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Research Article

Fe-Catalyzed C(sp^3)−H Diversification toward γ-Functionalized Amides via Iron Nitrenoid: Mechanistic Insights and Applications

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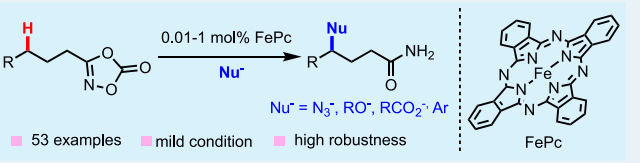
ABSTRACT: Access to γ-functionalized amides represents a challenge in organic synthesis. The recent upsurge of biomimetic metal nitrenoid-mediated C−H functionalization offers a method for producing *N*-containing molecules. Here, we describe an iron-catalyzed γ-C(sp^3)−H diversification of dioxazolones to access γ-functionalized amides. The C−H activation step proceeds via the formation of an iron nitrenoid species, followed by 1,5-hydrogen atom transfer (1,5-HAT). A crucial dihydrofuranimine species is isolated and characterized. This intermediate undergoes nucleophilic substitution to furnish the desired product through a S_N2 mechanism. This reaction obviates the need for external chemical oxidants and exhibits compatibility with electron-rich substrates and various nitrogen, oxygen, and carbon nucleophiles. The catalyst also offers up to 9500 turnovers on complex natural products, emphasizing its utility in organic synthesis and drug development.



KEYWORDS: *C−H functionalization, iron catalysis, nitrene, radical intermediates, reaction mechanisms*

The functionalization of C(sp^3)−H bonds offers an efficient means to harness simple feedstocks and has thus become a long-sought-after goal in synthetic chemistry.[1−7] However, the chemically inert C(sp^3)−H bond (bond dissociation energy = 90−104 kcal/mol)[8] severely limits its application. In contrast, nature utilizes metalloenzymes to effect C−H functionalizations through a high-valent iron oxo intermediate.[9,10] The enzymatic reactions are so effective in breaking C−H bonds that various synthetic metal complexes have been used as models to replicate the reactivity of enzymes,[9,11] and recently the reactivity has been extend to halogenation,[12,13] azidation[14] and thiocyanation.[15] Consequently, these biologically inspired direct functionalizations of unactivated aliphatic C−H bonds have emerged as one of the most powerful and straightforward gateways for altering the physical and/or biological properties of bioactive molecules.[5−7] Nevertheless, most C−H functionalization reactions involving the highly reactive metal oxo intermediate require the addition of a strong oxidant.[10] The oxidizing conditions restrain the reactions to substrates without electron-rich functionalities and subsequently limit their synthetic applications.

In contrast, the electronic structure of the iron oxo complex, along with its reactivity in C−H functionalization, can be replicated by the isolobal iron nitrenoid species.[16,17] Leading works by Breslow showed that an iron porphyrin complex Fe(TPP)Cl (TPP = tetraphenylporphyrinato) could break the aliphatic[18] and benzylic[19] C−H bonds via an iron nitrenoid intermediate. Subsequently, an intramolecular amination product was observed. Inspired by these seminal works, intramolecular C(sp^3)−H amination via iron nitrenoids has been extensively explored.[20−26] Moreover, the generation of iron nitrenoid does not require the addition of an oxidant. Bromamine,[27] sulfonamide,[23] azide,[28] and N-benzoyloxyurea[25] have all proven to effect iron nitrenoids. A much broader substrate scope with electron-rich substituents can thus be tolerated in these C−H amination reactions. Compared to the intramolecular reaction, the analogous intermolecular transformations by iron, however, are sparse.[29−31] A common disadvantage of these intermolecular transformations is that an oxidant is often required in company with the nitrogen source, which will severely limit the functional group tolerance.[21,32−35] Unlike metal oxos, most of the reactivity of metal nitrenoids is limited to C−H aminations. The only exception came very recently by Houk and Meggers who demonstrated that a Ru-acylnitrenoid mediated the direct intramolecular C(sp^3)−H oxygenations (Scheme 1a).[36]

