

Cycloaddition

International Edition: DOI: 10.1002/anie.201805908
German Edition: DOI: 10.1002/ange.201805908

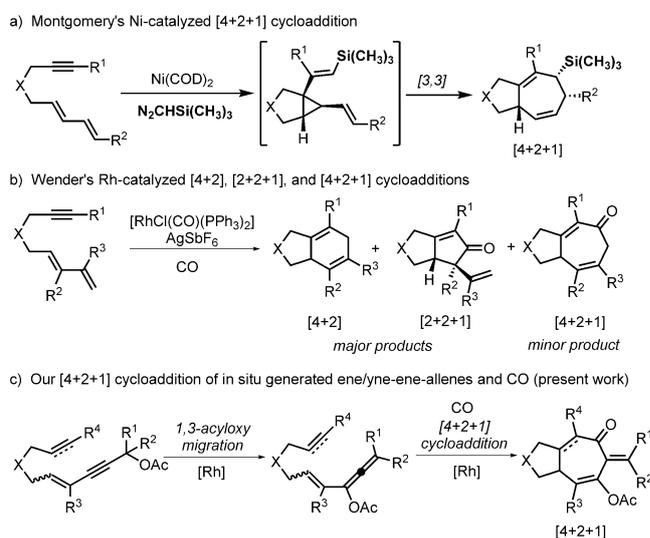
Rhodium-Catalyzed [4+2+1] Cycloaddition of In Situ Generated Ene/Yne-Ene-Allenenes and CO

Zi-You Tian, Qi Cui, Cheng-Hang Liu, and Zhi-Xiang Yu*

Abstract: Reported herein is the first rhodium-catalyzed [4+2+1] cycloaddition of in situ generated ene/yne-ene-allenes and CO to synthesize challenging seven-membered carbocycles fused with five-membered rings. This reaction is designed based on the 1,3-acyloxy migration of ene/yne-ene-propargyl esters to ene/yne-ene-allenes, followed by oxidative cyclization, CO insertion, and reductive elimination to form the final [4+2+1] cycloadducts. The possible competing [4+1], [4+2], and [2+2+1] cycloadditions were disfavored, making the present reaction an efficient way to access functionalized 5/7 rings.

Seven-membered carbocyclic rings are privileged skeletons widely found in natural products^[1] with biological and medicinal significances (for example, colchicine, guanacastepene, ingenol). However, the synthesis of seven-membered carbocycles is still posing challenges^[2] to chemists due to the facts that 1) only limited number of reactions and strategies are available; and 2) many molecules with seven-membered carbocycles have different substitution patterns and stereocenters, which could be difficult or impossible to achieve by the previously reported methods and strategies for seven-membered ring synthesis. Therefore, developing new reactions to access seven-membered carbocycles, which could either expand or complement previous reactions, is an important frontier in reaction development.

In recent years, transition-metal-catalyzed cycloadditions such as [5+2],^[3] [6+1],^[4] [4+3],^[5] [3+2+2],^[6] etc. have emerged as powerful tools to synthesize various seven-membered carbocycles. One easy way to synthesize seven-membered carbocycles is to develop transition-metal-catalyzed [4+2+1] cycloaddition of ene/yne-dienes with one-carbon synthons (such as CO, carbenes^[7]), considering that both ene/yne-dienes and CO (or carbenes) are readily accessible. These [4+2+1] cycloadditions, which are easily conjectured but difficult to realize, have only one successful methodology (Scheme 1 a). Montgomery's group showed that under Ni catalysis, yne-diene and trimethylsilyldiazomethane can give seven-membered carbocycles.^[8a] This Ni catalyzed [4+2+1] cycloaddition was proposed to occur through



