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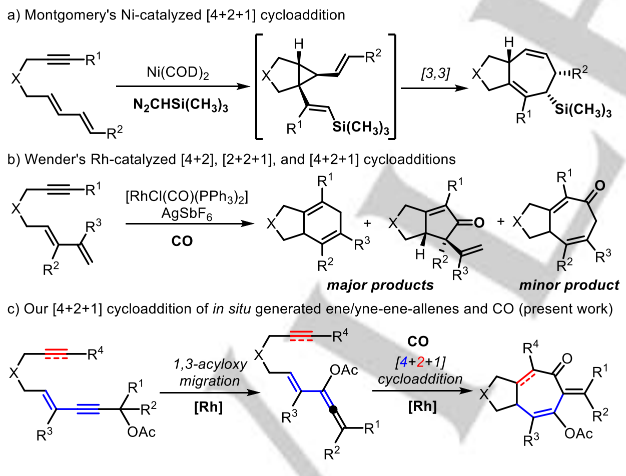
COMMUNICATION

Rh-Catalyzed [4+2+1] Cycloaddition of *in situ* Generated Ene/Yne-Ene-Allenes and CO

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

Abstract: We report here the first Rh-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 as an efficient way to access functionalized 5/7 rings.

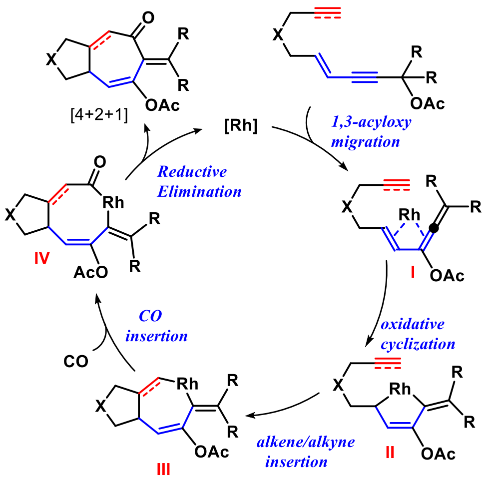
Seven-membered carbocyclic rings are privileged skeletons widely found in natural products[1] with biological and medicinal significances (for example, colchicine, guanacastepene, ingenol). However, the synthesis of seven-membered carbocycles is still posing challenges [2] to chemists due to the facts 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 by the previously reported methods and strategies of 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.



Scheme 1. [4+2+1] cycloadditions.

In recent years, transition metal catalyzed cycloadditions such as [5+2],[3] [6+1],[4] [4+3],[5] [3+2+2],[6] et al. have emerged as powerful tools to synthesize various carbocycles. One easy way to synthesize seven-membered carbocycles is to develop transition metal-catalyzed [4+2+1] reaction 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. This [4+2+1] cycloadditions, which are easily conjectured but difficult to be realized, have only one successful methodology (Scheme 1a). Montgomery's group showed that under Ni catalysis, yne-diene and trimethylsilyldiazomethane can give seven-membered carbocycles.[8a] This Ni catalyzed [4+2+1] reaction was proposed to occur through [3, 3] sigmatropic rearrangement of *in situ* generated divinylcyclopropanes.[8b] In 2003, Wender's group proposed a creative [4+2+1] reaction of yne-dienes and CO, but the major products in their reaction were [4+2] and Pauson–Khand [2+2+1] cycloadducts (Scheme 1b)[9a]. They then optimized this reaction and expanded the 2C synthon to alkenes and allenes to develop several powerful [2+2+1] reactions.[9b-e] Herein we report the second successful reaction 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 1c).

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 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



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

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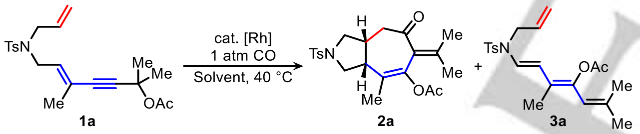
possible to form another intermediate **IV'**, which is not present in this Scheme but in Scheme S1 of the Supporting Information, by CO insertion into another C–Rh bond in intermediate **III**). Finally, reductive elimination from intermediate **IV** generated the final [4+2+1] cycloadduct. Several possible side reactions such as [4+1] (from intermediate **II**),[13] [4+2] (from intermediate **III**)[11] and [2+2+1] (from intermediate **IV**),[9] which had been previous 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 intramolecular [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] Our group will investigate these hypotheses by DFT calculations in the future. Fortunately, we were happy to find that the present [4+2+1] cycloaddition worked. Therefore, we report our experimental results of the [4+2+1] cycloaddition here.

