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The Allenic Pauson-Khand Cycloaddition. Dependence in π-Bond Selectivity on Substrate Structure.

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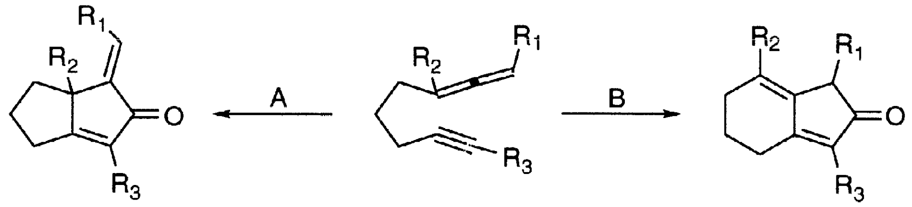
Abstract: Alkynyl allenes undergo intramolecular Pauson-Khand (P-K) cycloadditions to provide functionalized α-methylene and 4-alkylidene cyclopentenones in good yields. These studies have demonstrated a dependence of the π-bond selectivity of this cycloaddition on the substitution pattern of the allene.

The Pauson-Khand (P-K) reaction is a multi-component reaction that has been exploited extensively in the synthesis of natural products.[1] We have successfully demonstrated that the standard alkene moiety can be replaced by an allene functionality in intramolecular P-K cycloadditions which thereby constitutes a novel route to α-methylene cyclopentenones.[2] In these previously reported examples it was found that the internal π-bond of the allene selectively engages in the molybdenum-mediated cyclizations (Scheme 1, path A). In order to expand the overall utility of this methodology, we sought control elements which might induce preferential cyclization with the terminal π-bond (Scheme 1, path B). Moreover, an underlying motive for this investigation is the eventual application of this method to natural product synthesis.[3] As a first step toward this goal, we describe herein the substitution profile required in order to selectively accomplish this novel intramolecular allenic Pauson-Khand cyclization.[4]

Scheme 1



Substitution patterns on the allenes were varied in an effort to direct the regiochemical outcome of the cycloaddition. Initially, the cyclizations of 1,3-disubstituted allenes were examined. These cycloadditions were effected with molybdenum hexacarbonyl/DMSO[5] with four and seven carbon chains appended to the terminus of the allene so volatility of the starting materials and the products would not affect the observed yields. Treatment of the 1,3-disubstituted allenynes with molybdenum hexacarbonyl/DMSO[6] gave a mixture of products consisting of the *E* and *Z* isomers of the bicyclo[3.3.0]octane ring systems in 75% yield (entry 1, Table 1).[7,8] The *E*-isomer of the α-methylene cyclopentenone was obtained as the major product. The stereoselectivity of this

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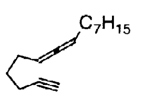
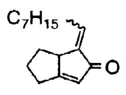
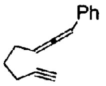
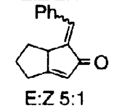
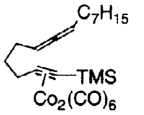
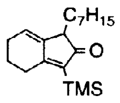
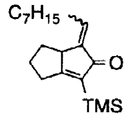
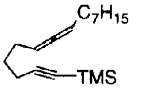
cyclization was slightly higher (*E:Z*, 5:1) when the heptyl moiety on the allene was replaced with a phenyl group (entry 2, Table 1). Since we are interested in using the P-K cycloaddition to prepare chiral α-methylene cyclopentenones this lack of facial selectivity concerned us. Thus in an effort to increase the facial selectivity, we turned to dicobaltoctacarbonyl as a metal promoter, since this metal has been used in the selective formation of diastereomers.[1,9] These cyclizations proceeded more stereoselectively, but gave nearly 1:1 mixtures of bicyclo[4.3.0]nonane and the *E*-bicyclo[3.3.0]octane ring systems with trace amounts of the *Z*-bicyclo[3.3.0]octane system. The highest yields were obtained when the alkynes were precomplexed with the cobalt, purified and subjected to cyclization conditions. The reaction proceeds much more quickly and in a slightly higher yield when trimethylamine-N-oxide is used as the promoter instead of DMSO (compare entries 3 and 4, Table 1).[10]

