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Palladium(II)-Catalyzed Aerobic Dialkoxylation of Styrenes: A Profound Influence of an *o*-Phenol

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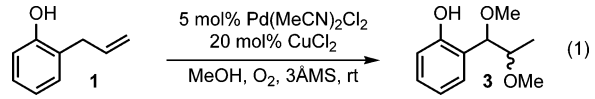
Controlling the rate of β-hydride elimination is an underlying concern in Pd-catalyzed reactions. This issue is highlighted by a desired slower rate of β-hydride elimination in cross-coupling of sp^3 hybridized substrates[1] and a faster rate in oxidative processes[2] (i.e., Wacker and Heck) where the expected Pd(II) intermediates for these two reactions should only have subtle structural differences. With this in mind, we wanted to integrate Pd-catalyzed cross-coupling and oxidation chemistry in the realm of olefin functionalization. In exploring this idea, we found a surprising outcome: exposing **1** to catalytic Pd(II) in methanol results in isomerization to 2-propenyl phenol (**2**),[3,4] followed by the dialkoxylation of the internal olefin with two equivalents of methanol (eq 1).[5] Herein, we present the initial scope of this transformation and a preliminary mechanistic study revealing that the *o*-phenol prevents β-hydride elimination.

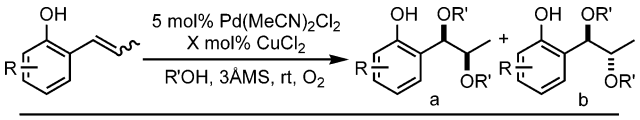


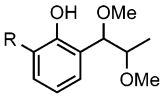
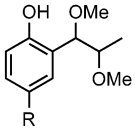
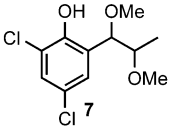
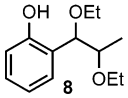
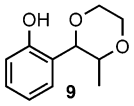
(1)

Reaction optimization using **2** led to a procedure utilizing 5 mol % $Pd(MeCN)_2Cl_2$, 40 mol % $CuCl_2$, with 3 Å molecular sieves in alcoholic solvent under a balloon pressure of O_2 to yield the dialkoxylation product with a syn to anti ratio of 4.5 to 1 (Table 1, entry 1).[6] Both catalytic $CuCl_2$ and molecular oxygen were required since removal of either reagent resulted in significant catalyst decomposition. Application of the optimized conditions to various substituted phenols proved challenging requiring adjustment of the reaction conditions to achieve satisfactory yields. Specifically, more electron-rich substrates initially led to poor mass balance attributed to substrate polymerization (entries 2 and 3). Lowering the $CuCl_2$ concentration and/or the initial temperature increased the mass recovery, resulting in enhanced isolated yields. Additionally, an increase in diastereoselectivity was observed at lower temperature with a syn to anti ratio of 6 to 1 (entry 2). In contrast to more electron-rich substrates which tended to polymerize under the standard conditions, the dialkoxylation of electron-poor substrates led to reduced selectivity for the desired product due to formation of several byproducts (vide infra). It was found that addition of catalytic amounts of Cs_2CO_3 (10 mol %) increased the selectivity of these reactions, leading to improved isolated yields (entries 4 and 5). Unfortunately, vinylphenols do not undergo dialkoxylation under similar conditions.

Ethanol and ethylene glycol were also surveyed to test if other alcohols could be used as nucleophiles in the dialkoxylation reaction. Both solvents led to successful dialkoxylation albeit in modest yields (entries 6 and 7). Of note, dialkoxylation with ethylene glycol gave the highest diastereoselectivity measured with a syn to anti ratio of 7.5 to 1. Unfortunately, the use of more hindered alcohols such as benzyl alcohol and 2-propanol proved unsuccessful for the dialkoxylation of **2**.

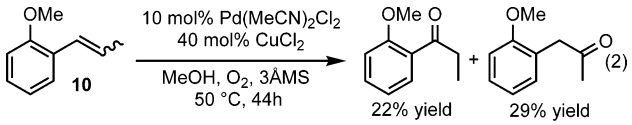
Table 1. Scope of Pd-Catalyzed Aerobic Dialkoxylation



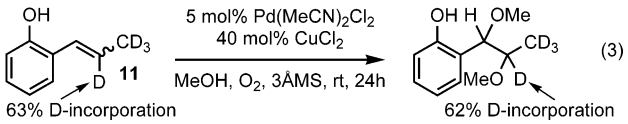
Entry	X	Product	Time (h)	% Yield[a]	a : b[b]
1	40	 R=H (**3**)	24	70	4.5 : 1
2[c]	10	R=Me (**4**)	6	70	6 : 1
3	20	 R=Me (**5**)	6	62	4.5 : 1
4[d]	40	R=Cl (**6**)	24	63	3.8 : 1
5[d]	40		24	72	3.8 : 1
6	20		36	50	2.9 : 1
7	20		24	43	7.5 : 1

[a] Average isolated yield of two reactions. [b] Measured by ^1H NMR. [c] Substrate was added at 0 °C. [d] 10 mol% Cs_2CO_3 was added.

The current results contrast Hosokawa and co-workers observations where, under similar reaction conditions, simple styrene derivatives were converted to the *anti*-Markovnikov acetals.[7] This lead us to question whether the *o*-phenol is required for dialkoxylation. Therefore, substrate **10** was tested to ascertain if the phenol was essential (eq 2). Upon exposure of **10** to the reaction conditions, a mixture of regioisomeric Wacker products resulted via hydrolysis of the acetals upon workup.



