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Pd(II)-Catalyzed Conversion of Styrene Derivatives to Acetals: Impact of (−)-Sparteine on Regioselectivity

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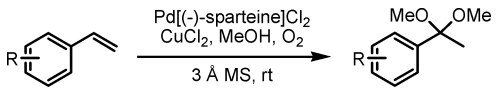
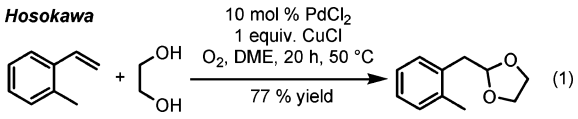
ABSTRACT



Pd[(−)-sparteine]Cl_2 catalyzes the formation of dialkyl acetals from styrene derivatives with Markovnikov regioselectivity. The substrate scope of this reaction has been investigated, and initial mechanistic studies indicate that the reaction proceeds through an enol ether intermediate and a Pd-hydride.

The Wacker oxidation has been widely utilized in target-orientated synthesis because of its ability to transform terminal olefins mildly and chemoselectively into methyl ketones.[1] One modification of this reaction involves substituting an alcohol for water to access the carbonyl as its acetal.[2] For example, Hosokawa and Murahashi[3] demonstrated that α,β-unsaturated carbonyl compounds and styrenes oxidize to acetals in good yields and with high regioselectivity for the anti-Markovnikov product (eq 1).[4,5] While investigating aerobic oxidative transformations of styrene derivatives using Pd[(−)-sparteine]Cl_2 (**1**) in methanol, we discovered that dimethyl acetals form under mild reaction conditions (Table 1). Surprisingly, a reversal in product regioselectivity was observed to yield the Markovnikov acetal when using (−)-sparteine as a ligand on Pd. Herein, we report the substrate scope and a preliminary mechanistic study to elucidate the salient features of this process.



(1)

Optimized conditions allowed styrene derivatives **2a**−**e** to be oxidized to the Markovnikov acetals using 4 mol % **1**, 5 mol % $CuCl_2$, and 3 Å molecular sieves in methanol under an O_2 atmosphere at room temperature in 24 h (Table 1). Removal of $CuCl_2$ or O_2 results in rapid decomposition of the Pd catalyst, and molecular sieves were required to achieve complete conversion.[6] In entries 1−5, the Markovnikov acetal was produced in excellent yields with little anti-Markovnikov product observed. Methyl ketone was

(1) For a review of Wacker oxidation, see: Takacs, J. M.; Jiang, X.-T. *Curr. Org. Chem.* **2003**, *7*, 369−396 and references therein.

(2) (a) Moiseev, I. I.; Vargaftik, M. N.; Syrkin, Y. K. *Dokl. Akad. Nauk SSSR* **1960**, *133*, 377−380. (b) Lloyd, W. G.; Luberoff, B. J. *J. Org. Chem.* **1969**, *34*, 3949−3952.

(3) (a) Hosokawa, T.; Ohta, T.; Murahashi, S.-I. *J. Chem. Soc., Chem. Commun.* **1983**, 848−849. (b) Hosokawa, T.; Ohta, T.; Kanayama, S.; Murahashi, S.-I. *J. Org. Chem.* **1987**, *52*, 1758−1764. (c) Hosokawa, T.; Ataka, Y.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 166−169. (d) Hosokawa, T.; Shinohara, T.; Ooka, Y.; Murahashi, S.-I. *Chem. Lett.* **1989**, 2001−2004. (e) Hosokawa, T.; Yamanaka, T.; Itotani, M.; Murahashi, S.-I. *J. Org. Chem.* **1995**, *60*, 6159−6167.

(4) For examples of acetal formation used in synthesis, see: (a) Hosokawa, T.; Murahashi, S.-I. *Acc. Chem. Res.* **1990**, *23*, 49−54. (b) Lai, J.-Y.; Shi, X.-X.; Dai, L.-X. *J. Org. Chem.* **1992**, *57*, 3485−3487. (c) Byrom, N. T.; Grigg, R.; Kongkathip, B.; Reimer, G.; Wade, A. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1643−1653. (d) Kasahara, A.; Izumi, T.; Murakami, S.; Miyamoto, K.; Hino, T. *J. Heterocycl. Chem.* **1989**, *26*, 1405−1413.

