Letter

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Iron-Catalyzed Arene C—H Amidation using Functionalized Hydroxyl Amines at Room Temperature

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ABSTRACT: *Herein, we report $Fe^{(III)}$(TPP)Cl as an effective catalyst for promoting arene C-H amidation through intramolecular cyclization of N-Tosyloxyarylcarbamate substrates. The reaction proceeds via nitrene (outer sphere pathway) C(sp^2)—H insertion to yield benzoxazolones under external oxidant free condition at ambient temperature. The method is operationally simple and scalable with high functional group tolerance. Preliminary experimental and computational data indicates involvement of electrophilic aromatic substitution mechanism for this aryl C—H amidation transformation, distinct from operating mechanism reported previously in aryl C—H amination using azide based substrates.*

KEYWORDS: C—H amidation, iron-catalysis, benzoxazolone, chemoselective, nitrene insertion, DFT calculations

Transition metal catalyzed direct C—H bond amination is an attractive strategy for constructing N-containing molecules.[1] In this context, arene C(sp^2)—H bond amination constitutes a valuable transformation for synthesizing benzannulated N-heterocycles.[2] In recent years hydroxyl amine derived aminating agents have gained significant prominence and several catalytic systems have been developed for the construction of N-scaffolds using arene C—H bond functionalization strategy which mostly occur via manifold outside with that of nitrene intermediate.[4] The relatively weak N-O bond of this aminating agent functions as internal oxidant when cleaved under reaction condition thus obviating the need for exogenous oxidant. Recently, Glorius [with $Rh^{(III)}$][5a, b] and Chang [with $Ir^{(III)}$ and $Co^{(III)}$][5c, d] demonstrated the *directed (via inner sphere pathway)*[5e] arene C—H amidation using N-acyloxy and N-aryloxy carbamates respectively as putative N-(nitrene) source (eq 1 and 2, Figure 1, respectively). However, utilization of hydroxyl amine derivatives as discrete N-(nitrene) source for arene C—H amidation are only handful[6, 7] which includes Yu et al's[8a] (outer sphere pathway) $Pd^{(II)}$-catalyzed and Nicholas et al's[8b] (inner sphere pathway) $Cu^{(I)}$-catalyzed intermolecular arene C—H amidation using N-Nosyloxy and N-Tosyloxycarbamate respectively (eq 3 and 4, Figure 1). Where considerable progress has been made in the direction of intermolecular transformation, *no report of intramolecular arene C—H amidation exists (via outer sphere pathway) with this system leading to valuable N-heterocycle.*[5f, 6a] More so, all the reactions mentioned above are associated with one or more limitations like requirement of either 2nd or 3rd row transition metal catalysts/additives (or specialized catalyst), harsh conditions (high temperature), and high catalyst loading for efficient transformation (Figure 1). Therefore, development of mild reaction conditions[4h] using earth abundant 1st row transition metal especially iron would be advantageous for cost effective and efficient synthesis of N-heterocycles.[9]

On the other hand, since the Breslow's seminal report of Fe^{III}(TPP)Cl as a catalyst for C(sp^3)—H bond amination using iminoiodinane as N(nitrene)-source,[10] Fe-porphyrin based catalytic system has found extensive usage for many different transformations[11] but aromatic C—H amidation. To the best of our knowledge no report exists with *$Fe^{(III)}$(TPP)Cl as an inexpensive, non-toxic and biocompatible catalyst for aromatic C—H amidation*.[12a, b]

