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Mild and Efficient Molybdenum-Mediated Pauson–Khand-Type Reaction

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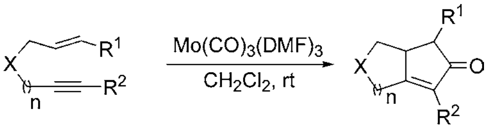
ABSTRACT



n= 1, 2; R^1= H, EWG; R^2= H, alkyl, aryl

The molybdenum-mediated Pauson–Khand reaction promoted by $Mo(CO)_3(DMF)_3$ takes place under very mild conditions in the absence of any promoter. High yields in Pauson–Khand adducts are obtained in the cyclization of a wide variety of functionalized 1,6- and 1,7-enynes. Enynes bearing electron withdrawing groups at the alkene terminus are particularly good substrates.

The formal transition metal mediated [2 + 2 + 1] cycloaddition of an alkyne, an alkene and carbon monoxide is nowadays one of the most convergent and practical methods for cyclopentenone synthesis.[1] The cobalt-mediated process known as the Pauson−Khand reaction (PKR), first reported in 1973,[2] was originally carried out by heating a mixture of stoichiometric amounts of dicobalt octacarbonyl, an alkyne and an alkene. The further development of new reaction conditions, such as the use of amine-*N*-oxides,[3] amines,[4] or thioethers[5] as promoters, allowed the reaction to be performed at lower temperatures (usually rt or 0 °C), greatly improving the scope and synthetic utility of the process.

In the past decade, an area of active research in the PKR has been the use of other transition metals, including titanium, nickel, iron, tungsten, rhodium, ruthenium, zirconium, or iridium species.[6] Every metal in these Pauson−Khand-type processes has its own advantages/limitations in terms of scope, cost, reaction conditions and functional group compatibility. In 1992, Hanaoka et al.[7] reported the first example of a molybdenum-mediated Pauson−Khand reaction by heating (110−160 °C) a mixture of bis(cyclopentadienyl)-tetracarbonyldimolybdenum-alkyne complex and norbornene or norbornadiene. One year later, Jeong et al. reported a more practical and general method using $Mo(CO)_6$.[8] The reaction was performed in toluene at 100 °C for 8−24 h in the presence of a large excess of DMSO to promote the initial CO decomplexation step required for the coordination of the alkyne and alkene partners to the metal center. These conditions [$Mo(CO)_6$, toluene, DMSO, 100 °C] were later

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(1) For recent reviews on PKR, see: (a) Geis, O.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **1998**, *37*, 911−914. (b) Jeong, N. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 1998; pp 560−577. (c) Chung, Y. K. *Coord. Chem. Rev.* **1999**, *188*, 297−341. (d) Fletcher, A. J.; Christie, S. D. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1657−1668. (e) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263−3283. (f) Sugihara, T.; Yamaguchi, M.; Nishizawa, M. *Chem. Eur. J.* **2001**, *7*, 3315−3318. (g) Hanson, B. E. *Comments Inorg. Chem.* **2002**, *23*, 289−318. (h) Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32−42. (i) Boñaga, Ll. V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795−9833.

(2) (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 975−977. (b) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977−981.

(3) (a) Shambayati, P. S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289−5292. (b) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S.-E. *Synlett* **1991**, 204−207.

(4) Sugihara, T.; Yamada, M.; Ban, H.; Yamaguchi, M.; Kaneko, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2801−2804.

(5) Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771−773.

(6) For a recent review on Pauson−Khand-type reactions, see: Buchwald, S. L.; Hicks, F. A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 2, pp 491−510.

(7) Mukai, C.; Uchiyama, M.; Hanaoka, M. *J. Chem Soc., Chem Commun.* **1992**, 1014−1015.

(8) Jeong, N.; Lee, J. S.; Lee, B. Y.; Chung, Y. K. *Tetrahedron Lett.* **1993**, *36*, 2407−2410.

