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Fe-catalyzed Amination of (Hetero)Arenes with a Redox-active Aminating Reagent under Mild Conditions

Jianzhong Liu, [a] Kai Wu, [a] Tao Shen, [a] Yujie Liang, [a] Miancheng Zou, [a] Yuchao Zhu, [a] Xinwei Li, [a] Xinyao Li, [a] and Ning Jiao [a], [b]*

Abstract: A novel and efficient Fe-catalyzed direct C-H amination (NH_2) of arenes is reported using a new redox-active aminating reagent. The reaction is operationally simple, and can be performed under air, mild, and redox-neutral conditions. This protocol with broad substrate scope could be used in the late stage modification of bioactive compounds. Mechanistic studies demonstrate a radical pathway involved in this transformation.

Primary amines are among the most important chemicals and have been widely applied in the synthesis of natural products, pharmaceuticals, agrochemicals, dyes, and polymers.[1] Moreover, primary anilines are various synthons for the preparation of functional arenes such as aryl halides, aromatic nitriles, phenols, azides, boronates, etc. through aryldiazonium intermediates.[2] Traditionally, primary anilines were prepared from arenes through the relay of nitration under strong acidic conditions and the subsequent reduction processes,[3] or the electrophilic amination with limited substrates.[4] In the past century, many approaches to primary anilines including Ullmann-Type cross coupling,[5] Buchwald-Hartwig amination[6] using aryl halides (or pseudohalides), Chan-Lam amination,[7] and metal free reactions using boronic acids as nuclephile,[8] have been significantly developed (Scheme 1a). In these cases, the preactivated arene substrates were required.

Alternatively, direct C-H bond functionalization provides an attractive strategy for C-N bond formation.[9] However, the construction of primary anilines through C-H bond activation is still challenging and has rarely been reported,[10-13] because: 1) The amine precursors and the primary anilines products are usually unstable under the strong oxidative conditions required in most C-H activation reactions; 2) The aniline products may chelate to the metal center and poison the transition metals. According to these problems, by using mild electrocatalysis and photocatalysis, the groups of Yoshida,[10] Nicewicz,[11] as well as Wu and Tung,[12] significantly achieved the amination (NH_2) of normal arenes (Scheme 1b). So far, to the best of our knowledge, the direct C-H primary amination of arenes without the assistance of directing group is still challenging and very desired.

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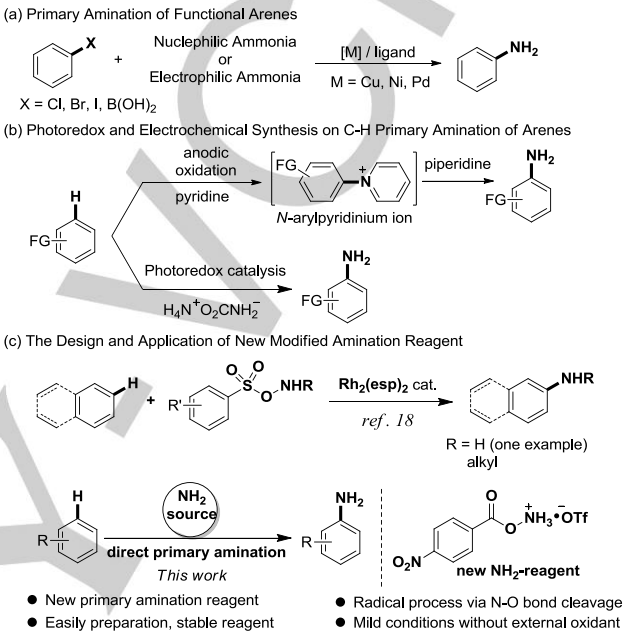

Scheme 1. The Construction of Primary Anilines.

Recently, through the weak N-O bond cleavage, the substrates containing N-O bond could be employed in C-H functionalization obviating the addition of external oxidant.[14,15] This kind of redox-active oxime reagents with N-O bond were elegantly used in C-N [16] bond and C-C bond [17] formations. Inspired by these works, we envisioned that the suitable amine reagent containing N-O bond may provide N-radical through N-O bond cleavage for the amination of arenes. More recently, a significant dirhodium catalyzed arene C-H amination with hydroxylamines was reported by Falck et. al.[18] Herein, we report an efficient Fe-catalyzed primary amination of (hetero)arenes with a redox-active aminating reagent under mild conditions (Scheme 1c).

