The Interrupted Pauson−Khand Reaction

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The thermal or amine oxide promoted Pauson−Khand reaction[1] of a dicobalt hexacarbonyl complexed enyne normally gives rise to bicyclic enones (eq 1).[2,3] During the course of our studies on the Pauson−Khand reaction we discovered a new enone from the thermal reaction of dicobalt hexacarbonyl complexed enyne **1**. Thermolysis of **1** under a nitrogen atmosphere yielded not only the bicyclic enone **2** but also enone **3** in 20−40% yields as a byproduct of the reaction. Inspection of the unexpected monocyclic product revealed that oxygen had been incorporated without carbon monoxide insertion and that cyclization to form the second ring had not proceeded in the normal fashion. This presumably occurs via enyne cycloaddition and subsequent oxidation, via adventitious oxygen, generating only one ring instead of the anticipated two. Metal−carbon bonds formed in transition metal mediated insertions or cycloadditions are generally functionalized to give products resulting from carbonyl insertion,[1−4] reduction,[5] β-elimination,[6] or further cycloaddition reactions.[7,8] However, fewer examples of subsequent oxidative functionalization of the metal−carbon bond have been reported.[9−11] Herein we describe the development of the interrupted intramolecular Pauson−Khand reaction.

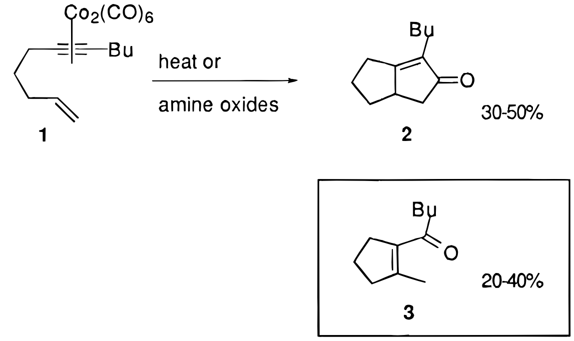
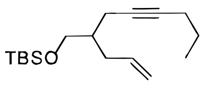
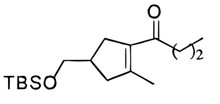
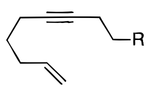
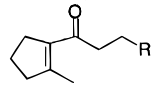
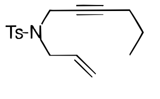
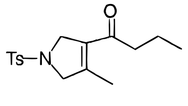
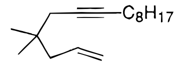
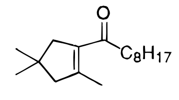
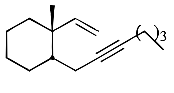
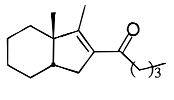
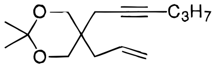
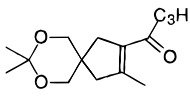
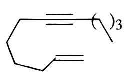
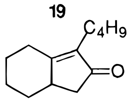
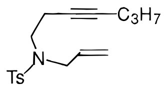
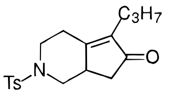


Table 1

Entry	Enyne[a]	Cyclopentenone	Yield[b,c]
1	 **4**	 **5**	67 [6]
			
		R	
2	**6**	CN **9**	75 [15]
3	**7**	(CH$_2$)$_2$OTBS **10**	59
4	**1**	Et **3**	54
5	**8**	CH$_2$Ph **11**	70
6	 **12**	 **13**	55 [10]
7	 **14**	 **15**	52
8	 **16**	 **17**	80
9	 **18**	 **19**	56 [18][d]
10	 **20**	 **21**	-- [40]
11	 **22**	 **23**	-- [30][e]

[a] Refers to the dicobalthexacarbonyl complexed enyne. [b] Yields in the table refer to isolated, chromatographically purified products. The number in brackets is the percent of Pauson−Khand enone isolated. [c] See ref 12 for general reaction conditions. [d] 18% of the corresponding diene was also isolated, see ref 13. [e] 30% of the corresponding diene was isolated, see ref 13.

