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Butenolide Synthesis by Molybdenum-Mediated Hetero-Pauson−Khand Reaction of Alkynyl Aldehydes

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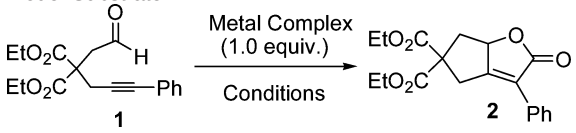
The Pauson−Khand reaction (PKR), the formal transition-metal-mediated three-component cycloaddition of an alkyne, an alkene, and carbon monoxide, constitutes one of the most useful and convergent methods for cyclopentenone synthesis.[1] In contrast, the hetero variant of this process,[2] and especially that involving the use of a carbonyl partner instead of the alkene component, has been much less studied despite the synthetic and natural product relevance of the resulting butenolide unit.[3] The first isolated example of this strategy was reported by Buchwald in 1996 by a low-yielding titanocene-mediated cyclocarbonylation of an alkynyl ketone under a carbon monoxide atmosphere.[2a] One year later, Murai described a more general protocol by the Ru-catalyzed hetero-PKR of alkynyl aldehydes under a carbon monoxide atmosphere and a high temperature (160 °C).[4] However, as an important drawback, this procedure cannot be applied to terminal alkynes. To the best of our knowledge, the only CO gas-free carbonylation of alkynes and aldehydes to give butenolides has been recently reported by Morimoto using a Rh-catalyzed process, albeit this procedure is limited to intermolecular processes involving formaldehyde as the carbonyl partner.[5]

Recently, we reported that the readily available molybdenum complex $Mo(CO)_3(DMF)_3$ efficiently promotes the intramolecular PKR of enynes in the absence of any promoter.[6] Extending the synthetic relevance of this highly reactive molybdenum carbonyl complex, we describe herein a very mild and general CO gas-free procedure for the synthesis of fused α,β-butenolides by the hetero-PKR of alkynyl aldehydes.

As a starting point, the alkynyl aldehyde **1** was selected as a model substrate for the cyclocarbonylation process (Table 1). Preliminary experiments showed that no reaction was observed when stoichiometric amounts of $Co_2(CO)_8$ or $Mo(CO)_6$ were used under usual cobalt- or molybdenum-mediated PKR conditions[7] (entries 1 and 2). On the contrary, in the presence of the commercially available complex $Mo(CO)_3(CH_3CN)_3$, the reaction occurred at room temperature in THF[8] to provide the butenolide **2** in 53% yield after 3 h (entry 3), showing the necessity of having labile ligands at the molybdenum atom. To our delight, the complex $Mo(CO)_3(DMF)_3$ proved to be even more reactive (15 min) and efficient (71% yield, entry 4).

With these optimal reaction conditions in hand, Table 2 summarizes the results obtained in the hetero-PKR of a variety of 5-yne aldehydes. Remarkably, in contrast to the previously reported Ru-catalyzed cyclocarbonylation process,[4] where alkyne disubstitution is required, this Mo-promoted reaction led to the butenolide adducts in high yields (60−71%) with both terminal (entries 3, 5, and 7) and disubstituted alkynes (entries 1, 2, 4, and 6). It is also interesting to note that the presence of substituents in the tether to restrict the conformational mobility of the substrate is not necessary for the success of the cyclization, albeit higher reaction times are required

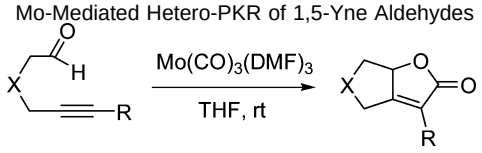
Table 1. Screening of Reaction Conditions for the Hetero-PKR of the Model Substrate **1**



entry	metal complex	conditions	yield (%)[a]
1	$Co_2(CO)_8$	NMO, rt, CH_2Cl_2, 16 h	0
2	$Mo(CO)_6$	toluene, DMSO, 100 °C, 16 h	0
3	$Mo(CO)_3(CN)_3$	THF, rt, 3 h	53
4	$Mo(CO)_3(DMF)_3$	THF, rt, 15 min	71

[a] Isolated yield after column chromatography.