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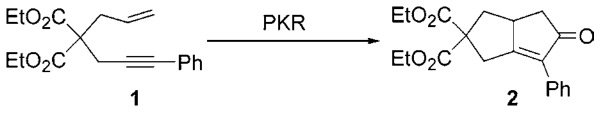
applied by other authors, especially Brummond and Cook, to the intramolecular reaction of alkynyl allenes.[9]

Since molybdenum complexes could be an attractive alternative to the classical dicobalt species $Co_2(CO)_8$, the development of new and milder reaction conditions for molybdenum-promoted PKR, which could enhance the synthetic scope of the process would be of great interest. In this context, we envisaged that, instead of $Mo(CO)_6$, the use of the much more ligand labile molybdenum carbonyl species $Mo(CO)_3(L)_3$ could greatly improve the reactivity of the process without the need of adding any type of promoter or additive.[10]

To test this assumption we selected as a model substrate the readily available 1,6-enyne **1**. We found that the reaction of **1** with $Mo(CO)_6$ under the usual conditions (toluene, DMSO, 100 °C) required 16 h for complete conversion, giving **2** in 53% yield (Table 1, entry 1). To our delight we observed that the reaction of **1** with the readily available complex $Mo(CO)_3(DMF)_3$[11] in toluene at rt afforded 75% conversion after 3 h (entry 2). To optimize the reactivity of this reaction, we briefly explored the effect of the solvent (entries 3−8). While no reaction was observed in CH_3CN or DMF, and incomplete conversions were observed in MeOH, THF, and AcOEt, a complete transformation was achieved in CH_2Cl_2 after 3 h (entry 8), providing the PK adduct **2** in 88% isolated yield.[12]

Table 1. Molybdenum Mediated Pauson−Khand Reaction of Model Enyne **1**

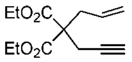
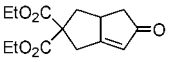
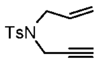
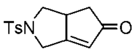
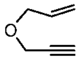
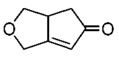
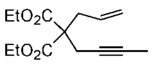
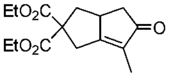
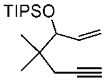
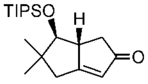
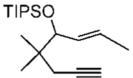
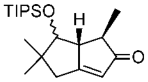
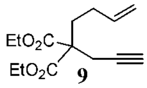
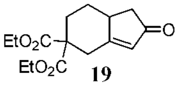
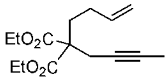
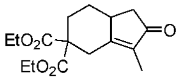
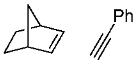
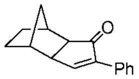
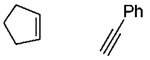
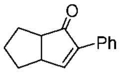


entry	metal complex	conditions	conv	yield[a]
1	$Mo(CO)_6$	toluene,100 °C DMSO, 16 h	73	53
2	$Mo(CO)_3(DMF)_3$	toluene, rt, 3 h	75	61
3	$Mo(CO)_3(DMF)_3$	CH_3CN, rt, 3 h		
4	$Mo(CO)_3(DMF)_3$	DMF, rt, 3 h		
5	$Mo(CO)_3(DMF)_3$	MeOH, rt, 3 h	53	38
6	$Mo(CO)_3(DMF)_3$	THF, rt, 3 h	70	59
7	$Mo(CO)_3(DMF)_3$	AcOEt, rt, 3 h	89	69
8	$Mo(CO)_3(DMF)_3$	CH_2Cl_2, rt, 3 h	>99	88

[a] Yields (%) after chromatographic purification on silica gel.

With these reaction conditions in hand we next explored the scope of the process by studying a wide variety of substrates (Table 2).

Table 2. $Mo(CO)_3(DMF)_3$-Mediated Pauson−Khand Reaction of Different Substrates[a]

entry	enyne	product	time	yield[b]
1	 **3**	 **13**	15min	83
2	 **4**	 **14**	15min	81
3	 **5**	 **15**	15min	78
4	 **6**	 **16**	2 h	85
5	 **7**	 **17**	1 h	75
6	 **8**	 **18**	7 h	0
7	 **9**	 **19**	4 h	61
8	 **10**	 **20**	5 h	60
9	 **11**	 **21**	5 h	62
10	 **12**	 **22**	7 h	0

[a] All reactions were carried out in dichloromethane at room temperature. [b] Yields (%) after chromatographic purification on silica gel.

