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Regiospecific Three-Component Aminofluorination of Olefins via Photoredox Catalysis

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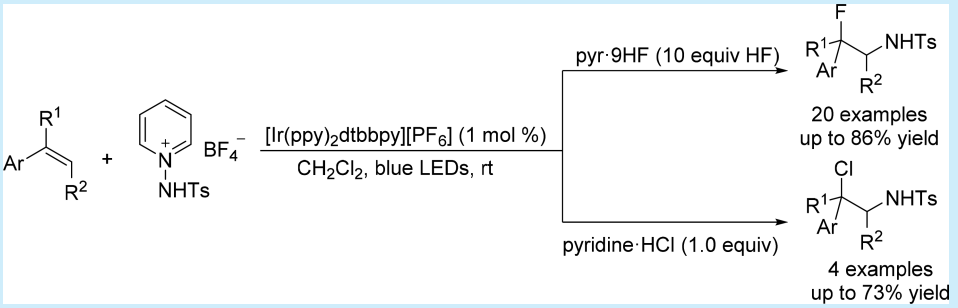
Supporting Information

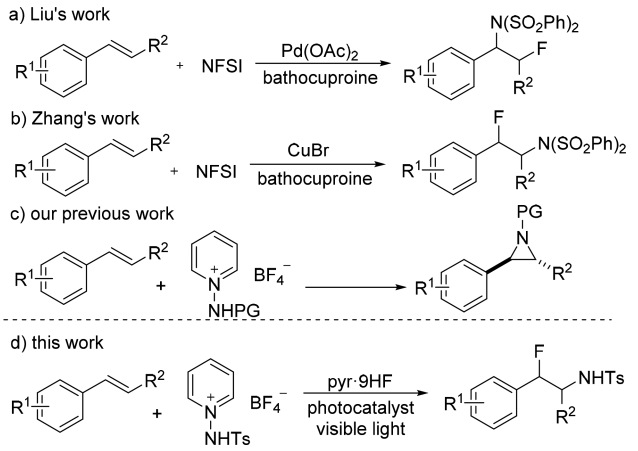


ABSTRACT: Direct visible-light-mediated aminofluorination of styrenes has been developed with high regioselectivity. Shelf-stable *N*-Ts-protected 1-aminopyridine salt was used as the nitrogen-radical precursor, and the commercially available hydrogen fluoride-pyridine was used as the nucleophilic fluoride source. The synthesis of an analogue of **LY503430** was performed to demonstrate the synthetic value of this strategy.

Alkenes are fundamental building blocks for the synthesis of complex molecules. Over the past several decades, vicinal difunctionalization of alkenes has become one of the most versatile approaches to install two functional groups simultaneously to a carbon−carbon double bond.[1] Much attention has been paid to the direct aminofluorination of olefins[2] since the molecules containing the 1,2-aminofluoro moiety constitute the key building blocks for the synthesis of anticancer,[3] anticholinergic, and anti-inflammatory drugs, as well as therapeutic β-peptides.[4]

To synthesize the compounds possessing vicinal amino and fluorine moieties efficiently, a wide variety of olefin amino-fluorination approaches have been developed.[5] For example, one of the most widely used methods is tandem intramolecular amination cyclization followed by intermolecular fluorination.[6] In contrast, only a few methods are currently available to generate β-fluoroamines in an intermolecular three-component fashion.[7] Recently, Liu and co-workers reported an efficient intermolecular aminofluorination of styrenes using *N*-fluoro-benzenesulfonimide (NFSI) as both an amino[8] and a fluorine source by fluoropalladation (Scheme 1a).[9] In addition, Zhang developed a highly regioselective copper-catalyzed radical aminofluorination of styrenes with NFSI, wherein the regioselectivity was complementary to that of palladium catalysis (Scheme 1b).[10] However, significant challenges still exist in the nucleophilic fluorination process because of the high electronegativity and low nucleophilicity of the solvated fluoride ion in organic solvents.[11] We herein describe an efficient visible-light-mediated aminofluorination reaction of styrenes with the fluoride ion (Scheme 1d).

