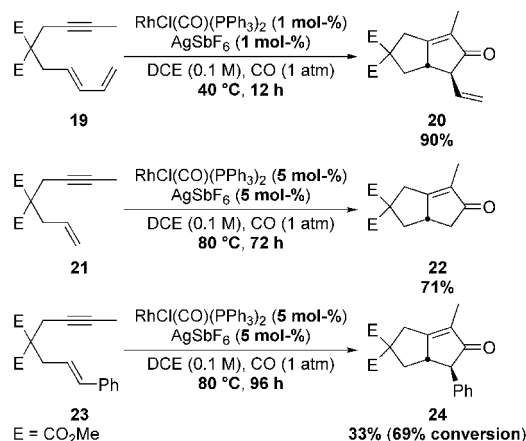

Scheme 4. Comparison of the [2+2+1] reactions of a diene-yne with ene-ynes.

3.2.1 Reaction Optimization

As anticipated from the previously discussed work, dienes provided the necessary reactivity enhancement for the intermolecular (three-component) dienyl-Pauson– Khand reaction, affording cycloadducts in excellent yield. This reaction was found to work best with $[RhCl(CO)_2]_2$ relative to other Rh^I catalysts in TCE (Scheme 5: 1,1,2,2- tetrachloroethane) or DCE (1,2-dichloroethane). Significantly, the intermolecular dienyl-Pauson—Khand reaction can be conducted in the absence of solvent, providing cyclopentenone 27 in good yield. While the role of solvent in modulating heat transfer on a large scale reactions must be considered, solventless reactions offer a green approach to some problems, particularly with respect to atom economy,[6] since they avoid atom loss from solvent, typically the largest atom loss in most reactions. As yet unoptimized in this reaction is the need for excess diene, due in part to its volatility and in part to its competing oligomerization under the reaction conditions. Finally, the intermolecular dienyl-Pauson—Khand reaction was found to be scalable with only a modest decrease in efficiency (Scheme 6).
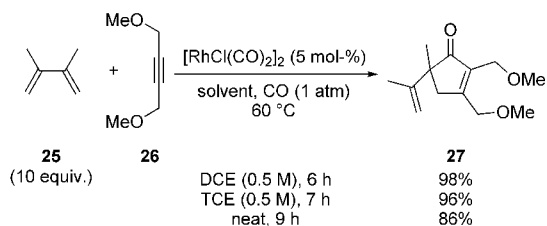
Scheme 5. Solvent study with the intermolecular dienyl-Pauson–Khand reaction.
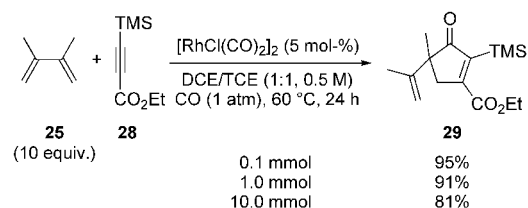
Scheme 6. Scalability of the intermolecular dienyl-Pauson–Khand reaction.

3.2.2 Alkyne Scope

Different alkynes were examined using 2,3-dimethyl-1,3- butadiene as the diene component and previously optimized conditions (Scheme 7). In most cases the reactions were high yielding and tolerated different functional groups. The reaction with 1,4-dichloro-2-butyne is less efficient but provides a product, compound 35, with a remarkable array of differentiated functionalities, a valuable building block for synthesis.
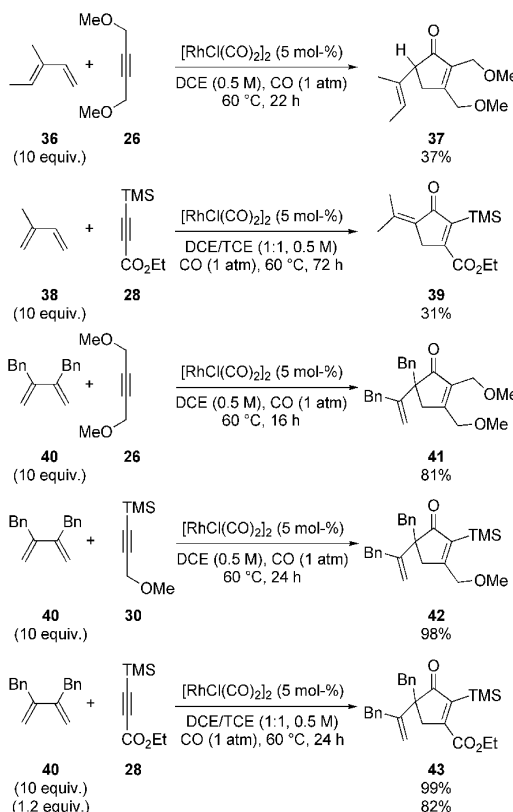
3.2.3 Diene Scope

The initial diene examined in the intermolecular dienylPauson—Khand reaction was 2,3-dimethyl-1,3-butadiene, a choice that was advantageous because reactions with this diene are higher yielding than reactions

with most of the other dienes examined (Scheme 8). This diene is probably optimal under the current conditions due to the slow rate of oligomerization of both the initial diene and the resultant olefin of the product. It was observed that other dienes used in this intermolecular dienyl-Pauson—Khand reaction are more prone to these side reactions. An exception, 2,3- dibenzyl-1,3-butadiene, was comparable in reactivity to 2,3- dimethyl-1,3-butadiene. Significantly, when only 1.2 equiv. of this nonvolatile diene were used with alkyne 28, an 82% yield of cyclopentenone 43 was obtained.
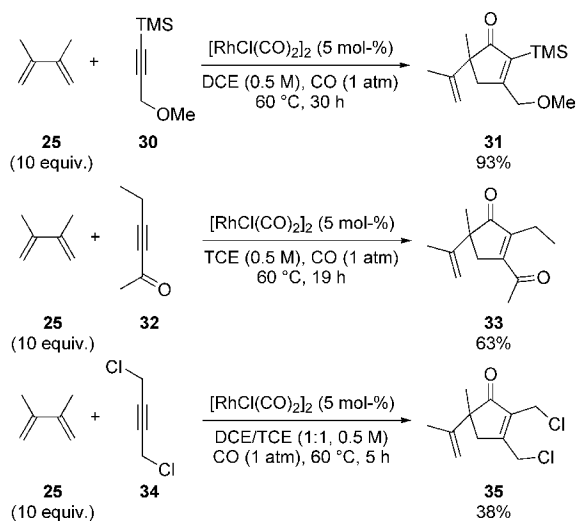

Scheme 7. Alkyne scope in the dienyl-Pauson–Khand reaction.

