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Strain-Release-Controlled [4 + 2 + 1] Reaction of Cyclopropyl-Capped Diene-ynes/Diene-enes and Carbon Monoxide Catalyzed by Rhodium

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ABSTRACT: Achieving transition-metal-catalyzed reactions of diene-ynes/diene-enes and carbon monoxide (CO) to deliver [4 + 2 + 1] cycloadducts, rather than the kinetically favored [2 + 2 + 1] products, is challenging. Here, we report that this can be solved by adding a cyclopropyl (CP) cap to the diene moiety of the original substrates. The resulting CP-capped diene-ynes/diene-enes can react with CO under Rh catalysis to give [4 + 2 + 1] cycloadducts exclusively without forming [2 + 2 + 1] products. This reaction has a broad scope and can be used to synthesize useful 5/7 bicycles with a CP moiety. Of the same importance, the CP moiety in the [4 + 2 + 1] cycloadducts can act as an intermediate group for further transformations so that other challenging bicyclic 5/7 and tricyclic 5/7/5, 5/7/6, and 5/7/7 skeletons, some of which are widely found in natural products, can be accessed. The mechanism of this [4 + 2 + 1] reaction has been investigated by quantum chemical calculations, and the role of the CP group in avoiding the possible side [2 + 2 + 1] reaction has been identified, showing that the [4 + 2 + 1] is controlled by releasing the ring strain in the methylenecyclopropyl (MCP) group (about 7 kcal/mol) in the CP-capped dienes.
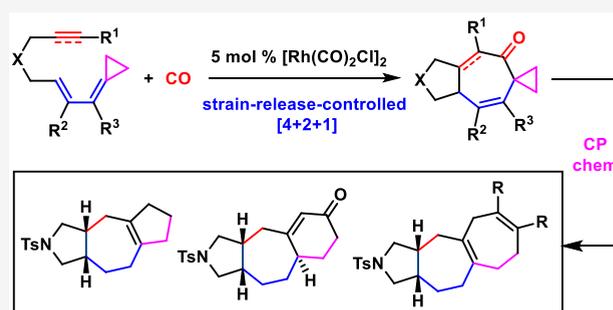
INTRODUCTION

Many bi- and polycyclic natural products with seven-membered carbocycles (Figure 1) have significant biological activities. However, synthesizing these molecules and their analogues is still posing challenges to chemists.[1,2] One of the major reasons is that the available reactions, methods, and strategies to build seven-membered carbocycles are limited.[1,2] Therefore, developing new reactions to synthesize seven-membered carbocycles with different substituents and stereo-chemistry, compared to those reached by the known methods, is important to advance the science of synthesis.

In our opinion, one of the most efficient and straightforward reactions, needed to be developed for the synthesis of seven-membered carbocycles, is the transition-metal-catalyzed [4 + 2 + 1] cycloaddition of diene-enes/diene-ynes/diene-allenes and carbon monoxide (CO), considering that these substrates are readily accessible and CO is cheap and abundant.[3−7] However, realization of this reaction has obstacles, since [4 + 2], [2 + 2 + 1] cycloadditions and other side reactions could overwhelm the desired [4 + 2 + 1] cycloaddition.

It was reported by Wender and coworkers[3] that the [2 + 2 + 1] reactions were usually the outcomes for the reactions of diene-enes/diene-ynes/diene-allenes and CO under the rhodium catalysis. Only in one example, the [4 + 2 + 1] product was observed as a side product (Scheme 1a).[3a] This observation prompted us to propose two strategies to overcome the regiochemistry issue in the future design of [4 + 2 + 1] reactions.[4] The first strategy named as catalyst-

Figure 1. Natural products containing bicyclic 5/7 and tricyclic 5/7/5 and 5/7/6 rings.

Scheme 1. Endeavors to Realize [4 + 2 + 1] Cycloadditions

a) [2+2+1] reaction of ene/yne/allene-dienes and CO (Wender et al.)

ene/yne/allene-dienes   [2+2+1]   [4+2+1] not favored

b) [4+2+1] of in situ generated ene/yne-ene-allenes and CO (our previous work)

ene/yne-ene-allenes in situ generated   [4+2+1]   [2+2+1] not observed

c) [4+2+1] reaction of cyclopropyl-capped diene-ynes/diene-ene and CO (this work)

cyclopropyl-capped diene-ynes/diene-ene

group required in the substrates for the [4 + 2 + 1] reaction can have rich chemistry of transformations, which in turn will significantly access many other useful skeletons. For example, our previous [4 + 2 + 1] reaction of in situ generated ene/yne−ene−allenes with CO belongs to the SDS (Scheme 1b).[4−6] In this reaction, the traditional dienes are changed to ene−allenes, where allenes are in situ generated. The allene is critical to provide additional coordination to help this [4 + 2 + 1] reaction.[4] We can envision that this intermediate group can be further transformed into other useful groups, which is our ongoing research. Here, we report a serendipitously discovered [4 + 2 + 1] reaction of cyclopropyl-capped diene-ynes/diene-enes with CO, which also belongs to the SDS (Scheme 1c).

