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Redox-Selective Iron Catalysis for α-Amino C−H Bond Functionalization via Aerobic Oxidation

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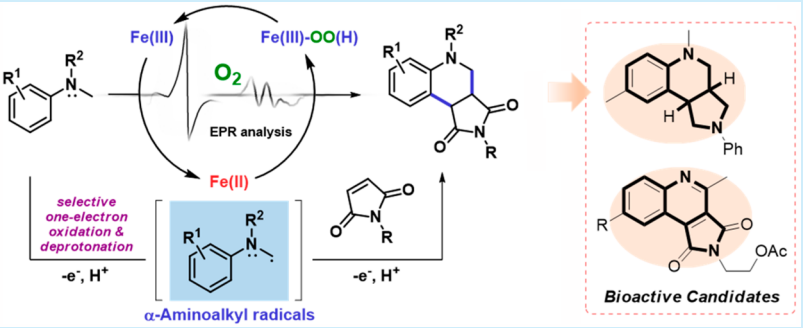
Supporting Information



ABSTRACT: Single-electron oxidation and α-deprotonation of tertiary anilines using $Fe(phen)_3(PF_6)_3$ afford α-aminoalkyl radicals, which can be coupled with electrophilic partners to afford various tetrahydroquinolines. Mechanistically, the $Fe(phen)_n^{2+/3+}$ catalytic cycle is maintained by O_2 or a TBHP oxidant, and the presence of the oxygen bound iron complex, Fe(III)−OO(H), was elucidated by electron paramagnetic resonance and electrospray ionization mass spectrometry. This redox-selective nonheme iron catalyst behaves similarly to bioinspired heme iron catalysts.

Transition-metal catalyzed C−H bond functionalization is an important synthetic strategy that still suffers from some impediments:[1] (1) a directing group is needed to control the chemo-, regio-, and stereoselectivity; (2) expensive and rare transition metals (Pd, Ru, Rh, and Ir) are often used; (3) reactions typically focus on $C(sp^2)$−H bonds; and (4) dual functionalization of both a $C(sp^3)$−H and a $C(sp^2)$−H bond in a single step is rare. Therefore, the continued development of economical and sustainably novel methods for the functionalization of $C(sp^3)$−H bonds is highly desirable, employing the more abundant metals.[2]

A one C−H bond functionalization method, preparation of the carbon radical, has become an essential synthetic tool,[3] and activating the α-amino $C(sp^3)$−H bond to convert it to the α-aminoalkyl radical would be a valuable endeavor due to the versatile reactivity and valuable compounds produced.[4] Functionalization of α-amino $C(sp^3)$−H bonds typically occurs via the oxidation of amines. However, thoughtful design of amine oxidation is important due to the competitive oxidative routes possible for amines. Single-electron oxidation of amines and subsequent deprotonation convert the amine radical cation to the nucleophilic α-aminoalkyl radical, which can add to electron-deficient alkenes or aromatics.[5] Additionally, hydrogen atom abstraction of the amine radical cation readily forms the electrophilic iminium ion.[6] Alternatively, single electron oxidation of the α-aminoalkyl radical can also give the iminium ion. Various metal oxidants (Mn, Cu, Co, Ce)[7] and nonmetal oxidants ($K_2S_2O_8$, TBAI/TBHP)[8] have been explored under nonirradiative conditions for the cycloaddition reactions of α-aminoalkyl radicals. However, in most of these cases, more than 10 mol % of the metal oxidant and superstoichiometric amounts of a co-oxidant were employed. While recent research has also been directed toward photocatalysis by UV[9] or visible light irradiation with Ru, Ir, Cu, Ni,[10] and an organic photosensitizer,[11] the use of iron catalysts for the activation of α-amino $C(sp^3)$−H bonds deserves further investigation due to the sustainable and redox properties of iron.

