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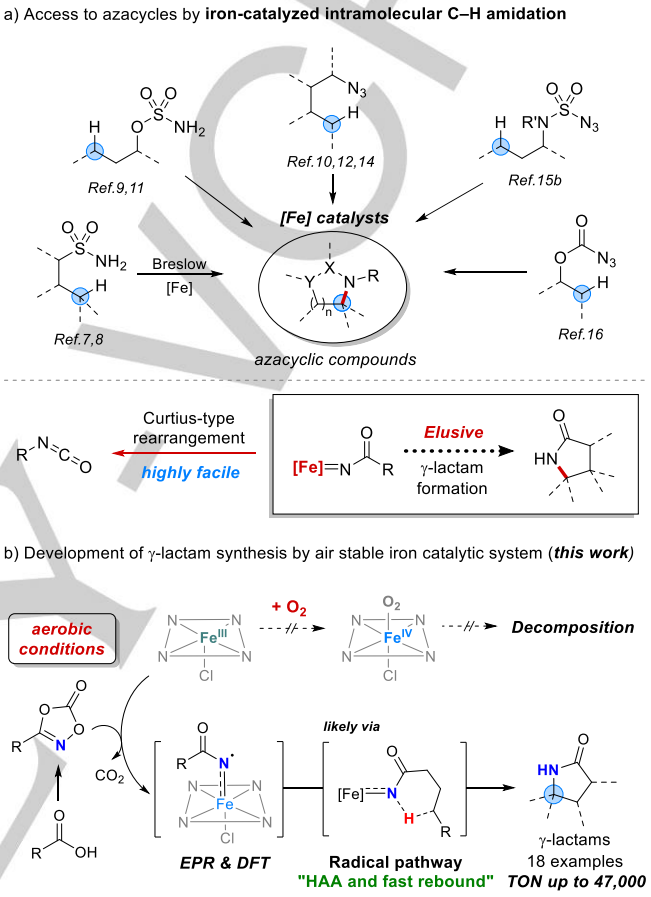
Highly Robust Iron Catalyst System for Intramolecular C(sp^3)–H Amidation Leading to γ-Lactams

Jeonguk Kweon [a,b] and Sukbok Chang [b,a,*]

Abstract: We herein disclose the use of an iron catalyst system for an intramolecular C–H amidation toward γ-lactam synthesis from dioxazolone precursors. (Phthalocyanine)Fe(III)Cl was found to catalyze this cyclization with extremely high turnover numbers up to 47,000 under mild and aerobic conditions. On the basis of experimental and computational mechanistic studies, the reaction was suggested to proceed via a stepwise radical pathway involving fast hydrogen atom abstraction followed by radical rebound. Plausible origin of extremely high turnover numbers along with air-compatibility was also rationalized.

Direct introduction of an amino group into hydrocarbon backbones has been extensively investigated as the carbon-nitrogen bonds are prevalent in pharmaceuticals and natural products.[1] As a result, transition metal-catalyzed amino group transfer is a promising approach especially for achieving high regio- and stereoselectivity.[2] While precious metals have been widely utilized for the C–H amination procedures, base metal catalysts display distinctive advantages in terms of their natural abundance and environmental sustainability.[3] In particular, based on the various C–H oxygenation systems via well-characterized iron oxo complexes,[4] their isolobal nitrenoid intermediates have been regarded as an attractive "stepping stones" to enable the C–N bond formation.[5]

On the other hand, construction of azacyclic structures via C–H amination is an appealing synthetic strategy as it does not require prefunctionalization of the substrates.[6] Since the Breslow's pioneering works on the nitrene transfer using (tetraphenylporphyrin)Fe(III) catalyst (5 mol%)[7] or isolated cytochrome P450[8] to obtain cyclic sulfonyl amides, significant advances have been made in the iron-catalyzed intramolecular C–H amidation reactions (Scheme 1a). For instance, Che employed a hepta-coordinated Fe(II) catalyst (5 mol%) for the synthesis of 6-membered oxathiazinanes via *in situ*-generated nitrene intermediate using hypervalent iodine as an oxidant at 80 °C.[9] The same group also reported the synthesis of pyrrolidine derivatives from alkyl azides using NHC-porphyrin (NHC = N-heterocyclic carbene) ligand system under the microwave conditions.[10] White group achieved highly selective allylic C–H amidation with a cationic (phthalocyanine)Fe(III) catalyst (10 mol%) under inert conditions.[11]



Scheme 1. a) Access to azacyclic compounds by Fe catalysis. b) Current approach to γ–lactams from dioxazolones by a robust iron catalyst under air.

