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Chelation-Assisted Transformation: Synthesis of 1,4-Dicarboxylate Esters by the Rh-Catalyzed Carbonylation of Internal Alkynes with Pyridin-2-ylmethanol

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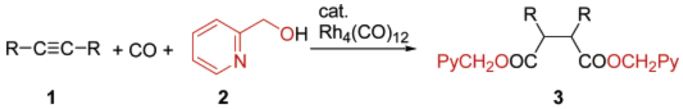
ABSTRACT



PyCH$_2$ = pyridin-2-yl-methyl

The reaction of internal alkynes 1 with CO and pyridin-2-ylmethanol (2) in the presence of $Rh_4(CO)_{12}$ results in a double-hydroesterification leading to 1,4-dicarboxylate esters 3. The reaction does not proceed via two consecutive hydroesterifications of alkynes, but the intermediacy of ketene intermediates is proposed. The coordination of the pyridine nitrogen in 2 to rhodium is essential for the reaction to proceed.

The carbonylation of alkynes with alcohols has been extensively studied because a variety of carbonyl compounds can be obtained depending on the reaction system.[1] A number of research groups, both academic and industrial, have made important contributions, and a variety of transformations have been developed through carbonylation of alkynes with alcohols. The hydroesterifications of alkynes to α,β-unsaturated esters are well-known reactions that proceed in the presence of nickel-, cobalt-, iron-, platinum-, or palladium-based catalyst systems.[2] The intramolecular version of hydroesterification using acetylenic alcohols is a useful method for the construction of unsaturated lactones.[3] 3-Haloacrylates can be produced by the Pd(II)-catalyzed carbonylation of terminal alkynes with alcohols in the presence of copper halides.[4] The introduction of more than one molecule of CO is important in preparing multifunctional compounds from relatively simple substrates. The oxidative carbonylation of alkynes catalyzed by palladium complexes gave 2-alkynoates via monocarbonylation, maleic acid derivatives via dicarbonylation, and tricarbonylation products, depending on the reaction conditions employed.[5] Mise reported that the Rh-catalyzed carbonylation of diphenylacetylene in ethanol gives

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(2) Knifton, J. F. *J. Mol. Catal.* **1977**, *2*, 293−299. Tsuji, Y.; Kondo, T.; Watanabe, Y. *J. Mol. Catal.* **1987**, *40*, 295−304. Ali, B. E.; Alper, H. *J. Mol. Catal.* **1991**, *67*, 29−33. Drent, E. I.; Arnoldy, P.; Budzelaar, P. H. M. *J. Organomet. Chem.* **1993**, *455*, 247−253. Ali, B. E.; Tijani, J.; El-Ghanam, A. M. *Tetrahedron Lett.* **2001**, *42*, 2385−2387.

(3) For a review, see: El Ali, B.; Alper, H. *Synlett* **2000**, 161−171. Murry, T. F.; Norton, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 4107−4119. Murry, T. F.; Samsel, E. G.; Varma, V.; Norton, J. R. *J. Am. Chem. Soc.* **1981**, *103*, 7520−7528. Yu, W. Y.; Alper, H. *J. Org. Chem.* **1997**, *62*, 5684−5687. Consorti, C. S.; Ebeling, G.; Dupont, J. *Tetrahedron Lett.* **2002**, *43*, 753−755.