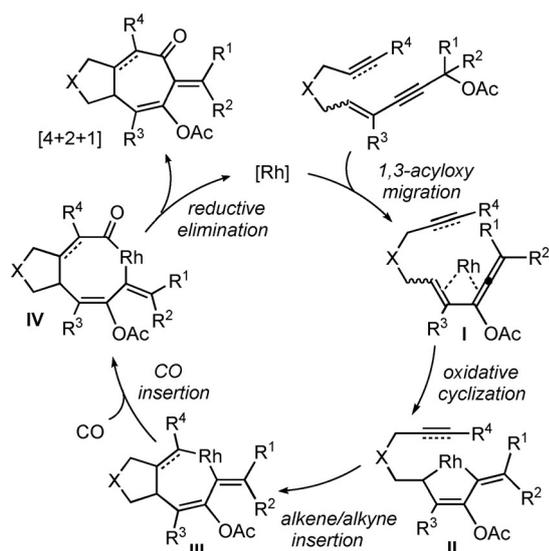
Scheme 1. [4+2+1] cycloadditions. COD = 1,5-cyclooctadiene.

[3,3] sigmatropic rearrangement of in situ generated divinyl-cyclopropanes.^[8b] In 2003, Wender's group proposed a creative [4+2+1] cycloaddition of yne-dienes and CO, but the major products in their reaction were [4+2] and Pauson-Khand [2+2+1] cycloadducts (Scheme 1 b).^[9a] Then they optimized this reaction and expanded the 2C synthon to alkenes and allenes to develop several powerful [2+2+1] reactions.^[9b-c] Herein we report the second successful methodology of transition-metal-catalyzed [4+2+1] cycloaddition of in situ generated ene/yne-ene-allenes and CO to achieve the synthesis of bicyclic 5/7 ring system (Scheme 1 c).

Scheme 2 shows our design of the present [4+2+1] cycloaddition. Ene/yne-ene-propargyl esters were used as the substrates and we reasoned that under Rh catalysis, 1,3-acyloxy migration^[10] of ene/yne-ene-propargyl esters could occur to give Rh and ene/yne-ene-allene complex **I**.^[11] Then oxidative cyclization took place to give five-membered rhodacycle **II**,^[12] which was then converted to intermediate **III** via alkene/alkyne insertion. After that, CO inserted into the C–Rh bond to form intermediate **IV** (it is also possible to form another intermediate, **IV'**, which is presented in Scheme S1 in the Supporting Information, by CO insertion into another C–Rh bond in intermediate **III**). Finally, reductive elimination from intermediate **IV** generated the final [4+2+1] cycloadduct. In the present design, we proposed that the internal alkene in the ene/yne-ene-propargyl ester substrates could be in an either *Z* or *E* configuration. Both *E*- and *Z*-ene/yne-ene-propargyl ester substrates would reach the same intermediate **II** and finally give the same [4+2+1]

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Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
<https://doi.org/10.1002/anie.201805908>.



Scheme 2. Proposed reaction pathway for the [4+2+1] cycloaddition.

cycloadducts. Several possible side reactions such as [4+1] (from intermediate **I**),^[13] [4+2] (from intermediate **III**)^[11] and [2+2+1] (from intermediate **IV**),^[9] which had been previously realized separately by similar intermediates, could occur in this situation and completely make our efforts to [4+2+1] cycloaddition fruitless.

We hypothesized that transformation from **I** to **II** is an intramolecular process and could be favored over possible competing intermolecular [4+1] reaction pathway of **I** with CO. Intermediate **III** has a strong Rh–C bond with the original allene moiety and would not be easy to undergo reductive elimination to give [4+2] cycloadduct.^[12] Instead, CO insertion to give intermediate **IV** could be preferred over the competitive [4+2] reaction. In theory, intermediate **IV** could undergo reductive elimination to give [2+2+1] reaction, but we hypothesized that **IV** is an eight-membered rhodacycle with strong Rh–C bond of the allene moiety (not a Rh–allylic bond). Consequently, generation of seven-membered product via [4+2+1] pathway should be favored for **IV**. Generation of [2+2+1] product could have a six-membered rhodacycle with a Rh–allylic bond, as hypothesized in previous [2+2+1] reaction of yne-dienes,^[9,14] and this is not present in intermediate **IV**. Our group will investigate these hypotheses by DFT calculations in the future. Fortunately, we were happy to find the designed [4+2+1] cycloaddition succeeded. Therefore, we report our experimental results of the [4+2+1] cycloaddition here.

