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Intermolecular Pauson–Khand Reactions of Cyclopropene: A General Synthesis of Cyclopentanones

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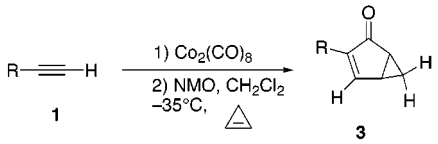
ABSTRACT



The Pauson–Khand reaction of cyclopropene with a variety of terminal alkynes has been studied. The best reaction conditions involve NMO activation in CH_2Cl_2 at −35 °C. In this way, 3-substituted-bicyclo[3.1.0]hex-3-en-2-ones have been obtained in good to excellent yields. As a synthetic application, several types of substituted cyclopentenones have been prepared from these cycloadducts by protocols involving conjugate addition and reductive ring opening.

One of the most significant characteristics of the Pauson−Khand (PK) reaction[1] is its broad applicability, tolerating many functional groups. Up to now, a great variety of structural patterns and functionalities have been described in intramolecular PK cyclizations, giving rise to a plethora of structures. In the intermolecular version of the reaction, however, the diversity of alkynes that have been successfully used is in sharp contrast with the small number of the alkene counterparts. It is well-known that only strained alkenes, such as cyclobutenes, or bicyclic olefins with a norbornane skeleton are good substrates for intermolecular PK reactions.[1] Although substituted ethylenes and some cyclic olefins such as cyclopentenes or dihydrofuranes can give the reaction, on most occasions the yields using unstrained olefins are low. Theoretical [DFT//PM3(tm)] calculations[2] provide an adequate explanation for this behavior and suggest that cyclopropene should be an excellent substrate for intermolecular PK cyclizations. Somewhat surprisingly, there are only few reports on the use of cyclopropenes in PK reactions,[3] and to the best of our knowledge the simplest member of this type of compound has never been tested in the reaction. Bicyclo[*n*.1.0]alkenones, such as those that could result from the PK reaction of cyclopropene, are synthetically useful compounds which, taking advantage of their ring strain, have been used in a variety of reactions featuring nucleophilic ring opening or reductive ring expansions.[4] We describe herein our results in the study of the Pauson−Khand reaction of cyclopropene which provide a useful preparation of bicyclo[3.1.0]hexenones and the regio- and stereoselective transformation of those systems into polysubstituted cyclopentanones.

Following the procedure described by Binger,[5] a solution of cyclopropene in toluene was prepared by treating a

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(2) Vazquez, J.; Moyano, M.; Pericàs, M. A.; Riera, A., unpublished results.

(3) (a) Kireev, S. L.; Smit, V. A.; Ugrak, B. I.; Nefedov, O. M. *Bull. Acad. Sci USSR (Engl. Transl.)* **1991**, 2240−2246. (b) Nüske, H.; Bräse, S.; de Meijere, A. *Synlett* **2000**, 1467−1469. (c) Witulski, B.; Gossmann, M. *Synlett* **2000**, 1793−1797.

(4) (a) Baird, M. S. *Top. Curr. Chem.* **1988**, *144*, 137−209. (b) Padwa, A.; Fryxell, G. E. *Adv. Strain Org. Chem.* **1991**, *1*, 117−166.

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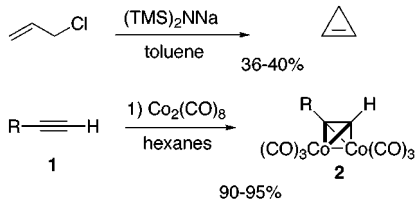
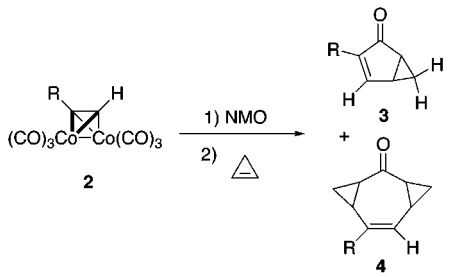
solution of allyl chloride in toluene at reflux with sodium bis(trimethylsilyl)amide and trapping the gas in toluene at −78 °C. On the other hand, the hexacarbonyl−dicobalt complexes **2** were prepared by treatment of the corresponding alkyne **1** with octacarbonyl dicobalt in hexanes at room temperature (Scheme 1).

Scheme 1



The Pauson−Khand reaction between cyclopropene and *tert*-butylacetylene was first attempted under purely thermal conditions. A solution of cyclopropene in toluene was added to a solution of hexacarbonyl dicobalt complex **2a** (R = *t*-Bu) in toluene at −78 °C, and the mixture was slowly allowed to warm with stirring. However, no trace of PK cycloadducts was observed in the crude by TLC. Since it is known that cyclopropene polymerizes at temperatures above −30 °C, we reasoned that the reaction had to be performed below this temperature and that *N*-oxide promotion could help in this task.[6,7] Thus, a solution of cyclopropene in toluene (aproximately 5−7 equiv) was added to a stirred solution of **2a** in methylene chloride at −78 °C and a solution of NMO (6 equiv) in methylene chloride was next added. The mixture was allowed to warm to −30 °C and stirred until the starting complex was consumed. In this way, a moderate 42% yield of 3-*tert*-butylbicyclo[3.1.0]hex-3-en-2-one (**3a**) could be isolated by chromatography of the reaction crude (Scheme 2). However, under the same reaction conditions, the cobalt