In 2013, Betley group prepared pyrrolidine derivatives from aliphatic azides using an iron(II) dipyrinato catalyst (>10 mol%),[12] proposing that it operates through an antiferromagnetically coupled iron imido species in a quintet spin state (S = 2).[13] An air-stable catalytic system allowing for the analogous pyrrolidine synthesis was reported by van der Vlught *et al.* with redox-active semiquinonato ligands (TON, up to 620).[14] Recently, Arnold[15] and Fasan[16] independently demonstrated that cytochrome P450 derivatives, containing a heme-Fe(II) cofactor as catalytic center, can construct carbon-nitrogen bonds under anaerobic conditions. However, to our best knowledge, there is no example of iron-catalyzed lactam synthesis via direct C–H amidation reaction (Scheme 1a, bottom). In fact, Curtius type rearrangement of the key acyl nitrenoid intermediate usually hampers the desired nitrene insertion, leading the formation of isocyanate byproducts.[17]

Inspired by the precedent works on the oxygen and nitrogen atom transfer processes using iron porphyrin derivatives, we envisaged that analogous catalytic systems would mediate an intramolecular C–H amidation to obtain γ-lactam compounds from

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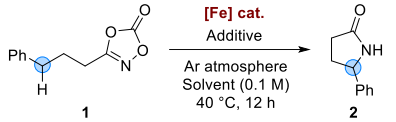
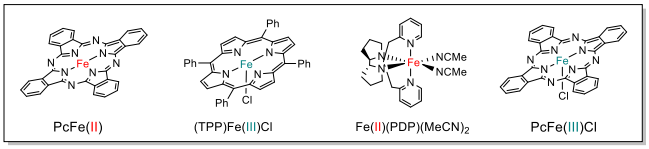
easily accessible dioxazolone precursors[18] via the acyl nitrenoid intermediates. (Scheme 1b). While most known iron catalysis requires anaerobic environment,[9, 11-12, 15-16] our current amidation procedure with neutral (phthalocyanine)Fe(III)Cl catalyst is operative under aerobic conditions with extremly high catalytic turnover (up to 47,000). Experimental and computational studies suggested that the key C–N bond-forming step proceeds in a stepwise fashion through a radical intermediate, and the observed high turnover numbers of the catalytic system was also rationalized in terms of the oxygen durability and catalyst regeneration.

Table 1. Optimization of reaction conditions





Entry	[Fe] cat. (mol%)	Additive (mol%)	Solvent	Yield[a] (%)
1	PcFe(II) (5)	-	HFIP	71 (<5)
2	(TPP)Fe(III)Cl (5)	-	HFIP	9 (<5)
3	Fe(II)(PDP)(MeCN)$_2$ (5)	-	HFIP	17 (<5)
4[b]	PcFe(II) (5)		HFIP	45 (<5)
5	PcFe(III)Cl (5)	$NaSbF_6$ (5)	HFIP	63 (<5)
6	PcFe(III)Cl (5)	$NaSbF_6$ (5)	CH_2Cl_2	34 (<5)
7	PcFe(III)Cl (5)	$NaSbF_6$ (5)	THF	17 (29)
8	PcFe(III)Cl (5)	$NaSbF_6$ (5)	MeCN	7 (80)
9	PcFe(III)Cl (5)	$NaSbF_6$ (5)	C_6H_6	N.D. (>95)
10	PcFe(III)Cl (5)	$NaSbF_6$ (5)	$PhCF_3$	<5 (92)
11	PcFe(III)Cl (5)	$NaSbF_6$ (5)	PhCl	<5 (58)
12	PcFe(III)Cl (5)	-	HFIP	62 (<5)
13[b]	PcFe(III)Cl (0.0055)	-	HFIP	83 (<5)[c]
14[b]	PcFe(III)Cl (0.0011)	-	HFIP	52 (47)[d]

[a] Determined by ^{1}H-NMR analysis (internal standard: 1,1,2-trichloroethane). The numbers in parentheses are the amounts of remaining starting material. N.D.: Not detected. [b] Reaction was conducted under air. [c] Turnover number (TON) was calculated to be 15,000 on the basis of the product formation. [d] TON was 47,000.

