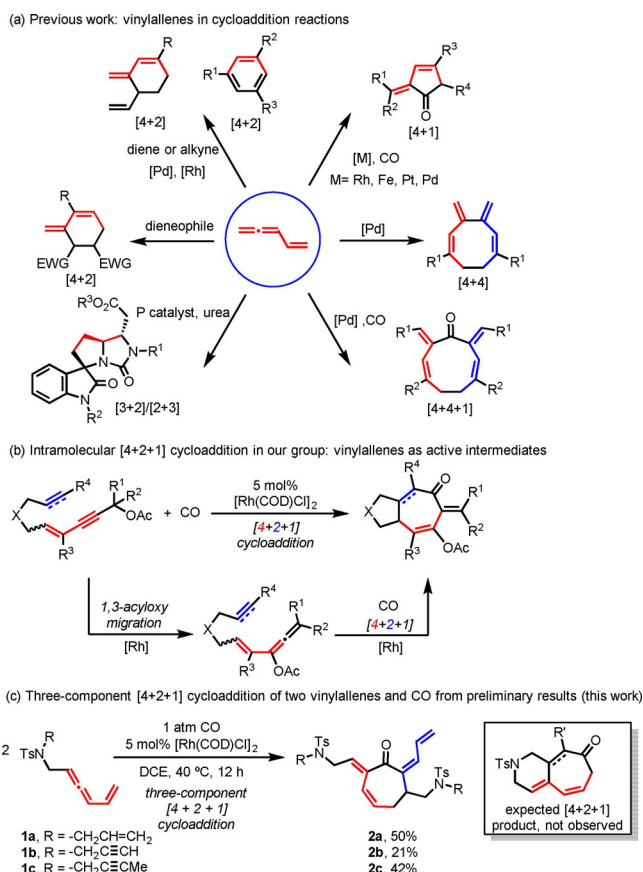Europe
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Rhodium(I)-Catalyzed Three-Component [4+2+1] Cycloaddition of Two Vinylallenes and CO

Qi Cui, Zi-You Tian, and Zhi-Xiang Yu*[a]

Abstract: Transition metal-catalyzed [4+2+1] reactions of dienes (or diene derivatives such as vinylallenes), alkynes/alkenes, and CO (or carbenes) are expected to be the most straightforward approach to synthesize challenging seven-membered ring compounds, but so far only limited successes have been realized. Here, an unexpected three-component [4+2+1] reaction between two vinylallenes and CO was discovered to give highly functionalized tropone derivatives under mild conditions, where one vinylallene acts as a C_4 synthon, the other vinylallene as a C_2 synthon, and CO as a C_1 synthon. It was proposed that this reaction occurred via oxidative cyclization of the diene part of one vinylallene molecule, followed by insertion of the terminal alkene part of the allene moiety in another vinylallene, into the Rh–C bond of five-membered rhodacycle. Then, CO insertion and reductive elimination gave the [4+2+1] cycloadduct. Further experimental exploration of why ene/yne-vinylallenes and CO gave monocyclic tropone derivatives instead of 6/7-bicyclic ring products were reported here.

Scheme 1. Vinylallenes in cycloaddition reactions and a new development.

Vinylallenes have been considered as the active 4π or 2π component in many reactions such as cycloadditions,[1] electrocyclizations,[2] rearrangement reactions,[3] and conjugated additions.[4] Many important skeletons or potentially useful compounds in drug discovery have been synthesized by these methods.[5] Especially, intermolecular or intramolecular cycloaddition reactions using vinylallenes, such as [4+1],[1a–f] [4+2],[1g–m] [4+4],[1n] [4+4+1],[1o] and [3+2]/[2+3][1p] cycloadditions, developed, respectively by Siegel et al., Murakami et al., and Lee and co-workers, have become powerful methods to synthesize various ring compounds (Scheme 1a). It is interesting to note that all these ring formation reactions (except one in Scheme 1b, see below) using vinylallenes cannot be used to synthesize seven-membered rings. Realization of this unmet

goal would push the frontiers of development and application of ring formation reactions further, considering that synthesis of seven-membered rings is still posing great challenges to the synthetic community.[6]

Transition metal-catalyzed [4+2+1] reactions of dienes, alkynes/alkenes, and CO (or carbenes), which are all easily accessible, are expected to be the most straightforward approach to synthesize challenging seven-membered ring compounds, but so far only limited successes have been realized.[7] Recently, we achieved the first synthesis of a seven-membered ring by using in situ-generated vinylallenes in the [4+2+1] reaction of ene/yne-ene-propargyl esters and CO, where vinylallenes, alkenes/alkynes, and CO act as C_4, C_2, and C_1 synthons, respectively (Scheme 1b).[1q] In this [4+2+1] reaction, the vinylallene intermediates were generated by the 1,3-acyloxy migration of propargyl esters (Scheme 1b).[3,8] Encouraged by this success, we further envisioned that the allene and alkene moieties of