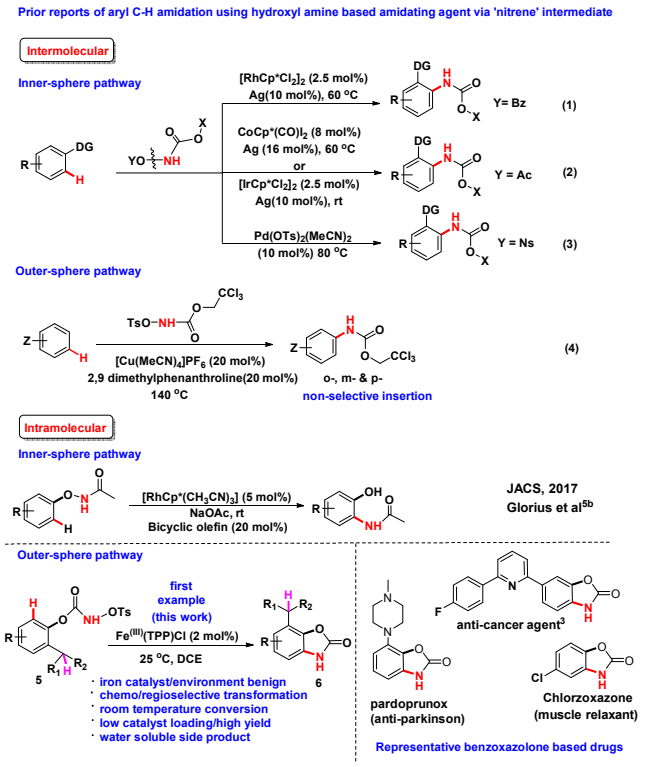
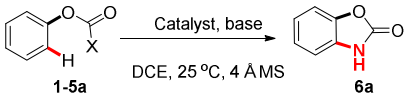


Figure 1. Prior art of arene C-H amidation with hydroxylamine derived aminating agents via nitrenoid insertion, this work and benzoxazolone based bio-active scaffolds

Therefore, towards our research interest for development of new sustainable amidation chemistry, herein, we wish to report $Fe^{(III)}$(TPP)Cl catalyzed conversion of N-Tosyloxyaryl carbamates to biologically important benzoxazolones[3, 13, 14] *via* intramolecular aryl C(sp^2)—H amidation under extremely mild reaction condition (at room temperature, external oxidant free, low catalyst loading, and water soluble side product) (Figure 1).

Our studies began with catalyst screening for decomposition of O-phenyl azidoformate (**1**) an ideal substrate, at room temperature for benzoxazolone synthesis, unfortunately, none of the catalysts screened including $Rh_2(OAc)_4$ were able to decompose this substrate at rt (entries 1-3; Table 1). This prompted us to introduce other leaving groups like an ester or a sulfonate in place of $–N_2$ as potential N-source. Although, N-acetoxy based carbamate (**2**) remained inert with all the catalyst screened, we were pleased to observe decomposition of N-Tosyloxy based carbamate (**5**) with $Fe^{(III)}$(TPP)Cl using K_2CO_3 as base under ambient condition providing benzoxazolone (**6a**) in excellent yield of 94% (entry 8, Table 1). K_2CO_3 proved as optimal base for current transformation (see ESI for details). $Rh_2(OAc)_4$ on the other hand could only provide modest (35%) yield upon full conversion (entry 7, Table 1). Among other catalytic systems screened, $Cu^{(II)}$ failed to provide any desired product (entry 9, Table 1) whereas non-heme iron based catalyst ($FeCl_2$ and $FeCl_3$) tested under otherwise similar reaction condition failed to initiate the reaction at rt (entries 15 and 16, Table 1) or gave. Catalytic activity of $Fe^{(III)}$ with other ligands (salen and box) gave inferior results (entry 10 and 11, Table 1, respectively).[12c]

Table 1. Optimization of arene C—H amidation with different carbonyl based nitrene precursors[a]



