

## A Titanocene-Catalyzed Intramolecular Ene Reaction: Cycloisomerization of Enynes and Dienynes

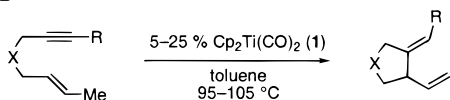
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The ene reaction involves the addition of a group possessing a  $\pi$ -bond (enophile) to a group possessing an allylic hydrogen (ene), with concomitant transfer of the allylic hydrogen to the enophile.<sup>1</sup> When performed in an intramolecular fashion, the ene reaction is referred to as a cycloisomerization and can serve as an efficient method for the construction of carbocyclic frameworks.<sup>2</sup> The need for high reaction temperatures and substrate activation has limited the applicability of the thermal reaction in the synthesis of complex structures. The use of transition-metal catalysts<sup>3</sup> has provided a means for performing cycloisomerizations<sup>4</sup> under mild conditions with enhanced selectivity and a wider substrate scope than was previously possible.<sup>5</sup> Most notably, the use of palladium for the cycloisomerization of enynes has been elegantly demonstrated by Trost<sup>6</sup> and has proven to be a valuable tool for the synthesis of natural products.<sup>7</sup> The Pd-catalyzed reaction has also provided encouraging results in enantioselective cycloisomerizations.<sup>8,9</sup> Although early transition metal complexes have been extensively applied to the cyclization of enynes,<sup>10</sup> no early transition-metal-mediated or -catalyzed cycloisomerization reactions have been reported. In the course of our studies on the titanocene-catalyzed Pauson–Khand type reaction,<sup>11</sup> we found that  $\text{Cp}_2\text{Ti}(\text{CO})_2$  can serve as a catalyst for the cycloisomerization of enynes (Scheme 1). We have examined the scope of this

### Scheme 1



process with respect to structural variations on the enyne and have observed unique selectivities for the titanocene-catalyzed reaction.

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 (3) (a) Ni: Radetich, B.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 8007. (b) Ni–Cr: Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 5268. (c) For a cobalt-mediated process, see: Llerena, D.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1996**, *37*, 7027 and Krafft, M.; Wilson, A.; Dasse, O.; Bonega, L.; Cheung, Y.; Fu, Z.; Shao, B.; Scott, I. *Tetrahedron Lett.* **1998**, *39*, 5911.  
 (4) For related enyne metathesis reactions, see: (a) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305 and references therein. For metallo-ene and related reactions, see: (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38. (c) Takayama, Y.; Gao, Y.; Sato, F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 851.  
 (5) See: Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1 and references therein.  
 (6) (a) Trost, B. M.; Lautens, M.; Chan, C.; JeBaratnam, D. J.; Mueller, T. *J. Am. Chem. Soc.* **1991**, *113*, 636. (b) Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268 and references therein.  
 (7) Trost, B. M. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1991; Vol. 8; p 277.  
 (8) Goeke, A.; Sawamura, M.; Kuwano, R.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 662.  
 (9) Trost, B. M.; Czeskis, B. A. *Tetrahedron Lett.* **1994**, *35*, 211.  
 (10) (a) For a review of zirconium-mediated cyclizations, see: Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 5, pp 1163–1184. (b) Titanium-mediated cyclization: Urabe H., Hata, T., Sato, F. *Tetrahedron Lett.* **1995**, *36*, 4261. (c) Titanium-catalyzed cyclization: Berk, S. C.; Grossman, R. B.; Buchwald, S. *J. Am. Chem. Soc.* **1994**, *116*, 8593.  
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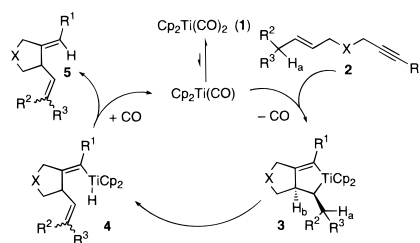


Figure 1. Proposed catalytic cycle for the cycloisomerization of enynes.

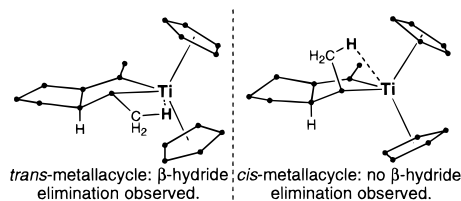


Figure 2. Calculated structures of proposed intermediate metallacycles derived from *trans*- and *cis*-enynes.

We have also been able to effect the cycloisomerization of dienynes to form allenes, a metal-catalyzed transformation which, to our knowledge, has not previously been reported.