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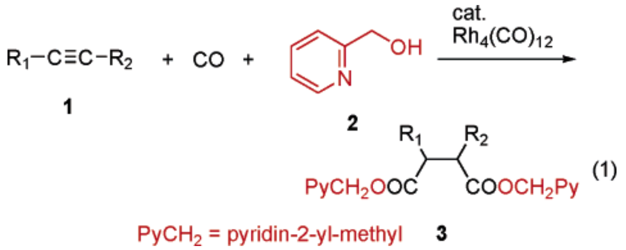
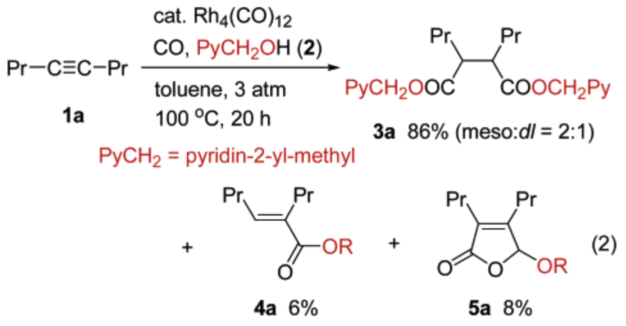
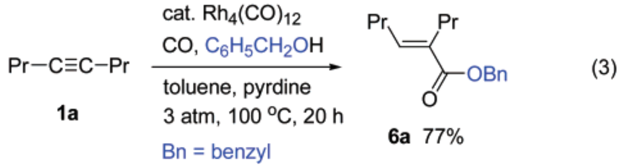
a 5-ethoxy-5*H*-furan-2-one derivative as the main product, along with a small amount of 2,3-diphenylsuccinic acid diethyl ester as a double-hydroesterification product.[6] Tsuji reported that the reaction of diethyl acetylenedicarboxylate in the presence of $PdCl_2$/HCl involves a double-hydroesterification, but no examples of the production of 1,4-dicarboxylates from simple alkynes appear to have been reported.[7] To the best of our knowledge, no effective example of the formation of 1,4-dicarboxylate esters by the double-hydroesterification of simple alkynes exists. We previously reported a series of chelation-assisted carbonylation reactions at C−H bonds[8] and O−H bonds[9] in which the coordination of the sp^2 nitrogen in the substrates to the catalysts is a key step for the reaction to proceed. No reaction occurred when chelation was not involved. The chelation method opens up new possibilities for exploring new types of catalytic reactions, which cannot be achieved using the conventional methods.[10,11] We wish to report herein on the Rh-catalyzed reaction of internal alkynes **1** with CO and pyridin-2-yl-methanol (**2**) leading to 1,4-dicarboxylate esters **3** (eq 1). The reaction does not proceed via two consecutive hydroesterifications of the alkyne, but the formation of ketene intermediates is proposed. The coordination of the sp^2 nitrogen in **2** is a key step for the reaction to proceed.



The reaction of 4-octyne (**1a**, 2 mmol) with pyridin-2-ylmethanol (**2**, 2 mmol) under CO (3 atm) in toluene (1 mL) at 100 °C in the presence of $Rh_4(CO)_{12}$ (0.04 mmol) for 20 h gave 2,3-dipropylsuccinic acid di(pyridin-2-ylmethy)l ester (**3a**) in 86% isolated yield in a 2:1 ratio of *meso* and *dl*,[12] along with the simple hydroesterification product **4a** in 6% and furanone **5a**[6b] in 8% yield (eq 2). A decrease in the reaction temperatures decreased the yield of **3a** (77% at 80 °C; 43−79% at 60 °C, low reproducibility). It was found that $Rh_6(CO)_{16}$ can also be used as a catalyst (49%), but rhodium phosphine complexes, such as $RhCl(PPh_3)_3$ and $HRh(CO)(PPh_3)_3$, were not active. The use of other complexes, such as $Co_2(CO)_8$ and $PdCl_2$ did not lead to the production of carbonylation products. Higher CO pressures had no effect on the yields of **3a**; 49% (1 atm), 86% (3 atm), 82% (5 atm), 85% (10 atm).





In contrast to **2**, the use of benzyl alcohol did not give the corresponding 1,4-dicarboxylate esters. When the reaction of **1a** (2 mmol) was carried out using benzyl alcohol (2 mmol) and pyridine (2 mmol), the 1,4-dicarboxylate ester was not obtained, but instead the monohydroesterification product **6a** was produced in 77% yield (eq 3).[13] This result shows that the double-hydroesterification of alkynes to 1,4-dicarboxylate esters **3** is achieved only when **2** is used.

To gain insight into the reaction mechanism, some control experiments were performed. The reaction of **4a** (1 mmol) with **2** (1 mmol) in the presence of $Rh_4(CO)_{12}$ (0.02 mmol) under otherwise identical conditions did not result in the formation of **3a**, and **4a** was recovered in 96% yield (eq 4). In addition, the reaction of **1b** (1 mmol) with **2** (1 mmol) in

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[5] Gabriele, B.; Sarerno, G.; De Pascali, F.; Costa, M.; Chiusoli, G. P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 147−154. Alper, H.; Des peyroux, B.; Woell, J. B. *Tetrahedron Lett.* **1983**, *24*, 5691−5694. Izawa, Y.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 2033−2045. Izawa, Y.; Shimizu, I.; Yamamoto, A. *Chem. Lett.* **2005**, 1060−1061.

[6] (a) Hong, P.; Mise, T.; Yamazaki, H. *Chem. Lett.* **1981**, 989−992. (b) Mise, T.; Hong, P.; Yamazaki, H. *J. Org. Chem.* **1983**, *48*, 238−242. (c) Joh, T.; Doyama, K.; Onitsuka, K.; Shiohara, T.; Takahashi, S. *Organometallics* **1991**, *10*, 2493−2498.

[7] Tsuji, J.; Nogi, T. *J. Org. Chem.* **1966**, *31*, 2641−2643.

