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Palladium-Catalyzed Carbonylation of Yne Esters Leading to γ-Alkylidene α,β-Unsaturated γ-Lactones

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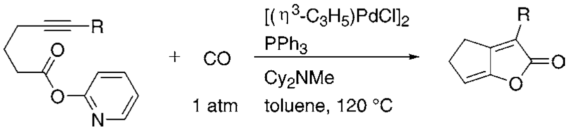
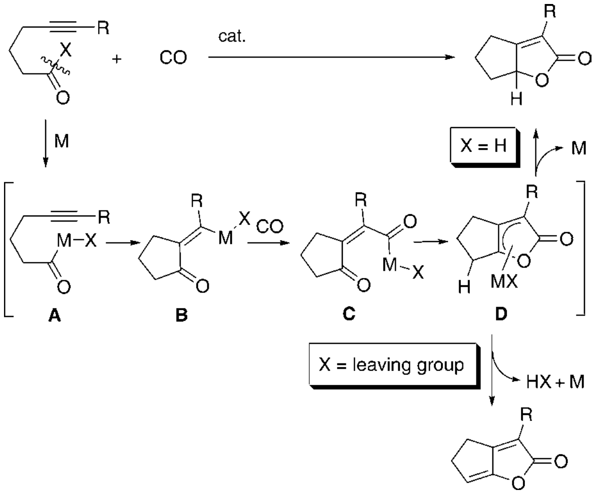
ABSTRACT



The reaction of yne esters with carbon monoxide (1 atm) in the presence of palladium complexes gives bicyclic unsaturated lactone derivatives in good to high yields. The 2-pyridinyloxy group is a good leaving group among leaving groups examined.

Unsaturated lactones are important subunits in naturally occurring as well as biologically active compounds.[1−3] While numerous methods have been developed for the synthesis of such skeletons, cyclocarbonylation continues to be a method of choice for the construction of lactone rings.[3] A variety of substrates, such as alkynols,[4] allenyl alcohols,[5] halo alkenes,[6] α-keto alkynes,[7] and β-iodo enones,[8] have been used thus far in the preparation of unsaturated lactones via cyclocarbonylation.[3] We previously reported on the $Ru_3(CO)_{12}$-catalyzed cyclocarbonylation of 1,6-alkynals leading to α,β-unsaturated bicyclic lactones.[9] One of the proposed mechanisms for this reaction is shown in Scheme 1. The oxidative addition of an aldehyde C−H bond to ruthenium gives acyl ruthenium species **A**, which undergoes carbometalation, CO insertion, cyclization, and a reductive elimination of **D** to afford the final product. If X, such as a halide or pseudohalide, is the leaving group, the final step,

Scheme 1



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(1) Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707−6738.

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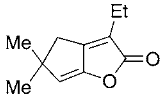
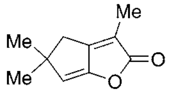
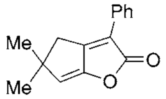
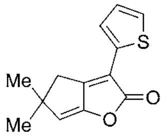
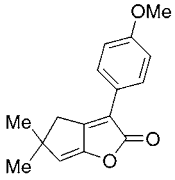
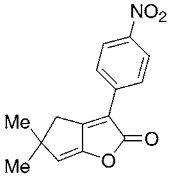
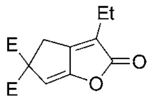
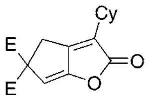
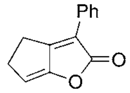
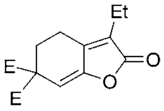
Table 1. Cyclocarbonylation of Yne Esters

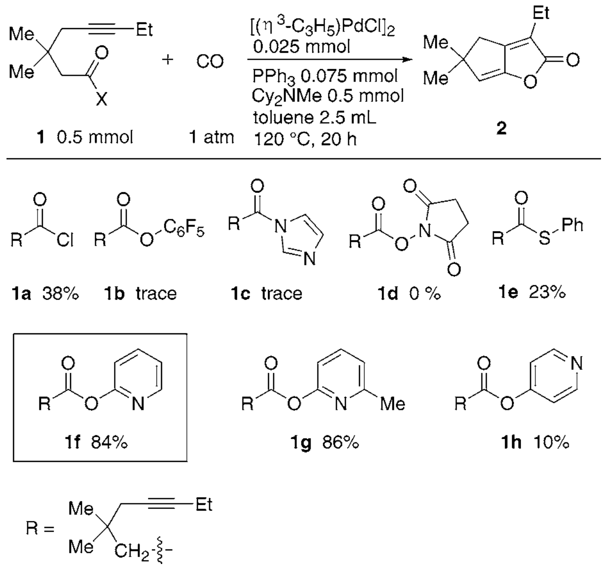
product	yield (time)	product	yield (time)
 **2**	94% (40 h)	 **3**	90% (40 h)
 **4**	80% (40 h)	 **5**	70%
 **6**	66%	 **7**	57%
 **8**	66%	 **9**	51%
 **10**	60% (40 h)	 **11**	18%

[a] Reaction conditions: substrate (0.5 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (0.025 mmol), PPh_3 (0.075 mmol), Cy_2NMe (0.5 mmol), toluene (2.5 mL) at 120 °C under CO (1 atm) for 20 h.

reductive elimination, does not proceed,[10] but instead a β-hydride elimination leading to unsaturated lactones would be expected to occur. Herein, we report on the successful use of this approach for the construction of unsaturated, fused bicyclic γ-lactones via the Pd-catalyzed cyclocarbonylation of hex-5-ynoic acid pyridin-2-yl esters (X = a 2-pyridyloxy group).