Table 1 Optimization of reaction conditions for **1a** and CO.[a]

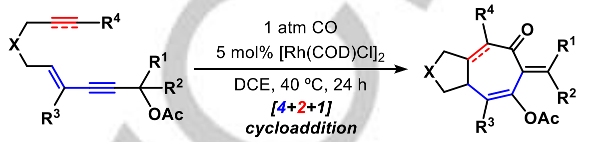


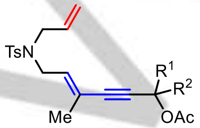
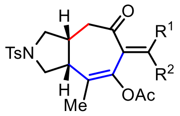
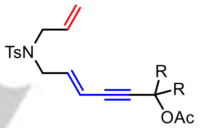
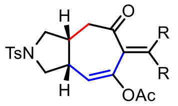
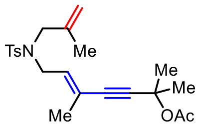
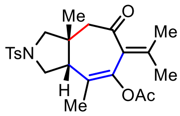
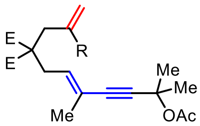
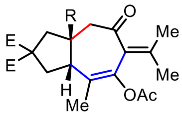
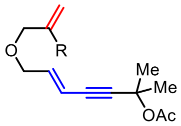
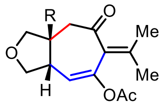
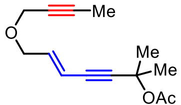
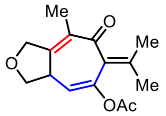
entry	catalyst (mol%)	solvent	time	yield of **2a**[b]	**2a**/**3a**[c]
1	$[Rh(CO)_2Cl]_2$ (10 mol%)	DCE	12 h	81%	10/1
2	$[Rh(COD)Cl]_2$ (10 mol%)	DCE	12 h	83%	10/1
3	$[Rh(COE)_2Cl]_2$ (10 mol%)	DCE	12 h	82%	10/1
4	$[Rh(NBD)Cl]_2$ (10 mol%)	DCE	12 h	78%	10/1
5	$Rh(CO)(PPh_3)_2Cl$ (20 mol%)	DCE	12 h	N.R.	-
6	$[Rh(COD)Cl]_2$ (10 mol%)	DCM	12 h	complex mixture	-
7	$[Rh(COD)Cl]_2$ (10 mol%)	THF	12 h	40%	1/1
8	$[Rh(COD)Cl]_2$ (10 mol%)	DME	12 h	62%	5/3
9	$[Rh(COD)Cl]_2$ (10 mol%)	dioxane	12 h	30%	1/1
10	$[Rh(COD)Cl]_2$ (10 mol%)	toluene	12 h	56%	5/4
11[d]	$[Rh(COD)Cl]_2$ (10 mol%)	DCE	12 h	82%	10/1
12[e]	**$[Rh(COD)Cl]_2$ (5 mol%)**	**DCE**	**24 h**	**79%**	**10/1**
13[f]	$[Rh(COD)Cl]_2$ (5 mol%)	DCE	24 h	69 %	10/1
14	$[Ir(COD)Cl]_2$ (5 mol%)	DCE	24 h	59%(**3a**)	-

[a] The reaction was carried out in 0.1 mmol in 2 mL solvent. [b] Isolated yield of **2a**. [c] The ratio of **2a**/**3a** was determined by crude NMR and **3a** was not isolated. [d] The reaction was perfomed in 60 °C. [e] Average yield of three runs. [f] 0.2 atm CO was used. N. R.= No Reaction

We tested our designed [4+2+1] cycloaddition using the N-Ts tethered ene-ene-propargyl ester **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] 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] product was observed (Table 1, entry 1). The triene byproduct **3a** was obtained by isomerization from intermediate **I** (see Scheme S1 in Supporting 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

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



entry	substrate	product, yield[b, c]
		
1	**1a** $R^1 = R^2 = Me$	**2a**, 79%
2	**1b** $R^1 = R^2 = Et$	**2b**, 63%
3	**1c** $R^1 = R^2 = -CH_2(CH_2)_2CH_2-$	**2c**, 42%
4	**1d** $R^1 = R^2 = -CH_2(CH_2)_3CH_2-$	**2d**, 70%
5[d]	**1e** $R^1 = Me, R^2 = H$	**2e**, 44% (2.5 : 1)
		
