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An Allenic Pauson–Khand-Type Reaction: A Reversal in π -Bond Selectivity and the Formation of Seven-Membered Rings

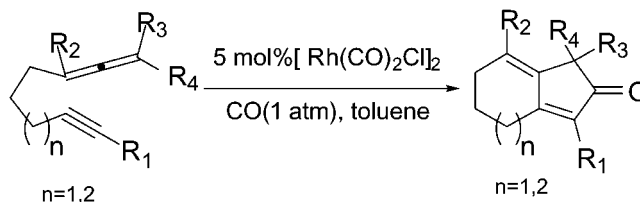
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Received April 1, 2002

ABSTRACT



Treatment of alkynyl allenes with $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ results in a formal $[2 + 2 + 1]$ cycloaddition reaction. This reaction occurs with complete regioselectivity for a variety of substrates affording only 4-alkylidene cyclopentenones in good yields. Moreover, seven-membered rings have been prepared in high yields.

The formal $[2 + 2 + 1]$ cycloaddition reaction involving alkenes, alkynes, and a CO source is a powerful strategy for effecting formation of cyclopentenones.¹ Research in our laboratory provided the first examples of an intramolecular, metal-mediated allenic $[2 + 2 + 1]$ cycloaddition reaction for the synthesis of α -alkylidene cyclopentenones² and 4-alkylidene cyclopentenones.³ This strategy has subsequently been developed as a generally useful synthetic method.⁴ It was demonstrated that the substitution profile

of the allene had an influence on the regiochemical course of this reaction. While this regiochemical control element proved to be exceedingly useful in the synthesis of hydroxymethylacetylfulvene^{4a,b} and our approach to 15-deoxy- $\Delta^{12,14}$ -PGJ₂, the allenic Pauson–Khand reaction would be more versatile and amenable to target-oriented synthesis if the regioselectivity could be controlled by simply altering the reaction conditions.

To amplify the overall utility of this method, we sought control elements that might induce preferential cyclization with the terminal π -bond of the allene, affording 4-alkylidene

† Corresponding author for information regarding X-ray crystallographic data.

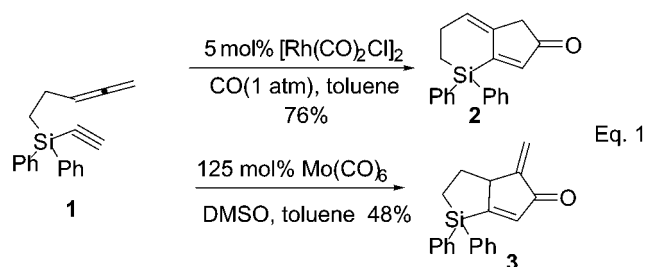
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cyclopentenones. While exploring the silicon-tethered allenic Pauson–Khand reaction, we screened numerous metals other than $\text{Mo}(\text{CO})_6$ in an effort to find reaction conditions that would be compatible with the silicon tether. During the course of these investigations, we found that upon treatment of the silicon-tethered alkynyl allene **1** with $[\text{Rh}(\text{CO})_2\text{Cl}]_2$, conditions reported independently by Narasaka⁵ and Jeong⁶ the reaction occurred exclusively with the external π -bond of the allene to give only the 4-alkylidene cyclopentenone **2** in 76% yield with no formation of the α -alkylidene cyclopentenone (eq 1).⁷ In contrast, $\text{Mo}(\text{CO})_6$ gives only α -alkylidene cyclopentenone **3** in 48% yield. Observations have been made that are consistent with this reactivity pattern; for instance, rhodium-vinylallene complexes have been investigated and a crystal structure was obtained indicating an η^2 coordination of the rhodium at the terminal allenic π -bond.⁸ However, reactivities inconsistent with our observations have also been reported.⁹



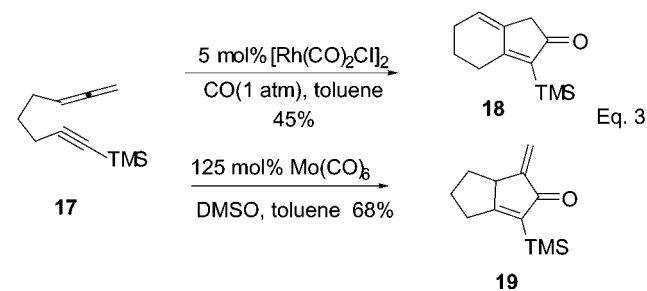
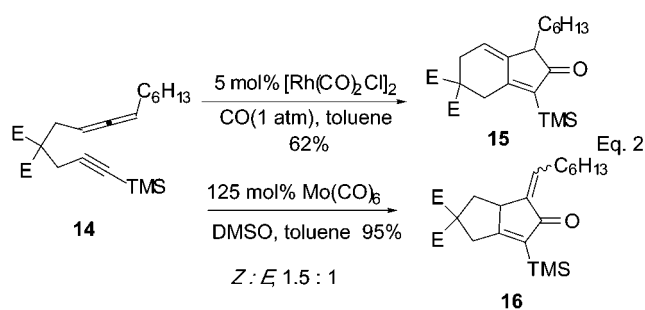
Similarly, in a more functionalized example, alkynyl allene **4** gave only 4-alkylidene cyclopentenone **5** in 64% yield (entry 1, Table 1). A variety of functional groups on the terminus of the alkyne were tolerant of the reaction conditions. For example, replacement of the hydrogen with a trimethylsilyl (**6**), *n*-butyl (**8**), or phenyl (**10**) group gave good yields of the corresponding cycloadducts **7**, **9**, and **11** (entries 2–4, Table 1). Subjection of alkynyl allenes **6**, **8**, and **10** to $\text{Mo}(\text{CO})_6$ afforded only recovered starting material.¹⁰ Substituting the terminus of the allene with a longer alkyl chain gave **12** that cyclized to afford the cycloadduct **13** in 55% yield (entry 5, Table 1).

