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**Title:** A Fe(II)-Based Metalloradical Activation Approach: Overriding Traditional Click Chemistry Towards Denitrogenative Annulation

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# A Fe(II)-Based Metalloradical Activation Approach: Overriding Traditional Click Chemistry Towards Denitrogenative Annulation

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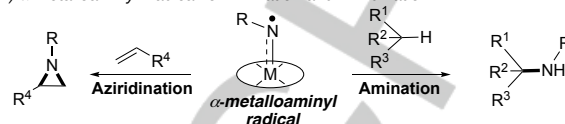
**Abstract:** A unique concept for the intermolecular denitrogenative annulation of 1,2,3,4-tetrazoles and alkynes is discovered using catalytic amount of Fe(TPP)Cl and Zn dust. The developed concept overrides the traditional more favored click reaction between organic azide and alkynes. It has been proved that the reaction underwent via an unprecedented metalloradical activation mechanism, which successfully overturn the ionic click reaction. We anticipate that the method will advance access for the construction of important basic nitrogen heterocycles, which will enable to discover new drug candidates.

The concept of metalloradical activation for radical cyclization has recently been demonstrated as one of the most advanced strategies. The groups of Zhang and de Bruin have given a new dimension of this concept based on the Co(II)–metalloradical chemistry for numerous synthetic transformations.<sup>[1,2]</sup> Moreover, it has also been shown that the concept of metalloradical activation could efficiently be employed for the radical C–H amination<sup>[3]</sup> and radical olefin aziridination<sup>[4]</sup> via the generation of  $\alpha$ -metalloaminy radical as the key intermediates derived from the organic azides (**Scheme 1A**). In this context, we have reported a Co(II)-based metalloradical activation of 2-(diazomethyl)pyridines resulting from the 1,2,3-triazoles for the denitrogenative radical transannulation and cyclopropanation.<sup>[5–7]</sup> Nevertheless, synthetic utility of these approaches is far from being fully investigated.

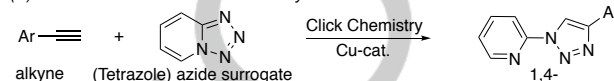
On the other hand, metalloradical activation of 1,2,3,4-tetrazoles (surrogates of organic azides) for radical annulation with terminal alkynes is entirely underdeveloped till date. Owing to the high reactivity of the 2-azidopyridine (1,2,3,4-tetrazole), it readily undergoes the traditional click reaction with alkyne in presence of transition metal catalysts (**Scheme 1B**).<sup>[6]</sup> As a result, it was impossible to think about other types of synthetic transformations between the reaction of 2-azidopyridines (1,2,3,4-tetrazoles) and alkynes. Moreover, over the past forty years, the chemistry of 1,2,3,4-tetrazole was mainly explored as denitrogenative photochemical and thermal nitrene-nitrene rearrangement pioneered by the Wentrup group.<sup>[7]</sup> Furthermore, while 1,2,3-triazoles are known<sup>[8]</sup> to undergo denitrogenative annulation with metal catalysts, 1,2,3,4-tetrazoles proved entirely inactive for annulation, except our recently developed intramolecular annulation via metal-nitrene formation (**Scheme 1C**).<sup>[9]</sup> Thus, it would be highly interesting to design a concept for the intermolecular denitrogenative annulation, which would override the traditional click reaction. Herein, we report a novel concept for the denitrogenative intermolecular annulation between 1,2,3,4-tetrazole (an azide surrogate) and alkyne via a Fe(II)-based metalloradical activation mechanism, which completely overturn the traditional click reaction (**Scheme 1D**).<sup>[10]</sup>

Previous work:

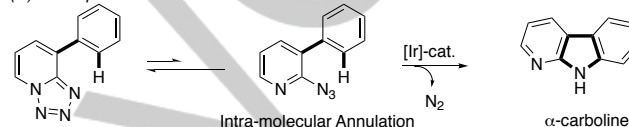
(A)  $\alpha$ -Metalloaminy Radical for Amination and Aziridination



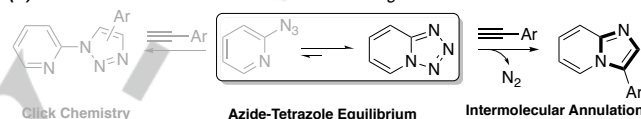
(B) Click Reaction of Tetrazole and Alkyne



