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Communication

Catalyst-Enabled Chemoselective Metalloradical Activation for Molecular Rearrangement via Ester Migration and Allylic C(sp^3)−H Amination

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ABSTRACT: An iron-based metalloradical activation concept is developed for an intramolecular molecular rearrangement via ester migration and an allylic C(sp^3)−H amination using tetrazole as a nitrene precursor. It has been shown that an appropriate choice of catalyst can switch the chemoselectivity of a particular substrate from molecular rearrangement toward allylic C(sp^3)−H amination. The scope of the reactions has been demonstrated by the use of a wide number of tetrazoles and aryl azides. Preliminary mechanistic studies revealed that while molecular rearrangement proceeds via an electrophilic nitrene transfer mechanism, C(sp^3)−H amination follows a distinctive metalloradical activation mechanism controlled by the electronic properties of the iron−porphyrin catalysts. Collectively, this discovery highlights the advancement of chemoselective metalloradical catalysis, which should find wide application in medicinal chemistry and drug discovery.

Nitrogen-containing molecular scaffolds are an important class of building blocks that are often seen in numerous biologically active compounds and pharmaceuticals.[1] Among various N-heterocycles, the indolenine or 3(*H*)-indole framework, along with its aza analogue, is prevalent in various natural compounds and is often used as a precursor for various indole derivatives (Chart 1A).[2] Although several methods exist for synthesizing the indolenine framework, the preparation of azaindolenines or diazaindenes (the aza analogues of indolenine) is limited.[3] This difficulty arises from the presence of an additional nitrogen atom, significantly altering the chemical properties of the molecule and posing a substantial challenge to the chemical community.[4]

Interestingly, while nitrene transfer reactions have emerged as powerful tools for constructing nitrogen-rich heterocycles,[5] achieving precise control over the product distribution in catalytic nitrene transfer reactions remains an ongoing challenge.[6] Despite significant advances in substrate modification for diverse complex molecular architectures through rearrangements,[7] achieving complete control over chemoselectivity, particularly by adjusting the electronics of metal catalysts through ligand design to obtain distinct scaffolds from common substrates and reagents, remains a crucial and largely unresolved challenge.

Both noble metals[8] and base metals[9] have demonstrated high potential in this area, but increasing focus on sustainability, cost-effectiveness, and metal abundance has recently shifted significant attention toward base metal catalysis. Within base metal strategies, metalloradical catalysis (MRC) has emerged as a versatile approach that uniquely regulates reactivity and selectivity through metal-stabilized organic radicals.[10] Notably, pioneering contributions from the groups of Zhang, de Bruin, and others have established cobalt-based MRC as an effective platform for nitrene transfer reactions.[11] Motivated by these advances, our group has been developing iron-based metalloradical systems[5d,10b] as a sustainable alternative (Chart 1B).

Despite iron's high potential in nitrene transfer reactions, documented examples of iron-catalyzed nitrene transfer reactions—particularly those exhibiting robust chemoselective control—are still fairly rare. Furthermore, although diazo compounds[12] and 1,2,3-triazoles[13] have been extensively explored as radical precursors in synthetic transformations, tetrazoles remain significantly less studied.[5d] As part of our continuing efforts on iron−metalloradical catalysis, we focus on using tetrazoles as nitrene precursors to develop strategies for the precise control of product chemoselectivity. In our earlier reports, we studied the reactivity of C8-alkene-substituted tetrazoles with a Cp*Ir catalyst.[14] We observed that *β*-monosubstituted alkenes readily underwent electrocyclization to furnish the desired products, whereas *β*,*β*-disubstituted alkenes were unreactive under the same conditions (Chart 2A, eq 1). Subsequently, we noticed that iron-based MRC is highly efficient for selective C(sp^3)−H bond amination (Chart 2A, eq 2).[15] The earlier limitation of specific substrate design (Chart 2A, eq 1) was successfully overcome using iron-based metalloradical catalysis, which facilitated a radical substitution pathway leading to a 1,2-migration product (Chart 2A, eq 3).[7c] Remarkably, despite the presence of a competitive C(sp^3)−H site, the iron-based MRC system exhibited remarkable selectivity, favoring 1,2-shifts over

