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Development of a General Pd(II)-Catalyzed Intermolecular Hydroalkoxylation Reaction of Vinylphenols by Using a Sacrificial Alcohol as the Hydride Source

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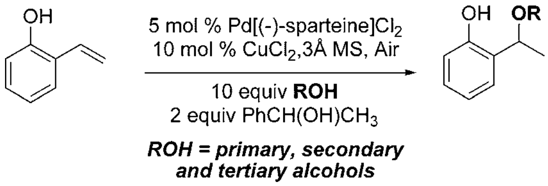
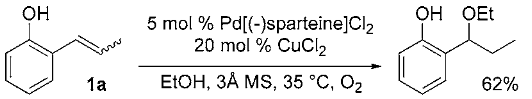
ABSTRACT



A general hydroalkoxylation of vinylphenols has been successfully developed wherein primary, secondary, and tertiary alcohols can be used as nucleophiles. The key conceptual breakthrough is the use of *sec*-phenethyl alcohol at relatively low concentrations as the sacrificial alcohol to undergo oxidation and provide the proposed Pd−H intermediate.

Transition-metal-catalyzed direct addition of N−H or O−H bonds across olefins represents an attractive method for C−N[1] or C−O[2] bond construction. Although significant advancements have been reported in the area of metal-catalyzed hydroamination processes,[3] transition-metal-catalyzed hydroalkoxylation reactions are much less common and remain a challenging transformation presumably due to the weaker Lewis basicity and the decreased nucleophilicity of oxygen nucleophiles, especially employing simple alcohols.[4,5] Recently, as part of our program aimed at the development of Pd(II)-catalyzed olefin functionalization reactions, we discovered a hydroalkoxylation reaction of *o*-vinylphenols (eq 1).[6] Initial mechanistic studies suggest a unique process in which a Pd(II)-catalyzed alcohol oxidation of the solvent was proposed to generate a Pd(II)-hydride **B**, followed by olefin insertion and formation of an *o*-quinone methide intermediate **D** (Scheme 1). The addition of a second equivalent of the alcohol solvent to the *o*-quinone methide intermediate is proposed to lead to product formation.



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(1) For recent reviews, see: (a) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (b) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368. (c) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673.

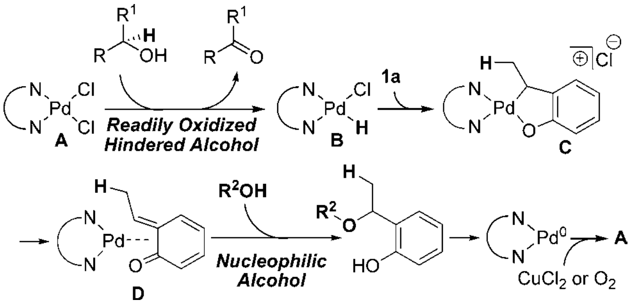
(2) For recent reviews, see: (a) Messerle, B. A.; Vuong, K. Q. *Pure Appl. Chem.* **2006**, *78*, 385. (b) Wolfe, J. P.; Thomas, J. S. *Curr. Org. Chem.* **2005**, *9*, 625.

(3) For recent examples, see: (a) Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828. (b) Patil, N. T.; Lutete, L. M.; Wu, H.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 4270. (c) Hii, K. K. *Pure Appl. Chem.* **2006**, *78*, 341. (d) Abbiati, G.; Beccalli, E.; Broggini, G.; Martinelli, M.; Paladino, G. *Synlett* **2006**, 73.

(4) For intramolecular hydroalkoxylation reactions, see: (a) Oe, Y.; Ohta, T.; Ito, Y. *Synlett* **2005**, 179. (b) Taylor, J. G.; Whittall, N.; Hii, K. K. *Chem. Commun.* **2005**, 5103. (c) Grant, V. H.; Liu, B. *Tetrahedron Lett.* **2005**, *46*, 1237. (d) Coulombel, L.; Favier, I.; Dunach, E. *Chem. Commun.* **2005**, 2286. (e) Yang, C. G.; Reich, N. W.; Shi, Z.; He, C. *Org. Lett.* **2005**, *7*, 4553. For intermolecular hydroalkoxylation reactions, see: (f) Qian, H.; Han, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536. (g) Matsukawa, Y.; Mizukado, J.; Quan, H.; Tamura, M.; Sekiya, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1128. (h) Yang, C. G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966.