Scheme 1. Direct Aminofluorination of Alkenes for the Construction of the C(sp^3)−F Bond



For the past several years, photoredox catalysis has become one of the fastest growing fields in organic chemistry.[12] Particularly, extensive research efforts have been directed toward visible-light photocatalytic olefin difunctionalization reactions.[13] More recently, the Akita group[14] and our group[15] have developed a series of reactions using shelf-stable *N*-Ts-protected 1-aminopyridine salt as the nitrogen-radical precursor by photoredox catalysis. The precursor, which was

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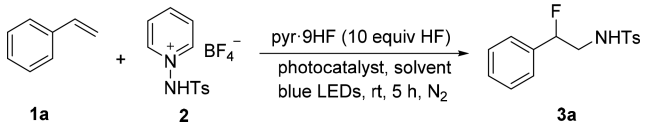
different from the other *N*-radical precursors, could only generate pyridine with concomitant formation of *N*-radicals.[16] Due to the poor nucleophilicity of pyridine, these methods inspired us to construct the C−F bond using hydrogen fluoride-pyridine (Olah's reagent) as the nucleophilic fluorine source.[17]

Initially, the aminofluorination reaction was carried out with styrene (**1a**), *N*-Ts-protected 1-aminopyridine salt (**2**), and pyr·9HF (Olah's reagent) as model substrates. The representative results are summarized in Table 1. When the reaction was performed using $Ir(ppy)_3$ as the photocatalyst at room temperature under irradiation with 25 W blue LED for 5 h, the reaction proceeded to give the expected product **3a** in 37% yield (entry 1). A simple screening of reaction showed that $[Ir(ppy)_2(dtbbpy)][PF_6]$ gave rise to superior results with **3a** being obtained in yield of 79% (entries 2−4). Encouraged by this result, we continued to optimize the reaction conditions to improve the yield. Solvent screening showed that CH_2Cl_2 was an optimal solvent for this transformation (Table 1, entries 5−10). Modulating the ratio of **1a** to **2** led to higher yields (Table 1, entries 11−13). Whether we increased or decreased the amount of pyr·9HF, the yields were significantly reduced (Table 1, entries 14 and 15). Either slight dilution of the reaction mixture or more catalyst loading resulted in a slight decrease of the yield (Table 1, entries 16 and 17). Control experiments clearly confirmed that both the photocatalyst and visible-light irradiation were critical for this process (Table 1, entries 18 and 19).

Table 1. Optimization of the Reaction Conditions[a]



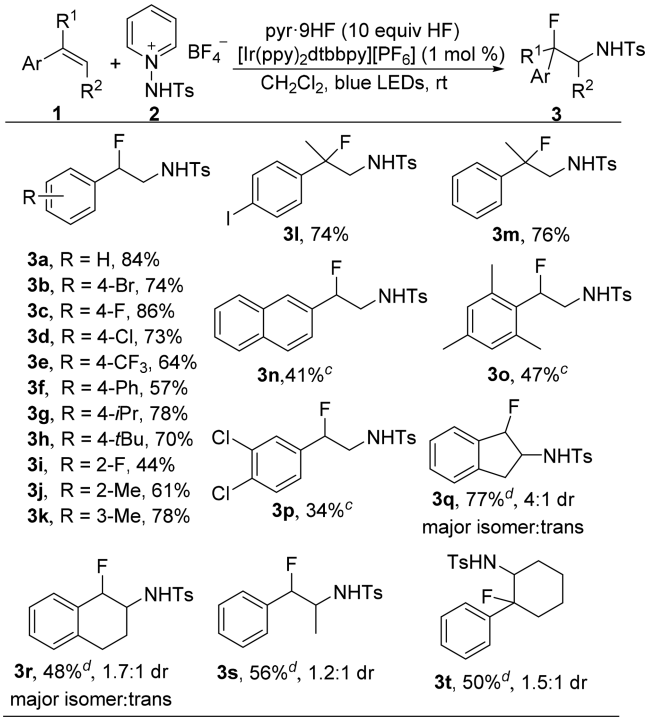
1a **2** **3a**

entry	photocatalyst	1a/2	solvent	yield[b] (%)
1	$Ir(ppy)_3$	1:1.5	CH_2Cl_2	37
2	$Ru(bpy)_3(PF_6)_2$	1:1.5	CH_2Cl_2	trace
3	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$	1:1.5	CH_2Cl_2	trace
4	$Ir(ppy)_2(dtbbpy)\ PF_6$	1:1.5	CH_2Cl_2	79
5	$Ir(ppy)_2(dtbbpy)\ PF_6$	1:1.5	DCE	13
6	$Ir(ppy)_2(dtbbpy)\ PF_6$	1:1.5	$CHCl_3$	23
7	$Ir(ppy)_2(dtbbpy)\ PF_6$	1:1.5	EA	14
8	$Ir(ppy)_2(dtbbpy)\ PF_6$	1:1.5	toluene	N.R.
9	$Ir(ppy)_2(dtbbpy)\ PF_6$	1:1.5	THF	N.R.
10	$Ir(ppy)_2(dtbbpy)\ PF_6$	1:1.5	DMF	N.R.
11	$Ir(ppy)_2(dtbbpy)\ PF_6$	1:1	CH_2Cl_2	67
12	$Ir(ppy)_2(dtbbpy)\ PF_6$	1:1.75	CH_2Cl_2	84
13	$Ir(ppy)_2(dtbbpy)\ PF_6$	1:2	CH_2Cl_2	72
14[c]	$Ir(ppy)_2(dtbbpy)\ PF_6$	1:1.75	CH_2Cl_2	28
15[d]	$Ir(ppy)_2(dtbbpy)\ PF_6$	1:1.75	CH_2Cl_2	9
16[e]	$Ir(ppy)_2(dtbbpy)\ PF_6$	1:1.75	CH_2Cl_2	60
17[f]	$Ir(ppy)_2(dtbbpy)\ PF_6$	1:1.75	CH_2Cl_2	73
18	—	1:1.75	CH_2Cl_2	N.R.
19[g]	$Ir(ppy)_2(dtbbpy)\ PF_6$	1:1.75	CH_2Cl_2	N.R.