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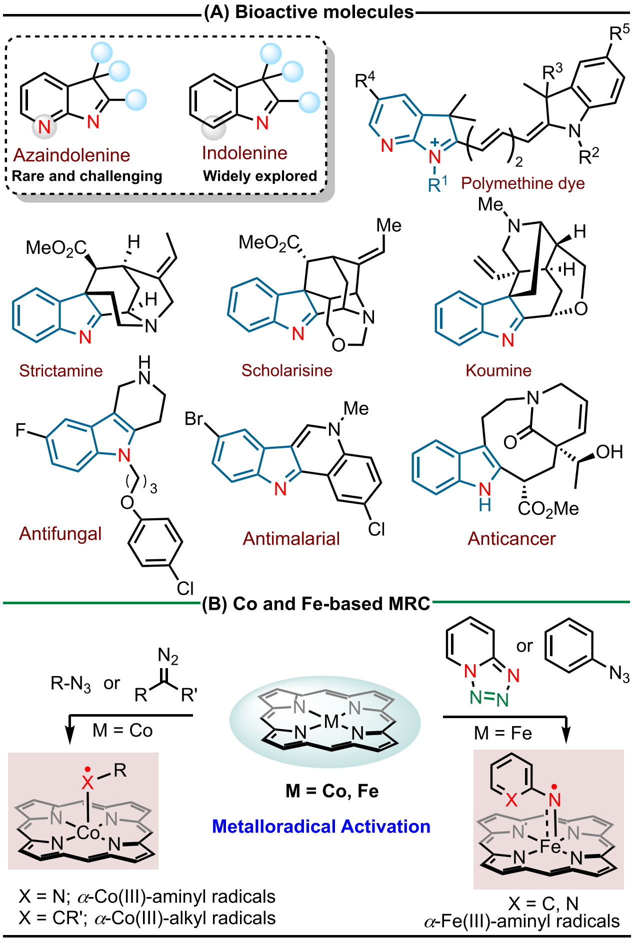
Chart 1. (A) Bioactive Molecules with an Azaindolenine or Indolenine Moiety; (B) Co- and Fe-Based MRC



direct C(sp^3)−H bond amination. Thus, we became interested in how to control the reaction chemoselectively to access either a rearrangement product or an allylic C(sp^3)−H amination product from the same substrate (Chart 2A, eq 4). To achieve this, we aimed to modulate the electronic properties of the catalyst to direct the reaction pathway of substrates featuring multiple competitive reactive sites.

Specifically, our target substrate design includes three competing reaction modes: (i) a rearrangement via ester migration, (ii) a ring migration yielding a spirocyclic scaffold, or (iii) an allylic C(sp^3)−H amination (Chart 2B). Through this work, we seek to develop a robust, tunable catalytic system that allows precise control over reaction outcomes, further advancing the potential of iron-based metalloradical catalysis in nitrene transfer chemistry and expanding the synthetic utility of tetrazoles as versatile nitrene sources. Moreover, we also envisioned that if tetrazole-crafted substrates successfully work, then in principle several other aromatic azides should also work, which would eventually further expand the scope of the reaction. Collectively, herein we report an iron-based metalloradical activation strategy for the molecular rearrangement reaction via an unprecedented ester migration as well as allylic C(sp^3)−H amination leading to the construction of N-heterocycles having a quaternary carbon center attached with a modifiable ester group for further synthetic transformation.

We started our initial optimization using substrate **1a**, utilizing iron-based porphyrin catalysts that are well-known for nitrene transfer reactions and their high stereo-, regio-, and chemoselectivity.[16] Accordingly, a catalytic amount of Fe(TPP)Cl with Zn dust was tested and afforded three possible products, with the ester migration product being the major isomer (66%; Table 1, entry 1). For further improvement, we then examined reactions with catalysts bearing substitutions at the meso position of the porphyrin by tuning the substituents of the phenyl ring at the periphery that are known to enable specific substrate−catalyst interactions. As the porphyrin catalysts such as Fe(TBPP)Cl, Fe(*p*-ClTPP)Cl, and Fe(TMPP)Cl failed to provide improved chemoselectivity (entries 2−4), we redesigned the catalyst structures by modifying the porphyrin ligands. While Fe(Por)-cat-I resulted in poor selectivity, Fe(Por)-cat-II-bearing two electron-donating 4-*tert*-butylphenyl groups and two electron-withdrawing pentafluorophenyl groups afforded the desired product with 73% conversion and 69% isolated yield (entries 5 and 6). We also noticed that the reaction does not require a long time; instead, it takes only 3.5 h to reach completion (entry 7). Further lowering the temperature resulted in the same selectivity, although the conversion was compromised (entries 8 and 9).

