The Allenic Pauson−Khand Reaction in Synthesis

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Keywords: Allenes / Carbonylation / Cycloaddition / Organometallics / Synthetic methods

The Pauson–Khand (PK) reaction is a formal [2+2+1] cycloaddition involving an alkene, an alkyne and carbon monoxide. The allene moiety represents a versatile and useful building block in organic synthesis. In place of the usual alkene, allene reagents are fascinating substrates in the Pauson–Khand-type reaction because of their unique reactivity and the synthetic utility of the final products. However, there are significant problems of selectivity. Several studies, most of them recent, have greatly enhanced the synthetic utility of this reaction by the use of allenes instead of alkenes. This paper presents recent advances in the less exploited allenic and dienic variants of the Pauson–Khand-type cycloaddition.

Introduction

The Pauson−Khand (PK) reaction is a formal [2+2+1] cycloaddition involving an alkene, an alkyne and carbon monoxide, which has become one of the most versatile methods for the synthesis of cyclopentenones.[1] Although the classical PK reaction was originally carried out by simply heating a mixture of stoichiometric amounts of dicobalt octacarbonyl, alkyne and alkene,[2] several improvements have been made in the execution of the PK cyclization.[3] Mechanistically, the pathway suggested in 1985 by Magnus and co-workers is widely accepted.[4] These authors proposed that a stable alkyne−[$Co_2(CO)_6$] complex initially suffers loss of a CO ligand from one of the two Co atoms. This is followed by olefin coordination and insertion into a Co−C bond forming a cobaltacycle, which suffers a reductive elimination to give the final cyclopentenone. Mass

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MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

 DOI: 10.1002/ejoc.200400023

spectrometric evidence in support of this mechanism has been reported recently.[5]

With regard to the substrate scope of the PK reaction, a wide variety of substituents are tolerated at the alkyne moiety, while the range of compatible substituents is more restricted for the alkene reagent.[6] In the conventional PK reaction, the alkene is typically substituted with hydrogen, alkyl, aryl, or ether groups. Several studies, most of them recent, have greatly enhanced the synthetic utility of this process by the use of allenes in place of alkenes. The aim of this article is to summarize the recent advances of the less exploited allenic and dienic variants of the Pauson−Khand-type cycloaddition, with special focus on their synthetic applications.

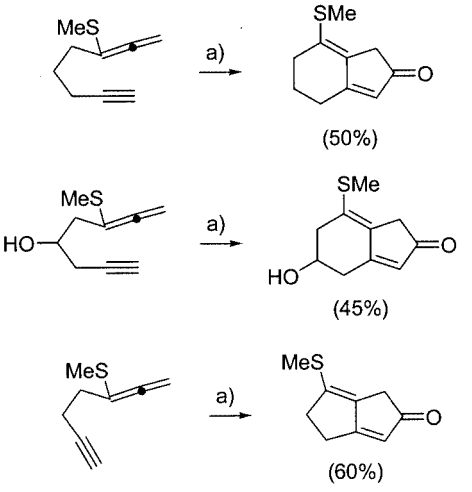
Discussion

The allene moiety represents a versatile and useful building block in organic synthesis.[7] In addition, the use of allenes in transition metal catalyzed cyclization reactions is of great interest.[8] However, there are significant problems in selectivity. Instead of the usual alkene, allene reagents are fascinating substrates in the Pauson−Khand-type reaction because of their unique reactivity and the synthetic utility of the final products.

Intramolecular Allenic Pauson−Khand Reaction

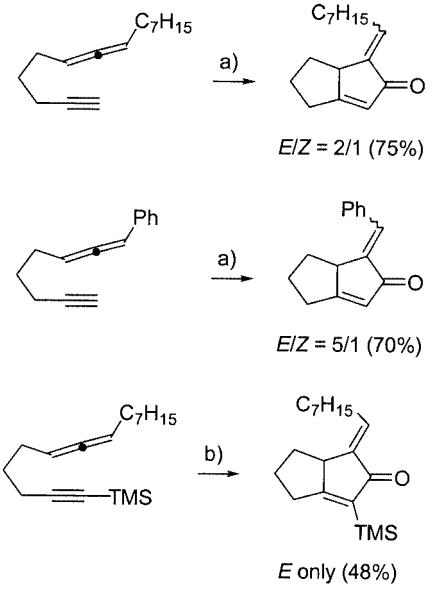
The intramolecular allenic PK reaction was described for the first time in 1994 by Narasaka[9] and shortly thereafter by Brummond.[10] These authors pioneered the replacement of the standard alkene moiety with an allene functionality in the intramolecular PK reaction.