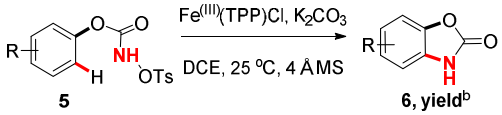
Entry	X (substrate)	Catalyst (mol%)	Base (equiv)	Time (h)	Yield[b] (%)
1	-N_3 (1)	$Rh_2(OAc)_4$(5)	none	24	NR
2	-N_3 (1)	Fe(TPP)Cl(5)	none	24	NR
3	-N_3 (1)	$Cu(OTf)_2$(5)	none	24	NR
4	-NHOAc**(2)**	$Rh_2(OAc)_4$(5)	K_2CO_3(2)	24	NR
5	-NHOAc**(2)**	Fe(TPP)Cl(5)	K_2CO_3(2)	24	NR
6	-NHOAc**(2)**	$Cu(OTf)_2$(5)	K_2CO_3(2)	24	NR
7	-NHOTs**(5a)**	$Rh_2(OAc)_4$(5)	K_2CO_3(2)	2	35
8	-NHOTs**(5a)**	Fe(TPP)Cl(5)	K_2CO_3(2)	2	**94**
9	-NHOTs**(5a)**	$Cu(OTf)_2$(5)	K_2CO_3(2)	2	NR
10	-NHOTs**(5a)**	$Fe^{(III)}$-(salen)Cl(5)	K_2CO_3(2)	2	42
11	-NHOTs**(5a)**	$Fe^{(III)}$-(box)Br(5)	K_2CO_3(2)	2	34
10	-NHONs**(3)**	Fe(TPP)Cl(5)	K_2CO_3(2)	2	52
11	-NHOMs**(4)**	Fe(TPP)Cl(5)	K_2CO_3(2)	2	64
12	-NHOTs**(5a)**	Fe(TPP)Cl(5)	none	24	NR
13	-NHOTs**(5a)**	none	K_2CO_3(2)	24	NR
14[c]	-NHOTs**(5a)**	Fe(TPP)Cl(5)	K_2CO_3(2)	2	82
15	-NHOTs**(5a)**	$FeCl_2$(5)	K_2CO_3(2)	24	NR
16	-NHOTs**(5a)**	$FeCl_3$(5)	K_2CO_3(2)	24	NR
17	-NHOTs (5a)	Fe(TPP)Cl(2)	K_2CO_3(2)	6	**93**
18	-NHOTs (5a)	Fe(TPP)Cl(1)	K_2CO_3(2)	18	84
19	-NHOTs**(5a)**	Fe(TPP)Cl(5)	K_2CO_3(1)	24	51
20[d]	-NHOTs **(5a)**	Fe(TPP)Cl(2)	K_2CO_3(2)	2	90

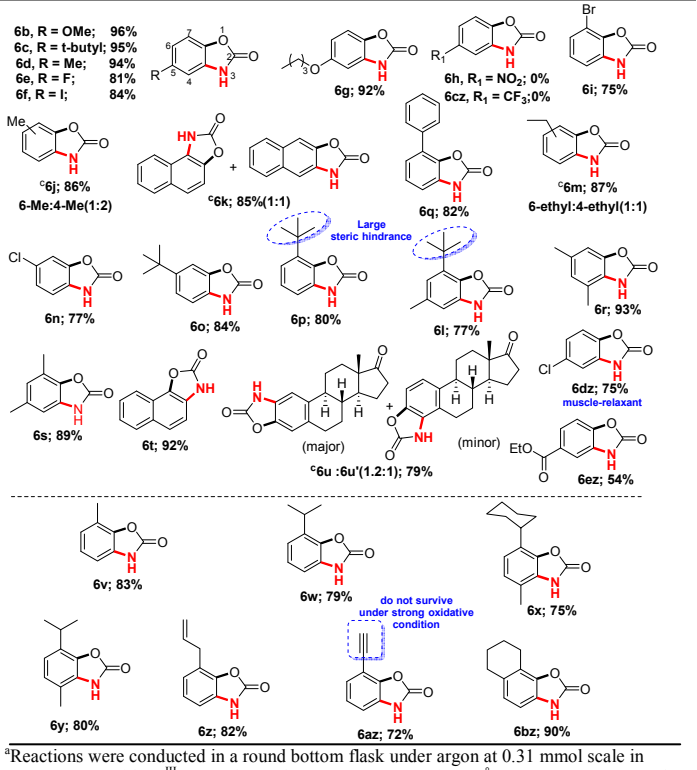
[a]Reactions were conducted in a round bottom flask under argon at 25 °C with substrate (0.31 mmol), cayalyst (1-5 mol%), 4 Å MS (100 wt %), base (1-2 equiv), in anhyd DCE (2.0 mL) (see ESI for details). [b]Isolated yields. [c]Conducted in open atmosphere. [d]7 mmol scale. NR = No Reaction