Table 1. Pauson-Khand Cycloaddition of 1,3-Disubstituted Allenes

entry	allenyne	cyclopentenone		conditions	yield
1		 E:Z 2:1		A	75%
2		 E:Z 5:1		A	70%
3		 45%	 55% E:Z 10:1	B	60%
4		40%	60% E:Z 5:1	C	62%
5		5%	95% E only	D	48%

Conditions: A: $Mo(CO)_6$/DMSO,tol,Ar,100°C,10h; B: DMSO,CH_2Cl_2,air,40°C,22h; C: Me_3NO,CH_2Cl_2,Ar,1.3h; D: 1. Cp_2ZrCl_2/n-BuLi, 2. CO,2h

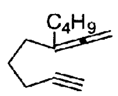
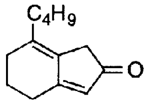
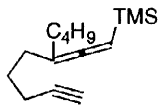
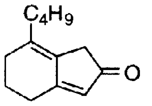
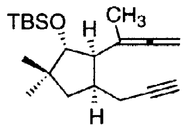
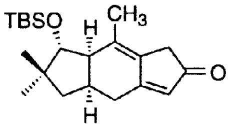
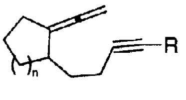
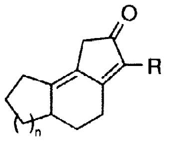
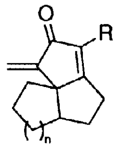
Finally, when the cyclization was effected in the presence of $Cp_2Zr(n\text{-}Bu)_2$,[11] the *E*-bicyclo[3.3.0]octane ring system was isolated as the major product in good yields (entry 5, Table 1). Thus, we have been able to successfully direct the allenic P-K cycloaddition of 1,3-disubstituted allenes to react stereoselectively with the internal π-bond of the allene to afford α-methylene cyclopentenones by simply changing the metal catalyst.

Next the cyclizations of 3,3-disubstituted allenes were investigated. The inefficient processing of 2,2-disubstituted olefins appears to be a weakness in many P-K systems[12] and was predicted to be the case for 3,3-disubstituted allenes. However, unlike the olefinic P-K reaction, in the allenic variant cycloaddition can occur with an alternate double bond. The allenynes utilized in this study were prepared via the addition of the requisite alkynyl magnesium bromide to the appropriate propargylic mesylate in the presence Cu(I).[13] Treatment of 3-butyl-1,2-octadiene-7-yne to molybdenum conditions resulted in the formation of the bicyclo[4.3.0]nonane ring system as the only product in a 60% yield (entry 1, Table 2). *This result demonstrates a dependence of the* *π-bond selectivity of this cycloaddition on the substitution pattern of the allene.* There are only a few examples of this type of selectivity dependence in the P-K reaction.[9,14]

In an attempt to sterically direct the cyclization reaction toward the internal double bond of the allene, we placed a silicon moiety at the terminus of the allene. Treatment of the trisubstituted allene to molybdenum conditions gave the desilylated bicyclo[4.3.0]nonane ring system in 59% yield (entry 2, Table 2). Similarly, the cyclization of a more functionalized precursor occurred to give the [5.6.5] ring system in 42% yield (entry 3, Table 2).

This cycloaddition process has also been used to prepare some interesting carbocyclic skeletons possessing functionality that can easily be manipulated to other substrates (entries 4-6, Table 2). Exposure of these allenynes to the molybdenum hexacarbonyl/DMSO conditions affords the tricyclic cycloadducts. The rapid assembly of these ring systems demonstrates the applicability of this method and provides skeletons visible in naturally occurring compounds.[15]

Table 2. Pauson-Khand Cycloaddition of 3,3-Disubstituted Allenes

entry	allenyne	cyclopentenone	yield
1			60%
2			59%
3			42%[a]
		 	
