

## C-H Activation

# Iron-Catalyzed Intermolecular C–H Amination Assisted by an Isolated Iron-Imido Radical Intermediate

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**Abstract:** Here we report the use of a base metal complex  $[(^t\text{Bu}(\text{pyrpyrr}_2)\text{Fe}(\text{OEt}_2)]$  (**1-OEt<sub>2</sub>**) ( $(^t\text{Bu}(\text{pyrpyrr}_2)^{2-} = 3,5\text{-}t\text{Bu}_2\text{-bis}(\text{pyrrolyl})\text{pyridine}$ ) as a catalyst for intermolecular amination of  $\text{C}_{\text{sp}^3}\text{-H}$  bonds of 9,10-dihydroanthracene (**2a**) using 2,4,6-trimethyl phenyl azide (**3a**) as the nitrene source. The reaction is complete within one hour at 80°C using as low as 2 mol% **1-OEt<sub>2</sub>** with control in selectivity for single C–H amination versus double C–H amination. Catalytic C–H amination reactions can be extended to other substrates such as cyclohexadiene and xanthene derivatives and can tolerate a variety of aryl azides having methyl groups in both ortho positions. Under stoichiometric conditions the imido radical species  $[(^t\text{Bu}(\text{pyrpyrr}_2)\text{Fe}=\text{N}(2,6\text{-Me}_2\text{-4-}t\text{Bu-C}_6\text{H}_2)]$  (**1-imido**) can be isolated in 56% yield, and spectroscopic, magnetometric, and computational studies confirmed it to be an  $S = 1$   $\text{Fe}^{\text{IV}}$  complex. Complex **1-imido** reacts with **2a** to produce the ferrous aniline adduct  $[(^t\text{Bu}(\text{pyrpyrr}_2)\text{Fe}\{\text{NH}(2,6\text{-Me}_2\text{-4-}t\text{Bu-C}_6\text{H}_2)(\text{C}_{14}\text{H}_{11})\}]$  (**1-aniline**) in 45% yield. Lastly, it was found that complexes **1-imido** and **1-aniline** are both competent intermediates in catalytic intermolecular C–H amination.

Since Breslow's initial reports on catalytic C–H amination using an iron porphyrin catalyst<sup>[1,2]</sup> there has been substantial interest in directly converting hydrocarbons into amines.<sup>[3,4]</sup> In subsequent reports, late transition metals such

as Ru,<sup>[5–7]</sup> Rh,<sup>[8,9]</sup> Mn,<sup>[10]</sup> Co,<sup>[11–14]</sup> Ni,<sup>[15,16]</sup> and Cu<sup>[17–22]</sup> have been successfully utilized as catalysts for C–H amination reactions. Iron remains of particular interest due to its relevance in cytochrome P450 enzymes that catalyze the analogous hydroxylation of C–H bonds.<sup>[23,24]</sup> Iron catalysts have been successfully used in a variety of intramolecular C–H amination reactions to produce cyclic products.<sup>[25–32]</sup> However, iron-catalyzed intermolecular C–H amination reactions, are rare<sup>[33–37]</sup> and have drawbacks including long reaction times, high temperatures, high catalyst loadings, limited scope of nitrene precursors, and require additional oxidants. Other advances in this area have come from photocatalysis,<sup>[38]</sup> microwave radiation,<sup>[39]</sup> and enzyme catalysis.<sup>[40,41]</sup>