Pioneered by the Chang group,[37] dioxazolones have emerged as stable nitrene precursors[38] for redox-neutral C−N bond-forming reactions catalyzed by transition metal complexes (Fe,[26] Co,[39] Ni,[40] Ru,[41] Rh[42−47] and Ir[44,48−56]). A more recent report from the Chang group has shown that (phthalocyanine)iron(III) chloride (FePcCl) can catalyze an intramolecular C−H amidation reaction of dioxazolones in

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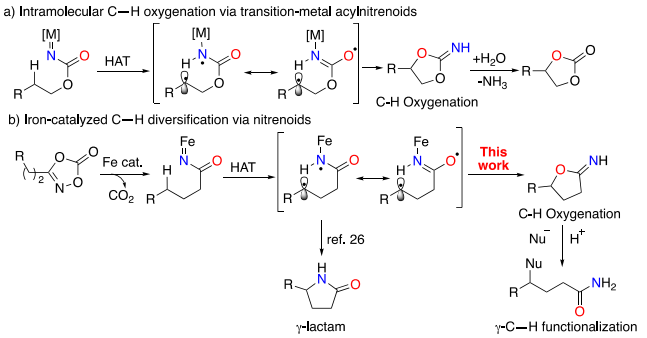
Scheme 1. Concept of Transition-Metal-Catalyzed C(sp^3)−H Functionalizations via Metal Nitrenoid Species

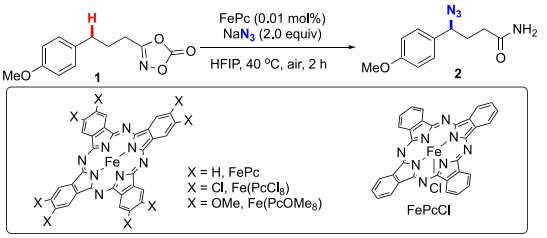


hexafluoroisopropanol (HFIP) (Scheme 1b).[26] This reaction, presumably via an iron nitrenoid intermediate, also provided some γ-hexafluoroisopropoxylated amide product if an electron-rich substrate is used. This important work inspires us to explore the possibility of developing a C−H functionalization process to access the challenging γ-functionalized amides, which remains one of the formidable challenges in synthetic chemistry.[57−67] Herein, we report the selective formation of γ-C(sp^3)−H functionalized amides catalyzed by a simple (phthalocyanine)iron(II) (FePc) complex from dioxazolone substrates. Without the addition of an external oxidant, this methodology enables C−H azidation, hydroxylation, alkoxylation, acyloxylation, and arylation with a broad scope of benzylic and allylic substrates selectively at the γ-position of amides (Scheme 1b). Mechanistic studies show that the reaction occurs initially with a 1,5-hydrogen atom transfer (1,5-HAT) process where an iron nitrenoid abstracts an H atom from the C−H bond, followed by an interesting radical cyclization onto carbonyl. The reactivity is further realized by a nucleophilic attack process through an S_N2 mechanism.

We commenced this study by investigating the γ-C(sp^3)−H functionalization of dioxazolone substrate **1** with an iron catalyst in the presence of a nucleophile. Due to the ease of handling azide sources and the application of organic azides in organic synthesis and pharmaceutical research,[53,68−70] azidation was chosen as an initial reaction to explore. The results of the model reaction between diaoxazolone substrate **1** and sodium azide (NaN_3) were listed in Table 1. **Caution!** *The azidation reaction should be handled with care due to the risk of explosion!*[71]

To our delight, FePc exhibits high catalytic activity in the γ-C(sp^3)−H azidation reaction, even at an extremely low catalyst loading (0.01 mol %). By introducing 2 equiv of NaN_3 in HFIP, the desired azidation product **2** was achieved in 92% yield with minimal formation of any undesired side product (Table 1, entry 1). A high turnover number (TON) of 9200 was obtained, indicating the high robustness of this catalytic system. Increasing the catalyst loading slightly decreased the yield, albeit the reaction time was reduced to 30 min (Table 1, entry 2). Either electron-poor catalyst Fe($PcCl_8$) or electron-rich catalyst Fe($PcOMe_8$) resulted in a slight decrease in yield (Table 1, entries 3−4). The analogous Fe(III) catalyst, FePcCl, was also effective, providing an 87% yield (Table 1, entry 5). It was noticed that the solvent significantly influenced the reaction outcomes. Only 10% yield of the desired product was observed if 1,4-dioxane was used, while no desired product was detected when switching to 1,2-dichloroethane (DCE) or acetonitrile (MeCN) (Table 1, entries 6−8), which indicates