(2)



(3)

These observations allude to a fundamentally different mechanistic pathway as compared to Wacker-type reactions where β-hydride elimination is implicated. Thus, we questioned: (1) what

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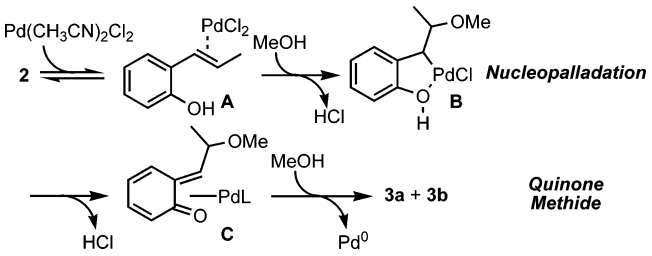
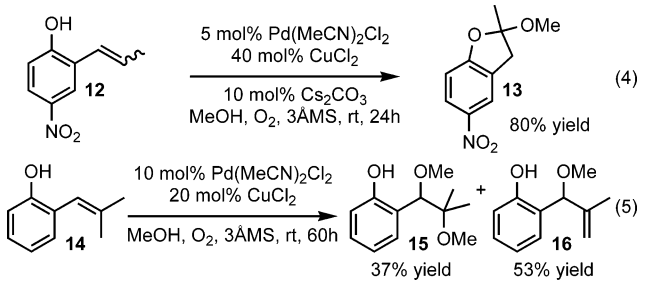
Scheme 1. Proposed Mechanism for the Pd-Catalyzed Dialkoxylation of Olefins



is the role of the *o*-phenol, and (2) if the first C−O bond is formed by nucleopalladation, how does the second C−O bond form?

To help address these questions, isotopic labeling experiments were performed to determine whether palladium-hydride chemistry is involved. Substrate **2** was submitted to the dialkoxylation reaction in CD_3OD. No deuterium was incorporated into the propane chain of the product. Additionally, exposure of the isotopically labeled substrate **11** to the reaction conditions resulted in no deuterium transfer within the product (eq 3). Together, these data rule out β-hydride elimination of solvent or substrate during the dialkoxylation reaction.

On the basis of these results, a mechanism is proposed that includes two intimately coupled steps: (a) regioselective nucleopalladation of **A** via MeOH addition to the β-carbon of the styrene yielding **B** and (b) subsequent formation of a quinone methide[8] species **C** with concomitant reduction of palladium (Scheme 1). Dialkoxylation is achieved by addition of a second equivalent of MeOH to **C**, leading to rearomatization.[9] Previously, a propenyl phenol derivative, upon treatment with stoichiometric Pd(II) and a base, is proposed to undergo a similar conversion into a quinone methide by Chapman in his classic synthesis of Carpanone.[10] Although alternative mechanistic proposals cannot be discounted, possibilities such as direct nucleophilic substitution or oxidatively induced reductive elimination[11] of a Pd-alkoxide to form the second C−O bond do not account for the requirement of the phenol or the mild reaction conditions.



The sensitivity of the reaction[12] to substrate electronic character supports a quinone methide intermediate. This is highlighted by the formation of cyclic acetal **13** when evaluating the electron-poor substrate **12** (eq 4). The cyclic acetal is a common byproduct for electron-poor substrates and is presumably formed by a combination of β-hydride elimination and insertion steps rather than a quinone methide intermediate.[13] This competing pathway presumably arises from the slow formation of the electron-poor quinone methides. Additionally, since the propenyl phenol derivatives isomerize rapidly to the *E*-isomer, we attribute the modest diastereoselection to the influence of the chiral center on **C** during MeOH attack.[14]

If the reaction is proceeding through a quinone methide, this intermediate can only be accessed by addition of MeOH to the β-carbon. Both Hosokawa's results of addition to the β-carbon of styrenes[5] and the formation of product **13** support this proposal. Further evidence for MeOH attack at the β-carbon is derived from the experiment in eq 5 where the trisubstituted olefin **14** is converted to a mixture of dialkoxylation product **15** and allylic ether **16**. The formation of **15** would result from the mechanism proposed in Scheme 1, while the allylic ether **16** would result from competitive attack of MeOH at the less hindered α-position followed by β-hydride elimination. Alternative processes to form these products are difficult to envision.

In conclusion, we have discovered a new Pd(II)-catalyzed dialkoxylation of styrene derivatives containing an *o*-phenol. These products are attributed to nucleopalladation at the β-carbon of the styrene followed by attack of a second equivalent of MeOH to a quinone methide species. A key finding is that β-hydride elimination is avoided in the dialkoxylation process, revealing the potential for integration with cross-coupling chemistry. This possibility and evaluation of other nucleophiles in enantioselective variants will be the subject of future research.

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

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(4) Byproducts of this reaction resulted from Wacker-type cyclizations.
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(6) The relative stereochemistry was assigned by comparison to an independently prepared syn product. The diastereomeric ratio was measured via ^{1}H NMR. See Supporting Information for details.
(7) Hosokawa, T.; Ohta, T.; Kanayama, S.; Murahashi, S.-I. *J. Org. Chem.* **1987**, *52*, 1758−1764.
(8) For a review on quinone methides, see: Van de Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367−5405.
(9) Chapman has reported methanol attacking a similar quinone methide, see: Chapman, O. L.; McIntosh, C. L. *Chem. Commun.* **1971**, 383−384.
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(12) Evaluation of a *p*-phenol did not lead to product but instead to significant substrate and catalyst decomposition.
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