Scheme 8. Diene scope in the dienyl-Pauson–Khand reaction.

3.2.4 Diene and Alkene Comparison

Because the intermolecular dienyl-Pauson–Khand reaction was high yielding when dienes were used in the place of an alkene, the reactivity difference between a diene and an alkene was evaluated. For this comparison, norbornene was chosen as the alkene since it was previously found to be one of the best alkenes in the intermolecular Pauson– Khand reaction.[22] Under identical reaction conditions, 2,3-dimethyl-1,3-butadiene produced a 98% yield of cyclopentenone 27, whereas norbornene generated less than 5% of cycloadduct 45 at full conversion (Scheme 9). Furthermore, the reaction with norbornene required twice as much time to consume the starting materials as compared to the reaction with a diene.
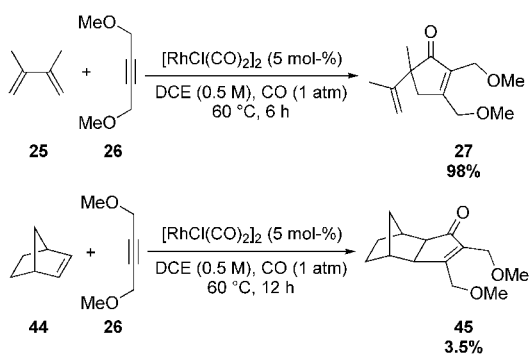
Scheme 9. Comparative reactivities of 2,3-dimethyl-1,3-butadiene and norbornene.
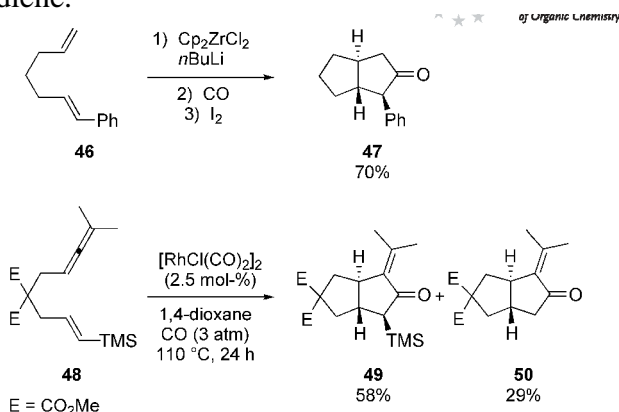
Scheme 10. Prior reports of [2+2+1] reactions to form cyclopentan-ones.

4. Diene-ene [2+2+1] Reaction[19c]

## 4.1 Introduction and Initial Results

A longstanding limitation of the [2+2+1] reaction of π-systems with CO is the necessity of using an alkyne as one of the two-carbon components. Previously, there were only two methods for the coupling of two alkenes and CO: a multiple-step procedure using stoichiometric zirconium[26] and a procedure involving cyclocarbonylation of an alkene tethered to an allene (Scheme 10).[27] In the latter case, Itoh and co-workers report that an ene-type cyclization reaction occurs with all other allene-enes (discussed later in Scheme 20) instead of a [2+2+1] cycloaddition reaction, [28] an observation that has also been reported by Brummond and co-workers.[29]

Given the accelerating effect of the diene on the Pauson Khand reaction involving a diene-yne (Scheme 4 and Scheme 9), the first metal-catalyzed [2+2+1] reaction of a diene-ene and CO was attempted (Scheme 11). Gratifyingly, the diene-ene [2+2+1] reaction proved to be an efficient process. For dienes with smaller substituents at the 2-position (such as 53), the β,γ-olefin of the [2+2+1] reaction product isomerized to the more thermodynamically stable α,β-unsaturated position.[22c] This was found to occur under the reaction conditions and on purification.
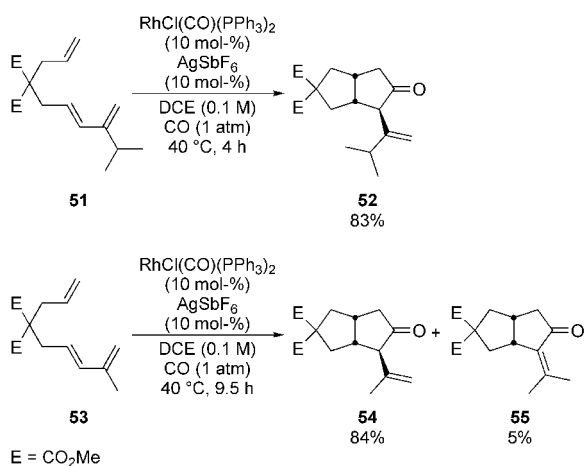
Scheme 11. Initial conditions for the diene-ene [2+2+1] reaction.
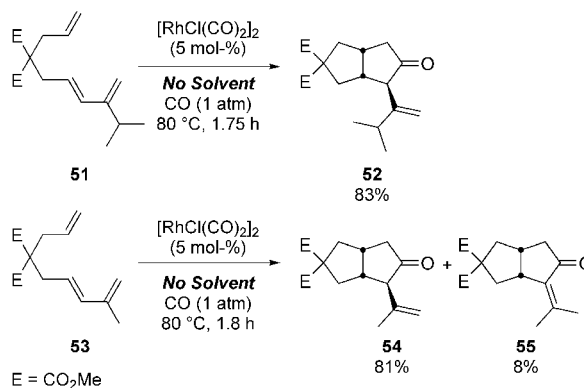
Scheme 12. Solvent-free diene-ene [2+2+1] reactions.