Table 2. Mo-Mediated Hetero-PKR of 1,5-Yne Aldehydes



entry	X	R	substrate	time (min)	product	yield (%)[a]
1	$C(CO_2Et)_2$	Ph	**1**	15	**2**	71
2	$C(CO_2Et)_2$	Me	**3**	15	**4**	63
3	$C(CO_2Et)_2$	H	**5**	15	**6**	61
4	*N*-Boc	Ph	**7**	15	**8**	70
5	*N*-Boc	H	**9**	15	**10**	66
6	CH_2	Ph	**11**	120	**12**	68
7	CH_2	H	**13**	120	**14**	60

[a] Isolated yield after column chromatography.

(entries 6 and 7). Disappointingly, no cyclization at all was observed when an alkynyl ketone substrate was tested under the same reaction conditions.[9]

Next, we extended the procedure to the cyclocarbonylation of 6-yne aldehydes (Table 3). Although the reaction also occurred mildly under the standard reaction conditions, with these substrates, a variable amount of the *exo*-methylene alcohol **B**, the result of a noncarbonylative reductive cyclization, was formed as a minor product. In an attempt to inhibit this competitive process, several additives were studied.[10] Interestingly, the use of Et_3B as a Lewis acid additive[11] produced a significant enhancement of the selectivity in favor of the butenolide formation. Under these new reaction conditions, the five tested yne aldehydes provided the corresponding butenolides in satisfactory isolated yields (63−73%), regardless of the substitution at the tether and alkyne terminus (entries 3−7).

To enlarge the structural scope of this Mo-mediated cyclocarbonylation, we turned our attention to the synthesis of chiral nonracemic butenolides from readily available enantiopure α-substituted yne aldehydes (Table 4). Thus, aldehyde **25** was readily prepared in three steps from (*S*)-ethyl lactate and subjected to the usual hetero-PKR conditions, providing the butenolide **26** as the only detectable product in good yield (68%) and high *exo* selectivity (*exo*/*endo* = 92:8, entry 1).[12] An even better chemical and

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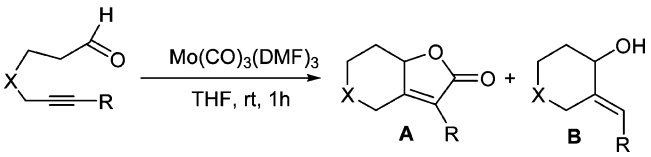
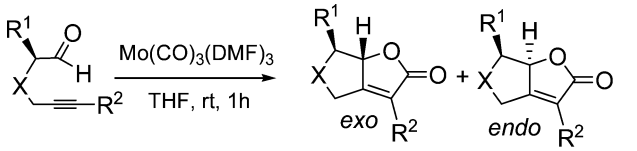
Table 3. Mo-Mediated Hetero-PKR of 1,6-Yne Aldehydes



entry	X	R	substrate	additive	product	A:B[a]	yield (%)[b]
1	$C(CO_2Et)_2$	H	**15**		**16**	82:18	69
2	$C(CO_2Et)_2$	H	**15**	Et_3B[c]	**16**	88:12	65
3	$C(CO_2Et)_2$	H	**15**	Et_3B[d]	**16**	92:8	63
4	$C(CO_2Et)_2$	Me	**17**	Et_3B[d]	**18**	>98:<2	73
5	*N*-Boc	H	**19**	Et_3B[d]	**20**	>98:<2	72
6	*N*-Boc	Ph	**21**	Et_3B[d]	**22**	93:7	70
7	$C(SO_2Ph)_2$	H	**23**	Et_3B[d]	**24**	90:10	65[e]

[a] Determined by ^{1}H NMR of the crude mixtures. [b] Isolated yield in adduct **A** after column chromatography. [c] 10 mol % of Et_3B. [d] 100 mol % of Et_3B. [e] Yield in **A** + **B** mixture.