Current Fe catalytic systems for the oxidation of amines only involve iminium ion intermediates, which usually undergo Mannich reactions with various carbon and heteroatom nucleophiles.[12] When the *N*-aryl iminium ion reacts with dienophiles as described in Scheme 1a, cross-dehydrogenative coupling (CDC) or dehydrogenative [4 + 2] cycloaddition reactions proceeded to produce quinolines and tetrahydroquinolines.[13] Our strategy, described herein, is *the first α-aminoalkyl radical formation under Fe catalysis with O_2 to afford tetrahydroquinolines via addition to electron-deficient alkenes and subsequent cyclization reactions*. In this letter, Fe-polypyridyl complexes are shown to be a single-electron oxidant of *N*,*N*-dialkylanilines, and the role of O_2 as the terminal oxidant is shown using several analytic experiments including electron paramagnetic resonance (EPR).

We initially focused our studies on the reaction of 4-methyl-*N*,*N*-dimethylaniline (**1a**) and *N*-phenylmaleimide (**2a**) with

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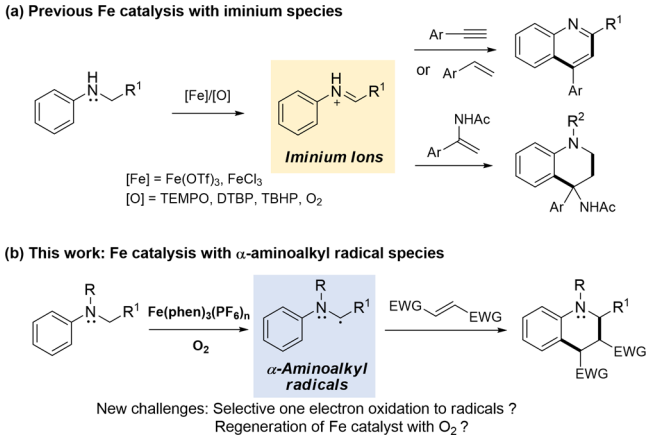
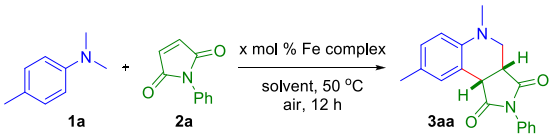
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Fe-Catalyzed α-Amino C(sp³)−H Functionalization in [4 + 2] Cycloaddition



the iron complex $Fe(phen)_3(PF_6)_3$ under air (Table 1). To our delight, tetrahydroquinoline (**3aa**) was produced in 77% yield,

Table 1. Optimization of the Reaction Conditions[a]



