A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202009078

Link to VoR: https://doi.org/10.1002/anie.202009078

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Dual Reactivity of 1,2,3,4-Tetrazole: Manganese-Catalyzed Click Reaction and Denitrogenative Annulation

*Hillol Khatua, Sandip Kumar Das, Satyajit Roy, and Buddhadeb Chattopadhyay**

Abstract: *A general catalytic method using Mn-porphyrin-based catalytic system is discovered that enables two different reactions (click reaction and denitrogenative annulation) affording two different classes of nitrogen heterocycles, such as 1,5-disubstituted 1,2,3-triazoles (with a pyridyl motif) and 1,2,4-triazolo-pyridines. Mechanistic investigations suggest that while click reaction likely proceeds through an ionic mechanism, which is different from the traditional click reaction, denitrogenative annulation undergoes likely via an electrophilic metallonitrene intermediate rather than the metalloradical intermediate. Collectively, the discovered method is highly efficient that offer obvious advantages over other methods, as it excludes multi-step synthesis of these classes of N-heterocyclic molecules and produces only environmentally benign N_2 gas by-product.*

Introduction

In the chemical community, organic azide is considered as one of the most intriguing and versatile synthetic intermediates[1] that have a profound role in diverse fields of research. These are the key components for the construction of complex *N*-heterocycles[2,3] owing to the high reactivity, easy availability, empowerment of exhibiting different kinds of synthetic transformations via either click reaction (1,3-cycloaddition) or the formation of metal-nitrene with transition metal catalysts.[4] Similarly, it has also been demonstrated that 1,2,3-triazoles could be utilized as an important precursory platform for a wide number of useful reactions,[5,6] which undergo via the generation of metal-carbene with transition metal catalysts. In sharp contrast, whereas the chemistry of organic azides and 1,2,3-triazoles studied extensively, 1,2,3,4-tetrazole (a surrogate of azide[7] bearing an important pyridyl unit) remained almost unutilized. In 1969, Huisgen and Fraunberg for the first time studied[8] the reactivity of 1,2,3,4-tetrazole (**Figure 1A**) and developed three important reactions, such as, (i) Cu-powder-catalyzed synthesis of nitrogen heterocycles at 120 °C, which undergo via a Cu-nitrene intermediate (ii) cycloaddition reactions with alkynes, and (iii) intermolecular aminations. While these pioneering results revealed excellent opportunity for the development of new synthetic methods, unfortunately, the chemistry was not developed. On the other hand, since the last four decades, only nitrene-nitrene rearrangement of 1,2,3,4-tetrazole has been investigated using flash vacuum process at high reaction temperature (>500 °C), pioneered by Wentrup group (**Figure 1B**).[9] Thus, these experimental findings by Huisgen and Fraunberg, and Wentrup led us an important conclusion that the nitrene generated by the FVT at high reaction temperature, if trapped by catalytic amount of transition metal, could be utilized as an important intermediate for the organic synthesis, although extremely difficult and challenging.

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Thus, considering this challenge, we initiated an investigation to capture the *N*-pyridyl metal-nitrene from this 1,2,3,4-tetrazole hypothesizing that the *N*-pyridyl metal-nitrene would be applied for the construction of various *N*-heterocyclic scaffolds. To our delight, we discovered a new method to access *N*-pyridyl metal nitrenes using an Cp*Ir(III) cation through an electrocyclization to construct aza-carbazoles and aza-indoles (**Figure 1C**).[10] Although, this was the first catalytic method of capturing productively a *N*-pyridyl nitrene from a 1,2,3,4-tetrazole, where the presence of the pyridine changes the fragmentation to produce a nitrene instead of the metal carbene as reported earlier by Murakami and co-workers,[11] the method suffer from many shortcomings, such as, highly expensive Cp*Ir catalyst, high catalyst loadings, high reaction temperature, only applicable for the intramolecular amination/annulation and limited scope for other synthetic transformations. Using that developed method, we attempted to make many important and valuable *N*-heterocyclic molecules, for example, 1,5-disubstituted-1,2,3-triazoles (bearing the pyridyl handle in one side of the triazole for the medicinal applications), although, we did not get any success. Moreover, attempted synthesis of the 1,2,4-triazoles that are the main API of many scaffolds were unsuccessful (**Figure 1D**).[12] To overcome these shortcomings, we also developed a method using Fe-based metalloradical strategy,[3] where we have demonstrated a complete switch from the traditional click reaction towards the intermolecular denitrogenative annulation (**Figure 1E**).[13] The reaction underwent via the generation of the metalloradical radical intermediate. Unfortunately, this method also does not solve the problems as stated earlier. Here, we report a general Mn-catalyzed system that enables a highly site selective 1,3-cycloaddition (click reaction) giving exclusively the 1,5-disubstituted click reaction product and a denitrogenative annulation for the quick access of 1,2,4-triazoles[14] (**Figure 1F**). Importantly, these are the core structural unit of numerous medicinally important molecules (**Figure 1D**). The discovered method is highly efficient and offer obvious advantages over other methods, as it excludes multi-step synthesis of these classes of *N*-heterocyclic molecules and produces only environmentally benign N_2 gas by-product.

