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Palladium-catalyzed inter- and intramolecular hydroamination of styrenes coupled with alcohol oxidation using *N*-fluorobenzenesulfonimide as the oxidant

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ABSTRACT

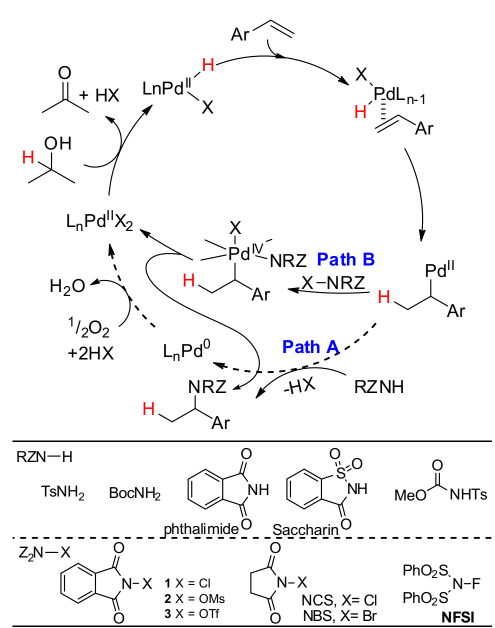
Palladium-catalyzed inter- and intramolecular hydroaminations of styrenes that are coupled to alcohol oxidation under oxidative condition are reported. The fluorination reagent NFSI is used as the nitrogen source as well as the oxidant. Bidental nitrogen ligand bathocuproine plays a crucial role in this transformation.

1. Introduction

Hydroamination is a powerful strategy to generate nitrogen–carbon bond [1]. Catalyst systems for this type of transformations have been extensively developed. Although lanthanides and group IV transition metal are among the most reactive catalyst systems [2,3], the synthetic utility of these protocols is relatively limited due to the poor functional group compatibility and extremely air- and moisture-sensitive properties. In contrast, late-transition metals have been shown to have better functional group tolerance. For instance, late transition-metal catalyzed addition of amines to vinylarenes [4], additions of amides and sulfonamides to alkenes, allenes, and dienes have been reported recently [5,6]. However, these reactions are not compatible with aerobic reaction condition because of the inherent limitation of the utilized phosphine ligands which are readily degradate under aerobic condition. Nitrogen-containing ligands, which are generally stable under oxidative reaction conditions [7], have rarely been used in hydroamination reactions [8]. Herein, we report a novel Pd(II)-catalyzed inter- and intramolecular hydroamination of styrenes using bathocuproine [9] as the ligand.

2. Results and discussion

Recently, our group reported a novel palladium-catalyzed intramolecular hydroamination of allenes, which is coupled to aerobic alcohol oxidation [10]. This reaction was demonstrated that a π-allyl-Pd(II) intermediate was generated from the addition of Pd^{II}-hydride



Scheme 1. The strategy for palladium-catalyzed hydroamination of styrenes.

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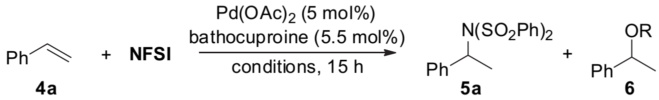
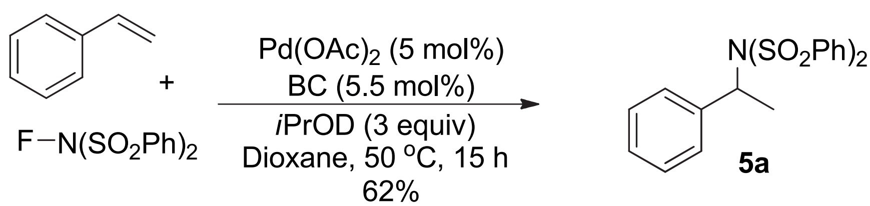


