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$Mo(CO)_6$- and $[Rh(CO)_2Cl]_2$-Catalyzed Allenic Cyclocarbonylation Reactions of Alkynones: Efficient Access to Bicyclic Dienediones

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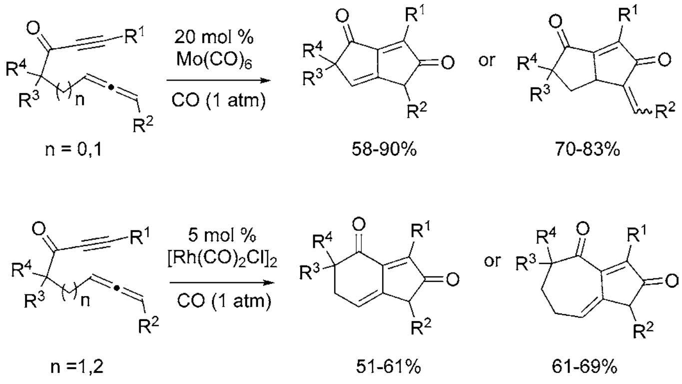
ABSTRACT



Allenyl alkynones are efficiently transformed into fused bicyclic dienediones via cyclocarbonylation reaction conditions. $Mo(CO)_6$/DMSO reaction conditions result in the formation of a bicyclo[3.3.0]octenone ring system, and the $[Rh(CO)_2Cl]_2$-catalyzed reaction affords bicyclo[4.3.0]-nonenone and bicyclo[5.3.0]decenone scaffolds.

Efficient construction of polycyclic cyclopentane-containing skeletons is a continual interest to the synthetic community.[1] Among numerously important cyclopentane derivatives, a fused bicyclic enedione represents an essential framework and versatile intermediate in natural product syntheses.[2] One common strategy for accessing the enedione moiety is by multistep annulation reactions, as demonstrated by Danishefsky[3] and Hassner.[4] Another strategy utilizes dicobaltoctacarbonyl $[Co_2(CO)_8]$[5] or tungstenpentacarbonyl·THF $[W(CO)_5\cdot THF]$[6] mediated cyclocarbonylation reactions on electron-deficient alkynones. However, the latter protocol has been limited to the preparation of bicyclo[3.3.0]oct-1-en-3-ones.

An important variant of the Pauson−Khand-type reaction involves substituting the alkene moiety with an allene,[7] thus enabling the formation of larger rings. The utility of this version of the Pauson−Khand-type reaction has been expanded by our ability to control the reacting double bond of the allene via the transition metal catalyst.

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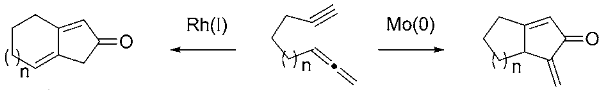
For example, the reaction of alleneyne **A** under molybdenum hexacarbonyl conditions affords α-alkylidene cyclopentenone **B** via a selective reaction of the proximal double bond of the allene (eq 1).[8] Alternatively, reaction of alleneyne **A** under rhodium(I) conditions gives 4-alkylidene cyclopentenone **C** resulting from a selective reaction with the distal double bond of the allene.[9] We have extended the scope of this regioselective cyclocarbonylation reaction to the preparation of indene-, pentalene-, and azulenediones. These diones were achieved by an intramolecular reaction of an allene with an ynone, a rarely used moiety in Pauson−Khand (P−K) reactions. The results of this study are reported within.



(1)

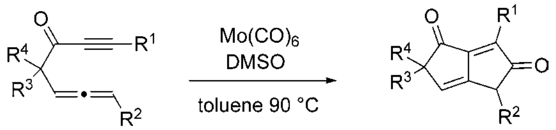
C n = 0,1,2 **A** n = 0,1,2 **B** n =1,2

The P−K reaction is one of the most extensively investigated methods for the formation of cyclopentenones.[10] However, limited attention has focused on electron-deficient alkynes as a reacting partner[11] and very few examples have been reported on the transition metal-*catalyzed* P−K reaction of ynones. Moreover, there have been no reports of a P−K reaction of alleneynones to form richly functionalized bicyclic dienediones.

The $Mo(CO)_6$-mediated reaction of alkynone **1** to form bicyclo[3.3.0]octadienedione **2** was first examined. To our delight, when **1a** was subjected to the standard reaction conditions (1.2 equiv of $Mo(CO)_6$, 10 equiv of DMSO), product **2a** was isolated in 90% yield in less than 10 min (entry 1, Table 1).