[8] Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 493−494. Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. J. *Org. Chem.* **1997**, *62*, 2604−2610. Fukuyama, T.; Chatani, N.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997**, *62*, 5647−5650. Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S. *Organometallics* **1997**, *16*, 3615−3622. Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S. *Tetrahedron Lett.* **1997**, *38*, 7565−7568. Fukuyama, T.; Chatani, N.; Tatsumi, J.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 11522−11523. Chatani, N.; Ishii, Y.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1998**, *63*, 5129−5136. Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D. R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 1475−1488. Chatani, N.; Fukuyama, T.; Tatamidani, H.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4039−4047. Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12882−12883. Chatani, N.; Yorimitsu, S.; Asaumi, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2002**, *67*, 7557−7560. Asaumi, T.; Chatani, N.; Matsuo, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2003**, *68*, 7538−7540. Asaumi, T.; Matsuo, T.; Fukuyama, T.; Ie, Y.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* **2004**, *69*, 4433−4440. Chatani, N.; Uemura, T.; Asaumi, T.; Ie, Y.; Kakiuchi, F.; Murai, S. *Can. J. Chem.* **2005**, *83*, 755−763.

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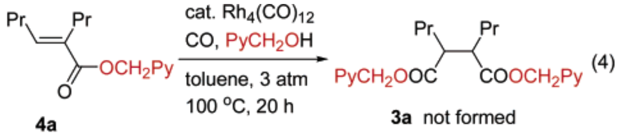
[10] For recent papers on chelation-assisted transformations, see: Yoon, J. H.; Park, Y. J.; Lee, J. H.; Yoo, J.; Jun, C.-H. *Org. Lett.* **2005**, *7*, 2889−2892. Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330−7331. Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154−13155. Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2005**, *127*, 13498−13499. Itami, K.; Yoshida, J. *Synlett* **2006**, 157−180.

[11] Chang reported on the Ru-catalyzed hydroesterification of alkenes using pyridin-2-yl-methyl formate. Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc.* **2002**, *124*, 750−751. Na, Y.; Ko, S.; Hwang, L. K.; Chang, S. *Tetrahedron Lett.* **2003**, *44*, 4475−4478.

[12] The stereochemistry was confirmed by ^{13}C NMR. Quermann, R.; Maletz, R.; Schäfer, H. J. *Liebigs Ann. Chem.* **1993**, 1219−1223.

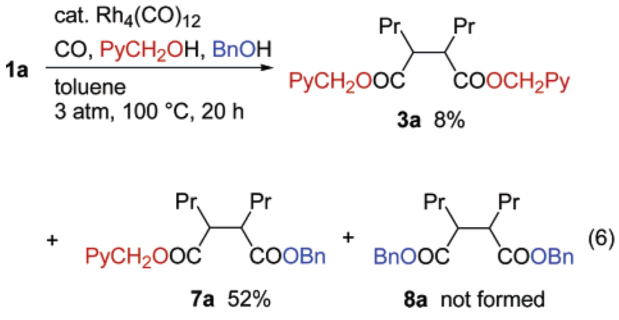
[13] The reaction of **1a** with benzyl alcohol in the absence of pyridine resulted in no reaction.

the presence of **4a** (1 mmol) gave **3b** in 56% yield, and **4a** was recovered in 83% yield along with no formation of **3a**. Mise reported that 2,3-diphenylsuccinic acid diethyl ester (related to **3a**) is a secondary product from 5-ethoxy-3,4-diphenyl-5*H*-furan-2-one (related to **5a**).[6b] A controlled experiment was performed using furanone **5a**; no evidence for the conversion of **5a** to **3a** was found (eq 5). The reaction of **1b** in the presence of **5a** gave only **3b** (70% yield) with **5a** remaining unreacted. According to the results obtained, the monohydroesterification products **4a** and **5a** do not appear to be intermediates in the formation of **3a**.



Some results for the reaction of various alkynes are shown in Table 1. Both aliphatic and aromatic internal alkynes gave the corresponding 1,4-dicarboxylate esters in good to high yields. The presence of a *tert*-butyl group on the acetylenic carbon, as in *tert*-butylphenylacetylene and 2,2-dimethyl-3-pentyne, had a significant effect on the efficiency of the reaction; the expected products were produced in less than 10% yield (not shown in Table 1). A terminal alkyne, such as octyne, or diethyl acetylenedicarboxylate gave complex mixtures. The use of trimethylsilylpropyne resulted in no reaction.

