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# $\text{Rh}^{\text{I}}$-Catalyzed C−C Bond Activation: Seven-Membered Ring Synthesis by a [6+1] Carbonylative Ring-Expansion Reaction of Allenylcyclobutanes[**]

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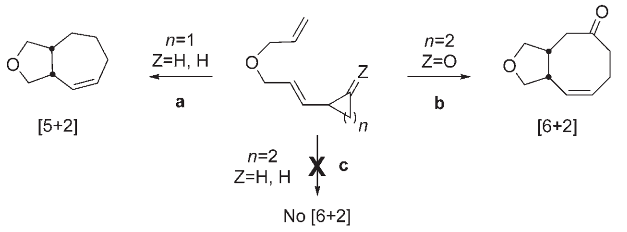
The transition-metal-catalyzed activation of carbon–carbon (C−C) sigma bonds represents an important and fundamental challenge in organometallic chemistry that has the potential to broaden how we approach problems in organic synthesis.[1] We have previously shown that transition metals can be used to catalyze the strain-assisted C−C bond activation of vinylcyclopropanes (VCPs) to produce organometallic intermediates that can be intercepted with various trapping agents to afford new two-, three-, and four-component cycloadditions. Representative examples include the [5+2] cycloaddition of VCPs and π systems (Scheme 1a);[2] the [5+2+1] cycloaddition of VCPs, alkynes (and allenes), and CO;[2c,3] and the [5+1+2+1] cycloaddition of VCPs, alkynes, and CO,[4] thus providing new routes to seven-, eight-, and nine-membered rings and their derivatives.[5] Whereas the extension of this five-carbon VCP chemistry to simple six-carbon vinylcyclobutanes has failed thus far (Scheme 1c), the metal-catalyzed activation of the C−C bond of vinylcyclobutanones has been successful, thus leading to a new [6+2] cycloaddition for the formation of eight-membered rings (Scheme 1b).[6,7]



**Scheme 1.** [5+2], [6+2], and attempted [6+2] reactions.

To explore whether vinylcyclobutanes could be activated for use as six-carbon components in metal-catalyzed reactions, we examined the reaction of 1-siloxy-1-vinylcyclobu-

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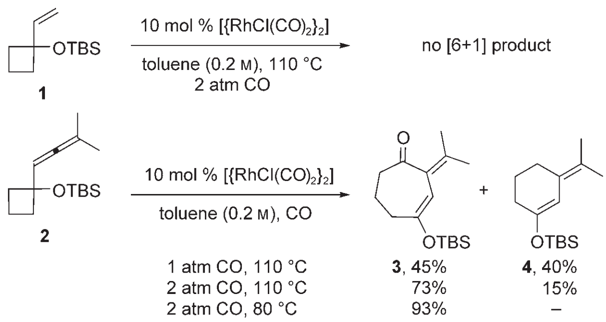
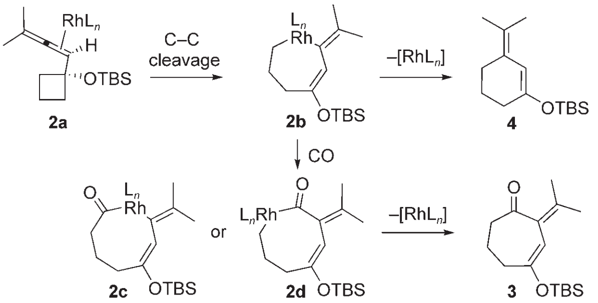
tane **1** (Scheme 2) with $\text{Rh}^{\text{I}}$ catalysts. Although we had previously shown that similar siloxy-substituted (and alkoxy-substituted) VCPs are more reactive than their non-oxygenated counterparts in metal-catalyzed [5+2] cycloadditions,[8] the corresponding 1-siloxy-1-vinylcyclobutane **1** was unreactive. Given that the requisite C–C cleavage process would likely be assisted by metal coordination to the π system and that allenes are often better coordinators than alkenes, the reaction of 1-siloxy-1-allenylcyclobutane **2** was examined. In contrast to vinylcyclobutane **1**, allenylcyclobutane **2** reacted readily through a metal-catalyzed C–C activation process and, in the presence of CO, produced both six- and seven-membered ring products (Scheme 2).[9] We describe herein our studies on this new class of metal-catalyzed C–C activation reactions and its incorporation into a new method for seven-membered ring synthesis through a carbonylative ring expansion reaction, a formal [6+1] cycloaddition.[10]