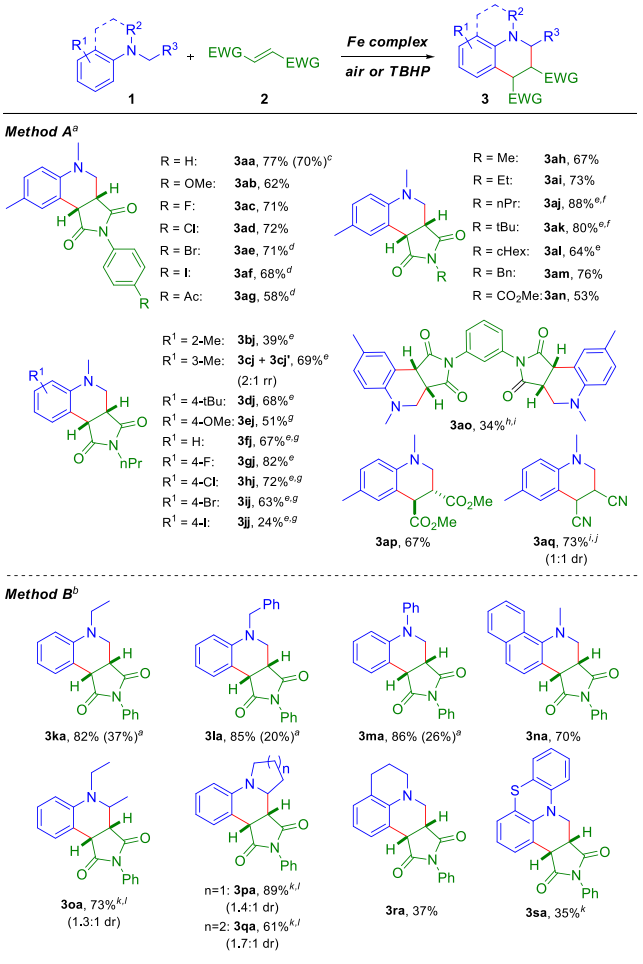
entry	Fe complex (*x*)	solvent	yield (%)[b]
1	$Fe(phen)_3(PF_6)_3$ (5)	DMSO	77
2[c]	$Fe(phen)_3(PF_6)_3$ (5)	DMSO	62
3[c]	$Fe(phen)_3(PF_6)_3$ (10)	DMSO	49
4[d]	$Fe(phen)_3(PF_6)_3$ (5)	DMSO	74
5	$Fe(Me_4phen)_3(PF_6)_3$ (5)	DMSO	67
6	$Fe(Ph_2phen)_3(PF_6)_3$ (5)	DMSO	58
7	$Fe(bpy)_3(PF_6)_3$ (5)	DMSO	59
8	$Fe(^tBu_2bpy)_3(PF_6)_3$ (5)	DMSO	60
9	$Fe(phen)_3(PF_6)_2$ (5)	DMSO	69
10	$Fe(phen)_3(PF_6)_3$ (5)	NMP	47
11	$Fe(phen)_3(PF_6)_3$ (5)	DMF	27
12	$Fe(phen)_3(PF_6)_3$ (5)	CH_3CN	6
13	$Fe(phen)_3(PF_6)_3$ (5)	DCE	4
14	$Fe(phen)_3(PF_6)_3$ (5)	DCM	2
15	–	DMSO	–
16[e]	$Fe(phen)_3(PF_6)_3$ (5)	DMSO	trace

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.1 mmol), solvent (0.1 M), 50 °C, under air for 12 h. [b]Isolated yield. [c]Reaction with 0.2 mmol of **1a**. [d]Reaction at 70 °C. [e]Under N_2. phen = 1,10-phenanthroline, Me_4phen = 3,4,7,8-tetramethyl-1,10-phenanthroline, Ph_2phen = 4,7-diphenyl-1,10-phenanthroline, bpy = 2,2′-bipyridine, $^tBu_2$bpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine.

suggesting that the Fe(III) complex could act as a single-electron oxidant and selectively oxidize the dimethylaniline to a nucleophilic α-aminoalkyl radical species (entry 1). Increasing the amount of the iron complex or the reaction temperature did not satisfactorily improve the isolated yield (entries 3−4). Furthermore, various polypyridyl ligands were utilized, but the $Fe(phen)_3(PF_6)_3$ catalyst was determined to be the optimal Fe(III) complex to effect this selective oxidation to radical intermediates (entries 5−8).[14] Remarkably, the Fe(II) complex also afforded the formation of **3aa**, which suggests that Fe(III) and Fe(II) may be simultaneously involved in the aerobic catalytic cycle (entry 9). Similar to previous studies,[10a,c,11b] solvent selection was shown to have a significant effect on the reaction (entries 10−14). While moderate results were observed in polar solvents such as NMP and DMF, the use of nitrile-containing and chlorinated solvents provided only trace amounts of product **3aa**. Control experiments verified the importance of each reaction component. Experiments conducted in the absence of the Fe catalyst failed to generate any product (entries 15−16).[15]

With the best reaction conditions established, the generality of this novel aerobic Fe catalysis was investigated with different anilines **1** and alkenes **2** (Scheme 2). *N*-Arylmaleimides substituted with electron-donating or -withdrawing groups were tested, and the corresponding addition/cyclization sequence products **3aa**−**ag** were obtained in good yields, while *N*-arylmaleimides incorporating 4-Br, I, and Ac functional groups required a larger amount of the catalyst and a longer reaction time. Reaction with *N*-aliphatic maleimides as