Scheme 2



complex **2b** (R = Ph) prepared from phenylacetylene afforded the tricyclic ketone **4b** in 50% yield as a main product. This unprecedented adduct[8] should arise from the abnormal evolution of the key cobaltacycle intermediate of the reaction: Due to the high reactivity of cyclopropene, a further olefin insertion competes with the normal CO insertion, leading to a cyclopentenone.[9] Disappointingly, the cobalt complex derived from 1-hexyne did not afford any cycloadduct under the same reaction conditions.

Since the reaction was taking place near the onset temperature for cyclopropene polymerization, we reasoned that, to improve the yield, the PK reaction should proceed as fast as possible. Perhaps the low solubility of the NMO in the mixture of toluene and methylene chloride at −30 °C could be responsible for the low rate and consequently for low yields. The reaction conditions were thus modified again: Cyclopropene was condensed neat, dissolved in CH_2Cl_2, and added to a mixture of NMO and cobalt complex **2a** in CH_2Cl_2 at −35 °C. The reaction took place in only 5 min, yielding enone **3a** in 93% yield. Under these optimized conditions, the standard PK adducts **3b** and **3c** could be finally obtained, although in both cases small amounts of the tricyclic products **4b** and **4c** were also formed (Table 1).

Table 1. Pauson−Khand Reaction of Cyclopropene with Hexacarbonyl−Dicobalt Complexes **2** Derived from Terminal Alkynes **1**[a]

	starting complex, R =	**4**, % yield	**3**, % yield
2a	*tert*-butyl		93
2b	phenyl	15	50
2c	*n*-hexyl	10	60
2d	Ph_3Si		82
2e	$PhCH_3C(OH)$		45
2f	*p*-tolyl	23	26
2h	$(CH_3)_2C(OH)$		51

[a] Reaction conditions. A solution of the hexacarbonyl−dicobalt complex **2** in CH_2Cl_2 was cooled to −35 °C. To this solution were sequentially added, via cannula, 6 equiv of NMO (2 M solution in CH_2Cl_2) and 7 equiv of cyclopropene (ca. 6−10 M solution in CH_2Cl_2). After 5 min of stirring at −35 °C, the mixture was filtered through Celite and evaporated. The crude was chromatographed on silica gel, eluting with EtOAc/hexanes.

These optimized conditions were tested on a series of cobalt complexes **2d**−**h** derived from commercially available terminal alkynes. In the case of bulky substituents (**2a**,**d**), the yields of bicyclo[3.1.0]hex-3-en-2-ones are very high. The cobalt complex of *p*-tolylacetylene exhibits the lowest yield of bicyclic adducts due to the significant amount of tricyclononanone **4h** formed in the reaction. In summary, the Pauson−Khand of cyclopropene with bulky terminal alkynes gives good to excellent yields of cycloadducts, whereas in the case of aromatic and *n*-alkyl-substituted alkynes the yields are good to moderate.

(5) Binger, P.; Wedemann, P.; Goddard, R.; Brinker, U. H. *J. Org. Chem.* **1996**, *61*, 6462−6464.

(6) At this temperature, the purely thermal dissociative loss of CO required for the reaction is extremely slow and NMO-promoted dissociation can provide an appropriate reaction rate.

(7) (a) Shambayati, 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**, 204−206.

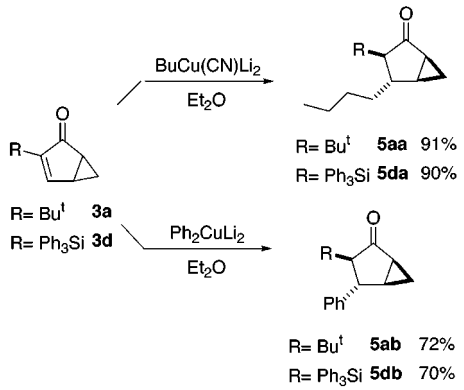
(8) Only one stereoisomer of **4b** was observed by ^1H and ^{13}C NMR. The stereochemistry of this adduct could not be unambiguously established.

(9) For a complete theoretical study of the mechanism, see: Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **2001**, *123*, 1703−1708.