To determine if this reversal in the regioselectivity was a consequence of the silicon tether, cyclization substrates containing all-carbon tethers were examined. Treatment of alkynyl allene **14** with 5 mol % $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ (toluene, CO (1 atm), 90 °C) produced compound **15** in 62% yield along with a 30% yield of a byproduct that was characterized as a

Table 1. Rhodium-Catalyzed Silicon-Tethered Allenic Pauson–Khand Reaction

entry	substrate	product	yield
1	4 R = H, R' = CH ₃	5 R = H, R' = CH ₃	64%
2	6 R = TMS, R' = CH ₃	7 R = TMS, R' = CH ₃	74%
3	8 R = <i>n</i> -Bu, R' = CH ₃	9 R = <i>n</i> -Bu, R' = CH ₃	75%
4	10 R = Ph, R' = CH ₃	11 R = Ph, R' = CH ₃	51%
5	12 R = H, R' = C ₅ H ₁₁	13 R = H, R' = C ₅ H ₁₁	55%

cross-conjugated triene (eq 2). This triene also results from a selective reaction with the distal double bond of the allene and will be reported on shortly.¹¹ Allene **14** gave only the α -alkylidene cyclopentenone **16** in 95% yield when 125 mol % $\text{Mo}(\text{CO})_6$ (DMSO, toluene, 100 °C) was used for the cyclization reaction (eq 2).³ Similarly, allene **17** was subjected to $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ and afforded only **18** in 45% yield (eq 3). This somewhat low yield was attributed to the volatility of compound **18**. We have reported previously that treatment of alkynyl allene **17** with $\text{Mo}(\text{CO})_6$ gives a 68% yield of **19**.³



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Table 2. Allenic Pauson–Khand Reaction

entry	substrate	product	conditions	yield
1			A	64%
2			A	22%
3			A	56%
4			A	32%
5			B	88% ^a
6			B	47%
7			B	60%
8			A	67%
9			A	75%

^a 4:1 mixture of **29**: desilylated enone (R=H), A: 5 mol% [Rh(CO)₂Cl]₂, toluene, CO (1 atm), B: 10 mol% [Ir(COD)Cl]₂, toluene, CO (1 atm)

On the basis of the examples in eqs 1–3, we continued to examine the regioselectivity issue using other alkynyl allenes, and these are depicted in Table 2. Allene **20** cyclized to give only **21** in 64% yield, for which an X-ray crystal structure was obtained (entry 1, Table 2). Allenyne **22**, possessing a *tert*-butyl group on the terminus of the allene, cyclized to give only a 22% yield of the [6–5] ring system **23** (entry 2, Table 2). This same allene cyclized to give only the corresponding α -alkylidene cyclopentenone in 56% yield using Mo(CO)₆.¹² 1,1,3-Trisubstituted allene **24** cyclized using [Rh(CO)₂Cl]₂ in 56% yield affording spirocycle **25** (entry 3, Table 2). 3,3-Disubstituted allene **26** cyclized to give **27** in 32% yield (entry 4, Table 2). An allene possessing an heptyl group at the terminus, **28**, cyclized to give a 30%

yield of cycloadduct **29** using [Rh(CO)₂Cl]₂ (entry 5, Table 2) and a 50% yield of a cross-conjugated triene.¹¹ Conditions to control the formation of this byproduct were found. Treatment of **28** with 10 mol % [Ir(COD)Cl]₂ in toluene and 1 atm of CO afforded an 88% yield of a 4:1 ratio of **29** (R = TMS) to desilylated enone (R = H).¹³ Alkynyl allene **30** possessing a methyl group on the terminus of the alkyne cyclized to give **31** in 47% yield using [Ir(COD)Cl]₂ (entry 6, Table 2). Similarly, **32** possessing a phenyl group on the alkyne afforded **33** in 60% yield (entry 7, Table 2). Moreover, [Rh(CO)₂Cl]₂ shows good functional group compatibility. For example, alkynyl allene **34** possessing a carboxylic acid side chain cyclized to give only compound **35** in 67% yield (entry 8, Table 2). Treatment of **34** with Mo(CO)₆ resulted in decomposition of the starting material. Alkynyl allene **36** cyclized to afford only 4-alkylidene cyclopentenone **37** in 75% yield (entry 9, Table 2).