Scheme 2. Substrate Scope of Anilines with Maleimides



[a]Reaction conditions (Method A): **1** (0.5 mmol), **2** (0.1 mmol), $Fe(phen)_3(PF_6)_3$ (5 mol %), DMSO (0.1 M), 50 °C, 12 h, under air. [b]Reaction conditions (Method B): **1** (0.5 mmol), **2** (0.1 mmol), $Fe(phen)_3(PF_6)_2$ (1 mol %), TBHP (0.15 mmol), CH_3CN (0.1 M), rt, 12 h, under N_2. [c]Reaction with 1 mmol scale of **2a**. [d]Reaction with 15 mol % of $Fe(phen)_3(PF_6)_3$. [e]Reaction with 7 mol % of $Fe(phen)_3(PF_6)_3$. [f]Reaction for 16 h. [g]Reaction at 70 °C. [h]Reaction with 1 mmol of **1a**. [i]Reaction for 24 h. [j]Reaction at 90 °C. [k]Reaction in DCE (0.1 M). [l]Reaction at 45 °C.

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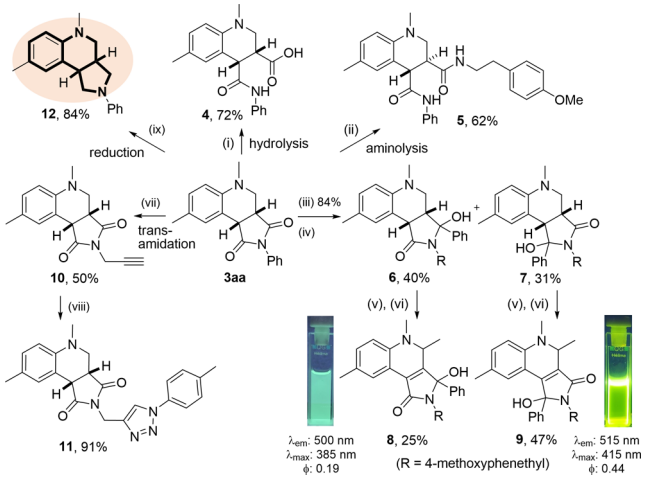
Org. Lett. XXXX, XXX, XXX−XXX

well as *N*-methoxycarbonylmaleimide also proceeded smoothly to afford the desired heterocyclic scaffolds (**3ah**−**an**). The radical addition/cyclization reaction with *ortho*-methyl substituted anilines proceeded sluggishly (**3bj**, 39%), most likely due to steric effects. The cyclization of 3-methyl substituted dimethylaniline occurred both ortho and para to the methyl substituent with a 2:1 regioisomeric ratio (**3cj** and **3cj′**). Various *N*,*N*-dimethylanilines incorporating 4-^{t}Bu, 4-OMe, 4-H, and 4-X delivered a range of tetrahydroquinolines in good to high yield. When bismaleimide was used, dimeric product **3ao** was formed. The reaction with (*E*)-fumaronitrile required a higher temperature (90 °C) to proceed and resulted in the formation of a 1:1 diastereomeric mixture, indicating that this addition/cyclization reaction is performed in a stepwise manner rather than a concerted one.

Substrates other than dimethylanilines were more challenging. In the reaction of **1k**−**m** having two different *N*-alkyl groups, aminomethyl radicals were exclusively generated and C−C bond formation took place on the *N*-methyl carbon. Owing to the low yield (20−37%) for the formation of **3ka**−**ma** under the Fe(III)/O_2 system (Method A), additional oxidants were examined to further promote the catalytic cycle (Table S3). Among the peroxide oxidants tested, the best result was obtained when TBHP was used with only 1 mol % of $Fe(phen)_3(PF_6)_2$ in MeCN (Method B). The reaction of *N*-methyl-lacking tertiary anilines generated the corresponding tetrahydroquinolines **3oa**−**qa** in good to excellent yield under elevated temperature (45 °C), as a roughly 1.3:1−1.7:1 mixture of diastereoisomers. It is noteworthy that the generation of secondary aminoalkyl radicals is limited to access by the previously reported SET oxidation of amines.[10a] Complex heterocyclic skeletons could be constructed, resulting in hexahydropyridoquinoline **3ra** and dihydropyridophenothiazine **3sa** in moderate yields.

