Titanocene-Catalyzed Conversion of Enynes to Bicyclic Cyclopentenones

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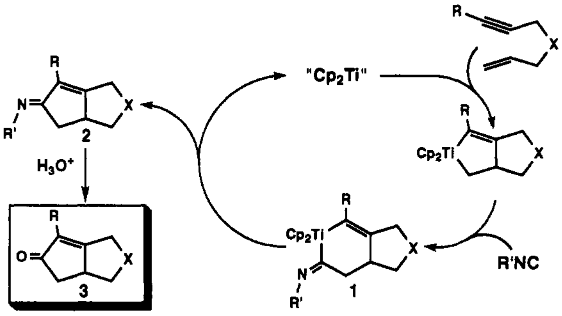
The early transition metal-induced reductive cyclization of enynes to produce metallacyclopentenes, followed by their subsequent transformation to a variety of organic products, has been the subject of numerous recent reports.[2,3] In the majority of these, a stoichiometric quantity of the metal reagent was employed. Recently, workers in several laboratories have demonstrated the viability of catalytic carbon–carbon bond formation in zirconocene systems under conditions where an excess of a trialkylaluminum or Grignard reagent is present.[4] Herein we describe the first early transition metal-catalyzed transformation of enynes to bicyclic cyclopentenones.

We recently reported that a stoichiometric titanocene equivalent could be utilized in the conversion of enynes to bicyclic iminocyclopentenes and cyclopentenones.[3,5] In comparison to the previously reported zirconocene systems,[2] this method tolerated a greater level of polar functionality, including esters. Integral to this process, in the instance of iminocyclopentene formation, was the conversion of **1** to **2** (Scheme I), during which some "titanocene" species was eliminated.[6] If this fragment could be trapped by enyne prior to its decomposition or conversion to "dead-end" products, the system would be rendered catalytic.[7]

Scheme I



Attempts to achieve such a system through the use of conventional isocyanides proved fruitless, presumably due to irreversible reaction of the nascent catalyst and excess isocyanide. After much experimentation, it was found that $Cp_2Ti(PMe_3)_2$[8] (10 mol %) catalytically converted enyne and a slight excess of Me_3SiCN to the corresponding iminocyclopentene.[9] The (trialkylsilyl)cyanide–(trialkylsilyl)isocyanide tautomeric equilibrium,[10] which largely favors the (trialkylsilyl)cyanide tautomer, conveniently limited the concentration of free isocyanide. Unfortunately, use of Me_3SiCN gave variable results, although in some cases complete consumption of the enyne was observed when slow addition of the Me_3SiCN was employed (Table I, entries 1 and 3). Reactions employing i-Pr_3SiCN were too slow to be useful, but t-$BuMe_2SiCN$ proved to be a good compromise with respect to reactivity and compatibility. Using 10 mol % $Cp_2Ti(PMe_3)_2$ and a slight excess of t-$BuMe_2SiCN$, conversion of enyne to **2** was nearly quantitative (^1H NMR) in all cases shown in Table I.[11] Hydrolytic workup of **2** provided cyclopentenones **3** in good yield.[9] The functional group toleration which we observed in the stoichiometric case[3] was retained in the present catalytic system, as could be seen for the diester substrates (entries 4, 5 and 7). Levels and sense of diastereoselectivity for this process were similar to those observed in the related stoichiometric process, as was seen for entry 6.[2b,c,12]

In summary, we have developed the first early transition metal system for the catalytic formation of bicyclic cyclopentenones from enynes and a carbon monoxide equivalent.[5b–e] The demonstrated utility of the analogous stoichiometric processes[2a,b] speaks to the potential for this new catalytic method in natural product synthesis. Examination of the scope of this novel process with regard to substrate structure, level of functionality tolerated, and the use of *in situ* generated, phosphine-free, and enantiopure catalysts of titanium and other metals is under investigation.

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[2] Representative lead references: (a) For a recent review, see Negishi, E. I. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 1163–1184. (b) Agnel, G.; Owczarczyk, Z.; Negishi, E. I. *Tetrahedron Lett.* **1992**, *33*, 1543. See also (c) RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128. (d) Davis, J. M.; Whitby, R. J.; Jaxa-Chamiec, A. *Tetrahedron Lett.* **1992**, *33*, 5655. (e) For the use of $Cp_2Ti(PMe_3)_2$ in a related stoichiometric carbonyl–olefin/alkyne cyclization, cf. Hewlett, D. F.; Whitby, R. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1684.

[3] (a) Grossman, R. B.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 5803 and references therein. (b) Grossman, R. B. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA 1992.

[4] (a) Dzhemilev, U. M.; Ibragimov, A. G.; Zolotarev, A. P.; Muslukhov, R. R.; Tolstikov, G. A. *Bull. Acad. Sci. U.S.S.R., Chem. Sci.* **1989**, *38*, 194. Dzhemilev, U. M.; Ibragimov, A. G.; Zolotarev, A. P.; Tolstikov, G. A. *Ibid.* **1989**, *38*, 1324. (b) Knight, K. S.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6268. Wischmeyer, U.; Knight, K. S.; Waymouth, R. M. *Tetrahedron Lett.* **1992**, *33*, 7735. (c) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. I. *J. Am. Chem. Soc.* **1991**, *113*, 6266. (d) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079. Hoveyda, A. H.; Xu, Z.; Morken, J. P.; Houri, A. F. *J. Am. Chem. Soc.* **1991**, *113*, 8950. *Ibid.* **1992**, *114*, 6692. (e) Lewis, D. P.; Muller, P. M.; Whitby, R. J.; Jones, R. V. H. *Tetrahedron Lett.* **1991**, *32*, 6797.

