

# Rh(I)-Catalyzed Formal [5 + 1]/[2 + 2 + 1] Cycloaddition of 1-Yne-vinylcyclopropanes and Two CO Units: One-Step Construction of Multifunctional Angular Tricyclic 5/5/6 Compounds

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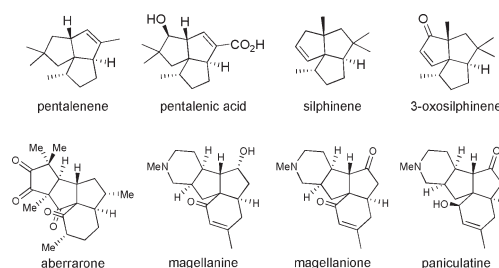
**S** Supporting Information

**ABSTRACT:** A novel Rh(I)-catalyzed formal [5 + 1]/[2 + 2 + 1] cycloaddition of 1-yne-vinylcyclopropanes and two CO units for the construction of multifunctional angular tricyclic 5/5/6 skeletons with one or two adjacent bridgehead quaternary all-carbon stereocenters in one step has been developed. Preliminary density functional theory calculations have been carried out to investigate the reaction mechanism and the substituent effects.

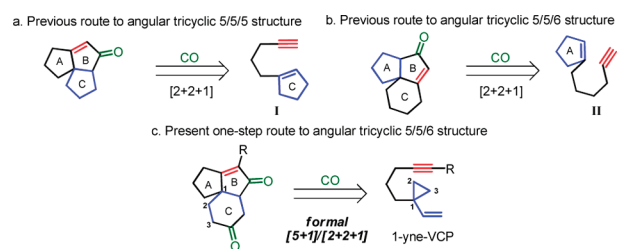
A preeminent goal of organic synthesis is to reach structural complexity in step- and atom-economical manners, preferably using a single-step reaction with all atoms embedded in the desired products.<sup>1,2</sup> This concept and its practice are influencing today's science of synthesis. Tricyclic and polycyclic carbocyclic ring skeletons are widely found in natural products with significant biological properties, such as the 5/5/5 systems of angular triquinanes and the 5/5/6 systems of the lycopodiaceae family (Scheme 1).<sup>3</sup> One of the challenges in the synthesis of these natural products and their analogues for biological and medicinal studies is usually related to finding one or a series of reactions to construct these ring systems. The widely applied approaches for constructing the tricyclic carbocyclic skeletons involve either building each ring independently, single-step building of two rings first and then the third ring, or building one ring first and then the other two rings in one step. An ideal way to build a tricyclic skeleton that would have step- and atom-economical characters would be to build the three rings in one step from readily available starting materials.

Modern transition-metal-catalyzed cycloadditions<sup>4</sup> represent powerful tools enabling quick and efficient access to mono-, bicyclic, and sometimes tricyclic structures<sup>5</sup> in one step. However, few methods have been developed for the one-step synthesis of compounds with angular tricyclic skeletons (such as those embedded in angular triquinanes and the lycopodiaceae family). Previously, the construction of angular tricyclic compounds using transition-metal-catalyzed cycloadditions has involved Pauson–Khand reactions of substrates that already have one five-membered ring (Scheme 2a,b).<sup>6,7</sup> We envisioned that a one-step construction of an angular tricyclic 5/5/6 skeleton would be the most efficient strategy to achieve this goal. Here we report an unexpected and unprecedented novel Rh(I)-catalyzed formal [5 + 1]/[2 + 2 + 1] cycloaddition of 1-yne-vinylcyclopropanes

## Scheme 1. Natural Products Containing Angular Tricyclic Systems



## Scheme 2. Previously Reported Syntheses of Angular Tricyclic Systems and Our New Work



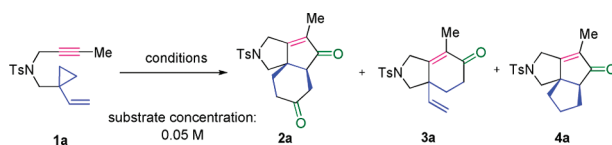
(1-yne-VCPs) and two CO units for the synthesis of multifunctional angular tricyclic 5/5/6 compounds (Scheme 2c).