We investigated the synthetic usefulness of the tetrahydroquinoline core structure (Scheme 3). Treatment with NaOH afforded the hydrolyzed product **4**,[16] and stereoselective aminolysis was performed to afford diamide **5** via the

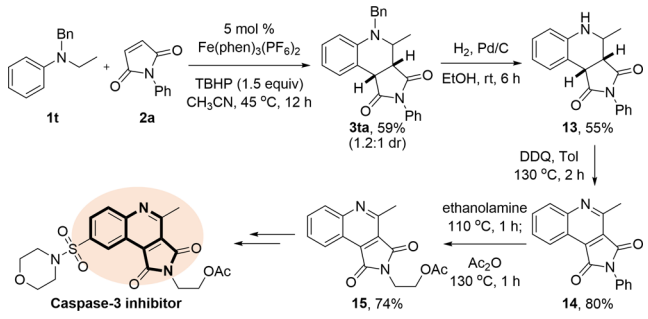
Scheme 3. Synthetic Application[a]



[a]Conditions: (i) NaOH, H_2O, rt; (ii) 4-methoxyphenethyl amine, DMAP, rt; (iii) 4-methoxyphenethyl amine, DMAP, 110 °C; (iv) PhMgBr, THF, 0 °C; (v) TFA, 90 °C; (vi) MeMgBr, THF, 0 °C; (vii) propargyl amine, DMAP, 110 °C; (viii) $CuSO_4$−$5H_2O$, tolyl azide, sodium ascorbate, DCM/H_2O, rt; (ix) DIBAL, DCM, 0 °C.

ring-opened ketene intermediate.[17] Furthermore, higher reaction temperatures promoted the recyclization to the *N*-phenethylmaleimide, which is expected to be a useful late stage strategy to convert the aryl amide to an alkyl amide. *N*-Phenethylmaleimide was transformed into the regioisomeric mixture of hydroxy pyrrolidinones **6** and **7**, and further oxidation followed by methylation produced photophysically attractive compounds **8** and **9**, respectively. The propargyl group introduced through transamidation smoothly reacted with the aryl azide affording product **11**. DIBAL reduction selectively furnished the hexahydropyrroloquinoline **12**, the core structures of which are mainly found in 5-HT_{2c} antagonists or serotonin receptors.[18] This methodology could also be used to synthesize the caspase-3 inhibitor, Ivachtin (Scheme 4). Benzylated tetrahydroquinoline **3ta** was formed in

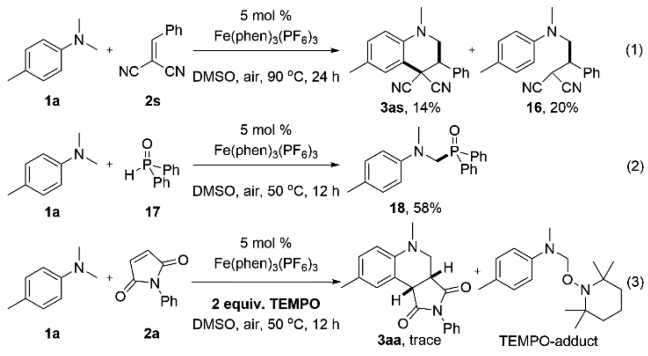
Scheme 4. Synthesis of Pyrrolo[3,4-*c*]quinolone-1,3-dione



good yield from benzylethylaniline **1t**. Cleavage of the Bn group and subsequent DDQ oxidation afforded pyrrolo[3,4-*c*]quinoline-1,3-dione **14**. Late-stage transamidation and acylation produced the desired precursor **15**, which could be transformed into the capase-3 inhibitor.[19]

