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Palladium(II)-Catalyzed Aerobic Hydroalkoxylation of Styrenes Containing a Phenol

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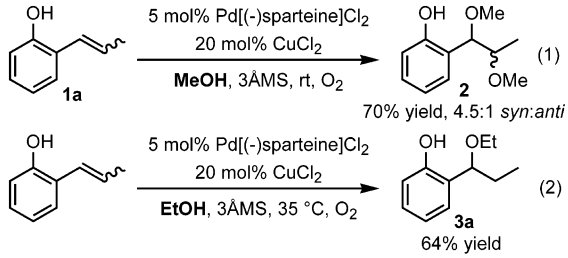
Considering the ubiquitous nature of carbon−oxygen bonds in biologically interesting compounds, developing new catalytic methods for the efficient construction of such bonds is desirable. One approach is metal-catalyzed addition of an alcohol across an olefin, which offers considerably enhanced synthetic versatility compared to the related Brønsted acid variants.[1] Recently, there have been several reports of catalytic olefin hydroalkoxylation processes,[2] which are thought to proceed via nucleophilic attack on a metal-coordinated olefin followed by protonation of the M−C bond.[3,4] In light of this and as expected, Pd(II) complexes[5] have not been reported to catalyze olefin hydroalkoxylation due to facile β-hydride elimination.[6] Herein, we disclose a mild new Pd(II)-catalyzed aerobic hydroalkoxylation reaction of styrene derivatives containing a phenol. In contrast to previous methods, the initial mechanistic studies support a process in which alcohol oxidation is coupled to the functionalization of the olefin.

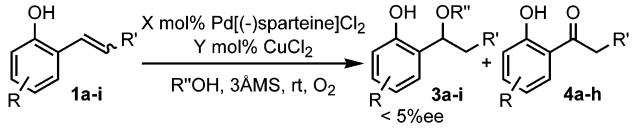
While exploring the scope of a recently discovered $PdCl_2$-catalyzed dialkoxylation reaction of propenyl phenol **1a**,[7] we found that the complex Pd[(−)-sparteine]Cl_2[8] catalyzed the transformation in MeOH, resulting in a 70% yield with a 4.5:1 syn-to-anti ratio in <5% ee (eq 1). Interestingly, switching the solvent to EtOH led to an unanticipated change in reaction outcome providing a 64% yield of the hydroalkoxylation product **3a** in <5% ee (eq 2).[9] Notably, without (−)-sparteine as a ligand, dialkoxylation was the major product.[7]

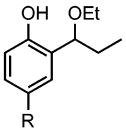
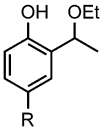
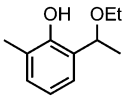
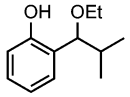
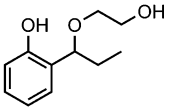
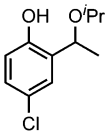


Optimization for hydroalkoxylation of **1a** led to the use of 5 mol % Pd[(−)sparteine]Cl_2, 20 mol % $CuCl_2$, and 3 Å molecular sieves at 35 °C under an O_2 atmosphere in ethanol (Table 1, entry 1). Removal of catalytic $CuCl_2$ or molecular oxygen resulted in significant catalyst decomposition and low yields. Expansion of the scope to include *o*-vinylphenols revealed these substrates are significantly more reactive and allowed the use of lower catalyst loadings (entries 3−5). The main byproduct of the reaction with *o*-vinylphenols is the ketone, which is inseparable by chromatography.[10] Unexpectedly, the hydroalkoxylation of **1f** led to low mass recovery, presumably due to polymerization of the substrate (entry 6). A trisubstituted styrene derivative **1g** undergoes hydroalkoxylation in 48% yield at a longer reaction time (entry 7).

Both ethylene glycol and 2-propanol were successful nucleophiles for hydroalkoxylation (entries 8 and 9), while benzyl alcohol and acetic acid did not lead to appreciable product formation. Use of

Table 1. Scope of Pd-Catalyzed Hydroalkoxylation



Entry	X	Y	Product		Time (h)	% Yield[a]	3 : 4[b]
1[c]	5	20		R = H (**3a**)	24	64	>19 : 1
2[c]	5	20		R = Cl (**3b**)	48	70	>19 : 1
3	2.5	7.5		R = H (**3c**)	12	72	12 : 1
4	2.5	7.5		R = Cl (**3d**)	14	82	19 : 1
5	2.5	7.5		R = Br (**3e**)	14	84	>19 : 1
6	2.5	10		**3f**	20	41	10 : 1
7[c]	5	20		**3g**	48	48	>19 : 1
8	5	20		**3h**	48	52	>19: 1
9[c]	2.5	7.5		**3i**	48	57	13 : 1

[a] Average isolated yield of two reactions. [b] Ratio measured by ^{1}H NMR. [c] Reaction carried out at 35 °C.

2-propanol as a nucleophile is noteworthy in that secondary alcohols are typically not viable in related nucleopalladation reactions.[11]

After exploring the initial scope of the Pd-catalyzed hydroalkoxylation, we were interested in elucidating the mechanistic features of the reaction. Specifically, we wanted to address three questions: (1) What is the source of the incorporated proton? (2) What is the role of the phenol, considering simple styrenes produce the acetal under the same conditions?[12] (3) What is the role of the solvent on reaction outcome?

