

Transition Metal-Catalyzed [6+2] Cycloadditions of 2-Vinylcyclobutanones and Alkenes: A New Reaction for the Synthesis of Eight-Membered Rings

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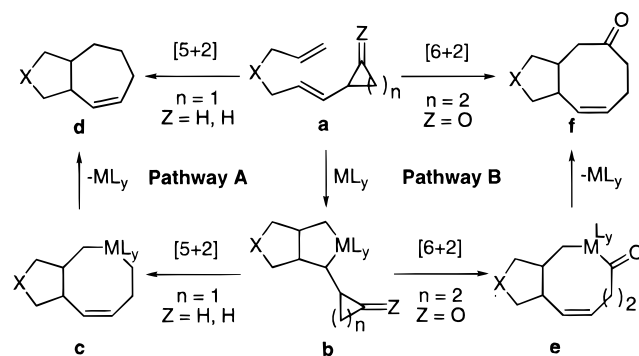
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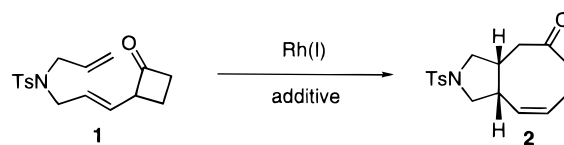
We previously reported the first examples of the transition metal-catalyzed intramolecular [4+4] cycloaddition of bis-dienes,¹ the transition metal-catalyzed intramolecular [4+2] cycloaddition of dienes with alkynes² or allenes,³ and the transition metal-catalyzed [5+2] cycloaddition of vinylcyclopropanes and π -systems,⁴ reactions which in the absence of catalysts are forbidden or require forcing conditions. Collectively, these reactions⁵ can be considered to proceed by the initial formation of a five-membered metallacycle. When flanked by a strained cyclopropane as is the case in the [5+2] cycloaddition (Scheme 1, pathway A), this intermediate (**b**) would undergo ring expansion to an eight-membered metallacycle **f** from which a seven-membered ring product **d** would be derived.⁶ We now report that replacement of the cyclopropane with a strained cyclobutane moiety provides a new reaction for the formation of eight-membered rings⁷ involving the transition metal-catalyzed [6+2] cycloaddition of vinylcyclobutanones and alkenes (Scheme 1, pathway B).

Our initial attempts to effect the [6+2] cycloaddition with simple vinylcyclobutanones (e.g., Scheme 1, **a**: X = O, Z = H,H, $n = 2$) were unsuccessful. The substrates were either unreactive

Scheme 1



Scheme 2^a



^a Ts = *p*-CH₃C₆H₄SO₂.

Table 1. Cycloaddition of 2-Vinylcyclobutanone **1**^a

entry	mol % [Rh(CO) ₂ Cl] ₂ ^b	concn (M) ^c	time (h)	yield (%) ^d
1	5	0.01	3	92
2	2.5	0.05	6.5	82
3	2.5	0.1	9	48
4	2.5	<0.1 ^e	9	81
5	5	0.5	4	39
	mol % RhCl(PPh ₃) ₃ ^f			
6	10	0.014	3	95
7	5	0.05	7.5	86

^a Reactions were run at 110 °C in PhMe. ^b mol % AgOTf and mol % PPh₃ = 2 × mol % [Rh(CO)₂Cl]₂. ^c Concentration of **1**. ^d Isolated yield of **2**. ^e Slow addition (5.5 h) of substrate **1**. Concentration of substrate is less than [0.1 M]. ^f mol % AgOTf = mol % RhCl(PPh₃)₃.

or complex mixtures were produced. In our previous work on [5+2] cycloadditions of vinylcyclopropanes we found that such reactivity problems can be significantly modulated by substitution of the cyclopropane subunit.⁴ This result combined with the observations of Huffman and Liebeskind⁸ that rhodium inserts efficiently into cyclobutenones suggested that the desired cycloaddition could be achieved through the use of vinylcyclobutanones as the 6-carbon component. This proved to be a key to success. Thus, when vinylcyclobutanone **1** is treated with 5 mol % [Rh(CO)₂Cl]₂, 10 mol % PPh₃, and 10 mol % AgOTf in toluene at 110 °C for 3 h, cyclooctenone **2** is obtained in 92% isolated yield as a single diastereomer (Scheme 2).⁹ The stereochemistry of **2** was assigned on the basis of an X-ray crystal structure of its alcohol reduction product.