At the outset, we envisioned that an iron(II) phthalocyanine (Pc) complex, PcFe(II), would catalyze an intramolecular C–H amidation via an acyl nitrenoid intermediate. When 3-phenylpropyl dioxazolone **1** was employed as a model substrate, PcFe(II) catalyst (5 mol%) provided the desired γ-lactam product **2** in high yield at 40 °C, using hexafluoro-2-propanol (HFIP) as the reaction solvent under argon atmosphere (Table 1, entry 1). Other types of iron complexes such as (TPP)Fe(III)Cl (H_2TPP = 5,10,15,20-tetraphenylporphyrin)[7] and a non-heme Fe(II) species, Fe(II)(PDP)(MeCN)$_2$ (PDP = *N,N′*-bis(pyridin-2-ylmethyl)-2,2′-bipyrrolidine),[19] were less effective for the lactam synthesis (entries 2 and 3, respectively). However, the high air-sensitivity of PcFe(II) necessitates inert conditions to suppress the catalyst deactivation (see the Supporting Information for details). In fact, when the same reaction as of entry 1 was performed under air, the catalytic reactivity was decreased (entry 4).[20]

Therefore, we envisioned that the higher-valent Fe(III) analogue of PcFe(II) would permit better air-compatibility to the current iron-catalyzed C–H amination, being less vulnerable to the oxidative deactivation.[21] PcFe(III)Cl catalyst was found to be also effective for the lactam cyclization under argon atmosphere in the presence of $NaSbF_6$ as the chloride abstractor (entry 5). Other reaction solvents instead of HFIP were not effective for the desired cyclization process (entries 6–11). It was found that the $NaSbF_6$ additive is not essential for the catalytic reactivity (entry 12). Moreover, the reaction was highly efficient with extremely low catalyst loading under air atmosphere. For instance, excellent product yield was obtained with 0.0055 mol% of PcFe(III)Cl catalyst at 40 °C when the reaction was performed open to the air (entry 13**,** TON = 15,000). The maximum turnover number was determined to be 47,000 based on the product yield (entry 14), which would be comparable to the reactivity of protein-based catalyst system.[15b]

We next explored the substrate scope under the currently optimized aerobic reaction conditions (Table 2). It is noteworthy that dioxazolones can be easily prepared in two steps from the corresponding carboxylic acid feedstocks. The amination at the benzylic C–H bonds proceeded with excellent turnover numbers, and the efficiency was not significantly affected by the electronic perturbation at the phenyl substituents (**2**–**5**) except the highly electron-withdrawing CF_3 group (**6**). Furthermore, high diastereoselectivity was observed when a β-methyl-substituted dioxazolone was subjected to the reaction conditions (**7**, *d.r.*>20:1)**.** A benzofused lactam product **8** was efficiently obtained also with excellent catalytic turnover (TON = 13,000).

Substrates bearing various types of aliphatic C–H bonds were also smoothly cyclized. For instance, an amination at the tertiary C–H bond afforded a spirocyclic lactam **9** with turnover number of 1,300. Secondary methylene and primary methyl C–H bonds were also readily amidated by the air-compatible PcFe(III)Cl catalyst system (**10**–**12**). Moreover, polycyclic γ-lactam skeletons were easily accessible by the current C–H amidation approach (**13**–**14**). Interestingly, when an optically active substrate (>99% ee) was subjected to the amidation conditions, the lactam formation took place at the chiral C–H bond without racemization (**15**, TON = 1,200). Dioxazolone compounds bearing propargylic γ-C–H bonds were cyclized in the presence of $NaSbF_6$ additive (**16**–**17**). It should be noted that an unprotected terminal alkyne functional group was tolerated under the current aerobic reaction conditions. However, dioxazolone bearing a thienyl moiety was converted to a solvent adduct only, suggesting that the acyl nitrenoid intermediate undergoes a Curtius rearrangement.