	Conditions	Yield (%) 5a	6
1	iPrOH (1 mL)	13	18 (**6a** R= ^{i}Pr)
2	Toluene (0.9 mL), ^{i}PrOH (3 equiv)	39	15 (**6a** R= ^{i}Pr)
3	DME (0.9 mL), ^{i}PrOH (3 equiv)	48	5 (**6a** R= ^{i}Pr)
4	CH_2Cl_2 (0.9 mL), ^{i}PrOH (3 equiv)	23	trace
5	DMSO (0.9 mL), ^{i}PrOH (3 equiv)	trace	trace
6	1,4-Dioxane (0.9 mL), ^{i}PrOH (3 equiv)	54	7 (**6a** R= ^{i}Pr)
7	1,4-Dioxane (0.9 mL), EtOH (3 equiv)	70	5 (**6b** R= Et)
8	1,4-Dioxane (0.9 mL), ^{n}PrOH (3 equiv)	63	8 (**6c** R= ^{n}Pr)
9	**1,4-Dioxane (0.9 mL), ^{n}BuOH (3 equiv)**	**75**	**6 (6d R= ^{n}Bu)**
10	1,4-Dioxane (0.9 mL), $PhCH_2OH$ (3 equiv)	67	4 (**6e** R= Bn)
11	Condition 6, ligand = (-)-Spartiene	trace	24 (**6a** R= ^{i}Pr)
12	Condition 6, ligand = 1,10-Phenanthroline	trace	trace

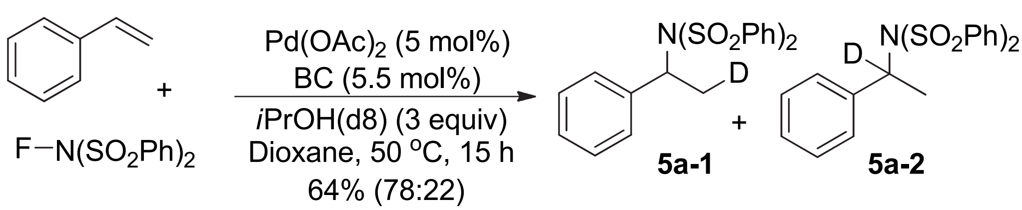
Scheme 2. Pd-catalyzed intermolecular hydroamination of styrene, screen results: **4a** (0.2 mmol), NFSI (0.5 mmol); ^{1}H NMR yield.

amount of hydroamination product **5a** (13% yield) [15]. The hydroalkoxylation of styrene simultaneously occurred to give side product **6a** (18% yield, Scheme 2, entry 1). To suppress this side reaction, the amount of isopropanol was reduced to 3 equivalents, and a variety of solvents were screened (entries 2–6). The reaction in 1,4-dioxane gave the best yield (entry 6). Furthermore, several alcohols were subsequently screened (entries 6–10), and *n*-butanol was found to be the best additive (**5a**, 75% yield, entry 9). The ligand screening results showed that bathocuproine is better than the others (entries 6, 11–12). It is worthy noted that the amino-fluorination product was obtained in the absence of alcohol [16].

Two deuterium-labelled isopropanols were used to determine the origin of the proton incorporated into the product. When $(CH_3)_2CHOD$ was used, no deuterium was incorporated into the product (eq 1). In the case of $(CD_3)_2CDOD$, the reaction afforded two isomers **5a-1** and **5a-2** with 100% deuterium incorporation (eq 2). These observations are consistent with the hypothesis that the intermediate Pd^{II}-hydride is generated from β-hydride elimination of alkoxypalladium species in the Pd-catalyzed alcohol oxidation, rather than from oxidative addition of HX (acid proton) to Pd(0) center [17].



(1)



(2)

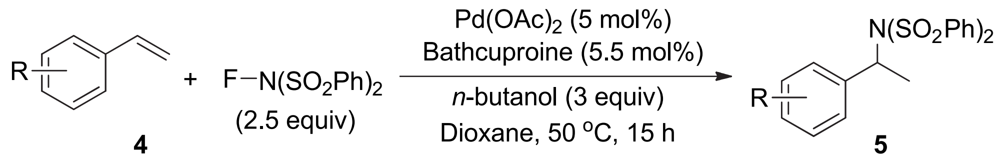
species to allene, in which bathocuproine (BC) plays a important role to promote Pd^{II}-hydride formation via alcohol oxidation. Thus, we assumed that the intermolecular hydroamination of styrenes might proceed through the similar pathway (Scheme 1, path **A**). Some nitrogen sources, such as tosylamide, *tert*-butyl carbamate and phthalimide were initially used to test this assumption. Treatment of styrene and nitrogen source by $Pd(OAc)_2$ (5 mol%), BC (5.5 mol%) in isopropanol under aerobic condition failed to achieve hydro-amination, and only trace alcohol oxidation product was detected. This observation possibly resulted from the stronger interaction between amide and palladium catalyst [11]. Therefore, weak coordinating nitrogen reagents, such as saccharin and methyl *N*-tosyl-carbamate, were subsequently studied. Unfortunately, no hydroamination product was observed. Moreover, the alcohol oxidation was completely inhibited, which could be attributed to the inhibitory effect of acidic proton on alcohol oxidation [12].