4.2 Reaction Optimization

A screening of catalysts, solvents, and temperatures resulted in the identification of the optimal conditions for this new process: [RhCl(CO)$_2$]$_2$ (5 mol-%) as catalyst in DCE (0.1 M) at 80 °C. Significantly, it was found that the concentration of the reaction could be increased to the point at which no solvent is required. In the case of diene-enes 51 and 53, solventless reactions resulted in 83% and 89% yields of product, respectively (including isomerized enone 55; Scheme 12). These two reactions were designed to be "green", especially in terms of atom-economy, [23] because no solvent atoms were wasted, no excess reagent was used, and the only lost atoms were from the rhodium catalyst, which was used substoichiometrically. It is important to note that in this and other cases the minimal catalyst loading could not be determined, as it would require the use of larger scale reactions than that acceptable in an academic setting. Loadings between 1–10 mol-% allowed for accurate weighing without using large quantities of starting materials.

4.3 Substrate Scope

With the optimized conditions for the diene-ene [2+2+1] reaction determined, variations in substitutions, tethers, and tether lengths were examined (Scheme 13). The reaction can be used to form heterocycles by incorporating an ether or sulfonamide group in the tether (56 and 58), quaternary centers by having additional substitution on the alkene (60), and [4.3.0] bicyclic products by having an additional methylene unit in the tether (62). The excellent yields for these reactions are significant because the formation of heterocycles, quaternary centers, and [4.3.0] bicycles has historically been difficult to accomplish with many transition-metal-catalyzed reactions, especially Pauson— Khand-type reactions.

Based on the success of the reaction of diene-ene 62 bearing a 4-atom tether, an intermolecular reaction was attempted using 2,3-dimethyl-1,3-butadiene, norbornene, and CO. Significantly, [2+2+1] reaction product 64 was formed in 73% yield with only the *exo*-product observed (Scheme 14).[30] This intermolecular reaction converts simple starting materials that are all commercially available into a product with a large increase in molecular complexity and therefore potential value.

4.4 Diene and Alkene Comparison

To determine if the diene is necessary for a [2+2+1] reaction to form a cyclopentanone, control reactions with bisenes were examined (Scheme 15). The bis-enes were similar to a diene-ene with respect to the electronics or coordinating ability of the diene. Of mechanistic significance, none of these reactions produced [2+2+1] cycloadducts; only slow decomposition of starting materials was observed. For the diene-ene [2+2+1] reaction, in contrast to the dienyl-Pauson—Khand reaction, the diene does more than accelerate the reaction; the diene enables the [2+2+1] reaction to occur.
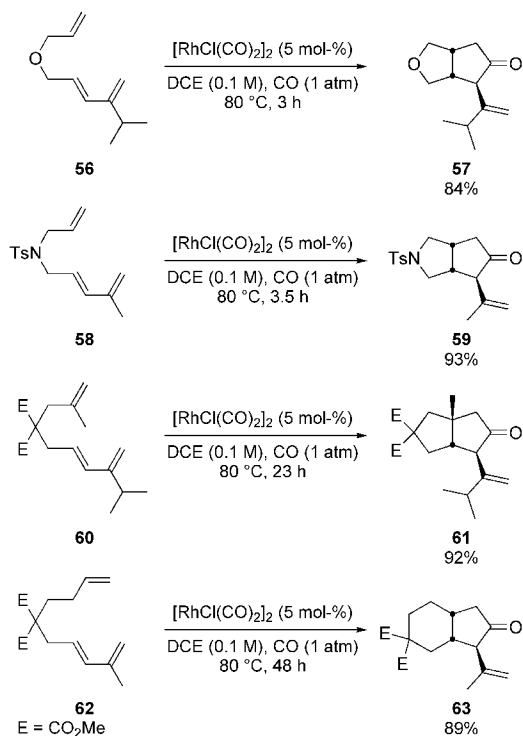
Scheme 13. Representative diene-ene [2+2+1] reactions.
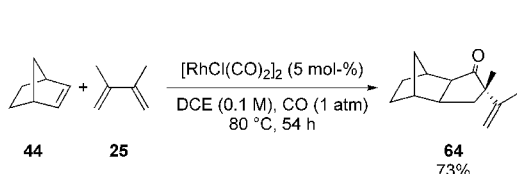
Scheme 14. Intermolecular diene-ene [2+2+1] reaction.
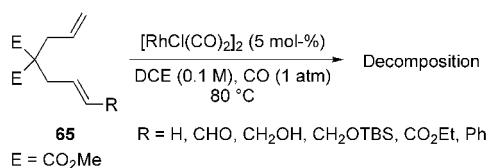
Scheme 15. Control reactions for the diene-ene [2+2+1] reaction.

4.5 Synthetic Utility

While examining the functionality produced by the diene-ene [2+2+1] reaction, it was noted that the core system of all medicinally used prostacyclin analogues contain a similar bicyclic structure (Figure 2). It was envisioned that reduction of the carbonyl group of a [2+2+1] product from the convex face would produce the stereocenters of such core structures. Additionally, the side chain could be attached via a cross-metathesis reaction.[31] Since remodulin (71) is one of the most successful prostacyclin analogues, and would pose a significant test for the diene-ene [2+2+1] reaction due to the bicyclo[4.3.0]nonane core, synthesis of its tricyclic core was chosen for study. The synthetic route used for large-scale production of remodulin,[32] reported in

2002, is 19 total steps (15 longest linear) and features a diastereoselective Pauson—Khand reaction using stoichiometric quantities of a cobalt catalyst.[33]

Figure 2. Structure of prostacyclin, carbacyclin, and medicinally examined prostacyclin analogues.