Subsequently, we briefly examined the site selectivity between potentially competing C–H bonds present in the same molecule. When a dioxazolone substrate bearing both benzylic and tertiary γ-C–H bonds was subjected to the catalytic conditions, the cyclization was favored toward the benzylic position (B) over the tertiary (T) site (**18**/**19**, 6.1:1). On the other hand, the amination was almost exclusive at the benzylic position in the presence of competing aliphatic 2° C–H bonds (**20**). Finally, the current [PcFe(III)Cl]-catalyzed aerobic C–H amidation process was shown to be readily performed in a gram scale (**2**, >99% yield, TON of 18,000).

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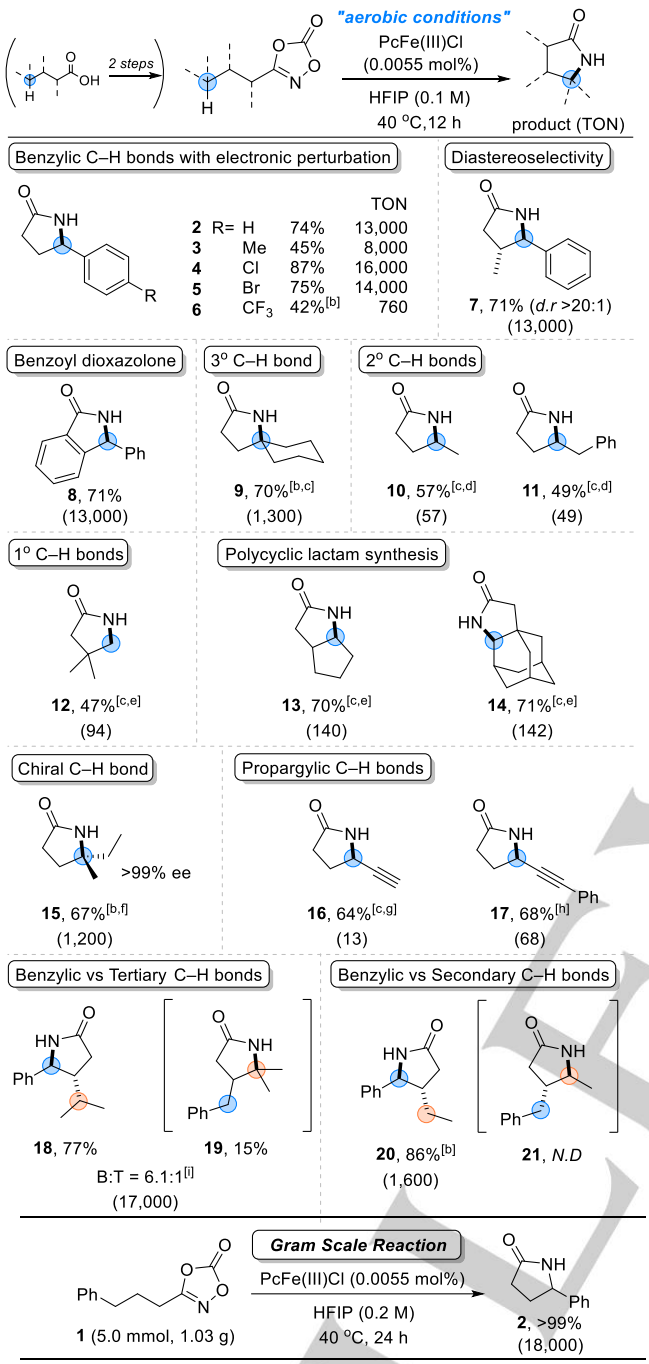
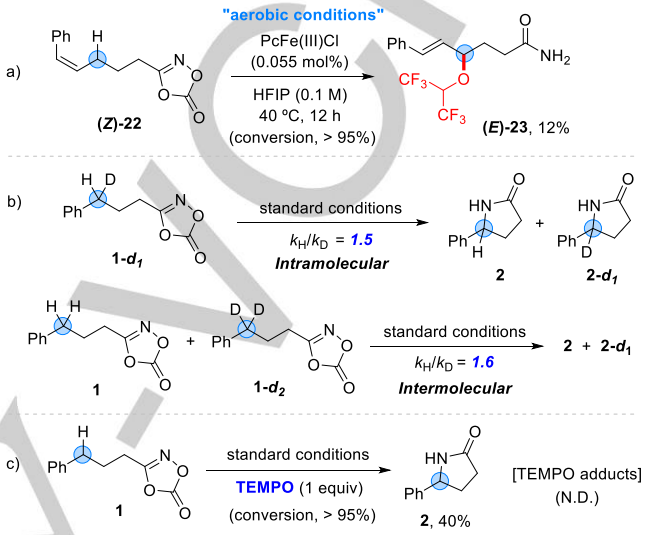
Table 2. Substrate scope of PcFe(III)Cl-catalyzed lactamization[a]