We tested our designed [4+2+1] cycloaddition using the N-Ts tethered ene-ene-propargyl ester **Z-1a** as the standard substrate (Table 1). Firstly, we tested our reaction using 10 mol% [Rh(CO)₂Cl]₂ catalyst, which was efficient for 1,3-acyloxy migration^[10,12] reaction, finding that 81% of the target product could be obtained in DCE after 12 hours, together with isomerization product **3a** with a ratio of 10:1, and no apparent [4+2] cycloadduct was observed (Table 1, entry 1). The triene byproduct **3a** was obtained by isomerization from intermediate **I** (see Scheme S1 in the Supporting

Table 1: Optimization of reaction conditions for **Z-1a** and CO.^[a]

Entry	Catalyst (mol%)	Solvent	<i>t</i> [h]	Yield 2a [%] ^[b]	2a/3a ^[c]
1	[Rh(CO) ₂ Cl] ₂ (10 mol%)	DCE	12	81	10:1
2	[Rh(COD)Cl] ₂ (10 mol%)	DCE	12	83	10:1
3	[Rh(COE) ₂ Cl] ₂ (10 mol%)	DCE	12	82	10:1
4	[Rh(NBD)Cl] ₂ (10 mol%)	DCE	12	78	10:1
5	Rh(CO)(PPh ₃) ₂ Cl (20 mol%)	DCE	12	n.r.	–
6	[Rh(COD)Cl] ₂ (10 mol%)	DCM	12	c.m.	–
7	[Rh(COD)Cl] ₂ (10 mol%)	THF	12	40	1:1
8	[Rh(COD)Cl] ₂ (10 mol%)	DME	12	62	5:3
9	[Rh(COD)Cl] ₂ (10 mol%)	dioxane	12	30	1:1
10	[Rh(COD)Cl] ₂ (10 mol%)	toluene	12	56	5:4
11 ^[d]	[Rh(COD)Cl] ₂ (10 mol%)	DCE	12	82	10:1
12 ^[e]	[Rh(COD)Cl] ₂ (5 mol%)	DCE	24	79	10:1
13 ^[f]	[Rh(COD)Cl] ₂ (5 mol%)	DCE	24	69	10:1
14	[Ir(COD)Cl] ₂ (5 mol%)	DCE	24	59 (3a)	–

[a] The reaction was carried out in 0.1 mmol scale in 2 mL solvent.

[b] Yield of isolated **2a**. [c] The ratio of **2a/3a** was determined by NMR

analysis of the crude reaction mixture; **3a** was not isolated. [d] The

reaction was performed in 60 °C. [e] Average yield of three runs.

[f] 0.2 atm CO was used. n.r. = no reaction. c.m. = complex mixture.

DCE = 1,2-dichloroethane, DME = 1,2-dimethoxyethane, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

Information) and the structure of product **2a** was further confirmed by X-ray analysis (see the Supporting Information). Several other Rh(I) catalysts with different ligands (COD, COE, and NBD) were also screened, finding that almost the same reaction yields (78–83%) and ratio of **2a/3a** (10:1) were realized (Table 1, entries 2–4). We hypothesized that these Rh catalysts gave the same catalytic species, through replacement of these ligands by CO molecule. In addition, catalyst Rh(CO)(PPh₃)₂Cl was found to be ineffective and the reaction substrate was recovered (Table 1, entry 5). Solvents other than DCE were found to be less effective for the [4+2+1] cycloaddition using [Rh(COD)Cl]₂ as the catalyst (Table 1, entries 6–10). For example, a complex mixture was obtained in DCM. In addition, the [4+2+1] cycloaddition can be carried out at higher temperature (60 °C), and a yield of 82% was reached (Table 1, entry 11). We were happy to find that the [4+2+1] cycloaddition can be operated by using 5 mol% of [Rh(COD)Cl]₂ to give comparable yield as that from the reaction using 10 mol% catalyst loading, even though the reaction had to extend to 24 h (Table 1, entry 12). Finally, we investigated how the CO pressure affected the reaction.^[3d] Using 0.2 atm CO pressure was less effective and the reaction yield was only 69% (Table 1, entry 13). Interestingly, the triene byproduct **3a** was isolated as the major product when using iridium catalyst instead of rhodium catalysts (Table 1, entry 14). Based on the results in Table 1, we then decided to study the scope of the [4+2+1] cycloaddition using the conditions in entry 12 of Table 1 for ene-ene-allene substrates (Table 2).