Initially, it was thought that the reaction was proceeding through a nucleopalladation/protonation process similar to that proposed by both Widenhoefer and co-workers[3] and Yang and He.[4] Therefore, the use of CH_3CH_2OD as the solvent should result in a single deuterium incorporation at the site of Pd−C protonation. However, submitting **5** to the hydroalkoxylation conditions in CH_3CH_2OD resulted in no deuterium incorporation into the product (eq 3).[9] In

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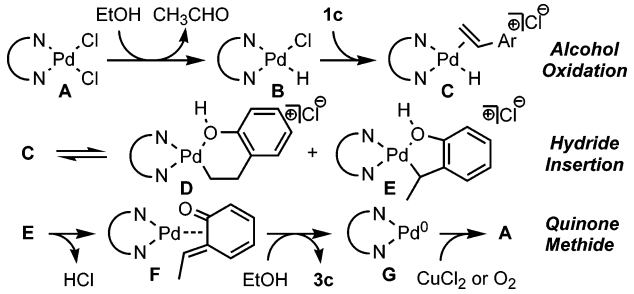
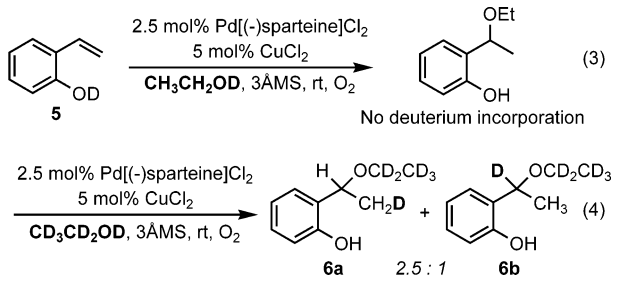
Scheme 1. Proposed Mechanism

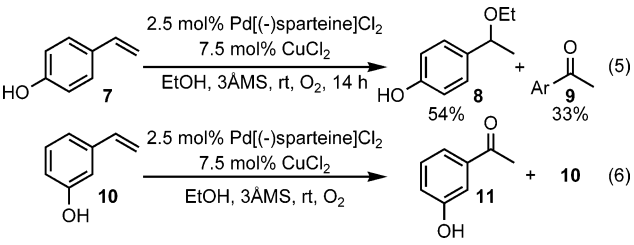


contrast, the use of CD_3CD_2OD produced isotopomers **6a** and **6b** in a 2.5:1 ratio (eq 4).



The labeling experiments suggest that the acidic proton from EtOH is not cleaving the Pd−C bond; rather, the incorporated hydrogen originates from the alkyl chain of a separate equivalent of ethanol. With this in mind, we propose a mechanism requiring the oxidation of ethanol to produce a Pd-hydride **B**, followed by coordination of the olefin to produce **C** (Scheme 1). On the basis of the isotopic labeling experiments, we propose that hydride insertion into the olefin yields a mixture of **D** and **E**, which interconvert through **C** via β-hydride elimination.[13] Since the products arise only from substitution at the α-carbon of the styrene, **E** is proposed to proceed to product via formation of an *ortho*-quinone methide intermediate **F** with concomitant reduction of the catalyst.[14,15] Ethanol would subsequently add into the *ortho*-quinone methide to form the carbon−oxygen bond.

To further explore the plausibility of intermediate **F**, both **7** and **10** were submitted to the reaction conditions (eqs 5 and 6). Reaction of **7**, which is able to form a *para*-quinone methide, resulted in the formation of a mixture of the hydroalkoxylation product **8** and ketone **9** in an overall 87% yield. However, reaction of **10**, which is unable to form a quinone methide, did not result in the formation of the hydroalkoxylation product, but instead generated ketone **11**. These experiments offer support for the formation of a quinone methide prior to addition of the alcohol. Additionally, a planar quinone methide intermediate or a weakly associated Pd complex may account for the lack of enantioselectivity observed.[9]



The final mechanistic question outlined above was how the subtle change in solvent influences the reaction outcome. Both Uemura and co-workers[10b] and Lloyd[16] have shown that methanol is not easily oxidized by Pd(II). On the basis of the proposed mechanism, we can attribute the change in reaction outcome from dialkoxylation in methanol to hydroalkoxylation in ethanol to the ability of the catalyst to oxidize the solvent to form the requisite Pd-hydride. Without a Pd-hydride, initial nucleopalladation by methanol is thought to be the first step of the dialkoxylation reaction.[7a]

In summary, we have discovered a novel intermolecular Pd-catalyzed hydroalkoxylation of styrene derivatives that contain a phenol. The hydroalkoxylation reaction can be performed on terminal, disubstituted, and trisubstituted olefins with several alcoholic solvents including 2-propanol. Mechanistic experiments support a pathway wherein the oxidation of an alcohol is coupled to olefin functionalization via a quinone methide intermediate. Future work will include further elucidation of the mechanism and utilizing coupled alcohol oxidations in olefin functionalization reactions.

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

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(9) See Supporting Information for details.
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