[a] Reaction conditions: substrate (0.1 mmol) and PcFe(III)Cl (0.0055 mol%) in HFIP (1.0 mL) for 12 h at 40 °C, open to the air. Isolation yields are reported. Turnover numbers (TONs) based on the product formation are shown in the parentheses. [b] 0.055 mol% of catalyst was used. [c] Substrate (0.2 mmol) and HFIP (2.0 mL) were used. [d] 1.0 mol% of catalyst was used. [e] 0.50 mol% of catalyst was used. [f] Substrate (0.15 mmol) and HFIP (1.5 mL) were used. [g] 5.0 mol% of catalyst and 5.0 mol% of $NaSbF_6$ were used. [h] 1.0 mol% of catalyst and 1.0 mol% of $NaSbF_6$ were used. [i] Determined by ^{1}H-NMR analysis of the crude reaction mixture.

The mechanistic aspect of the C–N bond-forming step was then investigated. When a substrate having a reactive allylic C–H bond **(*Z*)-22** was subjected to the reaction conditions, an olefin-isomerized solvent adduct **(*E*)-23** was obtained as an amide byproduct (12%, Scheme 2a). This result suggested that a stepwise process would be operative, presumably via an allylic radical species formed by the iron catalyst. Moderate KIE values were observed in both intra- and intermolecular competition of C–H and C–D amination (k_H/k_D = 1.5 and 1.6, respectively, Scheme 2b). When 1.0 equiv of TEMPO was added as an external radical scavenger, no TEMPO adduct was detected but diminished yield of the lactam product was obtained (Scheme 2c). This result, in parallel with the stereoretentive lactam cyclization (Table 2, **15**), led us to propose a rapid radical recombination after hydrogen abstraction process.[22]



Scheme 2. a) Olefin isomerization test on a substrate bearing allylic C–H bonds. b) Measurement of kinetic isotope effects (KIE). c) Radical trap experiment with TEMPO.

To elucidate the mechanistic details, we conducted a series of computational studies using a simplified ligand system (Pc′ = 5,10,15,20-tetraazoporphyrin). DFT calculations on the electronic structures of the putative iron nitrenoid intermediate, **[Pc′FeCl(NR)]** (R = $COCH_2CH_2CH_2C_6H_5$) revealed that an antiferromagentically coupled doublet (S = 1/2, AF) is thermodynamically most stable (Figure 1a). Mulliken spin density on the Fe center and the axial nitrogen (N_{ax}) atom was 1.891 and –0.786, respectively, substantiating the intermediacy of an imidyl radical species. In fact, the more soluble perchlorinated analogous catalyst Cl_{16}PcFe(III)Cl, which provided the lactam product **2** from the dioxazolone substrate **1** in 51% yield with 5 mol% catalyst loading, displayed a distinctive organic radical signal in the reaction mixture (g = 1.991, Figure 1b).[23] On the other hand, the γ-hydrogen atom abstraction by the iron nitrenoid was calculated to be almost barrierless (0.45 kcal/mol), suggesting that radical mechanism is operative in the current catalyst system. Furthermore, the significantly lower barrier of HAA than that of the CO_2 extrusion step (21.04 kcal/mol, Figure S6) implies that the oxidative decarboxylation is rate-limiting step, being in agreement with the moderate KIE values.[24]

To rationalize the plausible origin of the exceptionally high turnover numbers in the current iron-catalyzed lactamization process under aerobic conditions, further computational corroborations were performed on the model catalyst species, Pc′Fe. DFT calculations showed that while dioxygen binding to the lower valent Fe(II) center is energetically favored by 9.65 kcal/mol to form an end-on superoxo species, the analogous binding to the Fe(III) center turned out to be highly endergonic (Figure 2a). This result implies that the high air-compatibility of the