We previously developed a synthetically useful [(3 + 2) + 1] cycloaddition<sup>8</sup> that converts 1-yne-VCP derivatives and CO into bicyclic cyclohexenones in the presence of a catalytic amount of [Rh(CO)<sub>2</sub>Cl]<sub>2</sub>. It was found that all 1-yne-VCPs with terminal alkynes gave only [(3 + 2) + 1] cycloadducts, no matter whether a higher or lower CO pressure was applied. For 1-yne-VCP **1a**, which has an internal alkyne, the [(3 + 2) + 1] cycloadduct was obtained exclusively when a CO pressure of 1 atm was applied (Table 1, entry 1). However, to our surprise, when a CO pressure of 0.2 atm was applied, the reaction of **1a** afforded, in addition to the expected [(3 + 2) + 1] cycloadduct **3a** in 39% yield, the angular tricyclic 5/5/6 compound **2a** in 32% yield and the tricyclic 5/5/5 compound **4a** in 4% yield (Table 1, entry 2). Single-crystal X-ray diffraction analysis confirmed the

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Table 1. Optimization Studies



entry	catalyst (5 mol %)	solvent	CO pressure (atm)	temp (°C)	t (h)	yield (%) <sup>a</sup>		
						2a	3a	4a
1	[Rh(CO) <sub>2</sub> Cl] <sub>2</sub>	toluene	1	80	7	—	85	—
2	[Rh(CO) <sub>2</sub> Cl] <sub>2</sub>	toluene	0.2	80	19	32	39	4
3	[Rh(CO) <sub>2</sub> Cl] <sub>2</sub>	dioxane	0.2	80	13.5	48	49	—
4	[Rh(CO) <sub>2</sub> Cl] <sub>2</sub>	DCE	0.2	80	1	61	32	—
5	[Rh(CO) <sub>2</sub> Cl] <sub>2</sub>	DCE	1	80	1	32	31	—
6	[Rh(CO) <sub>2</sub> Cl] <sub>2</sub>	DCE	4	80	3	9	64	—
7	[Rh(COD)Cl] <sub>2</sub>	DCE	0.2	80	17.5	45	21	—
8	[Rh(dppp)Cl] <sub>2</sub>	DCE	0.2	80	24		no reaction	
9	[Rh(dppp)]SbF <sub>6</sub> <sup>b</sup>	DCE	0.2	80	24		no reaction	

<sup>a</sup> Isolated yield after column chromatography. <sup>b</sup> Using 10 mol % catalyst.

tricyclo[7.3.0.0<sup>4,9</sup>]dodecane skeleton of **2a**. Apparently, this unique angular tricyclic 5/5/6 compound originated from the cycloaddition of **1a** and two CO units, and the trace amount of the tricyclic 5/5/5 byproduct **4a** came from the cycloaddition of **1a** and one CO molecule. In view of the fact that this “dicarbonylative cycloaddition” process<sup>9</sup> is very rare in transition-metal-catalyzed cycloaddition chemistry and more importantly that the angular 5/5/6 tricyclic structure of **2a** could be reached in one step from easily prepared 1-yn-1-ene-VCP **1a**, we were eager to optimize and develop this reaction to a useful synthetic method in the laboratory.

Therefore, we employed 1-yn-1-ene-VCP **1a** as the model substrate and studied the influence of CO pressure, solvent, and catalyst on the reaction (Table 1). It was found that higher CO pressure usually facilitated the [(3 + 2) + 1] cycloaddition and inhibited the formation of the angular tricyclic cycloadduct **2a** (entries 1, 2, and 4–6). 1,2-Dichloroethane (DCE) was found to be an optimal solvent in comparison with toluene and 1,4-dioxane. A brief screening of different Rh(I) complexes indicated that [Rh(CO)<sub>2</sub>Cl]<sub>2</sub> was the best catalyst among those examined (entries 4 and 7–9).

