

Catalytic Intermolecular Hydroamination of Vinyl Ethers

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Abstract: This manuscript details the development of a palladium-catalyzed hydroamination of vinyl ethers. It is proposed that palladium catalyzes the hydroamination via Brønsted base catalysis, where palladium is protonated by the relatively acidic sulfonamide to generate a palladium hydride as well as the active anionic sulfonamide nucleophile. Thus, this process is distinct from known palladium-catalyzed hydroaminations of styrene derivatives that utilize less acidic amines.

Key words: hydroamination, vinyl ether, palladium, sulfonamide

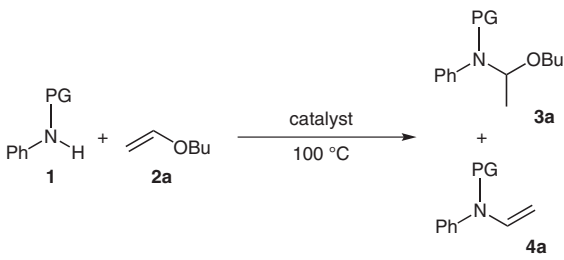
Transition-metal-catalyzed intermolecular hydroamination of alkenes has attracted a great attention in recent years.¹ Much research in this line has centered on the intramolecular hydroamination of simple alkyl-substituted α -olefins.^{2,3} The analogous intermolecular hydroamination of alkenes has been most successful with electron-deficient alkenes,⁴ dienes,⁵ and vinylenes.⁶ In contrast to these reactions, the related transition-metal-catalyzed hydroaminations of vinyl ethers have not been extensively investigated. Electron-rich olefins, such as vinyl ethers, undergo palladium-catalyzed intramolecular hydroamination;⁷ intermolecular hydroaminations are catalyzed by acid⁸ or bifunctional rhenium-oxo catalysts.⁹

At the outset of our investigations, it was known that palladium can catalyze the hydroamination of olefins by several mechanisms. For instance, palladium(II) catalyzes the intramolecular hydroamination of vinyl ethers.⁷ This reaction is thought to occur via Lewis acid catalysis where palladium coordinates the olefin, thus polarizing it toward nucleophilic attack by the amine.^{7c,10} In addition, Hartwig has developed a hydroamination of styrenes that is proposed to go via acid-induced formation of π -benzyl complexes.⁶ Herein we report a catalytic intermolecular hydroamination of vinyl ethers that we propose utilizes low-valent palladium as a specialized Brønsted base catalyst.

We began investigating the potential for hydroamination of 1-(vinyloxy)butane **2a** with a variety of aniline derivatives. Heating *N*-alkyl or *N*-acyl anilines in the presence of 5 mol% Pd(PPh₃)₄ at 100 °C resulted in no product formation. However, the more acidic *N*-tosyl aniline produced the corresponding addition product **3a**, which was obtained in excellent yield (Table 1, entry 4) when the reaction was performed in excess, neat vinyl ether. Lowering

the concentration of vinyl ether to 1.6 M (4 equiv) slightly lowers the yield (entry 5), while using just 2 equivalents considerably lowered the yield of aminol (entry 6) and increased the time necessary for reaction completion. Moreover, substantial quantities of enamine **4a** were formed. Further lowering the concentration of **2** to 0.5 M dramatically decreased the yield of **3**, and only a trace amount of enamine **4** was observed. Dioxane, MeCN, DCE, and THF were also tested as potential solvents; only dioxane provided any product. However, when 1,4-dioxane was used as solvent, a 1:1 mixture of **3a** and **4a** was obtained