We further modified the catalysts which shifted the selectivity toward the allylic C(sp^3)−H amination of tetrazoles (Table 1, entries 10 and 11; see the Supporting Information (SI) for details). Surprisingly, when we used electron-rich as well as sterically demanding Fe(Por)-cat.-VII, a significant shift of the product distribution ratio was observed toward the C(sp^3)−H allylic amination product as the major one (entry 12). This observed switch in chemoselectivity can be rationalized by considering the steric and electronic nature of the iron−nitrenoid intermediate.[17] Specifically, iron complexes bearing strongly electron-withdrawing substituents generate a highly electrophilic nitrenoid species that preferentially undergoes addition across the double bond. In contrast, catalysts featuring bulky electron-donating groups on the porphyrin ligand stabilize the iron−nitrenoid intermediate, making it more favorable for allylic C(sp^3)−H bond abstraction. Performing the reaction at relatively lower temperature, we noticed that while the selectivity remained the same, the conversion was decreased (entries 13 and 14). To confirm the role of the Zn dust, a reaction was carried out without Zn and resulted in no reaction (entry 15).

With the developed reaction conditions, the scope of the ester migration across a wide range of electronically varied 1,2,3,4-tetrazoles was studied (Table 2A), and it was found that both electron-donating and electron-withdrawing tetrazoles are well-tolerated under the developed reaction conditions to produce the desired products in good to excellent yields (**2a**−**2m**). In addition, various substituents on cyclohexane rings (**2n**−**2q**) and larger rings such as an eight-membered ring at C-8 of the tetrazole (**2r**) were also found to be suitable under these migration conditions. Notably, ethyl and isopropyl ester can also migrate to afford the desired amination products in 70% isolated yield (**2s** and **2t**). Surprisingly, a reaction with substrate **1u** featuring a sulfonyl ester group instead of the alkoxycarbonyl ester gave a 71% yield of the C(sp^3)−H aminated product **2u**, which is different from the allylic amination product.

Next, the scope of the iron-catalyzed rearrangement via ester migration was examined for a broad range of aryl azides (Table 2B). Importantly, we observed that aryl azide substrates smoothly underwent the ester migration reaction in the

