

Transition Metal Catalyzed [5 + 2] Cycloadditions of Vinylcyclopropanes and Alkynes: A Homolog of the Diels–Alder Reaction for the Synthesis of Seven-Membered Rings

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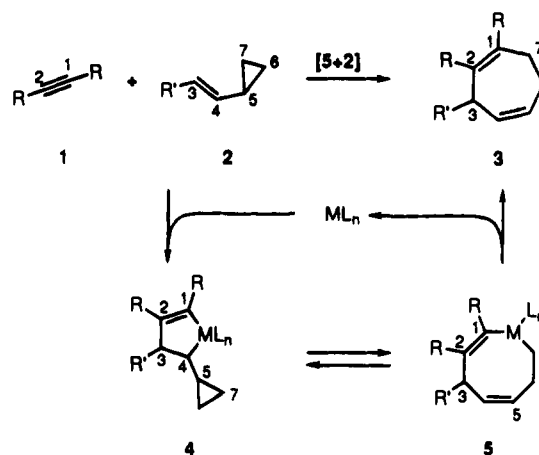
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The synthetic significance of the Diels–Alder cycloaddition coupled with the recognition that vinylcyclopropanes have diene-like properties has stimulated much interest over the past few decades in the development of a homolog of the Diels–Alder reaction for seven-membered-ring synthesis involving the cycloaddition of vinylcyclopropanes with π -systems (Scheme 1: $1 + 2 \rightarrow 3$).² Few examples of such cycloadditions have, however, been identified. As a continuation of our studies on transition metal catalyzed [4 + 4] and [4 + 2] cycloadditions,³ we describe herein the first examples of transition metal catalyzed cycloadditions of vinylcyclopropanes with alkynes, providing a conceptually new method for the synthesis of seven-membered rings based on a [5 + 2] cycloaddition.⁴

The design of this new cycloaddition was predicated on the mechanistic hypothesis outlined in Scheme 1.⁵ According to this sequence, oxidative addition of the metal catalyst to a vinylcyclopropane **2** and a suitable π -system **1** would provide metallacycle **4**. The juxtaposition of the carbon–metal bond

Scheme 1



and the cyclopropane in this intermediate would then be expected to lead to strain-driven cleavage of the cyclopropane,⁶ producing metallacycle **5**, from which cycloadduct **3** would be derived through reductive elimination.

Our test of this hypothesis started with vinylcyclopropane **6**. When treated with 10 mol % [RhCl(PPh₃)₃] in toluene at 110 °C for 2 days, **6** gave cycloadduct **7** as a single product in an isolated yield of 84% (at 100% conversion). With trifluoroethanol, a solvent whose polarity would favor formation of a cationic rhodium(I) catalyst, an increase in the reaction rate was observed, providing **7** in 90–95% yield in only 19 h at reduced temperature (55 °C). Further acceleration of this process was achieved by addition of silver triflate (0.5 mol %) to the reaction mixture in toluene, which allowed for the conversion of **6** to **7** in only 20 min at 110 °C (83% yield) with only 0.5 mol % catalyst.⁷ The yield of this reaction remained