The diene-ene required for synthesizing remodulin using a [2+2+1] reaction was assembled in only six steps from 3'- hydroxy acetophenone (Scheme 16). In this case, the cationic catalyst previously examined with the dienyl-Pauson— Khand reaction in Section 3 (Scheme 17) proved superior for the construction of the tricyclic core of remodulin.

With conditions determined for the diene-ene [2+2+1] reaction, a serial [2+2+1]/diastereoselective reduction was attempted (Scheme 18). Results showed that it was possible to form the tricyclic core of remodulin and install four of the five stereogenic centers in the molecule in a single operation. Importantly, this step converts a simple monocyclic starting material into an intermediate that can be used in the synthesis of remodulin or a variety of analogues, because the two sites required for diversification are readily functionalized from the completed core structure (mono-substituted olefin for cross-metathesis, and phenol for alkylation). More importantly, this study illustrates the value of the diene-ene [2+2+1] reaction as a method for the step-economical synthesis of complex targets.

Scheme 16. Synthesis of diene-ene for remodulin. (a) K$_2$CO$_3$, acetone, NaI, allyl bromide, 95%; (b) 220 °C (microwave), 75% (2:1 mixture of desired to undesired regioisomer); (c) LiHMDS, acrolein, 89%; (d) TsOH, 95%; (e) NaBH$_4$, CeCl$_3$·7H$_2$O, 89%; (f) TBSCl, imidazole, 64%.

Entry	Catalyst	Temp.	Time	Result
1[a]	[RhCl(CO)$_2$]$_2$	80 °C	6 days	<10% yield
2[b]	[RhCl(CO)$_2$]$_2$/AgSbF$_6$	r.t.	3 h	decomposition
3[c]	RhCl(CO)(PPh$_3$)$_2$/AgSbF$_6$	80 °C	6.5 h	73% yield[d]

[a] 5 mol-% [RhCl(CO)$_2$]$_2$; [b] 5 mol-% [RhCl(CO)$_2$]$_2$, 10 mol-% AgSbF$_6$; [c] 5 mol-% RhCl(CO)(PPh$_3$)$_2$, 5 mol-% AgSbF$_6$; [d] 0.85:1 ratio of epimers

Scheme 17. Screening of conditions for the [2+2+1] reaction.

Scheme 18. Construction of tricyclic core of remodulin.

Scheme 19. Reactions of allenes tethered to alkynes in the presence of CO.

## 5. The Diene-allene [2+2+1] Cycloaddition Reaction[19d]

5.1 Introduction and Initial Results

There are many reports of allene-yne [2+2+1] reactions (Scheme 19)[34] and their usefulness has been illustrated in total syntheses of several natural products.[20a] Notably, when a rhodium(I) catalyst is used, the allene reacts selectively with the distal olefin.[35] This behavior is clearly process-dependent, based on earlier reports from our group in which diene-allenes reacted in a [4+2] reaction with either the distal or proximal olefin of the allene depending on whether a Rh^I or Ni^0 catalyst is used.[17c] Despite the amount of research on the allenic Pauson—Khand reaction, there have not been any reports of an alkene reacting with a simple allene in a [2+2+1] fashion.[36] In fact, it has been reported independently by Brummond[27] and Itoh[26] that allenes tethered to alkenes preferentially and exclusively undergo an ene-type cyclization reaction, even under an atmosphere of CO (Scheme 20). Only in a single case was a [2+2+1] reaction of this type observed (discussed earlier in Scheme 10). Since a unique reactivity was observed for dienes with the diene-yne and diene-ene [2+2+1] reactions, a study of the diene-allene [2+2+1] reaction was undertaken.

Under the conditions optimal for the diene-ene [2+2+1] reaction, diene-allene 89 reacted with the proximal olefin of the allene in a [2+2+1] fashion (Scheme 21). Importantly, this reactivity is different from that of an allene-yne (Scheme 19) or allene-ene (Scheme 20). Diene-allene 89 also underwent a [4+2] reaction with the initial conditions; however, this type of reactivity was averted by lowering the reaction temperature from 80 °C to ambient temperature. In this case, a 99% yield of alkylidene cyclopentane 90 was produced.
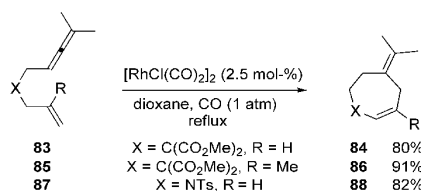
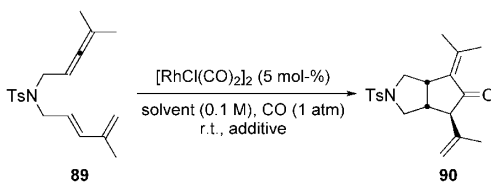Scheme 20. Reactions of allenes tethered to alkenes in the presence of CO.
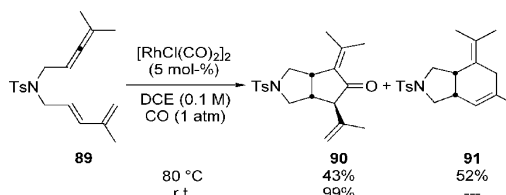
Scheme 21. Diene-allene [2+2+1] reaction.