Chart 2. Previous Reports and New Challenges

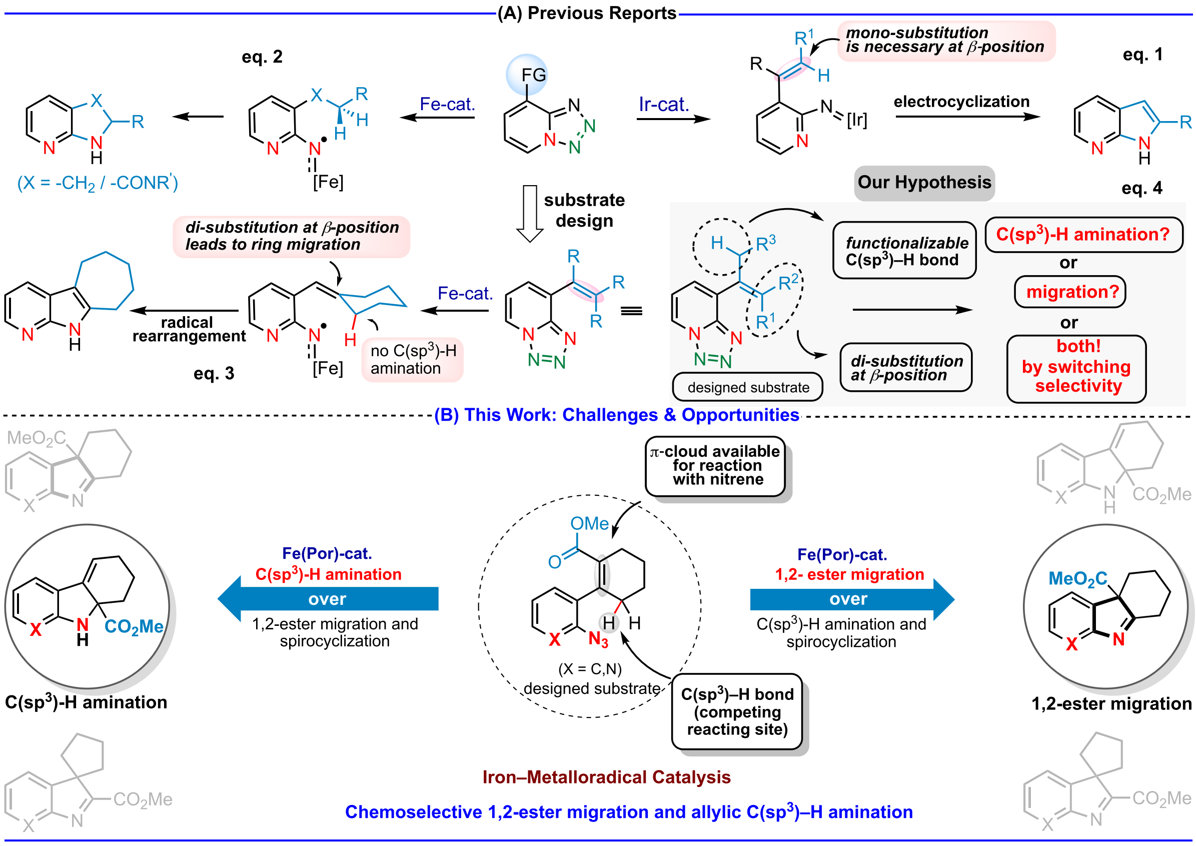
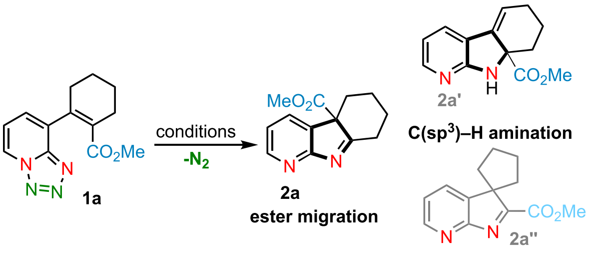
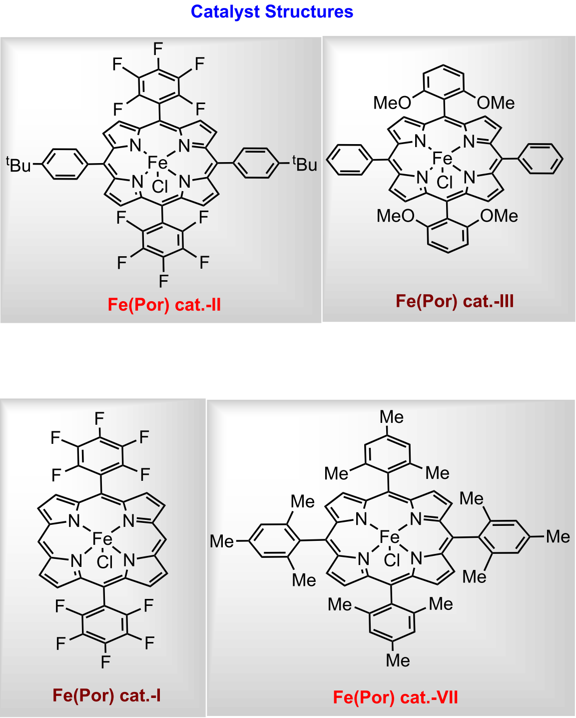


Table 1. Reaction Optimization[a]

