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COMMUNICATION

Metal-free C-H Amination of Arene with *N*-Fluorobenzenesulfonimide Catalysed by Nitroxyl Radical at Room Temperature

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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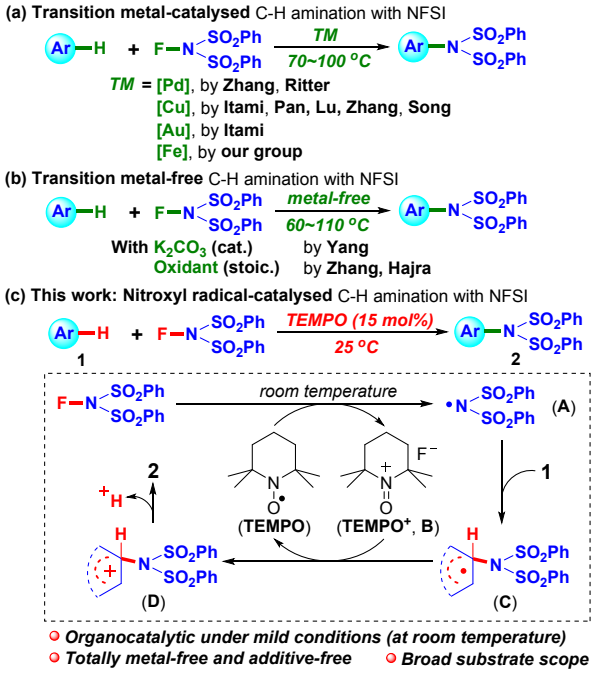
A TEMPO-catalysed direct amination of arene through C-H bond cleavage employing *N*-fluorobenzenesulfonimide (NFSI) as the amination reagent in good to excellent yields with broad arene scope in absence of any metal, ligand or additive is reported. Unlike previous transition metal-catalysed aminations in which high reaction temperatures were usually necessary, this novel reaction at room temperature is the first example of C-H amination with NFSI that is realised through organocatalysis. Probable mechanism of this concise amination is also proposed.

Aminoarenes are among the most privileged scaffolds not only due to their existence in miscellaneous bioactive molecules[1] and functional material,[2] but also owing to their broad application in organic synthesis such as ligands in organometallic chemistry.[3] The introduction of amino groups on arenes is therefore a very significant transformation in organic chemistry. Traditionally, aryl C-N bond formation can be achieved through carbon-halogen bond cleavage in aryl halides, such as copper-mediated Ullman-type amination or amidation,[4] and palladium-catalysed Buchward-Hartwig reaction.[5] However, preactivated arene substrates were required in these reactions. As a concise and atom-economic alternative to such aminations via carbon-halogen bond cleavage, tremendous progress in transition metal-catalysed direct amination of arenes with amines and stoichiometric oxidants through C-H/N-H cleavages has been witnessed during the past few decades.[6] Yet prerequisite directing groups, large excess of arenes, and/or stoichiometric amount of oxidants limited the wide applications of these efficient C-H aminations.

Recently, *N*-fluorobenzenesulfonimide (NFSI), which was usually employed as an electrophilic fluorination reagent, has been broadly used in a variety of aminative functionalization reactions including C-H amination of arenes[7-18] and aminative bisfunctionalization of alkenes[19] or alkynes[20], since it could easily generate an electrophilic amino radical through oxidative addition to transition metals. In 2011, a pioneering work on Pd-catalysed C-H amination of anilides with NFSI was disclosed by Zhang group,[7] followed by another report by Ritter group[8] on Pd- and Ag-cocatalysed C-N coupling with broader arene scope including simple benzenes and some heteroarenes at room temperature. Itami group[9] reported a couple of significant works on copper-catalysed C-H amination of both simple benzene derivatives and miscellaneous heteroarenes with NFSI. Such Cu-catalysed C-N couplings with NFSI have also been reported by Pan,[10] Lu,[11] Zhang,[12] and Song.[13] In addition, the first Au-catalysed and the first Fe-catalysed C-N coupling of



Scheme 1 C-H aminations of arenes with NFSI

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Electronic Supplementary Information (ESI) available: Detailed experimental procedures, ^{1}H and ^{13}C NMR data and spectra. See DOI: 10.1039/x0xx00000x

