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# Rhodium(I)-Catalyzed Intramolecular Ene Reaction of Vinylidenecyclopropanes and Alkenes for the Formation of Bicyclo[5.1.0]octylenes

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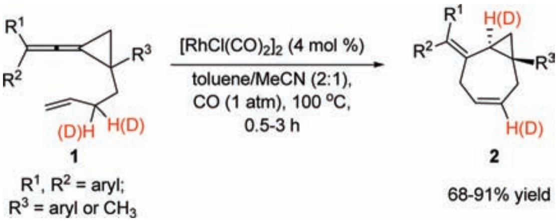
## ABSTRACT



**An efficient catalytic system for the intramolecular ene reaction of allene and alkene of diarylvinylidenecyclopropanes has been established. The reaction was achieved by using $[RhCl(CO)_2]_2$ as the catalyst in co-solvents of toluene and acetonitrile. MeCN was found to play a crucial role in controlling the reaction toward formation of bicyclo[5.1.0]octylene derivatives. An alternative system consisting of $[RhCl(CO)_2]_2$ and toluene in the absence of MeCN was found to give [2 + 2] cycloaddition adducts. The structures have been unambiguously determined by X-ray structural analysis. Deuterium labeling experiments were conducted to confirm the mechanism hypothesis.**

Transition-metal-catalyzed stereoselective creation of functionalized seven-membered rings has been challenging in modern organic chemistry because these rings belong to the carbocyclic cores of some of the most important and largest families of natural products such as frondosin A−E, guaianes, tiglianes, etc.[1,2] The most successful strategy to build these cores is to take advantage of the Rh-catalyzed and Ru-catalyzed [5 + 2] cycloadditions of cyclopropane-anchored olefins that were established by Wender[2,3] and Trost,[1,4] respectively.

In the past several years, we and others have been engaging in the study of a series of reactions involving vinylidenecyclopropanes (VDCPs) as the susbtrates in which allene moieties are connected onto the cyclopropane ring.[5,6] During continuing study of these reactions, we found that diarylvinylidenecyclopropanes can be readily converted into novel

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(1) (a) Trost, B. M.; Hu, Y.; Horne, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 11781. (b) *Transition Metals in the Synthesis of Complex Organic Compounds*, 2nd ed.; Hegedus, L. S., Ed.; University Science Books: Sausalito, CA, 1998. (c) *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed.; Collman, J. P., Hegedus, L. S., Norton, J. R., Finke, R. G., Eds.; University Science Books: Sausalito, CA, 1987.

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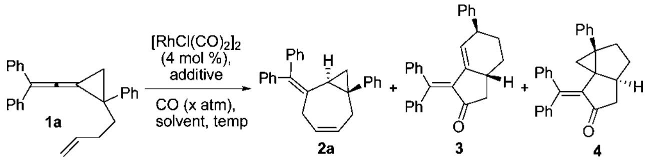
**Table 1.** Optimization of Conditions for Intramolecular Ene Reaction of Diphenylvinylidenecyclopropane **1a** in the Presence of $[RhCl(CO)_2]_2$

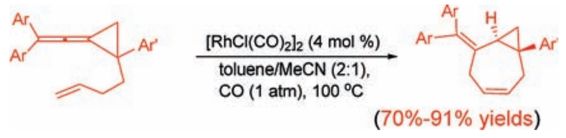


| entry[a] | solvent | $x$ | additive | temp (°C) | time | yield (%)[b] 2a | 3 | 4 |
|---|---|---|---|---|---|---|---|---|
| 1 | DCE | 1 | | 20 | 24 h | | trace | |
| 2 | DCE | 30 | | 20 | 6 d | | trace | |
| 3 | DCE | 1 | 2.0 equiv DMB | 20 | 7 d | | 23 | 43 |
| 4 | DCE | 30 | 2.0 equiv DMB | 20 | 7 d | | trace | |
| 5 | DCE | 1 | 2.0 equiv COD | 20 | 7 d | | trace | |
| 6 | DCE | 1 | 2.0 equiv DMB | 80 | 24 h | | complex | |
| 7[c] | DMF | 1 | | 100 | 2.5 h | 43 | trace | |
| 8 | MeCN | 1 | | 80 | 3 h | 89 | trace | |
| **9[d]** | **toluene/MeCN** | **1** | | **100** | **1 h** | **90** | **trace** | |

