



## Chemoselective hydroamination of vinyl arenes catalyzed by an NHC-amidate-alkoxide Pd(II) complex and *p*-TsOH



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### ARTICLE INFO

#### Article history:

Received 3 May 2013

Revised 13 May 2013

Accepted 23 May 2013

Available online 1 June 2013

#### Keywords:

Hydroamination

Vinyl arenes

Palladium catalyst

Brønsted acid

Sulfonamide

### ABSTRACT

The hydroamination of various substituted vinyl arenes with benzenesulfonamide was explored using an NHC-amidate-alkoxide palladium catalyst in conjunction with *p*-TsOH. Utilizing halide-substituted and electron-rich vinyl arenes, this methodology selectively furnished the cross-coupled hydroamination products in moderate to excellent yields in a Markovnikov fashion while greatly reducing undesired acid-catalyzed homocoupling of the vinyl arenes. Electron-rich vinyl arenes typically required milder conditions than electron-poor ones. While most effective for *para*-substituted substrates, the catalyst system also furnished the desired products from *ortho*- and *meta*-substituted vinyl arenes with high chemoselectivities.

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### Introduction

Hydroamination is an expeditious method to form carbon–nitrogen bonds from olefins. While this process is typically a challenging reaction due to its high barrier of activation, various methods have been successfully developed.<sup>1</sup> In particular, late transition metal catalysts have been extensively employed in hydroamination reactions due to their high reactivity, resistance toward degradation by water, and high functional group tolerance. Homogeneous intermolecular hydroamination of vinyl arenes with weakly basic nitrogen sources such as sulfonamides has been catalyzed by the salts of metals including platinum, copper, bismuth, hafnium, iron, gold, silver, and zirconium.<sup>2a–f</sup> However, most of these methods have shown limitations, especially with electron-rich vinyl arenes. These substrates, including methyl or methoxy-substituted styrenes, often furnished hydroamination products in low-to-intermediate yields along with large amounts of side products. In addition, some of these procedures were only effective under inert atmospheric conditions.

Other methods utilized to catalyze the homogeneous intermolecular hydroamination of vinyl arenes with sulfonamides include the use of *N*-bromosuccinimide,<sup>3</sup> molecular iodine,<sup>4</sup> *N*-fluorobenzenesulfonimide,<sup>5</sup> and ionic liquids.<sup>6</sup> Heterogeneous methods using gallium<sup>7</sup> and Amberlyst-15<sup>8</sup> have also been reported. Notably, the few homogeneous Brønsted acid-catalyzed examples that were reported were limited to simple unsubstituted styrenes.<sup>9a,b</sup> There have been several reasons for the dearth of these reactions,

including the tendency of the nitrogen sources to buffer the effect of the acids as well as the acid-catalyzed formation of undesired homocoupling products from vinyl arene substrates.<sup>2d,8</sup>

In order to avert these shortcomings, we actively pursued the development of new conditions by employing dual catalysts such as our NHC-amidate-alkoxide palladium complex **1** (Fig. 1)<sup>10</sup> and *p*-toluenesulfonic acid. When we used acids as the sole catalysts, 4-methylstyrene **2** underwent homocoupling to furnish dimer **5** predominantly (Scheme 1). However, our hybrid method facilitated the Markovnikov-type hydroamination efficiently and improved the yields of the hydroamination products (e.g., **4** in Scheme 1) while minimizing undesired homocoupling side products (e.g., **5** in Scheme 1).