These results clearly demonstrate the superiority of tetradentate (N,N,N,N) (porphyrin) ligand around the metal centre for this transformation, perhaps the electronics and structure of porphyrin plays crucial rolein stabilizing the high oxidation state Fe-intermediates during the course of the reaction.

Notably, this is the first report of Fe-porphyrin catalyzed decomposition of N-hydroxy substituted carbamates as nitrene source. N-Nosyloxy (**3**) and N-Mesyloxy (**4**) based substrates provided lower yield of the desired product **6** (entries 10 and 11, Table 1). Conducting the reaction in open atmosphere provided slightly diminished but practical yield of **6a**, thus making this protocol operationally convenient (entry 14, Table 1). Control reactions demonstrated the requirement of both base as well as catalyst for the success of this amidation reaction (entries 12 and 13, Table 1). Reducing the base (1 equiv) took longer time for full conversion, providing diminished yield of **6a** (entry 19, Table 1). However, comparable yields were obtained from 2 and 1 mmol catalyst, latter taking about 18 h for full conversion (entries 17 and 18, Table 1). Dichloroethane (DCE) turned out to be the best reaction medium among solvents screened (see ESI for details). Scale up of this reaction led to no significant change in isolated yield (entry 20, Table 1).

Table 2. Scope of $Fe^{(III)}$(TPP)Cl catalyzed C(sp^2)—H amidation on N-Tosyloxy arylcarbamates[a]





[a]Reactions were conducted in a round bottom flask under argon at 0.31 mmol scale in DCE (2 mL) with Fe^{III}(TPP)Cl(2 mol%), K_2CO_3 (2.0 equiv), 4 Å MS (100 wt %), 6-12 h; [b]Isolated yields. [c]Regioselectivity determined from ^{1}H NMR.

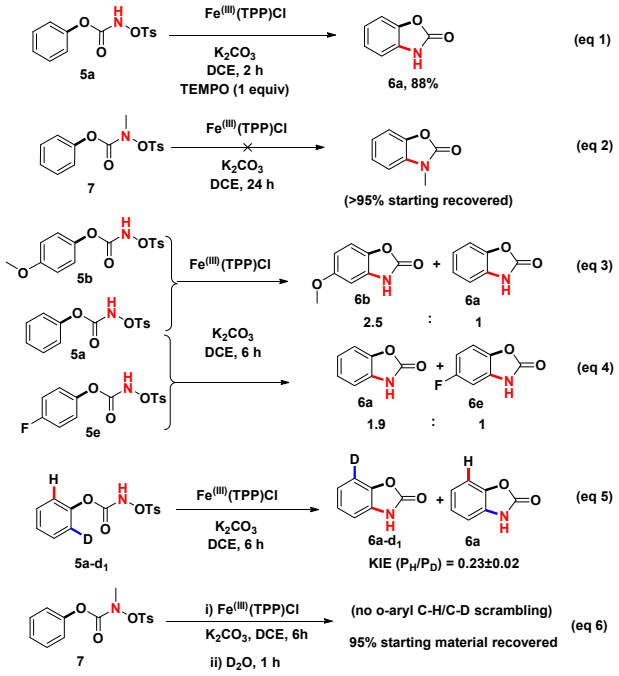
Subsequently, substrate scope was investigated with unoptimized reaction time. As observed from results shown in **Table 2**, various substituents like halogens, alkyl, aryl and alkoxy groups were well tolerated under the reaction condition. Influence of electronic effect was clearly observed on 4-substituted carbamates, where substrates with electron donating substitutents (alkoxy, Me, *t*-butyl) cyclized efficiently to provide desired products in good to excellent yields (entries **6b-6g**), while electron withdrawing substituted (F and I) substrates provided slightly diminished yields of their respective benzoxazolones (entries **6e** and **6f**).[13a, b] Strong electron withdrawing

