

Rhodium(I)-Catalyzed [2+2+1] Cycloadditions of 1,3-Dienes, Alkenes, and CO

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“Rhodium(I)-Catalyzed [2+2+1] Cycloadditions of 1,3-Dienes, Alkenes, and CO” Paul A. Wender, Mitchell P. Croatt, Nicole M. Deschamps Journal of the American Chemical Society 2004, 126, 5948-5949; <http://pubs.acs.org/doi/abs/10.1021/ja0489487>

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Abstract:

The evolution of organic synthesis relies heavily on the design and discovery of new reactions that generate structural complexity and value with step economy.¹ Toward this end, we previously reported studies on new [4+4],² [4+2],³ [5+2],⁴ and [6+2]⁵ cycloadditions and novel three-component [2+2+1],⁶ [4+2+1],⁶ and [5+2+1]⁷ reactions.⁸ In the course of our studies on the Rh-(I)-catalyzed dienyl Pauson-Khand [2+2+1] reaction, we observed that diene-ynes react significantly faster than alkene-ynes to produce cyclopentenone products. This enhanced reactivity suggests that dienes might be used instead of alkynes to effect a [2+2+1] reaction with simple alkenes and CO. Conventional Pauson-Khand reactions and more recent catalyzed variants have been limited almost exclusively to the use of alkynes as one of the two carbon components.^{9,10} Bis-alkenes do not undergo this three-component reaction, although useful alternative two-step stoichiometric processes have been reported in which a preformed metallacycle is converted with CO to a cyclopentanone.¹¹ We report herein the first examples of a metal-catalyzed [2+2+1] reaction involving a diene, an alkene, and CO.¹²

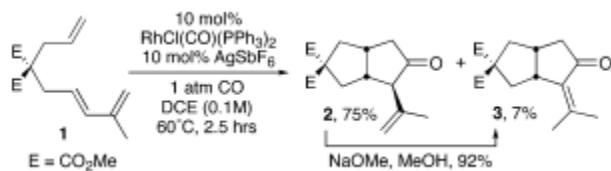
Keywords: organic synthesis

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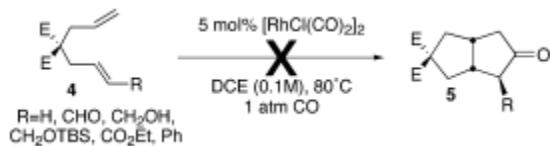
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Scheme 1. The Catalyzed [2+2+1] Reaction of Diene-ene 1



Diene-ene **1** (Scheme 1), readily available through alkylation of dimethyl allylmalonate, was selected as an initial test substrate. When treated with 10 mol % RhCl(CO)(PPh₃)₂ and AgSbF₆ under CO (1 atm), **1** was smoothly converted to the [2+2+1] products **2** and **3**, each a single diastereomer, in a combined yield of 82%. Control experiments have shown that **3** arises from the isomerization of **2** under the reaction conditions and is produced exclusively by treatment of **2** with sodium methoxide in methanol.

Scheme 2. The Control Reactions of Bis-enes



The presence of the diene moiety is crucial for the success of this process. In accord with previous studies,^{6,9,10} simple bis-enes **4** (Scheme 2), even those incorporating a coordinating heteroatom or conjugation to a phenyl group, failed to give [2+2+1] products under conditions thus far found to be optimum for the [2+2+1] reaction of diene-enes.

Exploration of the efficiency and scope of this novel process started with a screen of catalysts (Table 1). [RhCl(CO)₂]₂ (entry 6) has thus far been found to be the best catalyst for this process, producing **2** in the highest yield and with the best selectivity. It is noteworthy that [(COD)Rh(naph)]SbF₆^{4c} produces only the [4+2] product **6** (entry 3), indicating that the course of the reaction ([2+2+1] versus [4+2]) can be controlled by catalyst type.¹³

Table 1. Effect of Catalyst Variations on the Reaction of 1

entry	catalyst (10 mol % Rh)	<i>t</i> (h)	isolated yield (%)			
			1	2	3	6
1	RhCl(CO)(PPh ₃) ₂	38	80	<1	<1	—
2	above with AgSbF ₆	2.5	—	75	7	—
3	[(COD)Rh(naph)]SbF ₆	3	—	—	—	76
4	[RhCl(dppb)] ₂	45	5	61	29	—
5	[RhCl(BINAP)] ₂	41	—	73	15	—
6	[RhCl(CO) ₂] ₂	5.5	5	90	5	—