The proposed catalytic cycle, shown in Figure 1, proceeds through initial loss of CO from  $\text{Cp}_2\text{Ti}(\text{CO})_2$  (1) followed by reaction with enyne 2 to form titanacyclopentene 3.  $\beta$ -Hydride elimination exclusively of  $\text{H}_a$  (Figure 1) results in the formation of the vinyl titanocene hydride 4. This is in contrast to Pd-catalyzed systems in which  $\beta$ -hydride elimination of  $\text{H}_b$  to produce 1,3-dienes is a competitive pathway. Ligand-induced reductive elimination<sup>12</sup> provides the diene 5 and regenerates the catalytic titanium(II) species.

Table 1 illustrates the scope of the titanocene-catalyzed cycloisomerization reaction. It is striking that while *trans*-olefins are cycloisomerized, *cis*-olefins such as **6a** and **7** either do not react or are partially converted to cyclopentenones.<sup>11</sup> To investigate the reason for this dichotomy, metallacycles were prepared from both a *trans*-enyne (Table 1, entry 3) and a *cis*-enyne (**6a**) by addition of  $\text{Cp}_2\text{Ti}(\text{PMe}_3)_2$  to the enyne at room temperature in  $\text{C}_6\text{D}_6$ . Upon heating, the *trans*-metallacycle is converted to diene product, while the *cis*-isomer slowly decomposes, resulting in the release of the enyne from which it was formed. Energy minimization<sup>13</sup> of model metallacycles (Figure 2) suggests that in the metallacycle derived from a *trans*-olefin, the  $\beta$ -hydrogen is positioned close to the metal-center, while in a *cis*-metallacycle, the  $\beta$ -hydrogen is not geometrically disposed for overlap with the  $1a_1$  orbital necessary for  $\beta$ -hydride elimination.<sup>14</sup> The selectivity of the titanocene catalyst for the cyclization of *trans*-olefins is further demonstrated by the cycloisomerization of an enyne bearing both *cis*- and *trans*-3-pentene fragments (Table 1, entry 10). The *trans*-olefin is cycloisomerized while the *cis*-olefin, although it may undergo reversible conversion to the corresponding metallacycle, is recovered unchanged.

Phenyl-*n*-propyl-, and methyl-substituted alkynes are cyclized using the titanocene catalyst, but a trimethylsilyl-substituted alkyne could not be converted to product. A nitrogen-containing enyne was also successfully isomerized to the 1,4-diene (Table 1, entry 4). It should be noted that reaction of this substrate for

(12) Gell, K. I.; Schwartz, J. *J. Am. Chem. Soc.* **1981**, *103*, 2687.

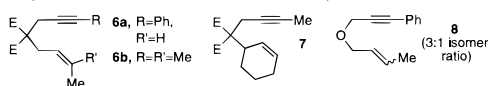
(13) Energy minimization was performed using MacSpartan Plus PM3 method.

(14) The LUMO corresponding to the titanocene fragment is of  $1a_1$  symmetry and is oriented perpendicular to the plane in which the metallacycles in Figure 2 are drawn. For a discussion of the structure of bis(cyclopentadienyl)-metal complexes, see: Lauher, J. W.; Hoffmann, R. *J. Am. Chem. Soc.* **1976**, *98*, 1729.

**Table 1.** Cycloisomerization of Enynes

Entry	Substrate <sup>a</sup>	Product	Mol % (1) <sup>b</sup>	Yield (%) <sup>16</sup> (isomer ratio)
1			R = Me	10 <sup>c</sup> 97
2			R = n-Pr	10 <sup>c</sup> 82
3			R = Ph	5 82
4			R = Ph	10 79
5				5 <sup>c</sup> 85
6				15 <sup>c</sup> 87 (1 : 3.5)
7				25 79
8				10 89 (1 isomer)
9				20 <sup>c</sup> 85 (1 : 1.3)
10				10 87 (1 : 1)
11				5 88 (1 : 1)
				5 85 (1 : 1)

<sup>a</sup> E = CO<sub>2</sub>Et. <sup>b</sup> Unless indicated otherwise, experimental method B (2 mM in **1**, 105 °C, 24–48 h) was employed. <sup>c</sup> Method A was employed (9–13 mM in **1**, 95 °C, 4–24 h).



4 h results in exclusive formation of the 1,4-diene product shown; however, heating for an additional 8 h results in isomerization to the 1,3-diene. A substrate which contains a methylene group in the allylic position undergoes cyclization with a moderate degree of selectivity with respect to the resulting olefin geometry (Table 1, entry 5). Notably, in the case of a substrate which contains a tertiary carbon in the allylic position (Table 1, entry 6), exclusive formation of the 1,4-diene is still observed. The trisubstituted enyne **6b** and the ether **8**<sup>15</sup> were not cycloisomerized with this catalyst system.

