

Palladium-Catalyzed Intramolecular Aminofluorination of Unactivated Alkenes

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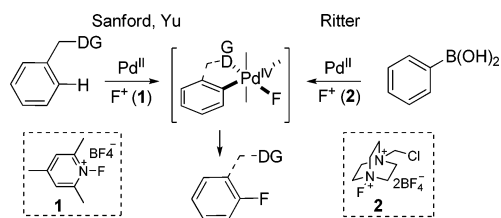
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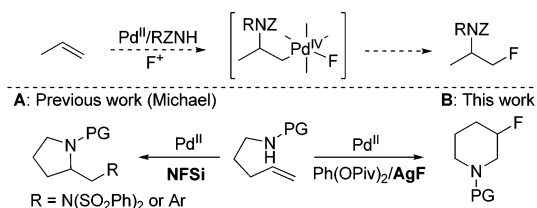
Molecules bearing a vicinal aminofluorine moiety have been extensively used as important building blocks for anticholinergic, antiemetic, and antispastic drugs as well as enzyme inhibitors.¹ However, very few effective approaches are available for the synthesis of these fluorinated molecules, and transition metal catalyzed methods are particularly rare.^{2,3}

Several groups recently described methods for Pd-catalyzed fluorination of aromatic compounds,^{4,5} in which the formation of C–F bonds have been demonstrated via Pd(II/IV) catalytic cycles, involving oxidative addition of Pd(II) to F⁺ reagents (Scheme 1).^{4a–d} For instance, Sanford^{4a} and Yu^{4b} have reported the use of **1** as an F⁺ source in the directed fluorination of C–H bonds, and Ritter has explored the stoichiometric fluorination of arylboronates with **2** (Scheme 1).^{5a} Meanwhile, similar Pd(II/IV) catalytic cycles have been successfully employed to achieve palladium-catalyzed difunctionalization of olefins,⁶ such as aminoxygenation,⁷ diamination,⁸ and chloroamination,⁹ which provide versatile strategies to prepare molecules with vicinal amino-heteroatom functionalities. We reasoned that if F⁺ reagents, such as **1** and **2**, were used as an oxidant, an aminofluorination product could be expected (Scheme 2, top). The same strategies have been studied using *N*-fluorobenzenesulfonimide (NFSi) as an oxidant by Michael and co-workers; however, the reaction exclusively afforded diamination^{8c} or carboamination¹⁰ products (Scheme 2A). Here, we describe a novel and highly regioselective palladium-catalyzed intramolecular aminofluorination of alkenes using AgF as the fluorinating reagent in the presence of PhI(OPiv)₂ (Scheme 2B).

Scheme 1. Palladium-Catalyzed Fluorination of Arenes via Pd(IV)F Complexes



Scheme 2. Hypthesis of Palladium-Catalyzed Aminofluorination of Alkenes



Our initial investigation focused on the reaction of amino-alkene **3a** with various F⁺ reagents, such as **1**, **2**, and NFSi, using Pd(OAc)₂ as the catalyst. However, none of the desired product was observed under such reaction conditions (Table 1, entries 1–3). When PhIF₂ was used as the oxidant, the reaction also failed to provide desired product **4a** (entry 4). Interestingly, a significant amount of aminofluorination product **4a** was observed with high regioselectivity when AgF was used as a fluorinating reagent in the presence of I(III) oxidants (entries 5–8); PhI(OPiv)₂ proved

to be the best oxidant, affording **4a** in 77% yield (entry 6). An aminocarboxylation side reaction generates small amounts of **5b**. No aminofluorination product was observed in the absence of I(III) oxidants (entry 9). Furthermore, other strong oxidants, such as oxone, NCS, and