(C) Concept of Intra-molecular Annulation



(D) This work: Intermolecular Annulation Overriding Traditional Click Reaction



Scheme 1. Previous Overviews and New Challenge

We started our initial studies selecting tetrazole (**1a**) and phenylacetylene (**2a**) as test substrates and the reactions were conducted using a variety of transition metal catalysts (**Table 1**, see SI, for detail). To our surprise, metal catalysts such as Rh, Ir (that are known<sup>[11]</sup> to produce metal-nitrene), Pd, Zn, Fe, In and Ru remain completely ineffective towards forming either the click product or the annulation product. For this extreme ineffectiveness of the tetrazole, we reasoned that strong coordination<sup>[12]</sup> of these metal catalysts with both azide and pyridine nitrogen atoms shut down the catalytic process for the formation of the metal-nitrene intermediate.

Table 1. Initial Screening of Denitrogenative Annulation<sup>[a]</sup>

	1.2 eq. $\equiv$ -Ph( <b>2a</b> )	2-20 mol% [M]-cat.	0-20 mol% additive solvent, T °C, 24 h	3a	3a'	3a''
<b>Initial Screening Results:</b>						
Rh-cat. (31 conditions)		Ir-cat. (7 conditions)		Ru-cat. (11 conditions)		
outcomes: 3a/3a'/3a'' = 0/0/0		outcomes: 3a/3a'/3a'' = 0/0/0		outcomes: 3a/3a'/3a'' = 0/0/0		
In-cat. (5 conditions)		Zn-cat. (7 conditions)		Fe-cat. (6 conditions)		
outcomes: 3a/3a'/3a'' = 0/0/0		outcomes: 3a/3a'/3a'' = 0/0/0		outcomes: 3a/3a'/3a'' = 0/0/0		
Pd-cat. (6 conditions)		Cu-cat. (37 conditions)		Ag-cat. (2 conditions)		
outcomes: 3a/3a'/3a'' = 0/0/0		outcomes: 3a/3a'/3a'' = 0/100/0		outcomes: 3a/3a'/3a'' = 0/70/30		
<b>Screening Results with Metal-porphyrin Catalysts:</b>						
#	[M(TPP)-cat]	solvent	T °C	ratio, 3a/3a'/3a''	conv. (%)	
1	Cu(TPP)	PhH	150	0/100/0	>99	
2	Fe(TPP)Cl	PhH	130	0/20/80	>99	
3	Co(TPP)	PhH	130	26/37/37	>99	

[a] Reactions were conducted with 0.5 mmol scale and GC/MS ratios were determined using dodecane as internal standard, for details reaction conditions, see: SI.

On the other hand, most of the Cu- and Ag-catalysts resulted only the regular click chemistry product. Thus, we turned our attention towards metalloporphyrin-based catalytic systems, which are well-known<sup>[3]</sup> to activate organic azide for C–H

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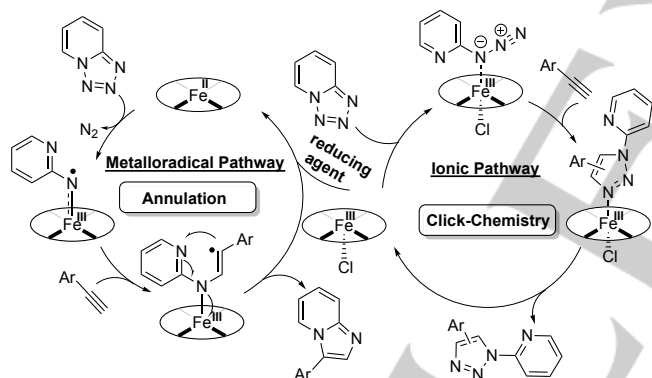
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<sup>†</sup>SR and HK contributed equally to this work.

amination via metal-nitrene generation. Thus, we first conducted a reaction employing Cu(TPP) at high temperature, which afforded energetically more favored click chemistry product quantitatively (Table 1, entry 1). Likewise, performing the same reaction using Fe(TPP)Cl, we did not see even a trace amount of the desired annulation product, instead, it afforded the 1,5-disubstituted click product as the major isomer (entry 2). To our delight, initial breakthrough was observed when the reaction was repeated with Co(TPP) as a metalloradical catalyst, which resulted the annulation product as minor and click chemistry product as the major one (entry 3).

