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Palladium-Catalyzed Intramolecular Aminofluorination of Unactivated Alkenes

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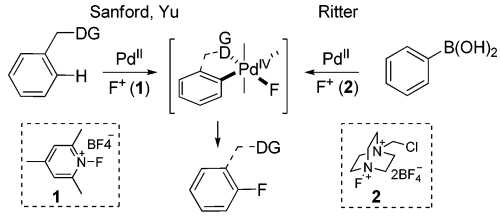
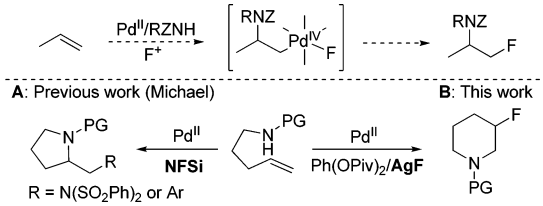
Molecules bearing a vicinal aminofluorine moiety have been extensively used as important building blocks for anticholinergic, antiemetic, and antispastic drugs as well as enzyme inhibitors.[1] However, very few effective approaches are available for the synthesis of these fluorinated molecules, and transition 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 aminooxygenation,[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 carboamination[10] 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

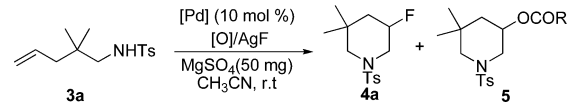


Scheme 2. Hypthesis of Palladium-Catalyzed Aminofluorination of Alkenes



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 $PhIF_2$ 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 H_2O_2, failed to result in product **4a** (entries 10−12). The additive of $MgSO_4$ 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).

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



entry	[Pd]	[O] (2 equiv)/MF (2.5 equiv)	yield (%)[b] 4a	yield (%)[b] 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	$Pd(OAc)_2$	$PhI(OCO^tBu)_2$/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_2O_2/AgF	0	--
13[e]	$Pd(OAc)_2$	$PhI(OCO^tBu)_2$/AgF	69	25 (**5b**)
14	--	$PhI(OCO^tBu)_2$/AgF	0	0 (**5b**)
15	$PdCl_2$	$PhI(OCO^tBu)_2$/AgF	65	20 (**5b**)
16	$Pd(OCOCF3)_2$	$PhI(OCO^tBu)_2$/AgF	33	9 (**5b**)
17	$PdCl2(CH3CN)_2$	$PhI(OCO^tBu)_2$/AgF	45	20 (**5b**)
18	$Pd(OAc)_2$	$PhI(OCO^tBu)_2$/Bu_4NF	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), $MgSO_4$ (50 mg) in 0.5 mL of CH_3CN at room temperature. [b] ^1H NMR yield with 1,3,5-trimethoxybenzene as internal standard. [c] **5a**: R = Me, **5b**: R = ^{t}Bu, **5c**: R = CF_3, **5d**: R = Ph. [d] AgF (5 equiv). [e] Without $MgSO_4$. [f] NFSi = *N*-fluorodibenzene-sulfonimide.

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 aminofluorinaton (entries 1−3). The reactions of **3d** and **3e** still afforded products **4d** and **4e** in 80% and 83% yields, respectively (entries 4−5). Subtrates **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

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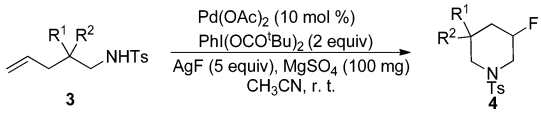
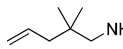
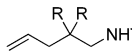
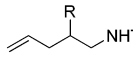
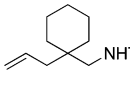
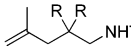
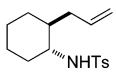
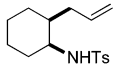
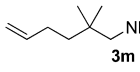
double bond exhibited high reactivity to form aminofluorination products **4i** and **4j** (entries 9−10). For the cyclic aminoalkenes, the reaction of *trans*-**3k** afforded bicyclic product **4k** at 87% yield with a 4:1 3,5-*trans*/*cis* isomer ratio (entry 11). As a comparison, the opposite diastereoselectivity (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% (1.3:1)[c]
7		**3g** R = Ph	**4g**	55% (2:1)[c]
8		**3h**	**4h**	79%
9		**3i** R = Me	**4i**	83%
10		**3j** R = Ph	**4j**	80%
11		*trans*-**3k**	**4k**	87% (4:1)[d]
12		*cis*-**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 ^{19}F 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**-d_1 was subjected to the standard reaction condition, and a successful aminofluorination afforded the mixture of *trans*-**4a**-d_1 and *cis*-**4a**-d_1 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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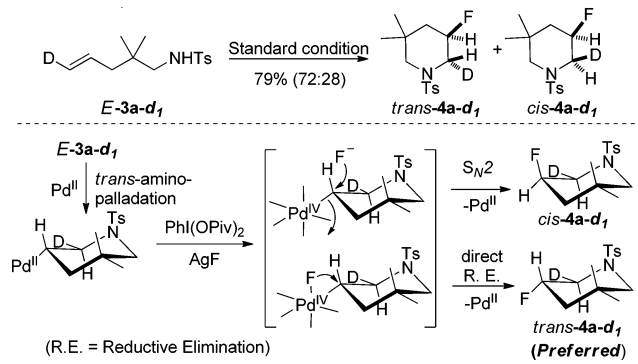
Scheme 3. Possible Mechanism for Aminofluorination of Alkenes



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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(11) A number of fluoride salts, such as CaF_2, CeF_2, NaF, ZnF_2, CuF_2, KF, NH_4F, PbF_2, BaF_2, were subjected to reaction conditions, and none of them are effective for aminofluorination.

(12) Although recent studies indicate that some *cis*-aminopalladation of alkenes occurred in the 5-*exo* fashion, the *6-endo* ring closure always proceeded via *trans*-aminopalladation; see: Watson, M. P.; Overman, L. E.; Bergman, R. G. *J. Am. Chem. Soc.* **2007**, *129*, 5031–5044.

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