Table 1. Palladium-Catalyzed Intramolecular Aminofluorination of Alkene **1a**^a

entry	[Pd]	[O] (2 equiv)/MF (2.5 equiv)	yield (%) ^b	
			4a	5 ^c
1	Pd(OAc) ₂	1	0	--
2	Pd(OAc) ₂	2	0	--
3	Pd(OAc) ₂	NFSi ^f	0	--
4	Pd(OAc) ₂	PhIF ₂	0	--
5	Pd(OAc) ₂	PhI(OAc) ₂ /AgF	38	24 (5a)
6	Pd(OAc) ₂	PhI(OCO ^t Bu) ₂ /AgF	77	17 (5b)
7	Pd(OAc) ₂	PhI(OCOCF ₃) ₂ /AgF	0	40 (5c)
8	Pd(OAc) ₂	PhI(OCOPh) ₂ /AgF	34	40 (5d)
9 ^d	Pd(OAc) ₂	-- /AgF	0	--
10	Pd(OAc) ₂	Oxone/AgF	0	--
11	Pd(OAc) ₂	NCS/AgF	0	--
12	Pd(OAc) ₂	H ₂ O ₂ /AgF	0	--
13 ^e	Pd(OAc) ₂	PhI(OCO ^t Bu) ₂ /AgF	69	25 (5b)
14	--	PhI(OCO ^t Bu) ₂ /AgF	0	0 (5b)
15	PdCl ₂	PhI(OCO ^t Bu) ₂ /AgF	65	20 (5b)
16	Pd(OCOCF ₃) ₂	PhI(OCO ^t Bu) ₂ /AgF	33	9 (5b)
17	PdCl ₂ (CH ₃ CN) ₂	PhI(OCO ^t Bu) ₂ /AgF	45	20 (5b)
18	Pd(OAc) ₂	PhI(OCO ^t Bu) ₂ /Bu ₄ NF	0	0 (5b)
19 ^d	Pd(OAc)₂	PhI(OCO^tBu)₂/AgF	86	10 (5b)

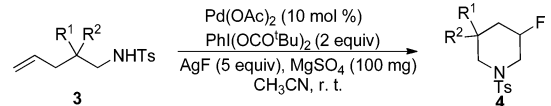
^a Reaction condition: **3a** (0.1 mmol), [Pd] (0.01 mmol), AgF (0.25 mmol), [O] (0.2 mmol), MgSO₄ (50 mg) in 0.5 mL of CH₃CN at room temperature. ^b ¹H NMR yield with 1,3,5-trimethoxybenzene as internal standard. ^c **5a**: R = Me, **5b**: R = ^tBu, **5c**: R = CF₃, **5d**: R = Ph. ^d AgF (5 equiv). ^e Without MgSO₄. ^f NFSi = *N*-fluorodiphenylsulfonimide.

H₂O₂, failed to result in product **4a** (entries 10–12). The additive of MgSO₄ is helpful to increase the yield of **4a** (entry 13). Control experiments indicated that no reaction occurred in the absence of Pd catalyst (entry 14). Among the palladium sources tested, Pd(OAc)₂ was the most effective catalyst (entries 6, 15–17). Screening of fluoride salts indicated that AgF is the only efficient reagent (entry 18).¹¹ Finally, the highest yield (86%) was obtained with 5 equiv of AgF (entry 19).

Under standard conditions, the substrate scope of the aminofluorination reaction was then investigated (Table 2). Compared to *N*-tosyl alkene **3a** with an 84% yield, the reaction of *N*-nosyl alkene **3b** gave **4b** in a slightly lower yield, and *N*-Boc alkene **3c** did not achieve aminofluorination (entries 1–3). The reactions of **3d** and **3e** still afforded products **4d** and **4e** in 80% and 83% yields, respectively (entries 4–5). Substrates **3f** and **3g**, with one substituent in the β-carbon position, underwent intramolecular aminofluorination to afford the corresponding products with moderate to good yields but poor diastereoselectivity (entries 6–7). The *spiro*-product **4h** could be obtained under the standard conditions (entry 8). Furthermore, substrates **3i** and **3j** bearing a methyl group at the internal carbon of the

