J|A|C|S COMMUNICATIONS

Published on Web 02/11/2010

Palladium-Catalyzed Intermolecular Aminofluorination of Styrenes

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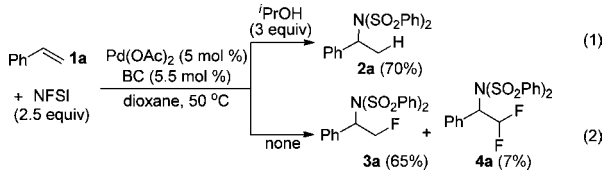
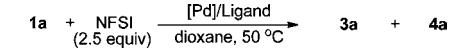
Palladium-catalyzed difunctionalization of olefins, such as aminooxygenation, diamination, and chloroamination, have been broadly studied.[1,2] These reactions provide versatile strategies to synthesize molecules with vicinal aminoheteroatom substitution. However, palladium-catalyzed aminofluorination of alkenes, which is the same strategy for the synthesis of vicinal aminofluorines,[3] is quite a challenge.

Several groups have recently reported palladium-catalyzed fluorination of aromatic compounds.[4,5] For instance, Buchwald has presented a coupling reaction of aryl triflates with CsF to give fluoroarenes.[4] Sanford[5a] and Yu[5b] have reported the use of *N*-fluoropyridinium reagents as a F^+ source in the directed fluorination of C−H bonds, and Ritter has explored the stoichiometric fluorination of arylboronates with SelectFluor.[5c] In most cases, the formation of a C−F bond is believed to proceed via a Pd(II/IV) catalytic cycle.[5d,e] Very recently, our group reported a palladium-catalyzed intramolecular aminofluorination of alkenes by PhI(OPiv)$_2$/AgF,[6] in which the C−F bond was also formed via reductive elimination from a Pd(IV) intermediate. In contrast, Sadighi reported a Au-catalyzed hydrofluorination of alkyne, where the formation of the C−F bond resulted from fluorogoldation of the triple bond.[7] Herein, we describe a novel palladium-catalyzed *intermolecular aminofluorination* of styrenes with *N*-fluorobenzenesulfonimide (NFSI) as the source of nitrogen and fluorine, in which *fluoropalladation* of styrenes is proposed as the key step to construct the C−F bond. In addition, a bidentate nitrogen ligand is crucial to the success of this reaction.



Recently, we explored a palladium-catalyzed hydroamination of styrenes.[8] In the presence of isopropyl alcohol and bathocuproine (BC), Pd(OAc)$_2$ could catalyze the reaction of styrene with NFSI to afford the desired product **2a** in a good yield (eq 1). Surprisingly, in the absence of the alcohol, a significant amount of compound **3a** was isolated with a small amount of difluoroamine **4a** (eq 2). To increase the yield of aminofluorination, several experiments were further investigated (Table 1). In comparison with BC (entry 1), none of the desired product was observed without a ligand (entry 2), or with various common nitrogen ligands, such as pyridine, bipyridine, and 1,10-phenanthroline (entries 3−5). A lower yield of **3a** was observed when other more sterically hindered ligands, neocuproine (NC) and 6,6′-dimethyl-bpy, were employed in the reaction mixture (entries 6−7). However, bathophenanthroline (BPH) which lacks the *ortho*-methyl groups was a poor ligand for this reaction (entry 8). Under these reaction conditions mentioned above, aminofluorination product **3a** was isolated as the single regioisomer (entries 1, 6−8). After screening, Pd(OAc)$_2$ was proven to be the most efficient catalyst; Pd(dba)$_2$, a precursor Pd(0), exhibited similar reactivity to that of the Pd(II) catalyst (entries 1, 9−12). A blank test showed that no reaction takes place without a palladium catalyst. Compared with the other solvents, dioxane is more suitable for the aminofluorination (entries 13−15). It should be noted that, in most cases, a small amount of side product **4a** was observed. With further optimization, the best yield (80%) was achieved under the reaction condition with Pd(OAc)$_2$ (5 mol %), BC (7.5 mol %), styrene (0.2 mmol), and NFSI (0.5 mmol) in dioxane at 0.4 M concentration (entry 16).