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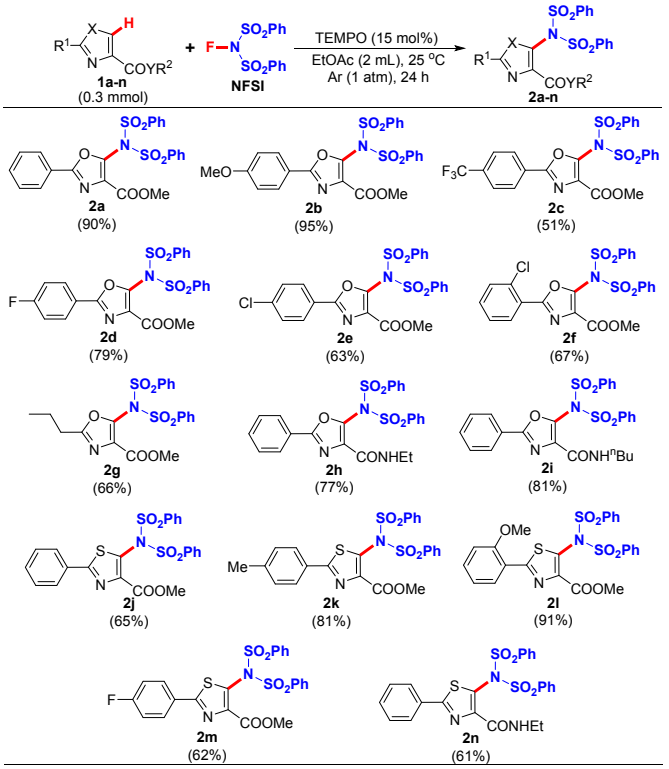
arenes with NFSI have been achieved by Itami[14] and our group[15], respectively, along with a Ni-promoted amidation reported by Wu[16]. Beside the above examples realised via transition metal catalysis (Scheme 1a), transition metal-free aminations with NFSI have been achieved in the presence of catalytic amount of inorganic base[17] or stoichiometric amount of oxidant[18] (Scheme 1b). Except for Ritter's study on the Pd/Ag-cocatalysed amination,[8] all these aminations with NFSI share a common drawback: high reaction temperatures were necessary, probably due to the good stability of NFSI itself, which required elevated temperatures to cleave its N-F bond to generate the active amino radical. Therefore, developing more efficient and environment-benign catalytic approaches to fulfil this C-H amination with broad arene scope under mild conditions is challenging but quite valuable.

Nitroxyl radicals, such as 2,2,6,6-tetramethyl-piperidine-1-oxyl (TEMPO) or its sodium salt (TEMPONa), are environment-benign and highly stable free radicals,[21] which have been widely used as efficient reagents catalysing or mediating miscellaneous oxidative organic reactions via single electron transfer (SET) redox process between TEMPONa and TEMPO, or between TEMPO and its oxoammonium counterpart (TEMPO$^+$). Notably, many of these reactions could be realised at low temperatures. Enlightened by these TEMPO-catalysed or mediated reactions, we proposed that (Scheme 1c), unlike previous transition metal-catalysed amination in which an oxidative addition of NFSI to transition metals at high temperatures provided an imidyl radical (**A**, Scheme 1a),[9b] this radical could alternatively be generated upon oxidation of TEMPO by NFSI at room temperature, along with TEMPO$^+$ (**B**, Scheme 1c),[22] followed by an electrophilic attack of radical **A** to arene substrate **1**, giving an aryl radical **C**.[9b] Subsequently, this aryl radical could be oxidized by **B** due to the high reductive tendency of **B**,[23] which gives an aryl cation **D**[9b] and TEMPO,[22-23] closing the SET redox cycle. The aminated product **2** would eventually be obtained after deprotonation and aromatization.[9b]

Herein, as an advancement of our previous works on aminative functionalization with NFSI,[15, 19i-j] as well as our continuous efforts on transition metal-catalysed C-H functionalizations,[15, 24] we would like to report our recent study on the metal-free TEMPO-catalysed[25] C-H amination of arene with NFSI as the amino precursor at room temperature (Scheme 1c). To our knowledge, C-H amination of arene with NFSI was rarely achieved at room temperature, and it has not yet been realized through organocatalysis.