Table 1 Conditions for Hydroamination^a



Entry	Catalyst	PG	Time (h)	Yield of 3a (%)	Yield of 4a (%)
1 ^b	Pd(PPh ₃) ₄	Ac	24	<5	<5
2 ^b	Pd(PPh ₃) ₄	Me	24	<5	<5
3 ^b	Pd(PPh ₃) ₄	Bn	24	<5	<5
4	Pd(PPh ₃) ₄	Ts	15	94	<5
5 ^c	Pd(PPh ₃) ₄	Ts	12	82	<5
6 ^d	Pd(PPh ₃) ₄	Ts	24	50	25
7	PdCl ₂ (PhCN) ₂	Ts	24	10	<5
8	Pd ₂ dba ₃ /BINAP	Ts	24	80	<5
9	Pd ₂ dba ₃ /dppb	Ts	24	72	<5
10	Pd ₂ dba ₃ /dppf	Ts	24	75	<5
11	none	Ts	17	<5	<5
12	TfOH (5 mol%)	Ts	12	<5	<5
13	TfOH/Pd(PPh ₃) ₄ (5 mol%)	Ts	12	<5	<5
14	PhCO ₂ H/Pd(PPh ₃) ₄ (10 mol%)	Ts	41	85	<5

^a Isolated yields of reactions carried out in a sealed vial with **1a** (0.2 mmol) and neat **2a** at 100 °C.

^b Starting material was recovered.

^c 1.6 M olefin in toluene.

^d Conditions: 2 equiv **2a**.

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as judged by ^1H NMR spectroscopy. In addition, a variety of other palladium catalysts were screened, but none was as effective at promoting the hydroamination as $\text{Pd}(\text{PPh}_3)_4$ (entries 7–10). Thus, reactions could be run in neat vinyl ether or in concentrated toluene solutions. For convenience, we chose to run reactions in neat vinyl ether for examination of the scope of the hydroamination.

Importantly, attempting to perform the same transformation without the addition of $\text{Pd}(\text{PPh}_3)_4$ produced <5% yield of **3a** over 17 hours at 100 °C (entry 11). Furthermore, since such a transformation could potentially be catalyzed by simple Brønsted acids,^{3,8} the reaction was run with 5 mol% TfOH with or without $\text{Pd}(\text{PPh}_3)_4$ and <5% product was observed (entries 12 and 13). Instead, TfOH promoted the decomposition of the butyl vinyl ether to acetaldehyde dibutyl acetal.¹¹ The reaction did proceed with $\text{Pd}(\text{PPh}_3)_4$ and 10 mol% benzoic acid (entry 14), however, the acid additive inhibited the reaction, and longer times were required for completion of the reaction. Importantly, the observed inhibition by acid contrasts with the $\text{Pd}(\text{PPh}_3)_4$ -catalyzed hydroamination of vinylarenes which requires strong acid additives.⁶ Thus, we propose that the mechanism of the palladium-catalyzed hydroamination of vinyl ethers differs from that of vinyl arenes.

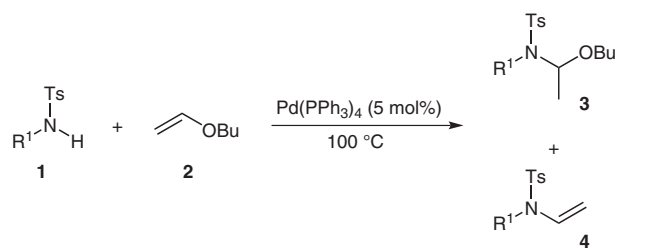
Given the inhibition of the reaction by added acid, we hypothesized that the Pd catalyst was behaving as a Brønsted base to facilitate the hydroamination. If this is the case, then the triphenylphosphine that accompanies the palladium may also be capable of acting as a base and catalyzing the reaction.⁸ Indeed, the reaction also proceeded in the presence of 20 mol% Ph_3P as a Lewis base, however, the conversion was only 25% after extended reaction time. Thus, phosphine catalysis does not account for our observed results.

Having the optimized conditions in hand, the scope and limitations of the hydroamination of butyl vinyl ether with a variety tosyl-protected amines was explored (Table 2). Both electron-rich and electron-poor anilines are good substrates for the reaction and groups like esters, nitro groups, and nitriles are compatible with the reaction conditions.