10.1021/ol062222t CCC: $33.50

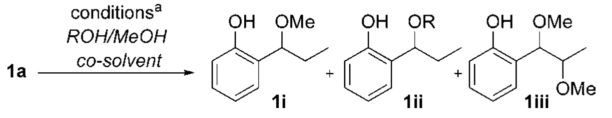
Scheme 1. Mechanistically Inspired Approach to an Improved Pd(II)-Catalyzed Hydroalkoxylation of *o*-Vinylphenols



Two issues limit the application of the current method: (1) only alcohols readily oxidized by Pd(II) are able to generate the proposed Pd−H intermediate,[7] therefore alcohols such as methanol or tertiary alcohols fail to yield the hydroalkoxylation product, and (2) the reaction utilizes a nucleophilic alcohol as solvent, which clearly prohibits the use of precious alcohols or alcohols in the solid state. To address these issues, we sought to develop a Pd(II)-catalyzed hydroalkoxylation reaction that exploits the use of a sacrificial alcohol to undergo Pd(II)-catalyzed alcohol oxidation promoting the formation of the requisite Pd−H intermediate **B** (Scheme 1). It was envisioned that using a hindered readily oxidized sacrificial alcohol in combination with a nucleophilic alcohol in higher concentrations would facilitate the hydroalkoxylation of a diverse set of alcohol substrates. Herein, we report a general hydroalkoxylation reaction of *o*-vinylphenols using *sec*-phenethyl alcohol as the sacrificial alcohol and offer new insights into the mechanistic features of the reaction.

Considering that secondary alcohols are more hindered nucleophiles and are also generally excellent substrates for Pd[(−)-sparteine]Cl$_2$-catalyzed alcohol oxidations,[7a] we reasoned they would be a logical choice for a sacrificial alcohol. To test this hypothesis, **1a** was subjected to Pd(II)-catalyzed hydroalkoxylation reaction conditions using mixtures of 2-propanol and methanol as the solvent (entries 1−3, Table 1). It was found that using a 5:1 methanol/2-propanol mixture resulted in high selectivity (94%) for the hydroalkoxylation product **1i** derived from the addition of methanol (entry 3). It should be noted that without added 2-propanol only dialkoxylation[8] of the olefin occurred, alluding to the necessity of a readily oxidizable alcohol to obtain the hydroalkoxylation product (entry 4).[7e,f] Although these experiments provide a proof of concept, the use of the nucleophile as the solvent still limits the scope of the reaction. Therefore, mixtures of methanol and several secondary alcohols in various solvents were examined (entries 5−9).[9] It was found that when CH$_2$Cl$_2$ or toluene was utilized as the cosolvent significantly lower levels of both the sacrificial alcohol and the alcohol nucleophile could be used (entries 5 and 6). Moreover, *sec*-phenethyl alcohol is an excellent sacrificial alcohol at low concentrations where only product **1i** is observed (entry 7). Under these reaction conditions, a balloon of air can be used in lieu of O$_2$ (entry 8).[10]

Table 1. Evaluation of the Solvent and Sacrificial Alcohol in the Hydroalkoxylation of 2-Propenyl Phenol with MeOH



entry	cosolvent	ROH	MeOH/ROH	1i/1ii/1iii[b]
1	–	(CH$_3$)$_2$CHOH	1:7 (M/M)	1:1:0
2	–	(CH$_3$)$_2$CHOH	1:1 (M/M)	3:1:0
3	–	(CH$_3$)$_2$CHOH	5:1 (M/M)	15:1:0
4	–	(CH$_3$)$_2$CHOH	100:0 (M/M)	0:0:>99
5	CH$_2$Cl$_2$	(CH$_3$)$_2$CHOH	10 equiv:2 equiv	12:1:0
6	toluene	(CH$_3$)$_2$CHOH	10 equiv:2 equiv	14:1:0
7	CH$_2$Cl$_2$	PhCH(OH)CH$_3$	10 equiv:2 equiv	>99:0:0
8[c]	CH$_2$Cl$_2$	PhCH(OH)CH$_3$	10 equiv:2 equiv	>99:0:0
9	CH$_2$Cl$_2$	PhCH(OH)CH$_3$	4 equiv:2 equiv	82:18:0