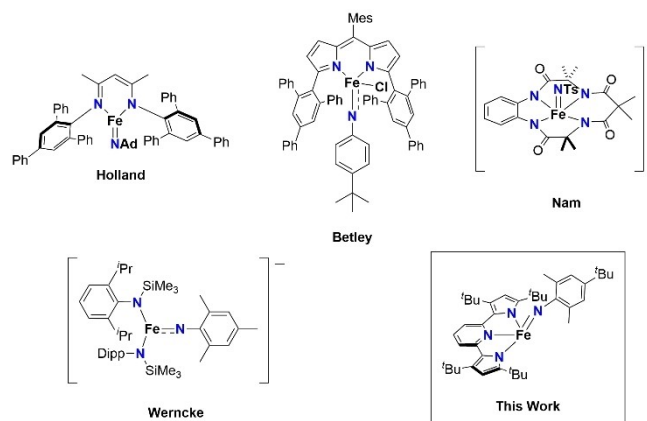
It is well documented that iron terminal imido complexes with spin density at the imido N atom can activate C–H bonds by either hydrogen atom abstraction<sup>[42–50]</sup> or nitrene insertion (Scheme 1).<sup>[34,35,51]</sup> Previously, we showed that a terminal iron imido can be stabilized with the  $(^t\text{Bu}(\text{pyrpyrr}_2)$  ( $(^t\text{Bu}(\text{pyrpyrr}_2)^{2-} = 3,5\text{-}t\text{Bu}_2\text{-bis}(\text{pyrrolyl})\text{pyridine}$ ) ligand platform  $[(^t\text{Bu}(\text{pyrpyrr}_2)\text{Fe}=\text{NAd}]$  (Ad=1-adamantyl), but this complex is a low-spin  $\text{Fe}^{\text{IV}}$  imido<sup>[52]</sup> with reactivity limited to intramolecular and oxidatively promoted N–N bond formation.<sup>[53]</sup> The cobalt analog, however, displays nitrene insertion into the ligand C–H bond under photolytic conditions.<sup>[54]</sup> Exploring different azides, we recently showed the catalytic competence of  $[(^t\text{Bu}(\text{pyrpyrr}_2)\text{Fe}(\text{OEt}_2)]$  (**1-OEt<sub>2</sub>**) in converting benzyl azide to benzaldimine.<sup>[55]</sup> Milsmann's work on related aryl-substituted pyrpyrr<sub>2</sub> systems show that

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**Scheme 1.** Examples of iron imido complexes capable of C–H activation.

small structural changes can lead to large differences in electronic structure and reactivity.<sup>[56–58]</sup> Furthermore, Betley showed that altering the substitution of iron aryl imidyl complexes supported by a dipyrromethene ligand can enable nitrene transfer reactivity over hydrogen atom transfer.<sup>[35]</sup> We hypothesized that with the proper choice of azide we could generate an iron terminal imido intermediate with the right electronic properties for catalytic intermolecular C–H amination.

In our initial explorations in catalytic C–H amination we treated equimolar 2,4,6-trimethyl phenyl azide (**3a**) and 9,10-dihydroanthracene (**2a**) with 10 mol % **1-OEt<sub>2</sub>** in C<sub>6</sub>D<sub>6</sub>. Rapid consumption of the starting materials was observed concomitant with the clean formation of a new organic product with <sup>1</sup>H NMR resonances at 5.12, 4.07, 3.67, and 2.99 ppm of equivalent integration (Figure S31). The product could be isolated in pure form by crystallization from pentane and confirmed to be the single insertion product HNMe(C<sub>14</sub>H<sub>11</sub>) (**4aa**) (Table 1, Figures S1 and S85). Interestingly, a minor byproduct could also be identified in the <sup>1</sup>H NMR spectrum with resonances at 5.70 and 3.27 ppm, and identified as the diaminated product *trans*-HNMe(C<sub>14</sub>H<sub>10</sub>)NHMe (**5aa**).

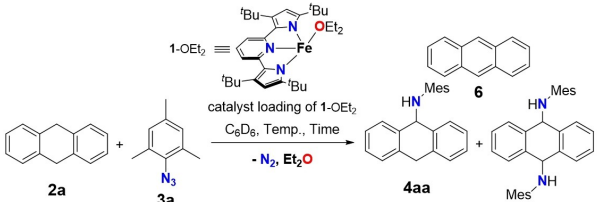
We next set out to optimize the reaction conditions for catalytic nitrene insertion (Table 1). Due to limited solubility of **2a** in common organic solvents, we only achieved substrate and azide concentrations as high as 0.9 M in C<sub>6</sub>D<sub>6</sub>. We found that catalyst loadings as low as 2 mol % could be tolerated over a temperature range from 25 to 80 °C with reaction times from 4 days to 1 h, respectively. Catalyst loadings lower than 2 mol % resulted in only trace formation of C–H amination products (Entries 6 and 7). The product distribution is quite consistent, even under differing reaction conditions, with yields of ≈90% **4aa**, ≈8% **5aa**, and ≈1–2% anthracene (**6**) when it reaches

completion. The selectivity can be tuned to favor the single insertion product **4aa** by using an excess of **2a** (Entry 8). The reactants and catalyst are also sufficiently soluble in toluene and THF for these solvents to be investigated. Performing the reaction in toluene resulted in essentially the same outcome as benzene, but the former allows for shorter reaction times to be achieved at 100 °C (Table S1). Unfortunately, THF is not a suitable solvent for this reaction likely due to catalyst inhibition.