We commenced our study by investigating the C-H amination of anisole (**1a**) with $PivONH_3OTf$ **2a** which was firstly used in the preparation of substrates containing internal oxidant by Fagnou et. al.[15e] and aminohydroxylation of alkenes by Morandi's group.[19] Unfortunately, no obvious product was obtained (entry 1, Scheme 2). We further prepared the 2,4-dinitrophenyl-hydroxylamine [8b,20] and its triflate derivative (**2b**), which could not produce the desired amination product either (entry 2). Then, we tried to design and prepare new NH_2-reagents by changing a series of good leaving groups on this kind of N-O chemicals. Initially, aminating reagent **2c** with a strong OTs leaving group was synthesized and tested to this reaction. Gratifyingly, the aniline product **3a** was obtained in 16% yield (entry 3). After a

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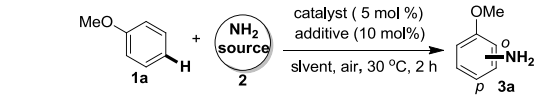
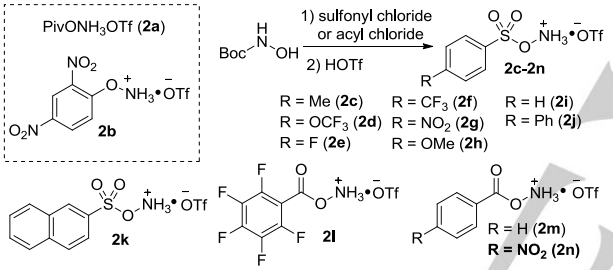
preliminary screening (entries 3-7, Scheme 2, and see SI), we were delighted to find the optimum conditions (entry 7, 48%). Obviously, the reaction did not work in the absence of iron catalyst (entry 6).

Scheme 2. New reagent synthesis and the direct C-H amination of anisole.[a]



entry	catalyst	solvent	additive	NH_2-source	yield of **3a** (%)[b]	*p* : *o*
1	$FeBr_2$	HFIP		**2a**	trace	–
2	$FeBr_2$	HFIP		**2b**	0	–
3	$FeBr_2$	HFIP		**2c**	16	1.8:1
4	$FeBr_2$	TFE		**2c**	40	1.7:1
5	$FeBr_2$	TFE/H_2O (2/1)		**2c**	43	2.0:1
6	–	TFE/H_2O (2/1)	$AgNTf_2$	**2c**	0	--
7	$FeBr_2$	TFE/H_2O (2/1)	$AgNTf_2$	**2c**	48	2.4:1
8	$FeBr_2$	TFE/H_2O (2/1)	$AgNTf_2$	**2d**	25	4.0:1
9	$FeBr_2$	TFE/H_2O (2/1)	$AgNTf_2$	**2e**	24	2.0:1
10	$FeBr_2$	TFE/H_2O (2/1)	$AgNTf_2$	**2f**	41	4.1:1
11	$FeBr_2$	TFE/H_2O (2/1)	$AgNTf_2$	**2g**	35	6.0:1
12	$FeBr_2$	TFE/H_2O (2/1)	$AgNTf_2$	**2h**	16	>50:1
13	$FeBr_2$	TFE/H_2O (2/1)	$AgNTf_2$	**2i-k**	trace	--
14	$FeBr_2$	TFE/H_2O (2/1)	$AgNTf_2$	**2l**	62	1.6:1
15	$FeBr_2$	TFE/H_2O (2/1)	$AgNTf_2$	**2m**	35	3.4:1
16	$FeBr_2$	TFE/H_2O (2/1)	$AgNTf_2$	**2n**	76	1.5:1

