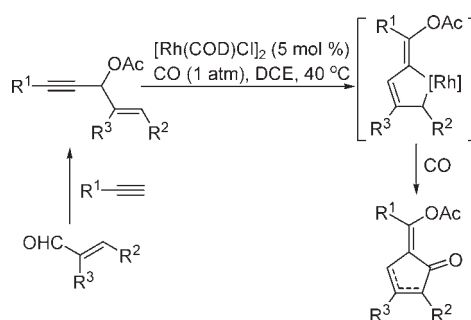# Rhodium-Catalyzed Carbonylation of 3-Acyloxy-1,4-enynes for the Synthesis of Cyclopentenones

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ABSTRACT

Functionalized cyclopentenones were synthesized by a Rh-catalyzed carbonylation of 3-acyloxy-1,4-enynes, derived from alkynes and α,β-unsaturated aldehydes. The reaction involved a Saucy−Marbet 1,3-acyloxy migration of propargyl esters and a [4 + 1] cycloaddition of the resulting acyloxy substituted vinylallene with CO.

The transition-metal-catalyzed cycloaddition reaction is one of the most efficient ways to access ring systems.[1] Formation of cyclopentenones *via* Pauson−Khand cycloaddition has proven to be extremely valuable for the synthesis of natural products and pharmaceutical agents.[2] However, transition-metal-catalyzed intermolecular Pauson−Khand reactions are still challenging for the synthesis of various monocyclic cyclopentenones. Even in the case of intramolecular reactions, the scope of alkenes is often limited. Efficient synthesis of cyclopentenones with diverse substitutions and functionalities are still highly desirable and continue to stimulate the development of novel cycloaddition reactions.[2f]

We herein report an efficient synthesis of highly functionalized cyclopentenones **4** and **5** from 3-acyloxy-1,4-enyne **3** *via* a Rh(I)-catalyzed carbonylation reaction (Scheme 1). Since substrate **3** could be conveniently prepared from the addition of terminal alkyne **1** to α,β-unsaturated aldehyde **2** followed by esterification, this carbonylation reaction offered an efficient protocol to access functionalized cyclopentenones, which are present in many bioactive natural products and pharmaceuticals. For examples, 5-alkylidene-cyclopent-2-enones such as clavulones[2g] and punaglandins[2h] display anti-inflammatory and antitumor activities respectively.

We and others have demonstrated that 3-acyloxy-1,4-enynes with a terminal alkyne (**3**, R[1] = H) can serve as

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(1) For selected reviews on transition metal catalyzed cycloadditions, see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Fruhauf, H. W. *Chem. Rev.* **1997**, *97*, 523. (c) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (d) Evans, P. A. *Modern Rhodium-Catalyzed Organic Reactions*: Wiley-VCH: Weinheim, 2005. (e) Michelet, V.; Toullec, P. Y.; Genet, J. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (f) Yu, Z.; Wang, Y.; Wang, Y. *Chem.—Asian J.* **2010**, *5*, 1072. (g) Inglesby, P. A.; Evans, P. A. *Chem. Soc. Rev.* **2010**, *39*, 2791. (h) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954.

(2) (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977. For selected reviews on Pauson−Khand reactions, see: (b) Gibson, S. E.; Mainolfi, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022. (c) Park, J. H.; Chang, K. M.; Chung, Y. K. *Coord. Chem. Rev.* **2009**, *253*, 2461. (d) Habermann, J. *Curr. Org. Chem.* **2010**, *14*, 1139. (e) Lee, H. W.; Kwong, F. Y. *Eur. J. Org. Chem.* **2010**, 789. For a recent review on synthesis of cyclopentenones, see: (f) Gibson, S. E.; Lewis, S. E.; Mainolfi, N. *J. Organomet. Chem.* **2004**, *689*, 3873. For selected bioactive cyclopentenones, see: (g) Kikuchi, H.; Tsukitani, Y.; Iguchi, K.; Yamada, Y. *Tetrahedron Lett.* **1982**, *23*, 5171. (h) Baker, B. J.; Okuda, R. K.; Yu, P. T. K.; Scheuer, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 2976.

