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Received 00th January 20xx, Accepted 00th January 20xx **Double C-H Amination by Consecutive SET Oxidations** 

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A new method for intramolecular C-H oxidative amination is based on a FeCl<sub>3</sub>-mediated oxidative reaction of anilines with activated sp<sup>3</sup> C-H bonds. The amino group plays multiple roles in the reaction cascade: 1) as the activating group in single-electrontransfer (SET) oxidation process, 2) as a directing group in benzylic/allylic C-H activation at a remote position, and 3) internal nucleophile trapping reactive intermediates formed from the C-H activation steps. These multielectron oxidation reactions proceed with catalytic amounts of Fe(III) and inexpensive reagents.

C-N bonds can be formed in a variety of ways, from the venerable Hofmann-Loffler-Freytag N-haloamine homolysis to oxidation of C,N-dianions and nitrene insertion.<sup>1</sup> The recent advances in direct functionalization of C-H bonds expanded the list of available chemical strategies.<sup>2,3</sup> The new C-H functionalization approach suggests that the methods for carbon-nitrogen double bond formation can go beyond the traditional condensation of an amine with a carbonyl.



Scheme 1 Two general strategies for C=N bond formation

Transition-metal-mediated (TMM) C-H amination represents a valuable method for adding functionality<sup>4</sup> dating back to the early reports of Fe- and Rh-mediated nitrene formation by Breslow and Gellman.<sup>5</sup> Unlike the most commonly used Rh-catalyzed C-H aminations,<sup>6</sup> the Co-,<sup>7</sup> Cu-,<sup>8</sup> Mn-,<sup>9</sup> and Fe-mediated<sup>10</sup> C-H aminations are believed to proceed through a single electron pathway (recent works illustrated in Figure 1).<sup>11</sup>

Herein, we describe a direct intramolecular C-H amination



Figure 1 Examples of intramolecular C-H aminations with present work.

involving *o*-substituted-anilines,FeCl<sub>3</sub>, and 2,3-dichloro-5,6dicyano-1,4-benzoquinone (DDQ) for the preparation of aromatic N-heterocycles.

When designing substrates for oxidative C-H amination, we started with *o*-functionalized anilines. When making this choice, we envisioned that the amino group can play three synergistic roles in the reaction cascade: 1) as the activating group in single-electron-transfer (SET) oxidation process, 2) as a directing group for C-H activation at a remote position, and 3) as the internal nucleophile trapping the cation formed from the C-H activation steps. Extended conjugation can stabilize the radical and cationic species formed after the initial SET oxidation/deprotonation steps (Scheme 2).<sup>12</sup>



Scheme 2 Strategy for intramolecular TMM SET oxidative amination

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<sup>+</sup> Electronic supplementary information (ESI) available: Experimental procedures and characterization data for new compounds. For ESI see DOI: 10.1039/x0xx00000x

Table 2 Optimization of reaction conditions





Experimental values were measured by differential pulse voltammetry with a glassy carbon working electrode, Pt counter electrode, and Ag wire reference electrode in a 0.1 M TBACIO<sub>4</sub> MeCN solution with ferrocene as an internal reference. <sup>a</sup>From reference 13.

The desired o-functionalized anilines are readily accessible via multiple robust routes derived from the Wittig, Grignard and Suzuki reactions (Scheme 3, full details in SI). These methods allowed us to prepare a diverse library of substrates in moderate to good yields. With substrates in hand, we first investigated the oxidation potentials of substrates 1a and 1p to test the feasibility of the initial SET step. The oxidation potentials for 1a and 1p (0.52V and 0.55V, respectively, vs. Fc/Fc<sup>+</sup>) suggesting that SET oxidation is a viable platform for the desired transformation.