5.2 Reaction Optimization and Co-Catalysis of the Reaction

Examination of solvents for this reaction led to the realization of a large rate increase for reactions run in TFE (2,2,2-trifluoroethanol) relative to those run in DCE (Table 1). This acceleration appears to be a case of acid co-catalysis since the addition of various acids to DCE also increased the reaction rate (compare entry 1 with entries 5– 10). Significantly, it was found that the rate enhancement is not linear with the pK_a of the acid used since the reaction is faster in TFE (aqueous pK_a of 12.5, entry 2) than in acetic acid (aqueous pK_a of 4.76, entry 8) or methanol (aqueous pK_a of 15.5, entry 3). Additionally, it was found that phenol (aqueous pK_a of 10), whose acidity is similar to TFE, had an analogous rate enhancement when used in the reaction as an additive (entries 9 and 10). Although this acceleration appears to be a result of the pK_a of the additive needing to be in an appropriate range, it could also be due to the hydrogen-bond-donating ability of the acids. [37] It was previously reported that hydrogen-bond donation does not correlate directly with acidity[38] and that TFE is a better hydrogen-bond donor than methanol or acetic acid. [37] Based on these results, it is hypothesized that the acid co-catalyst hydrogen-bonds with a CO ligand or rhodium–acyl species and therefore increases the rate of the reaction by lowering the barrier for CO insertion or reductive elimination. Importantly, this study illustrates the significance of screening different acids with transition-metal-catalyzed cycloaddition reactions, something

rarely evaluated. Benefiting from the acceleration, the diene-allene [2+2+1] reaction in TFE using only 0.1 mol-% catalyst was complete in eight hours at ambient temperature (97% yield of 90, entry 11).

Table 1. Acidic acceleration of the diene-allene [2+2+1] reaction.

Entry	Solvent	Additive (equiv.)	Time [h]	Yield of 90[a]
1	DCE	–	7	99%
2	TFE	–	0.25	92%
3	MeOH	–	12	96%
4	CH₃CN	–	45	77%
5	DCE	TsOH (0.05)	1.3	81%
6	DCE	AcOH (6)	4	93%
7	DCE	AcOH (100)	2.5	96%
8	AcOH	AcOH (neat)	2	93%
9	DCE	PhOH (14)	0.25	94%
10	DCE	TFE (14)	2	95%
11[b]	TFE	–	8	97%

[a] Isolated yield;. [b] 0.1 mol-% catalyst, 0.5 м.
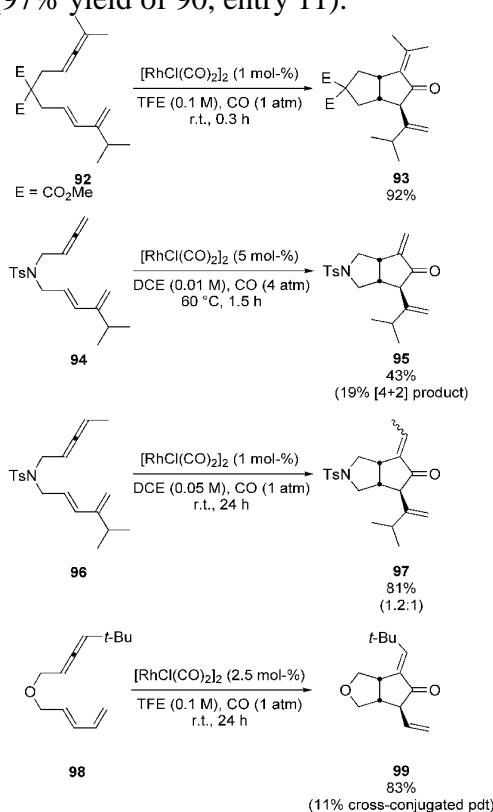
Scheme 22. Representative diene-allene [2+2+1] reactions.

5.3 Substrate Scope

Under the optimal reaction conditions {1–2.5 mol-% [RhCl(CO)₂]₂ in TFE or DCE at ambient temperature with 1 atm of CO}, different diene-allenes were examined. Similar to the other [2+2+1] reactions, the diene-allene [2+2+1] reaction tolerates a wide range of substitutions and tethers without significant decreases in efficiency (Scheme 22). It was observed that reactions were much higher yielding with substitution at the terminus of the allene, although the reaction of monosubstituted allene 94 was successful when slightly modified conditions were used. While the reaction of a substrate with methyl substitution at the terminus of the allene (96) was minimally selective, the reaction of a substrate with a larger *tert*-butyl group (98) produced a single diastereomer in 83% yield.

Importantly, dienes tethered to allenes allow for access to a different mode of reactivity when compared with reactions of alkynes or alkenes tethered to allenes (Scheme 19 and Scheme 20, respectively). Additionally, the reaction conditions are very mild (generally ambient temperature with 1 atm of CO) and produce products with a high level of molecular complexity.

6. Mechanistic Investigation of the [2+2+1] Reactions of Dienes Tethered to π-Systems
6.1 Introduction
Due to the reactivity enhancement observed with dienes in the [2+2+1] reactions,[39] a study was initiated to address the source of this effect and understand why the [4+2+1] reaction is generally not observed.[40] The proposed mechanism for the metal-catalyzed [2+2+1] reaction of a diene tethered to a π-system involves five main steps: (1) catalyst coordination,[41] (2) oxidative cyclization, (3) CO insertion, (4) reductive elimination, and (5) CO coordination (Figure 3). Each of these steps can be connected to additional steps (e.g. the conversion of A to C); however, for the sake of clarity, these five main steps will be discussed. Since changes in CO pressure do not have a significant effect on the rate of the reaction,[19] it is likely that CO coordination is not the rate-determining step (RDS). Therefore, it was decided to determine which of the other four steps is the RDS.

6.2 cis-Diene Results

To obtain information about the energy barriers for the steps described earlier, *cis*-dienes tethered to the respective π-systems were initially studied (Figure 4). If the energy barrier for ring expansion (I to C) is larger than the barrier for CO insertion and subsequent reductive elimination, *cis*-diene 100 should produce cycloadduct 101 wherein the vinyl substituent is epimeric to previously synthesized cycloadduct 3. Alternatively, if ring expansion to C[42] is facile and reversible, the geometry of the diene will rapidly be scrambled and the same product will be formed irrespective of the initial stereochemistry of the diene. It should be noted that cycloadducts corresponding to 3 are thermodynamically favored, but there is no interconversion between the two epimeric [2+2+1] reaction products since formation of the α,β-unsaturated system is a thermodynamic well.