[5] (a) For leading references to other transition metal-mediated methods for the synthesis of cyclopentenones, see ref 6 of 3a and Hoye, T. R.; Suriano, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 1154. For formation of related cyclopentenone skeletons catalyzed by late transition metals, see also: (b) Rautenstrauch, V.; Mégard, P.; Conesa, J.; Küster, W. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1413. (c) Eaton, B. E.; Rollman, B.; Kaduk, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 6245. (d) Ihle, N. C.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 560 and references therein. (e) Schore, N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 1037–1064, and references therein.

[6] Cámpora, J.; Buchwald, S. L.; Gutiérrez-Puebla, E.; Monge, A., manuscript in preparation.

[7] In initial experiments, sequential addition of enyne and t-BuNC to a stoichiometric amount of $Cp_2Ti(PMe_3)_2$, repeated 4 times, gave a 220% yield (by ^1H NMR) of **2** based on titanium.[3b]

[8] (a) Kool, L. B.; Rausch, M. D.; Alt, H. G.; Herberhold, M.; Thewalt, U.; Wolf, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 394. (b) Binger, P.; Müller, P.; Benn, R.; Rufinska, A.; Gabor, B.; Krüger, C.; Betz, P. *Chem. Ber.* **1989**, *122*, 1035.

[9] See supplementary information for experimental details. t-$BuMe_2SiCN$ was prepared as described in: Gassman, P. G.; Haberman, L. M. *J. Org. Chem.* **1986**, *51*, 5010.

[10] (a) Durig, J. R.; George, W. O.; Li, Y. S.; Carter, R. O. *J. Mol. Struct.* **1973**, *16*, 47. (b) Seckar, J. A.; Thayer, J. S. *Inorg. Chem.* **1975**, *14*, 573.

[11] Enynes containing trimethylsilyl-substituted alkynes are not converted to the corresponding iminocyclopentenes due to a ligand induced retrocyclization of the corresponding titanacycle which regenerates the enyne. We have also been unable to catalytically generate a 5,6-fused ring system from 3-(3-butenyloxy)-1-phenyl-1-propyne. However, this substrate was cleanly converted (as seen by ^1H NMR) to the corresponding iminocyclopentene by using a stoichiometric amount of $Cp_2Ti(PMe_3)_2$. To date, terminal alkynes are not successful substrates. This is similar to what is seen for stoichiometric cases.[2a,3] We are currently studying methods to circumvent the problems with these cases.

[12] For an important additional report on the stereochemical outcomes of enyne cyclizations, cf.: Lund, E. C.; Livinghouse, T. *J. Org. Chem.* **1989**, *54*, 4487.

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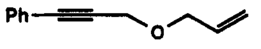
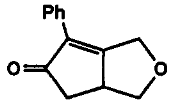
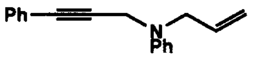
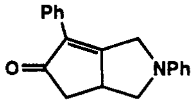
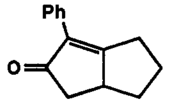
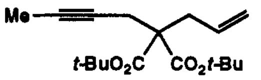
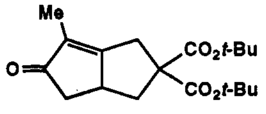
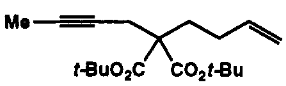
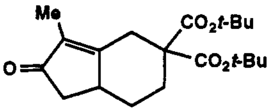
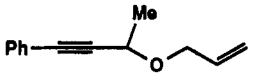
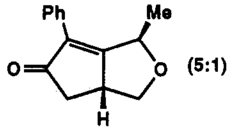
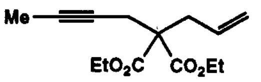
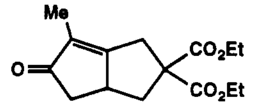
Table I. Titanocene-Catalyzed Conversion of Enynes to Bicyclic Cylopentenones

entry	starting material	cyanide[a]	product	isolated yield (%)
1		Me_3SiCN		80
2		Me_3SiCN		44[b]
3		Me_3SiCN t-$BuMe_2SiCN$		55 66
4		t-$BuMe_2SiCN$		70
5		t-$BuMe_2SiCN$		71
6		t-$BuMe_2SiCN$		71[c]
7		t-$BuMe_2SiCN$		65

[a] Me_3SiCN was added slowly over a 4–8 h period; t-$BuMe_2SiCN$ was added immediately at the beginning of the reaction. See supplementary material for full details. [b] 13% of starting material was also isolated. [c] Isolated as a 5:1 mixture of diastereoisomers. The major isomer, as assigned on the basis of NOE analysis, is shown.

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Supplementary Material Available: Representative experimental procedures for the catalytic preparation of bicyclic cyclopentenones and the preparation and spectroscopic characterization of the products listed in Table I (6 pages). Ordering information is given on any current masthead page.