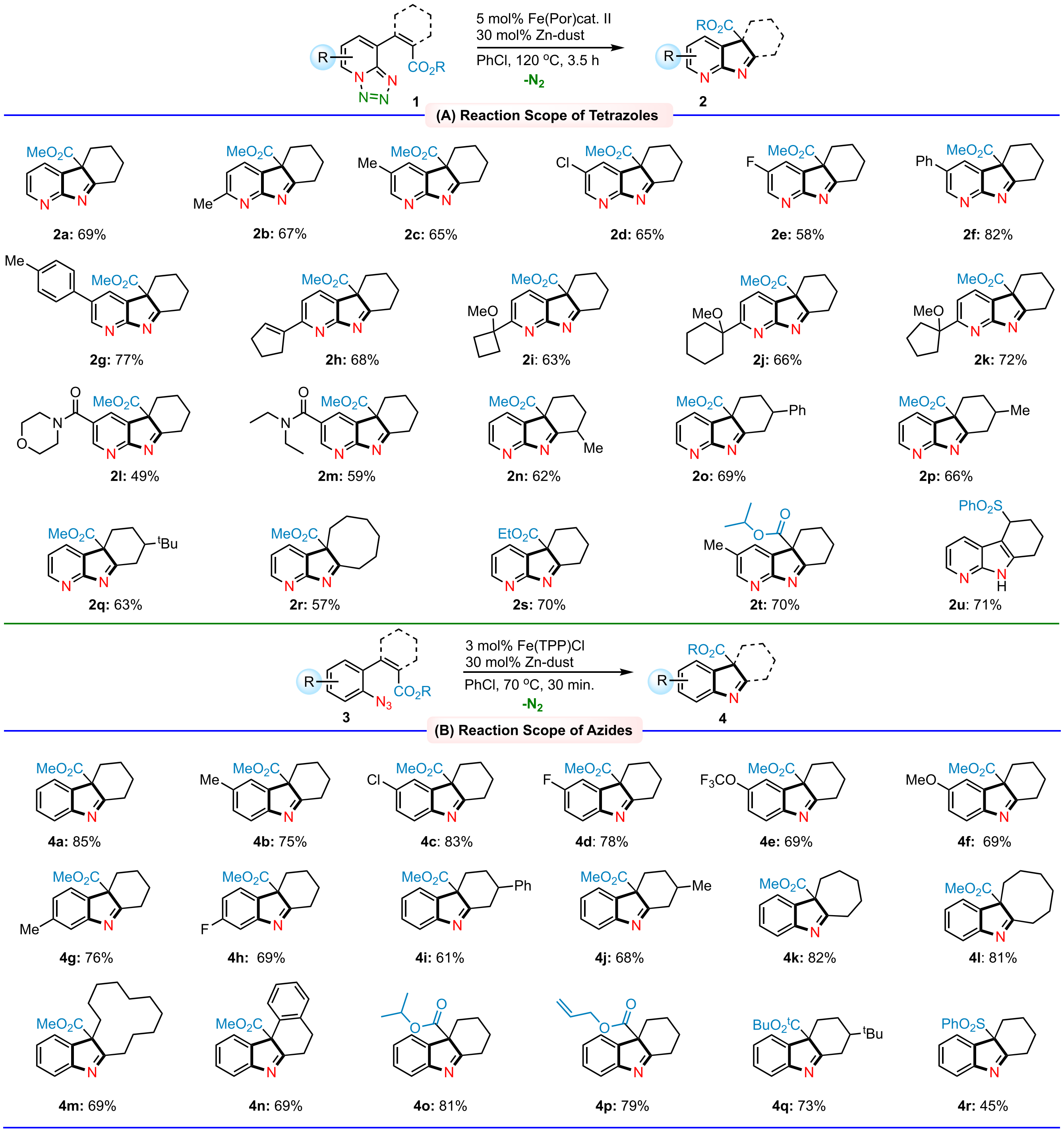




#	Catalyst (mol%)	Reductant (mol%)	Time (h)	Temp. (°C)	Conv. (%)	2a/2a'/2a''
1	Fe(TPP)Cl (5)	Zn(30)	12	120	100	66(61)[b]/21/13
2	Fe(TBPP)Cl (5)	Zn (30)	12	120	100	54/34/12
3	Fe(p-ClTPP)Cl (5)	Zn (30)	12	120	100	62/18/20
4	Fe(TMPP)Cl (5)	Zn (30)	12	120	100	53/34/13
5	Fe(Por) cat.-I (5)	Zn (30)	12	120	100	64/16/18
6	Fe(Por) cat.-II (5)	Zn (30)	12	120	100	73(69)[b]/09/18
7	Fe(Por) cat.-II (5)	Zn (30)	3.5	120	100	74(69)[b]/08/18
8	Fe(Por) cat.-II (5)	Zn (30)	3.5	100	76	75/09/16
9	Fe(Por) cat.-II (5)	Zn (30)	3.5	80	18	76/11/13
10	Fe(Por) cat.-IV (5)	Zn (30)	12	120	100	33/60/07
11	Fe(Por) cat.-VI (5)	Zn (30)	12	120	100	22/74/04
12	Fe(Por) cat.-VII (5)	Zn (30)	4	120	100	05/79(71)[b]/16
13	Fe(Por) cat.-VII (5)	Zn (30)	4	100	38	05/80/15
14	Fe(Por) cat.-VII (5)	Zn (30)	4	80	<5	–
15	Fe(Por) cat.-II, VII (5)	-	12	120	0	0/0/0

[a] The scale of the reaction was 0.25 mmol. NMR conversions (**2a** + **2a′** + **2a″**) were determined using 1,3,5-trimethoxybenzene as an internal standard. [b] The value in parentheses is the isolated yield. See the SI for details.

