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First Studies of the Transition Metal-Catalyzed [5+2] Cycloadditions of Alkenes and Vinylcyclopropanes: Scope and Stereochemistry

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As part of our continuing studies of transition metal-catalyzed [m+n] cycloadditions,[1] we recently reported the first examples of rhodium(I)-catalyzed [5+2] cycloadditions between vinylcyclopropanes and alkynes (**a**→**d**).[2] This new class of reactions has been shown to provide convenient access to 5,7-fused ring systems,[3] the commonly encountered bicyclic core of a variety of designed and natural molecules.[4] This reaction was formulated around the expectation that various metal catalysts (ML_n) could be used to mediate the formation of a metallacyclopentene (**b**) from vinylcyclopropanes and various π-systems (**a**).[5] Driven by the strain of the attached cyclopropane ring,[6] this metallacyclopentene intermediate (**b**) would ring expand to a metallacyclooctadiene (**c**) which, upon reductive elimination, would provide the seven-membered cycloadduct (**d**) and regenerate the metal catalyst. An alternative mechanism can be formulated around metallacycle **b′**. This reaction has been shown thus far to work with a wide range of alkynes, including terminal, internal, electron poor, electron rich, and conjugated systems. Prompted by the synthetic and mechanistic importance associated with the use of alkenes in this reaction and the attendant unexplored issues of stereochemistry, we report herein the first examples of rhodium(I)-catalyzed [5+2] cycloadditions between vinylcyclopropanes and alkenes and the first studies of the scope and stereochemistry of these remarkably efficient and selective processes.

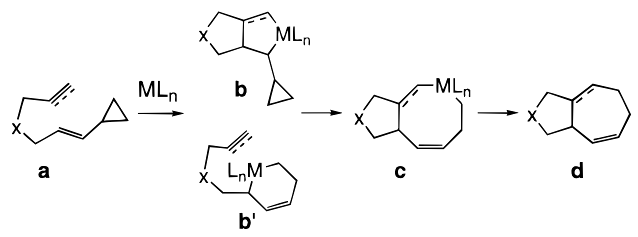
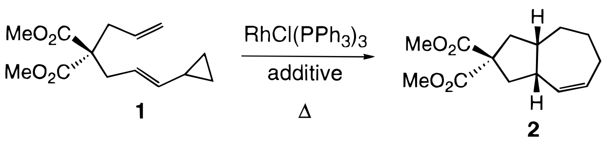


Table 1. Cycloaddition of Ene−Vinylcyclopropane **1**[a]



entry	mol % RhCl(PPh$_3$)$_3$	additive[b]	concn[c] (M)	time (h)	yield[d] (%)
1	0.1	AgOTf	1.0	15	90
2[e]	0.1	AgOTf	1.0	17	86
3	0.1	AgOTf	0.4	17	88
4	1	AgOTf	0.05	5	93
5	5	AgOTf	0.01	2	91
6	10	none	0.005	2.5	91

[a] Reactions were run at 110 °C in PhMe. [b] mol % AgOTf = mol % RhCl(PPh$_3$)$_3$. [c] Concentration of **1**. [d] Isolated yield of **2**. [e] Reaction run on 1 g scale.

Our investigation began with substrate **1** (Table 1).[7] In the presence of a catalyst system derived from 0.1 mol % tris(triphenylphosphine)rhodium(I) chloride and 0.1 mol % silver trifluoromethanesulfonate, ene−vinylcyclopropane **1** (1 g, 4 mmol, 1.0 M in toluene) gave after 17 h at 110 °C cycloadduct **2** in 86% isolated yield as a *single* diastereomer (entry 2).[8] The stereochemistry of cycloadduct **2** was assigned on the basis of the planar symmetry[9] of its hydrogenation product as determined by ^{13}C NMR spectroscopy. The remarkable stereoselectivity of this cycloaddition is consistent with the preferential formation and reaction of a *cis*-fused metallacyclopentane intermediate **b**.

Additional studies of the reaction variables revealed that the cycloaddition of **1** proceeds efficiently with substrate concentra-

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[1] For representative examples, see: [4+4] cycloadditions: Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678. Wender, P. A.; Correia, C. R. D.; Ihle, N. C. *J. Am. Chem. Soc.* **1988**, *110*, 5904. Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089. [4+2] cycloadditions: Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432. Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843. Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1995**, *60*, 2962. Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824.

[2] Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720.