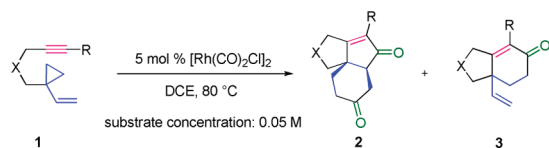
Various 1-yn-1-ene-VCP substrates were submitted to the optimal reaction conditions (5 mol % [Rh(CO)<sub>2</sub>Cl]<sub>2</sub> as catalyst, DCE as solvent, 80 °C). It was found that the yields of angular tricyclic 5/5/6 cycloadducts were generally good to excellent and that the [(3 + 2) + 1] cycloadducts were generated as byproducts in minor amounts (Table 2). In all cases except when **1k** was used as the substrate, the tricyclic 5/5/5 byproducts (of **4a** type) were not observed. Nitrogen-, oxygen-, and *gem*-diester-tethered substrates could afford hetero- and carbocyclic diones. The steric bulkiness of the alkyne substitution plays an important role in this reaction: bulky groups, such as <sup>i</sup>Pr, cyclohexyl (Cy), and <sup>t</sup>Bu, led to higher yields of the desired tricyclic cycloadducts (entries 2,3,5 and 8–11). Less bulky alkyne substituents such as Me resulted in diminished reaction yields (Table 1, entry 4, and Table 2, entry 7). A chloroalkyl substituent on the 1-yn-1-ene-VCP substrate could also be tolerated, producing the angular tricyclic product with a

chlorine-substituted alkyl chain, which could facilitate further modification of the cycloadduct (entry 4). A TMS-substituted 1-yn-1-ene-VCP could be employed to give a moderate yield; this could serve as a surrogate of the nonsubstituted 1-yn-1-ene-VCP, as the TMS group in the product can be easily removed afterward (entry 6). We also attempted to forge an angular tricyclic 6/5/6 skeleton using this formal [5 + 1]/[2 + 2 + 1] reaction of **1s** and CO (see ref 10). However, in this case only [(3 + 2) + 1] product instead of the tricyclic 6/5/6 compound was obtained.<sup>10</sup>

Further investigations of this [5 + 1]/[2 + 2 + 1] reaction showed that 1-yn-1-ene-VCP substrates with C $\alpha$  substituents are also compatible and afford C4-substituted tricyclic products, albeit in moderate yields and accompanied by remarkable amounts of [(3 + 2) + 1] products (Table 3). Significantly, these reactions allow the construction of angular tricyclic skeletons with two adjacent bridgehead quaternary all-carbon stereocenters (C4 and C9), which is a real challenge in cycloaddition reactions. This feature further enhances the synthetic utility of the present cycloaddition.

We refer to the present reaction as a formal [5 + 1]/[2 + 2 + 1] cycloaddition since we thought that this reaction could start from [5 + 1] reaction<sup>11</sup> of VCP and CO, which would be followed by a Pauson–Khand reaction<sup>12</sup> of the in situ-generated alkene, alkyne, and CO (Scheme 3a). However, a control experiment showed that an independently synthesized yne- $\beta,\gamma$ -cyclohexenone, **5**, could not afford the cycloaddition product **2a** under the optimal reaction conditions: 96% of **5** was recovered after 1 h, the same amount of time as required for the standard reaction in entry 4 of Table 1 (Scheme 3b). This result clearly indicated that this cycloaddition reaction does not proceed via a cascade [5 + 1]/[2 + 2 + 1] mechanism, even though after 24 h, a trace amount of **2a** was found in the reaction system. To present this reaction in an easily memorized way, we still name this reaction as a formal [5 + 1]/[2 + 2 + 1] cycloaddition.