Table 1. Screening Results: Pd-Catalyzed Fluoroamination of Styrene[a]



Entry	[Pd] (5 mol %)	Ligand (5.5 mol %)	Solvent	Yield[b] (%) 3a	4a
1	Pd(OAc)$_2$	bathocuproine (BC)	dioxane	65	7
2	Pd(OAc)$_2$	none	−	0	0
3	Pd(OAc)$_2$	pyridine[d]	−	0	0
4	Pd(OAc)$_2$	2,2′-bipyridine (BPy)	−	0	0
5	Pd(OAc)$_2$	1,10-phenanthroline	−	0	0
6	Pd(OAc)$_2$	neocuproine (NC)	−	44	5
7	Pd(OAc)$_2$	6,6′-dimethyl-bpy (DMBPy)	−	23	0
8	Pd(OAc)$_2$	bathophenanthroline (BPH)	−	11	0
9	PdCl$_2$	BC	−	62	7
10	Pd(PhCN)$_2$Cl$_2$	BC	−	52	6
11	Pd(OOCCF$_3$)$_2$	BC	−	51	5
12	Pd(dba)$_2$	BC	−	55	6
13	Pd(OAc)$_2$	BC	TBME	29	9
14	Pd(OAc)$_2$	BC	DCE	29	3
15	Pd(OAc)$_2$	BC	toluene	54	5
16[c]	Pd(OAc)$_2$	BC	dioxane	80	10

[a] Reaction condition: the reaction conducted in 0.2 mmol scale in 1 mL of solvent. [b] F NMR yield with trifluoromethylbenzene as internal standard. [c] Ligand BC (7.5 mol %) in 0.5 mL of dioxane. [d] Pyridine (11 mol %). TBME = *tert*-butyl methylether, DCE = dichloroethane.

With the standard condition, the substrate scope of the aminofluorination reaction was investigated with a variety of vinyl arenes (Table 2). Compared to styrene, the reactions of *p*-, *m*-, and *o*-methylstyrene afforded **3b**, **3c**, and **3d** at 80%, 70%, and 61% yields, respectively. Styrenes **1e**−**1h** with a halide in the benzene ring underwent intermolecular aminofluorination to afford the corresponding products **3e**−**3h** at moderate to good yields, in which there is no obvious halide effect on the reactivity. Furthermore, with different protected *p*-hydroxystyrenes **1i**−**1k**, similar results were obtained. However, the reaction of substrates **1l**−**1o** containing electron-withdrawing groups, such as ester, nitrile, nitro and trifluoro groups, exhibited slightly lower reactivity. The internal alkenes, such as **1p**−**1r**, were proven to be good substrates for the transformation to generate products **3p**−**3r** with excellent regioselectivity but with a moderate level of diastereoselectivity.[9] It is noteworthy that the reaction of diene *trans*-**1s** exhibited very good chemoselectivity, where aminofluorination exclusively occurred in the activated double bond. However, the unactivated olefins, such as 1-octene and allylbenzene, have no reactivity for the aminofluorination reaction.

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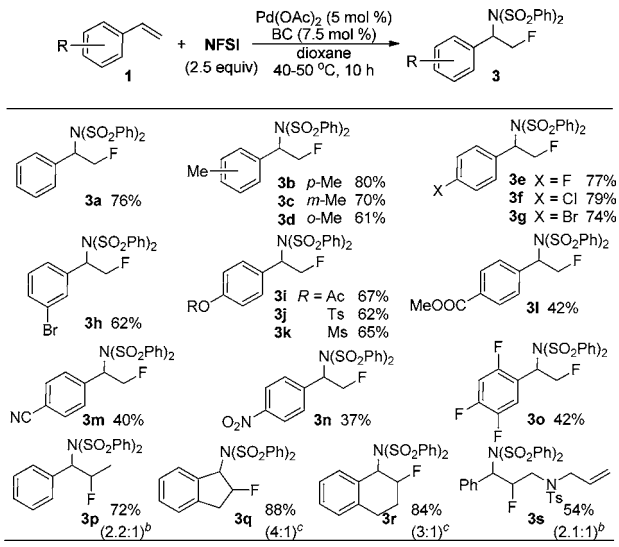
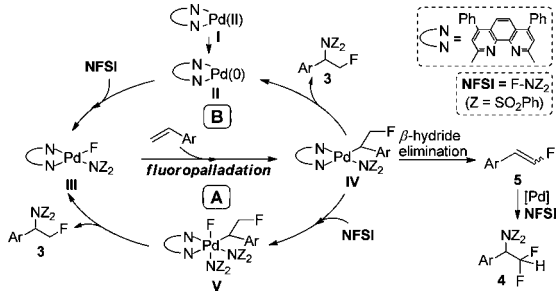
Table 2. Palladium-Catalyzed Aminofluorination of Styrenes[a]

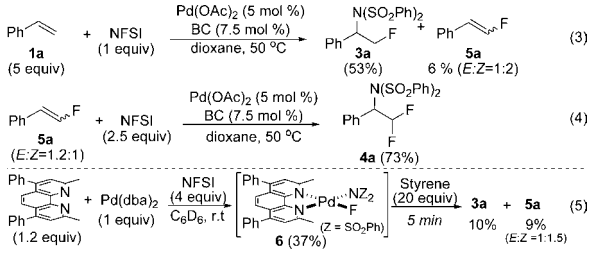


[a] Reactions were conducted in 0.4 mmol scale; isolated yield. [b] The data in parentheses are the ratio of *anti*:*syn*. [c] The ratio of *trans*:*cis*.

