

Rh(I)-Catalyzed Intramolecular [3 + 2] Cycloaddition of *trans*-Vinylcyclopropane-enes

Lei Jiao, Siyu Ye, and Zhi-Xiang Yu*

Beijing National Laboratory for Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China

Received February 4, 2008; E-mail: yuzx@pku.edu.cn

Developing methods to synthesize five-membered carbocycles has been intensively pursued by the synthetic community.¹ One spectacular achievement in this regard is witnessed by many [3 + 2] cycloadditions between various three-carbon and two-carbon components.² Among these three-carbon synthons, cyclopropane, a highly strained ring system expected to act as an efficient two-electron three-carbon synthon, has attracted tremendous attention. To date, various cyclopropane derivatives substituted with a wide range of activating functional groups have been successfully used in [3 + 2] cycloadditions.^{1c} For example, cyclopropyl ketones^{2g,h} and alkylidenecyclopropanes^{2j} have been shown to participate in several transition-metal catalyzed [3 + 2] cycloadditions. In contrast, vinylcyclopropanes (VCP) are less employed in the transition-metal catalyzed [3 + 2] cycloaddition, possibly because of the preference of VCP to act as a five-carbon component in the [5 + x] cycloadditions.³ Previous reports of VCPs as three-carbon units are only limited to those with one or two electron-withdrawing activating groups on the cyclopropane ring.⁴ Therefore, discovering new cycloaddition reactions in which unactivated VCP acts as a three-carbon unit will advance the cyclopropane chemistry. Herein, we wish to report a novel and unexpected Rh(I)-catalyzed intramolecular [3 + 2] cycloaddition of unactivated VCP-ene for the construction of bicyclic five-membered rings, where VCPs act as three-carbon synthons.

We recently demonstrated that ene-vinylcyclopropane (ene-VCP), which has an alkene tethered to the vinyl position of VCP, undergoes a Rh(I)-catalyzed two-component [(5 + 2) + 1] cycloaddition with CO to furnish bicyclic cyclooctenones (Scheme 1).⁵ We envisioned that, it might be an interesting extension to employ a new type of substrate, VCP-ene, which has an alkene tethered to the cyclopropane ring of VCP, in the [(5 + 2) + 1] cycloaddition to construct a bridged bicyclic cyclooctenone structure (Scheme 1). This hypothesis was tested with tosylamide-tethered VCP-ene **1** under the optimal [(5 + 2) + 1] cycloaddition conditions (0.2 atm CO, [Rh(CO)₂Cl]₂ as catalyst, dioxane as solvent, 80 °C).⁵ However, instead of the expected bridged [(5 + 2) + 1] cycloadduct, a symmetric bicyclic 5,5-ring compound **2** was obtained (Table 1), which was speculated to be generated via a [3 + 2] cycloaddition between alkene and cyclopropane moieties without incorporation of CO and the vinyl group of VCP.

Realizing that this unexpected result represents an important example where unactivated VCP participates in the [3 + 2] cycloaddition as a three-carbon component, we decided to further develop this reaction to a practical synthetic approach to bicyclic five-membered ring systems. We systematically optimized the reaction conditions for this new [3 + 2] cycloaddition using substrate **1**. It was found that, even under higher CO pressure, no CO-incorporated product was detected and only [3 + 2] cycloadduct **2** was obtained (Table 1, entry 2). Without CO atmosphere, the [3 + 2] reaction proceeded well (Table 1, entry 3). Wilkinson's catalyst could also catalyze this reaction, but was less efficient (Table 1, entries 4 and 5). Toluene as solvent was found to be better than 1,4-dioxane, producing cycloadduct **2** in 83% yield (Table 1, entry 6). Notably, Rh(I)⁺ species (generated through [Rh(CO)₂Cl]₂ + AgOTf) as catalyst was proved to be more active