Scheme 1. Carbonylation of 3-Acyloxy-1,4-enyne for the Synthesis of Cyclopentenones
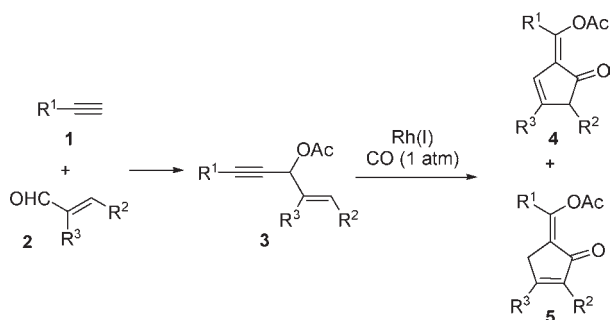
a five-carbon building block for [5 + 1][3] and [5 + 2][4] cycloadditions with CO and alkynes respectively. Both cycloadditions involved a Rh-catalyzed 1,2-acyloxy migration of propargyl esters, a process first described by Rautenstrauch in 1984 using a Pd(II) catalyst.[5]

We found that propargyl esters with an internal alkyne underwent 1,3-acyloxy migration to form an acyloxy substituted allene intermediate in several Rh-catalyzed cascade reactions.[6] The 1,3-acyloxy migration of propargyl esters was first discovered by Saucy and Marbet using a Ag(I) catalyst.[7] Trapping the resulting allene intermediate has been realized in tandem reactions catalyzed by Ag(I), Cu(I), Pt(II), and Au(I) complexes.[8] We envisioned that a new carbonylation method could be realized for the synthesis of cyclopentenones if a Rh(I) complex was able to catalyze the Saucy−Marbet rearrangement of 3-acyloxy-1,-4-enynes with an internal alkyne (**3**, $R^1 \neq H$) and a [4 + 1] cycloaddition of the resulting vinylallene with CO.[9]

(3) Brancour, C.; Fukuyama, T.; Ohta, Y.; Ryu, I.; Dhimane, A. L.; Fensterbank, L.; Malacria, M. *Chem. Commun.* **2010**, *46*, 5470.

(4) Shu, X.-Z.; Huang, S.; Shu, D.; Guzei, I. A.; Tang, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 8153.

(5) (a) Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950. (b) Rautenstrauch, V. *Tetrahedron Lett.* **1984**, *25*, 3845.

(6) (a) Shu, D.; Li, X.; Zhang, M.; Robichaux, P. J.; Tang, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 1346. (b) Li, X.; Zhang, M.; Shu, D.; Robichaux, P. J.; Huang, S.; Tang, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 10421. (c) Huang, S.; Li, X.; Lin, C. L.; Guzei, I. A.; Tang, W. *Chem. Commun.* **2012**, *48*, 2204.

(7) Saucy, G.; Marbet, R.; Lindlar, H.; Isler, O. *Helv. Chim. Acta* **1959**, *42*, 1945.

(8) For a leading review on π-acidic metal catalyzed 1,3-acyloxy migration of propargyl esters, see: (a) Wang, S.; Zhang, G.; Zhang, L. *Synlett* **2010**, 692. For selected related reviews on π-acidic metal catalyzed reactions, see: (b) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750. (c) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (d) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (e) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6754. (f) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (g) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351.

(9) For rhodium-catalyzed [4 + 1] cycloaddition of vinylallene with CO, see: (a) Murakami, M.; Itami, K.; Ito, Y. *Angew. Chem., Int. Ed.* **1995**, *34*, 2691. (b) Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 2950. (c) Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4130. (d) Murakami, M.; Itami, K.; Ito, Y. *Organometallics* **1999**, *18*, 1326. For iron-mediated [4 + 1] cycloadditions, see: (e) Sigman, M. S.; Kerr, C. E.; Eaton, B. E. *J. Am. Chem. Soc.* **1993**, *115*, 7545. (f) Sigman, M. S.; Eaton, B. E. *J. Org. Chem.* **1994**, *59*, 7488. (g) Sigman, M. S.; (h) Eaton, B. E.; Heise, J. D.; Kubiak, C. P. *Organometallics* **1996**, *15*, 2829. (i) Sigman, M. S.; Eaton, B. E. *J. Am. Chem. Soc.* **1996**, *118*, 11783.