6	**1f** R = Me	**2f**, 70%
7	**1g** R = Et	**2g**, 75%
		
8	**1h**	**2h**, 44%
	 E = CO_2Me	
9	**1i** R = H	**2i**, 94%
10	**1j** R = Me	**2j**, 85%
		
11	**1k** R = H	**2k**, 85%
12	**1l** R = Me	**2l**, 71%
13	 **1q**	 **2q**, 51%

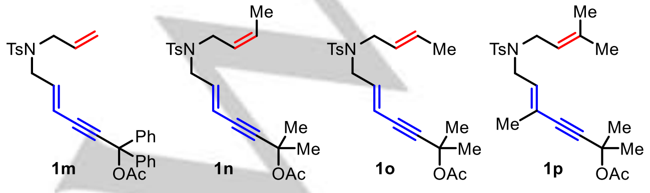
[a] The reaction was carried out in 0.1 mmol scale in 2 mL DCE. [b] Yield given in an average of two runs except for **2a**, average of three runs. [c] Trace [4+2] byproducts **4** and triene byproducts **3** could be detected by TLC and both were not isolated and characterized, except **3a** and **4a** (see SI). [d] With 10 mol% catalyst loading, under 75 °C for 24 h.

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 $Rh(CO)(PPh_3)_2Cl$ 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 catalyst (Table 1, entries 6 – 10). For example, a complex mixture was obtained for the reaction carried out in DCM. In additon, the [4+2+1] cycloaddition can be carried out at higher temperature, and a yield of 82% was reached as that from the reaction at 40 °C (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, 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). 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 susbtrates (Table 2). Interestingly, the triene byproduct **3a** was isolated as the major product when using iridium catalyst instead of rhodium catalysts (Table 1, entry 14).

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

We were happy to observe that substrates **1f** and **1g**, which did not have the substitution in the internal alkene part of ene-ene-ynes gave good yields (70% and 75%, respectively, see Table 2, entries 6 and 7). Substrate **1h** bearing methyl substitutions in alkene moiety of the ene-ene-ynes generated [4+2+1] cycloadduct **2h** with bridgehead quaternary carbon center in 44% yield (Table 2, entry 8).

We changed the N-Ts tether in the substrate to C and O tethers to further investigate the reaction scope. The [4+2+1] cycloadditions gave 94% and 85% reaction yields for **1i** (with C tether) and **1k** (with O tether), respectively (Table 2, entries 9 and 11). We were excited to note that substrates **1j** with C tether and **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 10 and 12).



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

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 because the corresponding allene insertion transition states in the [4+2+1] reaction could be difficult to be accessed. This was proved to be true because terminal diphenyl substituted substrate **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 could be achieved using substrates **1n** and **1o.** In addition, substrate **1p** with two methyl groups in the terminal position of the two-π ene part were 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).

We also synthesized yne-ene-propargyl ester substrate **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 **1q** can give product **2q** in 51% yield. Further study of [4+2+1] cycloaddition of more yne-ene-propargyl ester susbtrates 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, **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 optimization 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-enynes from conjugated ene/yne-yne propargyl esters has been developed. This reaction features easily prepared substrates and broad scope to reach 5/7 skeleton. Quaternary carbon centers can also be introduced at the bridgehead position of the bicyclic 5/7 system. This methodology 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 is ongoing.

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Keywords: [4+2+1] • rhodium • ene/yne-ene-allene • 1,3-acyloxy migration •cycloaddition

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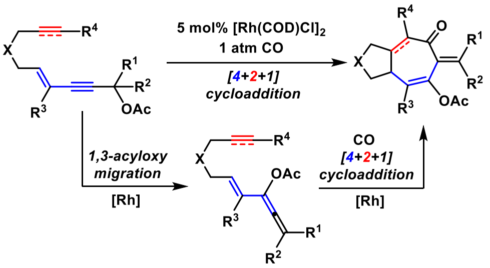

4+2+1=7, mathematically simple, but chemically difficult: Rh-catalyzed [4+2+1] cycloaddtion of *in situ* generated ene/yne-ene-allenes and CO to synthesize challenging seven-membered carbocycles fused with five-membered rings is reported, where ene-allene, alkene/alkyne and CO act as 4C, 2C, and 1C synthons, respectively.

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