[a] 5 mol % of Pd[(−)-sparteine]Cl$_2$, 10 mol % of CuCl$_2$, 3 Å MS, O$_2$, rt. [b] Ratios were determined by GC yields using 5-nonanone as the internal standard. [c] A balloon of air was used.

Using *sec*-phenethyl alcohol as the sacrificial alcohol with CH$_2$Cl$_2$ as the cosolvent, we explored the scope of this reaction with various vinylphenols and methanol as the nucleophilic alcohol (Table 2, entries 1−7). Both electron-rich and electron-poor substrates lead to good to excellent isolated yields of methanol hydroalkoxylation products. Interestingly, low enantiomeric excesses were measured for some of the hydroalkoxylation products implying that asymmetric catalysis may be possible (up to 9% ee for **3e**).[9] This is in contrast to our previous report.[6]

To further evaluate the scope, diverse alcohols were subjected to the reaction conditions using vinylphenol **1b** and 2 equiv of *sec*-phenethyl alcohol as the sacrificial alcohol (Table 2, entries 8−19). Secondary alcohols were found to be excellent substrates (entries 8−12), and using enantiomerically enriched secondary alcohols, we observed modest diastereomeric ratios (entries 11−13: **4d**, dr 1.4:1; **4e**, dr 1.9:1; and **4f**, dr 2.0:1).[9] It is interesting to consider that even large alcohols such as norborneol and menthol are successfully added to **1b** in the presence of *sec*-phenethyl alcohol (entries 10 and 13). This result is attributed to the lower concentration of *sec*-phenethyl alcohol relative to the nucleophile.

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(5) Hartwig and co-workers have recently reported that metal-triflate-catalyzed hydroalkoxylation reactions may proceed by simple Brønsted acid catalysis. See: Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179−4282.

(6) Gligorich, K. M.; Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2794.

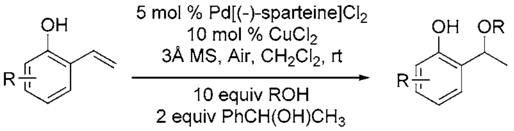
(7) For reviews of Pd(II)-catalyzed aerobic alcohol oxidation, see: (a) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221. (b) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (c) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362. (d) Muzart, J. *Tetrahedron* **2003**, *59*, 5789. For difficulties in the oxidation of methanol with Pd(II) catalysts, see: (e) Lloyd, W. G. *J. Org. Chem.* **1967**, *32*, 2816. (f) Nishimura, T.; Kakiuchi, N.; Onoue, T.; Ohe, K.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1915.

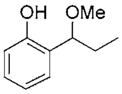
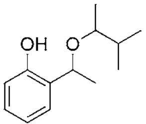
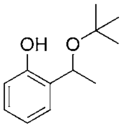
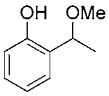
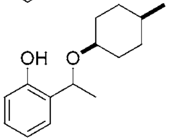
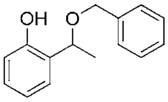
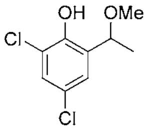
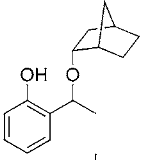
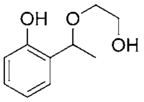
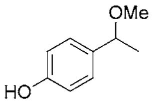
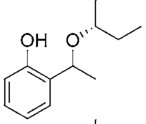
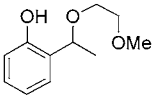
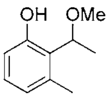
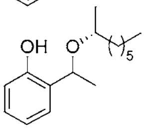
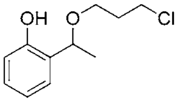
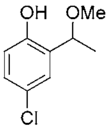
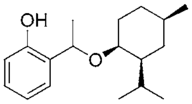
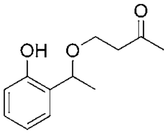
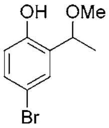
(8) Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 1460.