We were pleased to find that $[Rh(CO)_2Cl]_2$ was indeed able to facilitate both the 1,3-acyloxy migration of propargyl ester **3a** and [4 + 1] cycloaddition of the resulting vinylallene with CO (entry 1, Table 1). A mixture of isomeric alkylidene cyclopentenones **4a** and **5a** was observed. We then examined various other Rh(I) catalysts (entries 2−5). A slightly better yield was obtained using the $[Rh(COD)Cl]_2$ catalyst (entry 2). We also tried substrate **3b** bearing a pivalate group (entry 6). The combined yield and the ratio of **4b** and **5b** were similar to results from acetate shown in entry 2. Since acetate is generally easier to be removed, we decided to focus on acetate **3a** for further optimization of the conditions. Dichloroethane (DCE) provided the best results among solvents we screened (entries 2 and 7−9). We then examined the effect of temperature (entries 10−12). The best result was obtained at 40 °C (entry 11). Product **5a** could be separated from minor isomer **4a** and isolated in 70% yield.

For all entries in Table 1, the ratios of **4a/5a** did not change significantly. They ranged from 1:3 to 1:3.5. We observed no obvious change to the ratio of **4a/5a** when the mixture of two products was treated with bases (e.g., DBU, DBN, DMAP, DABCO, DIPEA, or Et_3N). When dppf was employed as the ligand, the ratio of **4a/5a** became 1:1 after the carbonylation. Most other ligands (e.g., dppe, dppp, and dppb) had no effect on the ratio.

Table 1. Screening of Catalysts and Conditions for Carbonylation of 3-Acyloxy-1,4-enynes[a]

3a, R = Ac, R¹ = PhCH₂CH₂   **4a**   **5a**
3b, R = Piv, R¹ = PhCH₂CH₂   **4b**   **5b**

(**4** / **5** = 1 : 3 - 3.5)
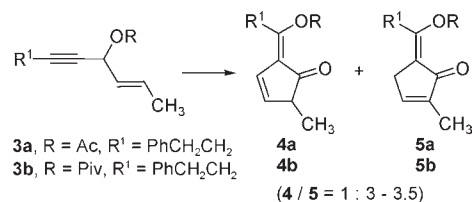
entry	conditions	yield (**4** + **5**)
1	$[Rh(CO)_2Cl]_2$ (5 mol %), DCE, 60 °C	53%
2	$[Rh(COD)Cl]_2$ (5 mol %), DCE, 60 °C	55%
3	$[Rh(CO)_2(acac)]$ (5 mol %), DCE, 60 °C	10%
4	$[Rh(PPh_3)_3Cl]$ (5 mol %), DCE, 60 °C	30%
5	$[Rh(COD)_2]BF_4$ (5 mol %), DCE, 60 °C	trace
6[b]	$[Rh(COD)Cl]_2$ (5 mol %), DCE, 60 °C	56%
7	$[Rh(COD)Cl]_2$ (5 mol %), toluene, 60 °C	43%
8	$[Rh(COD)Cl]_2$ (5 mol %), dioxane, 60 °C	46%
9	$[Rh(COD)Cl]_2$ (5 mol %), CH_3CN, 60 °C	33%
10	$[Rh(COD)Cl]_2$ (5 mol %), DCE, 80 °C	38%
11	$[Rh(COD)Cl]_2$ (5 mol %), DCE, 40 °C	81% (70%, Z/E = 7:1)[c]
12	$[Rh(COD)Cl]_2$ (5 mol %), DCE, rt	40%

[a] Unless noted otherwise, substrate **3a** was employed. The combined yield and the ratio of **4a** and **5a** were determined by ¹H NMR. The ratio of **4a/5a** ranged from 1:3 to 1:3.5. All reactions were carried out under a CO balloon for 8 h. [b] Substrate **3b** was employed. The ratio of **4b/5b** was 1:3.5. [c] Isolated yield of **5a**. The Z/E ratio was determined by ¹H NMR.