The incorporation of oxygen without carbon monoxide insertion strongly suggested that molecular oxygen could be responsible for altering the anticipated outcome of the normal intramolecular enyne cycloaddition. Following that assumption, thermal cycloaddition of **1** at 70 °C in an open flask yielded enone **3** as the major product along with small amounts of Pauson−Khand enone **2**. Further refinement and modification of the specific reaction conditions involved dilution of the cobalt complexed enyne to 0.003 M in toluene, use of a rapidly stirred heated oil bath, and an atmosphere containing controlled amounts of oxygen.[12] One atmosphere (balloon) of commercially available compressed gas mixtures were used, either

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(1) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977. Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Perkin Trans. 1* **1973,** 975.

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(3) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289. Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S. E. *Synlett* **1991**, 204. Krafft, M. E.; Scott, I. L.; Romero, R. H.; Feibelmann, S.; Van Pelt, C. E. *J. Am. Chem. Soc.* **1993**, *115*, 7199.

(4) Zr: Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8593 and references cited therein. Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon: Oxford, UK, 1991; Vol. 5, pp 1163−1184. W: Hoye, T. R.; Suriano, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 1154. Ti: Crowe, W. E.; Vu, A. T. *J. Am. Chem. Soc.* **1996**, *118*, 1557. Urabe, H.; Hata, T.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 4261 and references cited therein. Fe: Pearson, A. J.; Dubbert, R. A. *Organometallics* **1994**, *13*, 1656. Rh: Krafft, M. E.; Wilson, L. J.; Onan, K. D. *Tetrahedron Lett.* **1989**, *29*, 6421. Anastasiou, D.; Jackson, W. R. *Tetrahedron Lett.* **1990**, *31*, 4795. Ni: Oppolzer, W.; Bedoya-Zurita, M.; Switzer, C. Y. *Tetrahedron Lett.* **1988**, *29*, 6433. Pages, L.; Llebaria, A.; Camps, F.; Molins, E.; Miravitlles, C.; Moreto, J. M. *J. Am. Chem. Soc.* **1992**, *114*, 10449. Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1286. Pd: Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38.

(5) For examples, see: Kablauoni, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6785. Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787 and references cited therein.

(6) For representative examples, see: Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328. Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454.

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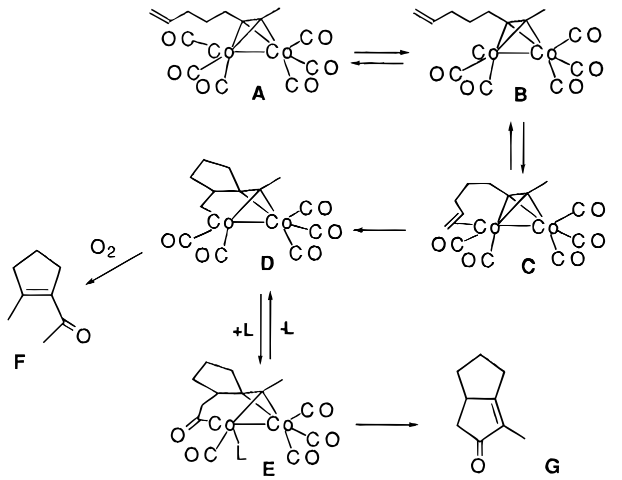
air, 5% oxygen in nitrogen, or pure oxygen. Results from reactions of a series of substituted enynes are listed in Table 1. In entries 1−9 we have successfully inhibited the “normal” Pauson−Khand process. However, the cobalt-complexed enyne in entry 9 began to form the Pauson−Khand product even at ambient temperature. Consequently, subsequent heating of the corresponding dicobalt−hexacarbonyl complex, under different oxygenated atmospheres, further promoted the undesired Pauson−Khand cycloaddition resulting in the formation of a 3:1:1 mixture of interrupted Pauson−Khand enone **19**: Pauson−Khand enone:1,3-diene[13] in 92% overall yield. As shown in entries 10 and 11, we found that, regardless of the reaction conditions used, substrates with 4 atom tethers between the alkene and alkyne did not give rise to the interrupted Pauson−Khand enone but rather gave the normal Pauson−Khand product (40 and 30% yields, respectively), and in the case of enyne **22**, 30% of the corresponding diene[13] was also observed.