Narasaka and co-workers converted various 1-(ω-alkynyl)propadienyl sulfides into bicyclic [*n*.3.0] dienones via intramolecular carbonylative allene−alkyne coupling reactions in the presence of $[Fe(CO)_4(NMe_3)]$ under photoirradiative conditions (Scheme 1).[9]



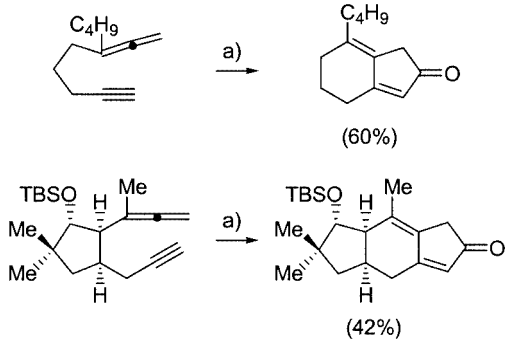
Scheme 1. Intramolecular carbonylative allene−alkyne coupling reaction in the presence of $[Fe(CO)_4(NMe_3)]$. Reagents and conditions: a) $[Fe(CO)_4(NMe_3)]$, hυ, THF, 20 °C

Brummond and co-workers were able successfully to direct the allenic PK cycloaddition of 1,3-disubstituted allenes to afford α-methylene cyclopentenones by a stereoselective reaction with the internal double bond of the allene (Scheme 2).[11]



Scheme 2. Pauson−Khand-type cycloaddition of 1,3-disubstituted allenes. TMS = trimethylsilyl. Reagents and conditions: a) $[Mo(CO)_6]$/DMSO, toluene, 100 °C. b) $[Cp_2ZrCl_2]$/*n*BuLi, then CO

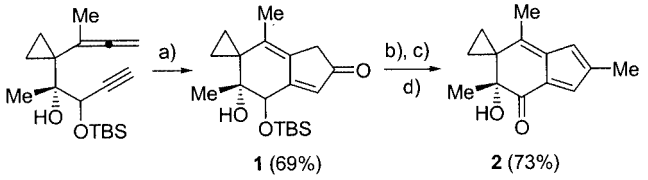
The inefficient conversion of 2,2-disubstituted olefins is a problem in many PK systems, as also appears to be the case for 3,3-disubstituted allenes. However, unlike the olefinic PK reaction, the allenic PK variant can occur with an alternate double bond. Thus, 3,3-disubstituted allenes undergo cycloaddition with the least substituted π-bond of the allene, affording the bicyclo [4.3.0]nonane ring system selectively. These studies demonstrate the dependence of the π-bond selectivity of this cycloaddition on the substitution pattern of the allene moiety (Scheme 3).



Scheme 3. Pauson−Khand-type cycloaddition of 3,3-disubstituted allenes. TBS = *tert*-butyldimethylsilyl. Reagents and conditions: a) $[Mo(CO)_6]$/DMSO, toluene, 100 °C

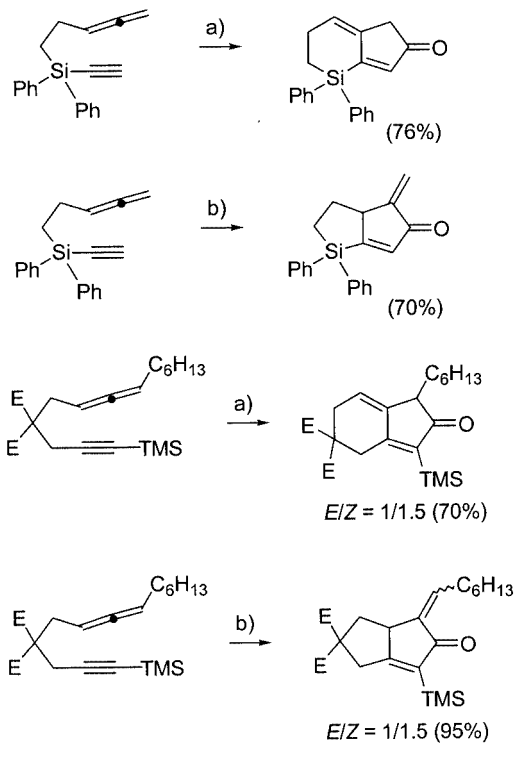
These results were utilized in the synthesis of analogues of illudins, a family of naturally occurring sesquiterpenes. The 3,6-dimethyl[4.3.0]nona-1,3,5-triene substructure em-