Two possible pathways (see Figure S1 in the Supporting Information) were proposed to account for this reaction. Preliminary density functional theory (DFT) calculations suggested that the

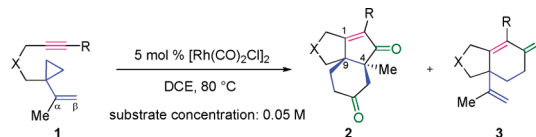
**Table 2. Rh(I)-Catalyzed Formal [5 + 1]/[2 + 2 + 1] Cycloaddition**

entry	substrate	CO pressure (atm)	t (h)	yield (%) <sup>a</sup>	
				2	3
X = TsN					
1	<b>1b</b> R = Et	0.5	2.5	58	4
2	<b>1c</b> R = <sup>i</sup> Pr	1	4	72	9
3	<b>1d</b> R = <sup>t</sup> Bu	1	3.5	71	26
4	<b>1e</b> R = (CH <sub>2</sub> ) <sub>3</sub> Cl	0.5	3.5	60	29
5	<b>1f</b> R = Cy	1	2	61	14
6	<b>1g</b> R = TMS	0.2	5	39	6
X = C(CO <sub>2</sub> Me) <sub>2</sub>					
7	<b>1h</b> R = Me	1	1	47	19
8	<b>1i</b> R = <sup>i</sup> Pr	1	1	91	—
9	<b>1j</b> R = <sup>t</sup> Bu	1	1.5	74	—
X = O					
10	<b>1k</b> R = <sup>i</sup> Pr	1	1.5	87	— <sup>b</sup>
11	<b>1l</b> R = Cy	1	2	77	—

<sup>a</sup> Isolated yield after column chromatography. <sup>b</sup> A tricyclic 5/5/5 product was obtained in 11% yield (see the Supporting Information for details).

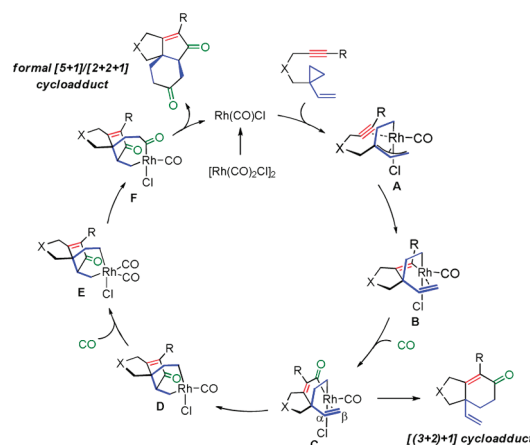
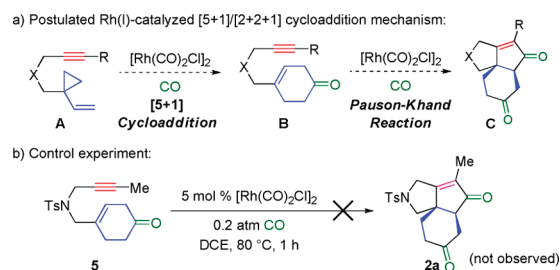
pathway shown in Figure 1 is reasonable (see the details in the Supporting Information). In this pathway, the 1-yn-1-ene-VCP and Rh(I) catalyst undergo complexation, cyclopropane cleavage, and alkyne insertion, generating intermediate **B**.<sup>13</sup> Insertion of CO into the Rh–C(sp<sup>2</sup>) bond gives rhodacycloheptenone **C**. If a direct elimination occurs on this intermediate, the [(3 + 2) + 1] cycloadduct could be generated. Alternatively, if insertion of the alkene C $\alpha$ =C $\beta$  double bond into the Rh–C(=O) bond in intermediate **C** takes place, a tricyclic rhodacyclohexane **D** could be generated. Next, another CO molecule could enter this process, and the final 5/5/6 product could be achieved through CO insertion and reductive elimination (via intermediates **E** and **F**, respectively).