Thus, inspired by these initial results using the metalloradical activation concept by Zhang and de Bruin,<sup>[1,2,3,4]</sup> and considering a pioneering work by Arnold and co-workers<sup>[13]</sup> using Fe(III) heme-enzyme (cytochrome-P411) biocatalyst to form nitrene intermediate from azide precursor in presence of NADPH reductant, we designed a blueprint (Scheme 2) for the intermolecular annulation, which might override the traditional click chemistry. Based on this blueprint, we hypothesized the following two important considerations, i) requirement of a metalloradical activation manifold, which would overpower the click chemistry enforcing the intermolecular annulation, and ii) replication of Arnold's Fe-heme enzyme/NADPH biocatalytic system by easily redox switchable Fe(TPP)Cl system in presence of a reductant, which could reduce the ferric state of the catalyst to the ferrous state overturning the ionic click chemistry towards the metalloradical activation strategy.



Scheme 2. Blueprint for Annulation Versus Click Chemistry Using Fe-Porphyrin Catalytic System

Accordingly, we performed a reaction using NaBH<sub>4</sub> as reductant in presence of Fe(TPP)Cl at 100 °C and found no reaction occurred (Table 2, entry 1). Employment of LiAlH<sub>4</sub> as reducing agent was also unsuccessful (entry 2). Remarkably, when the same reaction was carried out in presence of Fe(TPP)Cl in combination with a catalytic amount of Zn dust, we observed complete overturn of the reaction from click reaction to the intermolecular annulation affording quantitative conversion into the desired product (entry 3), which is in line with our proposed blueprint.<sup>[14]</sup> To verify the possibility of other reductant, we performed the same reaction using Mn dust, which resulted no reaction (entry 4). Moreover, for better understanding the role of the Zn dust, a control experiment was conducted without the Fe(TPP)Cl catalyst and observed that neither a annulation nor a click reaction occurred (entry 5). However, repeating the same

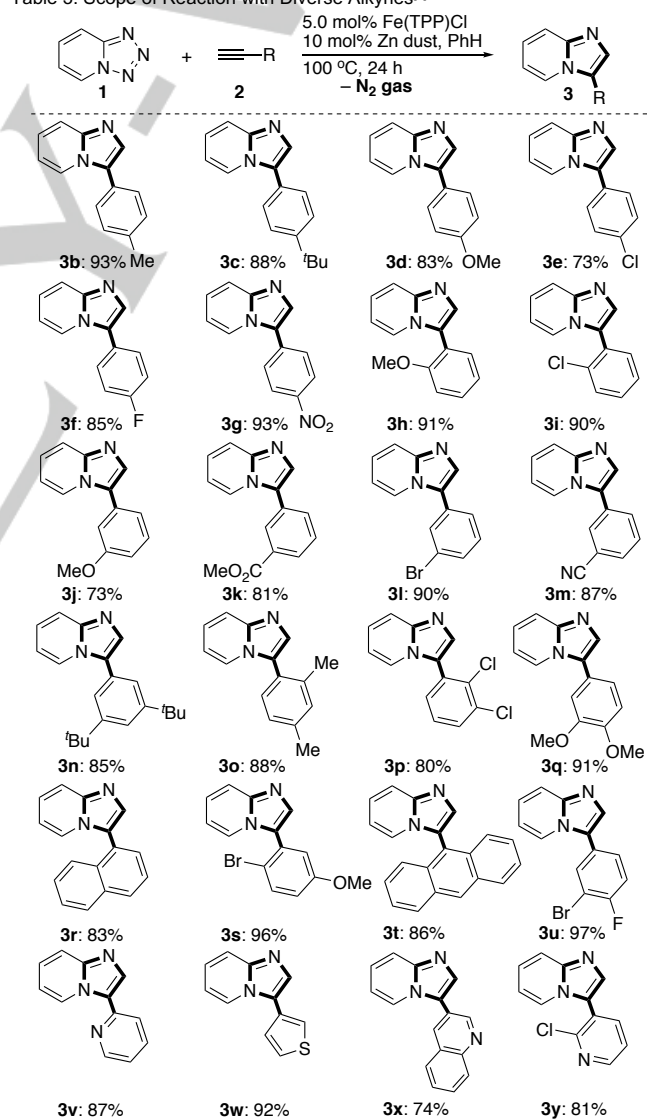
reaction at relatively high temperature (130 °C), we observed complete switching to the click reaction with moderate conversion (entry 6).<sup>[15]</sup>