bodied in the illudin skeleton is unique and Brummond and colleagues anticipated its accessibility by application of the allenic variant of the Pauson−Khand-type cycloaddition. The appropriate alkynyl allene undergoes a rapid [2+2+1] cycloaddition (10 min) to produce the 4-alkylidenecyclopentenone **1** as the only observed cycloadduct in 69% yield. After several further steps, this adduct was converted into the acylfulvene **2** which contains the illudin ring system (Scheme 4).[12]



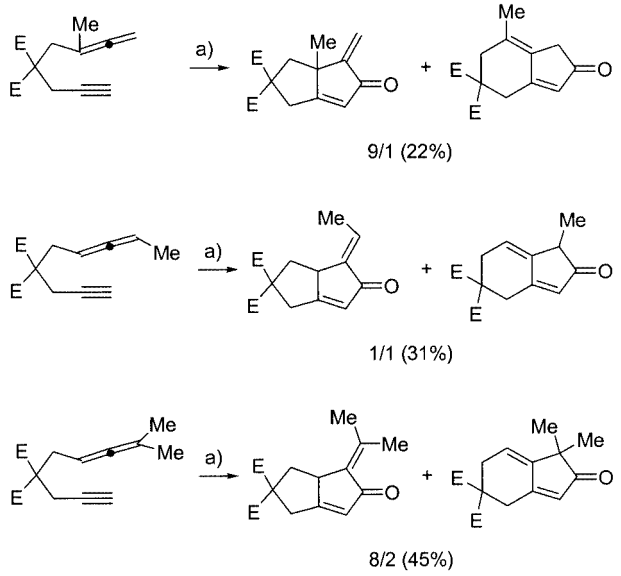
Scheme 4. Synthesis of illudin analogues. TBS = *tert*-butyldimethylsilyl. Reagents and conditions: a) $[Mo(CO)_6]$/DMSO, toluene, 100 °C. b) MeLi. c) TBAF. d) Dess−Martin oxidation

During the course of these investigations, Brummond and co-workers found that reaction of different alkynyl allenes with $[Rh(CO)_2Cl]_2$ occurs exclusively at the external π-bond of the allene giving the respective 4-alkylidenecyclopentenones with no formation of the α-alkylidenecyclopentenones (Scheme 5).[13] In contrast, $[Mo(CO)_6]$ gives only α-alkylidenecyclopentenones.



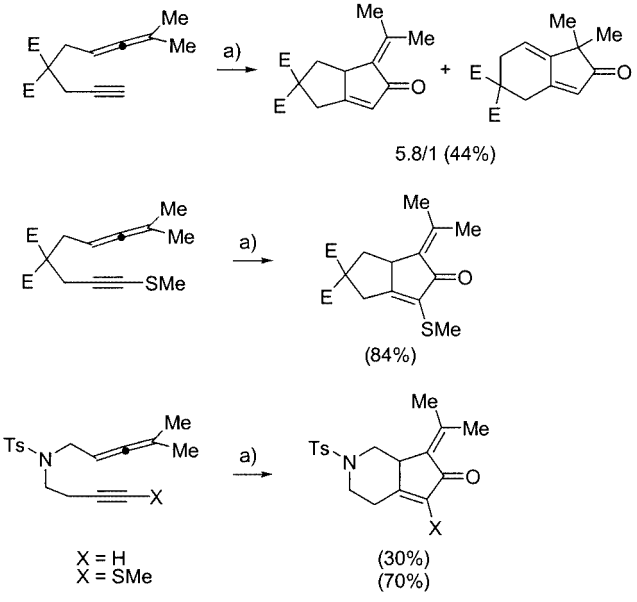
Scheme 5. Reversal in π-bond selectivity in the allenic Pauson−Khand reaction. E = CO_2Me. TMS = trimethylsilyl. Reagents and conditions: a) 5 mol % $[Rh(CO)_2Cl]_2$, CO (1 atm), toluene. b) 125 mol % $[Mo(CO)_6]$/DMSO, toluene

The feasibility of the intramolecular cobalt-mediated carbonylative cycloaddition of α,ω-allenynes promoted by *N*-methylmorpholine oxide was demonstrated for the first time by Cazes and co-workers, albeit with modest yields.[14] The regioselectivity of this reaction depends on the substitution pattern of the allenic moiety (Scheme 6).