Table 1. Optimization of Fe-Catalyzed C−H Azidation[a]



entry	deviation from standard condition	yield[b] (%)
1	none	92
2	FePc (1 mol %) for 30 min	81
3	Fe($PcCl_8$)	75
4	Fe($PcOMe_8$)	86
5	FePcCl	87
6	1,4-dioxane for 12 h instead of HFIP for 2 h	10
7	DCE for 12 h instead of HFIP for 2 h	trace
8	ACN for 12 h instead of HFIP for 2 h	trace
9	$TMSN_3$ instead of NaN_3	67
10	at 60 °C for 2 h	82
11	at 20 °C for 12 h	72
12	under O_2	91
13	under Ar	89

[a]Condition: **1** (47.0 mg, 0.2 mmol), azide (0.4 mmol) and Fe catalyst (0.01 mol %) in 2 mL solvent. [b]Yields based on ^{1}H NMR analysis of the reaction mixture with 4-bromobenzaldehyde as the internal standard.

solvent cage effect of HFIP could stabilize radical intermediate via the H-bonding network.[72] When $TMSN_3$ was used as the azide source, a lower yield of **2** (67%) was observed due to its decreased nucleophilicity (Table, entry 9). Increasing the reaction temperature to 60 °C slightly decreased the yield (Table 1, entry 10) while it took a much longer time to reach a similar yield if the temperature was decreased to 20 °C (Table 1, entry 11). The catalytic system is highly stable toward oxygen gas. Identical yields were observed when the reaction is conducted under air or even pure oxygen gas (Table 1, entry 12) when comparing to the reaction conducted under argon (Table 1, entry 13; see Table S1 in the Supporting Information for full data of reaction optimization). Furthermore, we studied the thermal decomposition of azide **2** by differential scanning calorimeter (DSC) and a thermal gravimeter analysis (TGA).[73] These analyses revealed that **2** remains inert until being heated to approximately 140 °C, showing its stability and safety under the reaction condition at 40 °C (see Figure S4 in the Supporting Information for detailed DSC/TGA analyses).

Under the optimized protocol for γ-C(sp^3)−H azidation, we examined a set of dioxazolone substrates with different substituents to explore the scope of the substrates (Table 2). Reactions generally went to completion within 0.25−6 h. Various substituted aryl substrates readily underwent azidations at the benzylic site, affording the corresponding products **2**−**15** in satisfying yields (38%−92%, respectively). Electronic properties played a crucial role in the reaction. Substrates with strong electron-donating groups on the phenyl ring (**2**, **10**, **11**, **13**, and **14**) reacted readily with sodium azide using extremely low catalyst loading (0.01 mol %), providing the desired azides in up to 93% yield with minimal side product within 1 h. Other substrates with the gentle electron-rich substituted phenyl or naphthyl substituents are also competent substrates (**3**−**5** and **15**) but required a higher catalyst loading (1 mol %) for