Interestingly, *ortho* substitution of the aniline lead to exclusive formation of the enamine product (entries 3 and 4, Table 2) in good to moderate yield. Unfortunately, high concentrations of the vinyl ether were often necessary to promote formation of the aminol over the enamine. Lastly, when an aliphatic amine was exposed, the anticipated addition product **3k** was isolated in moderate yield along with enamine **4k**.

Next we turned our attention to investigating the vinyl ethers that were compatible reaction partners in the hydroamination. Simple aliphatic vinyl ethers react smoothly to afford the desired aminols except in the case of vinyl cyclohexyl ether, which gives only a low yield of aminol (Table 3, entry 7). Interestingly, the bulkier *tert*-butyl ether forms the aminol in good yield (Table 3, entry 5).

Table 2 Scope of Hydroamination^a

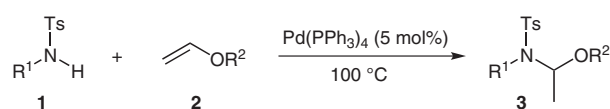


Entry	R ¹	2 (equiv)	Time (h)	Yield of 3 (%) ^b	Yield of 4 (%) ^b
1	4-BrC ₆ H ₄	19	14	3b 67	–
2	3-MeC ₆ H ₄	19	12	3c 92	–
3	2-MeC ₆ H ₄	19	20	–	4d 90
4	2-Me ₂ C ₆ H ₃	19	20	–	4e 45
5	4-MeOC ₆ H ₄	19	25	3f 80	–
6	4-MeOC ₆ H ₄	4 ^b	25	3f 70	–
7	3-MeOC ₆ H ₄	19	24	3g 80	–
8	3-MeOC ₆ H ₄	4 ^b	24	3g 60	–
9	4-O ₂ N-C ₆ H ₄	4 ^b	15	3h 60	–
10	4-NCC ₆ H ₄	19	26	3i 93	–
11	4-EtO ₂ CC ₆ H ₄	19	15	3j 93	–
12	4-EtO ₂ CC ₆ H ₄	4 ^b	15	3j 50	4j 50
13	CH ₂ (CH ₂) ₃ Me	19	24	3k 40	4k <20

^a All reactions were carried out in a sealed vial with **1** (0.2 mmol) and **2** in the presence of 5 mol% $\text{Pd}(\text{PPh}_3)_4$ at 100 °C unless otherwise indicated.

^b In toluene solvent.

Table 3 Scope of Vinyl Ethers^a

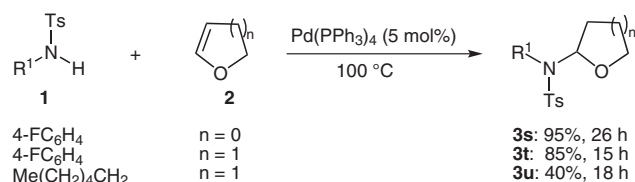


Entry	R ¹	R ²	2 (equiv)	Time (h)	Yield of 3 (%) ^b
1	Ph	<i>n</i> -Pr	19	36	3l 75
2	4-FC ₆ H ₄	<i>n</i> -Bu	8 ^b	14	3m 92
3	4-FC ₆ H ₄	<i>n</i> -Pr	4 ^b	14	3n 87
4	4-FC ₆ H ₄	Et	19	26	3o 89
5	4-FC ₆ H ₄	<i>t</i> -Bu	19	26	3p 82
6	4-F ₃ CC ₆ H ₄	<i>n</i> -Bu	8 ^b	14	3q 82
7	4-NCC ₆ H ₄	Cy	19	25	3r 30

^a All reactions were carried out in a sealed vial with **1** (0.2 mmol) in the presence of 5 mol% $\text{Pd}(\text{PPh}_3)_4$ at 100 °C.