[a] VDCP **1a** (0.2 mmol) and $[RhCl(CO)_2]_2$ (4 mol %) were dissoved in 3 mL of solvent under 1 atm CO and stirred for several hours at different temperatures. [b] Isolated yields. [c] 43% of the starting materials was recovered. [d] Toluene (2 mL) and MeCN (1 mL).

bicyclo[5.1.0]octylene core structures in toluene and MeCN as co-solvents at enhanced temperature in the presence of $[RhCl(CO)_2]_2$ as the catalyst. In addition, this catalytic system without using MeCN was found to result in intramolecular [2 + 2] cycloaddition adducts. In this paper, we would like to disclose the preliminary results of this study as represented by Schemes 1 and 4, with results summarized in Table 1 and 2.

**Scheme 1**



Diphenylvinylidenecyclopropane **1a** was utilized as the model substrate for screening conditions under carbon monoxide atmosphere in the presence of transition metal catalysts such as $PtCl_2$, $PdCl_2$, $Ru_3(CO)_{12}$, $RhCl(CO)(PPh_3)_2$, and $Rh_6(CO)_{16}$ that were then available to us in common solvents of *N*,*N*-dimethylformamide (DMF) and dichloroethane (DCE). Unfortunately, all of the above catalysts did not result in anticipated products, and most starting materials remained even at higher temperatures. We then turned attention to the use of $[RhCl(CO)_2]_2$, which has become a powerful transitional metal catalyst for similar cycloaddition reactions.[2,3] We found that bicyclic[5.1.0]octylene derivative **2a** was formed as a single diastereomer in a chemical yield of 43% when the reaction was performed in DMF at 100 °C in the presence of $[RhCl(CO)_2]_2$ (10 mol %) as the catalyst (entry 7 in Table 1 and Table SI in Supporting Information).[7]

Inspired by this initial result, we continued optimizing conditions using $[RhCl(CO)_2]_2$ as the catalyst. As revealed in Table 1, when the reaction was performed at room temperature (20 °C) under 1.0 or 30 atm of CO atmosphere (Table 1, entries 1 and 2), trace amounts of Pauson−Khand products **3** and **4** were detected without observing the intramolecular ene reaction products. However, when 2,3-dimethylbuta-1,3-diene (DMB, 2.0 equiv) was added into the catalytic system as an additive, Pauson−Khand products **3** and **4** were obtained in chemical yields of 23% and 43%, respectively (Table 1, entry 3).[7] Attempts to increasing the formation of these two products were unsuccessful under various catalytic conditions by using other additives even at enhanced temperature (Table 1, entries 4−6).

Pleasingly, we found that the combination of $[RhCl(CO)_2]_2$ and MeCN (as the catalyst and solvent, respectively) resulted in the intramolecular ene reaction product **2a** in 89% yield. This result was achieved by performing the reaction at 80 °C for 3 h (Table 1, entry 7). We also found the reaction occurred at a faster rate when a mixture of toluene and MeCN (2:1) was employed instead of acetonitrile itself. The reaction can be finished within 1 h leading to **2a** in 90% yield under this co-solvent system at slightly enhanced temperature

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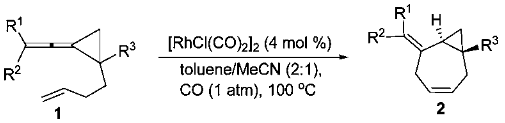
(7) See Supporting Information for the X-ray crystal data of products **2g**, **3**, and **5f** and the catalyst screening results.

(Table 1, entry 8). Under CO atmosphere, the $[RhCl(CO)_2]_2$ catalyst can be better stabilized, and the reaction rate be accelerated.