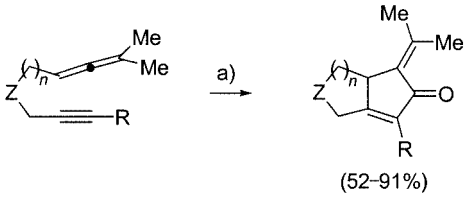
Scheme 6. *N*-Methylmorpholine oxide-promoted Pauson−Khand cycloaddition of α,ω-allenynes. E = CO_2Me. Reagents and conditions: a) $[Co_2(CO)_8]$, NMO, THF/CH_2Cl_2, −78 °C to 20 °C

Livinghouse and co-workers reported that (methylthio)alkynes are superior substrates for the thermally promoted, $[Co_2(CO)_8]$-catalyzed PK reaction of allenynes, providing cyclopentenones in higher yields and with enhanced regioselectivity.[15] This cyclization efficiency enhancement is illustrated in Scheme 7.



Scheme 7. Allenic Pauson−Khand cycloaddition of (methylthio)alkynes. E = CO_2Me. Ts = tosyl. Reagents and conditions: a) 10 mol % $[Co_2(CO)_8]$, CO (1 atm), 1,2-DME, 60 °C

It has been reported recently that Vaska's complex, $[IrCl(CO)(PPh_3)_2]$, efficiently catalyzes the intramolecular carbonylative [2+2+1] cycloaddition of allenynes.[16] Triphenylphosphane ligands in the iridium complex resulted in longer reaction times and gave the ene-product in significant yield. A two methyl substituents at the allene terminus and a low partial pressure of carbon monoxide realize the selective reaction of the internal π-bond of the allene Scheme 8.

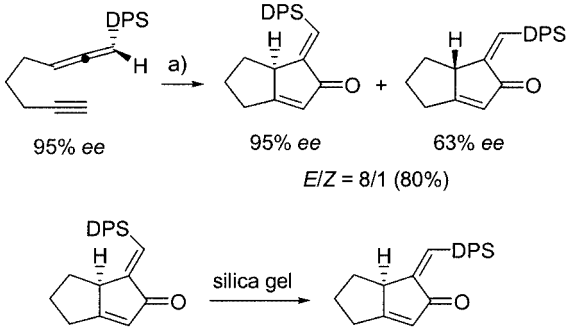


n = 1, 2
Z = O, TsN, $(EtO_2C)_2C$
R = Ph, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, Me, Me_2PhSi

Scheme 8. Iridum complex-catalyzed Pauson–Khand-type reaction of allenynes. Ts = tosyl. Reagents and conditions: a) 5 mol % $[IrCl(CO)(PPh_3)_2]$, CO (0.2 atm), xylene, 120 °C

Chiral Allenes in the Allenic PK Reaction

When using chiral allenes, the mechanism of intramolecular allenic PK-type cycloadditions has been indicated by the isolation of an (η^6-arene)-(tricarbonyl)molybdenum complex, which demonstrated, for the first time, that this is probably the active complex in the molybdenum-mediated reactions.[17] Brummond and co-workers have successfully affected a transfer of chirality from a non-racemic allene to an α-alkylidene- and an α-silylidenecyclopentenone in the molybdenum-mediated PK reaction. In substrates possessing a silyl group at the terminus of the allene, good facial selectivities were obtained but isomerization of the (*E*)-silylidenecyclopentenone to the (*Z*)-silylidenecyclopentenone occured when purification of these products was attempted (Scheme 9). On placing an alkyl group at the terminus of the allene, the cycloaddition proceeds with moderate selectivity but gives products that undergo an isomerization of the (*Z*)-alkylidenecyclopentenone to the (*E*)-alkylidenecyclopentenone when exposed to acidic conditions.[17] As a result of this isomerization, erosion of the enantiomeric excesses is observed for one of the two adducts making further studies necessary in order that synthetically useful levels of stereoselectivity are obtained.[18]