group (NO_2 and CF_3) substituted carbamates failed to undergo cyclization (entries **6h** and **6cz**). While substrate **5h** remained inert under reaction condition, **5cz** decomposed to give corresponding uncyclized carbamate (4-$CF_3C_6H_5OCONH_2$). However, ester substituted analog was readily synthesized in modest yield (entry **6ez**). These results are consistent with involvement of putative electrophilic aromatic substitution (EAS) pathway.[6] It is worth mentioning here that under present external oxidant free reaction condition even o-halo (entry **6i**) substituted derivative underwent smooth cyclization to give product in high yield. Further, Chlorzoaxazone, a muscle relaxant was efficiently accessed using this protocol in good yield (entry **6dz**). Halogen substituted benzoxazolones thus provides opportunity for further synthetic manipulations thereof. Regioselective product formation was observed on o-Phenyl substituted and α-naphthol derived carbamates in good yield (entries **6q** and **6t**).

Excellent yield with no side product formation was obtained under present protocol on dimethyl substituted substrates owing to non-oxidative and mild reaction condition (entries **6r** and **6s**). Likewise, sterically hindered o-alkyl and di-alkyl substituted substrates (entries **6p** and **6l**) furnished product in very good yields. Further, to observe the steric effect on the C—H bond amidation mediated cyclization process, *m*-substituted N-tosyloxycarbamates were tested. *m*-methyl substituted carbamate gave moderate regioselectivity with major C—H amidation product obtained from sterically more encumbered C—H site in good yields (entry **6j**). *m*-ethyl and *β*-naphthol derived carbamates furnished the regioisomeric products **6k** and **6m** respectively in 1:1 ratio. Although, *m*-t-butyl substituted substrate provided single regioisomer owing to its sterics (entry **6o**), unexpectedly, single isomer (from sterically less hindered C-H site) was isolated from the reaction of *m*-chloro carbamate (entry **6n**). Exact reason for observation of single isomer is unclear this stage.

Chemoselective transformation took place when we subjected various *o*-alkyl substituted carbamates with relatively weaker (1°, 2°, and 3°) C—H bonds under cyclization condition. Only *o*-aromatic C—H amidation products were obtained in excellent yields (entries **6v-6z**). Bicyclic substrate too provided chemoselective product in exellent yield (entry **6bz**). On contrary, under $Fe^{(III)}$(TPP)Cl catalytic condition it's sister analog carbene undergoes C(sp^3)—H insertion (major product) with alkyl benzenesin the absence of directing group.[11a] Substrates with sustituents like *ortho*-alkene and *ortho*-alkyne were well tolerated under present reaction condition and gave only chemoselective five membered products (entry **6z** and **6az**). The unsaturated moieties present in the molecule thus allow for generation of new scaffolds in chemical space. Noteworthily, alkyne moieties are often prone to undergo side reactions under oxidative reaction conditions,[15a] therefore, preferential *aromatic C(sp^2)—H bond nitrenoid insertion over more labile o-substitutents (C(sp^3)—H bond, alkene and alkyne) at room temperature demonstrates the uniqueness of the current system under Fe-porphyrin catalysis.* Finally, we investigated the application of this *C(sp^2)—H amidation* reaction to demonstrate late stage functionalization of a natural scaffold. Consequently, estrone derivative **5u**, was subjected under standard reaction condition which gave the regioisomeric products in 1.2:1 ratio (79% yield) (entry **6u** and **6u'**, Table 2).