### Results and discussion

As shown in Table 1, we embarked on a comparative study on hydroamination and homocoupling. Using DMF as an internal NMR standard, we recorded the conversion yields of **4** based on the sulfonamide as the limiting reagent and the mole ratios of **4** and **5** as the measure of chemoselectivity. Among several acids examined including TfOH and TFA, *p*-TsOH turned out to be the

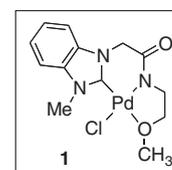
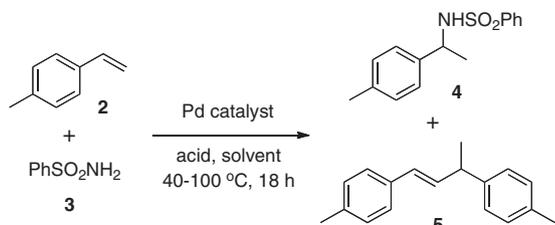


Figure 1. NHC-amidate-alkoxide Pd(II) catalyst **1**.

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**Scheme 1.** Hydroamination of 4-methylstyrene.

**Table 1**  
Effect of acids and palladium complexes on hydroamination of 4-methylstyrene<sup>a</sup>

Entry	Pd catalyst <sup>b</sup>	Acid	4 Yield (%)	4:5 (mol ratio)
1	--	<i>p</i> -TsOH	71	1:1.6
2	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	<i>p</i> -TsOH	81	1:1.6
3	Pd(OAc) <sub>2</sub>	<i>p</i> -TsOH	71	1:1.7
4	<b>1</b>	<i>p</i> -TsOH	95	7.9:1
5	<b>1</b>	MeSO <sub>3</sub> H	91	5.1:1

<sup>a</sup> All reactions were run using 0.25 mmol of benzenesulfonamide, 0.75 mmol of 4-methylstyrene, and 20 mol % of acids in toluene at 60 °C.

<sup>b</sup> 10 mol % of Pd catalysts were used.

most effective for hydroamination but still gave the dimer **5** as the major product (entry 1). We then investigated the use of palladium complexes as co-catalysts. When known palladium complexes were used (entries 2 and 3), both the yield of hydroamination product and the chemoselectivity remained similar to those of the acid-only conditions (entry 1). In sharp contrast, the addition of catalyst **1** led to a great improvement in hydroamination conversion and considerable reversal of chemoselectivity. Comparable results were observed with MeSO<sub>3</sub>H (entry 5). Unlike known catalysts, our catalyst **1** inhibited undesired Brønsted acid-catalyzed homocoupling of the olefin while promoting the desired hydroamination, implying that the structure and electronic properties of the ligand, rather than the simple presence of a palladium salt, could be the driving force behind the unique reactivity and selectivity.

With these trends noted, we endeavored to determine the influence of several other factors including solvent and substrate ratios (Table 2). Three distinct outcomes based on solvent effects were observed; the reaction was very active but not selective (1,2-dichloroethane, entry 1), no reaction occurred (dioxane, entry 2), and the reaction was efficient and highly selective toward the hydroamination product (toluene, entry 3). When we decreased the amount of the olefin to limit formation of dimer **5**, we observed much higher selectivities as anticipated. However, the yields of **4** diminished significantly, revealing the importance of using an excess of the olefin for optimal results (entries 4 and 5).

Subsequently, we investigated the effect of lowering catalyst **1** and acid loading at different temperatures (Table 3). When we used 5 mol % of *p*-TsOH, the chemoselectivities improved dramatically but the reactions were sluggish and provided much lower yields of the hydroamination product (entries 1 and 2). With

**Table 2**  
Effect of solvents and substrate ratios<sup>a</sup>

Entry	Ratio (2:3)	Solvent	4 Yield (%)	4:5 (mol ratio)
1	3:1	DCE	81	1.2:1
2	3:1	Dioxane	0	0:0
3	3:1	Toluene	81	20:1
4	1:1	Toluene	67	67:1
5	1:3	Toluene	61	61:1

<sup>a</sup> All reactions were run using 10 mol % of the catalyst and acid each at 60 °C.