Our study commenced with the optimization of reaction conditions for this novel nitroxyl radical-catalysed C-H amination, using methyl 2-phenyloxazole-4-carboxylate (**1a**) as the model substrate[15, 24a-g] as summarized in Table S1.[26] Initially, the C5-aminated product **3a** was obtained in 84% yield when **1a** was treated with 4 eq of NFSI and 40 mol% of TEMPO in 2mL of TCE at 25 °C under argon for 12 hours (entry 1), but the yield declined when the loading of TEMPO was decreased (entry 2). Then the screening of solvents (entries 3-8) revealed that, when the reaction time was prolonged to 24 hours, the yield of **3a** was elevated to 88% with 20 mol% of TEMPO in an environment-benign solvent EtOAc (entry 8). This excellent yield could be maintained when decreasing the loading of TEMPO to 15 mol% (entry 9), yet it would decline if further decreasing the loading of TEMPO to 10 mol% (entry 10) or decreasing the loading of NFSI to 3 eq (entry 12). No aminated product was generated in the absence of TEMPO, supporting our proposal that this amination is enabled by the SET redox cycle of TEMPO (entry 11). Therefore, reactions conditions in entry 9 were selected as the optimized conditions for this C-H amination.

Table 1 The TEMPO-catalysed C-H amination of azoles with NFSI[a]



[a] The reaction of azole **1** (0.3 mmol) was performed with NFSI (1.2 mmol) and TEMPO (0.045 mmol) in EtOAc (2 mL) under argon (1 atm) at 25 °C for 24 h. Isolated yields of **2** after column chromatography on silica gel.

With the optimized conditions acquired, miscellaneous substituted oxazoles were first explored for this nitroxyl radical-catalysed C-H amination as shown in Table 1. For 2-phenyloxazole-4-carboxylate substrates (**1a-f**), electron-rich methoxyl-substituted oxazoles provided correspond C5-aminated products **2a-b** in considerably higher yields than elctron-deficient ones did (**2c-f**), suggesting that this amination is probably an electrophilic substitution. However, steric hindrance showed little impact on this reaction, since the *otho*-substituted oxazole **1f** provided its aminated product (**2f**) in an approximate yield comparing to the para-substituted oxazole **1e** did. Beside 2-phenyloxazole-4-carboxylates, this efficient amination at room temperature could react smoothly on 2-alkyloxazole and oxazole-4-formamide, giving corresponding products **2g-i** in moderate to good yields. Moreover, thiazole substrates underwent this facile reaction effectively, providing C5-aminated thiazoles **2j-n** in moderate to excellent yields, and similar patterns on the influence of electron density and steric hindrance were also observed.

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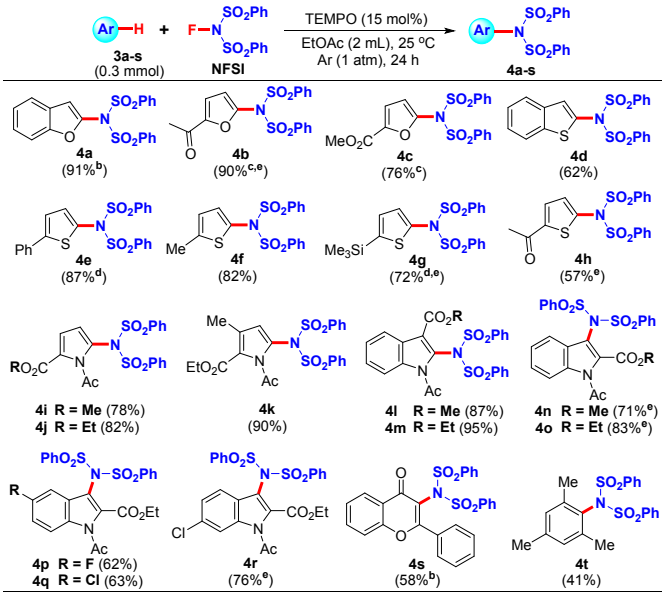
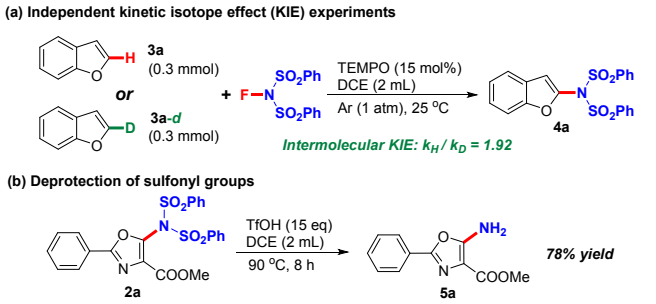
Table 2 The TEMPO-catalysed C-H animation on miscellaneous arenes[a]



[a] The reaction of arene **3** (0.3 mmol) was performed with NFSI (0.6 mmol) and TEMPO (0.045 mmol) in EtOAc (2 mL) under argon (1 atm) at 25 °C for 24 h. Isolated yields of **4** after column chromatography on silica gel. [b] The reactions were conducted in DCE (2 mL). [c] The reactions were conducted in MeCN (2 mL). [d] The reactions were conducted in 1,4-dioxane (2 mL). [e] With 1.2 mmol of NFSI.