Scheme 1. Possible Catalytic Cycles for Fluoroamination of Styrenes



Although the mechanistic details of this transformation are not clear at the moment, some preliminary studies indicated that *fluoropalladation* of styrene may be involved in the C−F bond formation (Scheme 1).[10] As mentioned above, the reaction of styrene afforded a small amount of byproduct **4a**, which is probably derived from aminofluorination of β-fluorostyrene **5a** generated from *fluoropalladation* of styrene and β-hydride elimination (Heck type reaction).[11] In addition, when an excess of styrene reacted with NFSI, a small amount of β-fluorostyrene **5a** was observed (eq 3), which can be subject to further reaction with NFSI to give **4a** in a good yield (73%, eq 4). Furthermore, the stoichiometric reaction of BC, $Pd(dba)_2$ with NFSI generated a Pd(II) complex **6**, which was characterized by ^{19}F NMR (a broad single peak at −381 ppm), ^{1}H NMR, and mass spectroscopy.[12] When excess styrene **1a** (20 equiv) was further added, products **3a** and **5a** were generated in 10% and 9% yields, respectively (eq 5).[13]



Based on the above observations, a possible catalytic cycle is shown in the Scheme 1: first, the oxidation of the Pd(0) complex **II** by NFSI generates Pd(II) species **III**; then fluoropalladation of styrene, which is similar to the addition of Pd hydride to styrene,[14] gives a palladium species **IV**. The following oxidation of **IV** by NFSI gives a Pd(IV) intermediate **V**, which conducts reductive elimination to form a C−N bond (pathway **A**).[2f,15] However, an alternative pathway cannot be excluded currently: the benzylic-Pd intermediate **IV** undergoes nitrogen nucleophilic attack to afford product **3** (pathway **B**).[14a,16] It is worth noting that both catalytic cycles involve fluoropalladation of styrenes as a key step to construct C−F bonds.

In conclusion, we have developed a novel palladium-catalyzed intermolecular oxidative aminofluorination of vinyl arenes, in which NFSI functioned not only as a fluorination but also as an amination reagent. The reaction afforded vicinal fluoroamine products with very high regioselectivity. This transformation may involve fluoropalladation of styrene as a key step for C−F bond formation. Further mechanistic research is in progress.

Acknowledgment. Dedicated to Prof. Li-Xin Dai on the occasion of his 85th birthday. This work was supported by CAS, NSFC (20821002, 20872155 and 20972175), 973-program (2009CB825300), and STCSM (08PJ1411600 and 08dj1400100).

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

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(9) The ratio of diastereoisomers of **3q** was slightly effected by ligand choice, for instance, BC 88% (4:1), BPH 62% (2:1), NC 75% (3.5:1), DMBPy 44% (1.2:1).
(10) There is no obvious effect on aminofluorination of styrene by addition of 2,4-dinitrophenol or 1,4-hydroquinone, which suggests against a radical mechanism. For the mechanism involving a β-fluorocarbocation intermediate that is also less likely, see the Supporting Information for details.
(11) Although fluoropalladation of alkenes is unknown, the fluorogoldation of alkyne have been reported; see ref 7.
(12) Some examples of PdFX (X = Ar or F) complexes are stabilized by nitrogen-containing ligands, see refs 5d−5e and Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2009**, *131*, 918–919.
(13) In the absence of BC, the stoichiometric reaction only afforded product **5a** in 8% yield. See the Supporting Information for the analysis.
(14) For selective examples, see: (a) Hartwig, J. F. *Pure. Appl. Chem.* **2004**, *76*, 507–516. (b) Gligorich, K. M.; Cummings, S. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 14193–14195.
(15) The intramolecular hydroamination of styrene takes place with NFSI as oxidant, but no reaction occurs with oxygen as sole oxidant. The observation indicated that the C−N bond formation is more likely to proceed through the Pd(II/IV) cycle; see ref 8.
(16) The π-benzyl-Pd intermediate **IV** has been invoked by Stahl to explain the regioselectivty of oxidative amination of styrenes; see: (a) Timokhin, V. I.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 17888–17893. For amination of the benzylic-Pd complex, see: (b) Johns, A. M.; Tye, J. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 16010–16011.

JA909716K