We initially tried to use cyclopropyl-capped dienes (CP-capped dienes in short)[8,9] and CO for the synthesis of eight-membered carbocycles, hypothesizing that the cyclopropyl (CP) group in the substrates can be cleaved, as many reactions of methylenecyclopropane (MCP) did.[10] Instead of CP cleavage, we found a [4 + 2 + 1] reaction of CP-capped diene-ynes/diene-enes with CO under the catalysis of rhodium, which is present in this paper (Scheme 1c). This unexpected and exciting [4 + 2 + 1] reaction belongs to the SDS due to the following reasons. The CP group as the intermediate group in the CP-capped dienes is critical to the success of the [4 + 2 + 1] reaction, which helps the [4 + 2 + 1] through strain release (see the computational understanding part in this paper). On the other hand, the CP group can be further converted to other functional groups by applying cyclopropane chemistry (CP chem in short here),[11] which is also communicated in this paper. Of the same importance, the highly functionalized bicyclic 5/7 molecules with the CP group will be valuable in medicinal chemistry because CP group is an important motif in many pharmaceutical compounds.[12]

searching strategy (CSS) is to find appropriate catalysts (and ligands). The second strategy is substrate-designing strategy (SDS), which involves designing substrates of diene-enes/diene-ynes/diene-allenes with special substituents to favor the [4 + 2 + 1] reactions.

Of course, the CSS is more attractive since this could realize [4 + 2 + 1] reactions with a broad scope of substrates, if successful. However, the SDS is also significant since the special [4 + 2 + 1] products from this strategy could be useful. The SDS could be more powerful if a special intermediate

■ RESULTS AND DISCUSSION

Reaction Optimization and Scope of the [4 + 2 + 1] Reaction. Table 1 lists our optimization efforts of the [4 + 2 + 1] reaction using CP-capped diene-yne **1a** and CO. In the presence of 5 mol % [Rh(CO)$_2$Cl]$_2$ as the catalyst in toluene at 80 °C, the [4 + 2 + 1] product **2a** was obtained in 60% NMR

Table 1. Optimization of [4+2+1] Reaction Conditions[a]

entry	catalyst	solvent	T (°C)	t (h)	yield[b]
1	5 mol % [Rh(CO)$_2$Cl]$_2$	toluene	80	15	60%
2	10 mol % Ir(CO)(PPh$_3$)$_2$Cl	toluene	80	15	5%
3	5 mol % Co$_2$(CO)$_8$	toluene	80	15	3%
4	5 mol % [Rh(CO)$_2$Cl]$_2$	DCE	80	15	45%
5	5 mol % [Rh(CO)$_2$Cl]$_2$	1,4-dioxane	80	15	42%
6	5 mol % [Rh(CO)$_2$Cl]$_2$	benzene	80	15	71%
7	5 mol % [Rh(CO)$_2$Cl]$_2$	toluene	100	2	55%
8	**5 mol % [Rh(CO)$_2$Cl]$_2$**	**toluene**	**40**	**24**	**81%[c]**
9	5 mol % [Rh(CO)$_2$Cl]$_2$	toluene	30	72	66%
10[d]	5 mol % [Rh(CO)$_2$Cl]$_2$	toluene	40	30	73%
11[e]	5 mol % [Rh(CO)$_2$Cl]$_2$	toluene	40	24	77%
12	1 mol % [Rh(CO)$_2$Cl]$_2$	toluene	40	24	12%

[a]Reaction conditions: 0.1 mmol **1a**, catalyst, 2 mL toluene (0.05 M), T °C, t h, 1 atm CO. [b]NMR yield, using 1,3,5-trimethoxybenzene as the internal standard. [c]Isolated yield: 76%. [d]4 mL toluene (0.025 M). [e]1 mL toluene (0.10 M).
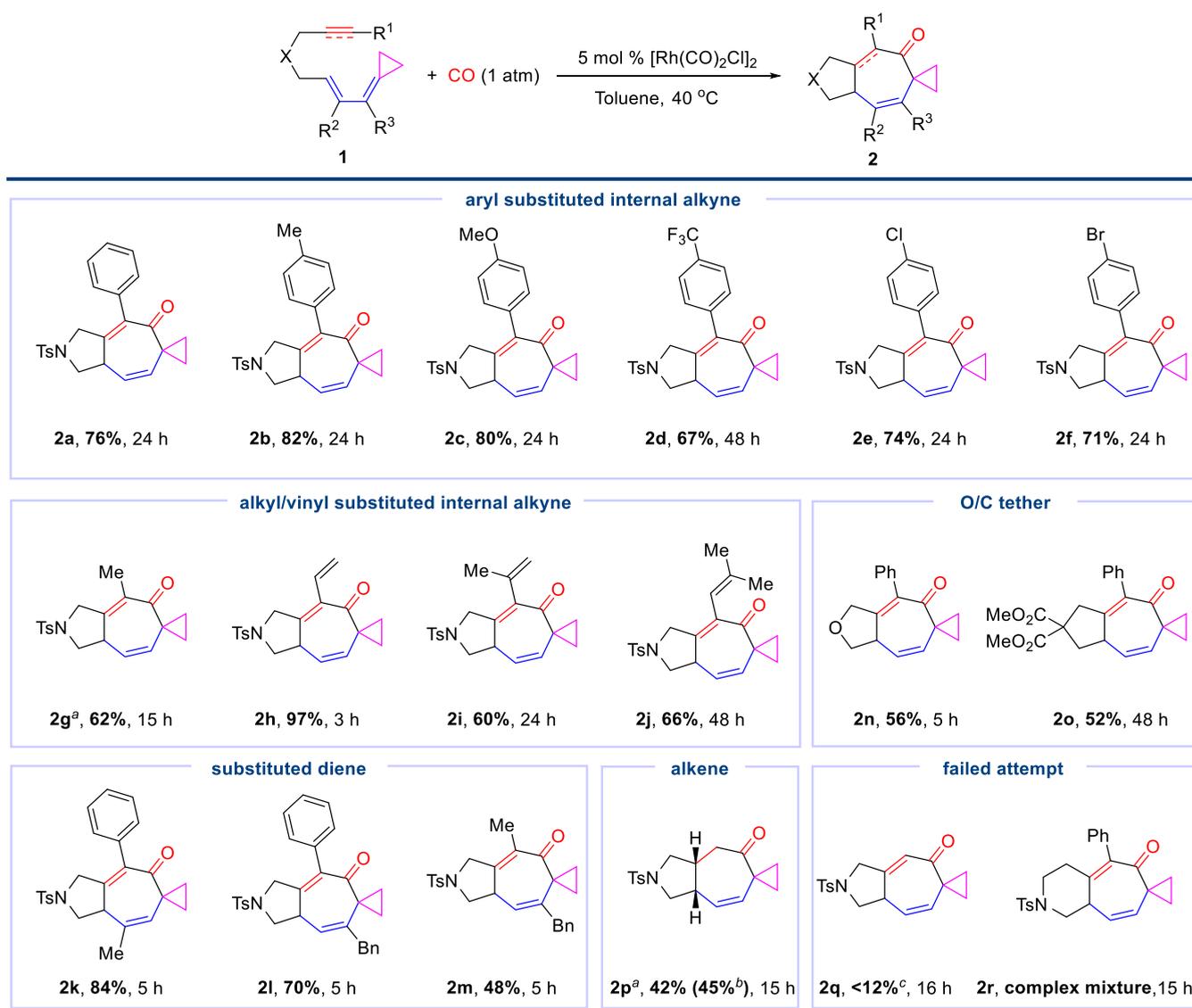
Figure 2. Reaction scope of [4 + 2 + 1] cycloaddition. Reaction conditions: 0.1 mmol **1**, 5 mol % [Rh(CO)₂Cl]₂, 2 mL toluene (0.05 M), 40 °C, 1 atm CO; The yields presented are an average of two runs. [a]80 °C; [b]at 3.5 mmol scale, 17 h; [c]with inseparable impurities.