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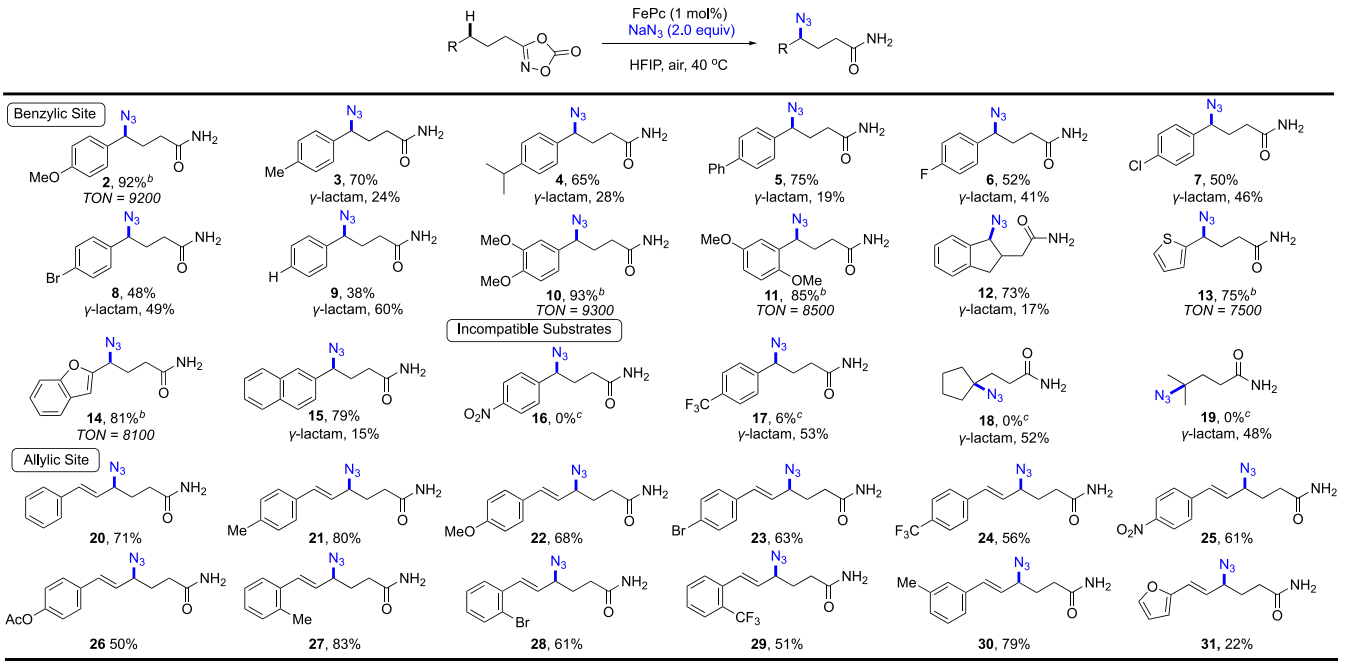
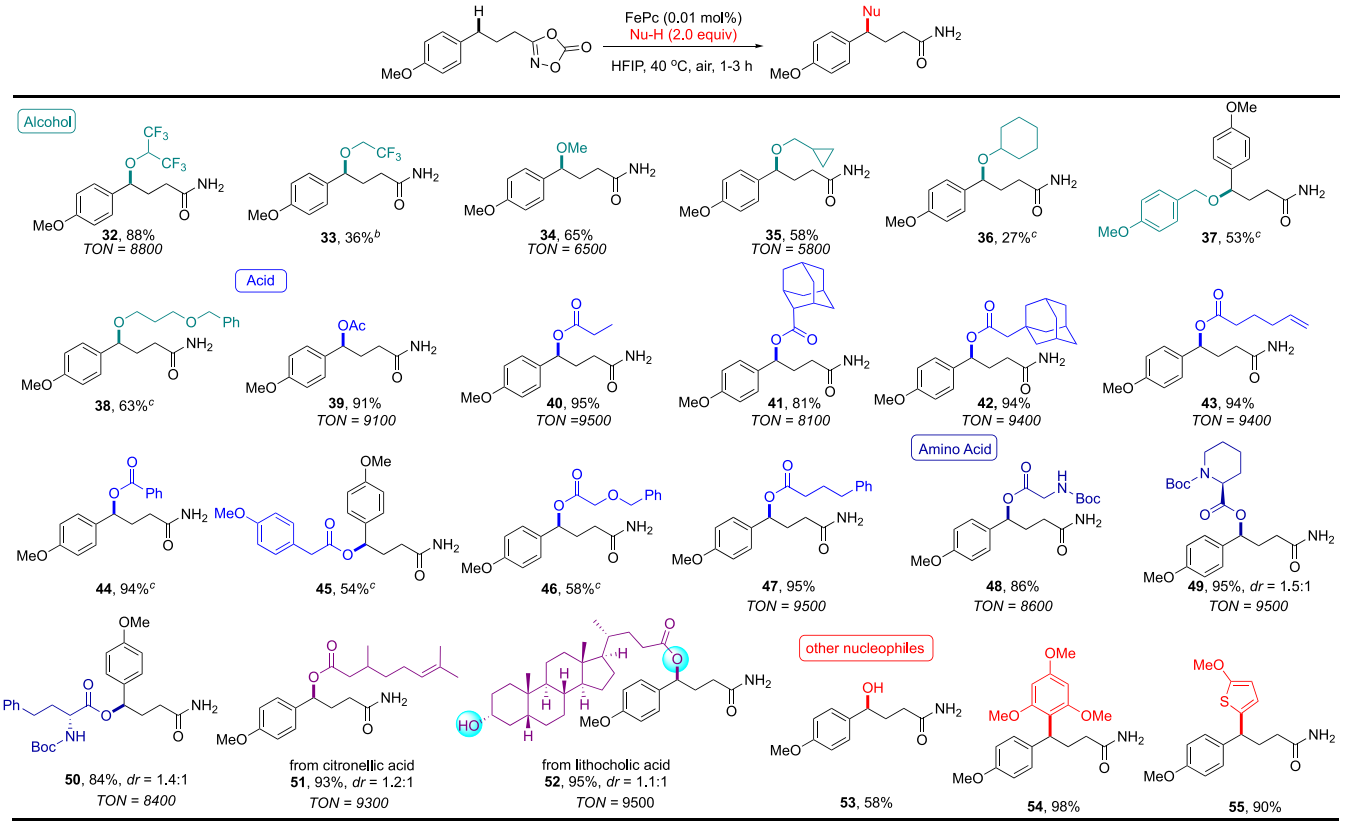
Table 2. Substrate Scope of Fe-Catalyzed Benzylic and Allylic γ-C(sp^3)−H Azidation Using Sodium Azide as an Azide Source[a]