Further studies with **1** as a representative substrate revealed that the reaction proceeds most efficiently for substrate concentra-

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(9) In a representative procedure, a solution of the vinylcyclobutanone **1** (0.01 M in dry toluene) is added to an oven-dried, base-washed Schlenk flask. Argon is bubbled through the solution for 10 min at room temperature, then [Rh(CO)₂Cl]₂ (5 mol %), PPh₃ (10 mol %), and AgOTf (10 mol %) are added sequentially. Argon is bubbled through the mixture for an additional 10 min. The resulting solution is heated at 110 °C for 3 h. After cooling, the reaction mixture is passed through a plug of neutral alumina and concentrated. Purification by flash chromatography (silica gel, 20% ethyl acetate in pentane) affords cycloadduct **2** in 92% yield as a white solid.

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(6) The path in Scheme 1 is one of several mechanistic hypotheses for this transformation. See ref 4 for further discussion.

(7) Various types of metal-catalyzed cycloadditions leading to the formation of eight-membered rings are described in the literature: including [2+2+2+2], [4+2+2], [4+4], and [6+2] cycloadditions. For examples and lead references, see: [2+2+2+2]: Boussie, T. R.; Streitwieser, A. *J. Org. Chem.* **1993**, *58*, 2377–2380. Colborn, R. E.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 5470–5477. Lawrie, C. J.; Gable, K. P.; Carpenter, B. K. *Organometallics* **1989**, *8*, 2274–2276. [4+2+2]: Greco, A.; Carbonaro, A.; Dall'Asta, G. *J. Org. Chem.* **1970**, *35*, 271–274. Lautens, M.; Tam, W.; Sood, C. *J. Org. Chem.* **1993**, *58*, 4513–4515. [4+4]: see ref 1. [6+2]: Feldman, K. S.; Wu, M. J.; Rotella, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 8490–8496. Rigby, J. H.; Kirova, M.; Niyaz, N.; Mohammadi, F. *Synlett* **1997**, 805–806. Rigby, J. H. *Acc. Chem. Res.* **1993**, *26*, 579–585 and references therein. Chaffee, K.; Huo, P.; Sheridan, J. B.; Barbieri, A.; Aistars, A.; Lalancette, R. A.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1995**, *117*, 1900–1907. Chaffee, K.; Sheridan, J. B.; Aistars, A. *Organometallics* **1992**, *11*, 18–19.

Table 2. Rh(I)-Catalyzed [6+2] Cycloaddition Reactions of 2-Vinylcyclobutanone Substrates^d

2-Vinylcyclobutanone Substrates	Cycloadducts, Yield ^a	Reaction Conditions, ^c Time
1: R ₁ =R ₂ =H	2: 95%	A, 3h
3: R ₁ =H, R ₂ =Me	4: 78%	B, 20h
5: R ₁ =Me, R ₂ =H	6: 71%	C, 26h
7:	8: 80% ^b	C, 14h
9: R ₁ =R ₂ =H	10a: 80% (cis) 10b: 6% (trans)	C, 17h
11: R ₁ =H, R ₂ =Me	12a: 77%	D, 20h
13: R ₁ =Me, R ₂ =H	14: 78%	C, 26h
15:	16: 91%	E, 0.75h

^a Isolated yield unless otherwise indicated. ^b Isolated yield as its dinitrophenyl hydrazone derivative. ^c A = 10 mol % RhCl(PPh₃)₃, 10 mol % AgOTf, PhMe (0.014 M), 110 °C. B = 10 mol % RhCl(CO)(PPh₃)₂, 10 mol % AgOTf, PhMe (0.014 M), 110 °C. C = 5 mol % [Rh(CO)₂Cl]₂, 10 mol % P(*n*-Bu)₃, 10 mol % AgOTf, PhMe (0.014 M), 110 °C. D = 5 mol % [Rh(CO)₂Cl]₂, 10 mol % P(*n*-Bu)₃, 10 mol % AgOTf, PhMe (0.010 M), 110 °C. E = 5 mol % [Rh(CO)₂Cl]₂, PhMe (0.010 M), 110 °C. ^d E = CO₂Me; Ts = *p*-CH₃C₆H₄SO₂.