yield (Table 1, entry 1). Neither iridium nor cobalt catalyst can achieve the [4 + 2 + 1] reaction in an acceptable yield (Table 1, entries 2 and 3). Other Rh catalysts were also tested using substrate **1g** (Figure 2) but cannot give better results than [Rh(CO)₂Cl]₂ did (see the Supporting Information (SI) for more optimization conditions on **1g**). We then screened other solvents (Table 1, entries 4−6), finding that benzene had the best performance, giving rise to **2a** in 71% yield (Table 1, entry 6). Replacing benzene by a less toxic solvent of toluene was tested, finding that higher reaction temperature (100 °C) and shorter reaction time (2 h) produced **2a** in 55% yield (Table 1, entry 7). To our delight, **2a** was obtained in 81% NMR yield and 76% isolated yield when the reaction was carried out at 40 °C for 24 h (Table 1, entry 8). Carrying out the [4 + 2 + 1] reaction at 30 °C failed to improve this cycloaddition reaction (Table 1, entry 9). Neither increasing nor reducing the concentration of the substrate can get a better yield of the [4 + 2 + 1] reaction (Table 1, entries 10 and 11). Further reducing the catalyst loading to 1 mol % gave a disappointing result because only 12% NMR yield of **2a** was obtained after 24 h

(Table 1, entry 12). Therefore, we chose the conditions shown in entry 8 of Table 1 for further investigation of the reaction scope. In addition, it is suggested that the substrates for the present reaction should be used as soon as possible, because the substrates can slowly decompose. For example, the yield of [4 + 2 + 1] cycloadduct **2g** decreased by 29% when using substrate **1g**, which had been stored at −20 °C for a week (see below and the SI).[9]

Figure 2 shows the scope of the present [4 + 2 + 1] reaction. For CP-capped diene-ynes **1b**−**1f** with a R¹=Ar group, the [4 + 2 + 1] products **2b**−**2f** were obtained in moderate to good yields, ranging from 67 to 82%. Among them, a longer reaction time (48 h) was essential to have a full conversion for **1d** bearing an electron-withdrawing CF₃ group on the aryl ring of its R¹ group. To our delight, the desired [4 + 2 + 1] cycloadduct can be generated at an elevated temperature of 80 °C when a methyl-terminated CP-capped diene-yne **1g** was employed as the substrate. Substrates **1h**−**1j** containing alkene substituents in the alkyne moiety of CP-capped diene-ynes also gave the corresponding products in moderate to excellent

yields (from 60 to 97%, **2h−2j**). In this case, substrates **1i** and **1j** had lower reactivities (their reaction times were 24 and 48 h, respectively) and gave moderate yields of 60 and 66%, respectively. In contrast, substrate **1h** with a vinyl group produced **2h** in 97% yield in 3 h. We reasoned that the steric effect introduced by the substituent was responsible for the less satisfactory reaction yields for both **1i** and **1j** compared to that for substrate **1h** with a vinyl group. We also tested **1k−1m** with R^2 or R^3 substituents in the diene moiety of the substrates, finding that all these reactions took place smoothly (**2k−2m**; the structure of **2m** was identified by X-ray crystallography; see the SI).