Good yields in bicyclo[3.3.0]octenones (75−85%) were obtained from all 1,6-enynes unsubstituted at the alkene

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(9) (a) Kent, J. L.; Wan, H.; Brummond, K. M. *Tetrahedron Lett.* **1995**, *36*, 2407−2410. (b) Brummond, K. M.; Wan, H. *Tetrahedron Lett.* **1998**, *39*, 931−934. (c) Brummond, K. M.; Wan, H.; Kent, J. L. *J. Org. Chem.* **1998**, *63*, 6535−6545. (d) Cao, H.; Van Ornum, S. G.; Cook, J. M. *Tetrahedron Lett.* **2000**, *41*, 5313−5316. (e) Brummond, K. M.; Lu, J.; Petersen, J. *J. Am. Chem. Soc.* **2000**, *122*, 4915−4920. (f) Brummond, K. M.; Sill, P. C.; Rickards, B.; Geib, J. S. *Tetrahedron Lett.* **2002**, *43*, 3735−3738. (g) Shen, Q.; Hammond, G. B. *J. Am. Chem. Soc.* **2002**, *124*, 6534−6535. (h) Cao, H.; Flippen-Anderson, J.; Cook, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 3230−3231. (i) Brummond, K. M.; Sill, P.; Chen, H. *Org. Lett.* **2004**, *6*, 149−152. (j) Brummond, K. M.; Mitasev, B. *Org. Lett.* **2004**, *6*, 2245−2248.

(10) For the use of (aryl)$Mo(CO)_3$/DMSO in related thermal cyclizations, see: (a) Brummond, K. M.; Kerekes, A. D.; Wan, H. *J. Org. Chem.* **2002**, *67*, 5156−5163. (b) Yu, C.-M.; Hong, Y.-T.; Yoon, S.-K.; Lee, J.-H. *Synlett* **2004**, 1695−1698. (c) Yu, C.-M.; Hong, Y.-T.; Lee, J.-H. *J. Org. Chem.* **2004**, *69*, 8506−8509.

(11) Pascuali, M.; Leoni, P.; Sabatino, P.; Braga, D. *Gazz. Chim. Ital.* **1992**, *122*, 275−279. Following this procedure $Mo(CO)_3(DMF)_3$ can be prepared from $Mo(CO)_6$ and DMF in multigram scale and stored under argon for months. For recent synthetic applications of $Mo(CO)_3(DMF)_3$ in organometallic chemistry, see: Arrayás, R. G.; Liebeskind, L. S. *J. Am. Chem. Soc*. **2003**, *125*, 9026−9027.

(12) **Typical Procedure.** An oven-dried Schlenk flask was charged under argon with $Mo(CO)_3(DMF)_3$ (0.57 mmol, 230 mg), capped with a rubber septum and twice evacuated and backfilled with argon. A solution of enyne **1** (0.57 mmol, 181 mg) in CH_2Cl_2 (5 mL) was added via syringe and the reaction mixture was stirred at room temperature for 3 h. The crude reaction mixture was filtered through a plug of Celite with the aid of CH_2Cl_2 and purified by flash chromatography (Hex/AcOEt 4:1) to afford cyclopentenone **2** (173 mg, 88%) as a colorless oil.