Table 2. Optimization of the Intermolecular Annulation<sup>[a]</sup>

#	[M]-cat.	reducing agent	T °C	ratio	conv. (%)
1	Fe(TPP)Cl	NaBH <sub>4</sub>	100	0/0/0	0
2	Fe(TPP)Cl	LiAlH <sub>4</sub>	100	0/0/0	0
3	<b>Fe(TPP)Cl</b>	<b>Zn</b>	<b>100</b>	<b>100/0/0</b>	<b>&gt;99 (95)<sup>[b]</sup></b>
4	Fe(TPP)Cl	Mn	100	0/0/0	0
5	no catalyst	Zn	100	0/0/0	0
6	no catalyst	Zn	130	0/100/0	>65

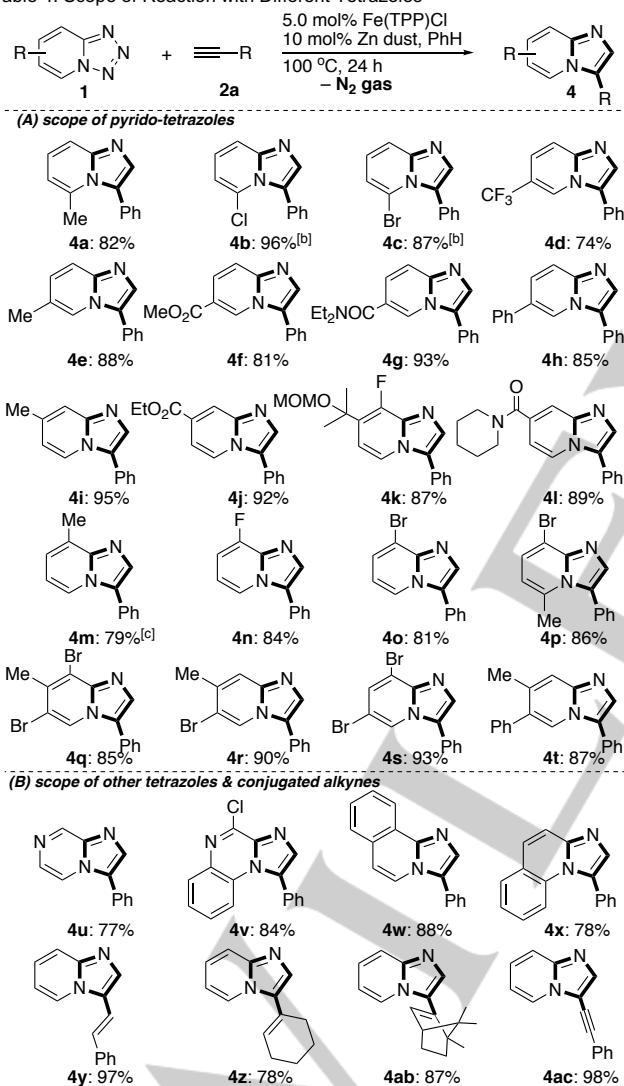
[a] Reactions were conducted with 0.5 mmol scale and GC/MS ratios were determined using dodecane as internal standard. [b] In parentheses, isolated yield is given.

Table 3. Scope of Reaction with Diverse Alkynes<sup>[a]</sup>



[a] Reactions were conducted with 0.5 mmol scale; isolated yields were reported after purification.

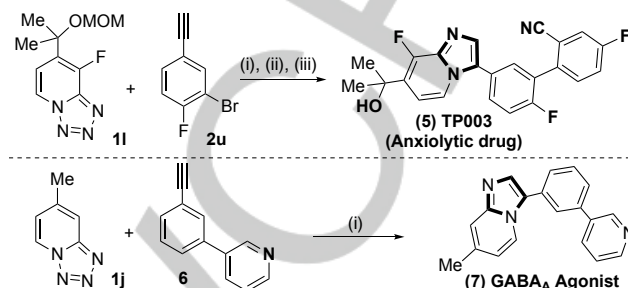
With these optimized conditions, Fe(II)-based metalloradical activation of the intermolecular denitrogenative annulation were performed for a series of terminal alkynes (**Table 3**), different tetrazoles and conjugated alkynes (**Table 4**). To our delight, this newly developed Fe(II)-based metalloradical approach appeared to be very general irrespective of the substituents present in the alkynes (such as halogen, alkyl, alkoxy, nitro, ester, nitrile etc.) producing diversely substituted imidazopyridines with excellent yields (see SI for details). In this context, it deserves mentioning that in all cases, we did not see even a trace amount of the click chemistry products. Finally, to highlight the utility of our newly discovered method, we have synthesized anxiolytic drug TP003 (**5**) and an important molecule which is GABA<sub>A</sub> agonist (**7**) with excellent yield from the corresponding tetrazoles (**Scheme 3**).