A series of radical inhibition experiments confirmed that the radical formation process occurs in Fe catalysis (Scheme 5). A

Scheme 5. Mechanistic Investigation



well-known radical scavenger of α-aminoalkyl radicals, 2-benzylidenemalononitrile **2s**, transformed to the cyclization product **3as** and the addition product **16** in a combined 34% yield.[10b] Additionally, α-aminoalkyl radicals were trapped by the electrophilic diphenylphosphine oxide radical, resulting in adduct **18** in 58% yield.[20] A radical trapping reagent, TEMPO, markedly suppressed the reaction, suggesting that α-aminoalkyl radicals are significant and responsible for the reactivity in this Fe(III)/O_2 system.

Next, the role of the iron catalytic cycle in this reaction was investigated. The initiation step is proposed to be an electron

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Org. Lett. XXXX, XXX, XXX−XXX

transfer between the Fe(III) complex and the amine to produce an amine radical cation intermediate. This proposal is compatible with the potentials of the Fe(III)/Fe(II) (1.10 V vs SCE)[21] and amine/radical cation redox pairs (0.78 V vs SCE),[22] and the ESI-MS spectrum of the reaction mixture of **1a** reveals an ion at m/z 135.1048 corresponding to the radical cation (Figure S5). Critically, the Fe(II) complex produced in this initiation step is known to be difficult to oxidize back to Fe(III) under air conditions. Thus, in the nonheme (N4)Fe catalysts that have been developed, O_2 is not utilized, but rather H_2O_2 is used to activate the catalyst in the oxidation reaction of C−H and C═C bonds.[23] For the $Fe(phen)_3^{2+}$ catalyst, the outer-sphere single electron transfer process with dioxygen is potentially mismatched ($O_2/O_2^{\bullet-}$ −0.33 V vs SCE)[24,13f] suggesting that this catalyst also might not readily react with O_2. However, in nature, the cytochrome P450 enzyme systems contain ferric (Fe(III)) and ferrous (Fe(II)) states that are coupled with oxygen and a tetradentate N4 ligand under equilibrium enabling an oxygenase cycle.[25] Inspired by the biological Fe heme systems, we envisioned that ligand dissociation of the unreactive $Fe(phen)_3^{2+}$ species may promote the requisite oxygen binding and oxidation needed to form the desired FeL_n^{3+} complex.

Spectroscopic studies (Figure 1) were carried out to determine which iron species were present in our Fe-

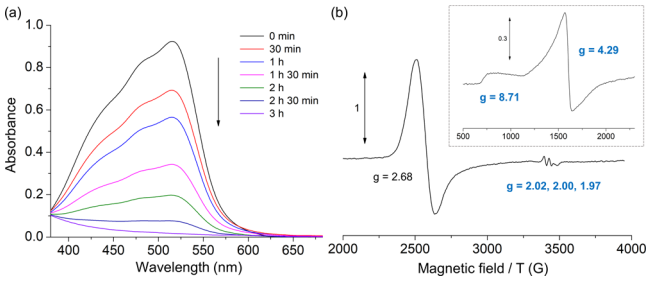

Figure 1. (a) UV−vis absorption spectra of $Fe(phen)_3(PF_6)_2$ in DMSO (1 mM) at 50 °C under air. (b) Low-temperature EPR spectrum of $Fe(phen)_3(PF_6)_3$ in DMSO (1 mM).