Table 2: Reaction scope of the [4+2+1] cycloaddition.^[a]

entry	substrate	product, yield ^[b,c]
1	Z-1a R ¹ = R ² = Me	2a , 79%
2 ^[d]	E-1a R ¹ = R ² = Me	2a , 88%
3	Z-1b R ¹ = R ² = Et	2b , 63%
4 ^[d]	E-1b R ¹ = R ² = Et	2b , 79%
5	Z-1c R ¹ = R ² = -CH ₂ (CH ₂) ₂ CH ₂ -	2c , 42%
6	Z-1d R ¹ = R ² = -CH ₂ (CH ₂) ₃ CH ₂ -	2d , 70%
7 ^[e]	Z-1e R ¹ = Me, R ² = H	2e , 44% (2.5:1)
8	E-1f R = Me	2f , 70%
9	Z-1f R = Me	2f , 62%
10	E-1g R = Et	2g , 75%
11	Z-1g R = Et	2g , 72%
12	Z-1h	2h , 44%
13	Z-1i R = H	2i , 94%
14	Z-1j R = Me	2j , 85%
15	E-1k R = H	2k , 85%
16	E-1l R = Me	2l , 71%
17	E-1q	2q , 51%

[a] The reaction was carried out in 0.1 mmol scale in 2 mL DCE. [b] Yield given is an average of two runs except for **2a** (average of three runs). [c] Trace amounts of the [4+2] byproducts **4** and triene byproducts **3** could be detected by TLC; neither were isolated nor characterized, except **3a** and **4a** (see the Supporting Information). [d] Reaction at 60 °C for 24 h. [e] With 10 mol% catalyst loading at 75 °C for 24 h. For **2e**, a mixture of the *Z* and *E* isomers for the alkene double bond with R¹ and R² substituents was obtained.

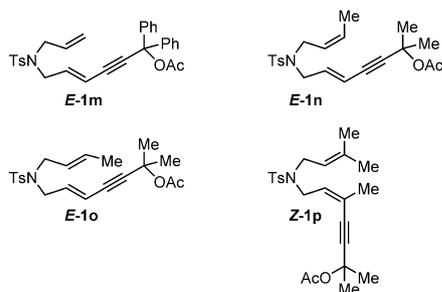
We first studied the [4+2+1] reaction of substrate **E-1a**, which is different from the standard substrate **Z-1a** in terms of the configuration of the internal alkene (Table 2, entry 2). Under the standard reaction conditions, the reaction substrate was majorly recovered (69%), together with 15% yield of [4+2+1] product **2a**, which is same as that from the reaction of **Z-1a**. We reasoned that this substrate with an *E* configuration could need more energy to undergo the 1,3-acyloxy migration. When we carried out the [4+2+1] reaction at 60 °C (instead of 40 °C), **E-1a** can deliver [4+2+1] cycloadduct **2a** in 88% yield.

We then investigated the influence of the substitution patterns in the propargyl ester moiety of the substrates with internal *Z*- and *E*-configured alkenes. Substrates with two substituted groups attached to the propargyl ester moiety showed good reactivity, and moderate to good reaction yields were obtained for **1b–e** (Table 2, entries 3–7). Both *Z*- and *E*-**1b** also gave the same product **2b** (in 63% and 79% yield, respectively). The reaction of substrate **Z-1e** with only one substituted group in the propargyl ester moiety was slow under the standard conditions. Consequently, higher reaction temperature (75 °C) and higher catalyst loading (10%) were applied for substrate **Z-1e**, which under the new conditions, gave a moderate yield (44%) and *Z/E* mixture of [4+2+1] cycloadducts.