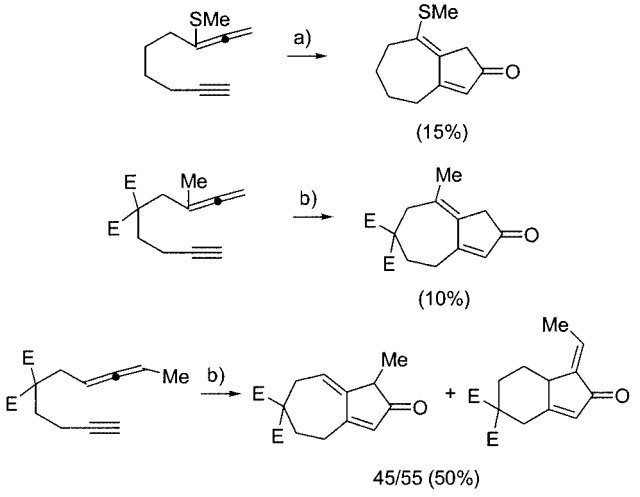


Scheme 9. Transfer of chirality from an allenylsilane to an α-silylidenecyclopentenone. DPS = dimethylphenylsilyl. Reagents and conditions: a) $[Mo(CO)_6]$/DMSO, toluene, 95 °C

Synthesis of Medium-Sized Rings via Allenic PK Reaction

Until recently and despite its synthetic potential, the intramolecular variant of the PK reaction has been largely restricted to the construction of bicyclo[3.3.0]octenones and bicyclo[4.3.0]nonenones. Difficulties achieving medium sized rings via PK reaction seem to be related to the low population of the appropriate reactive conformation. Given the large number of biologically active natural products that possess a medium-sized ring annulated with a cyclopentyl moiety, it should be of interest to develop a direct synthesis of this structural motif via an intramolecular PK reaction. Incorporation of structural features into the cyclization precursors that would reduce the entropic contribution to the free energy of activation might favour medium-sized ring formation. In fact, the planarity of aromatic rings appears to have a decisive influence on the reactivity of enynes connected through them.[19]

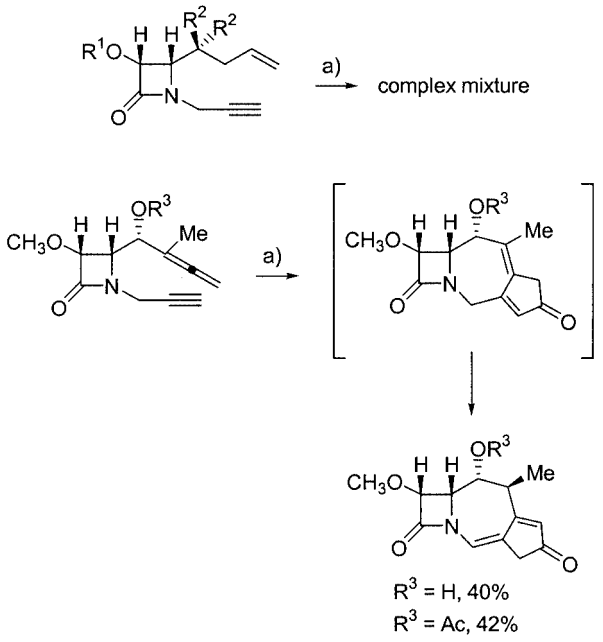
Alkyne derivatives with an allenyl functionality instead of an olefin group were found to produce the corresponding bicyclo[5.3.0] ring systems under different metal-mediated PK reaction conditions, although the yields were far from satisfactory (Scheme 10).[9b,14]



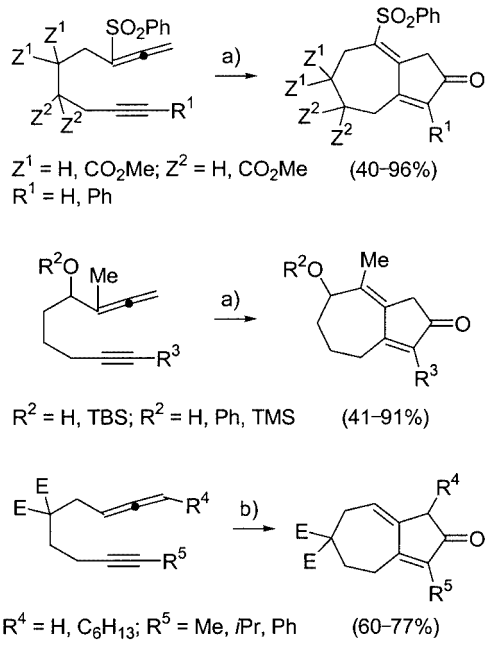
Scheme 10. Synthesis of medium-sized rings via iron- or cobalt-mediated Pauson–Khand cycloaddition of allenynes. E = CO_2Me. Reagents and conditions: a) $[Fe(CO)_4(NMe_3)]$, hυ, THF, 20 °C. b) $[Co_2(CO)_8]$, THF/CH_2Cl_2, −78 °C to 20 °C