[3] For reviews and lead references on seven-membered-ring syntheses via cycloadditions, see: Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. Herges, R.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 594. Mann, J. *Tetrahedron* **1986**, *42*, 4611. Herges, R. In *Chemical Structures*; Warr, W. A., Ed.; Springer-Verlag: Berlin, 1988; p 385. Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954. Giguere, R. J.; Tassely, S. A.; Rose, M. I. *Tetrahedron Lett.* **1990**, *31*, 4577. Hosomi, A.; Tominaga, Y. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5, p 593. Wender, P. A.; Siggel, L.; Nuss, J. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5, p 645. Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 4895. Trost, B. M.; Yamazaki, S. *Chem. Lett.* **1994**, 2245. Lange, G. L.; Gottardo, C. *Tetrahedron Lett.* **1994**, *35*, 8513. Davies, H. M. L.; Peng, Z.-Q.; Houser, J. *Tetrahedron Lett.* **1994**, *35*, 8939. Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2223. Takeda, K.; Takeda, M.; Nakajima, A.; Yoshii, E. *J. Am. Chem. Soc.* **1995**, *117*, 6400. Schwiebert, K. E.; Stryker, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 8275. Rigby, J. H.; Sugathapala, P.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 8851. Gwaltney, S. L.; Sakata, S. T.; Shea, K. J. *Tetrahedron Lett.* **1995**, *36*, 7177. Barluenga, J.; Aznar, F.; Martin, A.; Vasquez, J. T. *J. Am. Chem. Soc.* **1995**, *117*, 9419. Boger, D. L.; Takahashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12452. Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. Rigby, J. H.; Rege, S. D.; Sandanayaka, V. P.; Kirova, M. *J. Org. Chem.* **1996**, *61*, 842. Molander, G. A.; Eastwood, P. R. *J. Org. Chem.* **1996**, *61*, 1910. Trost, B. M.; Higuchi, R. I. *J. Am. Chem. Soc.* **1996**, *118*, 10094. Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774. Lautens, M.; Aspiotis, R.; Colucci, J. *J. Am. Chem. Soc.* **1996**, *118*, 10930. Harmata, M. *Tetrahedron* **1997**, *53*, 6235.

[4] For reviews and lead references on seven-membered-ring natural products, see: Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 47. Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Pavoac, F.; White, C. T. In *Total Synthesis of Natural Products;* Apsimon, J., Ed.; John Wiley and Sons: New York, 1983; Vol. 5, p 333. Rigby, J. H. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science Publishers B.V.: Amsterdam, 1988; Vol. 12, p 233. Fraga, B. M. *Nat. Prod. Rep.* **1996**, *13*, 307.

[5] The mechanistic pathway presented is intended only to facilitate synthetic application and guide mechanistic analysis. Other mechanisms are possible and await experimental investigation.

[6] For a review on metal-mediated cleavage of cyclopropanes, see: Khusnutidinov, R. I.; Dzhemilev, U. M. *J. Organomet. Chem.* **1994**, 1 and references therein.

[7] Substrate **1** was prepared in 41% yield by alkylation of allyl dimethylmalonate with 3-bromo-1-cyclopropyl-1-propene, which was prepared by the method of Fleming: Ward, S. C.; Fleming, S. A. *J. Org. Chem.* **1994**, *59*, 6476. Details are provided in the Supporting Information.

[8] In a representative procedure, tris(triphenylphosphine)rhodium(I) chloride (0.1 mol %) and silver triflate (0.1 mol %) are added sequentially, each in one batch, to a base-washed, oven-dried Schlenk flask under an argon atmosphere and are dissolved in freshly distilled, oxygen-free toluene (2 mL). The solution is stirred for 5 min at room temperature, after which ene−vinylcyclopropane **1** (1.0 g, 4.0 mmol in 2 mL of toluene) is added over 10 s and the solution is heated to 110 °C for 17 h. After cooling, the reaction mixture is filtered through a plug of alumina and concentrated. HPLC analysis of this mixture indicates that **2** is formed with >99% selectivity. Flash chromatography (silica gel, 5% ethyl acetate in hexane) gives cycloadduct **2** in 86% yield as a colorless oil.

[9] The corresponding hydrogenation product of the trans isomer would exhibit C_2 symmetry.

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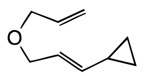
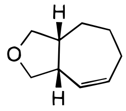
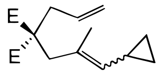
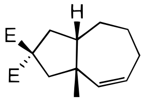
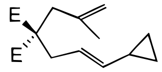
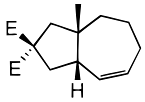
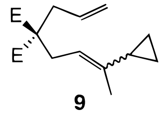
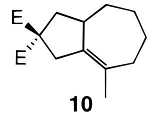
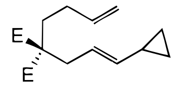
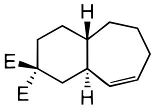
Table 2. Transition Metal-Catalyzed Intramolecular [5+2] Cycloadditions of Vinylcyclopropanes and Alkenes

	Vinylcyclopropane-Alkene[a]	Cycloadduct(s)	Reaction Conditions, Time, Isolated Yield
1.	**1**	**2**	A[b], 17 h 86-93% (see Table 1)
2.	 **3**	 **4**	B[c], 10 h 70% (94% by GC)
3.	 **5**	 **6**	C[d], 1 h 92%
4.	 **7**	 **8**	C[d], 1 h 94%
5.	 **9**	 **10**	D[e], 15 h 78%
6.	 **11**	 **12**	E[f], 5 d 77%