The actual role of molecular oxygen in interrupting the normal Pauson−Khand reaction is unclear. The generally accepted mechanistic hypothesis for the normal enyne to enone process is outlined in Scheme 1.[2,14] Initial ligand exchange (**A**−**C**) presumably occurs via a dissociative process. The following metallacycle-forming step (**C**−**D**) is proposed to be both rate limiting and product determining. Subsequent insertion of carbon monoxide into a cobalt carbon bond (**D**−**E**) and reductive coupling generates the observed Pauson−Khand bicyclic enone. While elaborating on the function of oxygen in the process is not possible at this time, it seems plausible to propose that both the normal and interrupted Pauson−Khand products arise via a common metallacyclic intermediate, i.e. **D** in Scheme 1. The interception of **D** by molecular oxygen, perhaps at the metal center, could inhibit carbon monoxide insertion, and therefore be responsible for driving the reaction toward the observed enone **F**.

Scheme 1



In summary, we have demonstrated that use of an oxygenated atmosphere can cause a change in the normal Pauson−Khand reaction pathway leading to monocyclic enones instead of the anticipated bicyclic ones from thermolysis of dicobalt hexacarbonyl complexed enynes. Further work on this reaction is in progress and other results will be reported in due course.

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Supporting Information Available: Spectral data and analyses for enones **3, 5, 9, 10, 11, 13, 15, 17,** and **19** (4 pages). Ordering information is given on any current masthead page.

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(7) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081.

(8) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 791.

(9) Sole, D.; Cancho, Y.; Llebaria, A.; Moreto, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133.

(10) Matsunaga, P. T.; Hillhouse, G. L. *J. Am. Chem. Soc.* **1993**, *115*, 2075.

(11) For representative oxidations of M−C bonds, see the following. C−Zn: Klement, I.; Lutjens, H.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 3161. C−Ni: Sole, D.; Cancho, Y.; Llebaria, A.; Moreto, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133. C−Pd: Kitching, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon: Oxford, UK, 1991; Vol. 7, pp 613−639. C−Al: Negishi, E-i.; Jensen, M. D.; Kondakov, D. Y.; Wang, S. *J. Am. Chem. Soc.* **1994**, *116*, 8404. Insertions that yield a π-allyl metal complex can be functionalized by nucleophilic addition to give C−N, C−O, or C−C bonds; for examples, see: Grigg, R.; Dorrity, M. J.; Malone, J. F. *Tetrahedron Lett.* **1990**, *31*, 1343. Takacs, J. M.; Zhu, J. *J. Org. Chem.* **1989**, *54*, 5193. C−Ti: Wilson, A. M.; West, F. G.; Arif, A. M.; Ernst, R. D. *J. Am. Chem. Soc.* **1995**, *117*, 8490.

(12) A typical general procedure for the synthesis of enone **5** follows: The dicobalt hexacarbonyl complex of enyne **4** (80 mg, 0.14 mmol) was dissolved in toluene (50 mL) to give a 0.003 M solution which was loaded into a pressure equalizing addition funnel. To the receiving flask 10 mL of toluene was added and the entire apparatus was placed under an atmosphere of air at room temperature for 10 min. The receiving flask was then allowed to come to 90 °C and the solution of the cobalt complex was added dropwise over a period of 20 min. The reaction was then stirred for 1 h at 90 °C under the atmosphere of air. The solution was allowed to cool, and the crude product was isolated after passage through a coarse frit with a Celite pad under aspirator pressure. Subsequent removal of the solvent followed by purification via radial chromatography (2-mm plate, 10% EtOAc in hexane) resulted in a 67% isolated yield of **5**. Experimental conditions used for the reactions listed in the table (enyne, atmosphere, temperature in °C) are as follows: **6**, air, 90; **7**, air, 90; **1,** air, 90; **8**, 5% O_2 in N_2, 100; **12**, O_2, 100; **14**, air, 70; **16**, air, 90; **18**, O_2, 100; **20**, air, 90; **22**, O_2, 100.

(13) 1,3-Dienes have frequently been observed as byproducts from the thermal Pauson−Khand cycloaddition. 1,3-Dienes are the only product formed when electron-deficient alkenes are used. See: Khand, I. U.; Pauson, P. L. *J. Chem. Soc., Chem. Commun.* **1974**, 379.

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