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vinylallenes could switch their positions in the substrates. The corresponding ene-vinylallenes could then give new bicyclic 6/7-membered ring compounds by a new [4+2+1] reaction, catalyzed also by Rh complex (Scheme 1c). However, to our surprise, no desired bicyclic 6/7 fused ring compounds were obtained for substrates **1a**–**1c** when treated by Rh catalyst. Instead, monocyclic seven-membered ring compounds **2a**–**2c**, which are highly functionalized tropones, were isolated. This can be regarded as a new three-component [4+2+1] reaction between two ene-allenes (one uses its C2-C3-C4-C5 as a C_4 synthon, and the other uses its C1-C2 as a C_2 synthon) and CO as a C_1 synthon (Scheme 2).
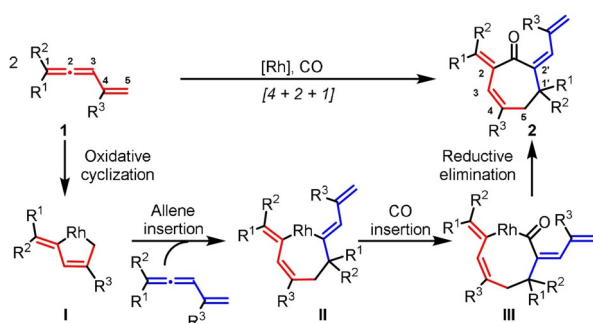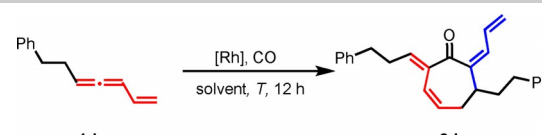
Scheme 2. Proposed mechanism of [4+2+1] reaction of two vinylallenes and CO.

We proposed that the new intermolecular [4+2+1] reaction starts from the oxidative cyclization reaction of vinylallene to form intermediate **I** (Scheme 2). Similar intermediate has been investigated experimentally and computationally.[9] Then another vinylallene's allene inserts into the Rh–C bond to form seven-membered rhodacyclic intermediate **II**. After that, CO insertion into Rh–C bond in **II** gives intermediate **III**,[10] which then undergoes reductive elimination to give final [4+2+1] reaction product. Murakami et al. found vinylallenes and CO gave [4+1] reaction under Rh catalysis, but here we obtained the [4+2+1] products.[1a] The different reactivity could be attributed to the differences of the used substrates and the ligands, which are coordinated to the rhodium center.

Therefore, we serendipitously found a three-component [4+2+1] reaction to synthesize seven-membered rings. We expected that this reaction, if it could have broad reaction scope, would enrich chemistry of vinylallenes and provide an efficient way to synthesize highly functionalized seven-membered ring compounds, which are analogues of biological important tropone molecules and could have great opportunity for medical chemistry study.[11] In what follows, we present details of screening the reaction conditions and investigating the reaction scope of this [4+2+1] reaction.

Vinylallene **1d** as the substrate was used for screening the reaction conditions of the [4+2+1] reaction. It was found that using 5 mol% [Rh(CO)$_2$Cl]$_2$ as the catalyst, [4+2+1] cycloadduct **2d** was obtained in 49% NMR yield in DCE (1,2-dichloroethane) solution at 60 °C (Table 1, entry 1). Low concentration of the substrate was detrimental to the reaction yield (Table 1,
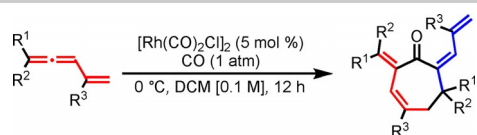
Table 1. Reaction condition optimization.[a]