Further studies demonstrated that both oxygen- and carbon-tethered substrates (**1n** and **1o**) can deliver the expected bicyclic 5/7 compounds successfully. The 2π component of the present [4 + 2 + 1] reaction can be an alkene, as exemplified by the reaction of **1p**, affording **2p** in an acceptable yield of 42%, even though the reaction temperature had to be 80 °C (the structure of **2p** was confirmed by X-ray crystallography; see the SI). In addition, a gram-scale reaction for **1p** was also carried out, giving **2p** in 45% yield. Unfortunately, the reaction of substrate **1q** with terminal alkyne was poor and gave a series of unidentified products, among which the [4 + 2 + 1] cycloadduct **2q** (in less than 12% yield) together with inseparable unknown impurities was obtained through column chromatography (see the SI for details). In addition, the present reaction cannot be applied to synthesize 6/7 products, as demonstrated by the reaction of substrate **1r**.

CP Chem of Transforming [4 + 2 + 1] Cycloadducts into Other Products.

We did some intermediate group transformations of cyclopropane (CP chem) using **2p**, to demonstrate that more functionalized molecules and challenging polycyclic skeletons can be built (Scheme 2). We used

Scheme 2. Intermediate Group Transformations of the Cyclopropyl Group (CP Chem) Using [4 + 2 + 1] Cycloadduct 2p
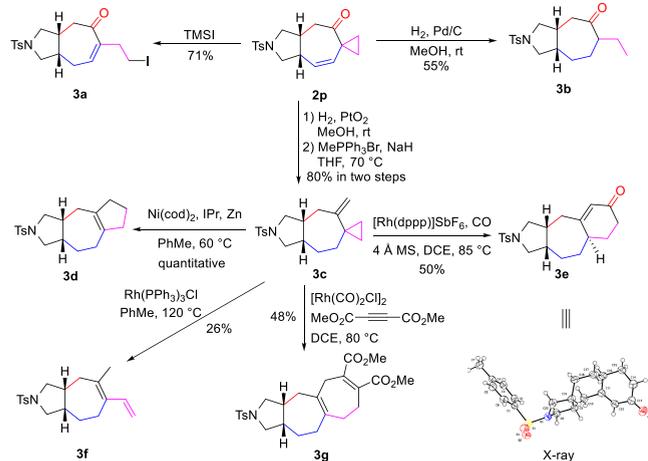
trimethyliodosilane (TMSI) to open the CP moiety in **2p** to afford **3a**. Under Pd/C and H_2, **2p** can be reduced to give **3b**. To construct the 5/7/5, 5/7/6, and 5/7/7 architectures, we first used reduction and Wittig reaction to synthesize **3c** bearing a vinyl cyclopropane group. We subsequently used Ni and Rh catalysts to convert **3c** to **3d−g**, via vinyl cyclopropane isomerization, [5 + 1], and [5 + 2] reactions, developed by

Louie and Zuo,[13] Yu et al.,[14] and Wender et al.,[15] respectively. Furthermore, vinyl cyclopropane isomerization was applied to convert **3c** to **3f** with a diene group when Wilkinson's catalyst was used. We can envision that **3f** can be further transformed into many other molecules if the rich chemistry of diene in **3f** can be utilized.

Mechanism of the [4 + 2 + 1] Reaction.

We carried out quantum chemical calculations to study the proposed mechanism of the [4 + 2 + 1] reaction of CP-capped diene-ynes shown in Scheme 1c and Figure 3. We proposed that the catalytic species of this reaction is a monomer of the catalyst, $[Rh(CO_2)Cl]$, similar to that in the [4 + 2 + 1] and [5 + 2 + 1] reactions.[4,5,16] The reaction starts from generating complex **IN1** from the dimeric $[Rh(CO)_2Cl]_2$ and model substrate with an oxygen tether. Then, **IN1** can dissociate a CO to generate **IN2**. This step has an estimated free energy of 15.9 kcal/mol (via **TSCO-diss**) if we assume that its reverse reaction of CO coordination is diffusion-controlled (the CO concentration is estimated to be 7.4 mM).[17] Intermediate **IN2**, which is a 16-electron species, is then coordinated by an alkyne moiety in the substrate to form an 18-electron complex **IN3**. After that, **IN3** undergoes oxidative cyclometalation to give intermediate **IN4** via transition state **TS1**, with an activation Gibbs free energy of 12.8 kcal/mol. **IN4** could undergo a direct reductive elimination (via **TS2**) to give the [4 + 2] cycloadduct, but this is disfavored (requiring an activation free energy of 17.2 kcal/mol, from intermediate **IN4**), implying that the [4 + 2] cycloaddition pathway can be ruled out.[18] This agrees with our experiments that no [4 + 2] products were observed. Instead of participating in the [4 + 2] cycloaddition, the 16-electron complex **IN4** prefers to be coordinated by a CO molecule to form an 18-electron complex, **IN5**, which then easily undergoes CO insertion reaction into the C1−Rh bond via the UP CO pathway, forming intermediate **IN6** via **TS3** (requiring an activation free energy of 19.2 kcal/mol, from **IN6** to **TS3**). In principle, the CO molecule could be inserted into the Rh−C2 bond in **IN5** (via the DOWN CO insertion pathway), but this is disfavored and excluded for further consideration (see the SI for the transition state), like that in the [4 + 2 + 1] reaction[3d,4] in Scheme 1b. To continue the [4 + 2 + 1] reaction, **IN6** then undergoes a reductive elimination (via **TS4**) to give intermediate **IN7**, which can be further coordinated by a CO molecule to generate **IN7-CO**, a complex between the [4 + 2 + 1] product and catalytic species. The final step of the [4 + 2 + 1] reaction is a ligand exchange to release the [4 + 2 + 1] product **P** and form complex **IN1**, which can then enter the next catalytic cycle (in principle, **IN7-CO**, **IN1**, and the unknown resting state are in equilibrium before the reaction starts the next catalytic cycle). **IN6** could be coordinated by CO to form **IN8**, but the followed-up reactions from **IN8** are kinetically disfavored (see discussion below). Therefore, the most difficult step in the catalytic cycle is reductive elimination with an activation free energy of 20.1 kcal/mol (from **IN8** to **TS4**). On the other hand, the resting state of this reaction is not known. The rate-determining step of the [4 + 2 + 1] reaction could also be the cyclometalation via **TS1**, if the required free energy from this resting state to **TS1** is higher than 20.1 kcal/mol. If not, the rate-determining step is the reductive elimination via **TS4**. We do not know the answer for this question at this moment.