(9) See Supporting Information for details.

(10) The use of Pd[(−)-sparteine]Cl$_2$ as the catalyst results in a simultaneous oxidative kinetic resolution of *sec*-phenethyl alcohol with k_{rel} values ~10. See ref 7 for details.

Table 2. Substrate Scope



entry	time (h)	product	% yield[a]	entry	time (h)	product	% yield[a]	entry	time (h)	product	% yield[a]
1	48	**3a** 	62	8	24	**4a** 	82	14	72	**4g** 	57
2	24	**3b** 	81	9	24	**4b** 	83	15	24	**4h** 	88
3	24	**3c** 	85	10	24	**4c** 	76	16	24	**4i** 	57
4	24	**3d** 	72	11	24	**4d** 	79	17	24[b]	**4j** 	74
5	40	**3e** 	74	12	24	**4e** 	76	18	48[b]	**4k** 	56
6	24	**3f** 	86	13	24	**4f** 	65	19	48[b]	**4l** 	66
7	24	**3g** 	83								

[a] Average isolated yield of two reactions. [b] Toluene was used as solvent, and the reaction was carried out at 45 °C.

Excitingly, *tert*-butanol was an effective nucleophile for the transformation (entry 14), which, to the best of our knowledge, represents the first example of a metal-catalyzed addition of a tertiary alcohol across an olefin. This result suggests that the size of the nucleophilic alcohol will have minimal impact on the future scope of this transformation. In contrast to our previous report, benzyl alcohol can now be utilized as a substrate leading to a high yield of the corresponding hydroalkoxylation product (entry 15). Alcoholic nucleophiles containing additional functional groups that may chelate or inhibit catalysis were also competent for the hydroalkoxylation reaction under slightly modified reaction conditions (entries 17−19).

After exploring the scope of the hydroalkoxylation reaction, we wanted to confirm our mechanistic rationale in designing this significantly improved method. Specifically, is the sacrificial alcohol acting as a hydride source in the hydroalkoxylation process? In the absence of the sacrificial alcohol and using only MeOH under the standard conditions, a <5% conversion of the starting material and no hydroalkoxylation product are observed which is consistent with the requirement of an alcohol that readily undergoes oxidation (eq 2). Additionally, methanol is not the source of the hydride incorporated into the product considering that the use of CD$_3$OD does not result in any deuterium incorporation into the olefin skeleton of **3h** (eq 3). This also rules out the action of Brønsted acid catalysis in the hydroalkoxylation process. As previously observed using CD$_3$CD$_2$OD as the solvent,[6] the use of PhCD(OH)CH$_3$ as the sacrificial alcohol results in two isotopomers **3i** and **3j** in a 2.5:1 ratio, consistent with the proton incorporated into the product being derived from the oxidation of *sec*-phenethyl alcohol (eq 4).[11]

As an additional experiment, the number of millimoles of sacrificial alcohol oxidized per millimole of product formed

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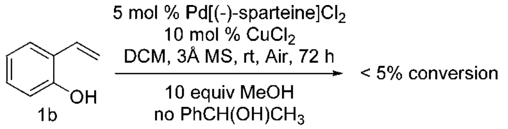
[11] The mixture of isotopomers is proposed to result from reversible hydride insertion (see ref 6). A total of 91% incorporation of a single deuterium atom is observed and consistent with reversible hydride insertion that does not include dissociation of the olefin.