Table 2. Effect of Reaction Condition Variations on the Reaction of 1^a

entry	solvent ^b	<i>T</i> (°C)	conc (M)	CO (atm)	<i>t</i> (h)	yield (%) ^c	
						2	3
1 ^d	DCE	60	0.1	1	5.5	90	5
2 ^e	toluene	60	0.1	1	50	<1	<1
3	TFE	60	0.1	1	37	28	4
4 ^f	dioxane	60	0.1	1	47	—	—
5	DCE	80	0.1	1	3	94	5
6	DCE	80	0.1	1	23	74	25
7	DCE	80	0.5	1	2.5	85	3
8	none	80	neat	1	1.75	81	8
9 ^g	DCE	80	0.1	0.5	8.5	74	4
10	DCE	80	0.1	2	3	91	6

^a [RhCl(CO)₂]₂ (5 mol %). ^b DCE) 1,2-dichloroethane, TFE) 2,2,2-trifluoroethanol. ^c Isolated yield. ^d 5% 1 was recovered. ^e 98% 1 was recovered. ^f 52% 1 was recovered. ^g 5% 6 was obtained.

Table 3. Substrate Scope of the Diene-ene [2+2+1] Reaction^a

entry	substrate	t (h)	product, isolated yield
1		3.8	8, 84% ^{b,c}
2		3	2, 94%
3		22	10, 0% 11, 71% ^d
4		23	13, 92% —
5		3.5	15, 93% —
6		3	17, 84% —
7		48	19, 89% —
8		48	— —
9		48	22, 28% ^e —
10	 10 + 2 equiv 52 —		23, 73% —

^a 5 mol % [RhCl(CO)2]2, CO (1 atm), DCE (0.1 M), 80 °C, unless otherwise noted. ^b 89% when run on 3.6 mmol scale with 2.5 mol % [RhCl(CO)2]2. ^c 83% yield when run neat. ^d Crude reaction contained a (4.5:1) mixture of 10 and Z-11. Upon purification, a (1.2:1) mixture of E-11 and Z-11 was obtained. ^e 10 mol % RhCl(CO)(PPh3)2, 10 mol % AgSbF6, 60 °C.

The effects of solvent, temperature, reaction time, concentration, and CO pressure variations on the efficiency of the reaction are summarized in Table 2. Of the solvents surveyed (entries 1-4), DCE gave the best yield. A temperature increase to 80 °C also proved beneficial, affording a 99% combined yield of **2** and **3** (entry 5). Prolonged reaction times led to an increase in isomerization, producing a 3:1 ratio of **2** and **3** (entry 6). Increasing the concentration to 0.5 M resulted in a slight decrease in yield (entry 7). Remarkably, when the reaction was conducted *without solvent* (the least atom economical component of most reactions), the product was obtained in an 89% yield (entry 8). Decreasing the CO pressure to 0.5 atm resulted in a slower reaction, a slightly lower yield of **2** and **3**, and the formation of **6** in 5% yield (entry 9), whereas increasing the CO pressure to 2 atm had no significant effect (entry 10).

Using the optimized conditions (Table 2, entry 5), the scope of the reaction with respect to substitution of the diene and alkene, the presence of heteroatoms, and tether length was investigated (Table 3). Substitution at the 2 position of the diene gave excellent yields of the corresponding alkenyl cyclopentanones (entries 1-3). Although on the scale of our exploratory studies (e1 mmol) catalyst loading was difficult to optimize fully, an increase in scale to 3.6 mmol (1 g) allowed for a decrease in catalyst loading to 2.5 mol % (entry 1). Further substitution

of the alkene portion was well tolerated, allowing for the diastereoselective and efficient formation of cycloadduct **13** incorporating a quaternary center and three contiguous stereocenters (entry 4). Diene-ene substrates incorporating heteroatoms in the tether reacted efficiently to produce heterobicyclic compounds in excellent yields (entries 5 and 6). In addition to its application to bicyclo[3.3.0] systems, this method can be extended to the synthesis of bicyclo[4.3.0] systems, such as **19** (89% yield, entry 7). Attempts to produce the bicyclo[5.3.0] system have thus far been unsuccessful. Substitution at diene positions 1 and 3 resulted in the formation of multiple products (entry 8) and only a moderate yield of the [2+2+1] product (entry 9). Significantly, this reaction can be carried out intermolecularly, as demonstrated in the efficient and diastereoselective conversion of norbornene, 2,3-dimethylbutadiene, and CO to **23** (entry 10).

In summary, initial examples of a metal-catalyzed [2+2+1] reaction of dienes, alkenes, and CO are described. This process allows for the facile, efficient, and diastereoselective construction of a variety of alkenyl cyclopentanones with the formation of three stereocenters. Further studies on the role of the diene in this and related processes are in progress.

Acknowledgment. This research was supported by a grant (CHE-9800445) from the National Science Foundation. Highresolution mass spectra were provided by the University of California, San Francisco. Fellowship support from Eli Lilly and Co. (N.M.D.) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data for **2**, **3**, **8**, **11**, **13**, **15**, **17**, **19**, **22**, and **23**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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