

Cobalt-Catalyzed Cycloisomerization of  
1,6-Enynes and Allyl Propargyl Ethers

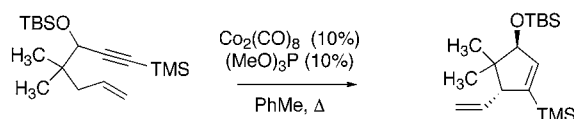
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## ABSTRACT

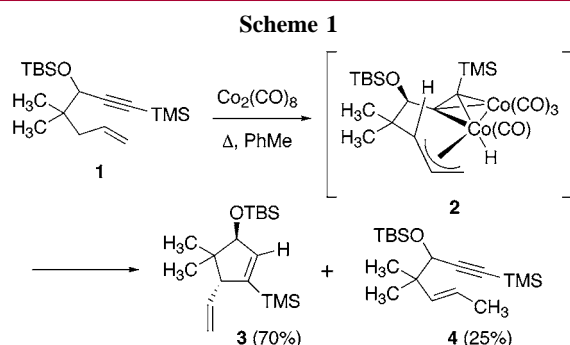


1,6-Enynes and allyl propargyl ethers undergo a cobalt-catalyzed formal 5-endo-dig cyclization to form vinyl cyclopentenes and dihydrofurans, respectively. The use of equimolar amounts of dicobalt octacarbonyl and trimethyl phosphite affords optimum yields and improved selectivity for cycloisomerization vs alkene isomerization.

Cycloisomerizations of acyclic dienes, enynes, and diyne are of tremendous interest in organic chemistry. Depending on the substrate, any one of a number of metal sources may catalyze such reactions.<sup>1</sup> In most cases, cycloisomerizations occur through exocyclic manifolds to give 1,2-substituted carbocycles and heterocycles. Recently, we disclosed a cobalt-mediated cycloisomerization of 1,6-enynes that proceeded through the less common endo-mode of cyclization (Scheme 1).<sup>2,3</sup> The reaction proceeds through an allylic C–H

bond formation to furnish vinyl cyclopentenes with excellent levels of diastereoselectivity. Subsequently, we showed that the reaction could be extended to allyl propargyl ethers to form vinyl dihydrofurans.<sup>4</sup> In both cases, the reactions used stoichiometric amounts of dicobalt octacarbonyl. In this letter, we report that the reactions may be made catalytic through the addition of an appropriate phosphorus ligand.

Significant effort has gone into the development of methods that enable the use of catalytic amounts of  $\text{Co}_2(\text{CO})_8$  in the Pauson–Khand reaction.<sup>5,6</sup> The most common methods have used high pressures of CO to regenerate  $\text{Co}_2(\text{CO})_8$ , although Krafft has recently shown that lower pressures may be used in conjunction with amine additives.<sup>4g,k</sup> Part of the difficulty in developing these methods has been



oxidative insertion to form an allylcobalt hydride intermediate (e.g., **2**). This species undergoes sequential C–C and C–H

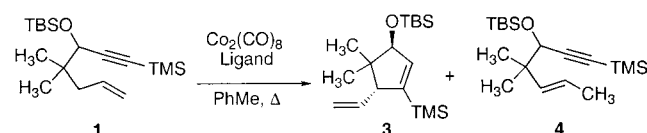
(1) Reviews: (a) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813.

(2) Dolaine, R.; Gleason, J. L. *Org. Lett.* **2000**, *2*, 1753.  
 (3) For a related endocyclic cycloisomerization, see: Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 9728.  
 (4) Ajamian, A.; Gleason, J. L. *Org. Lett.* **2001**, *3*, 4161.  
 (5) (a) Lee, B. Y.; Chung, Y. K. *J. Am. Chem. Soc.* **1994**, *116*, 8793. (b) Lee, N. Y.; Chung, Y. K. *Tetrahedron Lett.* **1996**, *37*, 3145. (c) Pagenkopf, B. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, *118*, 2285. (d) Sugihara, T.; Yamada, M.; Ban, H.; Yamaguchi, M.; Kaneko, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2801. (e) Jeong, N.; Hwang, S. H.; Lee, Y. W.; Lim, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 10549. (f) Krafft, M. E.; Bonaga, L. V. R.; Hirotsawa, C. *Tetrahedron Lett.* **1999**, *40*, 9171. (g) Krafft, M. E.; Bonaga, L. V. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3676. (h) Seung, U. S.; Lee, S. I.; Chung, Y. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 4158. (i) Kim, S. W.; Son, S. U.; Lee, S. I.; Hyeon, T.; Chung, Y. K. *J. Am. Chem. Soc.* **2000**, *122*, 1550. (j) Comely, A. C.; Gibson, S. E.; Stevenazzi, A.; Hales, N. J. *Tetrahedron Lett.* **2001**, *42*, 1183. (k) Krafft, M. E.; Bonaga, L. V. R.; Hirotsawa, C. *J. Org. Chem.* **2001**, *66*, 3004. (l) Gibson, S. E.; Johnstone, C.; Stevenazzi, A. *Tetrahedron.* **2002**, *58*, 10371. (m) Son, S. U.; Lee, S. I.; Chung, Y. K.; Kim, S. W.; Hyeon, T. *Org. Lett.* **2002**, *4*, 277.