***Scheme 2.*** Attempted [6+1] reaction of **1** and [6+1] reaction of **2**. TBS = *tert*-butyldimethylsilyl.

Our initial studies revealed that activation of **2** could be achieved with $[\{\text{RhCl(CO)}_2\}_2]$ (10 mol%) in toluene in the presence of CO (1 atm) to give cycloheptenone **3** in 45% yield along with the cycloisomerization product, cyclohexene **4**, in 40% yield (Scheme 2). Increasing the CO pressure to 2 atmospheres, improved the mode selectivity of the reaction, thus giving **3** and **4** in 73 and 15% yields, respectively. Significantly, decreasing the reaction temperature to 80°C decoupled the competing pathways, thus resulting in a completely selective and highly efficient trapping reaction to give **3** in 93% yield. Interestingly, although $[\text{IrCl(CO)(PPh}_3)_2]$ was the catalyst of choice in the [5+1] reaction of allenylcyclopropanes,[10] no reaction was obtained with **2** under the analogous reaction conditions.

As depicted in Scheme 3, this reaction putatively proceeds through pre-coordination of the $\text{Rh}^{\text{I}}$ center to the double bond of the allene that is proximal to the cyclobutane **2a**. This step leads to the metallacycle **2b** after insertion into the adjacent C–C bond. Reductive elimination affords the cycloisomerized cyclohexene **4**.[11] A competing CO insertion step, which is apparently favored at lower temperature followed by reductive elimination provides the [6+1] cycloadduct **3**. Metallacycles **2b** and **2c/2d** represent new reactive intermediates that could potentially be points of divergence to new classes of higher-order cycloaddition reactions.[7b,c]

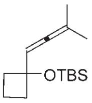
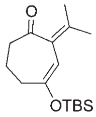
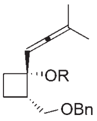
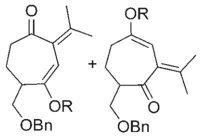
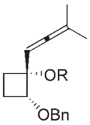
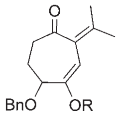
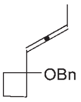
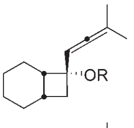
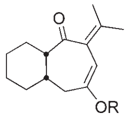
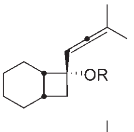
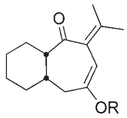
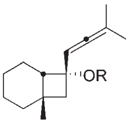
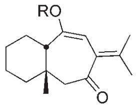
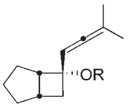
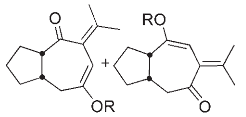
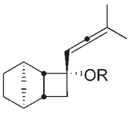
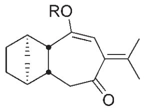


***Scheme 3.*** Mechanistic proposal for the [6+1] reaction.

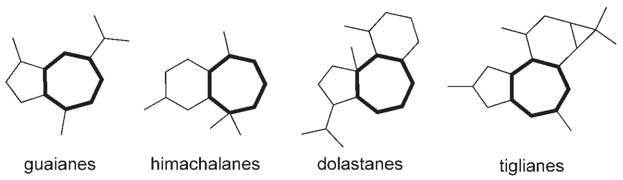
Studies on the scope of this new [6+1] reaction indicate that it can be used to synthesize various functionalized cycloheptenones (Table 1). Of the solvents surveyed, including 1,4-dioxane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, toluene, and *m*-xylene, aromatic solvents gave higher yields of the [6+1] products. Processes that required longer reaction times were carried out in *m*-xylene to minimize solvent loss. Monocyclic allenylcyclobutane **2** reacts to give a 93% yield of the cycloheptenone **3**. The substituted allenylcyclobutanes **5** and **8** react to give cycloheptenones **6**, **7**, and **9**. With the exception of **2**, better results were obtained using only 1 atmosphere of CO for the [6+1] reactions. In the case of **5**, two regioisomeric products were obtained, **6** which results from cleavage of the less-substituted C–C bond and **7** which results from cleavage of the more-substituted C–C bond. The benzyloxy-substituted allenylcyclobutane gave only **9**, the product that results from cleavage of the less-substituted C–C bond. Attempts to achieve a [6+1] reaction with allenylcyclobutane **10**, which has only one methyl group at the double bond distal to the cyclobutane have thus far been unsuccessful with $\text{Rh}^{\text{I}}$ catalysts.[12]