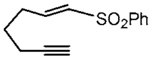
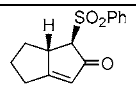
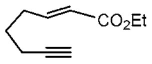
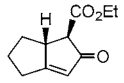
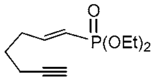
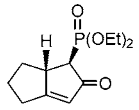
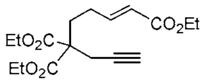
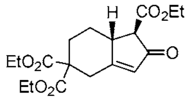
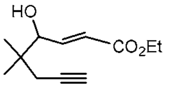
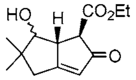
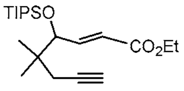
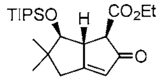
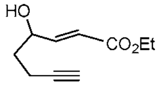
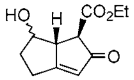
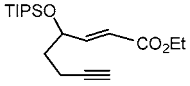
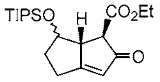
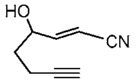
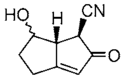
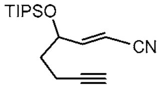
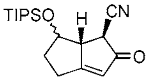
terminus regardless of the carbon or heteroatomic substitution at the enyne backbone studied (substrates **3**−**7**, entries 1−5). With most of these substrates the cyclization was very fast at rt (reaction times under 15 min), which allowed to perform the reaction at lower temperatures in quite reasonable times. For instance, the complete conversion of **3** took 30 min at 0 °C (81% yield) and 5 h at −20 °C (68% yield). It is also interesting to note that the cyclization of the allylic substituted enyne **7** was highly stereoselective, affording exclusively the *exo*-adduct **17**[13] (>98:<2 isomer ratio). In contrast, no reaction at all was observed in the case of the disubstituted alkene **8**, either at rt or 60 °C, showing the great sensitivity of the reaction to the steric effects at the alkene moiety.

On the other hand, 1,7-enynes **9** and **10** also proved to be suitable substrates in this reaction, albeit the reaction times were longer and the yields of the Pauson−Khand adducts somewhat lower (around 60% yield) than in the case of related 1,6-enynes. This is a particularly interesting result since this type of enyne failed to react under $Mo(CO)_6$/DMSO conditions.[8,14]

We also studied two examples of the intermolecular variant. In the presence of 5 equiv of norbornene the reaction with phenyl acetylene was complete within 5 h at rt, affording the expected *exo*-fused cyclopentenone **21** in 62% yield. In contrast, no reaction at all was observed in using cyclopentene as the olefin. This result parallels to the well-known low reactivity of non strained olefins in intermolecular PKR.[1]

Since the pioneering studies of Pauson and Khand,[15] it was generally assumed that electron poor olefins were not suitable substrates in Pauson−Khand reactions because the metallacycle intermediate was very prone to undergo a β-H elimination process, leading to the 1,3-diene instead of the cyclopentenone product.[16] Contrary to this belief, several interesting examples of successful Pauson−Khand reactions using electron poor olefins have been recently reported.[17] In connection with our previous work on the behavior of electron deficient substrates in Pauson−Khand reactions,[18] we decided to investigate the reaction of $Mo(CO)_3(DMF)_3$ with a variety of electron poor enynes (Table 3). With these substrates we had previously found that in their cobalt-mediated PKR the chemoselectivity of the process (cyclopentenone vs 1,3-diene formation) was deeply affected by the reaction conditions.[18e,19]

Table 3. $Mo(CO)_3(DMF)_3$-Mediated Intramolecular Pauson−Khand Reaction of Electron-Deficient Olefins

entry	enyne	product	t(h)	yield
1	 **23**	 **33**	3	80
2	 **24**	 **34**	3	72
3	 **25**	 **35**	3	65
4	 **26**	 **36**	5	55
5	 **27**	 **37** *exo*/*endo* 10/90	3	75
6	 **28**	 **38** *exo*/*endo* >98/<2	3	76
7	 **29**	 **39** *exo*/*endo* 11/89	3	64
8	 **30**	 **40** *exo*/*endo* 80/20	3	63
9	 **31**	 **41** *exo*/*endo* 15/85	3	62
10	 **32**	 **42** *exo*/*endo* 65/35	3	55

[a] All reactions were carried out in dichloromethane at room temperature. [b] Yields (%) after chromatographic purification on silica gel.