Although, 3-substituted bicyclo[3.1.0]hex-3-en-2-ones such as the PK adducts reported here are relatively unknown compounds,[10] other substances, either synthetic[11] or natural,[12] with the same bicyclic skeleton but with a different substitution pattern have been described in the literature. Most of these compounds have been prepared by photochemical rearrangement of enones[13] or phenols[14] and are used in mechanistic studies related to the photochemical conversion of santonin into lumisantonin.[15]

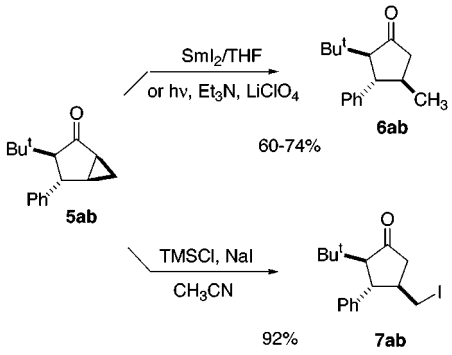
Once a practical procedure for the synthesis of 3-substituted bicyclo[3.1.0]hex-3-en-2-ones **3** was developed, their synthetic potential was subsequently explored. The photochemical behavior leading the corresponding *ortho*-substituted phenols is discussed in detail in the following Letter.[21] The combination of conjugate addition and ring expansion reactions also has potential applications for the synthesis of substituted cycloalkanones. The conjugate addition was studied on substrate **3a**, which by treatment either with $Bu_2Cu(CN)Li_2$ or Ph_2CuLi_2 afforded respectively the bicyclic cyclopentanones **5aa** or **5ab** in excellent yields (Scheme 3).

Scheme 3



The reaction was totally stereoselective, affording only one isomer. The stereochemistry of **5ab** (depicted in Scheme 3) was established by NOESY experiments and in the case of **5aa** was assigned by analogy. As expected, the conjugate addition took place from the less hindered *exo* face of the bicyclic structure, *trans* to the cyclopropane methylene group. The relative stereochemistry of the *tert*-butyl group was also determined to be *trans* to the phenyl. Semiempirical calculations using AM1[16] confirmed that this structure is the thermodynamically most stable isomer. Conjugate addition of the same cuprates on other adducts also gave excellent yields of cyclopentanones and followed the same stereochemical course. For instance, triphenylsilyl derivative **3d** afforded **5da** and **5db** in 90 and 70% yields, respectively. Compound **5ab** was used to explore ring opening reactions of the cyclopropane moiety. Unfortunately, all of our attempts to hydrogenate the cyclopropane ring under a variety of hydrogenation conditions (Pd/C or Pt_2O)[17] failed, leading to the recovery of unchanged starting material. Identical results were obtained by treatment with Zn in methanol in the presence of zinc chloride.[17] Quite gratifyingly, however, the reductive photoinduced electron transfer (*hν* 254 nm, Et_3N, $LiClO_4$, CH_3CN)[18] provided the methylcyclopentanone **6ab** in 60% yield. An even better yield was obtained by reductive cleavage using samarium iodide,[19] which afforded **6ab** in 74% yield. In both cases, the reduction took place with complete regioselectivity α to carbonyl *exo*-cyclic bond (Scheme 4). Even more surprising was the fact that electrophilic ring opening of **6ab** using the conditions developed by Dieter[20] (trimethylsilyl chloride/NaI/CH_3CN) afforded iodide **7ab** in 92% yield.

Scheme 4



The Pauson−Khand adducts of silylacetylenes such as **5d** can be used as a precursors of 3,4-disubstituted cyclopentanones through a sequence of conjugate addition, TBAF

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(16) As implemented in SPARTAN, version 4.1.1, Wavefunction, Inc.
(17) Attah-Poku, S. K.; Antzak, K.; Alward, S. J.; Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 1717−1721. (b) Attah-Poku, S. K.; Alward, S. J.; Fallis, A. G. *Tetrahedron Lett.* **1983**, *24*, 681−684.
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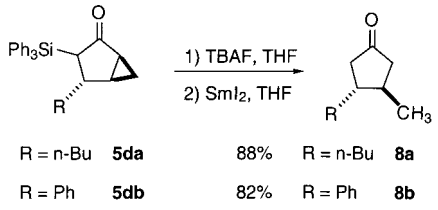
treatment to remove the silyl group, and reductive ring opening. In Scheme 5 is shown the transformation of **5da**

Scheme 5



R = n-Bu	**5da**	88%	R = n-Bu	**8a**
R = Ph	**5db**	82%	R = Ph	**8b**

and **5db** into 3-substituted 4-methylcyclopentanones in excellent overall yields.

In summary, we have found that cyclopropene is an excellent substrate for PK reactions. The appropriate conditions consist of performing the reaction in CH_2Cl_2 at −35 °C in the presence of NMO. The resulting 3-substituted bicyclo[3.1.0]-3-hexen-2-ones **3** are interesting intermediates that can be easily converted into di- or trisubstituted cyclopentanones in a totally controlled regio- and stereoselective manner by protocols involving conjugate addition, reductive ring opening, and silyl group removal.

These synthetic sequences provide a new strategy for the modular construction of substituted cyclopentanones which is currently being studied in our group. Thus, di- or trisubtituted cyclopentenones would be constructed from an alkyne, cyclopropene, carbon monoxide, and cuprate reagent as represented in Figure 1.

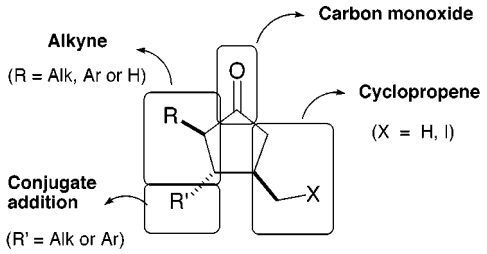


Figure 1.

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