$(phen)_n^{2+/3+}$ catalytic cycle. The UV−vis absorption spectrum obtained for the DMSO solution of the $Fe(phen)_3(PF_6)_2$ catalyst at 50 °C under air exhibited a strong absorption band with a peak wavelength at 508 nm, which gradually disappeared as time passed (up to 3 h). This observation was considered to be the result of the disappearance of the $Fe(phen)_3^{2+}$ catalyst; however, the catalyst did not seem to be directly oxidized to $Fe(phen)_3^{3+}$ as broad and weak absorptions at 527 and 586 nm, characteristic of $Fe(phen)_3^{3+}$, were not observed.[21a] Therefore, we hypothesized that the ligand dissociation of $Fe(phen)_3^{2+}$ complex occurred in the polar DMSO solvent. Decisively, the EPR spectrum of a DMSO solution of $Fe(phen)_3(PF_6)_3$ (g = 2.68) did show signals at g = 2.02, 2.00, and 1.97 that are associated with a representative S = 1/2 Fe(III)−OOH species, which was formed from in situ generated $Fe(phen)_3^{2+}$ species.[26] Other EPR active species observed at g = 4.29 and 8.71 were believed to be an S = 5/2 Fe(III)−OO peroxo species.[23,27] Furthermore, the ESI-MS spectrum strongly corroborated this hypothesis with several species including the $[Fe(phen)_2]^{2+}$ (ligand dissociated species) and $[Fe^{3+}(phen)_2{-}OO]^{+}$ (Fe-peroxo) complexes proposed in our mechanism (Figure S6).

Taken together, our proposed mechanism is as follows (Figure 2). Initiation occurs by electron transfer between the

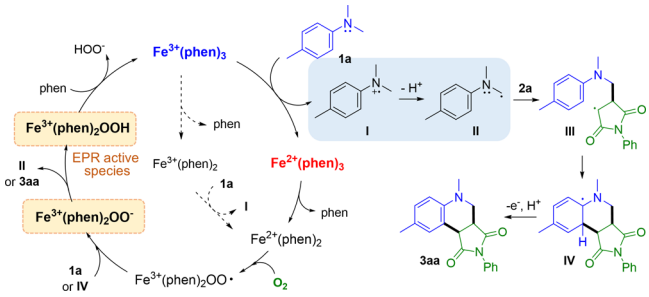

Figure 2. Proposed mechanism for radical addition/cyclization reactions in the Fe(III)−polypyridyl system.

amine and Fe(III) complex to produce radical cation **I** and the Fe(II) complex, which can be oxidized forming the Fe(III)-peroxo or Fe(III)−OOH complexes with O_2. The α-aminoalkyl radical **II** adds to alkene producing the alkyl radical **III**, which undergoes intramolecular radical arylation to furnish cyclohexadienyl radical **IV**. Single-electron oxidation of radical **IV** and subsequent deprotonation yield the tetrahydroquinoline product **3aa**. Importantly, the aforementioned Fe(III)−OO(H) complexes are believed to play an important role in the oxidations leading to the formation of both the initial α-aminoalkyl radical (**II**) and the product **3aa** by the single-electron oxidation/deprotonation of **1a** or cyclohexadienyl radical (**IV**). The HOO^- ligand can then exchange with a phen ligand to regenerate the $Fe(phen)_3^{3+}$ catalyst. The dissociated HOO^- ligand could also be protonated to form hydrogen peroxide, which would be rapidly consumed by Fenton-type oxidation with any Fe complex having an empty site, forming additional radical species.[28,29]

In conclusion, this work represents the first use of an Fe(III)−polypyridyl complex with an atom-efficient O_2 terminal oxidant to form α-aminoalkyl radicals for use in C−H bond functionalization, and the iron-peroxo species generated in the catalytic cycle were confirmed using a combination of EPR and ESI mass spectrometry data. Not only does this effort demonstrate the viability of designing catalysts utilizing sustainable first-row transition metals, but it also validates the notion that sensitive redox reactivity can still be discovered using the exceptionally simple procedure. We anticipate that Fe(III)-catalyzed single-electron oxidation will be applied to a wide range of transformations and expanded to more diverse reaction strategies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03542.

Experimental procedures and characterization data for new compounds (PDF)

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Org. Lett. XXXX, XXX, XXX−XXX

Notes

The authors declare no competing financial interest.

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