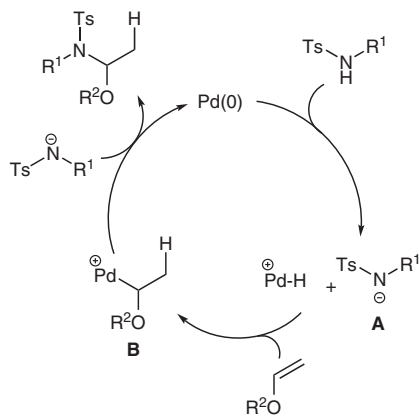
^b In toluene.

Cyclic vinyl ethers undergo the palladium-catalyzed hydroamination as well. Both five- and six-membered vinyl ethers undergo hydroamination to provide the cyclic aminols (Equation 1). An aliphatic amine also participates in this transformation, however, the product **3u** is formed in rather low yield.



Equation 1

A plausible mechanism for this transformation is outlined in Scheme 1. Protonation of Pd(0) with the tosyl aniline (pK_a ca. 11.5 in DMSO) produces a palladium hydride species^{12,13} which can undergo coordination of the vinyl ether followed by insertion to form an alkylpalladium intermediate **B**. Related carbopalladations of vinyl ethers have been proposed by Jordan.¹⁴ This intermediate can undergo nucleophilic substitution by the tosyl amide, probably via an S_N1 mechanism, to produce the observed product. The proposed intermediacy of the tosyl amide anion is supported by the fact that we observe acid inhibition. In addition, we observed near-quantitative formation of TsNHCH₂CH₂Cl when reactions were attempted in dichloroethane. Finally, the enamine byproduct may arise from elimination of alcohol from the aminol product, which is promoted by sterically bulky *ortho*-substituted anilines.



Scheme 1

In conclusion, we have developed a Pd(0)-catalyzed hydroamination of vinyl ethers. The reaction occurs under formally neutral conditions, and we propose that the Pd(0) catalyst acts as a Brønsted base to facilitate the hydroamination. This mechanism contrasts with that of the hydroamination of styrenes with less acidic amines.

General Procedure for the Hydroamination of Vinyl Ethers Representative Synthesis of Compound **3a**

To butyl vinyl ether (**2a**, 0.49 mL, 3.8 mmol) and Pd(PPh₃)₄ (11.55 mg, 0.01 mmol), was added *N*-tosylaniline (49.41 mg, 0.2 mmol) in a well-sealed pressure vial and heated to 100 °C in an aluminum block for the designated time. The completion of reaction was monitored via TLC, and the reaction stopped when amine was completely consumed. The reaction mixture was passed through a short pad of silica gel, and the product was isolated by flash column chromatography using silica gel as the stationary phase and hexane–EtOAc (4:1) as the eluent; 66 mg (94%) of the product *N*-(1-butoxyethyl)-4-methyl-*N*-phenylbenzenesulfonamide (**3a**) was obtained as a slightly yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.56 (d, *J* = 8.0 Hz, 2 H), 7.37–7.28 (m, 3 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 7.05–7.01 (m, 2 H), 5.69 (q, *J* = 6.0 Hz, 1 H), 3.77 (dt, *J* = 9.3, 6.7 Hz, diastereotopic 1 H), 3.56 (dt, *J* = 9.3, 6.7 Hz, diastereotopic 1 H), 2.43 (s, Ts CH₃), 1.58 (tt, *J* = 13.5, 4.0 Hz, 2 H), 1.37 (dq, *J* = 14.9, 7.3 Hz, 2 H), 1.14 (d, *J* = 6.0 Hz, 3 H), 0.94 (t, *J* = 7.3 Hz, 3 H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 143.17, 137.67, 134.44, 131.96, 129.18, 128.60, 128.54, 127.52, 85.06, 68.05, 31.51, 21.46, 20.62, 19.31, 13.88 ppm. IR (CH₂Cl₂): ν = 3259, 2931, 1598, 1494, 1338, 1091, 919, 813, 754 cm⁻¹. HRMS: *m/z* calcd for C₁₉H₂₅NO₃SNa [M + Na]: 370.1453; found: 370.1450.

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