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Fe(III) catalyst system compared to the lower-valent Fe(II) counterpart can be attributed to the energetically disfavored oxygen binding which would lead to the oxidative decomposition.[20]

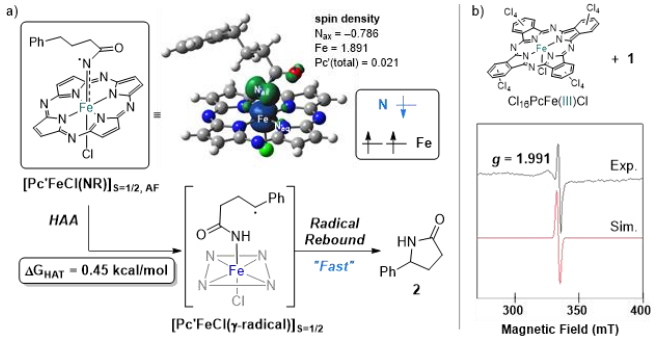


Figure 1. a) Mulliken spin density plot of **[Pc′FeCl(NR)]**$_{S=1/2}$ (α-spin density in blue and β-spin density in green) and proposed hydrogen atom abstraction (HAA) step. AF = Antiferromagnetically-coupled. b) Experimental (black) and simulated (red, g = 1.991) X-band EPR spectrum of the reaction mixture using Cl_{16}PcFe(III)Cl.

The dependence of the substrate coordination on the catalyst spin states was examined. The X-band EPR spectrum of PcFe(III)Cl in a frozen HFIP solvent showed admixed spin states of doublet and quartet, indicating the co-existance of the two electronic configurations (Figure S4).[25] However, DFT calculations revealed that the substrate coordination is energetically downhill only in the doublet spin surface (Figure 2b). Moreover, the calculated Fe–N_{ax} bond length of the dioxazolone adduct **[Pc′FeCl-1]** was significantly shorter in the doublet state (2.158 Å) compared to that of the quartet counterpart (2.759 Å), further suggesting that the substrate coordination on the iron metal center is favored in the doublet state.

On the other hand, the presupposed product-catalyst adduct **[Pc′FeCl-(*κN*-2)]**, was calculated to be most stable in the intermediate quartet spin state (IS, S = 3/2), rather than in its lower spin state (LS, S = 1/2, Figure 2c).[25] In the quartet spin state, the Fe–N bond length is calculated to be significantly elongated compared to that of the doublet analogue, as the Fe–N_{ax} σ^* antibonding orbital is partially populated. Moreover, the product dissociation from **[Pc′FeCl-(*κN*-2)]** is thermodynamically favored (ΔG = –17.39 kcal/mol, Figure 2c) in the quartet energy surface, thereby preventing the product inhibition even in the presence of large access amounts of the lactam species relative to the catalyst loading. The similar tendency was also observed when the *κO*-coordination mode of the product **2** was considered (Figure S8). In fact, even in the presence of product **2** (1.0 equiv) separately added to the reaction mixture, the PcFe(III)Cl catalyst still displayed high turnover numbers (= 12,000) in a reaction of a substrate **1**, indicating that the product inhibition is not significant during the course of reaction (see the Supporting Information). The plausible mechanism of the current catalytic system can be summarized in Scheme 3, showing that the key C–N bond formation involves a radical intermediate in doublet spin surface and that the facile product release for the catalyst takes place in the quartet spin state.