(6) For reviews and lead references on metal-mediated cleavage of cyclopropanes, see: Sarel, S. *Acc. Chem. Res.* **1978**, *11*, 204. Khusnutdinov, R. I.; Dzhemilev, U. M. *J. Organomet. Chem.* **1994**, *471*, 1. Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: New York, 1991; Vol. 5, pp 899–970. Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229. Moriarty, R. M.; Yeh, L. L.; Ramey, K. C. *J. Am. Chem. Soc.* **1971**, *93*, 6709. Powell, K. G.; McQuillin, F. S. *J. Chem. Soc., Chem. Commun.* **1971**, 931. Aumann, R. *J. Am. Chem. Soc.* **1974**, *96*, 2631. Russell, R. K.; Wingard, R. E.; Paquette, L. A. *J. Am. Chem. Soc.* **1974**, *96*, 7483. Pinke, P. A.; Stauffer, R. D.; Miller, R. G. *J. Am. Chem. Soc.* **1974**, *96*, 4229. Eilbracht, P. *Chem. Ber.* **1976**, *109*, 1429, 3136. Salomon, M. F.; Salomon, R. G.; Kachinski, L. C. *J. Am. Chem. Soc.* **1977**, *99*, 1043. Scharf, H. D.; Mattay, J. *Tetrahedron Lett.* **1977**, 401. Alcock, N. W.; Brown, J. M.; Conneely, J. A.; Williamson, D. H. *J. Chem. Soc., Perkin Trans. 2* **1979**, 962. Murakami, M.; Nishida, S. *Chem. Lett.* **1979**, 927. Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020. Doyle, M. P.; van Leusen, D. *J. Am. Chem. Soc.* **1981**, *103*, 5917. Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 2871. Binger, P.; Brinkmann, A.; Wedernann, P. *Chem. Ber.* **1983**, *116*, 2920. Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315, 2326. Larock, R. C.; Varaparth, S. *J. Org. Chem.* **1984**, *49*, 3432. Yamamoto, K.; Ishida, T.; Tsuji, J. *Chem. Lett.* **1987**, 1157. Fournier, G.; Balme, G.; Barieux, J. J.; Gore, J. *Tetrahedron* **1988**, *44*, 5821. Tumer, S. U.; Herndon, J. W.; McMullen, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 8394. Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 4895. Herndon, J. W.; Tumer, S. U.; McMullen, L. A.; Matasi, J. J.; Schattner, W. F. *K. Adv. Metalorg. Chem.* **1994**, *3*, 51. Dimmock, P. W.; Whitby, J. *J. Chem. Soc., Chem. Commun.* **1994**, 2323. Hanzawa, Y.; Harada, S.; Nishio, R.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 9421. Ryu, I.; Ikura, K.; Tamura, Y.; Maenaka, J.; Ogawa, A.; Sonoda, N. *Synlett* **1994**, 941. Hiroi, K.; Arinaga, Y. *Tetrahedron Lett.* **1994**, *35*, 153.

(7) In a representative procedure, tris(triphenylphosphine)rhodium(I) chloride (0.5 mol %) and silver trifluoromethanesulfonate (0.5 mol %) are added sequentially under an argon atmosphere to oxygen-free toluene (4 mL) in an oven-dried, base-washed Schlenk flask. After 5 min at room temperature, vinylcyclopropane **6** (0.9 mmol in 5 mL of toluene) is added and the resulting solution heated at 110 °C for 20 min. After cooling, the reaction mixture is passed through neutral alumina and concentrated. Chromatographic purification (silica gel, 5% ethyl acetate in hexanes) gave cycloadduct **7** in 83% yield as a colorless oil. All new compounds were characterized by IR and NMR spectroscopy and provided satisfactory elemental or exact mass analyses.

(1) (a) Visiting Scholar, Daiichi Pharmaceutical Co., Ltd. (1993–1995). (b) Feodor Lynen Fellow of the Alexander von Humboldt Foundation (1993–1994).