Table 4. Scope of Reaction with Different Tetrazoles<sup>[a]</sup>

[a] Reactions were conducted with 0.5 mmol scale; isolated yields. [b] Reaction completed within 12 h at 80 °C. [c] Reaction conducted at 120 °C.

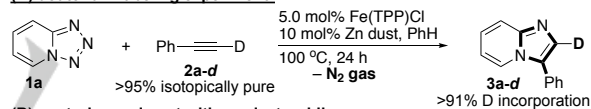
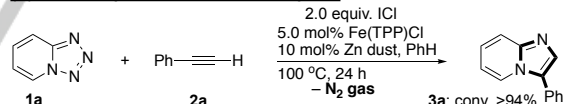
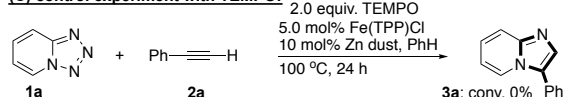
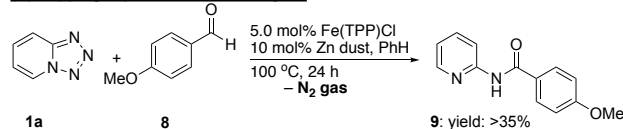
However, we did not see any halo-adduct, instead we found desired product formation quantitatively. Thus, this finding also discards the ionic mechanism. Third, as per our proposed blueprint (**Scheme 2**) for the metalloradical activation

mechanism, we performed a reaction in presence of TEMPO, which shut down the reaction completely (**Scheme 4C**). This outcome suggests the possibility of the proposed metalloradical activation mechanism. Fourth, to provide further proof of this radical activation mechanism, we attempted to trap the intermediate employing benzaldehyde, which is well-known<sup>[3f]</sup> to react with azide via acyl radical intermediate (**Scheme 4D**).



**Scheme 3. Short Synthesis of Important Molecules.** Conditions: (i) 5 mol% Fe( TPP)Cl, 10 mol% Zn, PhH, 100 °C, 24 h. (ii) 5.0 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 1.2 equiv. 2-cyano-4-fluoro phenylboronic ester, 2.0 equiv. Cs<sub>2</sub>CO<sub>3</sub>, 2/1 (PhMe/DMF), 100 °C, 12 h. (iii) 3.0 equiv. 4(N) HCl in dioxane, rt, 30 min.

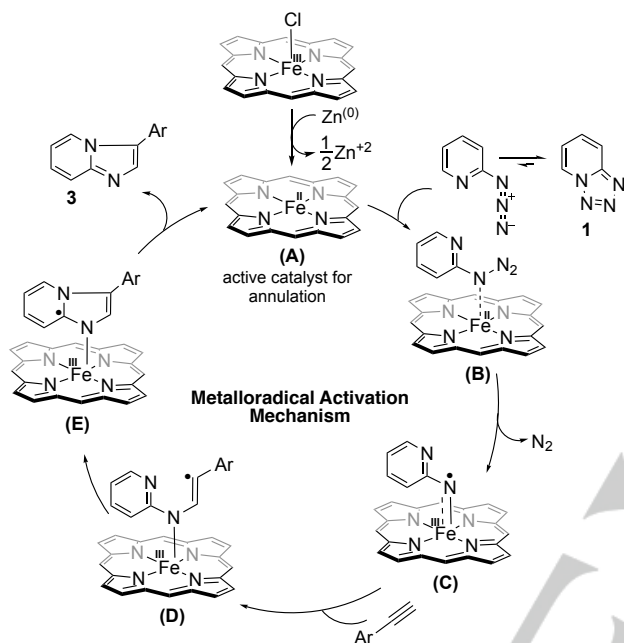
To provide mechanistic insight of the metalloradical annulation, we performed some preliminary control experiments (**Scheme 4**). First, a deuterium labeling experiment was carried out, which resulted almost complete preservation of the deuterium atom into the product (**Scheme 4A**). This result excludes the possible involvement of the ionic mechanism. Second, we conducted the annulation adding an electrophilic halogenating agent (ICI), hypothesizing that if the reaction follows an ionic mechanism, it should afford the corresponding halo-adduct (**Scheme 4B**).