When *cis*-diene-yne 102 and *cis*-diene-ene 103 were used in the [2+2+1] reaction, cycloadducts identical to those obtained from the corresponding *trans*-diene starting materials were generated and at approximately the same rates (Scheme 23). Importantly, the *trans*-diene starting materials were observed in both cases; however, a *cis*-diene without a tethered π-system (104) did not isomerize under the reaction conditions (Scheme 24). These results support a mechanism in which catalyst coordination and oxidative cyclization are rapid, reversible, and not the RDS. Thus, the remaining options for the RDS are CO insertion or reductive elimination.

6.3 Stoichiometric Use of Catalyst

In order to obtain more mechanistic information, a stoichiometric amount of catalyst was used in an attempt to observe intermediates in the diene-yne and diene-ene [2+2+1] reactions. Although the observation of intermediates does not imply that they are necessarily on the reaction pathway, [43] and often their presence indicates that they are not along the pathway,[44] it was envisioned that the observation of a metallacycle without CO inserted would substantiate the hypothesis that CO insertion or reductive elimination is the RDS. Alternatively, observation of an intermediate with a rhodium—acyl group would provide strong evidence against CO insertion being the RDS. For this reason, if a rhodium—acyl species is observed, it is likely that reductive elimination is the RDS.

Initially, diene-yne 11 was examined using the standard catalyst, [RhCl(CO)$_2$]$_2$, in a stoichiometric quantity (Scheme 25).[45] Based on the ^{1}H and 2D NMR spectroscopic experiments, two main intermediates were observed (Figure 5). These intermediates were converted into [2+2+1] reaction product 12 over time or upon heating. Unfortunately, the characterization of these intermediates proved difficult due to the low signal to noise ratio for ^{13}C NMR spectroscopic experiments.
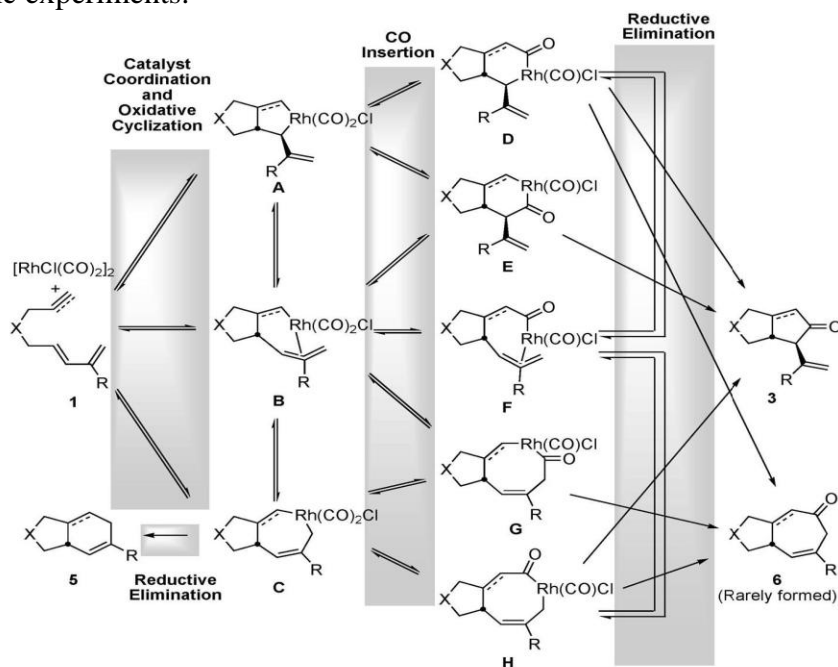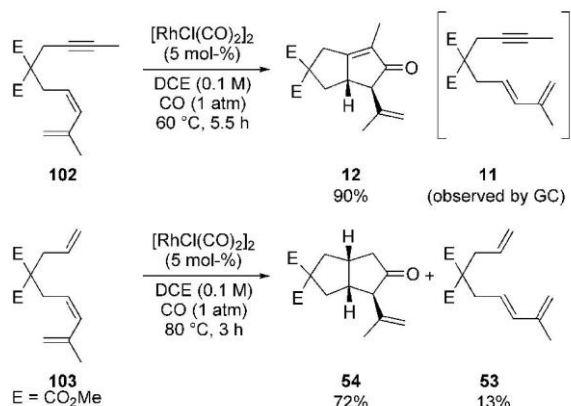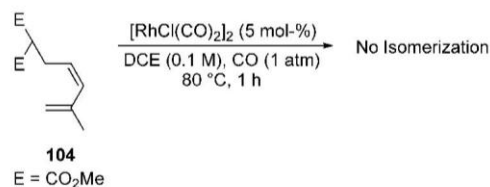

Figure 3. Proposed mechanistic overview of the [2+2+1], [4+2+1], and [4+2] reactions.

Scheme 23. Results of a *cis*-diene-yne and a *cis*-diene-ene.

Scheme 24. Reactivity of *cis*-diene without a tethered π-system.

To facilitate the characterization of the intermediates, a reaction was run with ^{13}C-labeled CO on the catalyst (Scheme 26). Significantly, this led to the determination that both of the intermediates in the diene-yne [2+2+1] reaction had inserted CO as evidenced by the shift and coupling in the ^{13}C NMR spectra (Figure 6).[46] As discussed earlier, this does not mean that these exact intermediates lie on the reaction pathway, but the evidence suggests that CO insertion and the steps prior to it are not the RDS.
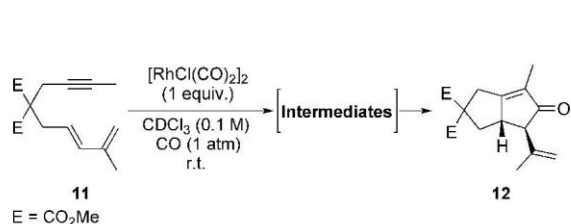
Scheme 25. Diene-yne [2+2+1] reaction with stoichiometric catalyst loading.
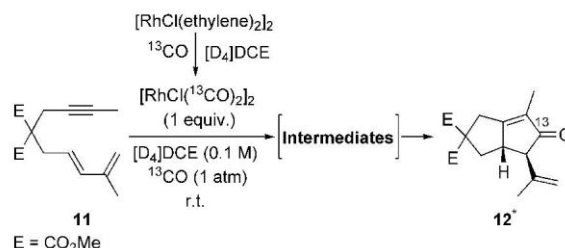
Scheme 26. Diene-yne [2+2+1] reaction with ^{13}C-labeled catalyst.