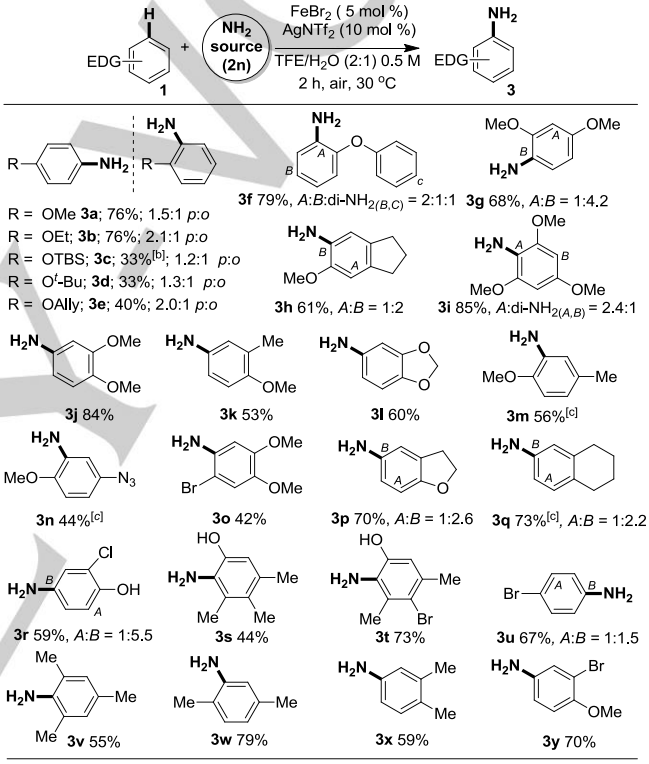


[a] Reaction conditions: **1a** (0.3 mmol), NH_2-source (0.6 mmol), catalyst (5 mol %), additive (10 mol %), solvent (0.5 M), stirred at 30 °C under air, 2h. [b] Isolated yields.

Encouraged by these results, we further modified the designed NH_2-reagent by increase or decrease the electronegativity of the leaving group. Notably, these new animation reagents **2c**-**2n** were easily prepared from readily available tert-butyl hydroxycarbamate and corresponding sulfonyl chlorides or acyl chlorides by two step reactions in gram scale without chromatography (Scheme 2), and were stable at room temperature for several months. Unexpectedly, the efficient improvement was not achieved by these aminating reagents **2d**-**2k**. It is noteworthy that NH_2-reagent **2h** could highly selectively acquire the *para*-amination product albeit in very low yield (entry 12). Although the reason is not clear yet, it may give a chance in the future for the regioselective amination of arenes which is still a challenging issue. Moreover, we employed acyl precursor instead of sulfonyl precursor to prepare aminating reagents **2l**-**2n** (Scheme 2). We were delighted to find that **2n** with *p*-nitrobenzoic acid anion exhibited the best efficiency in this transformation (76% yield, entry 16).

With the optimum conditions in hand, we next explored the scope of arenes with the strong electron-donating groups in the presence of NH_2-reagent **2n**. As summarized in Scheme 3, mono-, di-, tri- and cyclic-alkoxy-substituted arenes underwent the C-H amination quickly at room temperature in moderate to excellent yields (33-84%, **3a**, **3b**, **3g-3m**, **3p**, **3q**). Moreover, the protected phenols (**1c** ,**1d**, **1e**) could also afford the corresponding anilines respectively (**3c** ,**3d**, **3e**). In addition, the amination of 1-methoxy-2-methylbenzene **1k** highly selectively occurred at the para-position of methoxy group affording **3k** in 53% yield. The azido and bromo substituents could be containing in the substrate leading to the corresponding functional anilines **3n** and **3o, 3y** in moderate yields. The unprotected hydroxy group is also tolerated in this transformation (**3r**-**3t**).

Scheme 3. Substrate of arenes with strong electron-donating groups.[a]



[a] Reaction conditions: see entry 16, Scheme 2. [b] NH_2-source (0.45 mmol, 1.5 eq) was used. [c] NH_2-source (0.6 mmol, 2.0 eq) was used for 2 h, then NH_2-source (0.15 mmol, 0.5 eq) was added for another 1 h.

To highlight the broad substrate scope of this process (Scheme 4), we investigated the unactivated arenes without the strong electron-donating groups and heteroarenes which were not reported in previous reports.[10-12] The acetanilide was compatible in this transformation up to 92% yield (**5a**). Moreover, the amination of simple arenes proceeded well affording **5f** and **5g** in excellent yields (70% to 81%). It is noteworthy that C-H amination of benzene under our conditions was more efficient than that with ammonia developed by DuPont (NiO-ZrO_2 catalyst, 350 °C, 300 to 400 atm, 14% maximum yield).[21] In addition, arenes bearing halo substituent at *ortho*, *meta*, *para* (**5b**, **5c**, **5d**) position, steric hindered group (**3d**) were also tolerated. With respect to heteroarenes, we found pyridine, indole, thiophene could also be tolerated in spite of the low efficiency.