[a]Reaction conditions are as follows: **1a** (0.1 mmol), **2** (1−2 equiv), photocatalyst (1 mol %), solvent (2 mL), 25 °C, 25 W blue LEDs under N_2 atmosphere in a sealed plastic vial for 5 h. [b]Isolated yield. [c]5 equiv of HF. [d]15 equiv of HF. [e]4 mL of CH_2Cl_2. [f]2 mol % photocatalyst. [g]In the absence of a light source.

Under the optimized reaction conditions, the substrate scopes of the above aminofluorination reaction (Scheme 2) were explored. A range of styrenes with various electronic properties were compatible with the reaction, and the corresponding fluorosulfonamides **3a−3t** were produced in yields ranging from 34% to 84% with complete regioselectivity. Styrene derivatives carrying halogen substituents at the *para*-position of the arene such as F, Cl, Br, and I were successfully converted to the corresponding aminofluorination products (**3b−3d**, **3l**) in good yields (73%−86%). In addition, dihalosubstituted and trimethyl-substituted styrene also smoothly afforded **3p** and **3o** in 34% and 47% yields, respectively. The substrate bearing an electron-withdrawing CF_3 group provided the corresponding products **3e** in 64% yield. Furthermore, styrene derivatives bearing electron-donating substituents at the *p*-position of the arene ring provided the vicinal fluoroamines (**3f−3h**) in moderate to high yields (57−78%). *Ortho*- and *meta*-substituted styrene derivatives were well tolerated in this conversion (**3i−3k**). It is worth mentioning that 2-vinylnaphthalene afforded **3n** in a slightly lower yield (41%). Additionally, *α*-methylstyrene was also a good substrate (**3m**, 76%).

Scheme 2. Scope of Alkenes in the Intermolecular Aminofluorination Reaction[a]



[a]Reaction conditions: **1** (0.1 mmol), **2** (0.175 mmol), $[Ir(ppy)_2(dtbbpy)][PF_6]$ (1 mol %), CH_2Cl_2 (2 mL), 25 °C, 25 W blue LEDs. [b]Isolated yield. [c]8 h. [d]12 h. [e]Diastereomeric ratio was determined by ^{19}F NMR analysis of the mixture.

To gain more insight into the diastereoselectivity of the reaction, we investigated the aminofluorination of internal alkenes. With internal alkenes such as indene (**1q**), 1,2-dihydronaphthalene (**1r**), *β*-methylstyrene (**1s**), and cyclohexylbenzene (**1t**), the reactions also proceeded in a regiospecific manner, but the products were obtained as mixtures of two diastereomers (**3q−3t**). In addition, we also investigated trisubstituted unsymmetric alkenes such as but-2-en-2-yl benzene, but the reaction did not afford the desired product (see Supporting Information).

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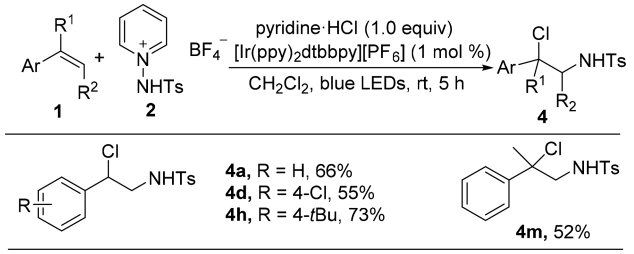
With the success of direct aminofluorination of styrenes, we further explored the possibility of achieving aminochlorination and aminobromination of olefins using nucleophilic halides. It was found that intermolecular aminochlorination of alkenes using pyridine hydrochloride as the Cl donor also demonstrated good efficiency, regioselectivity, and functional group tolerance, although the reactivities of these aminochlorination reactions were slightly lower than those of the corresponding aminofluorination reactions (Scheme 3). Additionally, we were

Scheme 3. Aminochlorination of Alkenes[a]