The formation of seven-membered carbocycles has been somewhat elusive compared to that of six-membered carbocycles. However, recent discoveries are beginning to change this reality. There are now a variety of methods, including [4 + 3]¹⁴ and [5 + 2]¹⁵ cycloaddition protocols, for the preparation of seven-membered carbocycles. Seven-membered rings have only recently been obtained using the Pauson–Khand reaction. Cazes was the first to demonstrate this using an alkynyl allene; however, the reactions lacked regioselectivity and as a result afforded mixtures of [5–7] and [5–6] ring systems in moderate yields.¹⁶ Perez-Castells has also shown that seven-membered rings can be formed with tethers possessing indoles and pyroles.¹⁷ Nevertheless, medium-sized rings remain decidedly difficult to obtain using the Pauson–Khand reaction.¹⁸ Since the rhodium(I)-catalyzed allenic Pauson–Khand reaction appears to be very selective toward the distal double bond of the allene in all cases, it was reasoned that this might be the case for alkynyl allenes possessing longer tethers. To test this generalization, alkynyl allene **38** was subjected to [Rh(CO)₂Cl]₂ and gave only the [5–7] ring system **39** in 60% yield. This remarkable reversal

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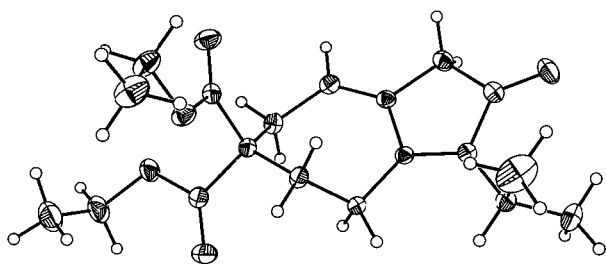


Figure 1. X-ray structure of **41**.

in regioselectivity has now resulted in a synthetic alternative for the preparation of seven-membered rings using an allenic Pauson–Khand-type reaction. Next, alkynyl allene possessing an isopropyl group on the terminus of the alkyne and only hydrogen on the distal position of the allene **40** was subjected to the same conditions to afford a 76% yield of the [5–7] ring system **41** as a crystalline compound from which an X-ray crystal structure was obtained (Figure 1). Similarly, **42** possessing a phenyl group on the terminus of the alkyne cyclized to afford only **43** in 77% yield.

In conclusion, we are examining the scope and limitations of the $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ -catalyzed allenic Pauson–Khand reaction. The results delineated above extend the scope and overall utility of the allenic Pauson–Khand reaction for the

(19) Sample experimental procedure for rhodium-catalyzed allenic Pauson–Khand reaction: 3-isopropyl-2-oxo-2,4,5,7-tetrahydro-1*H*-azulene-6,6-dicarboxylic acid diethyl ester (**41**). To a flame-dried test tube equipped with a magnetic stir bar were added 2-(2,3-butadienyl)-2-(5-methyl-3-hexynyl)malonic acid diethyl ester (**40**, 0.048 g, 0.16 mmol) and toluene (0.5 mL). The test tube was evacuated and charged with CO three times, and then $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ (3.2 mg, 0.008 mmol) was added. The mixture was stirred and heated at 90 °C overnight under CO (1 atm). The solvent was removed in vacuo, and the residue was purified by preparative TLC (SiO_2 , 75:25 hexanes/ether, R_f = 0.4) to afford title compound **41** as a pale yellow oil that solidified in the freezer to afford a colorless solid (0.0400 g, 76%): ^1H NMR (300 MHz, CDCl_3) δ 5.70 (t, J = 6.5 Hz, 1 H), 4.14 (q, J = 7.2 Hz, 4 H), 2.86–2.75 (m, 6 H), 2.30–2.26 (m, 2 H), 1.20 (t, J = 7.2 Hz, 6 H), 1.16 (d, J = 7.1 Hz, 6 H); ^{13}C NMR (75 MHz, CDCl_3) δ 204.6, 171.5, 165.7, 147.8, 138.9, 125.5, 120.9, 61.5, 58.2, 40.8, 31.0, 30.3, 24.8, 24.7, 20.3, 14.0; IR (neat) 1732, 1695, 1227, 1201, 1183, 1271, 2963, 2934, 2874 cm^{-1} ; EI-HRMS calcd for $\text{C}_{19}\text{H}_{26}\text{O}_5$ [M^+] m/z 334.1780, found 334.1787.

Table 3. [5–7] Ring System

entry	substrate	product	yield
1			60%
2			76%
3			77%

E = CO_2Et

assembly of substructures not readily obtained using alternative protocols. The ring systems prepared provide convincing evidence for the remarkable regiochemical preference for the reaction to occur with the distal double bond of the allene. Efforts to further delineate the scope of the allenic Pauson–Khand reaction and validate its usefulness in natural product synthesis are underway in our laboratories.

Acknowledgment. We thank the National Institutes of Health (GM54161) for financial support of this work.

Supporting Information Available: Characterization data and full experimental procedures are provided for compounds **14–18** and **20–45**.¹⁹ This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL025955W