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Regioselective palladium-catalyzed intramolecular oxidative aminofluorination of unactivated alkenes†

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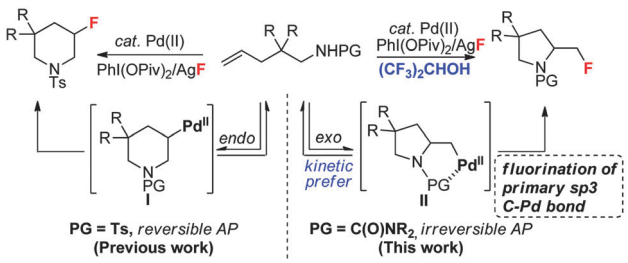
A novel Pd-catalyzed regioselective intramolecular aminofluorination of unactivated alkenes has been developed, which is an efficient method for the synthesis of a variety of monofluoromethylated nitrogen-containing heterocycles.

The challengeable transition metal-catalyzed C–F bond formation has received much attention during the last decade.[1] Recent studies demonstrated that C–F bond could be easily generated from the reductive elimination of high-valent palladium centers.[2,3] However, these processes were generally accompanied by other competitive reductive elimination pathways.[4] Thus, the development of catalytic methods for direct fluorination achieved little success.

Recently, our group[5] and Gagné[6a] demonstrated that oxidative fluorination of alkenes could be achieved by using transition metal, in which a secondary C_{sp^3}–M bond was effectively fluorinated. However, *the fluorination of a primary C_{sp^3}–M complex is quite challenging due to other competitive reactions.* For example, Gagné reported that treatment of primary C_{sp^3}–Pt complexes by NFSI afforded amination products, rather than fluorination products.[6b] Toste found that the reaction of primary C_{sp^3}–Au bonds with XeF_2 yielded β-hydride elimination products.[7a] Until recently, Sanford reported successful fluorination of Pd complexes with primary C_{sp^3}–Pd bonds without β-H by using strong PyF^+.[7b] But the related catalytic fluorination is quite rare.

In previous Pd-catalyzed aminofluorination, the reason for selective formation of the *endo*-product is that the reaction possibly involves reversible aminopalladation (AP) and oxidation of intermediate **I** due to higher electron density of the Pd^{II} centre than **II** (left, PG = tosyl, Scheme 1).[8] In regard to the chelating effect, replacing a tosyl group on nitrogen by a chelating protecting group could generate a primary C_{sp^3}–Pd species **II** from kinetically favoured *exo*-aminopalladation (AP). We speculated that if a $PhI(OPiv)_2$–AgF system can be applied to achieve selective fluorination of primary C_{sp^3}–Pd bonds, the regioselective formation of monofluoromethylated heterocycles might be expected.[9,10] Herein, we reported this study, and we found that addition of HFIP (hexafluoroisopropyl alcohol) is essential for highly selective fluorination of primary C_{sp^3}–Pd bond (right, PG = $C(O)NR_2$, Scheme 1).



Scheme 1 Pd-catalyzed regioselective aminofluorination of alkenes.

In order to test this hypothesis, a variety of substrates bearing different chelating protecting groups on nitrogen atoms were initially investigated. We are delighted to find that substrate **1a** with a urea protecting group underwent *exo*-cyclization, and gave fluorinated product **2a** in 13% yield in CH_3CN, without any *endo*-cyclization product. However, aminooxygenation product **3a** was obtained as a major product (26%, Table 1, entry 1). A similar result was obtained in the EtOAc solvent. The preference for formation of C–O bonds compared to C–F bonds is possible, resulting from the nucleophilic attack of carboxylate at the primary carbon centre of the Pd(IV) intermediate. If so, this process is favoured in polar solvent, and employment of nonpolar solvent should be helpful to suppress C–O bond formation. Gratifyingly, benzene, toluene and xylene were demonstrated to be good solvents to improve the yield of fluorination product **2a**, but still with a significant amount of product **3a** (around 20–30%, entries 3–5). Catalyst investigation showed that both $Pd(OAc)_2$ and $Pd(dba)_2$ presented good reactivities (entries 5–8). No aminofluorination reaction occurred in the absence of a palladium catalyst, even in the presence of Brønsted acid (HO_2CCF_3) or Lewis acid ($BF_3{\cdot}Et_2O$) (entry 9).[11] More efforts were devoted to improving the yield of fluorination product **2a**: addition of NaOPiv yielded a poor result; HOPiv just improved the yield of the oxygenation product **3a** (entries 10 and 11); *tert*-butyl alcohol gave aminofluorination product **2a** in slightly better yield (entry 12). Surprisingly, addition of fluorinated

