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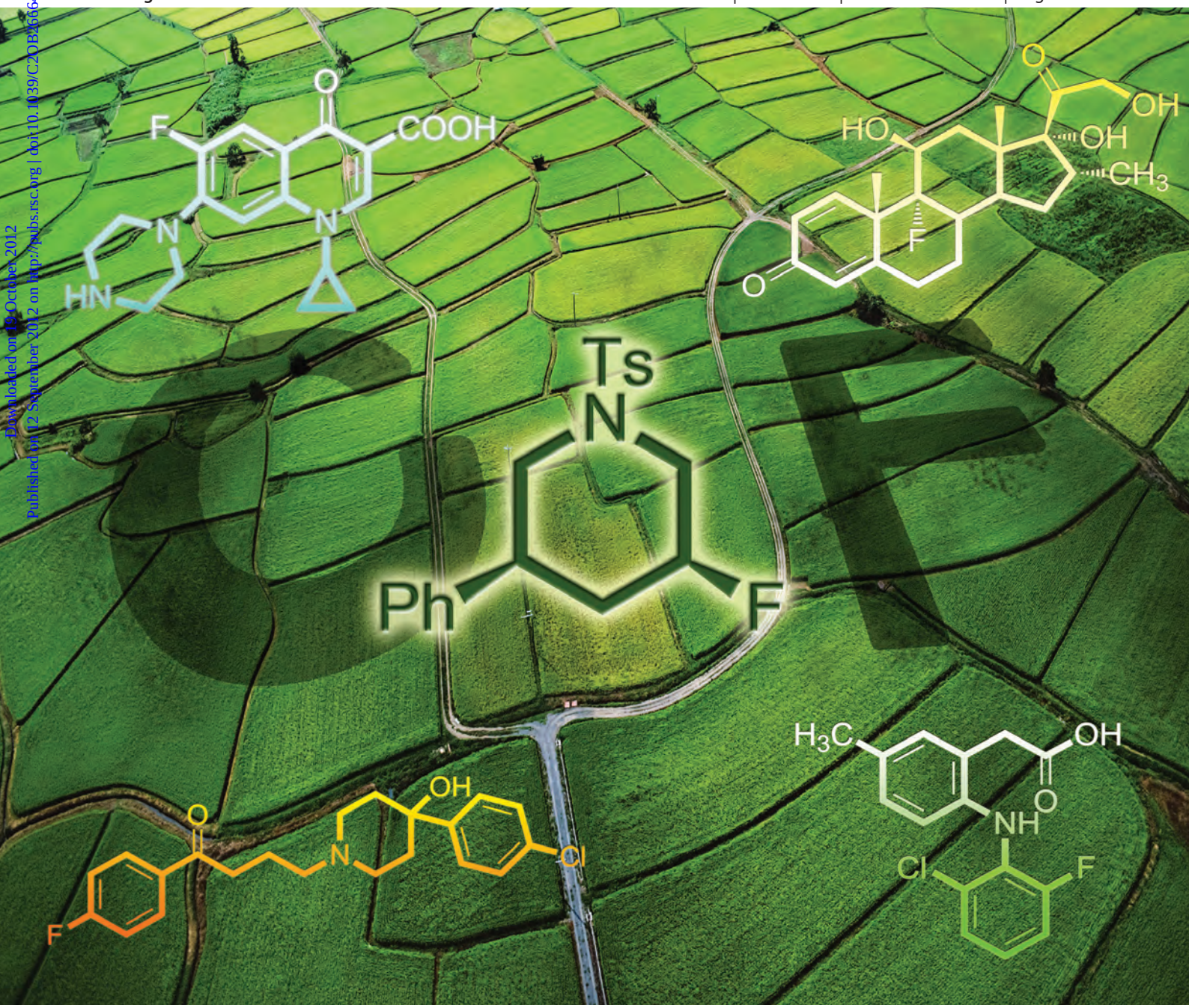

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COMMUNICATION

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COMMUNICATION

Metal-free intramolecular aminofluorination of alkenes mediated by PhI(OPiv)$_2$/hydrogen fluoride–pyridine system†