With our optimized reaction conditions in hand, we endeavored to extend this reaction to other hydrocarbons. We found that C–H insertion reactivity could be achieved with C–H bonds with a bond dissociation energy of less than 78 kcal/mol.<sup>[59]</sup> For instance, substrates with stronger C–H bonds than **2a** such as indene and fluorene showed only trace conversion to insertion products (Figures S60 and S61) and no C–H insertion activity was observed with substrates with even stronger C–H bonds. Substrates **2b** and **2c** yield exclusively the diamination products **5ba** and **5ca** showing that selective single insertion is only possible with more substituted 1,4-cyclohexadiene cores (Table 2). Xanthene (**2d**) and its dibromo derivative (**2e**) can be readily functionalized yielding the corresponding aminated products. Substrates containing heteroatoms such as sulfur (**2f**) or nitrogen (**2g**, **2h**) can also be functionalized to the respective secondary anilines. Spectroscopic yields are generally quantitative, except for substrates **2b** and **2c** where decomposition of the single insertion product intermediate is competitive with the second insertion step. In the case of competition between substrates **2a** and **2c** where either a benzylic or allylic C–H bond is aminated, the benzylic C–H bond of **2a** was the predominant site of reactivity, but the diamination product **5ca** was produced in greater spectroscopic yield than **5aa** (Figure S81). This speaks to faster reactivity of the smaller single amination product intermediate derived from **2c** despite its less reactive allylic C–H bond.

Having demonstrated C–H amination of a variety of substrates using **3a** as the nitrene source, we then probed

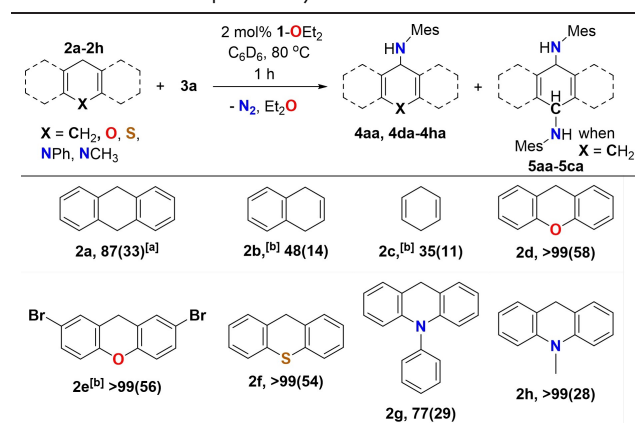
**Table 1:** Optimization of reaction conditions.



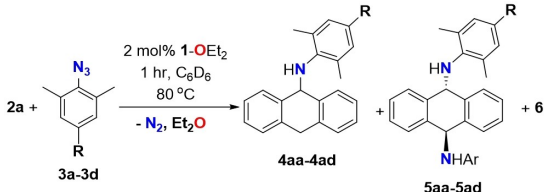
Entry	Temp. [°C]	Cat. Loading [mol %]	Time	% Yield <b>4aa</b>	% Yield <b>5aa</b>	% Yield <b>6</b>
1	RT	10	5 h	91	5	< 1
2	RT	2	96 h	91	8	< 1
3	40	2	28 h	91	8	< 1
4	60	2	4 h	91	8	1
5	80	2	1 h	87 <sup>[a]</sup>	11	2
6	80	1	24 h	45	< 1	< 1
7	80	0.5	24 h	< 1	< 1	2
8 <sup>[b]</sup>	80	2	1 h	96	2	1

[a] Spectroscopic % yield calculated with respect to 1,3,5-trimethoxybenzene as internal standard [b] This reaction was performed with 1.3 eq. 9,10-DHA.