The efficiency of the transformation of **1a** to **2a**, coupled with a report from Oh's laboratory[12] prompted us to investigate the catalytic version of the molybdenum cyclocarbonylation reaction. Lowering the quantity of molybdenum hexacarbonyl to 40 mol % and performing the reaction under an atmosphere of nitrogen gave product **2a** in 82% yield in 20 min (entry 2, Table 1). Equipping the reaction with a balloon of carbon monoxide and lowering the catalyst loading to 20 mol % produced **2a** in 81% yield in 1 h (entry 3, Table 1). Lowering the catalyst loading to 10 mol % gave varying quantities of product **2a** along with recovered starting material **1a** (entry 4, Table 1).

Table 1. $Mo(CO)_6$-Catalyzed Cyclocarbonylation Reactions



1a-g **2a-g**

entry	subst	prod	R¹	R²	R³	R⁴	time (min)	yield (%)
1[a]	**1a**	**2a**	*n*Bu	Me	Me	Me	10	90
2[b]	**1a**	**2a**	*n*Bu	Me	Me	Me	20	82
3[c]	**1a**	**2a**	*n*Bu	Me	Me	Me	60	81
4[d]	**1a**	**2a**	*n*Bu	Me	Me	Me		[e]
5[c]	**1b**	**2b**	H	Me	Me	Me	60	58
6[a]	**1c**	**2c**	Me	Me	$(-CH_2-)_5$		5	76
7[c]	**1c**	**2c**	Me	Me	$(-CH_2-)_5$		60	75
8[b]	**1d**	**2d**	Me	H	Me	BzNH	40	71
9[a]	**1e**	**2e**	H	H	Me	BzNH	10	59
10[a]	**1f**	**2f**	Me	Me	Me	BzNH	10	86[f]
11[a]	**1g**	**2g**	H	Me	Me	BzNH	10	63[f]
12[c]	**1g**	**2g**	H	Me	Me	BzNH	60	61[f]

[a] 120 mol % of $Mo(CO)_6$, 10 equiv of DMSO, 90 °C. [b] 40 mol % of $Mo(CO)_6$, 4 equiv of DMSO, 90 °C. [c] 20 mol % of $Mo(CO)_6$, 2 equiv of DMSO, CO (1 atm), 90 °C. [d] 10 mol % of $Mo(CO)_6$, 1 equiv of DMSO, CO (1 atm), 90 °C. [e] Reactions did not go to completion even after 5 h, see text for details. [f] Compounds **2f** and **2g** were obtained as ca. 1:1 mixtures of diastereomers, see the Supporting Information for details.

Next, the scope and limitation of this method for accessing other bicyclic dienediones was investigated by systematically varying the substitution on the allene, alkyne, and tether. Terminal alkynes are compatible with the Mo(0) reaction conditions but it was found that the yield decreased by 23% when compared to that of an internal alkyne (compare entries 3 and 5, and entries 10 and 11, Table 1). Interestingly, annulation of a cyclohexane ring on the tether produced spirotricyclic dienedione **2c** in comparable yield under both catalytic and stoichiometric reaction conditions (entries 6 and 7, Table 1). Substrates possessing a benzamide group on the tether afforded bicyclic dienediones **2d**−**g** (entries 8−12, Table 1).

Selective reaction of the distal double bond of the allene of substrates **1a**−**g** to give dienediones **2a**−**g** using the Mo(0) conditions is attributed to the developing strain in the bicyclo[3.2.0]heptenone, a product that would arise from the reaction with the proximal double bond of the allene. However, by lengthening the tether by one methylene unit, substrates **3a**−**d** afforded products resulting from the selective reaction with the proximal double bond of the allene, α-alkylidene enediones **4a**−**d** (Table 2). Alkyl-, phenyl-, and TMS-substituted ynones[13] all gave the corresponding CO insertion products (entries 1−6, Table 2). Substitution at the allene terminus with a methyl group provided only the

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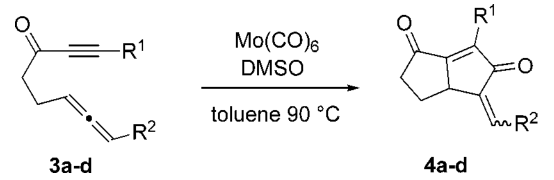
[12] Gupta, A. K.; Park, D. I.; Oh, C. H. *Tetrahedron Lett.* **2005**, *46*, 4171−4174.

