

Titanocene-Catalyzed Cyclocarbonylation of Enynes to Cyclopentenones

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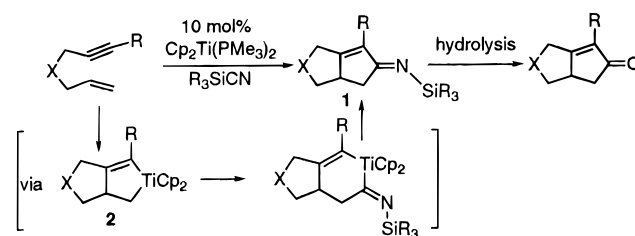
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The transition metal promoted condensation of an enyne with CO is a powerful and convergent method for the construction of bicyclic cyclopentenones.¹ While a number of middle and late transition metal carbonyl complexes can effect this transformation,² only the cyclization employing cobalt, the Pauson–Khand reaction, can be performed with a catalytic amount of the metal complex.³ We recently reported a titanocene-catalyzed cyclopentenone synthesis which proceeds *via* the yield-limiting hydrolysis of intermediate iminocyclopentenones **1** obtained from the cyclocondensation of an enyne with an isocyanide (Scheme 1).⁴ The moderate yields of cyclopentenones from this indirect route and our recent finding that Cp₂Ti(PMe₃)₂ catalyzes the conversion of allylacetophenones and CO to γ -butyrolactones⁵ encouraged us to reexamine the carbonylation of enyne substrates. We report here the first early transition metal catalyzed carbonylation of enynes which utilizes commercially available Cp₂Ti(CO)₂⁶ and CO to produce cyclopentenones.

The typical experimental conditions are outlined in Scheme 2;⁷ the results for enynes with monosubstituted alkenes are presented in Table 1. For those substrates cyclized with both the previous isocyanide and the present CO system (Table 1, entries 1, 7–9), the yields of the cyclocarbonylation are consistently higher^{8a} and less catalyst is required.^{8b} As for our other titanocene-catalyzed reductive cyclizations,^{4,9} polar functional groups such as ethers (entry 1), amines (entry 2), and esters (entry 3) are compatible with the Cp₂Ti(CO)₂ catalyst. Surprisingly, the carbonylation reaction also tolerates nitriles (entry 4)

Scheme 1



Scheme 2

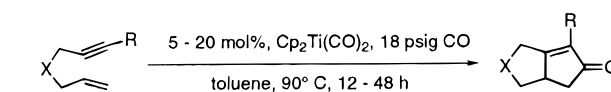


Table 1. Cyclopentenones from Enynes with Monosubstituted Alkenes

Entry	Substrate	Product	Mol% Cp ₂ Ti(CO) ₂	Yield (%) ^a
1			5	92
2			10	88
3			R = CO ₂ Et, 5	95
4			R = CN, 7.5	75 (1:1)
5			R = C(O)Me, 7.5	93 (1:1)
6			20	85
7			7.5	92 (3.5:1)
8			10	92 (8:1)
9			5	90 ^b
10			10	86

^a Isolated yields of products >95% purity as determined by ¹H NMR and GC or combustion analysis. Yields are an average of two or more runs. ^b Formed as a single isomer.

and ketones (entry 5), which lead to catalyst deactivation in our previous isocyanide condensations.¹⁰ The incompatibility of terminal alkynes with group 4 metallocene-catalyzed⁴ and even mediated¹¹ cyclopentenone syntheses has been one of the major drawbacks in comparison of this methodology to the Pauson–Khand reaction. As seen in entry 6, substrates containing terminal alkynes can be cyclocarbonylated with Cp₂Ti(CO)₂, although higher quantities of catalyst are required than for substrates with internal alkynes.

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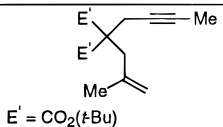
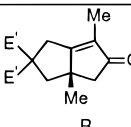
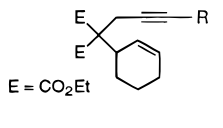
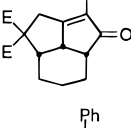
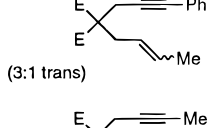
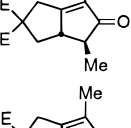
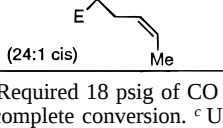
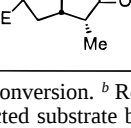
(6) (a) Commercial Cp₂Ti(CO)₂ (Strem Chemicals) was dissolved in hexane and filtered through Celite in a glove box under argon to remove insoluble materials prior to use. (b) Cp₂Ti(CO)₂ is also readily synthesized in one step from Cp₂TiCl₂. Sikora, D. J.; Moriarty, K. J.; Rausch, M. D. In *Inorganic Synthesis*; Angelici, R. J., Ed.; John Wiley and Sons, Inc.: New York, 1990; Vol. 28, p 248.

(7) See supporting information for a representative procedure. Note: Occasionally on very humid days, this procedure gave diminished conversion to product. In these cases, filtration of the substrate through alumina, in a glove box, restored full reactivity.