**Table 2:** Substrate scope of catalytic C–H aminations.



[a] Spectroscopic % yield calculated with respect to 1,3,5-trimethoxybenzene as internal standard (crystalline yield) [b] Reaction was performed with 10 mol % **1-OEt<sub>2</sub>**.

**Table 3:** Azide scope of catalytic C–H aminations.


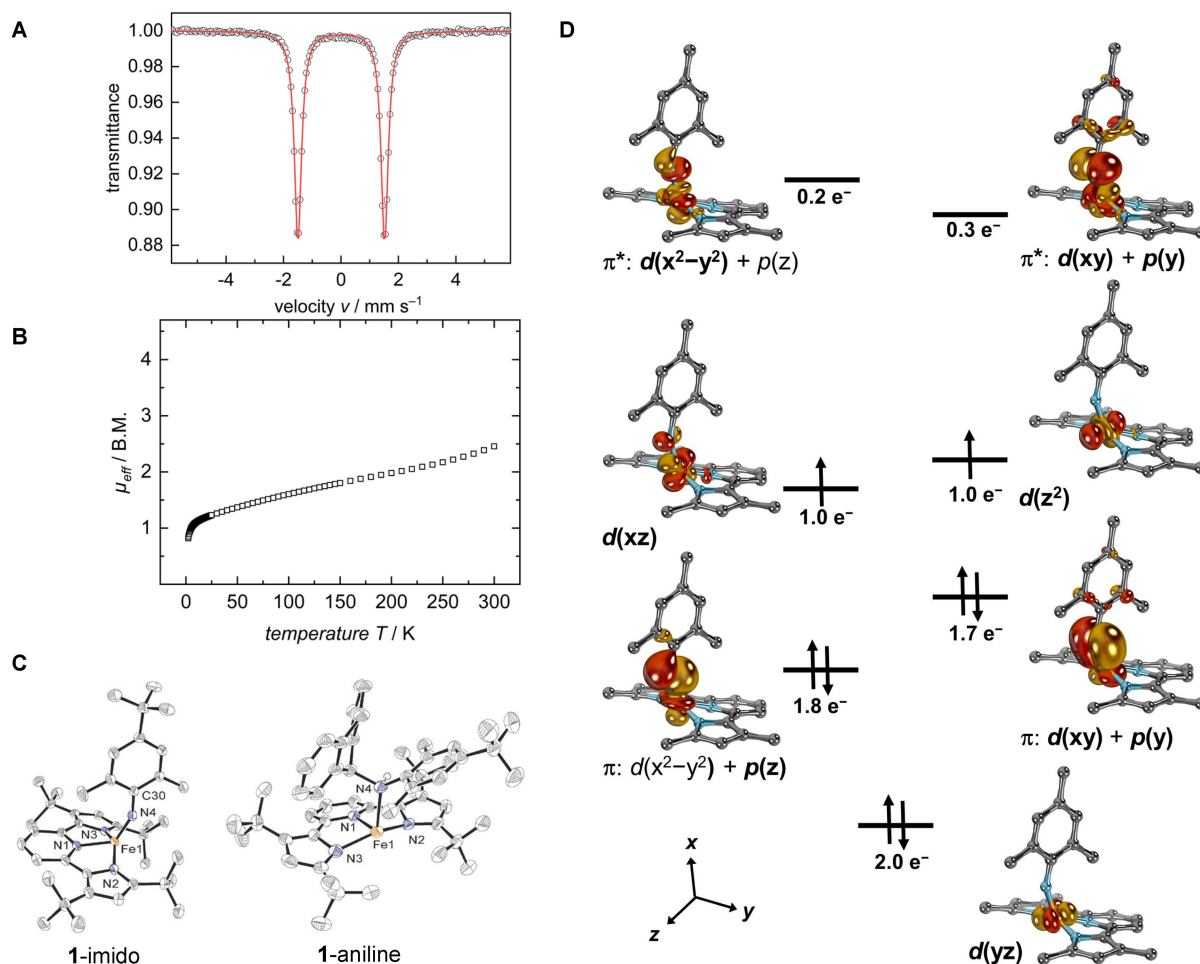
R	Azide	% Yield 4aa–4ad	% Yield 5aa–5ad	% Yield 6
Me	<b>3 a</b>	87.4 (33) <sup>[a]</sup>	8.5	1.8
<i>t</i> Bu	<b>3 b</b>	88.0 (44)	4.4	1.6
H	<b>3 c</b>	87 (50.)	3.4	3.2
Br	<b>3 d</b>	68 (41) <sup>[b]</sup>	2.6	8.2