[a]Reaction conditions: substrates (0.2 mmol), NaN_3 (0.4 mmol) and FePc (1 mol %) in HFIP (2 mL) at 40 °C for 0.25−6 h under air. Isolated yields were reported. [b]FePc (0.01 mol %) was used for 1 h. [c]Yields were determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard.

Table 3. Nucleophile Scope of Fe-catalyzed Benzylic γ-C(sp^3)−H Functionalization[a]



[a]Reaction conditions: substrates (0.2 mmol), Nucleophile (0.4 mmol) and FePc (1 mol %) in HFIP (2 mL) at 40 °C for 0.25−6 h under air. Isolated yields were reported. [b]FePc (0.01 mol %) was used for 1 h. [c]Yields were determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard.

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reaction to complete in 1 h. The yields also decreased slightly to 65%−79%. A structurally rigid indane substrate also reacted smoothly in 2 h, providing desired product **12** in 73% yield. In contrast, if no electron-rich substituent was presented or an electron-withdrawing group was presented on the phenyl ring (**6**−**9**), the yield of azidation products decreased drastically to about 50%; meanwhile up to 60% γ-lactam side products were observed, even though a higher catalyst loading (1 mol %) and a longer reaction time (6 h) were applied. Substrates with strong electron-withdrawing substituents on the phenyl ring (**16** and **17**) were not able to provide the desired azidation product, even after reacting for 24 h. Indeed, electron-deficient substrates will be converted to γ-lactam products rapidly, as shown by Chang.[26] Similarly, substrates with unactivated aliphatic C−H bonds (**18** and **19**) were tested, but no desired product was observed due to the rapid formation of γ-lactam products. It is noteworthy that heteroaromatic substrates (**13** and **14**), which are known to undergo Curtius rearrangement easily,[26] were well tolerated, affording the desired γ -azido amides in good yield (75% and 81%, respectively) under the optimized condition, highlighting the versatility of this azidation method in functionalizing pharmaceutically relevant molecules.

Inspired by the initial results, we questioned if this azidation protocol could be extended to allylic C−H bonds due to its tolerance on highly electron-rich functionalities. Only a handful of examples of allylic C−H azidation reactions have been documented to date.[24,74] Moreover, allylic C−H amination by nitrenoids, including azidation, presents a considerable challenge due to the competing olefin aziridination.[75] We envision that this bulky, electrophilic iron nitrenoid may prefer reacting with an electron-rich allylic C−H bonds to the electron-deficient and more sterically hindered C═C bond, similar to the manganese phthalocyanine catalyzed allylic C−H amination reaction reported by White.[76] To our delight, using the same protocol, allylic substrates (**20**−**31**) with different electronic properties were all able to provide the desired azidation product in satisfying yields (Table 2). It is noteworthy that even substrates with strong electron-withdrawing groups such as trifluoromethyl and nitro groups (**24** and **25**) were also tolerated with good yields (56% and 61%, respectively). It is also noteworthy that if triphenylphosphine was added to reduce the allylic azide **30**, rather than an amine product, γ-lactam **30′** was observed via reductive cyclization (see Supporting Information for details).