**Table 3**  
Effect of catalyst and acid at different temperatures<sup>a</sup>

Entry	1 (mol %)	<i>p</i> -TsOH (mol %)	Temp (°C)	4 Yield (%)	4:5 (mol ratio)
1	5	5	60	55	55:1
2	10	5	60	30	30:1
3	5	10	60	93	13:1
4	5	10	40	80	40:1
5	5	10	100	91	7:1

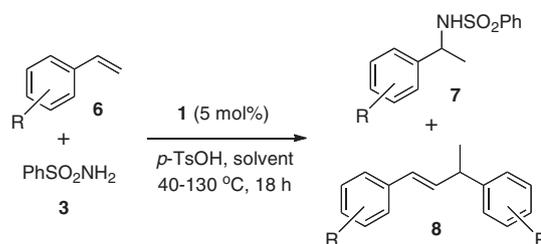
<sup>a</sup> All reactions were run using 0.25 mmol of benzenesulfonamide and 0.75 mmol of 4-methylstyrene in toluene.

10 mol % of the acid and 2–5 mol % of the Pd catalyst, we observed reasonably high yield and selectivity in favor of the hydroamination product (entry 3). Lower temperature improved the selectivity despite slightly lower yield (entry 4) while higher temperatures gave comparable yields with slightly lower selectivity (entry 5). Thus depending on the nature of the substrate, the temperature can be varied to improve either selectivity or yield as desired.

Under the optimized catalytic conditions, the substrate scope of this methodology was examined by screening various different vinyl arenes (Scheme 2 and Table 4).<sup>11</sup> Electron-rich vinyl arenes, including 4-methylstyrene (entry 1), 2,4-dimethylstyrene (entry 2), and 4-methoxystyrene (entry 3), furnished the hydroamination products in good yields and selectivities at relatively low temperatures (40–60 °C). 2,4-Dimethylstyrene in particular reacted in essentially quantitative yield under these conditions. 4-Methoxystyrene, in comparison, was much more sensitive to polymerization than any other substrates and required very mild conditions, including increased catalyst loading and a lower temperature, to give the hydroamination product in a decent yield. When the substitution pattern was changed from 4-methoxy to 3-methoxy (entry 4), the reactivity decreased dramatically and higher temperatures were required to afford comparable yields. 3-Methoxystyrene behaved similarly to unsubstituted and electron-neutral substrates encompassing styrene (entry 5) and 2-vinylnaphthalene (entry 6), which reacted smoothly at higher temperatures than electron-rich styrenes. Higher temperatures or increased amounts of *p*-TsOH resulted in significantly lower chemoselectivities, yielding increased amounts of homocoupled product **8**.

4-F-, Cl-, and Br-substituted vinyl arenes were subjected to the developed catalytic conditions and each of these substrates provided high yields and selectivities under conditions similar to those used for electron-neutral examples (entries 7–9).

As expected based on the aforementioned examples, the reactivities dropped significantly when the substitution pattern was changed from *para* to *ortho*. These substrates required higher temperatures in chlorobenzene solvent with higher loading of *p*-TsOH (entries 10–12). 2-Fluoro- and 2-bromostyrenes provided decent yields and selectivities at 130 °C. In contrast, 2-chlorostyrene underwent significant polymerization as well as hydroamination and dimerization (entry 11). 3-Chlorostyrene was a poor substrate