Similar results (yield of **5c** and ratios of **4c/5c**) were observed for substrate **3c** (Scheme 2). The conversion was low for substrate **3d** with a phenyl substituted alkene. After 40 h, product **5d** was isolated in 20% yield and 60% starting material was recovered. The yield of product **5d** could not be improved by varying the temperature or CO pressure.

For substrate **3e** with a trisubstituted olefin, isomer **4e** became the major product (condition a, Scheme 2). The ratio of isomers **4e/5e** was about 7:1 based on the ^{1}H NMR of the crude product. After purification by silica gel column chromatography, however, we found that the ratio of **4e/5e** varied each time. We suspected that isomer **5e** with a tetrasubstituted olefin might become more stable and the isomerization from **4e** to **5e** occurred during purification. Indeed, when the crude product from the Rh-catalyzed carbonylation was treated with 2.0 equiv of triethylamine, isomer **4e** was not detected and product **5e** was isolated in 86% yield. This greatly simplified the purification and characterization of the cyclopentenone product.

Scheme 2. Carbonylation of 3-Acyloxy–1,4-enyne with Di- and Trisubstituted Alkenes
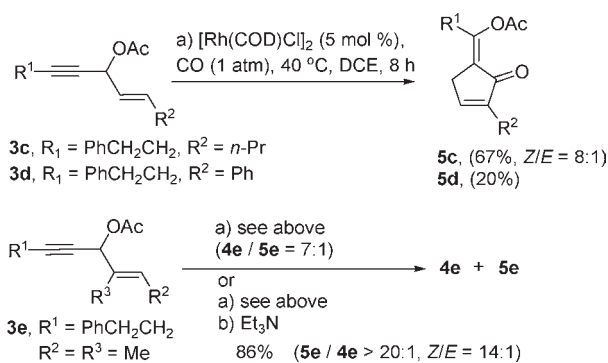
The scope of the carbonylation was examined more extensively for substrates with a trisubstituted olefin (Table 2). Substrates **3e**−**3k** could be easily prepared from the addition of various terminal alkynes to commercially available tiglic aldehyde followed by acetylation. For substrate **3f** with a phenyl substituted alkyne, a complex mixture was observed. Enynes **3g**−**3k** with various alkyl groups on the alkyne termini all participated in the tandem reaction. The yield became lower for substrate **3k** with a siloxy group on the propargylic position.

Substrate **3l** with an *n*-Bu group on the alkene could also be tolerated. Based on results for substrate **3d** in Scheme 2, it appeared that the introduction of a phenyl substituent to the terminal position of the alkene decreased the reactivity of the substrate significantly. We were pleased to find that product **5m** could be prepared in 51% yield under similar conditions. The yield of this product could be further improved to 65% with higher CO pressure. The carbonylation worked smoothly for substrates **3n** and **3o**, where the internal position of the alkene had an ethyl or aryl substituent.

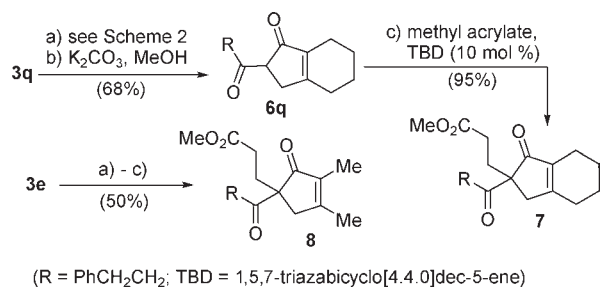**Table 2.** Carbonylation of 3-Acyloxy-1,4-enynes[a]

substrates	products	yield,[b] (Z/E)
3f	a complex mixture	-
3g	5g	72%,[c] (8:1)
3h	5h	55%, (3:1) / 12%[d]
3i	5i	68%, (8:1)
3j	5j	66%, (17:1)
3k	5k	48%, (13:1)
3l	5l	56%, (7:1)
3m	5m	51%,[c] (6:1) / 65%,[c,e] (6:1)
3n	5n	75%,[c] (11:1)
3o	5o	67%, (12:1)
3p, n = 1	5p, n = 1	84%,[c] (7:1)
3q, n = 2	5q, n = 2	82%,[c] (7:1)
3r, n = 3	5r, n = 3	70%,[c] (5:1)
3s	-	0%
3t	-	0%

