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Communication

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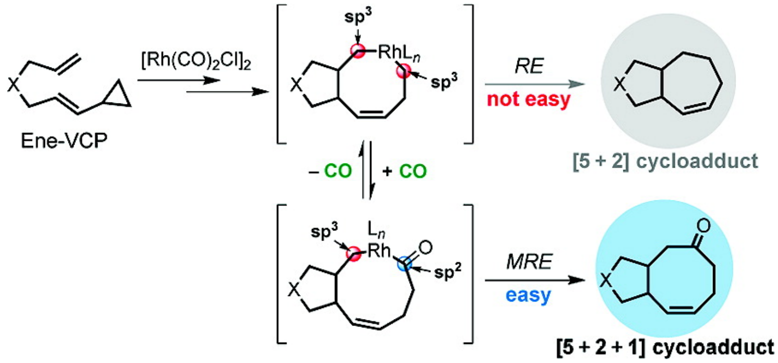

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COMMUNICATIONS

A Computationally Designed Rh(I)-Catalyzed Two-Component [5+2+1] Cycloaddition of Ene-vinylcyclopropanes and CO for the Synthesis of Cyclooctenones

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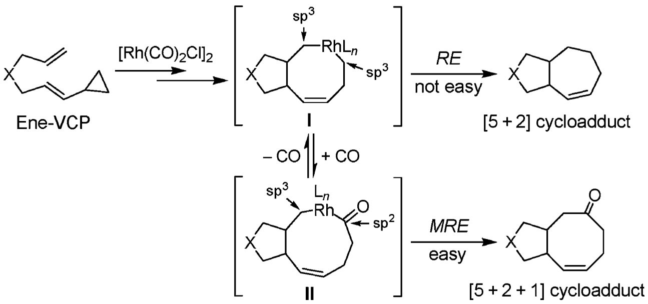
The design or discovery of new reactions for the synthesis of eight-membered rings has been stimulated by their occurrence in molecules of biomedical importance (e.g., taxol), ligands for catalysis (e.g., COT, COD), and precursors for natural products and novel materials (e.g., polyacetylenes).[1] The main difficulty encountered in the synthesis of eight-membered rings is the co-occurrence of unfavorable entropic and enthalpic factors associated with ring closure.[1] Several transition-metal-catalyzed cycloadditions[2] have been introduced in recent years to address this problem including Ni-, Rh-, or Ru-complex catalyzed [4+4], [6+2], [5+2+1], and [4+2+2] cycloadditions.[3] Herein we report a computationally designed and experimentally verified, new two-component [5+2+1] cycloaddition of tethered ene-vinylcyclopropanes (ene-VCPs) and CO that provides for the synthesis of ring-fused cyclooctenones, a ring system encountered in numerous natural products, non-natural targets, and their precursors (Scheme 1).

Our method is based on work from the Wender laboratory leading to the first metal-catalyzed [5+2] cycloadditions between vinylcyclopropanes and 2-π components (such as alkynes, alkenes, and allenes) which afford seven-membered ring cycloadducts.[4] $[Rh(CO)_2Cl]_2$ was found to be an especially effective and versatile catalyst for this and many related cycloadditions.[5] Importantly, however, the intramolecular [5+2] cycloaddition of ene-VCPs has not been realized using $[Rh(CO)_2Cl]_2$ as catalyst,[4b] even though this transformation can be achieved with $RhCl(PPh_3)_3$ or $[(arene)Rh(COD)]SbF_6$ catalyst.[4c]

We speculated that the failure of $[Rh(CO)_2Cl]_2$ to catalyze the [5+2] cycloaddition of ene-VCPs (relative to yne-VCPs and allenyl-VCPs) could be attributed to the reductive elimination (RE) step in the catalytic cycle (Scheme 1).[6] The RE step in the intramolecular [5+2] cycloaddition of ene-VCP would lead to the formation of an $(sp^3)C{-}C(sp^3)$ bond. However, it is known that this kind of RE reaction is not facile when compared to the migratory reductive elimination (MRE) of an $(sp^2)C{-}M{-}C(sp^3)$ subunit for the formation of an $(sp^2)C{-}C(sp^3)$ bond.[6,7] We hypothesized that raising the reaction temperature or extending the reaction time of the $[Rh(CO)_2Cl]_2$ catalyzed intramolecular [5+2] cycloaddition of an ene-VCP could enable this reaction to occur, if no side reactions compete (hypothesis A). We further hypothesized that the putative intermediate **I** (Scheme 1), whose RE to the [5+2] product is disfavored, would in the presence of CO be converted to intermediate **II**, whose MRE to a [5+2+1] cycloadduct would be favored by the formation of an $(sp^2)C{-}C(sp^3)$ bond (hypothesis B).