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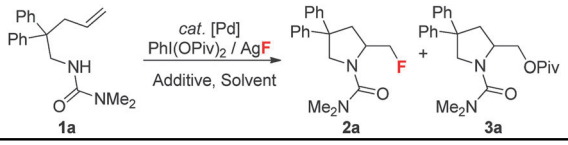
Table 1 Optimization of the reaction conditions[a]



Entry	[Pd] (5 mol%)	Additive (equiv.)	Solvent	Yield[b] (%) 2a	3a
1	$Pd(OAc)_2$	—	CH_3CN	13	26
2	$Pd(OAc)_2$	—	EtOAc	19	30
3	$Pd(OAc)_2$	—	Benzene	49	21
4	$Pd(OAc)_2$	—	Toluene	51	17
5	$Pd(OAc)_2$	—	Xylene	46	23
6	$PdCl_2(MeCN)_2$	—	Toluene	44	18
7	$PdCl_2(PhCN)_2$	—	Toluene	34	13
8	$Pd(dba)_2$	—	Toluene	50	16
9	—	—	Toluene	0	0
10	$Pd(OAc)_2$	NaOPiv (1)	Toluene	13	12
11	$Pd(OAc)_2$	HOPiv (1)	Toluene	45	34
12	$Pd(OAc)_2$	$HOBu^t$ (1)	Toluene	60	13
13	$Pd(OAc)_2$	TFE (2.5)	Toluene	62	6
14	$Pd(OAc)_2$	HFIP (2.5)	Toluene	73	Trace
15[c]	**$Pd(OAc)_2$**	**HFIP (2.5)**	**Toluene**	**81**	**Trace**

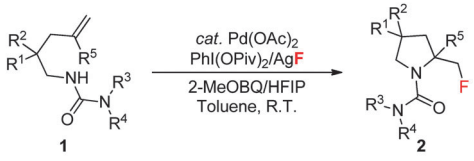
[a] Reaction conditions: **1a** (0.1 mmol), [Pd] (5 mol%), $PhI(OPiv)_2$ (3 equiv.), AgF (3 equiv.), solvent (0.5 mL), at r.t. for 24 h. [b] ^1H NMR yield with CF_3–DMA as internal standard. [c] 2-MeOBQ (1 equiv.).

alcohol, such as HFIP (hexafluoroisopropyl alcohol) and TFE (trifluoroethanol), significantly enhanced chemo-selectivity and HFIP gave the best yield (entries 13 and 14). Finally, we found that 2-methoxy-1,4-benzoquinone (2-MeOBQ) was a good additive to further improve the yield of **2a** to 81% (entry 15).[12]

With the optimal reaction conditions in hand, the scope of alkenes was further investigated (Table 2). For different substituents on urea protecting groups, the reactions of **1a** and **1b** afforded aminofluorination products in good yields (entries 1 and 2). Next, the substrates - **1c–1e** bearing dimethyl groups on the carbon chain provided the corresponding products in moderate yields (entries 3–5). Monofluoromethylated *spiro*-pyrrolidines **2f** and **2g** were also produced in this transformation with acceptable yields (entries 6 and 7). Substrate **1h** with one phenyl group at β-carbon provided **2h** in moderate yield but with poor diastereoselectivity (entry 8). Furthermore, due to steric hindrance, 1,1-disubstituted alkene **1i** exhibited slightly low reactivity to form desired product **2i** in 33% yield (entry 9). However, for an internal alkene substrate, the reaction did not afford the desired aminofluorination product.