In a study by our group on the use of the Pauson–Khand cyclization as an entry to fused tricyclic 2-azetidinones, attempts to generate central ring systems with more than six atoms proved unsuccessful.[20] This result was expected because the synthesis of azabicyclo[5.3.0]decenones had not yet been realized using the PK reaction. The substitution patterns of allenyne-β-lactams were selected in order

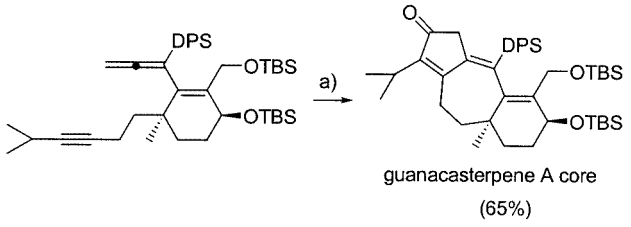
to direct the regiochemical outcome of the cycloaddition towards seven-membered central ring formation. Indeed, we found that the [2+2+1] cycloaddition produced tricycles bearing a central seven-membered ring as the only isomer (Scheme 11).[21] These tricycles presumably arise from the isomerization of the initially formed PK adducts because of the conjugation of the dienone moiety with the lone pair of the nitrogen atom.



Scheme 11. Synthesis of medium-sized tricyclic β-lactams via Pauson−Khand cyclization of 2-azetidinone-tethered allenynes. Reagents and conditions: a) $[Co_2(CO)_8]$, Me_3NO, dichloromethane, room temperature



Scheme 12. Rhodium-catalyzed Pauson−Khand-type reaction of allenynes. E = CO_2Me. Reagents and conditions: a) 2.5 mol % $[RhCl(CO)_2]_2$ or $[RhCl(CO)dppp]_2$, CO (1 atm), toluene, 110 °C. b) 5 mol % $[RhCl(CO)_2]_2$, CO (1 atm), toluene, 90 °C



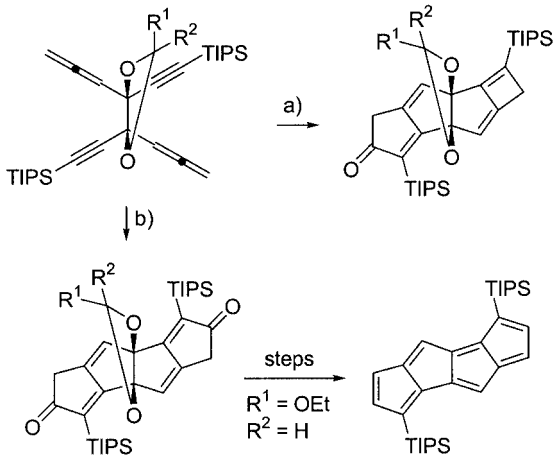
Scheme 13. Synthesis of the tricyclic core of guanacasterpene A. DPS = dimethylphenylsilyl. TBS = *tert*-butyldimethylsilyl. Reagents and conditions: 10 mol % $[RhCl(CO)_2]_2$, CO (1 atm), toluene, 80 °C

A more efficient procedure for constructing bicyclo[5.3.0]-deca-1,7-dien-9-one ring systems was initially described by Mukai in 2002,[22] shortly followed by Brummond.[13a] This reaction affords seven-membered rings in high yields via Rh^I-catalyzed intramolecular allenic PK reaction (Scheme 12). Complete chemoselectivity was observed in the formal [2+2+1] cycloaddition, leading to the exclusive construction of the bicyclo[5.3.0]deca-1,7-dien-9-one framework. The corresponding bicyclo[4.3.0]nonenone derivative was not detected in the reaction mixtures. Thus, rhodium(I) catalysts are regarded as superior catalysts for the construction of seven-membered rings from allenynes when compared with other metal catalysts.