tions of <0.05 M. At higher concentrations, the yield of cycloadduct decreases presumably due to the formation of oligomeric byproducts. This problem can be minimized by slow addition (5.5 h) of the substrate (Table 1, entry 4). Of the solvents studied, toluene is preferred for this reaction. Nitrobenzene (82%), chlorobenzene (72%), 9:1 toluene/dichloromethane¹⁰ (79%), and 9:1 toluene/dichloroethane¹⁰ (84%) can be used but afforded lower yields. Other solvents (e.g., acetonitrile, propanol, chloroform, and ethylene glycol dimethyl ether) gave incomplete conversion even after 18 h. The reaction of substrate **1** with Wilkinson's catalyst in the presence of silver triflate also gave the cycloadduct in high yield (Table 1, entries 6 and 7).¹¹

(10) The cycloaddition was carried out in a sealed tube.

Preliminary studies on the scope of the [6+2] cycloaddition reaction were conducted with substrates selected to investigate tether and substitution effects on the yield of the reaction. As illustrated in Table 2 with substrates **1**, **7**, and **9**, this novel cycloaddition proceeds efficiently with tethers incorporating sulfonamide, ether, and geminal diester functionalities.¹² Rhodium-catalyzed isomerization of the alkene, a potential competing reaction, is not observed. Methyl substitution of either alkene is also tolerated as seen for the cycloadditions of substrates **3**, **5**, **11**, and **13**, results that draw significance from the difficulty often encountered in the construction of quaternary centers and the presence of such centers in numerous natural and designed targets. Generally, the rates for methyl-substituted substrates are slower than those for their unsubstituted counterparts.

For substrates **9** and **11**, byproducts of mechanistic significance are also observed. Initially, treatment of **9** with 10 mol % RhCl(PPh₃)₃ and 10 mol % AgOTf in toluene at 110 °C for 19 h gave cyclooctenones **10a** and **10b** (**10a**:**10b** = 8:1) in 73% combined yield. Additionally, a 5,7 fused bicyclic compound (**10c**) was formed in 10% yield (Table 2). This compound is expected to arise through a rhodium(I)-catalyzed decarbonylation reaction involving metallacycle **e** (Scheme 1).⁶ Preliminary attempts to minimize formation of decarbonylated products by conducting the cycloaddition in an atmosphere of CO were not successful. However, this side product can be minimized through the use of 5 mol % [Rh(CO)₂Cl]₂, 10 mol % P(*n*-Bu)₃, and 10 mol % AgOTf in toluene at 110 °C for 17 h. Under these conditions, cycloadducts **10a** and **10b** are obtained in a combined yield of 86% (**10a**:**10b** = 13:1) along with only 8% of the 5,7 fused bicyclic cycloadduct **10c**. Under similar conditions, **11** gave only the cis cycloadduct **12a** in 77% and the decarbonylation product (**12b**) in 17% yield. Thus far, the reaction does not work with alkynes as 2C components, however, as represented in Table 2, allene **15** undergoes efficient cycloaddition to produce novel cycloadduct **16** in 91% yield.

In summary, this study provides the first examples of a flexible and efficient method for the construction of eight-membered-ring systems based on the Rh(I)-catalyzed [6+2] cycloaddition of 2-vinylcyclobutanones and alkenes. The reaction proceeds in good to excellent yields for a variety of tether types. In the cases studied, *cis*-fused products are formed exclusively or preferentially. Substitution of the alkene is tolerated although the reaction rates and yields are lowered. Methyl substitution allows for the preparation of 5–8-membered ring systems containing quaternary centers. Further mechanistic and synthetic studies on this new transition metal-catalyzed cycloaddition are in progress.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for compounds **1–16** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>. JA001483+

(11) Silver triflate is a required additive. It is found to facilitate the cycloaddition, presumably by opening a coordination site on the rhodium through removal of the chloride ligand.

(12) All new compounds were characterized by IR and NMR spectroscopy and provided satisfactory elemental or exact mass analyses.