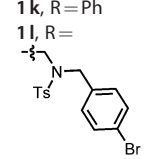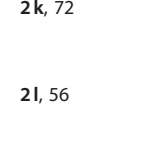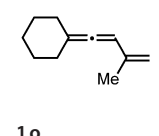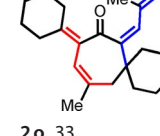| Entry	Catalyst [mol%]	$P_{(CO)}$ [atm]	Solvent	Conc. [M]	T [°C]	Yield[b] [%]
1	[Rh(CO)$_2$Cl]$_2$	5	1	DCE	0.1	60	49
2	[Rh(CO)$_2$Cl]$_2$	5	1	DCE	0.02	60	44
3	[Rh(CO)$_2$Cl]$_2$	5	1	toluene	0.1	60	12
4	[Rh(CO)$_2$Cl]$_2$	5	1	MeCN	0.1	60	60
5	[Rh(CO)$_2$Cl]$_2$	5	1	HFIP	0.1	60	27
6	[Rh(CO)$_2$Cl]$_2$	5	1	dioxane	0.1	60	76
7	[Rh(CO)$_2$Cl]$_2$	5	1	DCM	0.1	RT	78
8	[Rh(CO)$_2$Cl]$_2$	5	0.2	DCM	0.1	RT	62
9	[Rh(CO)$_2$Cl]$_2$	2	1	DCM	0.1	RT	76 (66)
10	[Rh(CO)$_2$Cl]$_2$	5	1	DCM	0.1	0	81 (70)
11	Rh(COD)$_2$SbF$_6$	10	1	DCM	0.1	RT	c.m.
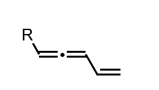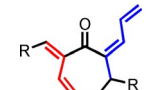
[a] All the reactions were performed on 0.1 mmol scale. [b] ^{1}H-NMR yield using 1,3,5-trimethoxybenzene as an internal standard; yields of isolated product based on a 0.3 mmol scale reaction were given in parentheses. c.m. = complex mixture.

entry 2). Other solvents such as toluene, MeCN, hexafluoroisopropanol (HFIP), and dioxane were found to be inferior compared to DCM for the target reaction (Table 1, entries 3–6). We were happy to note that the [4+2+1] reaction can also be carried out at room temperature in DCM in a decent reaction yield (Table 1, entry 7). Using 0.2 atmosphere CO pressure, which was effective in many other Rh-catalyzed cycloadditions such as [5+2+1] reaction,[12] gave **2d** only in 62% NMR yield (Table 1, entry 8). When the catalyst loading was lowered to 2 mol%, the [4+2+1] reaction gave the desired product in 76% NMR yield and 66% isolated yield (Table 1, entry 9). To avoid side reactions, we carried out the reaction at 0 °C, finding that **2d** can be generated in 81% NMR yield and 70% isolated yield (Table 1, entry 10).[13] Further study showed that Rh(COD)$_2$SbF$_6$ cannot catalyze the [4+2+1] reaction (Table 1, entry 11). Based on these results in Table 1, we decided to study the scope of this [4+2+1] reaction using reaction conditions in entry 10 of Table 1 as the optimal reaction conditions.

We performed 0.3 mmol scale reactions of all tested substrates for the [4+2+1] reaction shown in Table 2 for the study of reaction scope. First, we studied different substituents at the C1 position of vinylallenes. For n-hexyl group, the reaction yield of **2e** was 74% (Table 2, entry 2). For substrates **1f** and **1g** with bulky substituents, the reaction yields were 52% and 58%, respectively (Table 2, entries 3–4). Ester substituent and OTBS (TBS = tert-butyldimethylsilyl) group can be introduced to the substrates and the [4+2+1] reactions of the corresponding substrates went smoothly, giving **2h** in 55% yield and **2i** in 51% yield, respectively (Table 2, entries 5 and 6). For substrate **1j** with a cyclohexyl group, its [4+2+1] reaction gave the final product in 51% yield (Table 2, entry 7). Notably, [4+2+1] reaction of substrate **1k** with a phenyl group had a poor conversion under the standard reaction conditions. By increasing the catalyst loading to 10 mol%, conversion of **1k** to

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Table 2. Scope of the three-component [4+2+1] reaction.[a]

| Entry	Substrate	Product, yield[b] [%]
1	**1 d**, R = CH$_2$CH$_2$Ph	**2 d**, 70
2	**1 e**, R = n-C$_6$H$_{13}$	**2 e**, 74
3	**1 f**, R = CH$_2$Ph	**2 f**, 52
4	**1 g**, R = CH$_2$Cy	**2 g**, 58
5	**1 h**, R = CH$_2$OAc	**2 h**, 55
6	**1 i**, R = CH$_2$OTBS	**2 i**, 51
7	**1 j**, R = Cy	**2 j**, 51
8[c]	**1 k**, R = Ph	**2 k**, 72
9[d]	**1 l**, R =	**2 l**, 56
10	**1 m**, R = CH$_2$CH$_2$Ph	**2 m**, 72
11	**1 n**, R = n-C$_5$H$_{11}$	**2 n**, 68
12[d]	**1 o**	**2 o**, 33

[a] The reactions were carried out in 0.3 mmol scale; the substrates and products were not bench stable when stored for a long time. [b] Isolated yield for the average of two runs. [c] The reaction was performed at RT with 10 mol% catalyst loading. [d] The starting material remained and detected by TLC after 12 h at 0 °C, then the reaction was warmed to RT and stirred for 24 h.