Under the optimal condition, we next examined the scope of generality of this reaction by using a variety of diarylvinylidenecyclopropanes **1** as the substrates that were synthesized using known procedures;[5] the results are summarized in Table 2. As revealed in Table 2, the corresponding ene product, bicyclo[5.1.0]octylene **2**,[7] was obtained as a single diastereomer for each case in good to high yields (68 − 91%) that are not influenced by electron-donating or electron-withdrawing substituents on the aromatic rings (Table 2, entries 1−9). Even for the case of **1k** in which R3 was an aliphatic methyl group, the ene product (**2k**) can be obtained in 70% yield (Table 2, entry 10). In the case of unsymmetrical diarylvinylidenecyclopropane **1l**, the bicyclo[5.1.0] octylene (**2l**) was generated as *E*- and *Z*-isomeric mixtures in a combined yield of 88% (Table 2, entry 11).

**Table 2.** $[RhCl(CO)_2]_2$-Catalyzed Intramolecular Ene Reaction of Diarylvinylidenecyclopropane **1** under Optimal Condition

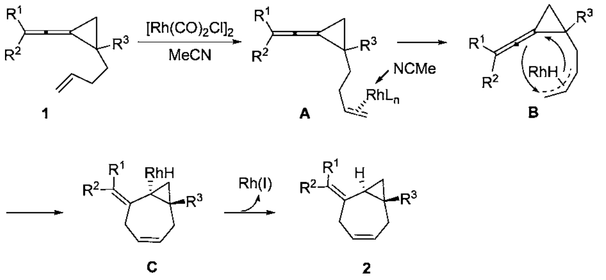


| entry[a] | $R^1/R^2/R^3$ | time (h) | **2**, yield (%)[b] |
|---|---|---|---|
| 1 | $C_6H_5/C_6H_5/p$-$CH_3C_6H_4$, **1b** | 1 | **2b**, 74 |
| 2 | $C_6H_5/C_6H_5/p$-$CH_3OC_6H_4$, **1c** | 6 | **2c**, 74 |
| 3 | $C_6H_5/C_6H_5/p$-$FC_6H_4$, **1d** | 0.5 | **2d**, 91 |
| 4 | $C_6H_5/C_6H_5/p$-$ClC_6H_4$, **1e** | 0.5 | **2e**, 87 |
| 5 | $C_6H_5/C_6H_5/p$-$BrC_6H_4$, **1f** | 1 | **2f**, 68 |
| 6 | $C_6H_5/C_6H_5/$m-$BrC_6H_4$, **1g** | 0.3 | **2g**, 73 |
| 7 | *p*-$CH_3C_6H_4/p$-$CH_3C_6H_4/C_6H_5$, **1h** | 2 | **2h**, 84 |
| 8 | *p*-$CH_3OC_6H_4/p$-$CH_3OC_6H_4/C_6H_5$, **1i** | 2 | **2i**, 72 |
| 9 | *p*-$ClC_6H_4/p$-$ClC_6H_4/C_6H_5$, **1j** | 2 | **2j**, 75 |
| 10 | $C_6H_5/C_6H_5/CH_3$, **1k** | 3 | **2k**, 70 |
| 11 | *p*-$ClC_6H_4/C_6H_5/C_6H_5$, **1l** | 1 | **2l**, 88[c] |

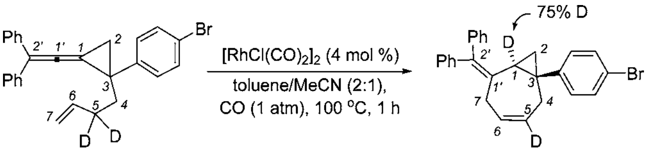
[a] Reaction conditions: VDCP 1 (0.2 mmol) and $[RhCl(CO)_2]_2$ (4 mg, 4 mol %) were dissolved in toluene (2 mL) and MeCN (1 mL), and then the mixtures were stirred for different times at 100 °C under 1 atm CO. [b] Isolated yield. [c] Ratio of *E*- and *Z*-isomers is 1:1, which was determined by $^1H$ NMR spectroscopic data.