[13] Terminal alkynones were not tested in this case due to the volatility of both starting material and product.

Table 2. Mo(CO)$_6$-Catalyzed Cyclocarbonylation Reactions



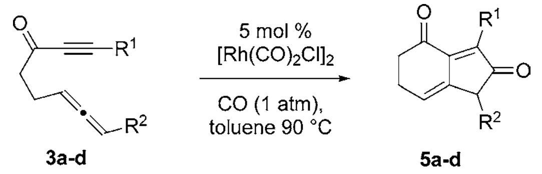
entry	subst	prod	R^1	R^2	time (min)	yield (%)
1^{c}	**3a**	**4a**	TMS	H	60	76
2^{b}	**3a**	**4a**	TMS	H	20	75
3^{c}	**3b**	**4b**	*n*Bu	H	60	70
4^{a}	**3b**	**4b**	*n*Bu	H	10	73
5^{b}	**3c**	**4c**	Ph	H	20	84
6^{a}	**3c**	**4c**	Ph	H	10	79
7^{a}	**3d**	**4d**	Ph	Me	10	83^{d}

^{a} 120 mol % of Mo(CO)$_6$, 10 equiv of DMSO, 90 °C. ^{b} 40 mol % of Mo(CO)$_6$, 4 equiv of DMSO, 90 °C. ^{c} 20 mol % of Mo(CO)$_6$, 2 equiv of DMSO, CO (1 atm), 90 °C. ^{d} Combined yield for a 3:1 (*E*/*Z*) mixture of two diastereromers.

cyclocarbonylation product **4d** in 83% yield (entry 7, Table 2) and none of the triene resulting from a competing cycloisomerization reaction.[14] Catalytic quanitities of molybdenum hexacarbonyl provided the products **4a**−**c** in 70−84% yield (entries 1−3 and 5).

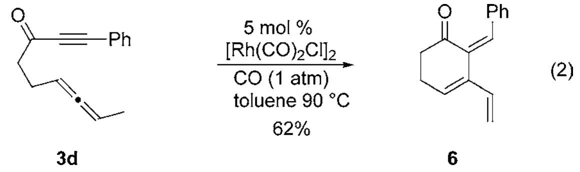
Next, we turned our attention to the formation of bicyclo[4.3.0]dienediones using substrates **3a**−**d**. On the basis of previous studies in our group,[9b] the [Rh(CO)$_2$Cl]$_2$-catalyzed conditions should selectively react with the distal double bond of the allene to afford [4.3.0] bicycles (Table 3). Indeed, reaction of **3a**−**c** produced the corresponding bicyclo[4.3.0]-nonadienediones **5a**−**c** in 51−61% yield and substitution at the alkyne terminus is generally tolerated (entries 1−3, Table 3). However, the methyl-substituted allene **3d** failed to give the dienedione product **5d** (entry 4, Table 3), but instead afforded the cross-conjugated triene **6** in 62% yield as the only isolated compound (eq 2). Triene **6** is formed as a result of the intermediate rhodum metallocycle undergoing a β-hydride elimination instead of a CO insertion.

Table 3. [Rh(CO)$_2$Cl]$_2$-Catalyzed Cyclocarbonylation Reactions



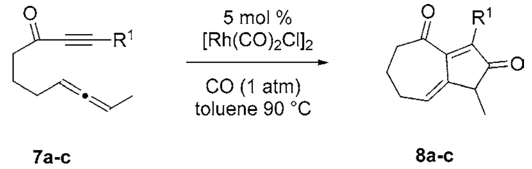
entry	subst	prod	R^1	R^2	time (min)	yield (%)
1	**3a**	**5a**	TMS	H	30	51
2	**3b**	**5b**	*n*Bu	H	30	61
3	**3c**	**5c**	Ph	H	30	55
4	**3d**	**6**	Ph	Me	15	62^{a}

^{a} Yield of the cycloisomerization product **6**.