Considering the similar nucleophilicity between azide and oxygen nucleophiles such as alcohol and carboxylic acids, we imagined that this azidation protocol would also enable the direct incorporation of a range of oxygen nucleophiles into C−H bonds. To our delight, by simply replacing NaN_3 with alcohol substrates in the azidation protocol, various alkoxide groups were successfully incorporated into model substrate **1** (Table 3, **32**−**38**). It is worth mentioning that except for hexafluoroisopropanol and trifluoroethanol, which were used as the solvents in the reactions, other alcohols were only used in 2 equiv. This protocol is highly beneficial as most established methods for C−H alkoxylation require solvent quantities of alcohols except few notable examples.[77−79] Thus, this protocol would allow the application of C−H alkoxylation in a more reasonable stoichiometry when structurally complicated alcohols are used. Moreover, carboxylic acids also showed a high reactivity. In fact, they are even better reaction partners than alcohols. Simple aliphatic and benzoic acids (**39**−**47**) and more functionalized acids including natural amino acids (**48**−**52**) all reacted smoothly, affording desired products in high yields. Notably, the structurally complicated steroid **52** was also tolerated. This steroid, containing both hydroxyl and carboxylic acid functional groups, provided only the acyloxylation product, presenting high chemoselectivity among nucleophiles. Moreover, the successful installation of natural products into the substrate in high efficiency indicated the potential application in bioactive molecule synthesis. A simple water molecule can react smoothly in the reaction, giving desired alcohol product **53** in good yield (58%). More significantly, carbon-based nucleophiles have also shown superb reactivity. Both a highly electron-rich substrate, trimethoxylbenzene, and a heteroarene substrate, 2-methoxythiophene, are well tolerated in the reaction, producing almost quantitative yields (**54** and **55**, 98% and 90%, respectively) under the optimized condition.

To gain more insight into the reaction mechanism, we next turned our attention to monitoring the process of catalytic reaction (eq 1 in Figure 1). Even in the absence of NaN_3,

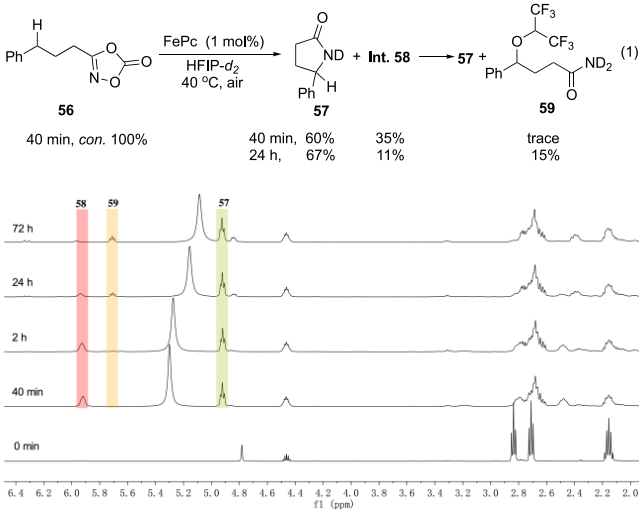
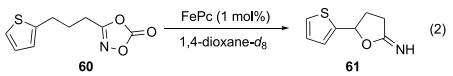


Figure 1. In situ ^{1}H NMR spectra of the catalytic reaction of substrate **56** with catalyst FePc (1 mol %) in HFIP-d_2.

substrate **56** was fully consumed in 40 min, along with the formation of lactam **57** in 60% yield. Additionally, intermediate **58** was also observed. This intermediate **58** will gradually convert to the desired products, mostly to **59** and a few **57**.