Given the potential of this process for access to the core ring systems of natural and non-natural targets containing seven-membered rings (e.g., Scheme 4),[13] the reactions of various allenyl-substituted [*n*.2.0] bicycles were also investigated. The cycloadducts **12** and **14**, which incorporate a himachalane core, were obtained in excellent yield using only 2 mol% of catalyst and a substrate concentration of 0.5 M (Table 1). A comparison of the [6+1] reactions of **11** and **13** illustrates that the replacement of the methoxyethyl protecting group with a benzyl group has a negligible effect on yield; however, a longer reaction time is required, thus possibly reflecting a chelating effect for the former group. It is noteworthy that the reaction proceeds with exclusive cleavage of the more-substituted bond in these cases. In contrast, the [6+1] reaction of **15**, which contains an angular methyl group, gave the bicyclo[5.4.0]undecenone product **16**, which arises from cleavage of the less-substituted bond in moderate yield. Interestingly, the bicyclo[3.2.0]heptane substrate **17** afforded the regioisomers **18** and **19** in a 3:4 ratio with a combined yield of 56%, both of which possess the bicyclo[5.3.0]decane system of pseudoguaianes, guaianes, tiglianes, daphnanes, and other natural products. The norbornene-derived substrate **20** provided only regioisomer **21**, which results from cleavage of the less-substituted C–C bond in 85% yield.

***Table 1:*** [6+1] Reaction of allenylcyclobutanes.

| Substrate | | Conditions[a] | $t$ | Product(s) | | Yield [%][b] |
|---|---|---|---|---|---|---|
|  | **2** | A | 24 |  | **3** | 93 |
|  | **5**[b] | B | 44 |  | **6**+**7** | 70 (5:1) |
|  | **8**[b] | C | 48 |  | **9** | 55 |
|  | **10** | D | 48 | decomposition | | |
|  | **11**[b] | E | 11 |  | **12** | 89 |
|  | **13**[c] | E | 22 |  | **14** | 90 |
|  | **15**[b] | B | 20 |  | **16** | 53 |
|  | **17**[b] | F | 40 |  | **18**+**19** | 56 (3:4) |
|  | **20**[b] | C | 44 |  | **21** | 85 |

[a] A: [{RhCl(CO)$_2$}$_2$] (10 mol%), toluene (0.1 M), CO (2 atm), 80°C; B: [{RhCl(CO)$_2$}$_2$] (2 mol%), *m*-xylene (0.5 M), CO (1 atm), 80°C; C: [{RhCl(CO)$_2$}$_2$] (10 mol%), *m*-xylene (0.1 M), CO (1 atm), 80°C; D: [{RhCl(CO)$_2$}$_2$] (10 mol%), toluene (0.1 M), CO (1 atm), 80°C; E: [{RhCl(CO)$_2$}$_2$] (2 mol%), toluene (0.5 M), CO (1 atm), 80°C; F: [{RhCl(CO)$_2$}$_2$] (10 mol%), *m*-xylene (0.1 M), CO (1 atm), 95 °C. [b] R = $(CH_2)_2OCH_3$. [c] R = Bn.



***Scheme 4.*** Representative natural product skeletons.

In summary, we have shown that allenylcyclobutanes undergo Rh$^I$-catalyzed C–C activation to generate intermediate metallacycles that can be trapped with CO to produce cycloheptenones in good to excellent yields. This novel [6+1] cycloaddition offers a new route to functionalized cycloheptenones that would be difficult to produce conventionally, including those corresponding to the bicyclo[5.4.0] and -[5.3.0] cores of a wide range of natural products. Further studies on the scope and applications of this reaction and the trapping of these intermediates to produce higher order cycloadditions are in progress.

## *Experimental Section*

Allenylcyclobutane **11** (41 mg, 0.163 mmol) was weighed into an oven-dried test tube equipped with a magnetic stir bar. The substrate was dissolved in toluene (0.33 mL), and [{RhCl(CO)$_2$}$_2$] (1.3 mg, 0.0033 mmol) was added in one portion. The test tube was capped with a rubber septum. The resulting yellow solution was stirred in an atmosphere of CO (balloon, 1 atm) vented to a bubbler through an outlet needle for 15 min. The outlet needle was removed and the test tube was partially immersed into a thermostat-controlled oil bath preheated to 80°C. The reaction mixture was stirred for 11 h, at which time TLC analysis indicated that the starting material was consumed. The solution was cooled to room temperature and was purified by column chromatography on silica gel ($Et_2O$/pentane, gradient elution: 5:95→10:90). Product-containing fractions were combined and concentrated to give **12** (40.3 mg, 89%) as a colorless oil. The compounds were chromatographically homogeneous.

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