limited information about the late intermediates and final fate of the cobalt species in the stoichiometric process. A similar situation arises with the cycloisomerization of 1,6-enynes and allyl propargyl ethers. As these reactions have been conducted in the absence of CO, the final product is often metallic cobalt, which either precipitates as a finely divided solid or plates out of solution as a mirror.

In early attempts to induce a catalytic process, we explored the use of phosphines as supporting ligands for cobalt. Preliminary studies were conducted on enyne **1** using 10 mol %  $\text{Co}_2(\text{CO})_8$  in refluxing toluene under an argon atmosphere. As shown in Table 1, triphenylphosphine was found to be a

**Table 1.** Survey of Supporting Ligands for Cobalt-Catalyzed Cycloisomerization



entry	ligand <sup>a</sup>	ratio of $\text{Co}_2(\text{CO})_8$ /ligand	<b>3</b> <sup>b</sup> (%)	<b>4</b> <sup>b</sup> (%)
1	$\text{Ph}_3\text{P}$	6	0	0
2	$\text{Ph}_3\text{P}$	2	15	6
3	$\text{Ph}_3\text{P}$	1	47	14
4	$\text{Ph}_3\text{P}$	0.5	45	11
5	$\text{Et}_3\text{P}$	1	12	6
6	$\text{Cyc}_3\text{P}$	1	25	7
7	<i>t</i> - $\text{Bu}_3\text{P}$	1	72	13
8	$(\text{PhO})_3\text{P}$	1	59	23
9	$(\text{MeO})_3\text{P}$	1	93	7
10	$(\text{EtO})_3\text{P}$	1	60	27
11	$(i\text{-PrO})_3\text{P}$	1	69	19
12	HMPT	1	6	1

<sup>a</sup> All reactions were conducted over a 5 h period using 10 mol %  $\text{Co}_2(\text{CO})_8$ . <sup>b</sup> Yields were determined by GC analysis versus a calibrated internal standard. Isolated yield for entry 9 was 97% of a 13:1 mixture of **3** and **4**.

competent supporting ligand, affording the highest yield of cyclopentene **3** when used in a 1:1 ratio with  $\text{Co}_2(\text{CO})_8$ . Other phosphines such as tricyclohexyl-, tri-*tert*-butyl-, and triethylphosphine also catalyzed the cycloisomerization. Although none went to completion, the best results were observed using the sterically hindered tri-*tert*-butylphosphine. Drawn by reports of the use phosphites in both catalytic Pauson–Khand reactions and cobalt-catalyzed expansion of alkynylcyclopropanols, we examined their use in the cycloisomerization process.<sup>7</sup> Several aryl and alkyl phosphites proved to be competent ligands. The most effective was trimethyl phos-

(6) For catalytic Pauson–Khand reactions that use metals other than cobalt: (a) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 9450. (b) Kondo, T.; Suzuki, N.; Okada, T.; Mitsudo, T. *J. Am. Chem. Soc.* **1997**, *119*, 6187. (c) Morimoto, T.; Chatani, N.; Fukumoto, Y.; Murai, S. *J. Org. Chem.* **1997**, *62*, 3762. (d) Morimoto, T.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *J. Am. Chem. Soc.* **2002**, *124*, 3806. (e) Brummond, K. M.; Chen, H.; Fischer, K. D.; Kerekes, A. D.; Rickards, B.; Sill, P. C.; Geib, S. J. *Org. Lett.* **2002**, *4*, 1931.