(5) For acetal formation with alkynes, see: Scheffknecht, C.; Peringer, P. *J. Organomet. Chem.* **1997**, *535*, 77−79.

(6) Without molecular sieves the reaction is considerably slower and the primary product is methyl ketone. However, the role of molecular sieves may not be as simple as a dehydrating agent; see: Steinhoff, B. A.; King, A. E.; Stahl, S. S. *J. Org. Chem.* **2006**, ASAP.

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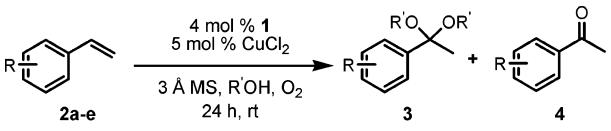
Table 1. Pd(II)-Catalyzed Acetalization of Styrenes in Various Alcohols



entry	styrene	alcohol	% yield[a]	3:4[b]
1	2a	MeOH	83	>19:1
2	2b	MeOH	97	9:1
3	2c	MeOH	95	>19:1
4	2d	MeOH	95	>19:1
5	2e	MeOH	90	>19:1
6	2c	EtOH	85	12:1
7[c]	2c	OH, OH	80	>19:1

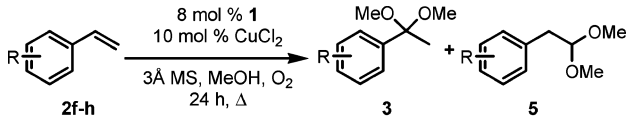
[a] Average isolated yield over two reactions. [b] Measured by ^{1}H NMR. [c] Reaction performed at 0.1 M with 20 mol % $CuCl_2$.

found to be a minor contaminant due to acetal hydrolysis during purification.[7] Additionally, the regioselectivity does not change as the reaction progresses. Switching the solvent to ethylene glycol or ethanol similarly provided the Markovnikov acetals in good yields (entries 6 and 7). However, an increased amount of $CuCl_2$ was required when using ethylene glycol, potentially due to low O_2 solubility. Unfortunately, larger nucleophiles such as 2-propanol did not react with styrenes under these conditions.

Formation of methyl acetals using electron-poor styrenes (**2f**, **2g**, and **2h**) required elevated temperatures and higher catalyst loadings (Table 2). In these examples, a mixture of Markovnikov and anti-Markovnikov acetals was obtained, with the most electron-poor substrate **2h** leading to a nearly equal mixture of the two regioisomers. Furthermore, a direct correlation between Hammett σ values and the log of the ratio of regioisomers is observed ($\rho \approx -2.0$).[8]

The above results contrast Hosokawa and Murahashi's observations in which styrene derivatives under similar conditions are converted preferentially to anti-Markovnikov acetals.[3] This ligand-dependent regioselectivity led us to ask the following questions: (1) what is a reasonable reaction mechanism and (2) what factors dictate regioselectivity?

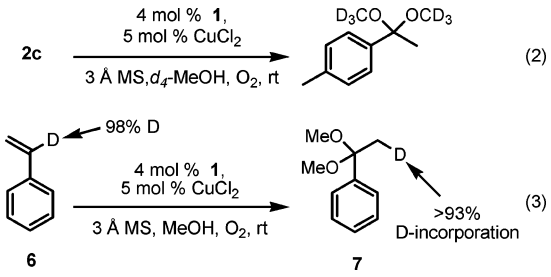
Table 2. Pd(II)-Catalyzed Acetalization of Styrenes Containing Electron-Withdrawing Functional Groups



entry	styrene	temp (°C)	% yield[a]	3:5[b]
1	2f	35	95	13:1
2	2g	50	87	2.4:1
3	2h	50	94	1.6:1

[a] Average isolated yield over two reactions. [b] Measured by ^{1}H NMR; **3** includes ~5% ketone.