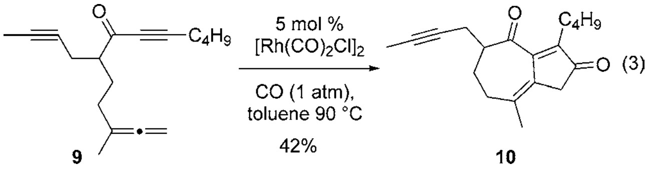
The Rh(I)-catalyzed allenic cyclocarbonylation reaction of alkynones was further explored by testing the feasibility of forming the bicyclo[5.3.0]decenone ring system. As shown in Table 4, the cyclization reactions of **7a**−**c** proceeded smoothly to give seven-membered rings **8a**, **8b**, and **8c** in 61%, 69%, and 68% yield, respectively.

Table 4. [Rh(CO)$_2$Cl]$_2$-Catalyzed Cyclocarbonylation Reaction



entry	subst	prod	R^1	time (h)	yield (%)
1	**7a**	**8a**	*n*Bu	12	61
2	**7b**	**8b**	Ph	6	69
3	**7c**	**8c**	1-cyclohexene	8	68

To the best of our knowledge, this is the first example of a cyclocarbonylation reaction to form a seven-membered ring that does not benefit from the Thorpe−Ingold effect or a conformational restriction imposed by an additional ring in the tether.[9a,b,15] Furthermore, a methyl group on the allene does not result in formation of the triene product. One exception occurs with the phenyl-substituted alleneyne **7b**, in which the unstable cross-conjugated triene was isolated in less than 5% yield (entry 2, Table 4). The carbonyl-containing tether appears to play an important role in facilitating the formation of the seven-membered ring, evidenced by the cyclocarbonylation of alleneyne **9**, which gives only the dienedione **10** in 42% yield (eq 3).



Attempts to prepare the bicyclo[6.3.0]undecadienedione skeleton from the corresponding alleneynone were unsuc-

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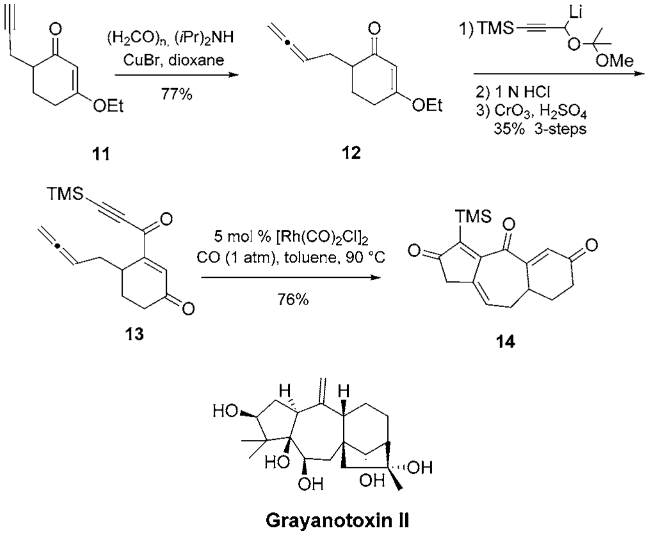
cessful. The starting material was partially recovered after 14 h under the standard Rh(I) reaction conditions.

Next, with an eye toward the synthesis of grayanotoxin II,[16] the Rh(I)-catalyzed allenic cyclocarbonylation reaction was tested on the model system **13** (Scheme 1). Allenic alkynone **13** was rapidly obtained from the known alkyne **11** in 4 steps. Subjecting this alleneynone to the standard Rh(I)-catalyzed cyclocarbonylation reaction conditions afforded the tricyclic core structure **14** in 76% yield. This ring-forming strategy provides a unique approach to functionally dense scaffolds that are otherwise difficult to access.

In summary, the scope of the allenyl cyclocarbonylation reaction has been extended to ynones, a functional motif that has seen limited use in Pauson−Khand reactions. The selective reaction of proximal and distal double bonds of the allene was controlled by the substrate and the transition metal catalyst. Substoichiometric quantities of $Mo(CO)_6$ afforded excellent yields of bicyclo[3.3.0]octadienediones and alkylidene bicyclo[3.3.0]octenediones. The $[Rh(CO)_2Cl]_2$-catalyzed reactions afforded bicyclo[4.3.0]nonadienediones and bicyclo[5.3.0]decadienediones. The utility of the resulting functionally dense scaffolds in natural product synthesis and library preparation will be reported in due course.

Scheme 1. Allenic Cyclocarbonylation Approach to Grayanotoxin II



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Supporting Information Available: Characterization data and full experimental procedures are provided for all new compounds in Tables 1−4, eq 3, and Scheme 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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