[a] Conditions: [Rh(COD)Cl]$_2$ (5 mol %), CO (1 atm), 40 °C, DCE, 8−20 h, then Et$_3$N (2.0 equiv). The ratios of Z/E isomer were determined by ^{1}H NMR of the crude product. [b] Isolated yield of the Z-isomer unless noted otherwise. [c] Isolated yield of the mixture of Z- and E-isomers. [d] Isolated yield of E-isomer. [e] The reaction was run at 5 atm of CO.
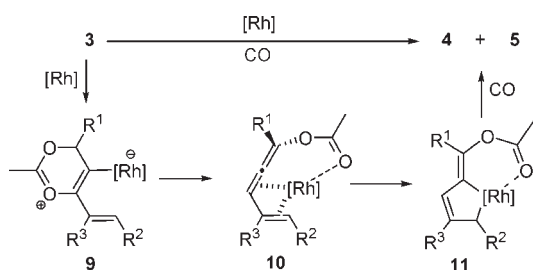
Bicyclic products **5p**, **5q**, and **5r** were also prepared in good yields from the corresponding 3-acyloxy-1,4-enynes. This provided an easy access to 5−5, 5−6, and 5−7 fused compounds with a highly functionalized cyclopentenone.

No desired cyclopentenone product was observed for substrates **3s** and **3t**. When we tried to prepare tertiary propargyl esters with a trisubstituted alkene, they underwent isomerization to form a mixture of conjugated enynes during the preparation.

Scheme 3. Functionalization of Cyclpentenones Derived Carbonylation of 3-Acyloxy-1,4-enynes

(R = PhCH$_2$CH$_2$; TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene)

Scheme 4. Proposed Mechamism for the Carbonylation of 3-Acyloxy-1,4-enynes

For many cyclopentenone products in Table 2, the major Z-isomer was separated and isolated for clear characterization. The combined yield of both isomers would be slightly higher. The Z/E ratio of product **5** is actually inconsequential after hydrolysis of the enol ester. The mixture of carbonylation products derived from substrate **3q** was then directly treated with K$_2$CO$_3$ in methanol

(Scheme 3). Product 1,3-diketone **6q** could be isolated in 68% yield after two steps. The NMR spectra of diketone **6q**, however, was complex due to the presence of different enols. The 1,3-diketone was then further alkylated with methyl acrylate.[10] Bicyclic compound **7** could be isolated in high yield and clearly characterized. Monocyclic cyclopentenone **8** was obtained in 50% overall yield from substrate **3e**.

The mechanism for the carbonylation of 3-acyloxy-1,-4-enynes was proposed in Scheme 4. The alkenyl substituted propargyl ester **3** could undergo a Rh-catalyzed 1,3-acyloxy migration to form allene intermediate **10**.[6] The coordination of the acyloxy group to Rh may favor the formation of metallocyclopentene intermediate **11**, which will produce the Z-isomer of cyclopentenones **4** or **5** after CO insertion and reductive elimination.

In summary, we have developed an efficient method for the synthesis of various highly functionalized monocyclic and bicyclic cyclopentenones from readily available 3-acyloxy-1,4-enynes. The combination of the novel reactivity of a Rh(I) catalyst for promoting 1,3-acyloxy migration of propargyl esters and its ability to facilitate a carbonylation reaction made this tandem transformation possible. The acyloxy group in the propargyl ester starting material not only eliminates the need for the preformation of allenes but also provides a useful handle for further selective functionalizations of the cyclopentenone products.

Supporting Information Available. ^{1}H NMR, ^{13}C NMR, IR, and HRMS for starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) Ye, W.; Xu, J.; Tan, C. T.; Tan, C. H. *Tetrahedron Lett.* **2005**, *46*, 6875.

The authors declare no competing financial interest.