Qing Wang, Wenhe Zhong, Xiong Wei, Maoheng Ning, Xiangbao Meng* and Zhongjun Li*

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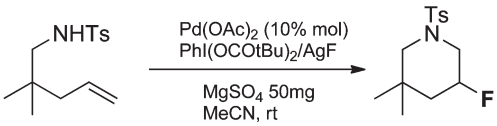
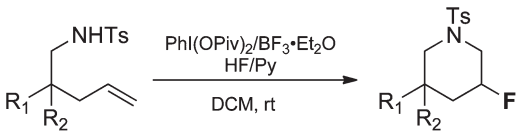
A convenient, metal-free intramolecular aminofluorination of alkenes has been developed. Employing readily available PhI(OPiv)$_2$ and hydrogen fluoride–pyridine in the presence of BF_3·OEt_2, tosyl-protected pent-4-en-1-amines were converted to 3-F-piperidines in one step in good yields as well as high stereoselectivity.

Carbon–fluorine bond formation is an integral reaction in the preparation of pharmaceuticals, agrochemicals, materials and tracers for positron emission tomography.[1] In recent years, many metal-catalyzed fluorination reactions have been studied for the efficient incorporation of fluorine.[2] Vicinal amino-fluoro-compounds, which contain a fluoro group adjacent to an amino group, have been used as an important intermediate in the synthesis of many pharmaceuticals.[3] Direct aminofluorination of alkenes could allow rapid access to this type of useful building block, but only a few methods have been reported. For instance, Liu and co-workers developed a palladium-catalyzed intramolecular aminofluorination of unactivated alkenes for the efficient construction of fluoro-containing cyclic amines. A palladium catalyst was crucial for this reaction and a Pd(II/IV) catalytic process was proposed in the presence of PhI(OPiv)$_2$/AgF (Scheme 1).[4]

Recently, hypervalent iodine reagents have been employed to mediate the difunctionalization of alkenes without the use of a noble metal catalyst. Lovick and Michael found that a highly regioselective aminotrifluoroacetoxylation of an unactivated alkene was achieved in the presence of hypervalent iodine(III).[5] Meanwhile, Wardrop and co-workers developed a method for the intramolecular oxamidation of unsaturated *O*-alkyl hydroxamates mediated by phenyliodine(III) bis(trifluoroacetate) (PIFA).[6] Furthermore, hypervalent iodine(III) also has been used in the stereoselective dioxygenation of alkenes and the mechanism has been clarified.[7] In addition, Muñiz *et al.* described a method for the enantioselective diamination of styrenes by employing a chiral iodine(III) reagent,[8] and the diamination of other alkenes



Scheme 1 Palladium-catalyzed intramolecular aminofluorination.



Scheme 2 Metal-free aminofluorination of alkenes.

was reported by the same group.[9] Gouverneur *et al.* reported an enantioselective intramolecular aminofluorination reaction of *N*-Ts indole derivatives by use of Selectfluor/(DHQ)$_2$PHAL and NFSI/(DHQ)$_2$PHAL.[10] The use of hypervalent iodine reagents, which are less toxic and readily available, represents a useful alternative to the metal-catalyzed procedures. Herein, we report a novel BF_3·OEt_2-catalyzed metal-free method for the intramolecular aminofluorination of unactivated alkenes mediated by a PhI(OPiv)$_2$/hydrogen fluoride–pyridine system (Scheme 2). Compared with previous reports,[4,11] this method is more regioselective and stereoselective, and in the absence of a noble metal catalyst.