**Scheme 2.** Hydroamination of vinyl arenes.

**Table 4**  
Hydroamination of various vinyl arenes with benzenesulfonamide

Entry	Vinyl arene	<i>p</i> -TsOH (mol %)	Solvent	Temp (°C)	Products	Yield <b>7</b> (%)	Ratio <b>7:8</b>
1	4-Methylstyrene ( <b>6a</b> )	10	Toluene	60	<b>7a, 8a</b>	93	13:1
2	2,4-Dimethylstyrene ( <b>6b</b> )	10	Toluene	60	<b>7b, 8b</b>	99	9:1
3	4-Methoxystyrene <sup>a</sup> ( <b>6c</b> )	5	Toluene	40	<b>7c, 8c</b>	70	7.8:1
4	3-Methoxystyrene ( <b>6d</b> )	15	Toluene	100	<b>7d, 8d</b>	73	12:1
5	Styrene ( <b>6e</b> )	15	Toluene	100	<b>7e, 8e</b>	84	9.3:1
6	2-Vinylnaphthalene ( <b>6f</b> )	10	Toluene	100	<b>7f, 8f</b>	57	14:1
7	4-Fluorostyrene ( <b>6g</b> )	15	Toluene	100	<b>7g, 8g</b>	95	9.5:1
8	4-Chlorostyrene ( <b>6h</b> )	15	Toluene	100	<b>7h, 8h</b>	83	28:1
9	4-Bromostyrene ( <b>6i</b> )	15	Toluene	100	<b>7i, 8i</b>	87	15:1
10	2-Fluorostyrene ( <b>6j</b> )	20	Chlorobenzene	130	<b>7j, 8j</b>	70	23:1
11	2-Bromostyrene ( <b>6k</b> )	20	Chlorobenzene	130	<b>7k, 8k</b>	63	16:1
12	2-Chlorostyrene <sup>b</sup> ( <b>6l</b> )	20	Chlorobenzene	130	<b>7l, 8l</b>	31	4.4:1
13	3-Chlorostyrene ( <b>6m</b> )	20	Chlorobenzene	130	<b>7m, 8m</b>	41	8.2:1
14	<i>cis</i> - $\beta$ -Methylstyrene ( <b>6n</b> )	20	Chlorobenzene	130	<b>7n, 8n</b>	13	13:1

<sup>a</sup> 10% catalyst loading was required.<sup>b</sup> Significant polymerization of starting material was observed.

(entry 13) while additional styrenes with electron withdrawing groups were also resistant to hydroamination conditions. These results suggest that the vinyl arenes play an electrophilic role in the hydroamination reaction and the electron-withdrawing substituents on the styrenes would slow their reactivities. In pursuit of wider applications, we sought to conduct hydroamination on disubstituted styrenes but failed to acquire satisfactory results. For instance, *cis*- $\beta$ -methylstyrene barely generated the desired product because of almost complete isomerization to a more stable *trans*-olefin (entry 14) which was largely resistant to these conditions.

## Conclusion

The combination of the tridentate NHC-amidate-alkoxide palladium complex **1** and *p*-TsOH efficiently catalyzed the Markovnikov-type hydroamination of electronically varying vinyl arenes with benzenesulfonamide. Our hybrid method improved the yields of the hydroamination products while minimizing the undesired homocoupling side products, which existing methods commonly produced in the presence of strong acids. In addition, while existing methods were generally limited to unsubstituted or *para*-substituted substrates, our method was highly efficient for vinyl arenes with *ortho*-, *meta*-, and *para*-substitutions. Electron-rich and electron-neutral vinyl arenes were well suited for the intended selective hydroamination. We hope that our ongoing studies could elucidate the mechanism of this transformation in due course.

## Acknowledgments

We acknowledge generous financial support from the Hydrocarbon Research Foundation and the National Institute of Health (S10 RR025432).

## Supplementary data

Supplementary data (<sup>1</sup>H and <sup>13</sup>C NMR spectra for new compounds synthesized) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2013.05.101>.

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- General conditions: to a mixture of **3** (0.25 mmol), **1** (10 mol %), and *p*-TsOH (5.00 × 10<sup>-2</sup> mmol) in a 2 dram vial were added toluene (3 mL) and **2** (0.75 mmol). After stirring for 18 h at 100 °C, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (3 mL), neutralized with Et<sub>3</sub>N (5.00 × 10<sup>-2</sup> mmol), and filtered through Celite. The resulting solution was concentrated in vacuo then purified using flash column chromatography with silica gel (4:1 hexanes/EtOAc).