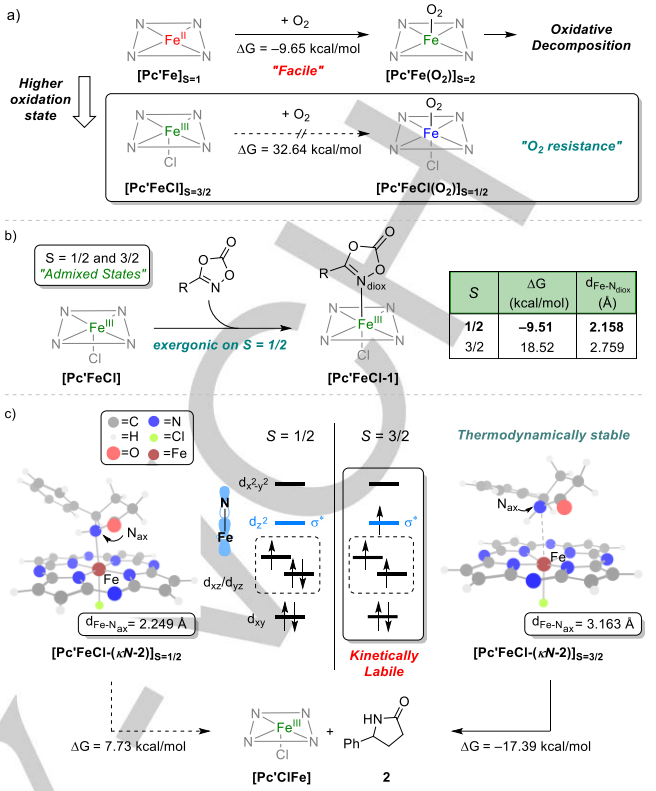
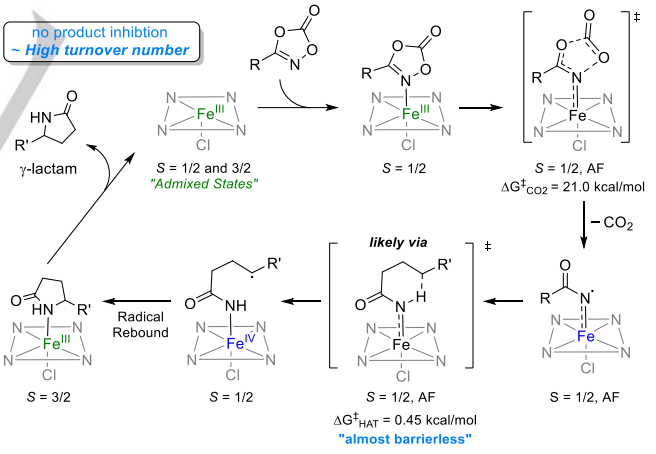


Figure 2. a) Computational comparison of dioxygen binding between Fe(II) and Fe(III) center of the model catalyst system, Pc′Fe. b) Free energy change of iron catalyst species in the dioxazolone coordination depicted with Fe–N_{ax} bond length in doublet (S = 1/2) and quartet (S = 3/2) spin states. c) Electronic configurations of the Pc′Fe-product adduct and the free energy change for the product release in each spin state.



Scheme 3. A plausible mechanistic pathway of the [PcFe(III)Cl]-catalyzed intramolecular C–H amidation with dioxazolone substrates to produce γ-lactams.

In conclusion, we successfully developed a PcFe(III)Cl-catalyzed intramolecular C–H amidation of dioxazolones to afford γ-lactam products with extremely high turnover numbers under aerobic conditions. The origin of the high catalytic activity was rationalized by the facile spin interconversion of the iron species. We believe that this study would pave a way for the use of easily accessible 1st row transition metal catalyst systems for the direct and practical C–H functionalizations.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Iron catalysis, nitrenoid transfer, aerobic conditions, dioxazolones, γ-lactam synthesis

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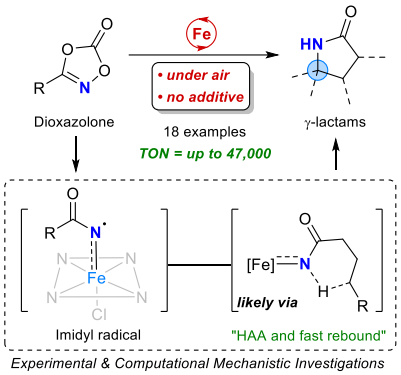

Experimental & Computational Mechanistic Investigations

*Jeonguk Kweon, and Sukbok Chang**

Page No. – Page No.
Highly Robust Iron Catalyst System for Intramolecular C(sp³)–H Amidation Leading to γ-Lactams

Herein, the highly robust air-stable iron-catalyzed C–H amidation is disclosed for the synthesis of γ-lactams. A series of experimental and computational mechanistic investigations suggested a radical stepwise pathway involving an imidyl nitrenoid intermediate. The air compatibility and high turnover numbers (up to 47,000) of the iron catalyst system were also rationalized by DFT calculations.

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