Scheme 1

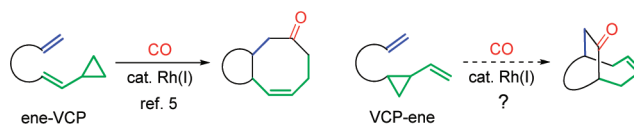


Table 1. Optimization Studies on the [3 + 2] Cycloaddition^a

entry	CO (atm)	catalyst (mol %)	T (°C)	solvent	T (h)	yield (%) ^b
1	0.2 ^c	5% [Rh(CO) ₂ Cl] ₂	80	dioxane	23	59
2	1.0	5% [Rh(CO) ₂ Cl] ₂	80	dioxane	17	28 ^d
3	0	5% [Rh(CO) ₂ Cl] ₂	80	dioxane	17	77
4	0	10% RhCl(PPh ₃) ₃	80	dioxane	23	13 ^d
5	0	10% RhCl(PPh ₃) ₃ + 10% AgOTf	80	dioxane	23	21 ^e
6	0	5% [Rh(CO) ₂ Cl] ₂	110	toluene	5.5	83
7	0	5% [Rh(CO) ₂ Cl] ₂ + 10% AgOTf	50	toluene	10	62

^a Racemic VCP-ene **1** was used. ^b Isolated yields. ^c Reaction run with 0.2 atm CO + 0.8 atm N₂. ^d Recovered 52% of **1**. ^e Recovered 31% of **1**.

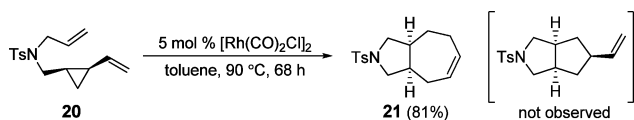
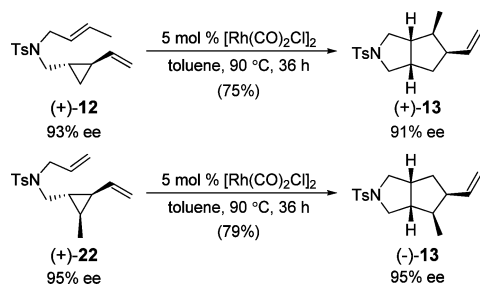
and thus allow the reaction to run at lower temperature (Table 1, entry 7). In all cases, the [3 + 2] cycloadduct **2** was obtained as a single diastereomer. When ene-cyclopropane **3** was submitted to the optimized conditions, the [3 + 2] cycloaddition could not occur and the substrate remained intact, highlighting the importance of the vinyl substitution in the [3 + 2] cycloaddition (Table 1).

A series of VCP-ene substrates was tested under the optimized reaction conditions to explore the substrate scope of this [3 + 2] cycloaddition (Table 2). The results indicated that this cycloaddition reaction is tolerant of different substitution on the VCP and ene moieties. Alkyl and aryl substituents on the vinyl functionality of VCP furnished the corresponding [3 + 2] cycloadducts in moderate to good yields (Table 2, entries 1 to 4). Alkyl substituent on ene moiety gave the cycloadduct with an additional stereocenter (Table 2, entry 5), and methyl substitution on cyclopropane moiety provided a similar cycloadduct (Table 2, entry 6). Bicyclic cycloadduct with a quaternary carbon could also be produced in a good yield from 1-methyl-substituted VCP-ene **16** (Table 2, entry 7). Interestingly, VCP-ene **18** with a special bicyclic VCP moiety afforded a linear-triquinane-like tricyclic [3 + 2] cycloadduct **19** in a good yield (Table 2, entry 8). Other tether in VCP-ene substrate, such as ether functionality, is also tolerated in this [3 + 2] cycloaddition (Table 2, entry 4). However, the VCP-ene substrates with an internal substitution on the ene moiety, an elongated tether (for 6,5-ring formation), or a carbon-tether failed to undergo the [3 + 2] cycloaddition.