Although difluoroiodoarenes (ArIF$_2$) have been widely used in fluorination reactions,[12] the preparation of ArIF$_2$ usually needs the use of powerful fluorinating reagents such as F_2,[13] XeF_2,[14] or toxic HgO.[15] Therefore, we initially used commercially available PhI(OAc)$_2$ (PIDA) as the oxidant and AgF as the fluorine source. Based on our previous work,[7] we chose BF_3·Et_2O as the promoter. To our delight, the aminofluorination product was obtained in the absence of palladium catalyst, albeit in 18% yield. Meanwhile, an aminohydroxylation byproduct was observed (Table 1, entry 1). We then used PhI(OPiv)$_2$ (PIDP) for its larger size to reduce the aminohydroxylation byproduct and the aminofluorination yield increased to 29% (Table 1, entry 2). Various fluorine sources were also tested to increase the aminofluorination yield. However, the reaction failed to provide desired product **2a** when several fluorides were employed as the

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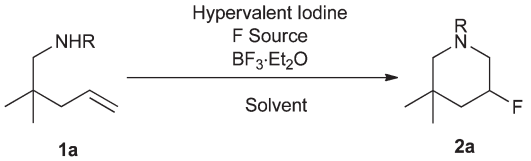
†Electronic supplementary information (ESI) available: Detailed experimental procedures and spectroscopic data. See DOI: 10.1039/c2ob26664d

Table 1 Hypervalent iodine(III) mediated intramolecular amino-fluorination of alkenes



Entry	[F] Source	Solvent	Hypervalent iodine(III)	R	Yield (%)
1	AgF (2.5 eq.)	DCM	PIDA	Ts	18
2	AgF (2.5 eq.)	DCM	PIDP	Ts	29
3	AgF (2.5 eq.)	DCM	PIDP	Ts	n.r.[a]
4	HF/H_2O (2.5 eq.)	DCM	PIDP	Ts	0
5	CaF_2 (2.5 eq.)	DCM	PIDP	Ts	0
6	NH_4HF_2 (2.5 eq.)	DCM	PIDP	Ts	0
7	$NEt_3{\cdot}3HF$ (2.5 eq.)	DCM	PIDP	Ts	0
8	TBAF (2.5 eq.)	DCM	PIDP	Ts	n.r.
9	HF–Py (2 eq.)	DCM	PIDP	Ts	35
10	HF–Py (3 eq.)	DCM	PIDP	Ts	70
11	HF–Py (4 eq.)	DCM	PIDP	Ts	76
12	HF–Py (5 eq.)	DCM	PIDP	Ts	81
13	HF–Py (10 eq.)	DCM	PIDP	Ts	85
14	HF–Py (15 eq.)	DCM	PIDP	Ts	85
15	HF–Py (10 eq.)	DCM	PIDA	Ts	39
16	HF–Py (10 eq.)	DCM	PIFA	Ts	59
17	HF–Py (10 eq.)	DMSO	PIDP	Ts	n.r.[b]
18	HF–Py (10 eq.)	DCM	PIDP	Cbz[c]	Complex

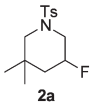
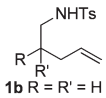
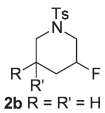
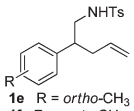
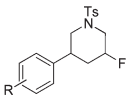
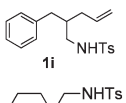
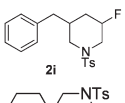
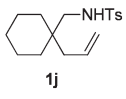
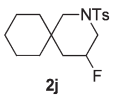
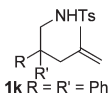
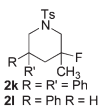
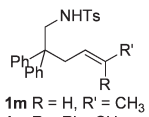
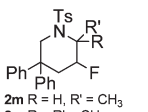
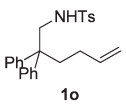
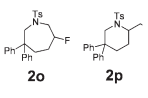
[a] Carried out without $BF_3{\cdot}Et_2O$. [b] No desired product was obtained when the reaction was carried out in DMSO, THF or MeCN. [c] The reactions of *N*-Bz, *N*-Ac and *N*-Boc protected amines also produced a complex mixture.

fluorine sources (Table 2, entries 4–9). Fortunately we found that the aminofluorination yield increased to 35% when HF–Py was used as a fluorinating reagent (Table 1, entry 9). The aminofluorination yield increased to 85% after we increased the amount of HF–Py to 10 eq. (Table 1, entry 13). $PhI(OAc)_2$ and PIFA were not as good as PIDP (Table 1, entries 15 and 16) in this procedure. When the reaction was carried out in DMSO, THF or MeCN, no desired product was obtained (Table 1, entry 17). Compared with *N*-tosyl alkene **1a** that produced 85% yield, the reactions of other protected amines such as *N*-Cbz, *N*-Bz, *N*-Ac and *N*-Boc produced a complex mixture (Table 1, entry 18).