During acetalization, a hydrogen atom is added to the β-carbon of the styrene. To elucidate the origin of this hydrogen atom, isotopic labeling experiments were performed.[9] Substrate **2c** was submitted to the reaction conditions in d_4-MeOH (eq 2). No deuterium atoms were incorporated in the methyl group of the product, indicating that the hydrogen atom does not originate from the solvent.[10] To investigate the origin of the hydrogen atom incorporated further, α-deuteriostyrene was subjected to the reaction conditions (eq 3). The resulting acetal retained >93% of the deuterium atom at the β-position in **7**, providing support for a hydride shift.



These experiments provide insight into a possible mechanism for acetalization that involves a palladium-assisted 1,2-hydride migration (Scheme 1). Following formation of the Pd-bound sytrene **A**, nucleopalladation of methanol can proceed with Markovnikov or anti-Markovnikov regioselectivity. In the presence of (−)-sparteine, it is believed a kinetically favored pathway is preferred to minimize steric interactions between substrate and catalyst.[11] Upon nu-

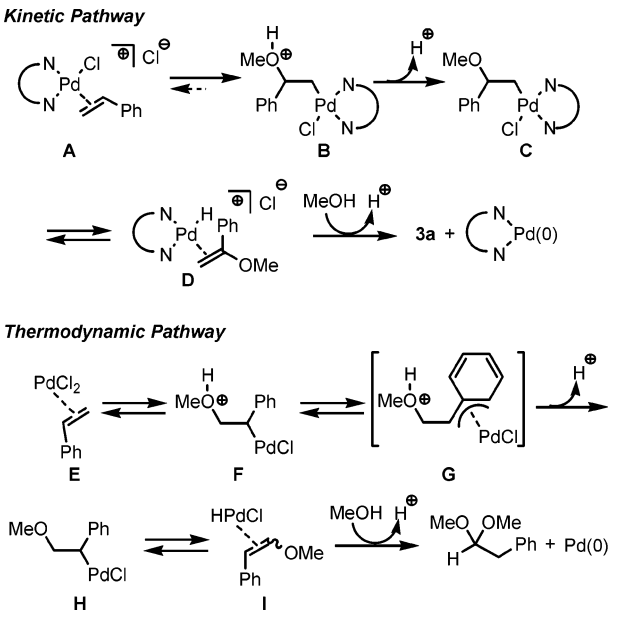
(7) It has also been shown that the methyl ketone could result from a Wacker coupled alcohol oxidation; see: Nishimura, T.; Kakiuchi, N.; Onoue, T.; Ohe, K.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1915−1918.

(8) See Supporting Information for details.

(9) For a review of previous isotopic labeling studies, see: Henry, P. M. *Palladium Catalyzed Oxidation of Hydrocarbons*; Reidel Publishing Company: Dordrecht, Holland, 1980.

(10) These results are consistent with previous isotope labeling experiments performed by Hosokawa and Murahashi on an α,β-unsaturated carbonyl substrate. See ref 3b for additional information.

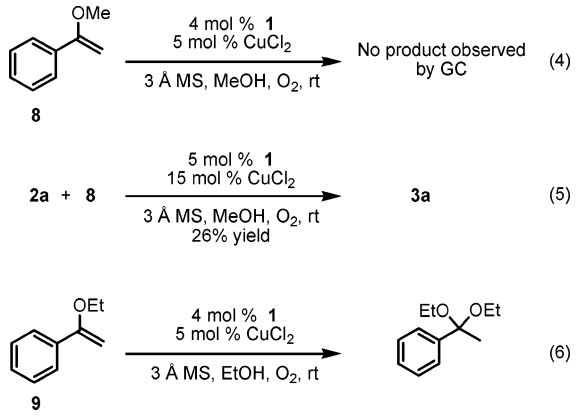
Scheme 1. Pd(II)-Catalyzed Acetalization of Styrene under Proposed Kinetic and Thermodynamic Control