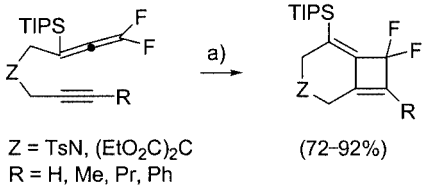
A synthesis of the highly functionalized tricyclic core of guanacasterpene A has been developed using the Rh^I-catalyzed intramolecular allenic PK reaction (Scheme 13).[23] This approach constitutes a conceptually novel strategy for the synthesis of this tricyclic framework, where initial formation of the six-membered ring is followed by the simultaneous formation of the five-and seven-membered rings.

The synthesis of a dicyclopenta[*a*,*e*]pentalene via a (hexacarbonyl)molybdenum-mediated tandem allenic PK reaction has been achieved recently.[24] When the starting diynediallenes were treated under the conditions reported by Brummond, the unexpected [5.5.5.4] tetracyclic systems were obtained in moderate yields (30−40%). On the basis of these results, Cook and colleagues affected the cyclization in a saturated solution of $[Mo(CO)_6]$ in toluene at 55 °C, obtaining the desired [5.5.5.5] ring system in yields ranging from 65 to 70% (Scheme 14). With the tetraenic PK adduct in hand, introduction of the additional three units of unsaturation was achieved in five steps.

Occasionally, the intramolecular PK reaction is not as predictable as it is desirable. After identifying an efficient synthesis of functionalized *gem*-difluoroallenes, Hammond and co-workers attempted the Co-mediated PK reaction. Despite their success in isolating the stable Co-alkyne complex, the subsequent [2+2+1] cycloaddition did not occur. Upon application of Brummond's (hexacarbonyl)molybdenum conditions, the intramolecular cyclization did not produce the expected PK product but gave a fused cyclobutene (Scheme 15).[25] This reaction represents a formal



Scheme 14. Molybdenum-catalyzed Pauson−Khand-type reaction of diyne-diallenes. TIPS = triisopropylsilyl. Reagents and conditions: a) 2.2 equiv. $[Mo(CO)_6]$, 10 equiv. DMSO, toluene, 100 °C. b) 10 equiv. $[Mo(CO)_6]$, 20 equiv. DMSO, toluene, 55 °C

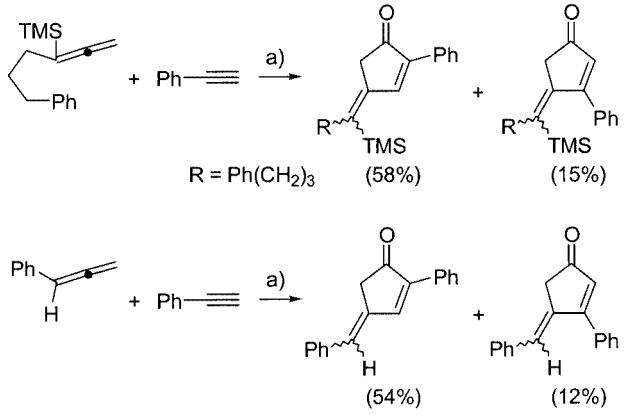


Scheme 15. Molybdenum-catalyzed intramolecular [2+2] cycloaddition reaction of fluoroallenes. TIPS = triisopropylsilyl. Reagents and conditions: a) $[Mo(CO)_6]$/DMSO, toluene, 100 °C

[2+2] cycloaddition, with the molybdenum metallacycle undergoing a reductive elimination rather than a CO insertion.

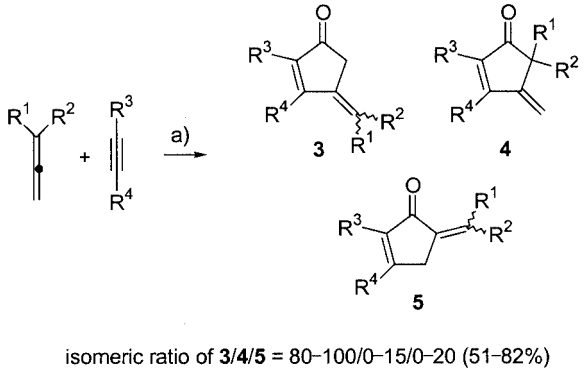
Intermolecular Allenic Pauson−Khand Reaction

Little was known about the synthetic application of the intermolecular allenic PK reaction until Cazes and colleagues entered this field,[26] excepting that Narasaka had reported a $[Fe(CO)_4(NMe_3)]$-mediated intermolecular carbonylative coupling (Scheme 16).[9]