We also tested substrates **1f** and **1g**, which did not have the substitution in the internal alkene part of ene-ene-yne. Both *E*- and *Z*-**1f** gave the same product in 70% and 62% yield (Table 2, entries 8 and 9). *E*- and *Z*-**1g** also afforded good yields of **2g** (75% and 72%, respectively; see Table 2, entries 10 and 11). Substrate **Z-1h** bearing methyl substitutions in alkene moiety of the ene-ene-yne generated [4+2+1] cycloadduct **2h** with bridgehead quaternary carbon center in 44% yield (Table 2, entry 12).

We changed the NTs tether in the substrate to C and O tethers to further investigate the reaction scope. The [4+2+1] cycloadditions gave 94% and 85% yields for **Z-1i** (with C tether) and **E-1k** (with O tether), respectively (Table 2, entries 13 and 15). We were excited to note that substrates **Z-1j** with C tether and **E-1l** with O tether can reach high yields of [4+2+1] products **2j** and **2l**, both of which have a methyl group at the bridgehead positions of the 5/7 skeleton (Table 2, entries 14 and 16).

It was anticipated that the allene moiety of the ene-ene-allene could not have two large groups, otherwise, the [4+2+1] cycloadduct could suffer from severe repulsion (and the corresponding alkene insertion transition states in the [4+2+1] reaction could be difficult to reach). This was proved to be true because terminal diphenyl substituted substrate **E-1m** decomposed under the standard reaction conditions (Scheme 3). We also tested whether the two- π component in the substrates can have substituents at its terminal position. Complex mixtures were obtained using substrates **E-1n** and **E-1o**. In addition, substrate **Z-1p** with two methyl groups in the terminal position of the two- π part was synthesized, and the corresponding triene product was isolated in 55% yield, without the formation of [4+2+1] cycloadduct (see the Supporting Information for details).



Scheme 3. Unsuccessful substrates for [4+2+1] cycloaddition.

We also synthesized yne-ene-propargyl ester substrate **E-1q**^[12] to study whether the 2C synthon of the [4+2+1] cycloaddition can be alkynes. To our delight, under the optimized reaction conditions for ene-ene-propargyl ester substrates, the [4+2+1] cycloaddition of **E-1q** can give product **2q** in 51% yield (Table 2, entry 17). Further study of [4+2+1] cycloaddition of more yne-ene-propargyl ester substrates will be carried out in the future.

Herein we want to point out that lower yields for some substrates in Table 2 usually had some isomerization products, as judged by TLC (for example, **Z-1h**). Since we only concentrated on developing a method for the 5/7 ring synthesis, we neither isolated nor characterized these side products (except **3a**). Under the optimized reaction conditions for all substrates in Table 2, only trace amount of [4+2] products could be detected by TLC.

In summary, a novel Rh(I)-catalyzed two-component [4+2+1] cycloaddition of CO and in situ generated ene/yne-allenes from ene/yne-ene propargyl esters has been developed. This reaction features easily prepared substrates and broad scope to reach a 5/7 skeleton. Quaternary carbon centers can also be introduced at the bridgehead position of the bicyclic 5/7 system. This method represents the second successful example of transition-metal-catalyzed [4+2+1] cycloaddition. Further study of the reaction scope, its application in synthesis, and understanding the reaction mechanism are ongoing.^[15]

Acknowledgements

We thank the National Natural Science Foundation of China (21472005) for financial support. We also thank Prof. Dr. Wen-Xiong Zhang and Dr. Neng-Dong Wang of Peking University for X-ray crystal analysis.

Conflict of interest

The authors declare no conflict of interest.

Keywords: conjugation · cycloaddition · fused-ring systems · reaction mechanisms · rhodium

How to cite: *Angew. Chem. Int. Ed.* **2018**, *57*, 15544–15548
Angew. Chem. **2018**, *130*, 15770–15774

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there are differences in the chemical structures of this version of record and the accepted article (published online on August 13, 2018).

Manuscript received: May 22, 2018

Accepted manuscript online: August 13, 2018

Version of record online: October 25, 2018