The scope of the aminofluorination reaction was also investigated under optimized conditions (Table 2).

Substrate **1b**, without a substituent at the β-carbon of the alkene, underwent an intramolecular aminofluorination to form the corresponding product in an excellent yield, while substrate **1c** with two phenyl groups at the β-carbon formed the corresponding product in a slightly lower yield. Gratifyingly, the monosubstituted product **2d** in sole *cis* configuration was obtained under the standard conditions in 81% yield (Table 2, entries 2–4). Substrates **1e**, **1f** and **1g** bearing a methylphenyl group at the β-carbon exhibited lower reactivity to furnish products **2e**, **2f** and **2g**, but maintained the high stereoselectivity (Table 2, entries 5–7). Substrate **1h** with one phenyl group and one methyl group at the β-carbon afforded product **2h** in 89% yield with a 1.6 : 1 (*cis* : *trans*) isomer ratio (Table 2, entry 8). Substrate **1i** with a benzyl group at the β-carbon produced **2i** in

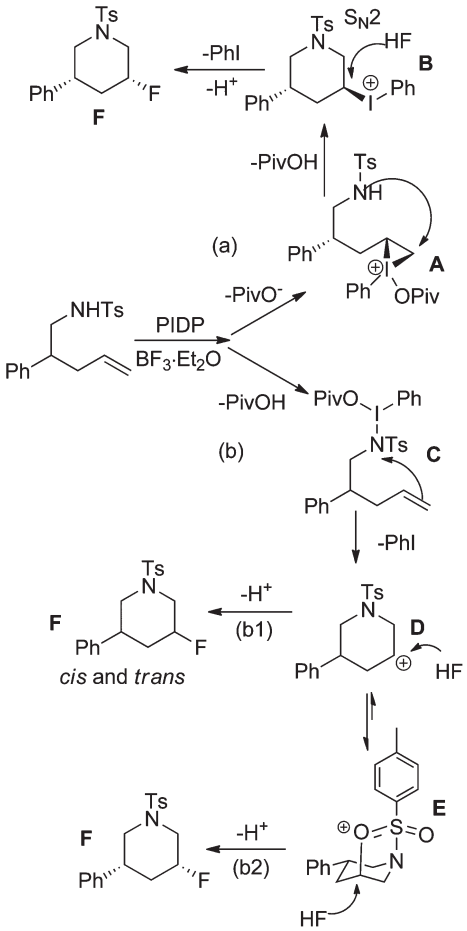
Table 2 Hypervalent iodine(III) mediated intramolecular amino-fluorination of alkenes[a]

Entry	Alkene	Product	Yield[b] (%)
1	 **1a**	 **2a**	85
2	 **1b** R = R' = H **1c** R = R' = Ph **1d** R = Ph R' = H	 **2b** R = R' = H **2c** R = R' = Ph **2d** R = Ph R' = H	90 81 81 (*cis* : *trans* > 99 : 1)
3			
4			
5	 **1e** R = *ortho*-CH_3 **1f** R = *meta*-CH_3 **1g** R = *para*-CH_3	 **2e** R = *ortho*-CH_3 **2f** R = *meta*-CH_3 **2g** R = *para*-CH_3	78 (*cis* : *trans* > 99 : 1) 75 (*cis* : *trans* > 99 : 1) 64 (*cis* : *trans* > 99 : 1)
6			
7			
8	 **1h**	 **2h**	89 (*cis* : *trans* = 1.6 : 1)
9	 **1i**	 **2i**	63 (*cis* : *trans* > 99 : 1)
10	 **1j**	 **2j**	80
11	 **1k** R = R' = Ph **1l** R = Ph R' = H	 **2k** R = R' = Ph **2l** R = Ph R = H	59 59 (*cis* : *trans* > 99 : 1)
12			
13	 **1m** R = H, R' = CH_3 **1n** R = R' = CH_3	 **2m** R = H, R' = CH_3 **2n** R = R' = CH_3	Complex mixture Complex mixture
14			
15	 **1o**	 **2o** **2p**	33 (**2o** : **2p** = 9.3 : 1)[c]

[a] Reactions were conducted at 0.25 mmol scale. [b] Isolated yield (the ratio of diastereoselectivity was determined by ^{19}F NMR). [c] Products **2o** and **2p** cannot be separated by column chromatography on silica gel.