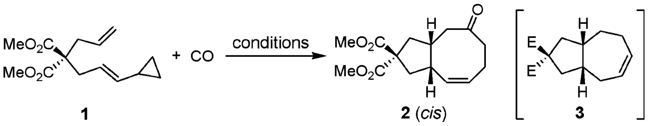
Scheme 1. Rationale for the Two-Component [5+2+1] Reaction



Before testing our hypotheses experimentally, we computed the energies for the RE, the CO insertion, and MRE steps shown in Scheme 1 ($X = CH_2$) using the B3LYP method.[8] The activation energies of the RE steps are about 25−30 kcal/mol, whereas the CO insertion and MRE steps have activation energies of about 13−14 and 23−24 kcal/mol, respectively, suggesting that the [5+2+1] path would be favored over the [5+2] path and the dominant product would be the [5+2+1] cycloadducts.[8]

Encouraged by the above preliminary calculations, we began our experimental test. We observed that, in the absence of CO, the $[Rh(CO)_2Cl]_2$ catalyzed (10 mol %) reaction of ene-VCP substrate **1** at 110 °C did indeed give a double-bond-isomerized [5+2] cycloadduct **3** in 59% isolated yield, together with 10% of the

Table 1. Optimization Studies of the [5+2+1] Cycloadditions



entry	CO [atm]	catalyst [mol %]	T [°C]	solvent	concn [M]	t [h]	yield [%]
1	0	10% $[Rh(CO)_2Cl]_2$	110	toluene	0.05	24	10[a]
2	1	5% $[Rh(CO)_2Cl]_2$	80	dioxane	0.05	5	44[b]
3	4	5% $[Rh(CO)_2Cl]_2$	80	dioxane	0.05	24	8
4	0.2[c]	5% $[Rh(CO)_2Cl]_2$	80	dioxane	0.05	5	70[d]
5	0.2	5% $[Rh(CO)_2Cl]_2$	60	dioxane	0.05	48	17
6	0.2	5% $[Rh(CO)_2Cl]_2$	90	dioxane	0.05	5	70
7	0.2	5% $[Rh(CO)_2Cl]_2$	100	dioxane	0.05	5	61
8	0.2	5% $[Rh(CO)_2Cl]_2$	80	DCE	0.05	5	62[e]
9	0.2	5% $[Rh(CO)_2Cl]_2$	80	toluene	0.05	12	14
10	0.2	5% $[Rh(CO)_2Cl]_2$	80	dioxane	0.01	5	68
11	0.2	5% $[Rh(CO)_2Cl]_2$	80	dioxane	0.20	5	34
12	0.2	10% $[Rh(CO)_2Cl]_2$	80	dioxane	0.05	5	72
13	1	10% $RhCl(PPh_3)_3$	80	dioxane	0.05	17	N.R.
14	1	10% $RhCl\ (PPh_3)_3$ + 10% AgOTf	80	dioxane	0.05	18	23[f]
15	1	5% $[Rh(CO)_2Cl]_2$ + 10% AgOTf	80	dioxane	0.05	13	7

[a] Accompanied with a [5+2] cycloadduct **3** (59%); see Supporting Information for details. [b] Cis/trans = 5:1. [c] Conditions: 0.2 atm CO + 0.8 atm N_2. [d] Cis/trans > 20:1. [e] Cis/trans = 4:1. [f] Cis/trans = 1:1.

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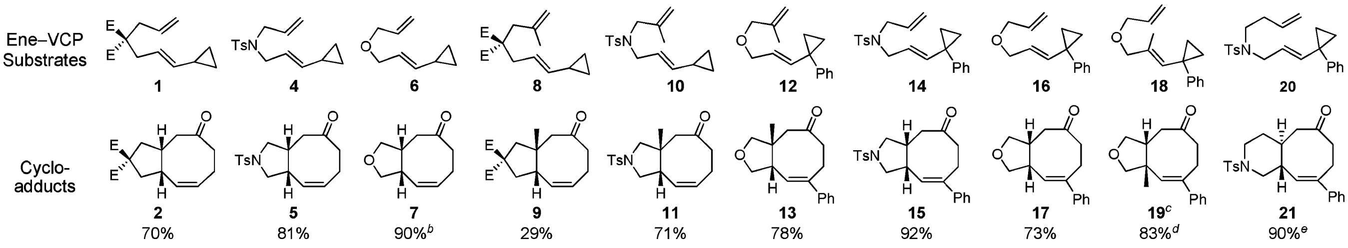
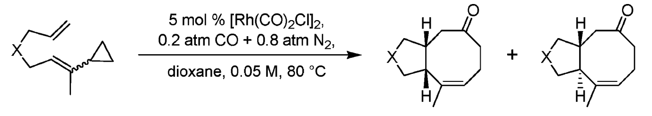
Table 2. Rh(I)-Catalyzed [5+2+1] Cycloaddition Reactions of Ene-vinylcyclopropane Substrates and CO[a]