(8) (a) The yields for the two processes compare as follows [old(new)]: entry 1, 80(92); entry 7, 67(90); entry 8, 45(92); entry 9, 54(92). (b) A comparison of the mole percent catalyst used [old(new)]: entry 1, 10(5); entry 7, 10(7.5); entry 8, 10(10); entry 9, 10(5).

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Table 2. Cyclopentenones from Enynes Containing Disubstituted Olefins

Entry	Substrate	Product	Mol % Cp ₂ Ti(CO) ₂	Yield (%)
1	 E' = CO ₂ (t-Bu)		5	94 ^a
2	 E = CO ₂ Et	 R = Ph, 10 R = Me, 10	10 10	91 ^b 86 ^b
3	 (3:1 trans)		20	67 ^b (4:1 trans)
4	 (24:1 cis)		20	58 ^{b,c} (2:1 cis)

^a Required 18 psig of CO for conversion. ^b Required 5 psig of CO for complete conversion. ^c Unreacted substrate by GC (30%).

Recently, the Mo(CO)₆-promoted conversion of 1,5-allenynes to α -methylene cyclopentenones has been reported.¹² In that report, Co₂(CO)₈ failed to effect cyclization, presumably due to competing allene polymerization. While Cp₂Ti(CO)₂ also promotes the cyclization of 1,5-allenynes,¹⁰ it catalyzes the cyclization of a 1,4-allenynes to a bicyclic dienone (entry 10). This represents the first transition metal catalyzed cyclocarbonylation of an allenynes.

One of the most significant features of this catalyst system is the ability to cyclize substrates containing substituted olefins. The earlier Cp₂Ti(PMe₃)₂-catalyzed isocyanide cyclocondensation is only effective for the cyclization of 1,1-disubstituted olefins, and then only when 20 mol % of catalyst is used.⁴ Only a single example of the successful catalytic Pauson–Khand-type transformation of an enyne containing a 1,2-disubstituted olefin has been reported.^{3a,d} This substrate contains both an α -acetoxy group capable of acting as a chelating ligand^{13a} and is a terminal alkyne.^{13b,14} Table 2 summarizes our work with substrates containing both substituted olefins and internal alkynes. Entry 1 shows an example of a 1,1-disubstituted olefin substrate which is cyclized using 5 mol % of catalyst. As shown in entry 2, tricyclic cyclopentenones are produced from the cyclic 1,2-disubstituted olefin substrates in excellent yields. Although stoichiometric Pauson–Khand cyclizations of this class of substrate have been realized,¹⁵ this is the first report of a catalytic variant of this transformation. The viability of this catalyst for the transformation of simple acyclic 1,2-disubstituted

olefin substrates is shown in entry 3. By utilizing a geometrically pure *cis* substrate, it was found that cyclization occurs with considerable olefin isomerization¹⁶ (entry 4). The reactions of 1,2-disubstituted olefin substrates did not go to completion at 18 psig of CO, but lowering the pressure to 5 psig led to complete consumption of substrate. Presumably, competition between CO and the 1,2-disubstituted olefin for coordination to the titanium center gives rise to the observed pressure dependence.

Despite the differences in substrate scope between the two titanium-catalyzed methodologies noted above, we initially assumed that the carbonylation proceeds *via* a mechanism similar to our previous iminocyclopentene synthesis, with CO replacing the isocyanide (Scheme 1). However, further evidence indicates the two systems are mechanistically distinct. Cyclocarbonylations employing Cp₂Ti(PMe₃)₂ or metallacycle **2**¹⁷ as the precatalyst require twice the amount of catalyst utilized by reactions employing Cp₂Ti(CO)₂. This implies that the carbonylation of enynes using Cp₂Ti(CO)₂ does not proceed *via* formation of metallacycle **2**. There is also a significant stereochemical variance between the two systems when chiral enyne substrates are cyclized (Table 1, entries 7, 8).¹⁸ If both systems proceed through the same intermediate metallacycle, the diastereoselectivities would be expected to be similar if both reactions are under thermodynamic (or kinetic) control. Further evidence against **2** as an intermediate is demonstrated in the cyclization of allenynes. While enynes which are carbonylated with Cp₂Ti(CO)₂ form metallacycles like **2** when treated with Cp₂Ti(PMe₃)₂, 1,5- and 1,4-allenynes show no evidence for metallacycle formation, although they are cleanly carbonylated by Cp₂Ti(CO)₂. We are currently seeking to clarify the mechanistic discrepancies between the two catalytic reactions.

In conclusion, we have developed the first early transition metal catalyzed carbonylative route to cyclopentenones. Besides demonstrating a novel reactivity mode for an early transition metal carbonyl, the Cp₂Ti(CO)₂ system displays an unexpectedly increased level of functional group compatibility as compared to other group 4 metallocene cyclizations and intriguing mechanistic differences from the related iminocyclopentene synthesis. Additionally, it shows a greater tolerance for substituted alkenes than related cobalt procedures.

Supporting Information Available: Complete experimental procedures as well as spectroscopic data for all new compounds and analytical data for most new compounds (8 pages). See any current masthead page for ordering and Internet access instructions.

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