Understanding Why [4 + 2 + 1] Is Favored over [2 + 2 + 1] and Finding that Strain Release Is the Key to Success.

The next question is to answer why the [2 + 2 + 1]
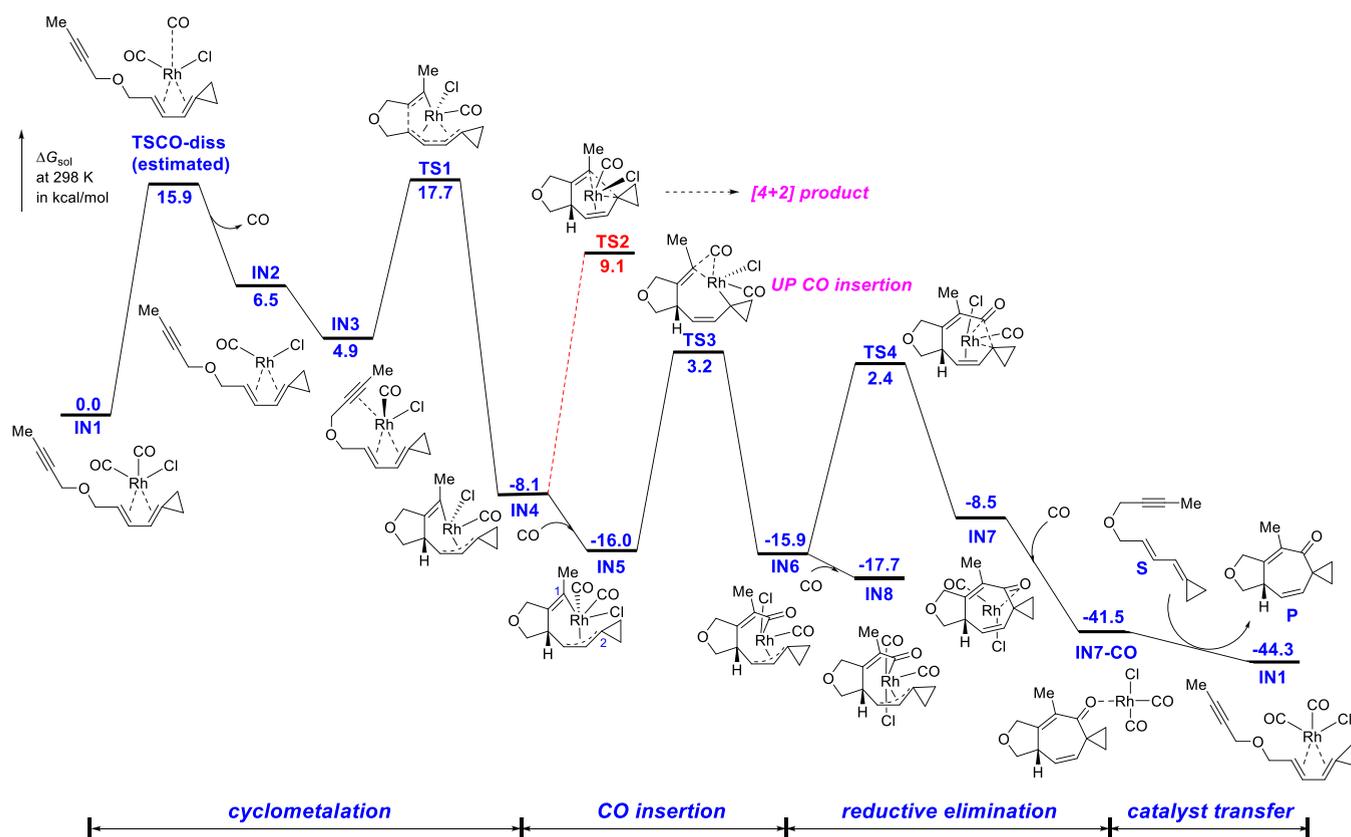
Figure 3. Gibbs energy profile for [4 + 2 + 1] cycloaddition of CP-capped diene-yne and CO computed at the DLPNO-CCSD(T)-SMD(PhMe)/def2-TZVPP//BMK/def2-SVP level.