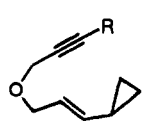
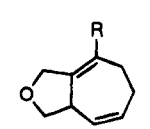
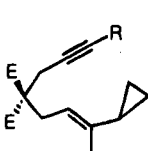
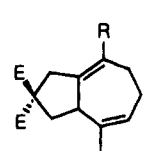
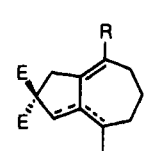
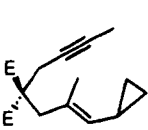
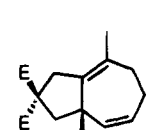
(2) (a) For examples, see: Sarel, S.; Breuer, E. *J. Am. Chem. Soc.* **1959**, *81*, 6522. Sarel, S.; Felzenstein, A.; Yovell, J. *J. Chem. Soc., Chem. Commun.* **1973**, 859. Sarel, S.; Felzenstein, A.; Yovell, J. *J. Chem. Soc., Chem. Commun.* **1974**, 753. Felzenstein, A.; Sarel, S.; Yovell, J. *J. Chem. Soc., Chem. Commun.* **1975**, 918. (b) Related work includes the following: Effenberger, F.; Podszun, W. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 976. Nishida, S.; Moritani, I.; Teraji, T. *J. Chem. Soc., Chem. Commun.* **1970**, 501. Baldwin, J. E.; Pinschmidt, R. K. *Tetrahedron Lett.* **1971**, 935. Shimizu, N.; Fujioka, T.; Ishizuka, S.-I.; Tsuji, T.; Nishida, S. *J. Am. Chem. Soc.* **1977**, *99*, 5972. Christl, M.; Brunn, E.; Lanzendörfer, F. *J. Am. Chem. Soc.* **1984**, *106*, 373.

(3) For representative examples, see: Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678. Wender, P. A.; Ihle, N. C. *Tetrahedron Lett.* **1987**, *28*, 2451. Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221. Wender, P. A.; Correia, C. R. D.; Ihle, N. C. *J. Am. Chem. Soc.* **1988**, *110*, 5904. Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432. Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089. Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843.

(4) There are only three possible two-component cycloadditions that lead to seven-membered rings: [6 + 1], [5 + 2], and [4 + 3]. For examples and lead references, see the following. [6 + 1] (in the form of carbene insertions into arenes): Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. [5 + 2]: Sánchez, I. H.; Yáñez, R.; Enríquez, R.; Joseph-Nathan, P. *J. Org. Chem.* **1981**, *46*, 2818. Sammes, P. G. *Gazz. Chim. Ital.* **1986**, *116*, 109. Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954. Padwa, A.; Hornbuckel, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1992**, *57*, 5747. Wender, P. A.; Siggel, L.; Nuss, J. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: New York, 1991; Vol. 5, pp 645–673. [4 + 3]: Noyori, R. *Acc. Chem. Res.* **1979**, *12*, 61. Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. Mann, J. *Tetrahedron* **1986**, *42*, 4611. Harmata, M.; Elahmad, S. *Tetrahedron Lett.* **1993**, *34*, 789. Giguere, R. J.; Tassely, S. M.; Rose, M. I.; Krishnamurthy, V. V. *Tetrahedron Lett.* **1990**, *31*, 4577. Trost, B. M.; MacPherson, D. T. *J. Am. Chem. Soc.* **1987**, *109*, 3483. Trost, B. M.; Schneider, S. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 213. Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. Davies, H. M. L. *Tetrahedron* **1993**, *49*, 5203. Hosomi, A.; Tomimaga, Y. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: New York, 1991; Vol. 5, pp 593–615. Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1985**, *50*, 3425.

(5) The mechanisms of these reactions and nature and geometry of the catalyst require further investigation. The path presented is intended only to facilitate synthetic application and guide mechanistic analysis. Other mechanisms include initial opening of the vinylcyclopropane to a σ,π -allyl complex and oxidative addition to the alkyne.

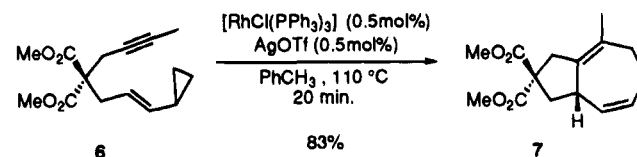
Table 1. Transition Metal Catalyzed Intramolecular [5 + 2] Cycloadditions of Vinylcyclopropanes and Alkynes