The reaction of diene-ene 53 with a stoichiometric amount of the ^{13}C-labeled catalyst was subsequently examined (Scheme 27). Similar to the diene-yne reaction, the ^{13}C NMR spectrum showed two rhodium–acyl intermediates (Figure 7). Therefore, since the rate of forming the CO-inserted intermediates is faster than the rate of product formation, the evidence again suggests that CO insertion is not the RDS.
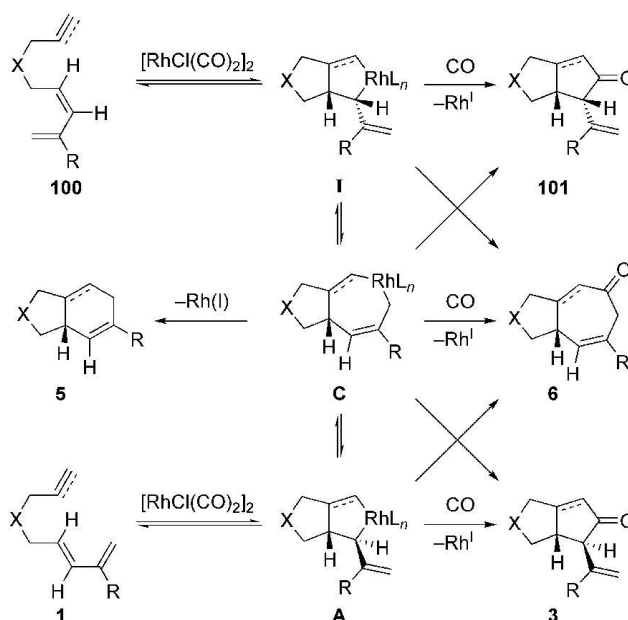

Figure 4. Reaction pathways for *cis*-dienes and π-systems.

6.4 Conclusions for the Mechanism of the [2+2+1] Reactions of Dienes Tethered to n-Systems

Based on the empirical data, it was previously determined that CO coordination is not the RDS. From the reactions run with *cis*-dienes tethered to -systems, it was found that catalyst coordination and oxidative cyclization are rapid and reversible for the diene-yne and diene-ene reactions. Finally, from the reactions using a stoichiometric amount of catalyst with ^{13}C-labeled CO, it was determined that the rate of CO insertion for the two intermediates in the dieneyne and diene-ene reactions was faster than the rate of product formation. Therefore, under these conditions, the evidence suggests that ***reductive elimination is the rate-determining step for the diene-yne and diene-ene [2+2+1] reactions***.
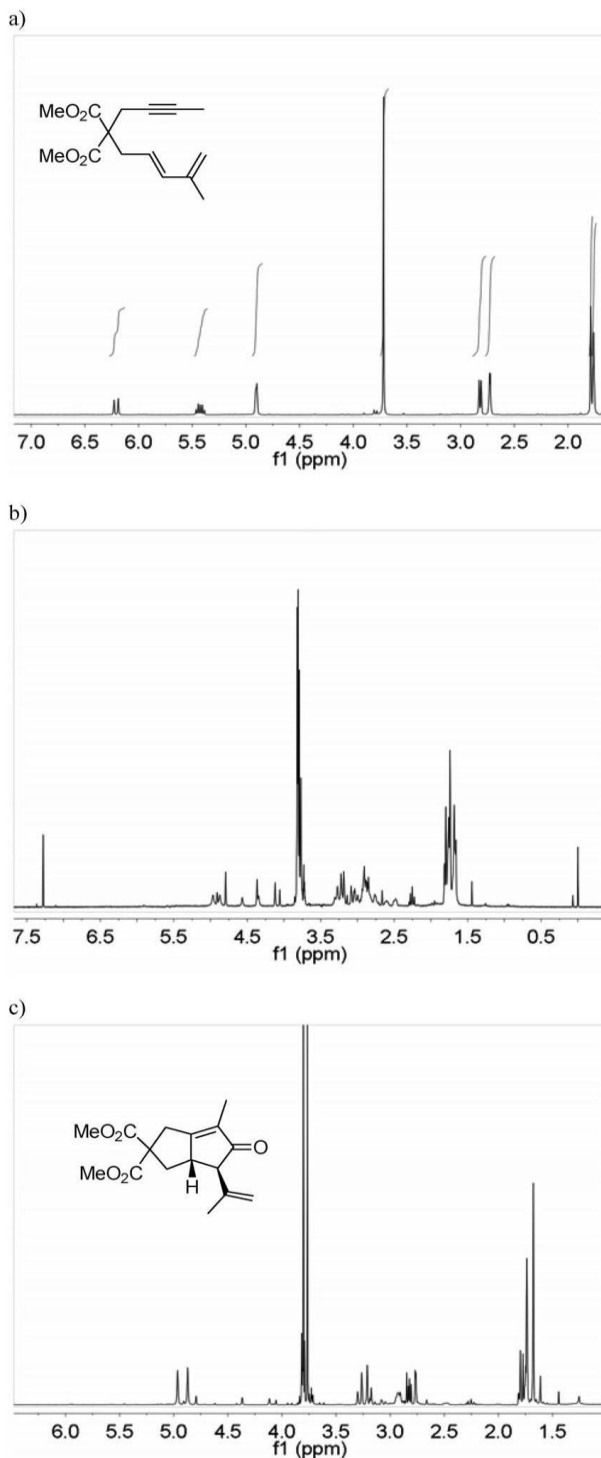