A plausible mechanism for this intramolecular ene reaction is outlined in Scheme 2. As in a similar mechanism proposed by Bergman,[8] acetonitrile and the tethered terminal alkene can be coordinated onto Rh(I) metal center to generate intermediate **A** *in situ*. Subsequently, the oxidative addition of rhodium(I) complex into the neighboring allylic C−H bond gives a $\pi$-allyl rhodium−hydrogen species **B**,[9] which leads to a seven-membered carbocyclic rhodium−hydrogen species **C** through an intramolecular cycloaddition to allene moiety. A reductive elimination affords the product **2** along with Rh(I) catalyst regeneration.

**Scheme 2.** Mechanism of $[RhCl(CO)_2]_2$-Catalyzed Intramolecular Ene Reaction



**Scheme 3.** Deuterium Labeling Study of Mechanism

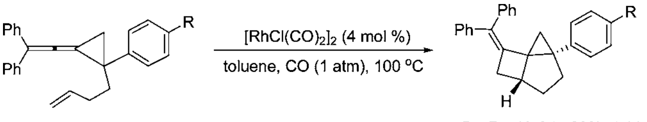


**1f-*d***, 75% D

**2f-*d***, 79% yield, 75% D

To obtain the evidence to support this mechanism, we conducted deuterium labeling experiments (Scheme 3). The labeling experiments were performed by subjecting deuterated substrate **1f**-*d* (75% D at the allylic C5 position) to the standard catalytic system. After the reaction was finished, the resulting deuterated product **2f**-*d* was determined to be in 79% yield along with 75% D contents at both C1 and C5 positions; this observation unambiguously confirms that the complete deuterium transferring in **1f**-*d* into bicyclo[5.1.0]-octylene, **2f**-*d*, via the Rh(I) complex catalyzed C−H activation does occur under the present catalytic condition.

**Scheme 4.** $[RhCl(CO)_2]_2$-Catalyzed Reaction Performed in Toluene



**1a** or **1f**

**5a**, R = H, 3 h, 29% yield;
**5f**, R = Br, 2 h, 24% yield.

To further confirm that MeCN acts as the ligand to Rh(I) metal center and plays a crucial role for the present $[RhCl(CO)_2]_2$-catalyzed intramolecular ene reaction, we next performed the reactions of diphenylvinylidenecyclopropane **1a** and **1f** under the standard conditions solely in toluene without the use of acetonitrile. Surprisingly, the reaction

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proceeded along another direction (Scheme 4), i.e., the corresponding bicyclo[5.1.0]octylene derivatives **2a** and **2f** were not observed. Instead, the intramolecular [2 + 2] cycloaddition reaction[10] took place and gave adducts **5a** and **5f** in chemical yields of 29% and 24%, respectively.

In conclusion, we have established a new efficient catalytic system for an intramolecular ene reaction of allene and alkene of diarylvinylidenecyclopropanes. In this new system consisting of $[RhCl(CO)_2]_2$, toluene, and acetonitrile, MeCN was found to play a crucial role in controlling the reaction toward formation of bicyclo[5.1.0]octylene derivatives (**2b**−**2l**). An alternative system consisting of $[RhCl(CO)_2]_2$ and toluene in the absence of MeCN leads to [2 + 2] cycloaddition adducts (**5a** and **5f**). The structures have been unambiguously determined by X-ray structural analysis. Deuterium labeling experiments were conducted to confirm the mechanism hypothesis. Further efforts on the scope and mechanistic details of this reaction are currently ongoing in our laboratories. Meanwhile, the intramolecular [2 + 2] cycloaddition and Pauson−Khand reaction of diarylvinylidenecyclopropanes under similar conditions will also be systematically investigated in the near future.

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**Supporting Information Available:** $^{13}C$ and $^{1}H$ NMR spectroscopic and analytic data for **1a**−**1l**, **2a**−**2l**, **3**, **4**, **5a**, and **5f**, as well as the X-ray crystal data of **2g**, **3**, and **5f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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