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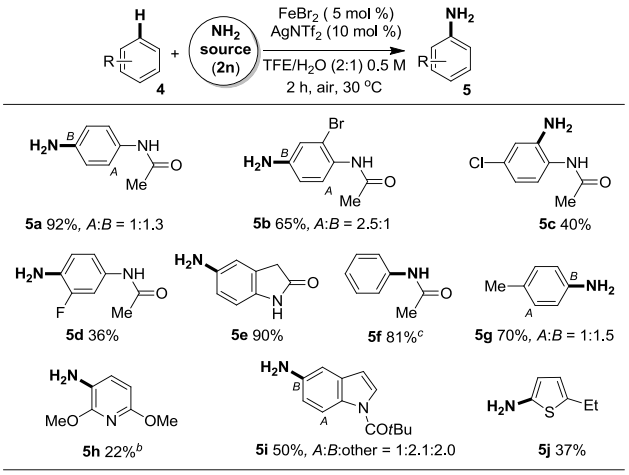
To evaluate whether this catalysis system could be applied to late-stage functionalization of bioactive compounds, we tested the amination protocol with several complex bioactive molecule derivatives (Scheme 5). For instance, ß-D-Galactopyra nocide with

Scheme 4. Substrate of arenes without strong electron-donating groups.[a]



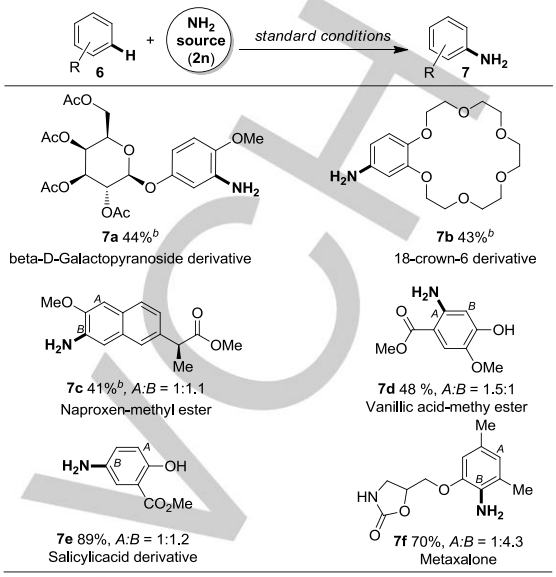
[a] Reaction conditions: 4 (0.3 mmol), NH_2-source (0.6 mmol, 2.0 eq), $FeBr_2$ (5 mol %), $AgNTf_2$ (10 mol %), TFE/H_2O (0.4/0.2, 0.5 M), stirred at 30 °C under air, 2 h, then NH_2-source (0.15 mmol, 0.5 eq) was added for another 1 h. [b] NH_2-source (0.6 mmol, 2.0 eq) was used. [c] The crude product was extracted by DCM, then acetylated by acetyl chloride.

aryl group (**6a**) and 18-crown-6 derivative (**6b**) could afford the single regioisomers of the amination adducts **7a** and **7b** in moderate yields. Naproxen methyl ester (**6c**), vanlliic acid-methyl ester (**6d**) and metaxalone (**6f**) with anti-inflammatory and analgesic effect could also transformed into the corresponding amination products (**7c, 7d, 7f**) in moderate to good yields. In addition, salicylicacid derivative was aminated in good yields albeit poor regioselectivity (**7e**). The *para*-amination-**7e** could be converted to Mesalazine through the simple hydrolysis, which was one of the top 200 pharmaceutical products by US retail sales in 2011 and 2012.

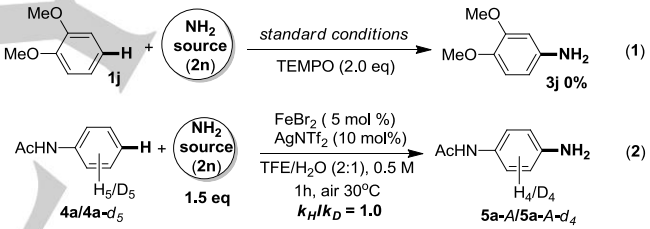
To gain insight into the mechanism, the reaction of **1a** in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) as the radical scavenger were tested, **2a** was completely inhibited in these reactions (eq 1), which suggests that a radical process may be involved in this process. an intramolecular kinetic isotope effect. (KIE) of k_H/k_D = 1.0 was consistent with that anticipated for a radical aromatic substitution pathway (eq 2). To get more information about this transformation, EPR (electroparamagnetic resonance) experiments were conducted with the addition of free radical spin trapping agent DMPO (5,5-dimethyl-1-pyrroline *N*-oxide). Fortunately, some signals of organic radical were observed (Figure 1), which was consistent with the amino radical in previous reports.[22]