[a] Spectroscopic % yield calculated with respect to 1,3,5-trimethoxybenzene as internal standard (crystalline yield). [b] Reaction was performed with 10 mol % **1**-OEt<sub>2</sub>.

the scope of the azides. We found that azides containing *two* *ortho*-methyl groups are needed for catalysis to proceed. In

fact, *ortho*-substituents such as *t*Bu and *i*Pr show no evidence of C–H amination reactivity, likely due to steric constraints. We think two *ortho* methyl groups are required to force the <Fe–N<sub>imide</sub>–C<sub>ipso</sub> angle of the imido intermediate to become more obtuse, leading to more triplet character in the ground state. Despite these limitations, we were able to vary *para* substitution of *ortho*-dimethyl substituted phenyl azides with electron donating (*t*Bu and Me) and electron withdrawing (Br) substituents using **2a** as the substrate (Table 3).

To investigate likely intermediates in the amination reaction, we treated **1**-OEt<sub>2</sub> with one equivalent of 2,6-Me<sub>2</sub>-4-*t*Bu-C<sub>6</sub>H<sub>2</sub>N<sub>3</sub> (**3b**), which is capable of catalytic C–H amination (Table 3, see above). This reaction resulted in rapid darkening of the reaction mixture with some notable effervescence. Following work-up, we could isolate a crystalline material which by <sup>1</sup>H NMR spectroscopy showed seven paramagnetically shifted and broadened resonances in the range 35.54 to –2.84 ppm indicative of a C<sub>s</sub> symmetric system (Figure S15). A solid-state structural study<sup>[60]</sup> re-



**Figure 1.** (A) Zero-field <sup>57</sup>Fe-Mössbauer spectrum of **1**-imido, recorded in the solid-state at 77 K. Red line is best fit with the parameters:  $\delta = 0.01 \text{ mm s}^{-1}$ ,  $\Delta E_Q = 3.02 \text{ mm s}^{-1}$ ,  $\Gamma_{\text{FWHM}} = 0.30 \text{ mm s}^{-1}$ . (B) Temperature-dependent SQUID DC field measurement of a powdered sample of **1**-imido recorded in 2 to 300 K range with an applied magnetic field of 1 T. (C) X-Ray structures of **1**-imido and **1**-aniline with 50% probability (H atoms and co-crystallized solvent molecules have been omitted). (D) CASSCF (10,8) molecular orbital diagram for **1**-imido. *t*Bu groups are truncated to CH<sub>3</sub>, but have been included in the calculations. H-atoms as well as one orbital are omitted for clarity (cf. Fig. S106).

vealed this species to be the terminal imido complex  $[(^t\text{Bu})\text{pyrpyrr}_2]\text{Fe}=\text{N}(2,6\text{-Me}_2\text{-4-}t\text{Bu-C}_6\text{H}_2)$  (**1-imido**) (Figure 1, C). Some salient features of **1-imido** include the  $\text{Fe}=\text{N}_{\text{imido}}$  bond length of 1.666(2) Å, akin to the low spin  $\text{Fe}^{\text{IV}}$  imido complex  $[(^t\text{Bu})\text{pyrpyrr}_2]\text{Fe}=\text{NAd}$  (1.640(4) Å), and a  $\tau_4$  value of 0.61 in accord with a *cis*-divacant octahedral coordination geometry.<sup>[52,55,61]</sup> The  $\langle \text{Fe}-\text{N}_{\text{imido}}-\text{C}_{\text{ipso}} \rangle$  angle of 150.9(2)° is larger than that in  $[(^t\text{Bu})\text{pyrpyrr}_2]\text{Fe}=\text{NAd}$  (140.5°) implying less  $\text{sp}^2$  hybridization of the imido N atom.<sup>[15,62–65]</sup> The solution state magnetic moment of 2.6  $\mu_{\text{B}}$ , determined by Evans method, indicates an  $S = 1$  system in contrast to the low-spin nature of  $[(^t\text{Bu})\text{pyrpyrr}_2]\text{Fe}=\text{NAd}$ .<sup>[52]</sup>