With the above results in hand, we turned our attention to the synthesis of monofluoromethylated imidazolidines. Initial studies focused on the reaction of substrate **4a**. We are delighted to find that substrate **4a** could be smoothly transformed into **5a** in 61% yield. Further optimization of reaction conditions indicated that the best yield (75%) was obtained by using $Pd(O_2CCF_3)_2$ as catalyst (Table 3, entry 1). Other substrates were then subjected to the modified reaction conditions. Urea substrates **4b–4f** with different substituents on nitrogen atoms gave the corresponding products in moderate to good yields (entries 2–6). When a methyl group was introduced at the *allylic* position, substrate **4g** presented slightly lower reactivity and selectivity (entry 7). In addition, 1,1-disubstituted substrate **4h** showed a similar reactivity to give the product in 56% yield (entry 8). Furthermore, substrates bearing one more carbon atom tethered

Table 2 Pd-catalyzed aminofluorination of alkenes[a]

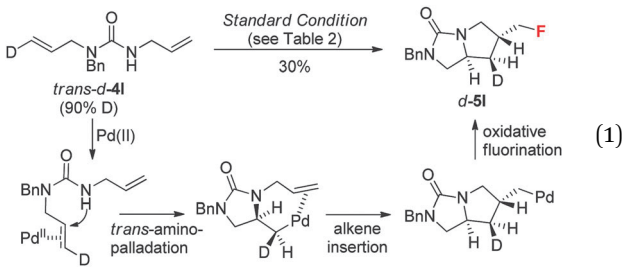


Entry	Substrate	Product	Yield[b]
1	**1a** $R^1 = R^2 = Me$	**2a**	82%
2	**1b** $R^1 = R^2 = {}^i Pr$	**2b**	78%
3	**1c** $R^1 = R^2 = Me$	**2c**	53%
4	**1d** $R^1 = R^2 = Bn$	**2d**	63%
5	**1e** $R^1 = Me$, $R^2 = Ph$	**2e**	61%
6	**1f** n = 0	**2f**	47%
7	**1g** n = 1	**2g**	51%
8	**1h**	**2h**	50% (1/1)[c]
9	**1i**	**2i**	33%

[a] All the reactions were conducted at the 0.2 mmol scale; reaction conditions are the same as those in entry 15 in Table 1. [b] Isolated yield. [c] Diastereoselectivity.

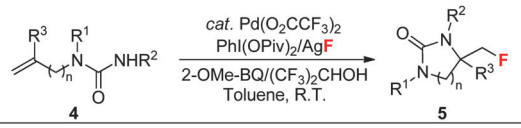
between amides and alkenes were also investigated. Substrate **4i** exhibited excellent reactivity to give the six-membered product in 80% yield (entry 9). Upon introducing a methyl group at the *allylic* position, the reaction of **4j** exhibited excellent diastereoselectivity to yield *trans*-**5j** as a single isomer (entry 10). In contrast, substrate **4k** with a phenyl group at the homoallylic position gave poor diastereoselectivity (entry 11). It is worth noting that excellent chemoselectivities were observed in all the above reactions to give fluorination products.

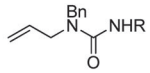
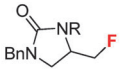
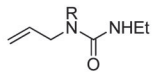
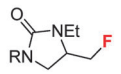
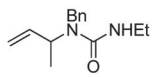
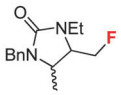
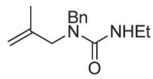
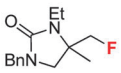
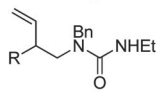
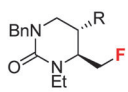
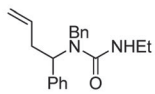
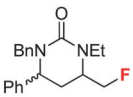
In regard to the reaction mechanism, deuterium-labelled diene *trans*-*d*-**4l** was subjected to standard conditions to give single isomer *d*-**5l** in 30% yield. This result indicated that an initial *trans*-aminopalladation step is involved in the catalytic cycle. The subsequent process included alkene insertion, oxidative fluorination to afford the desired product (eqn (1)).