Table 2. Substrate Scope of Ester Migration with Various Tetrazoles and Phenyl Azides[a]

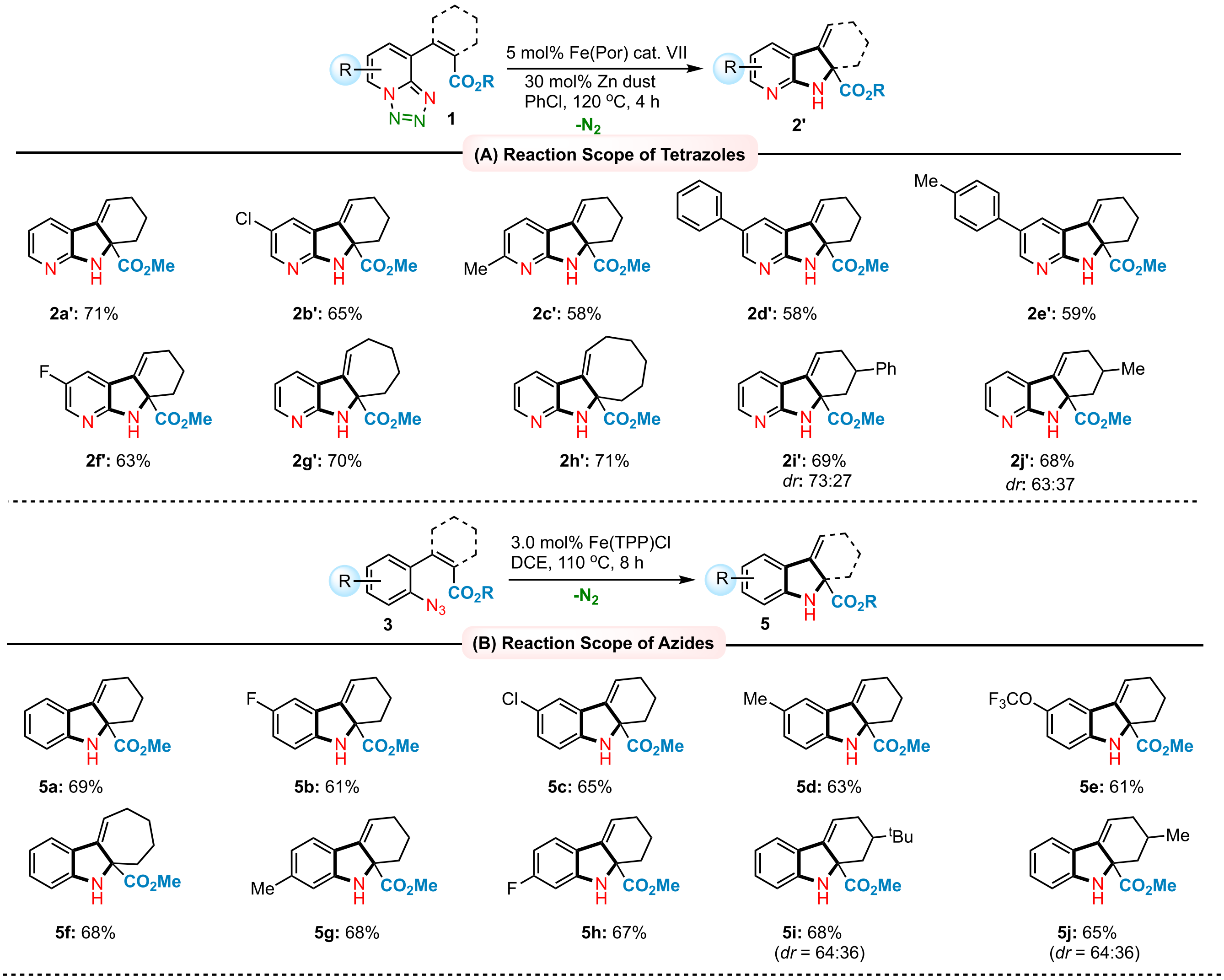


[a] Scale of reaction 0.25 mmol. Isolated yields are reported.

presence of 3 mol % Fe(TPP)Cl along with 30 mol % Zn dust at 70 °C. For instance, a number of electronically different and substituted aryl azides including variously substituted cyclohexenyl groups exhibited excellent reactivity for the ester migration (**4a**–**4j**). Expanding the *o*-cyclohexenyl group to cycloheptane, cyclooctane, and cyclododecanone also proved equally compatible and provided various medium to macrocyclic ring compounds (**4k**–**4m**). Notably, the method enables the formation of the tetracyclic core with the ester handle (**4n**). Apart from the methyl ester, the isopropyl, allyl, and *tert*-butyl esters also produced the migration products in satisfactory yields (**4o**–**4q**). Notably, instead of an ester group, a substrate bearing a $-SO_2Ph$ group can also undergo migration to give the 1,2-SO_2Ph migrated product (**4r**) in 45% yield.