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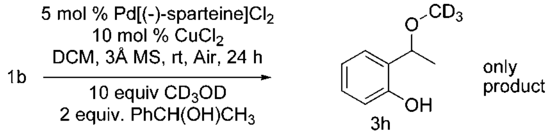

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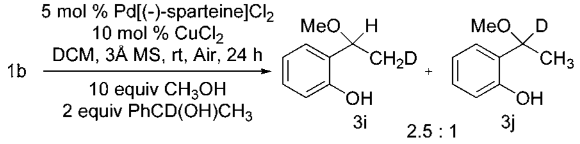


(4)

was measured. To achieve this, aliquots of the hydroalkoxylation reaction of *o*-vinylphenol with methanol were sampled over a period of time and analyzed by GC. The GC yield of acetophenone and the GC yield of hydroalkoxylation product **3b** were measured for each aliquot. By correlating the number of millimoles of each component at a given time, a linear relationship was observed (Figure 1). The slope (0.93) of the line indicates that for every molecule of *sec*-phenethyl alcohol oxidized nearly 1 equiv of olefin is converted to product. This result highlights why low levels of the sacrificial alcohol can be successfully used in this reaction and bodes well for the use of a sacrificial alcohol as a hydride source in related olefin functionalization reactions.

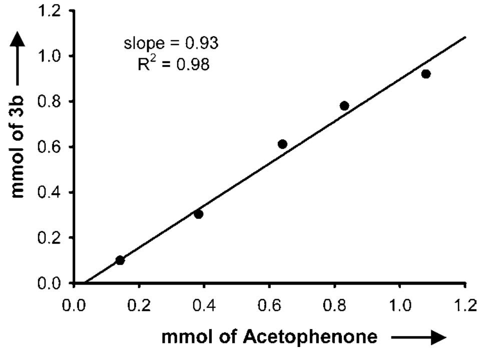
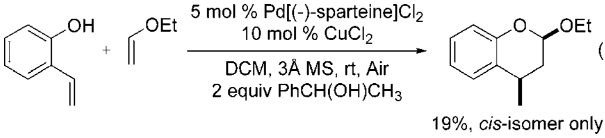


Figure 1. Correlation of the number of millimoles of the sacrificial alcohol oxidized per millimole of the product formed.

The final question we wanted to address is whether the hydroalkoxylation product does indeed arise from a well-defined quinone methide intermediate.[12] To probe this possibility, 2 equiv of ethyl vinyl ether, a commonly used dienophile in cycloaddition reactions with *o*-quinone methides,[13] was subjected to the reaction conditions using **1b** as the substrate in the absence of a nucleophilic alcohol (eq 5). The endo-cycloaddition product was isolated in 19% yield as a single diastereomer, and the yield of the cycloaddition product could be increased to 30% when 10% NEt$_3$ was added to the reaction. These results provide strong evidence for the intermediacy of an *o*-quinone methide under the hydroalkoxylation reaction conditions. Of particular interest, the use of styrenyl precursors to generate *o*-quinone methides is quite rare and typically requires forcing thermal conditions. Additionally, *o*-quinone methides derived from vinylphenols generally undergo dimerization reactions.[13] Therefore, the mild conditions under which we are able to generate and intercept *o*-quinone methide intermediates from vinylphenols may have future synthetic utility.



(5)

In conclusion, a general hydroalkoxylation of vinylphenols has been successfully developed wherein primary, secondary, and tertiary alcohols can be used as nucleophiles. The key conceptual breakthrough is the use of *sec*-phenethyl alcohol at relatively low concentrations as the sacrificial alcohol to undergo oxidation and provide the proposed Pd(II)−H intermediate. Isotopic labeling studies confirm that the hydrogen atom incorporated into the product is derived from oxidation of the sacrificial alcohol, and for every alcohol oxidation, approximately 1 equiv of olefin is converted to product. Evidence for a well-defined *o*-quinone methide intermediate was garnered through trapping the intermediate via a cycloaddition reaction with an enol ether. Future work will focus on exploiting the coupling of Pd(II)-catalyzed alcohol oxidations with new olefin functionalization processes and generating *o*-quinone methide intermediates under mild conditions.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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