Although the NMR experiment does suggest that intermediate **58** is stable in solution to some extent, our attempts to isolate **58** were not successful. We then tested the reaction using different dioxazolone substrates in different solvents in the hopes of obtaining a more stable intermediate. Delightfully, a similar intermediate was observed when a thiophene substrate **60** was used (eq 2). The corresponding



intermediate **61**, generated by reacting **60** with catalyst FePc in 1,4-dioxane, was stable for several hours in solution. While intermediate **61** still decomposed during isolation, its stability in 1,4-dioxane-d_8 allowed us to well characterize it by NMR (see pages S87−89 in Supporting Information). To our

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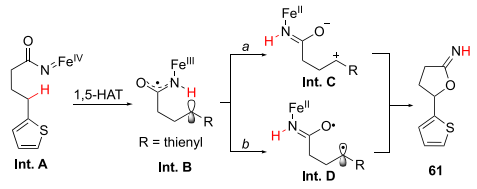
surprise, intermediate **61** proved to be a dihydrofuranimine derivative.

How the dihydrofuranimine intermediate **61** is formed is intriguing. Chang reported that the catalyst FePc can react with dioxazolones to form an iron nitrenoid.[26] This nitrenoid species subsequently abstracts a hydrogen atom from the benzylic C−H bond via a 1,5-hydrogen atom transfer (1,5-HAT) pathway to form a diradical species (Intermediate **B** in Scheme 2). There are two potential routes to the formation of

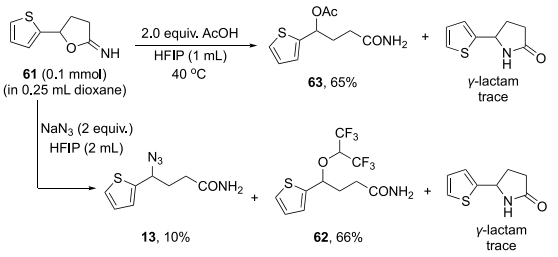
Scheme 2. Possible Pathways for the Formation of 61



dihydrofuranimine species **61** (Scheme 2). In pathway a, a single electron transfer (SET) process can transform **B** into zwitterion **C** that subsequently forms compound **61**. However, this pathway is unlikely because Arnold and Liu have shown in a heme iron nitrenoid system that the triplet state of the diradical intermediate **B** is more stable than the open-shell singlet state of the zwitterion **C**, which makes the SET process thermodynamically unfavorable.[20] On the other hand, in pathway b, the nitrogen radical in intermediate **B** is delocalized with the adjacent carbonyl due to the conjugation. The delocalization then enables radical recombination with the oxygen atom to yield the dihydrofuranimine compound **61** (pathway b in Scheme 2). A similar radical recombination to the oxygen moiety in a nitrene system was reported recently by Meggers and Houk in a ruthenium nitrenoid system.[36] It is noteworthy that Norton and co-workers have also reported a similar radical process where the radical cyclized onto the oxygen moiety of a carbonyl group.[80] This radical recombination with oxygen presumably favors electron-rich substrates which can provide a more stable benzylic radical, allowing for the slower but less steric hindered recombination with oxygen.[36] In contrast, the shorter lifetime of the benzylic radical from an electron-deficient substrate will favor the faster recombination with nitrogen, resulting in the formation of the γ-lactam product as reported by Chang.[26]

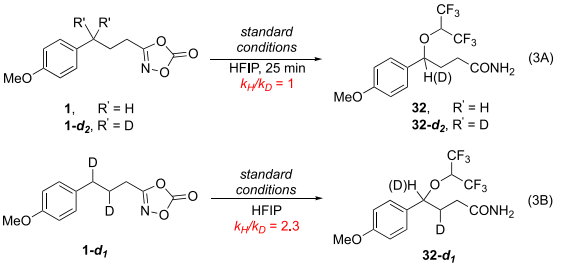
When the reaction in eq 2 was carried out in HFIP, intermediate **61** was quickly converted to the corresponding solvent adduct product **62**, indicating a nucleophilic attack step. To experimentally validate our hypothesis, various nucleophiles, including acetic acid and sodium azide, were added to the dioxane solution of **61** to see if the desired ester and azide products could be generated (Scheme 3). Notably, by simply adding 2 equiv of acetic acid in HFIP to **61**, the desired ester product **63** was isolated in 65% yield. Sodium azide, due to its low solubility in dioxane, has to be added along with HFIP. Nonetheless, the desired azide product **13** was observed in 10%, along with 66% yield of the HFIP adduct product **62**. It was important to point out that trace γ-lactam product was also observed in both reactions, indicating that this nucleophilic attack pathway could represent a minor pathway in the intramolecular C−H functionalization reported by Chang (see details in Figure S2 in Supporting Information).[26] To verify the mechanism, varying amounts of the nucleophile acetic acid (AcOH) were employed. A linear