reaction does not occur (Figure 4a). There are four pathways to give [4 + 2 + 1] and [2 + 2 + 1] products. Intermediate **IN6** directly undergoes reductive elimination via **TS4** to give [4 + 2 + 1] cycloadduct−Rh complex **IN7**. Intermediate **IN6** can also directly deliver [2 + 2 + 1] product−Rh complex **IN11** via **TS5**. In addition, **IN6** can be coordinated by a CO molecule to form **IN8**, which then delivers **IN7-CO**, the complex of [4 + 2 + 1] product **P** and catalyst, via **TS4-CO**. In addition, **IN8** can isomerize to **IN9**, which can then undergo reductive elimination via **TS5-CO** to form **IN10**, Rh complex with the [2 + 2 + 1] product. Our calculations indicated that the favored pathway to form the [4 + 2 + 1] product is through **TS4**, while the preferred pathway to form the [2 + 2 + 1] product is through **TS5-CO**. In the present case, **TS4** is lower than **TS5-CO** by 5.8 kcal/mol in terms of Gibbs free energy, suggesting that the [4 + 2 + 1] product is the exclusive product. This agrees with our experimental results.

To appreciate the reason of the regiochemistry, we must compare this with the [2 + 2 + 1] reaction of diene-yne and its competing but disfavored [4 + 2 + 1] reaction (Figure 4b). Similarly, there are intermediates **IN6-d**, **IN8-d**, and **IN9-d** and their corresponding transition states **TS4-d**, **TS5-d**, **TS4-CO-d**, and **TS5-CO-d**. For this substrate, our DFT calculations found that generation of the [2 + 2 + 1] product is favored because its transition state **TS5-CO-d** is favored over **TS4-d** (which leads to the [4 + 2 + 1] product) by 2.8 kcal/mol. This agrees with experiments of Wender et al.[3a]

First, we discuss Figure 4b for the substrate with a common diene. Consistent with the previous studies on the reductive elimination from the d^6 transition-metal complex,[19] the C−C bond formation through reductive elimination usually proceeds

through a 16-e five-coordinate Rh(III) complex (such as **IN6-d** and **IN9-d** here). The 18-e intermediate **IN8-d** dissociates a CO ligand to form 16-e complex **IN6-d**. Intermediate **IN6-d** undergoes reductive elimination via either transition state **TS4-d** or **TS5-d** to afford the [4 + 2 + 1] product or [2 + 2 + 1] product. **TS4-d** is more stable than **TS5-d** by 6.1 kcal/mol. The ring strain could be the reason for this preference because **TS5-d** is forming a Rh-embedded smaller ring compared to the ring formed in **TS4-d**: if there is no ring formation, both pathways have similar activation free energies, as can be appreciated by the model reactions shown in Figure S5 of the Supporting Information.

The 18-e complex **IN8-d** can also dissociate the vinyl ligand (C1=C2) to form a 16-e complex **IN9-d**. Then, **IN9-d** affords the [2 + 2 + 1] product through **TS5-CO-d**. In **TS5-CO-d**, the vinyl (C1=C2) group is weakly coordinated with Rh (the C2−Rh is 2.28 Å, 0.13 Å longer than that in **TS5-d**) and has little effect on the required geometry of reductive elimination from the Rh(III) complex (trigonal bipyramid). **TS5-CO-d** is much favored over **TS5-d** by 8.9 kcal/mol. This is because the additional strong π-acceptor ligands of CO and double bond in **TS5-CO-d** can stabilize the low-valent metal and facilitate the reductive elimination of the transition-metal complex.[20] **IN8-d** can also dissociate the vinyl ligand (C2=C3) and undergo the reductive elimination via **TS4-CO-d** to form the [4 + 2 + 1] product. Due to the required geometry of reductive elimination of the Rh(III) complex (trigonal bipyramid), **TS4-CO-d** loses the coordination of the vinyl group (C2=C3) completely (unlike **TS5-CO-d**), and one CO ligand in **TS4-CO-d** is close to the Rh-embedded eight-membered ring, leading to a large steric repulsion. That is why this process
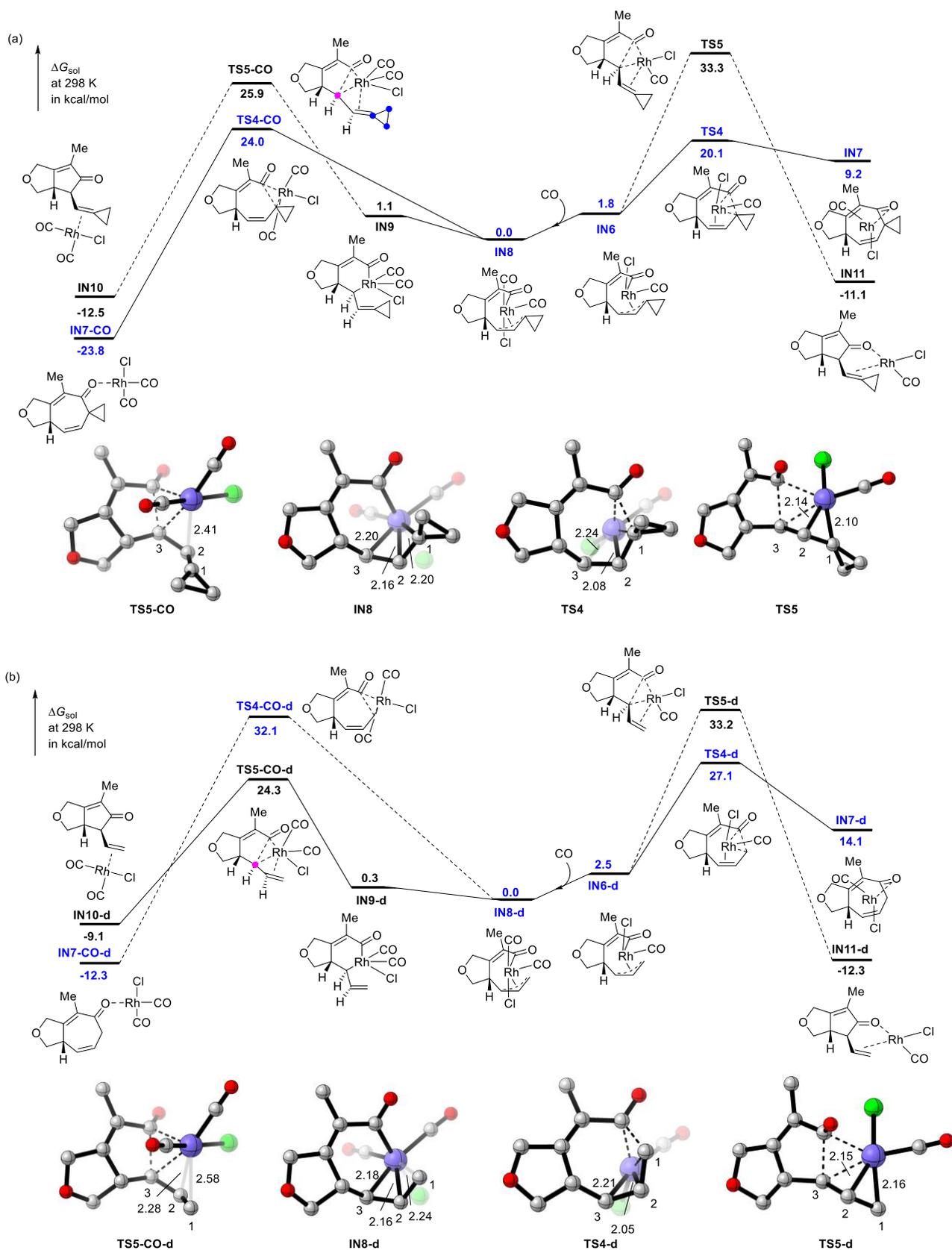
Figure 4. Competition of [4 + 2 + 1] and [2 + 2 + 1] cycloadditions for the reactions of CO and CP-capped diene-yne (a) and common diene-yne (b). All of them were computed at the DLPNO-CCSD(T)-SMD(PhMe)/def2-TZVPP//BMK/def2-SVP level.