Vinylcyclopropane-Alkyne	Cycloadduct(s), Yield	Reaction Conditions, time
<p>1.</p> <p>2.</p>  <p>8</p>	<p>7</p>  <p>9</p>	<p>A^a, 20 min.</p> <p>B^b, 2 d</p>
<p>3.</p> <p>4.</p> <p>5.</p> <p>6.</p> <p>7.</p> <p>a: R=Me b: R=TMS c: R=CO₂Me d: R=Ph e: R=H</p>  <p>10</p>  <p>11</p>  <p>12</p>	<p>88%</p> <p>83%</p> <p>74%</p> <p>80%</p> <p>50%^f</p>	<p>B^b, 1.5 h</p> <p>B^b, 3.5 h</p> <p>B^b, 1.25 h</p> <p>B^b, 1.5 h</p> <p>C^c, 1.5 h</p>
<p>8.</p> <p>9.</p> <p>10.</p> <p>11.</p> <p>12.</p> <p>a: R=Me a: R=Me b: R=H c: R=CO₂Me d: R=TMS</p>  <p>13</p>  <p>14</p>	<p>89% (11:12=3.5:1)</p> <p>92% (11:12=1:2)</p> <p>82% (only 11)</p> <p>81% (only 11)</p> <p>71% (only 12)</p>	<p>B^b, 2 d</p> <p>D^d, 2.5 h</p> <p>B^b, 2d</p> <p>B^b, 16 h</p> <p>B^b, 7 d</p>
<p>13.</p>	<p>82%</p>	<p>D^d, 30 min</p>

^a A = 0.5 mol % RhCl(PPh₃)₃, 0.5 mol % AgOTf, PhMe, 110 °C. ^b B = 10 mol % RhCl(PPh₃)₃, PhMe, 110 °C. ^c C = 10 mol % RhCl(PPh₃)₃, THF, 100 °C. ^d D = 10 mol % RhCl(PPh₃)₃, 10 mol % AgOTf, PhMe, 110 °C. ^e E = CO₂Me. ^f Lower yield in this case due to product volatility.

constant (82–84%) over the range of concentrations (0.05–0.1 M) studied.⁸

As illustrated by the entries of Table 1, this new cycloaddition allows for the flexible and efficient synthesis of a variety of cycloheptadienes. Entries 3–7 and 8–12 indicate that the cycloaddition is relatively insensitive to steric (hydrogen to trimethylsilyl groups) and electronic (electron-donating, electron-withdrawing, and conjugating groups) effects introduced by substituents on the alkyne. Similarly, substitution of the alkene



(entries 8–13) has little effect on the efficiency of the cycloaddition; in all cases, the yields are in the range 70–92%. However, in some cases (compounds 10a and 10d), isomerization of the double bond of the initial product is observed. For entries 8–12, the starting materials were mixtures of *E* and *Z* isomers. However, both isomers react to give the same cycloadducts, with the *Z* isomer reacting faster. Finally, the cycloaddition proceeds even with geminal dialkyl substitution of the alkene (entry 13), providing a simple and new route to pseudoguaianes and related compounds.

In summary, the transition metal catalyzed cycloaddition of vinylcyclopropanes to alkynes is shown to provide a flexible and efficient route to seven-membered rings. Except for the volatile product 9e, all cycloadditions studied thus far proceed in yields of 70–95% and appear to be relatively little influenced by steric and electronic effects. A secondary reaction involving positional isomerization of the product double bond is a limitation encountered in two cases. This method establishes the experimental framework for conceptually new approaches to natural and non-natural seven-membered-ring-containing compounds and suggests a greater role for vinylcyclopropanes as diene homologues in a wide range of transition metal catalyzed reactions and more generally for the catalyzed addition of strained rings across π -systems, ideas currently under investigation.

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Supplementary Material Available: Spectroscopic and analytical data for compounds 7, 9a–e, 11a–c, 12a,d, and 14 and the synthetic route to starting materials (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(8) At high concentrations (>0.1 M), the reaction mixture is heterogeneous but the cycloaddition proceeds uneventfully.