Ene–VCP Substrates	**1**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**
Cyclo-adducts	**2** 70%	**5** 81%	**7** 90%[b]	**9** 29%	**11** 71%	**13** 78%	**15** 92%	**17** 73%	**19**[c] 83%[d]	**21** 90%[e]

[a] E = CO_2Me. Isolated yields were reported unless otherwise indicated. [b] GC yield. Isolated yield is 44% owing to the volatility of the product. [c] Confirmed by X-ray analysis. [d] A [5+2] product was obtained in 11% yield. [e] Combined yield of diastereomers (trans/cis = 5:1).

Scheme 2



X = $C(CO_2Me)_2$	**23a** (*cis*)	**23b** (*trans*)[a]
22 (*E*/*Z* = 3:1)	16%	50%
24 (*E*/*Z* = 1:3)	52%	17%
X = NTs	**26a** (*cis*)[a]	**26b** (*trans*)
25 (*E*/*Z* = 3:1)	15%	44%
27 (*E*/*Z* = 1:3)	31%	10%

[a] Confirmed by X-ray analysis.

[5+2+1] cycloadduct **2** in which the carbonyl group comes from the CO ligand of the $[Rh(CO)_2Cl]_2$ catalyst (Table 1, entry 1). This result supported our hypothesis A that [5+2] ene-VCP cycloadditions can be achieved when the reaction temperature is increased. We then turned our attention to promoting the [5+2+1] cycloaddition. Gratifyingly, substrate **1** in the presence of CO (balloon, 1 atm) and 5 mol % $[Rh(CO)_2Cl]_2$ catalyst in dioxane, gave after 5 h at 80 °C the [5+2+1] cycloadduct, cyclooctenone **2** (cis/trans = 5:1), in 44% isolated yield (entry 2). We then systematically optimized the reaction conditions for this new [5+2+1] cycloaddition using substrate **1**. Comparison of the reactions in entries 2 to 12 suggested that the optimal conditions for the [5+2+1] cycloaddition were the use of a substrate concentration of 0.05 M, 5 mol % $[Rh(CO)_2Cl]_2$ catalyst, CO (delivered by balloon admixed with N_2 in the ratio of 1:4 at a pressure of 1 atm),[9] dioxane as solvent, and a reaction temperature of 80−90 °C (entries 4 and 6). Under these conditions, substrate **1** gave the cis-fused [5+2+1] cycloaddition product **2** as a single diastereomer. Other Rh(I) catalysts such as Wilkinson's complex and the cationic rhodium(I) catalysts were found ineffective for the [5+2+1] cycloaddition (entries 13, 14, and 15).

With the above optimal conditions in hand, we studied the Rh(I)-catalyzed [5+2+1] cycloadditions of diverse substrates (Table 2). The results indicate that the cycloaddition reactions are tolerant of tethers incorporating geminal diester, sulfonamide, and ether functionalities. Comparison of reaction yields of substrates with different tethers shows that heteroatom substitution in the tether results in higher yields of [5+2+1] cycloadducts. This [5+2+1] cycloaddition also tolerates methyl substitution on the alkene (substrates **8**, **10**, and **12**) and the VCP (substrates **18**, **22**, **24**, **25**, and **27**). Phenyl substitution of the cyclopropane leads efficiently to the [5+2+1] cycloadducts **13**, **15**, **17**, and **19**. In addition to the 5/8-ring system, the trans-fused 6/8-ring system can also be efficiently established in the cycloaddition reaction from **20** to **21**, albeit with decreased diastereoselectivity. It is noteworthy as well that the *E*/*Z* geometry of the C═C bonds in the VCP moieties of ene-VCPs affects the cis/trans stereochemistry of the bicyclic products (Scheme 2). In addition to its synthetic merit, this has mechanistic implications suggesting that the starting alkene geometry is conserved through the multistep pathway.

In conclusion, a new Rh(I)-catalyzed [5+2+1] cycloaddition has been designed computationally and verified experimentally. This study provides a flexible, convenient, and efficient method for constructing bicyclic cyclooctenones. The reaction proceeds in good to excellent yields with a variety of tether types and substitution patterns and allows for the preparation of 5/8- and 6/8-fused ring systems even those containing quaternary centers. Further studies of this reaction (scope, mechanism, and stereochemistry) and its synthetic applications to natural products are being pursued.

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Supporting Information Available: Computational and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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