[a] E = CO_2Me. [b] 0.1 mol % $RhCl(PPh_3)_3$, 0.1 mol % AgOTf, $PhCH_3$, 110 °C, 1.0 M. [c] 5 mol % $RhCl(PPh_3)_3$, 5 mol % AgOTf, THF, 65 °C, 0.01 M. [d] 10 mol % $RhCl(PPh_3)_3$, 10 mol % AgOTf, $PhCH_3$, 110 °C, 0.01 M. [e] 5 mol % $RhCl(PPh_3)_3$, 5 mol % AgOTf, $PhCH_3$, 110 °C, 0.01 M. [f] 10 mol % $RhCl(PPh_3)_3$, 10 mol % AgOTf, $PhCH_3$, 100 °C, 0.02 M.

tions ranging from 0.005 to 1.0 M and catalyst loads from 0.1 to 10 mol %, demonstrating catalyst turnovers of up to at least 1000 (Table 1). It is noteworthy that the cycloaddition occurs even with substrate concentrations of up to 5 M, in which case the substrate−solvent ratio is 1:1. However, at high concentrations (>1.0 M), the efficiency of the reaction decreases due to the formation of presumably oligomeric byproducts. Silver triflate is not a required additive, but in this and several other cases it is found to facilitate the reaction, putatively by opening a coordination site on the rhodium through removal of the chloride ligand. As would be expected, a reduction in the amount of catalyst alone leads to longer reaction times. However, when both the amount of catalyst is reduced and the concentration is increased, the reaction proceeds at reasonable rates. The efficiency of the cycloaddition is relatively unaffected by scale over the milligram to gram range studied thus far.

The scope of the cycloaddition reaction was explored with a variety of substrates selected in order to establish the generality of the process and its applicability to commonly encountered synthetic problems (Table 2). In accord with the results obtained with substrate **1**, vinylcyclopropane **3** (entry 2) produced exclusively *cis*-fused cycloadduct **4** in 94% yield by GC and in 70% isolated yield.[10] This result indicates that the cycloaddition is tolerant of heteroatom substitution in the tether and proceeds faster than alkene isomerization, a potentially competing process also mediated by Rh(I) catalysts.[11] The efficiency of this cycloaddition also indicates that the geminal diester substitution in the tether is not required for success. Substrates **5** (*E*:*Z* = 5.5:1) and **7** (entries 3 and 4) were selected for study due to the number of naturally occurring bicyclo[5.3.0]decanes bearing an angular methyl group and due to the general difficulties associated with quaternary center formation.[4] These methyl-substituted substrates (**5** and **7**) reacted rapidly (<1 h) and with high efficiency (>90%) to afford exclusively the *cis*-fused products **6** and **8**, respectively.[12] In these cases, AgOTf is required for clean conversion. In its absence, decomposition occurred more rapidly than cycloaddition. Thus far, we have been unable to effect the cycloaddition of substrates which would lead to cycloadducts bearing two angular methyl groups. Likewise, substrates bearing methyl groups at the alkene terminus did not undergo efficient cycloaddition, reacting instead to form predominantly products arising from β-hydride elimination pathways. In contrast, methyl substitution of the alkene group of the vinylcyclopropane is tolerated, as evidenced by the cycloaddition of **9** (*E*:*Z* = 6.5:1), which provides **10** in 78% yield (entry 5). In this case, the initially produced cycloadduct undergoes a secondary isomerization mediated by the Rh(I) catalyst to produce **10**. Finally, the reaction was also successful for substrates with 4-atom tethers (entry 6), although in this case a longer reaction time is required to offset the less favorable entropy. A single diastereomer with trans stereochemistry is formed, in accord with a *trans*-fused metalla[4.3.0]bicyclic system **b**.

In summary, this study establishes the rhodium-catalyzed intramolecular [5+2] cycloaddition of alkenes as a flexible, efficient, and practical method for the synthesis of seven-membered rings. All cycloadditions proceed in good to excellent yields (70−94%) and produce only one diastereomer. The cycloaddition proceeds even at high concentrations and low catalyst loads, and allows access to polycycles with angular methyl substitution. This procedure not only affords a novel process for seven-membered-ring formation, but also provides the framework and substitution patterns characteristic of many biochemically and medicinally significant natural products and designed analogues. Further efforts on the synthetic scope and mechanism of this reaction are in progress.

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Supporting Information Available: IR, NMR, and mass spec data for compounds **1**−**12** (13 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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[10] The difference in actual yield (by gas chromatography) and isolated yield in this case is principally a consequence of the product volatility.

[11] For representative examples, see: Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224. Gigg, R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 738.

[12] The stereochemistry of these cycloadducts was assigned on the basis of their conversion (hydrogenation) to a common product and the nOe exhibited between the angular methyl and ring junction proton of **8**.