During this process, combination of $PhI(OPiv)_2$ and AgF presented a good system to achieve fluorination.[5] In addition, only the

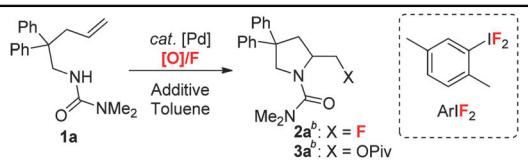
Table 3 Pd-catalyzed aminofluorination of alkenes[a]



Entry	Substrate	Product	Yield[b]
1	 **4a** R = ^{n}Pr	 **5a**	75%
2	**4b** R = Me	**5b**	72%
3	**4c** R = Et	**5c**	71%
4	**4d** R = Bn	**5d**	70%
5	**4e** R = Ph	**5e**	55%
6	 **4f** R = *c*-C_5H_9	 **5f**	58%
7	 **4g**	 **5g**	50% (2:1)[c]
8	 **4h**	 **5h**	56%
9	 **4i** R = H	 **5i**	80%
10	**4j** R = Me	**5j**	66%[d]
11	 **4k**	 **5k**	56% (2/1)[c]

[a] Reaction conditions: **4** (0.2 mmol), $Pd(O_2CCF_3)_2$ (5 mol%), $PhI(OPiv)_2$ (3 equiv.), AgF (3 equiv.), 2-MeO-BQ (1 equiv.), $(CF_3)_2CHOH$ (3 equiv.) in toluene (1.0 mL) at r.t. for 24 hours. [b] Isolated yield. [c] Diastereoselectivity. [d] Only *trans*-isomer detected.

Table 4 Pd-catalyzed aminofluorination with $ArIF_2$[a]



Entry	[Pd]	[O]/F	Additive	**2a**	**3a**
1	$Pd(OAc)_2$	$ArIF_2$	—	0	0
2	—	$ArIF_2$	—	0	0
3	$Pd(OAc)_2$	$ArIF_2$/AgOPiv	—	13%	0
4	$Pd(OAc)_2$	$ArIF_2$/AgOPiv	HFIP	45%	0
5	—	$ArIF_2$/AgOPiv	HFIP	0	0
6	$Pd(OAc)_2$	$ArIF_2$/AgF	HFIP	27%	0

[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), $ArIF_2$ (2 equiv.), AgOPiv (2 equiv.), additive (2 equiv.) in toluene (1 mL) at r.t. [b] NMR yield.

I(III) reagent could deliver fluorination products. Thus, it is possible that high-valent iodine reagent $PhIF_2$, generated *in situ*, might act as a true oxidant. In order to address the possibility, $ArIF_2$ (Ar = 2,4-xylenyl) was independently synthesized and subjected to standard conditions (see Table 4).[13] Unfortunately, the reaction of $ArIF_2$ failed to give fluorination product **2a** in the presence or absence of a palladium catalyst (entries 1 and 2). Interestingly, the reaction occurred in the presence of AgOPiv to give fluorination products as single products *in albeit* low yield (entry 3). And addition of HFIP could significantly enhance the yield to 45% (entry 4). Besides AgOPiv, the additive AgF also provided the desired product in 27% yield (entry 6). But CsOPiv was ineffective for this transformation. These results suggested that $ArIF_2$ may act as a true oxidant to achieve C–F bond formation.

In summary, we have developed a Pd-catalyzed regioselective intramolecular aminofluorination of unactivated alkenes, in which a primary C_{sp^3}–Pd bond was selectively fluorinated by AgF/$PhI(OPiv)_2$ in the presence of HFIP. Preliminary mechanistic studies demonstrated that $PhI(OPiv)_2$ and/or $PhIF_2$ might act as a real active oxidant. This methodology is an efficient route to synthesize a variety of monofluoromethylated nitrogen-containing heterocycles.

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