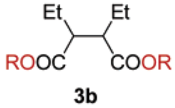
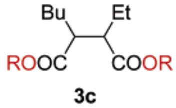
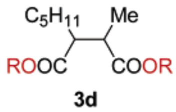
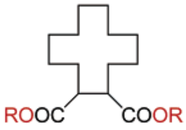
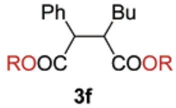
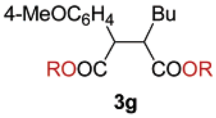
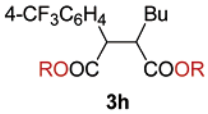
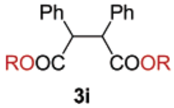
The reaction of **1a** with **2** (1 mmol) and benzyl alcohol (1 mmol) gave **3a** in 8% and **7a** in 52% yields (eq 6). It should be noted that **8a** was not detected. This shows that the reaction involves one step in which **2** is always required and that the subsequent step does not depend on the type of alcohol used.



A proposed reaction mechanism is shown in Scheme 1. The coordination of the pyridine nitrogen in **2** to the rhodium center facilitates the intramolecular attack of the alcohol on the coordinated carbon monoxide to give a rhodium hydride species **9**. The insertion of an alkyne into the acyl−Rh bond in **9** to give **10**, in which the CO insertion gives rise to the acyl complex **11**, which is then converted to a ketene intermediate **12**. Pyridin-2-ylmethanol or benzyl alcohol may both attack the ketene carbon to give **3a** and **7a**, respectively. The formation of a mixture of **3a** and **7a** in favor of **7a** is rationalized by the intermediacy of **12** and by an excess of benzyl alcohol remaining in the reaction system because the generation of **12** requires **2**. The coordination of **2** to rhodium is required to form an active species such as **9**, showing that at least one molecule of **2** is incorporated into the product.

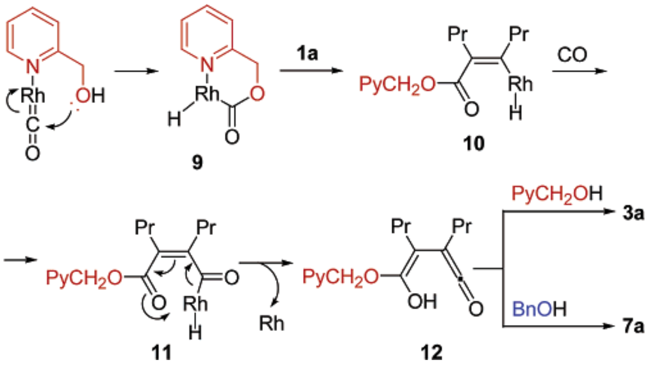
In summary, the reaction described here represents the first effective example of the double-hydroesterification of simple alkynes to 1,4-dicarboxylate esters, to the best our knowledge. Based on the controlled experiments, it can be

Table 1. $Rh_4(CO)_{12}$-Catalyzed Carbonylation of Alkynes with CO and Pyridin-2-ylmethanol (**2**)[a]

entry	alkyne	product	yield [b]
1	Et−C≡C−Et **1b**	 **3b**	83% (2:1)
2	Bu−C≡C−Et **1c**	 **3c**	75% (1.3:1)
3	C_5H_{11}−C≡C−Me **1d**	 **3d**	72% (nd)
4	 **1e**	 **3e**	57% (1.4:1)
5	Ph−C≡C−Bu **1f**	 **3f**	73% (1:2)
6	4-MeOC_6H_4−C≡C−Bu **1g**	 **3g**	55% (1:1.8)
7	$4\text{-CF}_3C_6H_4$−C≡C−Bu **1h**	 **3h**	56% (1:1.7)
8	Ph−C≡C−Ph **1i**	 **3i**	63% (1:2)

[a] Reaction conditions: alkyne **1** (2 mmol), pyridin-2-ylmethanol (**2**) (2 mmol), $Rh_4(CO)_{12}$ (0.04 mmol) in toluene (1 mL) under CO (3 atm) at 100 °C for 20 h. [b] Isolated yield by column chromatography. The number in parentheses is the ratio of *dl* and *meso* (or *threo* and *erythro*). nd: not determined.

Scheme 1. Proposed Reaction Mechanism



concluded that the reaction does not proceed via two successive hydroesterifications, but proceeds via the intermediacy of a ketene intermediate. In situ transesterification of products with methanol or ethanol would be expected to be catalytic with respect to **2**. However, all attempts to make catalytic use of **2** were in vain. Because the coordination of the sp^2 nitrogen of **2** is essential for the reaction to proceed, the use of **2** in place of methanol or ethanol, which are typically used in various catalytic reactions, might have led to a chance to explore new types of catalytic reactions.

Supporting Information Available: Experimental detailes and the characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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