4	n=1, R=H	7 : 1	73%
5	n=1, R=TMS	1 : 0	50%
6	n=2, R=H	6 : 1	62%

Conditions: Mo(CO)$_6$/DMSO/tol,Ar,100°C [a] Yield based upon recovered starting material

In summary, monosubstituted allenes afford α-methylene cyclopentenones as the only cycloadduct.[2] Disubstitution on the allene alters the course of the allenic P-K reaction. Cycloaddition of 1,3-disubstituted allenes afford mixtures of several possible cycloadducts. However, we have shown that good control over the product ratio can be obtained by altering the cycloaddition conditions and that the regiochemistry can be directed depending upon the metal used. 3,3-Disubstituted allenes undergo cycloaddition with the least substituted π-bond of the allene. This affords the bicyclo[4.3.0]nonane ring system selectively. We are currently utilizing this result in the synthesis of analogs of the illudins.[3] We are continuing to explore the scope and limitations of the allenic variant of the Pauson-Khand cycloaddition and the results of these studies will be reported shortly.

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6. Sample experimental details for the allenic P-K reaction: A mixture of 6,7-pentadecadien-1-yne (57 mg, 0.28 mmol), molybdenum carbonyl (118 mg, 0.45 mmol) and DMSO (200 μL, 2.8 mmol) in toluene (3 mL) was heated at 100 °C under argon for 15 h, during which a dark blue precipitate formed. The reaction mixture was passed through a small plug of silica gel eluting with ethyl acetate/hexane (1:1). The filtrate was concentrated *in vacuo* and the residue chromatographed on silica gel (eluting with 5% ethyl acetate/hexane) to furnish *Z*-4-[(heptyl)methylidenyl]-bicyclo[3.3.0]oct-1-en-3-one (15 mg, 25%) and *E*-4-[(heptyl)methylidenyl]-bicyclo[3.3.0]oct-1-en-3-one (28 mg, 50%).
7. All new compounds reported herein exhibit satisfactory spectral data (IR, ^{1}H NMR, ^{13}C NMR, GC/MS).
8. Representative spectral data: ***Z*-4-[(Heptyl)methylidenyl]-bicyclo[3.3.0]oct-1-en-3-one:** ^{1}H NMR (270 MHz, CDCl$_3$) δ 5.98 (s, 1H), 5.90 (t, *J* = 7.5 Hz, 1H), 3.33-3.23 (m, 1H), 2.74 (q, *J* = 7.1 Hz, 2H), 2.67-2.43 (m, 2H), 2.18-2.01 (m, 3H), 1.41-1.10 (m, 11H), 0.86 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (67.9 MHz, CDCl$_3$) δ 199.3, 183.9, 138.7, 138.3, 127.4, 51.1, 31.8, 29.5, 29.4, 29.2, 29.1, 27.0, 26.3, 26.1, 22.6, 14.1; IR (neat) 2926, 2855, 1695, 1654, 1623, 1458, 1325, 861 cm^{-1}; MS (GC/MS) *m/z* 232 (M$^+$), 203,189, 161, 147, 134, 105, 91, 77. ***E*-4-[(Heptyl)methylidenyl]-bicyclo[3.3.0]oct-1-en-3-one:** ^{1}H NMR (270 MHz, CDCl$_3$) δ 6.49 (dt, *J* = 1.8, 7.7 Hz, 1H), 6.03 (s, 1H), 3.35 (t, *J* = 9.8 Hz, 1H), 2.70-2.46 (m, 2H), 2.33-2.04 (m, 5H), 1.50-1.10 (m, 11H), 0.86 (t, *J* = 6.7, 3H); ^{13}C NMR (67.9 MHz, CDCl$_3$) δ 198.2, 184.9, 139.2, 134.3, 126.0, 48.8, 31.7, 29.7, 29.4, 29.2, 29.1, 28.8, 25.9, 25.7, 22.6, 14.0; IR (neat) 2926, 2855, 1701, 1655, 1620, 1458, 1256, 856 cm^{-1}; MS (GC/MS)*m/z* 232 (M$^+$), 203, 189, 161, 147, 134, 106, 91, 77.
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