requires an activation free energy of 32.1 kcal/mol and is disfavored compared to **TS4-d** and **TS5-CO-d**. Therefore,

TS5-CO-d, which gives the [2 + 2 + 1] product, is the most favored transition state for the common diene.

In Figure 4a for the substrate with a CP-capped diene, all the [2 + 2 + 1] pathways have similar activation free energies compared to those in Figure 4b for the substrate with a common diene: 25.9 kcal/mol (**TS5-CO**) vs 24.3 kcal/mol (**TS5-CO-d**); 33.3 kcal/mol (**TS5**) vs 33.2 kcal/mol (**TS5-d**). However, the [4 + 2 + 1] pathways for the substrate with a CP-capped diene compared to those for the substrate with a common diene are favored by around 7 kcal/mol: 20.1 kcal/mol (**TS4**) vs 27.1 kcal/mol (**TS4-d**); 24.0 kcal/mol (**TS4-CO**) vs 32.1 kcal/mol (**TS4-CO-d**).

We attribute the reduction of activation free energies in the [4 + 2 + 1] pathway to the strain release of the methylenecyclopropyl (MCP) part in the CP-capped diene.[21,8a] MCP is a strained molecule because the bond angle of its alkene is 60°. This ring strain can be reflected by the hydrogenation reactions a and b, showing that CP-capped diene is 11.7 kcal/mol more exergonic than a common diene (Scheme 3). Here, we just compare **IN8** to **TS4** to **IN7** and

Scheme 3. Evaluation of Strain Release of MCP by Comparing the Hydrogenation Reactions of a and b and Estimation of the Relative Coordination Ability of Alkene and MCP via Reaction c
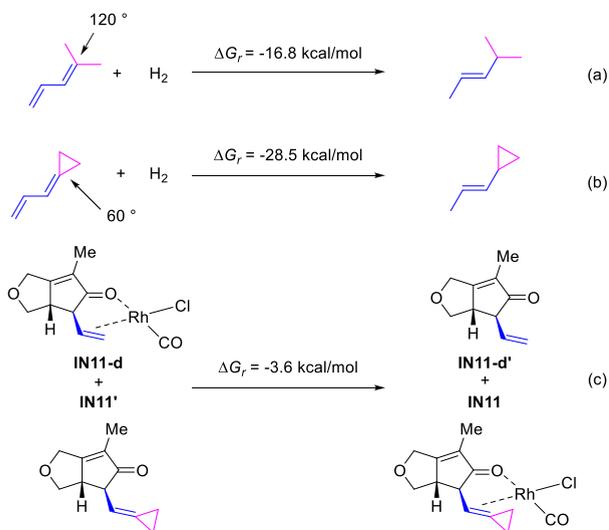
IN8-d to **TS4-d** to **IN7-d** to elucidate the strain release. First, MCP in **IN8** binds stronger than the alkene in **IN8-d**, and the Rh−C1 bond in **IN8** is shorter than that in **IN8-d** by 0.04 Å. Second, in the transition state and product, this strain release is more appreciated. The [4 + 2 + 1] reaction is less endergonic than that in the common diene shown in Figure 4b (**IN7** 9.2 vs **IN7-d** 14.1 kcal/mol). Following Hammond's postulate,[22a] the late transition state **TS4** is geometrically similar to **IN7**, while **TS4-d** is geometrically similar to **IN7-d**, indicating that strain release plays an important role in the [4 + 2 + 1] transition states. Indeed, consistent with the Bell−Evans−Polanyi principle[22b,c] indicating that more exergonic reaction is much more favored for similar reactions, the activation free energy for the CP-capped **TS4** is lower than its structurally similar diene **TS4-d** by 7.0 kcal/mol.