The set of enynes **23**−**32**, having different electron-withdrawing substitution at the alkene terminus (sulfone, phosphonate, ester, or nitrile) and length of the enyne (1,6- and 1,7-enynes), reacted completely within 3−5 h. Interestingly, these Mo-mediated reactions were completely chemoselective, affording the PK adducts (products **33**−**42**) in good isolated yields (55−80%). The possible conjugated 1,3-dienes were not detected in any case. This excellent reactivity is in

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(13) A 90:10 *exo*/*endo* ratio has been reported for the cobalt-mediated PKR of enyne **6.** See ref 18c.

(14) Only starting material was observed after heating **9** with $Mo(CO)_6$/DMSO in toluene at 100 °C for 24 h.

(15) (a) Khand, I. U.; Pauson, P. L. *J. Chem. Soc., Chem. Commun.* **1974**, 379. (b) Khand, I. U.; Pauson, P. L. *Heterocycles* **1978**, *11*, 59−67.

(16) 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*, 5911−5914.

(17) For a review see: Rodríguez Rivero, M.; Adrio, J.; Carretero, J. C. *Eur. J. Org. Chem.* **2002**, 2881−2889.

(18) (a) Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **1999**, *121*, 7411−7412. (b) Adrio, J.; Rodríguez Rivero, M.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2000**, *39*, 2906−2909. (c) Adrio, J.; Rodríguez Rivero, M.; Carretero, J. C. *Chem. Eur. J.* **2001**, *7*, 2435−2448. (d) Rodríguez Rivero, M.; de la Rosa, J. C.; Carretero, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 14992−14993. (e) Rodríguez Rivero, M.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 2975−2978.

(19) Hoye, T. R.; Suriano, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 1154−1155.

sharp contrast with the sluggish reaction of the sterically similar 1-alkyl substituted enyne **8** (Table 2), showing that electron-poor alkenes are particularly good substrates for this molybdenum-mediated PKR.

Of particular interest from a stereochemical point of view is the cyclization of the readily available γ-oxygenated enynes **27**−**32** (prepared by the one-step piperidine promoted condensation of the corresponding aldehyde with ethyl *p*-tolyl-sulfinyl acetate or *p*-tolyl-sulfinyl acetonitrile).[18e] We found that the relative configuration at C-5/C-6 (*endo*/*exo* selectivity) in the final PK adducts was highly dependent on the size of the oxygenated substitution at the γ-position, allowing the stereoselective preparation of either the *endo* or the *exo* isomer. Thus, in the case of the γ-hydroxy enynes the PKR occurred with a relatively high *endo*-selectivity (entries 5, 7 and 9), while the cyclization of the bulky OTIPS derivatives was always *exo*-selective (entries 6, 8, and 10).[20]

In conclusion we have developed a new version of the molybdenum-mediated PKR. This method is based on the use of $Mo(CO)_3(DMF)_3$ as a highly reactive carbonylmetal complex. Unlike the traditional PKR mediated by $Mo(CO)_6$/DMSO, the reactions with $Mo(CO)_3(DMF)_3$ take place under very mild conditions (CH_2Cl_2, rt or 0 °C) in the absence of any promoter. The scope of the intramolecular process is rather broad, tolerating the presence of a wide variety of substituents and functional groups at the 1,6- and 1,7-enyne framework, including electron-withdrawing groups at the alkene terminus.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[20] In the stereochemical assignment of the *endo/exo* adducts **39**−**42** the values of $J_{5,6}$ constitute a very useful diagnostic criteria: $J_{5,6}$ is significantly lower in the *endo* isomer ($J_{5,6}$ = 3.7−4.0 Hz, H_5/H_6 in *cis* arrangement) than in the *exo* isomer ($J_{5,6}$ = 8.9−9.3 Hz, H_5/H_6 in *trans* arrangement). On the other hand, the configuration of *endo*-**37** and *exo*-**38** was assigned by NOE experiments. Additionally, the OTIPS Pauson−Khand adducts were chemically correlated with the OH derivatives by desilylation (5 M HCl, THF, rt).