An intramolecular acetylene–acid chloride (X = Cl) was the first choice for a representative substrate to examine because acid chlorides are well-known to generate acyl complexes related to **A** via oxidative addition. Although extensive studies were carried out using $Ru_3(CO)_{12}$ as the catalyst, the expected product was not formed. However, the use of a palladium catalyst resulted in the formation of the expected unsaturated lactones. The reaction of 3,3-dimethyl-oct-5-ynoyl chloride (**1a**) with CO (1 atm) in the presence of a palladium catalyst gave 3-ethyl-5,5-dimethyl-4,5-dihydrocyclopenta[*b*]furan-2-one (**2**) in 38% yield. Other leaving groups, which have recently been developed for Pd-catalyzed cross coupling reactions with arylboronic acids, as in **1b**–**d**, did not give satisfactory results.[11] A thioester **1e** was also not a suitable substrate for the present carbonylation (23% yield), although catalytic reactions involving the oxidative addition of thioesters to palladium complexes are well-known.[12] We recently found that the 2-pyridinyloxy group is a good leaving group for Pd-catalyzed cross-coupling reactions of pyridin-2-yl esters with arylboronic acids leading to aromatic ketones.[13] We then prepared the yne ester **1f**. As expected, the reaction of **1f** at 120 °C at 1 atm led to dramatically improved yield of **2** of 84% yield. The use of higher CO pressures, such as 5 atm decreased the product yield to 71%. The use of a CO balloon gave **2** in 23% yield, indicating that a slight positive CO pressure is necessary for the reaction to proceed efficiently.

Scheme 2



Results for the carbonylation of various pyridinyl esters are shown in Table 1. Substrates having alkyl-, aryl-, and heteroaryl groups on the acetylenic carbon gave the corresponding unsaturated lactones in good to high yields. Certain additional functional groups, such as methoxy and nitro, are compatible for the present reaction. The presence of a geminal group at the tether is not essential for the reaction to proceed. The formation of a cyclohexyl-fused lactone failed to proceed smoothly.

The reaction appears to proceed in a manner consistent with the working hypothesis proposed in Scheme 1. A pyridinyl ester oxidatively adds to a palladium complex to give an acyl palladium complex **A**.[14] The complex **A** undergoes carbometalation to give the vinyl palladium complex **B**, in which CO is inserted to give an acyl complex **C**. The cyclization of **C** gives the π-allyl palladium complex

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(10) Roy, A. H.; Hartwig, J. *J. Am. Chem. Soc.* **2003**, *125*, 13944–13945. Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 1533–1541.

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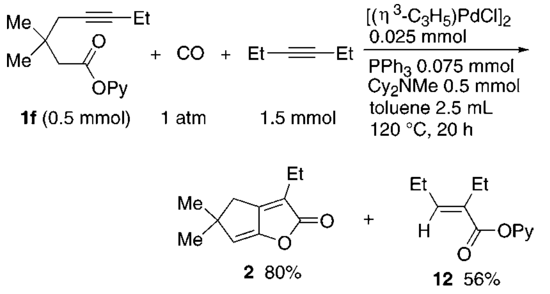
(12) For a recent paper, see: Fausett, B. W.; Liebeskind, L. S. *J. Org. Chem.* **2005**, *70*, 4851–4853. See also: Fukuyama, T.; Tokuyama, H. *Aldrichim. Acta* **2004**, *37*, 87–96.

(13) Tatamidani, H.; Kakiuchi, F.; Chatani, N. *Org. Lett.* **2004**, *6*, 3597–3599.

D, which then undergoes a β-hydride elimination to give the final product.[15] Based on the proposed mechanism, a catalytic amount of amine is sufficient for the reaction to proceed. However, the use of 10 mol % (0.05 mol) of amine decreased in the product yield to 52% yield. The exact reason for why the 2-pyridinyloxy group is the leaving group of choice is currently not clear. 2-Hydroxypyridine was not able to be isolated from the reaction mixture. However, when 3-hexyne was added to a reaction of **1f** under the reaction conditions shown in Scheme 2, the hydroesterification of 2-hydroxypyridine also took place to give **12** in 56% yield, along with **2** in 80% yield, indicating that 2-hydroxypyridine was formed and was sufficiently stable to be trapped (Scheme 3).[16,17]

In summary, we demonstrate the Pd-catalyzed cyclocarbonylation of yne esters leading to the formation of γ-alkylidene α,β-unsaturated γ-lactones. The 2-pyridinyloxy group was found to be a good leaving group for generating acyl palladium complexes via oxidative addition compared with other leaving groups in this cyclocarbonylation.[18] The applications of this method for generating acyl complexes from pyridin-2-yl esters to new catalytic reactions are under study.

Scheme 3



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

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(15) A similar mechanism was proposed for Pd and Rh catalysis. See refs 7 and 8. Kamitani, A.; Chatani, N.; Murai, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1397−1399.

(16) When twice the amount of palladium complex was used (0.05 mmol), **2** and **13** were obtained in 97% and 74% yields, respectively.

(17) Kushino, Y.; Itoh, K.; Miura, M.; Nomura, M. *J. Mol. Catal.* **1994**, *89*, 151−158.

(18) For papers on pyridinyl esters, see: Mukaiyama, T. *Chem. Lett.* **1980**, 709−712. Mukaiyama, T. *Chem. Lett.* **1980**, 905−906. Mukaiyama, T. *Chem. Lett.* **1981**, 531−534. See also refs 11b and 13.