Scheme 16. Intermolecular carbonylative allene−alkyne coupling reaction by the use of $[Fe(CO)_4(NMe_3)]$. TMS = trimethylsilyl. Reagents and conditions: a) $[Fe(CO)_4(NMe_3)]$, hυ, THF, 20 °C

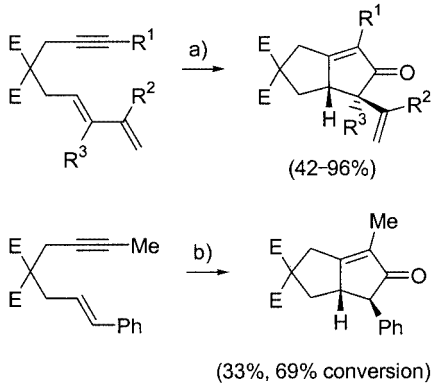
Cazes utilized a cobalt-mediated co-cyclization of alkynes and allenes promoted by *N*-methylmorpholine oxide to obtain alkylidene-2-cyclopentenones.[27] The regioselectivity of the PK reaction of alkynes with allenic hydrocarbons depends on the substitution pattern of both the acetylenic and allenic partners (Scheme 17). Competitive mechanistic pathways to the 4- or 5-alkylidene-2-cyclopentenones have been proposed for several allene-cobalt π-complexes.[28] In particular, 5-alkylidene-2-cyclopentenones (type **5**) are formed only from acetylene, which might be explained by an initial pseudoaxial coordination of the allenic unit to cobalt. The β-effect of silicon was shown to be a determining factor for the regioselectivity of the PK reaction of alkynylsilanes with allenes. This electronic effect accounts for the formation of 3-trimethylsilyl-4-alkylidenecyclopentenones (types **3** and **4**) from monosubstituted allenes.[29]



Scheme 17. Intermolecular cobalt-mediated Pauson−Khand cyclization of alkynes and allenes. Reagents and conditions: a) $[Co_2(CO)_8]$, Me_3NO, *N*-methylmorpholine oxide, dichloromethane, room temperature

1,3-Dienic Pauson−Khand Reaction

In the PK reaction, use of a 1,3-diene rather than an alkene or an allene has not been explored. In view of the potential synthetic utility of this dienic version, Wender and co-workers focused their attention on the selectivity of the reaction of dienynes for the intramolecular [2+2+1] pathway.[30] Internal alkynes gave excellent yields of the PK cycloadducts (85−96% yield), whereas terminal alkynes reacted less efficiently. Substitution at the 2- or 3-position of the diene was also tolerated well. The geometry of the alkene is conserved during the transformation. In addition to its synthetic value, the diene facilitates the rhodium-catalyzed cycloaddition relative to that of an alkene. For example, while the reactions of dienynes are all complete within 14 h at room temperature or 40 °C with 1−2.5 mol % catalyst, the reactions of the corresponding enyne require 3 days and much harsher conditions (80 °C, 5 mol % catalyst) (Scheme 18). Significantly, conjugation alone is not sufficient to facilitate the reaction, since under these same conditions the reaction of the related styrene substrate is even more sluggish, requiring 4 days to reach 69% completion.



Scheme 18. Rhodium-catalyzed intramolecular Pauson−Khand-type reaction of dienynes. E = CO_2Me. Reagents and conditions: a) 1−2.5 mol % $[RhCl(CO)(PPh_3)_2]$, 1−2.5 mol % $AgSbF_6$, CO (1 atm), 1,2-dichloroethane, 20 °C. b) 5 mol % $[RhCl(CO)(PPh_3)_2]$, 5 mol % $AgSbF_6$, CO (1 atm), 1,2-dichloroethane, 80 °C

Conclusions

Instead of the usual alkene, diene (allene or 1,3-diene) reagents are fascinating substrates in the Pauson−Khand-type reaction because of their unique reactivity and the synthetic utility of the final products. However, there are significant problems with selectivity. While the allenic variant of the Pauson−Khand reaction has been known for a decade and several studies have been made during this time, the PK reaction based on dienes has only recently been described. Progress on these less exploited variants of the Pauson−Khand reaction is likely to follow, and will contribute to its relevance as a versatile and effective tool in organic chemistry.

Acknowledgments

Support for this work by the DGI-MCYT (Project BQU2003−07793-C02−01) is gratefully acknowledged.

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Received January 14, 2004
Early View Article
Published Online April 20, 2004