After exploring the rearrangement reaction via ester migration for the tetrazoles, the scope of the C(sp^3)−H allylic amination was tested (Table 3A), where it was noticed that irrespective of the nature of the substituents, the reaction proceeds smoothly to afford exclusively the allylic C(sp^3)−H

Table 3. Catalyst-Controlled Allylic C(sp^3)−H Amination[a]



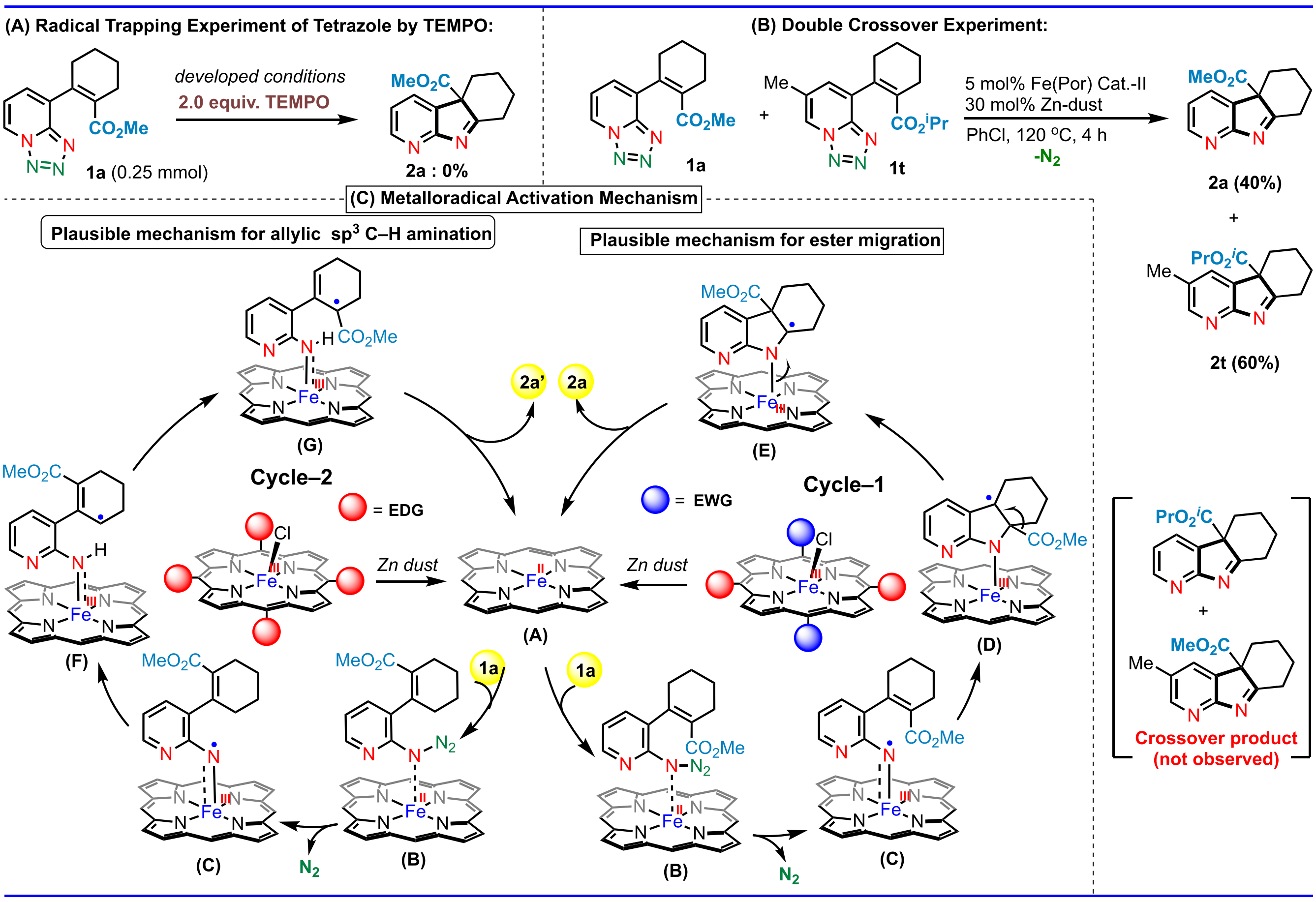
[a] Scale of reaction 0.25 mmol. Isolated yields are reported.