first attempt using Our FeCl₃ (1 eq.), tertbutylhydroperoxide (TBHP, 4 eq.) in acetonitrile (80°C) with 1a yielded 5a in 56% (see SI for full details). Encouraged by this result, we tested other oxidants in this reaction (DDQ (0.05 V vs. Fc/Fc<sup>+</sup>), TBHP (0.07 V), DTBP (-0.1 V))<sup>14</sup> and found that DDQ outperformed other oxidants. Two equivalents of DDQ were needed for full conversio transition metals that ha TMM-SET oxidation react as Ti<sup>IV</sup>, Zn<sup>II</sup>, Cu<sup>I</sup> and Co<sup>II</sup> sa were poor. However, Fe<sup>II</sup> transformation and provid product. FeCl<sub>3</sub> provided slightly higher yields over FeCl<sub>2</sub> (entries 8 and 5 in Table 2). Other Fe<sup>III</sup> salts (Fe(acac)<sub>3</sub>, FeCl<sub>3</sub>•6H<sub>2</sub>O) provide comparable yields of 62% and 60%, respectively. Aprotic solvents were favored with acetonitrile providing highest yields. At room temperature, only trace amounts of 5a were observed. Elevated temperatures were needed to achieve full conversion (see SI for full details). We found that sub-stoichiometric quantities (20 mol%, entry 12) were sufficient for driving reaction to completion. Under the optimal conditions, i.e, FeCl<sub>3</sub> (20 mol%), DDQ (2 eq.) in acetonitrile at 80°C gave the target product in 86% yield.

on of <b>1a</b> . We next tested first row					
we been shown to undergo similar					
ions. <sup>7</sup> For the other Lewis acids such					
alts, the observed conversions/yields					
and Fe <sup>III</sup> salts facilitated the desired					
ded high yields of the C-H amination					

	NH <sub>2</sub> Ph	Conditions	→	5CC03106D Ph 5a
Entry	Metal	Oxidant	Solvent	Yield% <sup>g</sup>
1	Co(acac) <sub>2</sub> <sup>a</sup>	DDQ <sup>c</sup>	CH₃CN	trace
2	TiCl <sub>4</sub> <sup>a</sup>	DDQ <sup>c</sup>	CH₃CN	20
3	Cul <sup>a</sup>	DDQ <sup>c</sup>	CH₃CN	60
4	ZnCl <sub>2</sub> <sup>a</sup>	DDQ <sup>c</sup>	CH₃CN	0
5	FeCl <sub>2</sub> <sup>a</sup>	DDQ <sup>c</sup>	CH₃CN	66
6	$FeCl_3 \bullet 6H_2O^a$	DDQ <sup>c</sup>	CH₃CN	60
7	Fe(acac)₃ <sup>a</sup>	DDQ <sup>c</sup>	CH₃CN	62
8	FeCl <sub>3</sub> <sup>a</sup>	DDQ <sup>c</sup>	CH₃CN	69
9	FeCl <sub>3</sub> <sup>a</sup>	<b>TBHP</b> <sup>c</sup>	CH₃CN	61
10	FeCl <sub>3</sub> <sup>a</sup>	DTBP <sup>c</sup>	CH₃CN	59
11	FeCl <sub>3</sub> <sup>a</sup>	BPO <sup>c</sup>	CH₃CN	51
12	FeCl <sub>3</sub> <sup>a</sup>	$Na_2S_2O_8^c$	CH₃CN	40
13	FeCl <sub>3</sub> <sup>b</sup>	DDQ <sup>c</sup>	CH₃CN	86
14	None	DDQ <sup>c</sup>	CH₃CN	31
15	FeCl <sub>3</sub> <sup>b</sup>	$DDQ^d$	CH₃CN	81
16	FeCl <sub>3</sub> <sup>b</sup>	DDQ <sup>e</sup>	CH₃CN	45
17	FeCl <sub>3</sub> <sup>b</sup>	None	CH₃CN	trace
18	FeCl <sub>3</sub> <sup>b</sup>	DDQ <sup>c</sup>	CIC <sub>6</sub> H <sub>6</sub>	78
19	FeCl <sub>3</sub> <sup>b</sup>	DDQ <sup>c</sup>	$C_6H_6$	75
20	FeCl <sub>3</sub> <sup>b</sup>	DDQ <sup>c</sup>	DMF	14
21	FeCl <sub>3</sub> <sup>b</sup>	DDQ <sup>c</sup>	EtOH	trace

Reaction conditions: 1a (1 eq.), specified amount of metal (a 100 mol%, b 20 mol%) and oxidant; <sup>c</sup> 2 eq., <sup>d</sup> 3 eq., <sup>e</sup> 1 eq.) in 4 mL of solvent. Reactions were allowed to stir for 4 hours with heating bath set to 80°C. <sup>g</sup> NMR yield based on 1a and determined by internal standard (Ph<sub>3</sub>CH).