**(A) deuterium labeling experiment:****(B) control experiment with an electrophile:****(C) control experiment with TEMPO:****(D) trapping experiment with aldehyde:**

Scheme 4. Mechanistic Studies: Control Experiments

Accordingly, a control experiment was performed using benzaldehyde instead of alkyne. To our delight, we were able to trap the intermediate (**9**), which is characterized by spectroscopic data. Finally, EPR spectroscopic data ( $g = 1.97$ ) of the crude reaction mixture (see SI for details) demonstrated the generation of the organic radical species. Thus, based on these experimental evidences, a metalloradical activation mechanism is proposed (**Scheme 5**). First, Zn reduces the Fe<sup>III</sup>(TPP)Cl to form the active catalyst Fe<sup>II</sup>(TPP) (**A**) via single electron transfer which was confirmed by a red-shift in the UV

spectra (SI for details). After coordination with azide nitrogen,  $\alpha$ -Fe(III)-nitrene radical intermediate (**C**) is formed by the loss of dinitrogen from species (**B**). Upon subsequent trapping with alkyne, the intermediate (**C**) produces  $\gamma$ -Fe(III)-vinyl radical intermediate (**D**), which undergo radical addition intramolecularly to the C=N bond to generate a new  $\beta$ -Fe(III)-alkyl radical intermediate (**E**) where the fused five-membered ring is constructed upon C-N bond formation. Subsequently, the beta-Fe(III)-alkyl radical intermediate (**E**) proceeds  $\beta$ -radical scission to break N-Fe bond and form C=N double bond, affording the product (**3**) regenerating the catalytic cycle.



Scheme 5. Proposed Metalloradical Activation Mechanism

In conclusion, we have developed a new metalloradical activation concept for the intermolecular denitrogenative annulation, which completely overturn the traditionally more favored click reaction. It has been demonstrated that the reaction proceeds via an unprecedented metalloradical activation mechanism. The method requires commercially available cheap Fe(TPP)Cl catalyst in combination of a catalytic amount of Zn dust as reducing agent. This is the first report for the denitrogenative intermolecular annulation via metal-nitrene formation. The developed method shows a wide range of substrate scope and functional group tolerance. The synthetic utility of the developed method is showcased with the short synthesis of valuable bioactive molecules.<sup>[16]</sup> We do believe that the developed concept will have extensive impact in this area for solving the long-standing challenging problem for the overriding the traditional click chemistry towards intermolecular annulation.

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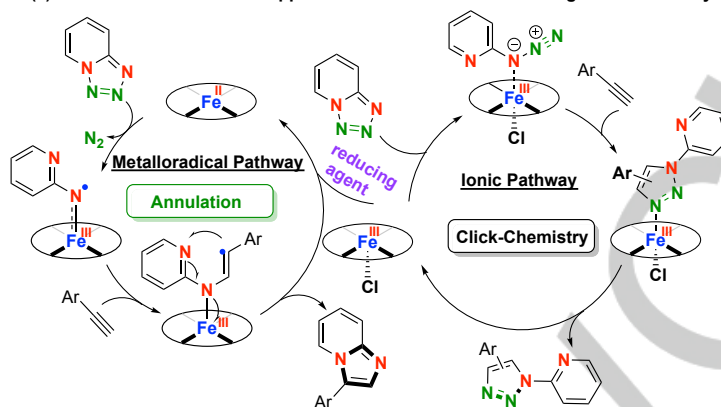
**Keywords:** Denitrogenative annulation • Fe-nitrene • catalysis • nitrogen-heterocycles • Metalloradical

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- [15] Importantly, performing a reaction at 130 °C temperature in presence of Fe(TPP)Cl and Zn dust, we observed only annulation product and no click reaction occurred, which is demonstrating that our reaction conditions is highly effective even at high reaction temperature.
- [16] For Fe-catalyzed nitrogen heterocycle synthesis, see: E. T. Hennessy, T. A. Betley, *Science* **2013**, *340*, 591.

## COMMUNICATION

A unique concept for the intermolecular denitrogenative annulation of 1,2,3,4-tetrazoles and alkynes is discovered employing a catalytic amount of  $\text{Fe}(\text{TPP})\text{Cl}$  and Zn dust. This concept overcomes the traditional click reaction between organic azide and alkynes.

**Fe(II)-Metalloradical Activation Approach for Annulation Overcoming Click Chemistry**

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**A Fe(II)-Based Metalloradical Activation Approach: Overriding Traditional Click Chemistry Towards Denitrogenative Annulation**