63% yield with excellent stereoselectivity (Table 2, entry 9). The spiro-product **2j** was obtained in 80% yield (Table 2, entry 10). The intramolecular aminofluorination of internal olefins **1m** and **1n** were unsuccessful (Table 2, entries 13 and 14); however, substrates **1k** and **1l** with disubstituted terminal olefin produced **2k** and **2l** in 59% yield (Table 2, entries 11 and 12). Lastly, the reaction of **1o**, which has one extra carbon between the amine and the olefin, provided a mixture of regioisomers **2o** and **2p** in a 9.3 : 1 ratio, indicating that the reaction favored the 7-*endo* ring closure (Table 2, entry 15).

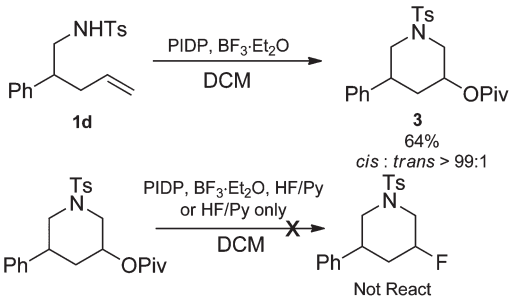
Based on the reaction mechanism of $PhI(OAc)_2$/TFA mediated intramolecular aminotrifluoroacetoxylation of alkenes,[5] two possible pathways are proposed for the aminofluorination reaction (Scheme 3). For pathway (a), the alkene is oxidized first to generate an iodonium ion **A**. This intermediate is



Scheme 3 Possible mechanism of $PhI(OPiv)_2/BF_3{\cdot}OEt_2$ mediated aminofluorination of alkenes.

intramolecularly attacked by the sulfonamide nitrogen to form the kinetically preferred intermediate **B**, which rapidly reacts with a fluoride ion to form the *cis* product through an S_N2 reaction. For pathway (b), the sulfonamide nitrogen is oxidized to generate an electrophilic species **C** first. Subsequent nucleophilic attack of the double bond of **C** generates the carbocation intermediate **D**, which is converted to the more stable **E** *via* the neighboring group participation of the tosyl group.[16] When intermediate **D** is stable, the attack by fluoride produces both *cis* and *trans* products. The fluoride attack of intermediate **E** *via* an S_N2 reaction produces the *cis* product only. When the substrate bears a quaternary β-carbon, the axial alkyl group would prevent the formation of intermediate **E**, thus producing a *cis*/*trans* mixture (**2h**, Table 2). Because of the high stereoselectivity of compounds **1d–g**, we tend to believe that pathway (b) is more probable than pathway (a).

In order to understand the reaction mechanism further, we carried out the reaction without the hydrogen fluoride–pyridine. The substrate **1d** underwent intramolecular aminopivaloylation to provide the corresponding *cis* product **3** in 64% yield, indicating a similar mechanism as the aminofluorination reaction. When the aminopivaloylation product **3** was treated with HF–Py, no reaction was observed. This phenomenon ruled out the aminopivaloxylation product as an intermediate in the reaction (Scheme 4).



Scheme 4 Intramolecular aminopivaloylation of alkenes mediated by $PhI(OPiv)_2/BF_3{\cdot}Et_2O$ system.

In conclusion, we developed a highly regioselective and stereoselective metal-free method for the intramolecular oxidative aminofluorination of unactivated terminal alkenes, in which HF–Py acted as the fluorine source in the presence of PhI $(OPiv)_2$ and $BF_3{\cdot}Et_2O$. Without the use of metal reagents, this new transformation represents an efficient method for the preparation of fluorine containing cyclic amines.

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