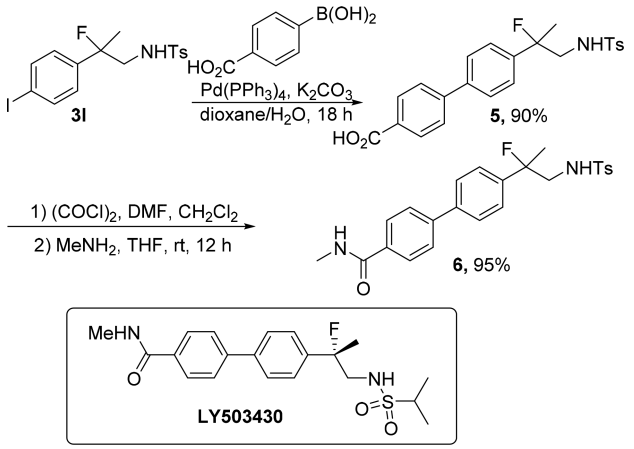


[a]Reaction conditions: **1** (0.1 mmol), **2** (0.175 mmol), [Ir(ppy)$_2$(dtbbpy)][PF$_6$] (1 mol %), CH_2Cl_2 (2 mL), 25 °C, 25 W blue LEDs. [b]Isolated yield.

pleased to find that this reaction system could also be modulated to obtain β-bromoamines using pyridine hydrobromide as the bromide donor, albeit with a low yield of 17% (**10**) (see Supporting Information). We speculated that the strong acidity of hydrobromic acid caused the poor yield.

Having established this strategy for generating the β-fluoroamine skeleton, we next sought to demonstrate the utility of this method in the rapid synthesis of an analogue of **LY503430**, which is a potential therapeutic agent for Parkinson's disease (Scheme 4).[18] The synthesis began with

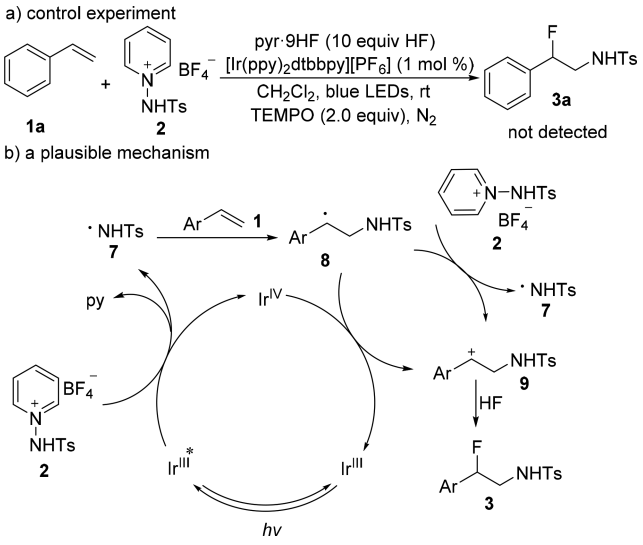
Scheme 4. Synthetic Utility of the Method



a Wittig olefination, which converted 4-iodoacetophenone into the corresponding alkene. Under the optimized conditions, product **3l** was afforded through the aminofluorination process as the key step.[19] Product **3l** was subsequently subjected to Suzuki coupling and amide coupling to provide product **6**, which is an analogue of **LY503430**.[20]

TEMPO trapping experiments were carried out to prove that the aminofluorination process was a radical one. On the basis of the aforementioned control experiments and other reported literature,[21] a putative mechanism is illustrated in Scheme 5. First, the photocatalyst Ir(ppy)$_2$ (dtbbpy)PF$_6$ (Ir^{III})

Scheme 5. A Proposed Mechanism



is excited by visible light to give the excited species (*Ir^{III}), which undergoes oxidative quenching with *N*-Ts-protected 1-aminopyridine salt **2** to give the corresponding radical **7** along with highly oxidizable Ir species Ir^{IV}. Subsequently, the N-centered radicals react with the alkene in a regiospecific manner to give stabilized radical intermediate **8**, which is oxidized by strongly oxidizing Ir species Ir^{IV} to a cationic intermediate **9**, which is trapped by hydrogen fluoride-pyridine to form the final product (**3**). Alternatively, the *N*-Ts-protected 1-aminopyridine salt **2** can act as a chain carrier, whereby it oxidizes benzyl radical intermediate **8** to provide the cationic intermediate **9**. Quantum yield measurements (Φ = 1.167) suggest a chain mechanism is possible (see the Supporting Information for further details).

To our knowledge, this is the first example employing commercially available hydrogen fluoride-pyridine as the nucleophilic fluorine source, thus making it an attractive reagent for synthetic purposes. The practicability of this transformation has also been demonstrated by the efficient synthesis of an **LY503430** analogue.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01760.

Experimental details on experimental procedures for the catalytic reactions and spectroscopic data for the products (PDF)

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Notes

The authors declare no competing financial interest.

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