The  $S = 1$  room temperature spin state was corroborated in the solid-state by DC SQUID magnetometry on two independently synthesized samples of **1-imido** (Figure 1, B) and shows a gradual, temperature-dependent increase in the magnetic moment from an averaged  $\mu_{\text{eff}}$  of 0.72  $\mu_{\text{B}}$  at 2 K to 2.49  $\mu_{\text{B}}$  at 300 K. Zero-field  $^{57}\text{Fe}$ -Mössbauer spectroscopy, recorded in the solid-state at 77 K (Figure 1, A) on two independently synthesized samples of **1-imido**, reveals a sharp quadrupole doublet with a  $\delta = 0.01 \text{ mms}^{-1}$  and  $\Delta E_{\text{O}} = 3.02 \text{ mms}^{-1}$ . These parameters are typical values for  $\text{Fe}^{\text{IV}}$  imido complexes,<sup>[66–69]</sup> including the related  $S = 0$   $\text{Fe}^{\text{IV}}$  imido complex  $[(^t\text{Bu})\text{pyrpyrr}_2]\text{Fe}=\text{NAd}$ ,<sup>[52]</sup> and are well reproduced by the BP86 functional (Table S7).<sup>[70]</sup>

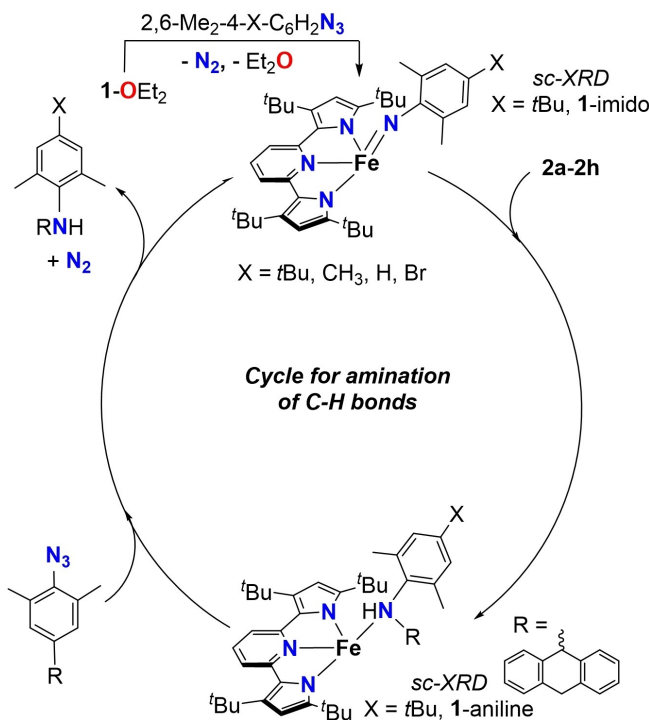
Quantum chemical calculations were performed on **1-imido** using density functional theory (DFT; PBE,  $r^2\text{SCAN-3c}$ , TPSSH, PBE0) and ab initio methods (CASSCF).<sup>[71]</sup> The DFT-calculated structural- (Table S5) and spectroscopic (Table S7, Figure S107–S110) parameters are consistent with the experiment. The Löwdin atomic spin-densities suggest two unpaired electrons to be metal centered, but with substantial delocalization to the imido nitrogen (Table S6, Figure S100). Orbital localization in the form of Intrinsic Bond Orbitals (IBOs)<sup>[72]</sup> substantiates the presence of four electrons at Fe with two of these electrons in a covalent metal-ligand  $\pi$ -orbital (Figure S101). CASSCF (Figure 1, D) calculations show two unpaired  $e^-$  populating  $d(xz)$  and  $d(z^2)$  orbitals and a doubly-occupied  $d(yz)$  orbital. The  $d(xy)$  mixes with the  $p(y)$  orbital of the imido ligand and was found to be covalent in nature (Figures S100, S103, S105). Such a feature indicates significant charge transfer to Fe, and substantial nitrene character (Table S8) in line with partial population of the antibonding combination ( $\pi$ : 1.7  $e^-$ ;  $\pi^*$ : 0.3  $e^-$ ) with accumulation of some spin density at the imido ligand (−0.16 a.u., Table S6). It is likely that the aryl imido substituent on **1-imido** imparts a weaker ligand field than the adamantyl substituted diamagnetic imido complex  $[(^t\text{Bu})\text{pyrpyrr}_2]\text{Fe}=\text{NAd}$ ,<sup>[52]</sup> leading to less  $d$ -orbital energetic splitting thereby making occupation of higher energy orbitals more favorable than spin pairing.