On the basis of above results and related work by others, a possible mechanism is proposed in Scheme 2. Outer-sphere single-electron transfer from $FeBr_2$ to the NH_2-reagent initiates the

Scheme 5. Late-stage functionalization.[a]



[a] Reaction conditions: see entry 16, Scheme 2. [b] NH_2-source (0.6 mmol, 2.0 eq) was used for 2 h under standard conditions, then NH_2-source (0.15 mmol, 0.5 eq) was added for another 1 h.



N-O bond cleavage, resulting in the formation of N-radical intermediate **A.**[23] Subsequently, the radical addition for the C-N bond formation between **A** and arene **1** delivers the radical intermediate **B**. Then intermediate **B** is oxidized via a single electron transfer (SET) process by Fe(Ⅲ) to form cationic intermediate **C,** which further undergoes deprotonation assisted by the generated benzoate ($ArylCO_2^-$) affords the product **3**. Alternatively, the deprotonation step by benzoate ($ArylCO_2^-$) might occurs with intermediate **B** to form a radical anion,[24a-b] which then reacts with NH_2-reagent through SET to finally produce **3** and the N-radical intermediate **A** for the next catalytic circle.[24] Besides the radical process, the alternative Friedel-Crafts reactions pathway could not be completely ruled out.

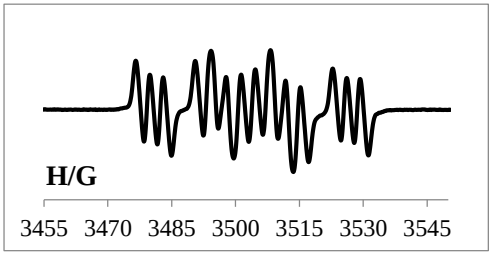


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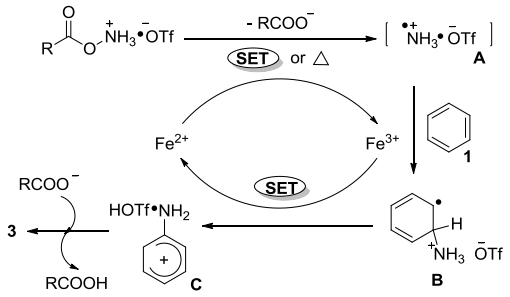
Figure 1. The EPR spectra (X band, 9.7 GHz, RT) of reaction mixture in the presence of the radical trap DMPO (2.5×10-2 M).



Scheme 6. Proposed Mechanism.

In conclusion, a novel and efficient C-H amination is developed by using a new NH_2-reagent. The reaction is operationally simple, and can be performed in air under mild and redox-neutral conditions and can be applied to the late stage modification of bioactive compounds. Preliminary EPR and control experiments indicate that an amino radical is involved. Further application of this aminating reagent are undergoing in our laboratory.

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Keywords: Amination • C-H functionalization • Radical • New reagents • Iron

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C-H Amination

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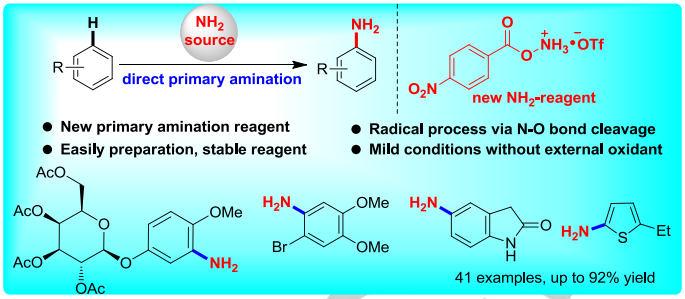
Fe-catalyzed Amination of (Hetero)Arenes with a Redox-active Aminating Reagent under Mild Conditions



A novel and efficient Fe-catalyzed direct C-H amination of arenes is reported using a n redox-active aminating reagent. Mechanistic studies demonstrate a radical pathw involved in this transformation.