double bond exhibited high reactivity to form aminofluorination products **4i** and **4j** (entries 9–10). For the cyclic aminoalkenes, the reaction of *trans*-**3k** afforded bicyclic product **4k** at 87% yield with a 4:1 *3,5-trans/cis* isomer ratio (entry 11). As a comparison, the opposite diastereoselectivity (1:5 for *3,5-trans/cis*) was achieved in the reaction of *cis*-**3k** with a similar reaction yield (entry 12). Finally, the reaction of **3m**, which has one more carbon atom tethered between the amide and alkene, provided a mixture of regioisomers **4m** and **4m'** at a 5:1 ratio, in which the reaction favors the *7-endo* ring closures (entry 13). For the 1,2-disubstituted alkene *N*-tosyl (*Z*)-4-hexenylamine, however, the reaction only afforded an aminopalladation/ β -hydride elimination product, rather than an aminofluorination product (See Supporting Information Table S2).

Table 2. Palladium-Catalyzed Intramolecular Aminofluorination of Alkenes^a



Entry	Alkene	Product	Yield ^b
1	3a Z = Ts	4a	84%
2	3b Ns	4b	74%
3	3c Boc	4c	0
4	3d R = H	4d	80%
5	3e R = Ph	4e	83%
6	3f R = Me	4f	89%
7	3g R = Ph	4g	(1.3:1) ^d (2:1) ^c
8	3h	4h	79%
9	3i R = Me	4i	83%
10	3j R = Ph	4j	80%
11	<i>trans</i> - 3k	4k	87% (4:1) ^d
12	<i>cis</i> - 3k	4l	82% (1:5) ^d
13	3m	4m + 4m'	58% (5:1) ^e

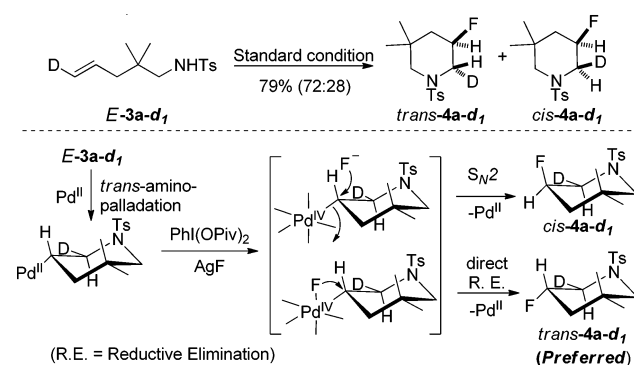
^a Reactions were conducted at 0.2 mmol scale. ^b Isolated yield (the ratio of diastereoselectivity which determined by ¹⁹F NMR). ^c The ratio of *trans* and *cis* isomers. ^d The ratio of *3,5-trans* and *3,5-cis* isomers. ^e The ratio of **4m**:**4m'**.

To gain some mechanistic insight into the aminofluorination process, deuterium-labeled alkene *E*-**3a-d₁** was subjected to the standard reaction condition, and a successful aminofluorination afforded the mixture of *trans*-**4a-d₁** and *cis*-**4a-d₁** in 79% yield with a 72:28 ratio (Scheme 3). A possible catalytic cycle based on our findings is shown below: Pd(II)-mediated *trans*-aminopalladation of the alkene with attack at the terminal carbon (6-*endo*)¹² generates a Pd(II) intermediate that undergoes an oxidation step by PhI(OPiv)₂/AgF.^{4c,d} Reductive elimination from the Pd(IV) intermediate generates the C–F bond, where direct reductive elimination is favored, but competing with S_N2 type nucleophilic attack by fluorine.

In conclusion, a highly regioselective palladium-catalyzed intramolecular oxidative aminofluorination of unactivated alkenes was reported, in which AgF functioned as a fluorinating reagent in the presence of PhI(OPiv)₂. This transformation represents a very efficient method to prepare fluoro-containing cyclic amine.

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Scheme 3. Possible Mechanism for Aminofluorination of Alkenes



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Supporting Information Available: Detail 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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