To establish if complex **1-imido** is indeed capable of C–H amination we treated this species with one equivalent of **2a** in  $\text{C}_6\text{D}_6$  at room temperature. This resulted in an immediate color change from dark to rusty red in addition to nine new paramagnetically shifted and broadened resonances in the  $^1\text{H}$  NMR spectrum in the range 114.53 to 0.12 ppm (Figure S74). Work-up and crystallization of the material from pentane resulted in the isolation of ferrous

$[(^t\text{Bu})\text{pyrpyrr}_2]\text{Fe}\{\text{NH}(2,6\text{-Me}_2\text{-4-}t\text{Bu-C}_6\text{H}_2)(\text{C}_{14}\text{H}_{11})\}$  (**1-aniline**), which was structurally confirmed.<sup>[60]</sup> The Fe–N(amine) bond length is 2.204(3) Å which implies a datively bound fragment and the  $\tau_4$  value of 0.72 is consistent with a *cis*-divacant octahedral coordination geometry (Figure 1C).<sup>[52,55,61]</sup> A solution state magnetic moment of 4.8  $\mu_{\text{B}}$ , determined by Evans method, is indicative of an  $S = 2$  spin state in accord with an  $\text{Fe}^{\text{II}}$  ion.<sup>[52,55,61]</sup>

To close the cycle we treated **1-aniline** with one equivalent of **3b** resulting in clean conversion to **1-imido** with concomitant release of the aniline  $\text{HN}(2,6\text{-Me}_2\text{-4-}t\text{Bu-C}_6\text{H}_2)(\text{C}_{14}\text{H}_{11})$  (**4ab**, Figures S75, S76). Complexes **1-imido** and **1-aniline** can be utilized as catalysts for C–H amination, proving their role in the simplified catalytic cycle shown in Figure 2 (Figures S78 and S79). We propose that azide oxidizes **1-OEt<sub>2</sub>** to form a terminal imido complex, followed by amination of the C–H bond to form the  $\text{Fe}^{\text{II}}$  aniline adduct. Akin to oxidation of **1-OEt<sub>2</sub>**, the aniline adduct could then be reoxidized with the azide to close the cycle. The nitrene insertion step from **1-imido** to **1-aniline** likely proceeds through a radical rebound mechanism as for cytochrome P450 enzymes.<sup>[23,73,74]</sup> Small amounts of anthracene (**6**) as a reaction product could stem from the radical disproportionation of a hydroanthracenyl radical.<sup>[75,76]</sup> However, polarized<sup>[77]</sup> and concerted<sup>[78–80]</sup> pathways are also possible.

In conclusion, we report the Fe-catalyzed intermolecular C–H amination reaction between aryl azides and organic substrates with  $\text{C}_{\text{sp}^3}\text{-H}$  bonds. This reaction proceeds cleanly at 80 °C in 1 h and functional groups can be delivered both from the azide and the hydrocarbon substrate. Furthermore,



**Figure 2.** Cycle for the formation of imido and aniline derivatives stemming from **1-OEt<sub>2</sub>**.

we were able to isolate and fully characterize some key intermediates in a tentative catalytic cycle, which includes an intermediate-spin Fe<sup>IV</sup> imido. Future work will involve a mechanistic study to more conclusively establish the pathway for C–H amination.

### Supporting Information

Supporting Information contains complete experimental and computational details and characterization of new molecules including X-ray crystal structures. The authors have cited additional references within the Supporting Information.<sup>[81–112]</sup>

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### Conflict of Interest

The authors declare no conflict of interest.

### Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** Amination · C–H Activation · Imido · Insertion · Nitrene

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