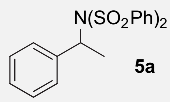
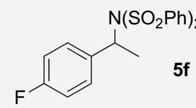
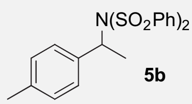
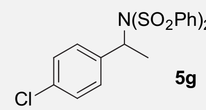
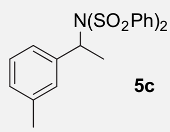
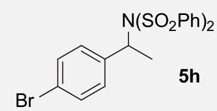
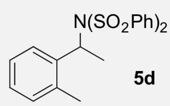
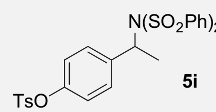
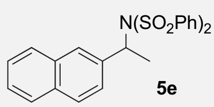
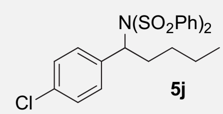
In order to eliminate the inhibitory effect of acid proton on alcohol oxidation, N–X reagents, such as compounds **1**–**3**, NCS, NBS and NFSI were considered as nitrogen sources (Scheme 1), which have been recently used as oxidant to carry out C–X or C–N bond formation [13]. We postulated that benzylic Pd(II) species, generated from the addition of Pd-hydride to styrene [14], could be oxidized by N–X reagent to form Pd(IV) species, and then underwent reductive elimination to generate C–N bond (Scheme 1, path **B**) [13]. When N–X reagents were treated with $Pd(OAc)_2$/BC in isopropyl alcohol, only the reaction with NFSI afforded a significant

Having established the optimal reaction condition, we thus investigated the substrate scope. As summarized in Table 1, the reaction is compatible with a variety of functional groups to afford the corresponding hydroamination products. Reactions of *m*- and *o*-methylstyrene afforded the corresponding products **5c**, **5d** in 70%, 61% yields, respectively (entries 3–4). However, the reaction of *p*-methylstyrene gave **5b** in low yield (entry 2) [18]. For vinyl-naphthylene **4e**, the reaction gave hydroamination product with moderate yield (entry 5). Styrenes bearing halide in aryl ring underwent hydroamination to afford the corresponding products **5f**–**5h** in moderate yields (entries 6–8). Similar result was obtained with tosyl protected *p*-hydroxystyrene **4i** (entry 9). Furthermore, hydroamination of internal alkene *E*-1-(4-chlorophenyl)-1-pentene **4j** also afforded imide **5j** in moderate yield (entry 10).

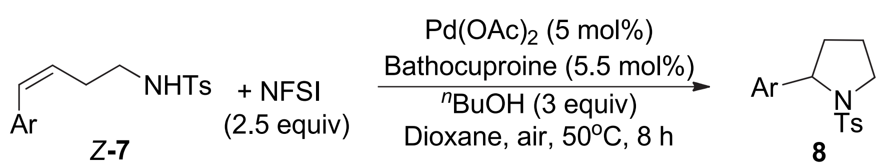
Based on the above results, we turned our attention to intra-molecular hydroamination of styrenes. Under the standard reaction condition, the reaction of *Z*-**7a** afforded a satisfying yield of cyclic product **8a** (eq 3, entry 1). For substrates **7b**–**7d**, hydroamination also proceeded efficiently to produce **8b**–**8d** with good yields (entries 2–4). For the substrates **7e**–**7g** bearing halides in phenyl ring, the intra-molecular hydroamination gave slightly higher yields than that of intermolecular cases (entries 5–7 versus entries 6–8 in Table 1). It is noteworthy that the 1,1-disubstituted styrene **7h** which was inert in the intermolecular hydroamination reaction also provided cyclic product **8h** in moderate yield (eq 4). However, the unactivated alkene *N*-tosyl-*Z*-3-pentenylamine did not show any reactivity for this transformation.