Table 1 also illustrates the scope of the cycloisomerization of a variety of chiral enyne substrates (entries 7–10). The cycloisomerization proceeded with complete diastereoselectivity when an enyne bearing a substituent  $\gamma$  to the alkyne was employed as a substrate (entry 7). However, the cyclization of substrates with chiral centers  $\alpha$  (entry 8) and  $\beta$  (entry 9) to the alkyne moiety proceeded with little or no diastereoselectivity. These results are consistent with stereoselectivity trends observed in other early metal-mediated cyclizations.<sup>10c,17</sup>

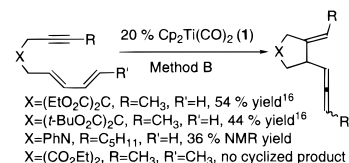
A novel feature of the titanocene system is its reaction with dienynes.  $\beta$ -Hydride elimination from metallacycle **3** (Figure 1),

(15) A complex mixture results when ether **8** is used as a substrate in the cycloisomerization reaction. Although titanium reagents have been shown to induce the cyclization of allylic ethers, these substrates are known to be problematic in reactions using zirconium reagents. Grossman, R. B.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 5803.

(16) Yields reported are the average of two experiments and represent isolated products of >95% purity by <sup>1</sup>H NMR and GC as well as an elemental analysis for one experiment with each substrate.

(17) RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128. Lund, E. C.; Livinghouse, T. *J. Org. Chem.* **1989**, *54*, 4487. Pagenkopf, B. L.; Lund, E. C.; Livinghouse, T. *Tetrahedron* **1995**, *51*, 4421.

formed from the reductive cyclization of a dienyne, results in the formation of an allene.<sup>18</sup> To our knowledge, formation of allenes via loss of a  $\beta$ -hydrogen from allyl-metal complexes is unknown.<sup>19</sup> Using late transition-metal catalysts, this class of substrates has been shown to undergo [4 + 2] intramolecular cyclizations.<sup>20</sup> The malonic ester-derived substrates shown below cycloisomerize to allenes, with either no detectable or trace



amounts of the thermal [4 + 2] reaction observed; however, an 11% yield of the Diels–Alder product was observed (<sup>1</sup>H NMR) for the reaction of the amine-containing enyne. Finally, attempts were made to cyclize a methyl-substituted dienyne, but only extensive isomerization of the uncyclized olefin was observed.

The amount of catalyst required for complete conversion of the enyne to product could be lowered by performing the reaction at relatively high dilution. Two reaction protocols have been employed: the procedure at a higher substrate concentration, method A, uses concentrations of **1** ranging from 9 to 13 mM. In method B, the concentration of **1** is reduced to 2 mM, but an increase in reaction time and temperature is also necessary. The success of this protocol may be due to the minimization of an intermolecular catalyst decomposition pathway, or it may be due to a decrease in the rate of the recombination of CO with a catalytically active titanocene species.

In conclusion, we have demonstrated Cp<sub>2</sub>Ti(CO)<sub>2</sub> to be the first early metal-based catalyst for the cycloisomerization of enynes and dienynes to 1,4-dienes and 1,4,5-trienes, respectively. Our findings illustrate that the titanocene system displays complementary reactivity and selectivity to analogous late transition-metal-catalyzed processes.

**Acknowledgment.** This research was supported by the National Institutes of Health (GM 34917), Pfizer, Novartis, and Merck. S.J.S. thanks the Ford Foundation for a predoctoral fellowship. N.M.K. was a National Cancer Institute Predoctoral Trainee supported by NIH Cancer Training Grant CI T32CA09112 and was a fellow of the American Chemical Society organic division supported by Smith-Kline Beecham and of Boehringer Ingelheim Pharmaceuticals, Inc. We are grateful to Dr. Frederick Hicks for many helpful conversations and to Dr. Attila Aranyos for assistance with computer modeling of metallacycles.

**Supporting Information Available:** Experimental procedures and characterization of cyclization products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(18) For reactions of allenes, see: Schuster, H. F.; Coppola, G. M. *Allenes In Organic Synthesis*; John Wiley & Sons: New York, 1984.

(19) (a) For the microscopic reverse of this reaction, the formation of metal-allyl complexes via metalation of an allene, see: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; pp 904–906. (b) For the preparation of  $\eta^2$ -allene complexes from  $\beta$ -hydride abstraction of divinyl zirconocene complexes, see: Yin, J.; Jones, W. M. *Tetrahedron* **1995**, *51*, 4395. (c) The formation of allenes via  $\beta$ -hydride elimination of vinyl complexes has been proposed as an intermediate step in several palladium-catalyzed reactions, see: Kadota, I.; Shibuya, A.; Gyoung, Y. S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1062 and references therein.

(20) (a) Rh: Jolly, R. S.; Leudtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965. McKinstry, L.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 6145. Gilbertson, S. R.; Hoge, G. S. *Tetrahedron Lett.* **1998**, *39*, 2075. (b) Ni: Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432. Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824. (c) Pd: Kumar, K.; Jolly, R. S. *Tetrahedron Lett.* **1998**, *39*, 3047.