2 k can be improved with an increased reaction yield of 72%, at room temperature (Table 2, entry 8). The structure of the [4+2+1] product **2 l** was further confirmed by X-ray analysis of its derivative (see Table 2, entry 9, and the Supporting Information).

Furthermore, vinylallene substrates with C4 substitution were tested for the [4+2+1] reaction, and the functionalized products **2 m** and **2 n** were obtained in good yields (Table 2, entries 10 and 11). We were delighted to observe that the present [4+2+1] reaction showed great regioselectivity and no other isomeric products of carbocyclic ketones were detected. Interestingly, the reaction was also effective for substrate **1 o** with two substituents in the allene moiety, because the [4+2+1] product **2 o** with a quaternary carbon can be generated in 33% yield (no [4+1] product was detected in the reaction system, see Table 2, entry 12). We found that substrates **1 a**–**1 c** gave similar yields to those obtained in Scheme 1 c,

under the optimized conditions, but at 40 °C (the reaction conversions were low at 0 °C and the reaction temperature had to be raised).

The above [4+2+1] reaction incorporated two vinylallenes, one as C$_4$ and the other as C$_2$ synthons, in the final cycloadducts. We wondered that, if other 2π and 4π components could replace one vinylallene of the reaction, then more diverse tropone derivatives could be synthesized by this new reaction. Unfortunately, allene, alkyne, and isoprene cannot be incorporated into the [4+2+1] cycloadducts (see Supporting Information for details). We reasoned that many side reactions could compete and give mixtures of different products when these new components were introduced in the reaction system. One support for this hypothesis came from the observation that the reaction of **1 h**, **3**, and CO gave 23% [2+2+1] Pauson–Khand reaction product **4** (Scheme 3, and the Supporting Information).
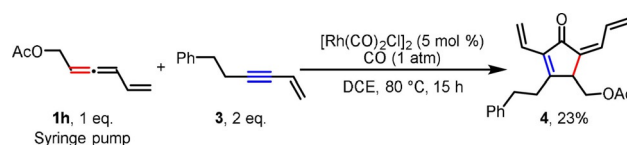
Scheme 3. The attempt of three-component [4+2+1] reaction gave a [2+2+1] product.

Scheme 2 is the proposed mechanism for the present [4+2+1] reaction. The reason why **1 a**–**1 c** failed to give desired 6/7 products could be the geometry of oxidative cycloaddition intermediate **I**, which is not appropriate for the further alkene and CO insertions because the used 2π component is *trans* to the Rh. We hypothesized that if a bulky group R^1 such as *t*Bu was introduced, the corresponding substrates **1 p**–**1 r** could have a *cis* configuration between rhodium and the linker moiety, which then has the possibility to give 6/7 ring product (Scheme 4). To our surprise, we found that **1 p** was converted to the [4+2] cycloaddition product **5** in 81% yield, and the desired 6/7 ring compound was not obtained.[14] Yne-vinylallene substrates **1 q** and **1 r** also failed to give [4+2+1] products. These results imply that, though the right configuration of oxi-
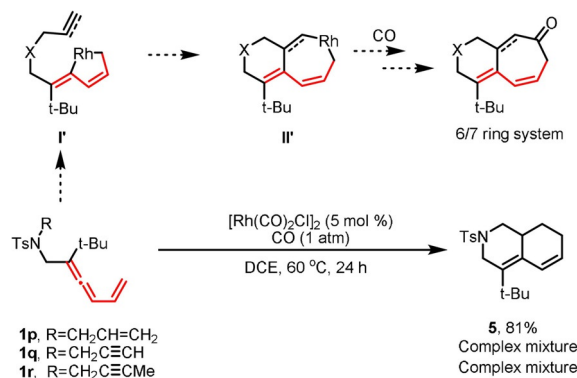
Scheme 4. Attempting to realize [4+2+1] reactions by introducing a bulky *t*Bu group in vinylallenes gave either a [4+2] product or complex mixtures.

dative cycloaddition has been introduced, other side reactions such as [4+2] reaction would interfere in the formation of [4+2+1] cycloadducts (Scheme 4).

In summary, a rhodium(I)-catalyzed three-component [4+2+1] cycloaddition reaction of two vinylallenes (as C₄ and C₂ synthons) and a CO (as a C₁ synthon) has been realized. This reaction provides a new reaction pattern for vinylallenes, which were in previous studies mainly restricted to [4+1] cycloaddition reactions for five-membered ring synthesis, not seven-membered ring synthesis. Of the same importance, the present reaction is of value for synthesis of highly functionalized tropone derivatives from the viewpoint of medical chemistry.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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[10] CO could insert into another Rh–C bond in intermediate III, and then similar processes followed could give the final [4+2+1] product.

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