But why does the [2 + 2 + 1] reaction not benefit from strain release? This is because the thermodynamic driving force for CP-capped diene and common diene is similar (11.1 kcal/mol from **IN8** to **IN11**, vs 12.3 kcal/mol from **IN8-d** to **IN11-d**). Though the MCP part could affect the [2 + 2 + 1] reaction

by coordinating to the rhodium center (such as **TS5** and **TS5-d**), here, we found that the difference in the coordination effect between MCP and common alkene is small. We computed the hypothesized reaction c in Scheme 3, showing that MCP is about 3.6 kcal/mol stronger than alkene when coordinating to Rh. This difference is much smaller than that of the hydrogenation reactions in Scheme 3 (3.6 kcal/mol vs 11.7 kcal/mol). Therefore, the activation free energies of the [2 + 2 + 1] reaction have little change when using MCP dienes instead of common dienes.

To exclude the electronic effects of the CP substituent on the regioselectivity, we also carried out the [4 + 2 + 1] reaction using dimethyl diene-yne/ene shown in Scheme 4. To our

Scheme 4. Attempts of [4 + 2 + 1] Reactions Using Dimethyl Diene-yne and Diene-ene as Substrates
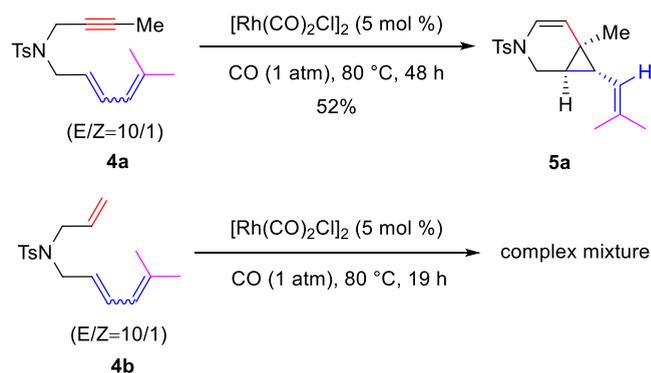
surprise, under the standard conditions at 80 °C, no [2 + 2 + 1] or [4 + 2 + 1] product was observed for dimethyl diene-yne substrate **4a**. Instead, a cycloisomerization product, **5a**, was obtained in 52% yield.[23] Meanwhile, for dimethyl diene-ene substrate **4b**, a similar isomerization did not happen. Checking the crude ^{1}H NMR of the reaction and TLC suggested that a complex mixture (without any carbonyl insertion product) was generated. These results indicated that the carbonyl insertion is difficult for dimethyl diene-yne/ene substrates. Our further DFT calculations found that the [2 + 2 + 1] reaction was favored over the [4 + 2 + 1] reaction for dimethyl diene-yne if a competition between them could happen (see the SI for details). Therefore, we conclude that ring strain release is the reason for the [4 + 2 + 1] reaction of CP-capped diene-ynes/diene-enes and CO.

Before we close this part, we point out that strain release[21,24] is considered as a thermodynamic concept, but in this paper, based on our analysis (Hammond's postulate and Bell−Evans−Polanyi principle), the present metal-catalyzed reaction can benefit from strain release in the reductive elimination so that the [4 + 2 + 1] pathway becomes kinetically preferred compared to the competing [2 + 2 + 1] reaction when using CP-capped dienes.

■ CONCLUSIONS

In summary, we have discovered a strain-release-controlled [4 + 2 + 1] reaction of CP-capped diene-ynes/diene-enes and CO catalyzed by [Rh(CO)$_2$Cl]$_2$. The reaction has a broad scope and various 5/7 bicyclic molecules with the CP group can be synthesized. Of the same importance, the 5/7 products can be further transformed into either functionalized 5/7 molecules or polycyclic 5/7/5, 5/7/6, and 5/7/7 compounds by using the CP group as an advanced intermediate group (CP chem).

Quantum chemical calculations have been carried out to understand the detailed steps of this [4 + 2 + 1] reaction. Especially, the role of CP group to avoid the possible competing [2 + 2 + 1] reaction has been identified, showing that the strain release of the MCP moiety in the CP-capped dienes (about 7 kcal/mol) is the key to prefer the [4 + 2 + 1] over the [2 + 2 + 1] reaction. Further study and application of this reaction are ongoing in our lab.

COMPUTATIONAL METHODS

ASSOCIATED CONTENT

SI **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c00134.

    Experimental procedures, characterization data, copies of NMR spectra, and computational details (PDF)

Accession Codes

CCDC 2201274−2201276 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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