Reaction of *cis*-substituted VCP-ene **20** was examined to see whether its [3 + 2] cycloaddition would produce a cycloadduct with

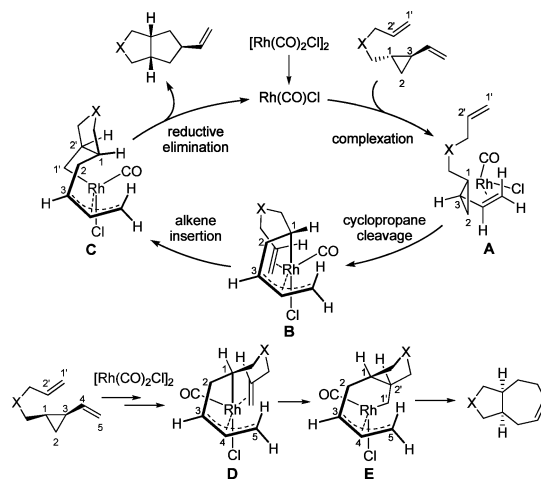
Table 2. Rh(I)-Catalyzed [3 + 2] Cycloaddition Reactions^a

substrate	condition	cycloadduct (yield)	substrate	condition	cycloadduct (yield)					
	A 110 °C 8 h			A 90 °C 32 h						
	A 110 °C 8 h			A 90 °C 26 h		B 30 °C 13 h			B 30 °C 41 h	
	B 30 °C 38 h			A 80 °C 24 h	<p>^a Racemic substrates were used. Condition A: 5 mol % [Rh(CO)₂Cl]₂ as catalyst, toluene as solvent, substrate concentration 0.025 M. Condition B: 5 mol % [Rh(CO)₂Cl]₂ + 10 mol % AgOTf as catalyst, toluene as solvent, substrate concentration 0.025 M. Isolated yields are reported. ^b Confirmed by X-ray crystallographic analysis. ^c dr = 7:1.</p>					

Scheme 2. Reaction of a *cis*-VCP-ene**Scheme 3.** Chirality Transfer in the [3 + 2] Cycloaddition

different stereochemistry (Scheme 2). To our surprise, *cis*-VCP-ene **20** did not afford the expected [3 + 2] cycloadduct; instead, a *cis*-fused 5,7-bicyclic compound **21** was obtained in 81% yield, which was supposed to be generated via a [5 + 2] cycloaddition. This indicated that the [3 + 2] cycloaddition is limited to *trans*-VCP-enes. Enantiomerically enriched VCP-enes (+)-**12** and (+)-**22** were also submitted to cycloaddition conditions. The corresponding [3 + 2] cycloadducts, (+)-**13** and (–)-**13** were obtained in optically active form (Scheme 3). The preservation of the enantiomeric excess in the products demonstrated complete chirality transfer in the present [3 + 2] cycloaddition.

A rationalization of [3 + 2] and [5 + 2] cycloadditions is given in Scheme 4. For the *trans*-VCP-ene substrate, the catalytic cycle starts with complexation of Rh(CO)Cl with the substrate to give complex **A**, followed by cyclopropane ring cleavage at C1–C3 to give a π -allyl Rh(III) intermediate **B** (Scheme 4).⁶ After *cis* insertion of the complexed alkene to Rh–C1 bond to form intermediate **C**, reductive elimination occurs to form the C1'–C3 bond, furnishing the [3 + 2] cycloadduct. It is important to point out that the *trans* configuration of VCP in the starting material makes the alkene chain stay at the opposite side of the π -allyl moiety, leading to a favored reductive elimination of the two proximal carbons, C1' and C3. However, when *cis*-VCP-ene is employed, intermediates **D** and **E** will be sequentially formed,

Scheme 4. Plausible Mechanism of the [3 + 2] Cycloaddition

where C1' and C5 are in close proximity. Thus, the final reductive elimination leads to the formation of C1'–C5 bond to produce the [5 + 2] cycloadduct, instead of the unfavorable formation of C1'–C3 bond to give the [3 + 2] cycloadduct.

In conclusion, we have described the first examples of an Rh(I)-catalyzed intramolecular [3 + 2] cycloaddition of VCP-enes, demonstrating that vinylocyclopropanes without electron-withdrawing activation groups can act as three-carbon synthons in transition-metal catalyzed cycloadditions. The present methodology provides an efficient and diastereoselective approach to fused five-membered ring systems. Further studies of this reaction (scope, mechanism, and application) are underway.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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