We then set out to investigate the role of C-H bond strength by varying substituents at the sp<sup>3</sup> carbon: from hydrogen to alkyl, aryl, vinyl, ether, and amine groups (Table 3). For the benz-allyl and bi-aryl substituents, the reaction works well to provide the corresponding aromatic products 5a, and 5I (Table 4). Mono-functionalized substrates 1b and 1c gave poor conversions with no detectable amounts of phenanthridine **5b** or quinoline **5c**.<sup>15</sup> Although C-H amination still occurred for substrates 1d and 1e, the heteroatom group was lost from the allylic and the benzylic positions via C-X bond

Table 3 Scope of sp<sup>3</sup>C-H activation



Reactions performed under conditions. optimized Complex mixture of byproducts with no detectible amount of desired aromatic product. Fragmented aromatic Nheterocycle was isolated as only product. <sup>c</sup> Substrate was synthesized via Wittig method as E:Z (1:3) mixture. <sup>D</sup> Substrate was prepared via Suzuki method as the pure Eisomer. e Yields are based on <sup>1</sup>H NMR with internal standard (CHPh<sub>3</sub>). f Yields are based on isolated products.

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scission to afford the quinoline **5d** and phenanthridine **5e**, respectively. This process is similar to deprotection of benzyl ethers and amines to the corresponding aldehyde under oxidative conditions, and is believed to proceed through a SET oxidation mechanism, which is consistent with the mechanistic hypothesis of the present work.<sup>16</sup>

In the case of the allyl systems, the alkene geometry was critical for the success of the reaction. When a E:Z (1:3) mixture of isomers of **1a** was used, full conversion of substrate **1a** was observed with a yield of 83% for quinoline **5a**. However, when the pure E isomer **1aE** was used instead, poor conversion of **1aE** and a low yield of 30% for quinoline **5a** were observed. Diminished yields are attributed to slow E:Z isomerization. Based on these results, we concentrated on benz-allylic (accessed via Z-selective routes) and di-benzylic substrates for the remainder of this work.

Substrate scope has shown that the reaction proceeds readily with di-functionalized sp<sup>3</sup> C-H bonds and accepts a variety of functional groups and substituent patterns. Interestingly, not only electron-withdrawing (e.g.,  $-CF_3$ , -CN) substituents but also moderately electron-donating groups (e.g., -OMe,  $-CH_3$ ) were compatible with the reaction conditions (Table 4). Halogens such as CI and F were tolerated in the reactants to afford products **5j** and **5l** in good yields. Efficiency was retained when substituents were introduced at the alkene (Me, Ph) to provide **5n** and **5o** in good yields. Ester functionality did not interfere with the preparation of compound **5n**.

Additionally, mechanistic studies were performed to detect key intermediates in this transformation. A plausible pathway is through the Fe-assisted SET oxidation with DDQ. Interestingly, when a control experiment was conducted using **6a** under modified reaction conditions with  $H_2O:CH_3CN$  (1:1),



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**6b** and **6c** were observed (equation (1)). Additionally, when **6a** was subjected to similar conditions with 1 eq. of 2-bromo-4-chloroaniline,<sup>17</sup> the reaction turned deep blue indicative of aniline polymerization.<sup>18</sup> Both **6a** and the aniline were partially reclaimed (equation (2)). It is possible that compound **3** is oxidized further under the reaction conditions. This scenario is supported by the rapid conversion of **3a** to the aromatic product **5a** under oxidative conditions.<sup>19</sup>

On the basis of the above results, product scope and literature precedents such as recent work by Pandey and Laha which describe an intermolecular visible light catalyzed benzylic C(sp<sup>3</sup>)-H amination by "anomeric" amides,<sup>20</sup> one can envision a mechanism proposed in Scheme 4.<sup>10,11</sup> Initially, **1** will undergo SET oxidation with DDQ to produce radical-cation **1'**, which is then deprotonated by DDQ radical-anion. Two sites of deprotonation are possible (nitrogen or benzylic carbon) but both paths converge to afford **2a** (with deprotonation at nitrogen followed by intramolecular H-atom transfer). This radical undergoes SET oxidation to cation **2b**. This cation can





Scheme 4 Proposed mechanism for product formation.

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be trapped by the pendant amine group to arrive, after the loss of H<sup>+</sup>, at a putative intermediate **3**. Another iron-mediated SET oxidation with DDQ converts **3** to radical **4a**. This cyclic radical then undergoes further oxidation to arrive at **5**.

In summary, we have developed a novel protocol for the preparation of N-heterocycles via intramolecular sp<sup>3</sup> C-H amination under Fe-assisted SET oxidation with DDQ. This methodology offers a novel approach to intramolecular C-H aminations in route to N-heterocyclic compounds.

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