Table 1
Pd-catalyzed intermolecular hydroamination of styrenes.[a]



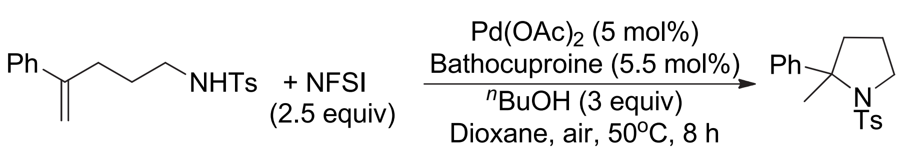
Entry	Product	Yield[b]	Entry	Product	Yield[b]
1	 5a	74%	6	 5f	57%
2[c]	 5b	31%	7	 5g	50%
3	 5c	70%	8[c]	 5h	48%
4	 5d	61%	9	 5i	67%[d]
5	 5e	58%	10[e]	 5j	40%

[a] Reaction condition: vinylarenes (0.2 mmol), $FN(SO_2Ph)_2$ (0.5 mmol), $Pd(OAc)_2$ (5 mol%), bathocuproine (BC, 5.5 mol%), ^{n}BuOH (0.6 mmol) in dioxane (2 mL) at 50 °C for 15 h.
[b] Isolated yield.
[c] ^{i}PrOH (0.6 mmol).
[d] ^{1}H NMR yield with 1,3,5-trimethylbenzene as internal standard.
[e] Product **5j** was transferred from (*E*)-1-(4-chlorophenyl)-1-pentene (**4j**).



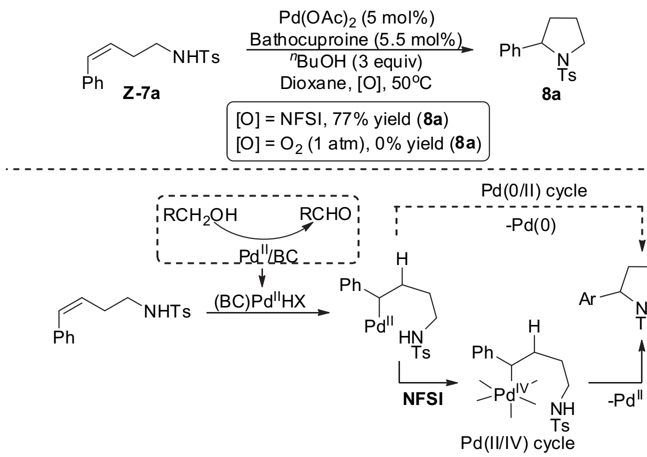
(3)

Entry	Substrates		Yield (%)
1	**7a**	Ar = C_6H_5	77
2	**7b**	*p*-MeC_6H_4	76
3	**7c**	*m*-MeC_6H_4	71
4	**7d**	*p*-$MeOC_6H_4$	83
5	**7e**	*p*-FC_6H_4	73
6	**7f**	*p*-ClC_6H_4	58
7	**7g**	*p*-BrC_6H_4	64



(4)

7h **8h** (54%)



Scheme 3. Pd-catalyzed intramolecular hydroamination of styrenes.

In contrast to our previous study on Pd-catalyzed intramolecular hydroamination of allene coupled with aerobic alcohol oxidation [10], neither the intramolecular nor intermolecualr hydroamination of styrene can proceed under aerobic reaction condition (Scheme 3). These results suggest that the C–N bond formation may undergo a nucelophilic attack of nitrogen nucleophile to the carbon center of C–Pd(IV) intermediate, which is generated from the oxidation of Pd(II) intermedaite by NFSI (the $Pd^{II/IV}$ pathway) [19].

In conclusion, we have developed a novel strategy for the palladium-catalyzed inter- and intramolecular hydroamination of styrenes that are coupled to alcohol oxidation under oxidative condition. This reaction employs a nitrogen-based ligand and NFSI as the oxidant. Further study on the asymmetric hydroamination of styrene is in progress.

3. Experimental

3.1. The typical procedures for intermolecular hydroamination of styrenes

In a dried glass tube, $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 5 mol%), bathocuproine (0.011 mmol, 5.5 mol%), *N*-fluorobenzenesulfonimide (157 mg, 0.5 mmol, 2.5 equivalents) were dissolved in 1,4-dioxane (2.0 mL), and then styrene **4a** (0.2 mmol, 1.0 equivalent) and butanol (0.6 mmol, 3 equivalents) were added. After the mixture was stirred at 50 °C for 15 h, the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel with a gradient eluant of petroleum ether and ethyl acetate to afford the hydroamination product **5a** in 74% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (bs, 4H), 7.56 (t, $J = 7.6$ Hz, 2H), 7.46–7.40 (m, 6H), 7.30–7.27 (m, 3H), 5.63 (q, $J = 7.6$ Hz, 1H), 1.65 (d, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 137.3, 133.5, 128.8, 128.7, 128.2, 128.1, 128.0, 60.3, 18.0; HRMS (ESI) calculated $[M + Na]^+$ 424.0648, measured 424.0648.

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Appendix. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2010.07.015.

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