Figure 5. ^{1}H spectra using stoichiometric catalyst loading: (a) starting diene-yne; (b) intermediates formed; (c) further reaction forms product.
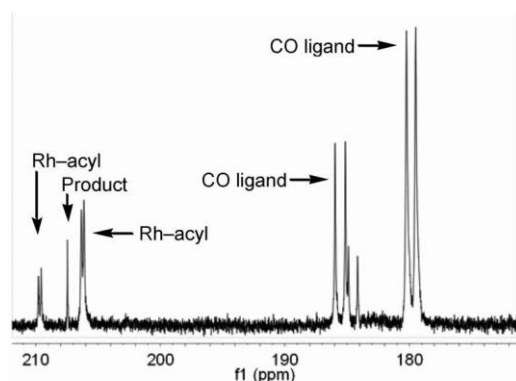
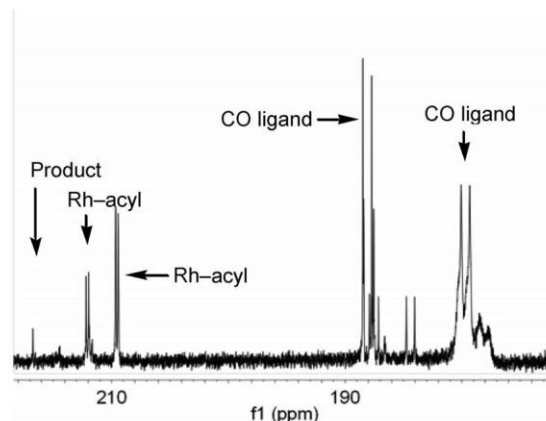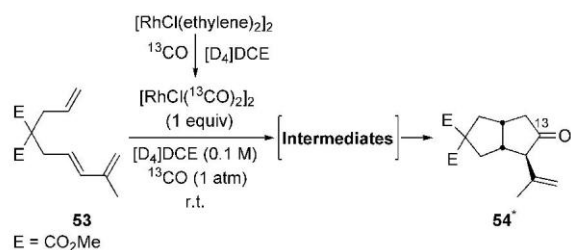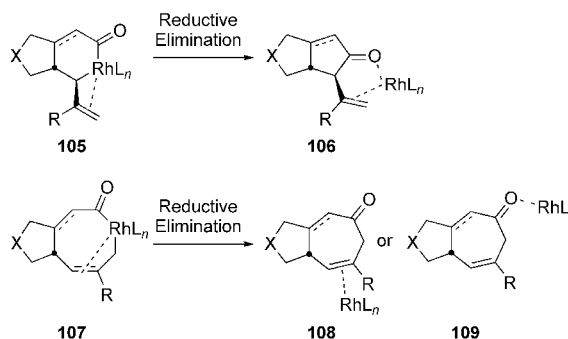Figure 6. ^{13}C NMR spectrum for a diene-yne reaction.

Figure 7. ^{13}C NMR spectrum for a diene-ene reaction.

Scheme 27. Diene-ene [2+2+1] reaction with ^{13}C-labeled catalyst.

Scheme 28. Assisted reductive elimination.

Since reductive elimination appears to be the RDS, two hypotheses can be made as to why a [2+2+1] reaction is favored over a [4+2+1] reaction. First, reductive elimination with an exocyclic vinyl group would provide the catalyst with bidentate coordination to stabilize the transition state as compared to single ligation for the [4+2+1] reaction (Scheme 28). A similar result has been observed with the [5+2] reaction whereby a "migratory reductive elimination" was found to be much lower in energy when the rhodium could bind to another olefin within the molecule.[47] Another possibility is that the reductive elimination occurs with 1,3-transposition of the olefin. In other words, intermediate 110 directly forms 111 (Scheme 29) in a similar mechanism as an allylation of a ketone with an allyl–metal species. Either of these hypotheses can be used to explain why the diene is important since the olefin is intricately in volved in both of the mechanisms. These hypotheses are also consistent with the observed absence of reactivity when the diene of the starting material is replaced with an isolated alkene or styrene.
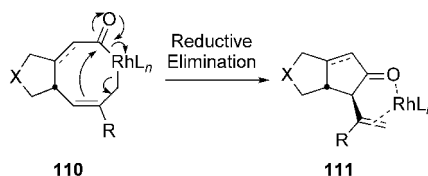
Scheme 29. Allylic transposition and reductive elimination.

7. Conclusions

The mechanism of the [4+2] cycloaddition of dienes and π-systems has been used as a conceptual starting point for the design of an unexplored variant of the Pauson–Khand [2+2+1] reaction involving dienes and of a new [4+2+1] reaction. The intramolecular metal-catalyzed [4+2] reaction introduced in our earlier work[17] is a very efficient process, often serving as an alternative or preferred option to a Diels–Alder process. Significantly, capture of intermediates along the [4+2] reaction pathway with CO has been possible using commercially available, bench-stable rhodium(I) catalysts, resulting in diene-yne, diene-ene, and diene-allene [2+2+1] reactions. It is also noteworthy that capture can be conducted with other π-systems. [48] The [2+2+1] reactions

discussed herein convert relatively simple starting materials into mono- or bicyclic molecules with significantly increased molecular complexity including three new bonds, up to four new stereocenters, and functional groups including ketones and olefins that allow for facile subsequent functionalization. Mechanistic studies suggest that with the diene-yne and diene-ene [2+2+1] reactions the rate-determining step is reductive elimination. It is therefore hypothesized that the additional olefin of the diene is beneficial for these reactions because it provides for bidentate binding to the catalyst during the reductive elimination. Thus, as has even been observed in other systems with different catalysts, [39] the diene exhibits unique reactivity compared to an isolated alkene even though one of the n-systems of the diene is unchanged by the reaction. This observation (diene effect) should have widespread use in other cycloaddition processes, especially those for which simple monoalkenes are poor substrates.

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