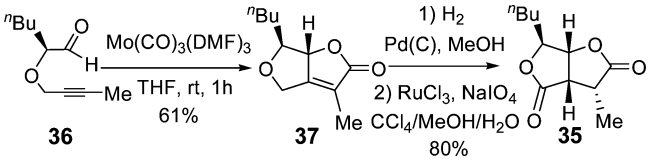
Table 4. Mo-Mediated Hetero-PKR of Enantiomerically Pure Yne Aldehydes



entry	X	R^1	R^2	substrate	product	*exo*:*endo*[a]	yield (%)
1	O	Me	H	**25**	**26**	92:8	68[b]
2	O	Me	Me	**27**	**28**	>98:<2	71
3	O	Me	Ph	**29**	**30**	>98:<2	76
4	*N*-Boc	^{i}Pr	H	**31**	**32**	14:86	62[b]
5	*N*-Boc	^{i}Pr	Ph	**33**	**34**	30:70	73[c]

[a] Determined by ^{1}H NMR of the crude mixtures. [b] Yield in the mixture *exo*/*endo* after column chromatography. [c] Yield of 51 and 22% of *endo* and *exo* adducts, respectively, after column chromatography.

Scheme 1. Synthesis of the (+)-Dihydrocanadensolide Epimer **35**



stereochemical outcome was obtained with the phenyl- and methyl-substituted alkynes **27** and **29**, which provided the *exo* adducts with complete selectivity (entries 2 and 3). In contrast, the *N*-Boc aldehydes derived from L-valine (**31** and **33**, entries 4 and 5) led to the corresponding butenolides with similar yields but reversed diastereoselectivity, showing the sensitivity of the *exo*/*endo* ratio to the substitution at the α-position and tether.[13] We also checked that the hetero-PKR takes place without racemization at the α-position of aldehydes **29** and **33**, as confirmed by the very high enantiopurity of the butenolides **30** and *endo*-**34** (96 and 98% ee, respectively, HPLC).

To highlight its synthetic potential, this highly convergent approach to the synthesis of bicyclic butenolides was finally applied to the straightforward synthesis of an epimer of dihydrocanadensolide (**35**), a biologically active bislactone metabolite isolated from *Penicillium canadense* (Scheme 1).[14] The exposure of the enantiomerically pure aldehyde **36** to the usual Mo-mediated reaction conditions afforded the butenolide **37** (61% yield) with complete *exo* selectivity. Hydrogenation of the C−C double bond followed by Ru-catalyzed ether-to-ester oxidation under Sharpless' conditions[15] gave rise to the bislactone **35** as a single stereoisomer in 80% overall yield.

In summary, we have developed an efficient and general Mo-mediated cyclocarbonylation of 1,6- and 1,7-yne aldehydes. This novel hetero-PKR occurs under very mild conditions in the absence of a carbon monoxide gas atmosphere. Starting from readily available chiral aldehydes, highly valuable, enantiomerically pure fused butenolides are obtained.