Due to virtue of present reaction conditions being extremely mild, no side products with substrates capable of forming benzoxazinone as well as aziridine derivatives (entries **6v-6z**)were observed. Such results also points towards non-involvement of free nitrene intremediate in this process as free nitrene generated under thermolytic conditions often lead to non-selective product formation.[15b] Thereafter, a set of experiments were conducted to underpin the rationale mechanism prevalent in this $Fe^{(III)}$-porphyrin catalyzed transformation. Subjecting the substrate **5a**, with free radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine-1-oxy radical) (eq 1, Scheme 1)under standard reaction condition did not hamper the reaction and cyclized product **6a**, was obtained in good yield, indicating no involvement of free radical in the transformation.[15c] In addition, no product formation from N-methyl O-tosylated carbamate, **7** under similar reaction conditions (eq 2, Scheme 1), indicated putative involvement of Fe-nitrenoid species incurrent aromatic C—H bond amidation, as **7** is incapable of generating nitrene intermediate. Experiments were then conducted to gather evidence for involvement of Fe-nitrenoid species undergoing stepwise, (either electrophilic or H atom abstraction/radical rebound (HAA/RB))[11g, 16, 17] or concerted asynchronous pathway. Consequently, two set of one pot competition reactions were conducted under standard reaction condition. Substrate with electron donating group (**5b**) and electron neutral substrate (**5a**) provided product in the ratio of 2.5:1(eq 3, Scheme 1, see ESI for details), whereas, substrate with electron withdrawing group (**5e**) provided product ratio of 1:1.9 with respect to **5a** (eq 4, Scheme 1, see ESI for details).This indicated the beneficial effect of electron donating groups.



Scheme 1.Mechanistic investigation experiments

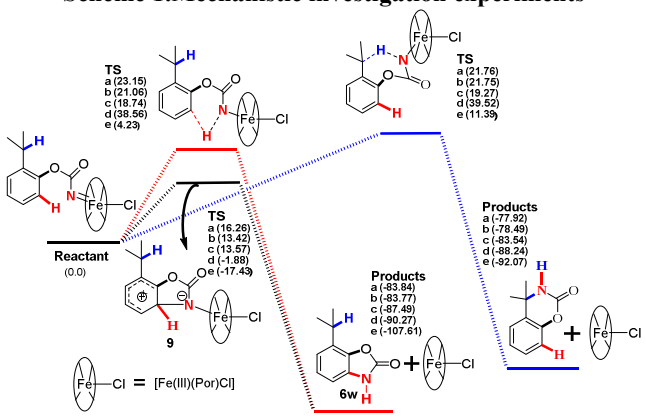
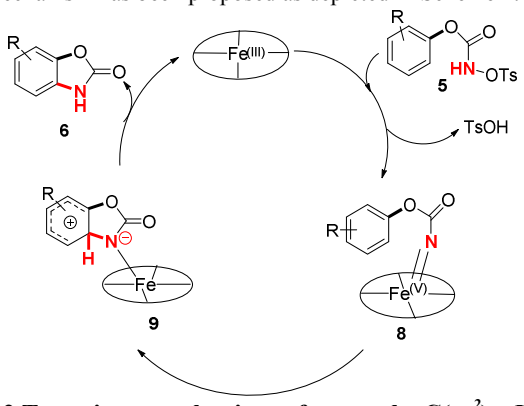


Figure 2. DFT calculated energy profiles of C(sp^2)—H bond amidation (red and black colour) and C(sp^3)—H bond amidation (blue colour) reaction on substrate 5w. Relative energies (kcal/mol) are in parentheses using various methods (see Table S2 in ESI for details)

Next, Kinetic Isotopic Effect (KIE) study was conducted on a deuterated substrate (**5a-d$_1$**).[2e] Observation of inverse secondary KIE (P_H/P_D = 0.23±0.02 at 25 °C), under standard reaction condition indicated that cleavage of C—H bond is not involved in rate determining step, and suggested involvement of stepwise mechanism favoring EAS pathway in $Fe^{(III)}$-porphyrin catalyzed cyclization (eq 5, Scheme 1, see ESI for details).