amination products. Notably, this is the first example of metalloradical catalysis where two different types of transformation can be achieved by the appropriate choice of two different catalysts. To our delight, it has been observed that a large number of phenyl azides can also be used under the iron-based metalloradical catalysis for the C(sp^3)−H allylic amination (Table 3B). Notably, for switching the molecular rearrangement of phenyl azides toward the allylic amination, we noticed that the requirement of Zn dust is not necessary.

To gain insight into the reaction mechanism, we conducted several control experiments. For example, the reaction with TEMPO did not form the desired product, which suggested the radical nature of the 1,2-ester migration reaction (Chart 3A). Notably, while the TEMPO-trapped products can be detected by HRMS, several attempts to isolate the trapped products failed, perhaps due to the unstable nature of the products. The radical nature was further confirmed by EPR experiments (see the SI). To understand the nature of the migration step, a double crossover experiment (Chart 3B) was performed that afforded exclusively two products (**2a** and **2t**), without any crossover, which indicates that the 1,2-ester migration is either concerted or the 1,2-shift occurs faster than diffusion. Next, to understand the electronic effect of the reaction, a series of competitive experiments were performed with the systematically varied substitution (both electron-donating and electron-withdrawing groups) at the *para* position of the pyridine ring of the tetrazole substrates. We noticed that both electron-donating and -withdrawing substituents increase the rate of the reaction over the unsubstituted substrate (**1a**). Analyzing the reaction rates using the Hammett equation, we observed a V-shaped curve (SI Figure 1), which either indicates that the reaction might be the consequence of two distinct mechanisms depending on the electronics of the substrates or alternatively suggests that the reaction follows a radical mechanism.[18]

Based on these experimental findings and literature precedents,[7c,9l,19] we proposed a radical activation mechanism (Chart 3C). At first, Zn reduces Fe^{III}(Por)Cl to produce the active catalytic species Fe^{II}(Por) (**A**) through a single electron transfer. Then substrate coordination occurs, generating a metal-bound complex (**B**), which upon loss of N$_2$ forms the Fe^{III}−nitrene radical intermediate (**C**). Intermediate **C** can participate in two distinct reaction pathways, leading to different product outcomes such as ester group migration

Chart 3. Mechanistic Studies



and allylic C(sp^3)−H bond amination. In Cycle 1, nitrene **C** readily reacts with the adjacent π cloud to produce intermediate **D**. A subsequent 1,2-ester migration then occurs, affording the desired product **2a** via intermediate **E** along with regeneration of the catalytic cycle. In Cycle 2, intermediate **C** abstracts an allylic hydrogen to generate allyl radical **F**. Through allylic resonance, this radical is delocalized to form intermediate **G**, and radical recombination leads to the formation of the desired allylic amination product **2a′**. The observed chemoselectivity switch can be attributed to the different electronic natures of the iron−nitrenoid intermediates. Based on literature precedents,[17,20] we postulate that the the iron complex (Fe(Por)-cat-II) bearing two C_6F_5 substituents renders the iron−nitrenoid intermediate highly electrophilic, thereby promoting nitrene addition across the double bond. In contrast, the catalyst (Fe-(Por)-cat-VII) featuring electron-donating substituents on the porphyrin ligand makes the iron−nitrenoid intermediate energetically favorable toward allylic C(sp^3)−H bond abstraction.

In conclusion, an iron-based catalyst-controlled chemoselective intramolecular molecular rearrangement via an ester migration and an allylic C(sp^3)−H amination has been developed. Using the developed strategies, two different product classes have been achieved that were inaccessible by previously reported methods. Mechanistic investigations disclosed that while both reactions follow a metalloradical activation mechanism, the nature of the iron−nitrene intermediate is entirely different, which is postulated to be the driving force for these two unique transformations. Collectively, this discovery highlights the development of iron-based MRC that would uncover wide applications in the context of drug discovery research and natural product synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c07955.

Full characterization, copies of all spectral data, and experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

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