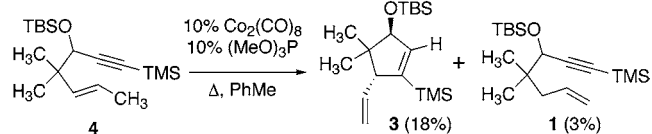
(7) (a) Jeong, N.; Hwang, S. H.; Lee, Y.; Chung, Y. K. *J. Am. Chem. Soc.* **1994**, *116*, 3159. (b) Iwasawa, N.; Matsuo, T.; Iwamoto, M.; Ikeno, T. *J. Am. Chem. Soc.* **1998**, *120*, 3903.

phite, which afforded complete conversion of the starting material after 5 h to a 13:1 mixture of cyclopentene **3** and isomerization product **4** in 97% isolated yield after chromatography.<sup>8</sup> More basic ligands such as HMPT were not effective, while the addition of pyridines completely inhibited the reaction.

A study of solvents showed that the trimethyl phosphite catalyst system was competent in ethereal solvents as well as in benzene, but in all cases, incomplete conversion to product was observed. It is interesting to note, however, that the reaction does proceed to an appreciable extent in benzene (76%), whereas conducting the reaction in benzene using stoichiometric amounts of  $\text{Co}_2(\text{CO})_8$  (in the absence of ligand) affords only minute amounts of product. Thus, the role of the phosphite in these reactions is not only to support the metal, preventing it from precipitating from solution, but also to accelerate the cycloisomerization process. Examining the catalyst loading, it was found that the reaction could be conducted equally well with 5% catalyst, although as expected the reaction required longer reaction periods (9 h for the reaction shown in Table 1). Use of lower catalyst loadings was less successful. The reactions may be conducted in open air, but higher yields are usually observed if the reaction is conducted under an argon atmosphere.

An important observation in the cyclization utilizing  $(\text{MeO})_3\text{P}$  as ligand was that the reaction produced only 7% of alkene isomerization product **4**, which is a significant improvement over the stoichiometric process. Following this reaction over time by gas chromatography showed that within 2 h, the starting material had been almost completely consumed and compounds **3** and **4** were present in a 69:25 ratio. Further heating improved the ratio in favor of the desired cyclization product, and at the end of 5 h, the ratio was 93:7. These results indicate that **4** is a substrate for the cobalt-catalyzed cycloisomerization. Independent synthesis of **4** and submission to the reaction conditions produced the cycloisomerization product **3** in 18% yield along with 3% enyne **1** and 79% recovered **4** after 5 h of reaction time (Scheme 2).<sup>9</sup> The slower isomerization rate of the 1,5-enyne