Scheme 3. Intermediate Trapping Experiments with Various Nucleophiles



dependence on the nucleophile was observed, which implies that the formation of γ-functionalized amides is through an S_N2 mechanism (See details in Figure S3 in Supporting Information). This outcome, different from the report of Meggers and Houk,[36] can be attributed to the potent nucleophilicity of the HFIP solvent, which can destabilize a carbocation intermediate, effectively hindering the S_N1 mechanism.[81]

The observation of this dihydrofuranimine intermediate **61** during the reaction also suggests that the step to break a C−H bond might not be the rate-determining step (RDS). To further probe the mechanism, we carried out an intermolecular competitive reaction and an intramolecular competitive reaction respectively. A kinetic isotope effect (KIE) was observed (k_H/k_D = 2.3) in eq 3B. This is in sharp contrast with



eq 3A, where a KIE was not observed. A possible explanation is that an irreversible binding of the substrate and catalyst is not involved in the cleavage of the C−H bond.[82] The same KIE values were also observed in the intermolecular competitive reactions when other nucleophiles were used (see Scheme S2 in Supporting Information) because two different hydrogen isotopes at the benzylic site of substrate **1-d_1** are present in equal environment after the substrate-binding step generating iron-nitrenoid intermediate.[82] Collectively, the RDS occurs before the cleavage of C−H bond.[82] As a result, the generation of iron nitrenoid species between the substrate and the iron catalyst is the rate-determining step in this C−H functionalization reaction.

The kinetic isotope effect result, in parallel with the observation of a dihydrofuranimine intermediate in the reaction, enables us to propose a mechanism for this iron-catalyzed C(sp^3)−H functionalization reaction (Scheme 4). An initial iron-mediated decarbonation of the substrate generates iron-nitrenoid complex **I**. This complex readily abstracts a hydrogen atom via a 1,5-HAT process to provide diradical species **II**. As stated in Scheme 2b, a delocalized system promotes the formation of diradical resonance structure **III**, which subsequently is converted to dihydrofuranimine **IV**. Finally, facilitated by a proton, a nucleophilic substitution

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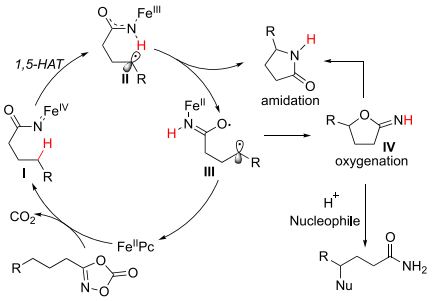
Scheme 4. Proposed Mechanism for the Fe-Catalyzed C−H Functionalization



(S_N2) gives rise to the desired C(sp^3)−H functionalized product.

In conclusion, we have successfully developed a conventional iron-catalyzed γ-C−H functionalization of dioxazolones via an iron-nitrenoid intermediate toward the γ-functionalized amides. Mechanistic studies suggest this reaction undergoes a 1,5-HAT process to cleave the C−H bond by the iron nitrenoid species, followed by a radical cyclization to form a dihydrofuranimine intermediate. This intermediate would be subjected to nucleophilic attack to provide the desired C−N, C−O, and C−C bond formation at the g position of amides via an S_N2 mechanism. The reaction employs various nucleophiles including easily handled solid sodium azide NaN_3, oxygen nucleophiles (alcohols and carboxylic acids), and various carbon-based nucleophiles and is operationally simple. It is noteworthy that this reaction does not require the addition of a strong chemical oxidant and thus tolerates highly electron-rich substrates including heteroaryl and olefin. The broad substrate scope of this method renders it amenable toward complicated molecule synthesis as well as late-stage functionalization of bioactive compounds. We will thus envision a broad utility of this methodology in synthetic and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c03679.

Experimental details, materials and methods, characterization data, NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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