Subsequently, a variety of different categories of arenes were explored for this nitroxyl radical-catalysed C-H amination with NFSI as shown in Table 2. Generally, this TEMPO-catalysed C-H amination was conducted efficiently on furan (including benzofuran), thiophene (including thianaphthene), pyrrole, indole and flavone. To our delight, most furans and thiophenes could be aminated effectively with 2 eq of NFSI, while electron-withdrawing acetyl substituted arenes **3b** and **3h** required 4 eq of NFSI to guarantee the good yields. Although the conversions of furans were poor in ethyl acetate, these substrates underwent this C-H amination smoothly in 1,2-dichloroethane or in acetonitrile, affording corresponding C2-aminated furans (**4a-c**) in excellent yields. Likewise, some thiophenes also converted poorly in ethyl acetate, but their C2-aminated thiophenes **4d** and **4g** were obtained in good yields using 1,4-dioxane as the solvent instead. When pyrroles and indoles were employed as the substrates, the C2-aminated products **4i-m** were acquired in good to excellent yields with 2 eq of NFSI. On the other hand, C3-aminated indoles **4n-r** were generated in slightly lower yields when the C2-position was substituted, and increasing the loading of NFSI could elevate their yields (**4n-o**, **4r**). Beside these five-membered heterocyclic arenes, a six-membered heterocyclic arene, flavone, and an electron rich benzene derivative, mesitylene, could also underwent this amination, affording **4s** and **4t** in moderate yields.

To gain more evidence supporting the reaction mechanism proposed in Scheme 1c, several control experiments were conducted. A competition experiment was performed to further elucidate the electronic preference of this amination (Scheme S1).[26] When an equimolecular mixture of oxazoles **1b** and **1d**, or thiophene **3f** and **3h** (0.25 mmol each) was subjected to insufficient loadings of NFSI (0.4 mmol), the electron-rich product **2b** and **4f** was isolated predominantly, indicating that this novel nitroxyl radical-catalysed amination with NFSI is an electrophilic substitution. Meanwhile, when the amination was conducted with D_2O for insufficient reaction time, no deuterium incorporation was observed either on the recovered substrate or the amination product (Scheme S2),[26] suggesting that the cleavage of C-H bond in this amination is irreversible. Interestingly, the value of intermolecular kinetic isotope effect (KIE) was calculated to be 1.92 (Scheme 2a),[26] indicating that the final deprotonation process might be involved in the rate-limiting step in this nitroxyl radical-catalysed amination, which is different from Ritter's Pd/Ag-cocatalysed amination wherein the oxidative addition of NFSI to the palladium catalyst is the rate-limiting step,[8] or from Itami's Cu-catalysed amination wherein the addition of the imidyl radical to the arene is the rate-determining step.[9] It is rather uncommon that the re-aromatisation step from **D** (Scheme 1) should be rate-determining, and the precise mechanism of this amination requires further studies. In addition, the sulfonyl groups could be effectively deprotected with TfOH in DCE while the vulnerable methyl ester group remained intact (Scheme 2b),[26] demonstrating the promising potentials in the application of this TEMPO-catalysed amination.



Scheme 2 KIE and deprotection experiments

In conclusion, a novel nitroxyl radical-catalysed C-H amination with NFSI at room temperature has been described, providing a concise and efficient C-N coupling methodology under mild conditions in absence of any metal, ligand or additive, which is the first example of organocatalysed C-H amination with NFSI. Further studies to fully uncover the precise mechanism of this amination, as well as to expand the arene scope from heteroarenes to simple benzenes, are undergoing.

This work is financially supported by the National Natural Science Foundation of China (No. 21801177). We thank Tao Lu and Dong Yang in this group for reproducing the results of **2b**, **2d**, **2k**, **4c** and **4m**.

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- ***The first C-H amination with NFSI via organocatalysis***
- ***Totally metal-free, ligand-free and additive-free***
- ***Broad substrate scope***
- ***At room temperature***

The first C-H amination of arene with NFSI through organocatalysis is disclosed, which can be achieved at room temperature with broad substrate scope.

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