A rationalization of why the angular tricyclic 5/5/6 products are usually accompanied by the [(3 + 2) + 1] cycloadducts and how the steric bulkiness of the alkyne substituent R of the 1-yn-1-ene-VCP influences the results of these two competitive pathways are proposed (see Figure 2 and Figure S2). DFT calculations indicated that no matter whether R is small or big, the activation enthalpies (from **IN4** to **TS4**–[(3 + 2) + 1]) required for the [(3 + 2) + 1] pathway are almost the same (~23.0 kcal/mol). However, as R becomes bigger, the activation enthalpies (from **IN4** to **TS4**) required for the formal [5 + 1]/[2 + 2 + 1] pathway are reduced from 24.6 to 22.8 to 21.8 kcal/mol, making the formal [5 + 1]/[2 + 2 + 1] pathway gradually preferred over the [(3 + 2) + 1] pathway. A cursory examination of **IN4**, **TS4**, and **TS4**–[(3 + 2) + 1] shows that when a bulky R group is introduced in the 1-yn-1-ene-VCP, the alkene group in **IN4** coordinates to the Rh atom much more strongly. This stronger coordination makes alkene insertion into the Rh–C(=O) bond easier, and consequently, the formal [5 + 1]/[2 + 2 + 1] cycloaddition becomes favored.

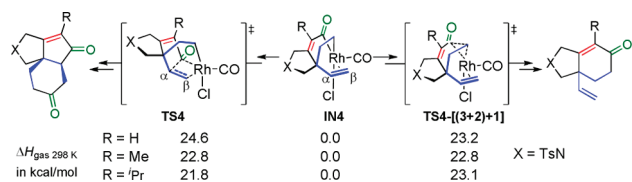
**Table 3. Exploration of Substrate Scope for Formation of Two Adjacent Bridgehead Quaternary All-Carbon Stereocenters**

entry	substrate	CO pressure (atm)	t (h)	yield (%) <sup>a</sup>	
				2	3
X = TsN					
1	<b>1m</b> R = Me	0.2	4	36	61
2	<b>1n</b> R = <sup>i</sup> Pr	1	1.5	31	46
3	<b>1o</b> R = <sup>t</sup> Bu	1	1.5	32	59
4	<b>1p</b> R = Cy	1	1.5	39	57
X = C(CO <sub>2</sub> Me) <sub>2</sub>					
5	<b>1q</b> R = <sup>t</sup> Bu	1	1.5	55	18
X = O					
6	<b>1r</b> R = <sup>i</sup> Pr	1	1.5	57	27

<sup>a</sup> Isolated yield after column chromatography.

**Figure 1. Catalytic cycle supported by DFT calculations.****Scheme 3. Preliminary Mechanistic Study**

In summary, a novel Rh(I)-catalyzed formal [5 + 1]/[2 + 2 + 1] cycloaddition of 1-yn-1-ene-VCPs and two CO units has been developed, yielding multifunctional angular tricyclic 5/5/6 diones in



**Figure 2.** DFT study showing how the R group influences the selectivity.

generally good to excellent yields and providing a one-step, efficient, versatile, and diastereoselective approach to carbo- and heteroangular tricyclic 5/5/6 compounds with one or two bridge-head quaternary all-carbon stereocenters. Preliminary DFT calculations have been carried out to investigate the reaction mechanism and the substituent effects. Further studies of this reaction (scope, mechanism, and application) are underway.

## ASSOCIATED CONTENT

**S Supporting Information.** Experimental and computational details; crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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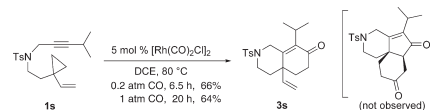
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