**Scheme 2**

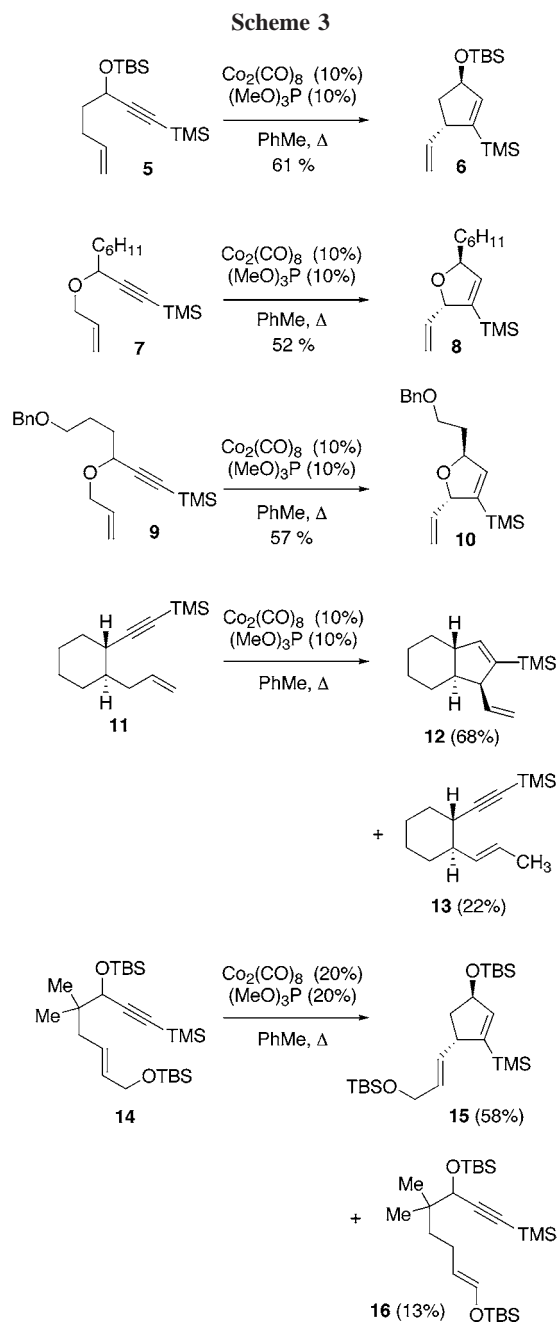


**4** relative to that of the 1,6-enyne **1** suggests that in the normal cycloisomerization mode, **4** may act as a catalyst “sink”, thus reducing catalyst turnover efficiency.

(8) Products **3** and **4** were not separable by chromatography. Treatment of the mixture with  $\text{K}_2\text{CO}_3$  in methanol to remove the acetylenic TMS group allowed **3** to be removed as a volatile component. This allowed **4** to be isolated in pure form in 91% yield. The reaction can be conducted on >1 mmol scale with ease (see Supporting Information).

(9) Although initial studies (ref 2) did not reveal any cyclization of **4** under stoichiometric conditions, subsequent studies have shown that **4** does indeed slowly cyclize to **1** in low yield (20%) under stoichiometric conditions.

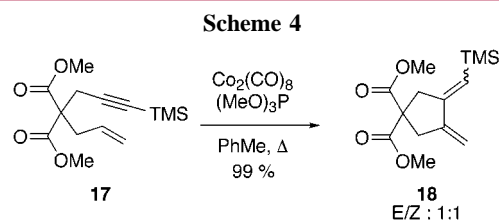
The reaction works well with a range of 1,6-enynes and allyl propargyl ethers to form vinyl cyclopentenes and dihydrofurans (Scheme 3). Although isomerization products



are observed in some cases (e.g., cyclizations of **11** and **14**), this observation is not universal. In the case of the allyl propargyl ethers, this may be due to the fact that the isomerization product would be a potentially unstable enol ether. As in the stoichiometric version of the reaction, the presence of a trimethylsilyl group on the alkyne terminus is required for cycloisomerization to take place. The reaction is highly stereoselective, affording 1,3-trans-substituted products in all cases. The geometric constraints of the C–H

activation process are underscored by the case of cyclohexane substrate **11**. While the trans-substituted enyne cyclizes cleanly to form 5,6-fused bicycle **12**, the corresponding cis-substituted enyne does not undergo cyclization. Presumably, this reflects a nonoptimal alignment of the C–H bond in the cobalt–alkyne complex of the cis-isomer.

Finally, we examined the cyclization of malonate-derived **17**, which under stoichiometric conditions affords the Pauson–Khand cycloadduct rather than the cycloisomerization product even if the reaction is conducted under an argon atmosphere.<sup>2</sup> Under catalytic conditions, the reagent does not have sufficient CO to allow high conversion to the Pauson–Khand product, and thus it was hoped that the lack of CO would allow this substrate to proceed down the cycloisomerization pathway. However, subjecting **17** to the catalytic cycloisomerization conditions again failed to produce the desired product and, instead, diene **18** was produced in >99% yield as a 1:1 mixture of *E:Z* isomers (Scheme 4).<sup>10</sup> Similar



diene formation has been reported when unactivated and electron-deficient alkenes are used in the presence of  $\text{Co}_2(\text{CO})_8$ .<sup>11</sup>

In conclusion, we have developed practical catalytic conditions for the cycloisomerization of 1,6-enynes and allylpropargyl ethers to their corresponding vinyl cyclopentene and dihydrofuran derivatives using dicobalt octacarbonyl and trimethyl phosphite. The reaction is high-yielding and highly diastereoselective. Importantly, the observation that the phosphite ligand accelerates the cycloisomerization reaction may allow development of a catalytic enantioselective cyclization based on this methodology. Further work toward this end will be reported in due course.

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**Supporting Information Available:** Experimental procedures and characterization for all new materials. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(10) Malonates similar to **14** possessing an –OTBS group at the propargylic position also fail to give the desired cycloisomerization product.

(11) Krafft, M. E.; Wilson, A. M.; Dasse, O. A.; Bonaga, L. V. R.; Cheung, Y. Y.; Fu, Z.; Shao, B.; Scott, I. L. *Tetrahedron Lett.* **1998**, 39, 5911.