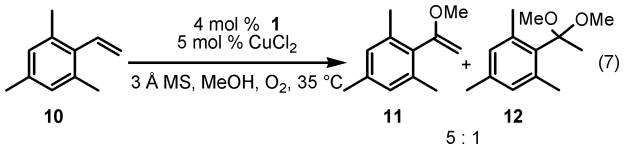
cleopalladation at the α-position, methanol is deprotonated followed by β-hydride elimination to afford **D**. Nucleophilic attack of methanol[12] onto **D** or a related intermediate results in the formation of the Markovnikov acetal and release of Pd(0). Several mechanistic pathways have been proposed to describe addition of the second methanol, including nucleopalladation of the enol ether or hydride insertion into the enol ether followed by oxonium formation.[3,8] We are currently unable to differentiate these possibilities.

In the absence of ligand, Pd-catalyzed acetalization of **2a** results in the anti-Markovnikov product. To account for this reversal in regiocontrol, we propose that nucleopalladation proceeds reversibly. It has been proposed by Stahl in a related transformation that the thermodynamically favorable intermediate arises from anti-Markovnikov addition. This proposal requires reversable nucleopalladation where **F** can be stabilized by a Pd-benzylic species similar to **G**.[13] Considering that electron-poor substrates require more forcing reaction conditions leading to erosion of regioselectivity, entry into the proposed thermodynamic pathway is reasonable. However, an alternative explanation for the electronic correlation on regioselectivity is a change in polarization of the Pd-bound olefin affecting kinetic nucleopalladation.

To examine whether the methyl enol ether proposed in Scheme 1 is a viable intermediate for acetalization, **8** was synthesized[14] and exposed to the Pd(II)-catalyzed reaction conditions in methanol (eq 4). No product was detected after 24 h, indicating that acetal formation does not proceed in the absence of a Pd−H species.[15] To promote Pd−H formation, an equal mixture of **2a**[16] and **8** was subjected to similar reaction conditions (eq 5). After 14 h, only 26% of the enol ether was converted to **3a**, suggesting that **8** becomes tightly associated with **1** and inhibits the reaction. Interestingly, exposure of ethyl enol ether **9**[17] to the acetalization conditions in ethanol (eq 6) results in complete conversion to the diethyl acetal. Under these conditions, ethanol is proposed to undergo oxidation[18] to form a Pd−H species that can react with **9** to facilitate acetal formation.



Further evidence for an enol ether intermediate was obtained upon oxidation of the sterically demanding 2,4,6-trimethyl sytrene **10** (eq 7). Under the optimized acetalization conditions, a 5:1 mixture of enol ether **11** and dimethyl acetal **12** was observed by ^{1}H NMR. It is believed that after β-hydride elimination, **11** disassociates from the Pd, thus limiting formation of **12**.



In summary, the Pd(II)-catalyzed oxidation of styrenes in alcoholic solvents proceeds under mild conditions to afford the corresponding Markovnikov acetal in excellent yields. Initial mechanistic studies indicate that the reaction proceeds through a methyl enol ether intermediate and Pd−H species. When (−)-sparteine is used as a ligand on Pd, a change in regioselectivity favoring the Markovnikov product is observed. Elucidating the precise reasons for the control of

(11) For crystal structure of **1**, see: Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475−7476.

(12) Portney, M.; Milstein, D. *Organometallics* **1994**, *13*, 600−609.

(13) Similar studies regarding the mechanism of styrene amination were recently reported; see: Timokhin, V. I.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 17888−17893.

(14) Gassman, P. G.; Burns, S. J.; Pfister, K. B. *J. Org. Chem.* **1993**, *58*, 1449−1457.

(15) Methanol does not readily oxidize under these conditions. For further evidence, see: Lloyd, W. G. *J. Org. Chem.* **1967**, *32*, 2816−2819.

(16) In the absence of **8**, substrate **2a** is >95% consumed as observed by GC.

(17) A 1.3:1 mixture of enol ether **9** and its corresponding diethyl acetal was used in this experiment.

(18) For alcohol oxidations using Pd[(−)-sparteine]Cl_2, see: Mueller, J. A.; Cowell, A.; Chandler, B. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 14817−14824 and references therein.

regioselectivity and applying this information to related transformations is a subject of future research.

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

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