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Supporting Information Available: Experimental procedures, characterization data of new compounds, copies of NMR spectra, and X-ray crystallography data of *exo*-**34** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a recent review on PKR, see: Struebing, D.; Beller, M. In *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 619−632.
(2) Main versions of oxa-hetero-PKR and related processes. For Ti-mediated cyclocarbonylation of alkenyl ketones and aldehydes, see: (a) Kablaoui, N. M.; Hicks, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 5818−5819. (b) Crowe, W. E.; Vu, A. T. *J. Am. Chem. Soc.* **1996**, *118*, 1557−1558. (c) Kablaoui, M.; Hicks, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4424−4431. (d) Mandal, S. K.; Amin, S. R.; Crowe, W. E. *J. Am. Chem. Soc.* **2001**, *123*, 6457−6458. For Ru-catalyzed cyclocarbonylation of allenyl aldehydes and ketones, see: (e) Kang, S.-K.; Kim, K.-J.; Hong, Y.-T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1584−1586. For Ni-mediated cyclocarbonylation of alkenyl aldehydes, see: (f) Ogoshi, S.; Oka, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2004**, *126*, 11802−11803. For Mo-mediated cyclocarbonylation of allenyl or cyclopropylidenyl aldehydes, see: (g) Yu, C.-M.; Hong, Y.-T.; Yoon, S.-K.; Lee, J.-H. *Synlett* **2004**, 1695−1698. (h) Yu, C.-M.; Hong, Y.-T.; Lee, J.-H. *J. Org. Chem.* **2004**, *69*, 8506−8509.
(3) (a) Bruckner, R. *Curr. Org. Chem.* **2001**, *5*, 679−718. γ-Butyrolactones are present in about 10% of all natural products. See: (b) Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol.* **2002**, *6*, 453−458.
(4) Chantani, N.; Morimoto, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 5335−5336.
(5) Fuji, K.; Morimoto, T.; Tsutsumi, K.; Kakiuchi, K. *Chem. Commun.* **2005**, 3295−3297.
(6) Adrio, J.; Rodríguez-Rivero, M.; Carretero, J. C. *Org. Lett.* **2005**, *7*, 431−434.
(7) For leading references on Mo-mediated PKR of enynes, see: (a) Brummond, K. M.; Curran, D. P.; Mitasev, B.; Fischer, S. *J. Org. Chem.* **2005**, *70*, 1745−1753. (b) Cao, H.; Van Ornui, S. G.; Deschamps, J.; Flippen-Anderson, J.; Laib, F.; Cook, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 933−935.
(8) Lower yields were obtained in other solvents, such as toluene, CH_2Cl_2, or CH_3CN.
(9) No reaction at all occurred when diethyl 2-(2-oxopropyl)-2-propargylmalonate was used as substrate.
(10) For example, the addition of isopropanol or water produced a decrease in the reaction yield, while the use of PPh_3 did not significantly affect the **A**/**B** selectivity.
(11) For an example of the use of boranes as Lewis acid in metal-mediated aldehyde cyclizations, see: Yu, C.-M.; Youn, J.; Lee, M.-K. *Org. Lett.* **2005**, *7*, 3733−3736.
(12) The *endo*/*exo* configurational assignment was established by ^{1}H NMR experiments and by X-ray diffraction analysis of *exo*-**34** (see Supporting Information for details).
(13) Although the Co-mediated PKR of allylic-substituted 1,6-enynes is usually *exo* selective (see for instance (a) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851−4854. (b) Mukai, C.; Kim, J. S.; Sonobe, H.; Hanaoka, M. *J. Org. Chem.* **1999**, *64*, 6922−6832), some examples of *endo* selective PKR have been reported (see for instance (c) Adrio, J.; Rodriguez-Rivero, M.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2000**, *39*, 2906−2909. (d) Rios, R.; Pericàs, M. A.; Moyano, A.; Maestro, M. A.; Mahia, J. *Org. Lett.* **2002**, *4*, 1205−1208).
(14) For the isolation of dihydrocanadensolide, see: (a) McCorkindale, N. J.; Wright, J. L.; Brian, P. W.; Clarke, S. M.; Hutchinson, S. A. *Tetrahedron Lett.* **2001**, *42*, 6183−6186. (b) Kato, M.; Kageyama, M.; Tanaka, R.; Kuwahara, K.; Yoshikoshi, A. *J. Org. Chem.* **1975**, *40*, 1932−1941. For recent synthesis, see: (c) Mulzer, J.; Kattner, L. *Angew. Chem., Int. Ed.* **1990**, *29*, 679−680. (d) Chen, M.-J.; Narkunan, K.; Liu, R.-S. *J. Org. Chem.* **1999**, *64*, 8311−8311. (e) Sharma, G. V. M.; Gopinath, T. *Tetrahedron* **2003**, *59*, 6521−6530.
(15) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

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