Theoretical studies were then conducted to obtain further mechanistic insight, as well as for rationalization of selective C(sp^2)—H amidation over more labile and weaker C(sp^3)—H bond. Therefore, DFT calculations were performed with substrate **5w** and Fe^{III}(por)Cl as simplified catalyst model, which in accordance with the earlier report,[10] indicated slight preference for C(sp^3)—H amidation over C(sp^2)—H in gas phase. However, C(sp^2)—H amidation reaction path was found to be energetically more favourable when calculations were performed in solution phase using DCE as solvent (Figure 2). Probably solvent plays a major role and controls the path of this reaction. *Interestingly, the energy barrier height is the lowest for the formation of C-N bond (via intermediate **9**) followed by H-shift in gas phase as well as in solvent. Thus, product **6w** follows the EAS path depicted with black line in Figure 2*. Calculations were performed at a few different levels and methods in DCM solvent which clearly show that the level of the calculation does not affect the overall trend of the results. M06 level DFT calculations indicate clearer picture compared to B3LYP level; however both the levels show the same trend.

Based on the experimental observation and theoretical calculations in this report and previous literature reports,[18a, b, 5f, 6] a tentative mechanism has been proposed as depicted in Scheme 2.



Scheme 2.Tentative mechanism for aryl C(sp^2)—H amidation

Initial co-ordination of N-Tosyloxy carbamate **5** with $Fe^{(III)}$-porphyrin would lead to $Fe^{(V)}$–nitrenoid intermediate species **8**, which undergoes *aromatic* C—H bond nitrenoid insertion *via* stepwise electrophilic substitution pathway through arenium ion intermediate **9**, to furnish the benzoxazolones **6** (Scheme 2). Finally, an evidence was gathered for prevalence of outer sphere-pathway in this transformation by subjecting substrate 7, using stoichiometric $Fe^{(III)}$-porphyrin, followed by quenching with D_2O, where no *o*-C-H/D bond scrambling was observed (eq 6, Scheme 1, see ESI for details).

It is worth to mention here that previous reports on intramolecular aryl C(sp^2)—H amination with azidebased substrates have revealed different (stepwise) mechanistic scenarios under Rh_2(II)[16a] and $Fe^{(III)}$-porphyrin[16b] catalysis. Electrocyclization is the preferred pathway in Rh=Nirenoid catalyzed transformation whereas in the case of Fe=nitrenoid species 1,2-H shift precedes C-N bond formation i.e HAA/RB mechanism prevails. Thus, *clearly pointing towards a distinct mechanistic (EAS) manifold in current arene C—H amidation system*. As a further extrapolation of this methodology, benzoxazolone 5a was readily cleaved under standard reaction condition to provide o-hydroxyl aniline, thus providing a complementary approach to access substituted o-hydroxyl anilines.[5b] (see ESI; Scheme S2).

In conclusion, we have developed an iron (heme) based catalytic system for efficient aryl C(sp^2)—H bond amidation on aryl N-tosyloxycarbamates to access privileged benzoxazolones. Experimental findings were validated by DFT calculations. $Fe^{(III)}$(TPP)Cl as earth abundant and innocuous catalyst decomposes N-tosyloxycarbamates under external oxidant free reaction condition at room temperature. Low catalyst loading (2 mol%) along with generation of water soluble side product underscores the importance of current transformation. Moreover, this transformation adds to the repertoire of Fe-catalyzed reactions in an effort towards development of sustainable amidation chemistry. Further exploration and deep mechanistic insight of this relatively new transformation is currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

General and experimental information on preparation of carbamates, optimization studies, procedure for C—H amidation, details for mechanism studies and characterization data (^{1}H NMR, ^{13}C NMR, HRMS) for all new compounds. This material is available free of charge on the ACS Publications website. Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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