Result and Discussion

At the outset of this investigation, we first attempted the proposed click reaction between the tetrazole (**1a**) and phenylacetylene (**2a**) using the reported reaction conditions.[13] However, what we observed is either no reactions or a traditional click reaction for the preparation of 1,4-disubstituted 1,2,3-triazoles and in some cases a mixture of 1,4- and 1,5-disubstituted-1,2,3-triazoles (**Table 1**, entries 1-3, see SI for details). Since, Ru complexes are known[4h] to produce the 1,5-click product from simple organic azides, thus we were curious whether the Ru-catalyzed conditions would be applicable for this complex tetrazole system. Accordingly, we tested various Ru-based catalytic systems. Unfortunately, none of them exhibited their catalytic activity towards the formation of the trace amount of the products (entries 4-5).

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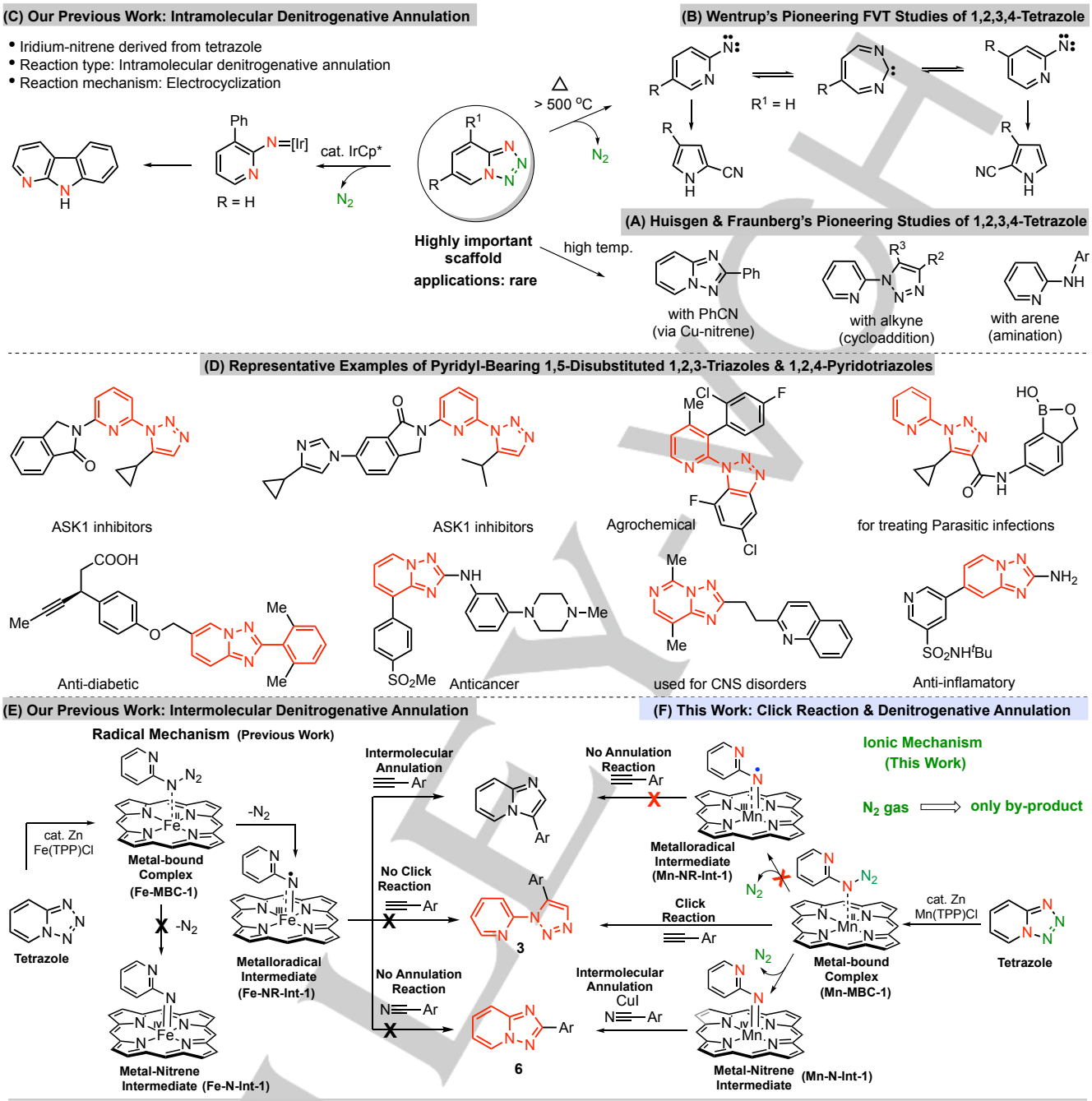
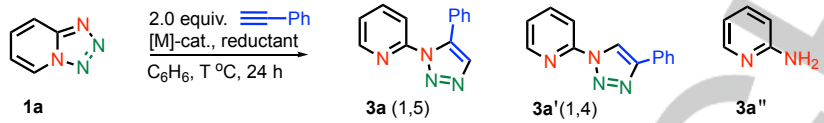


Figure 1. (A), Huisgen and Fraunberg's pioneering work of 1,2,3,4-tetrazole. **(B),** Wentrup's pioneering work for nitrene-nitrene rearrangement of 1,2,3,4-tetrazoles via FVT process. **(C),** First report of pyridyl-bearing Ir-nitrene intermediate derived from 1,2,3,4-tetrazoles for organic synthesis. **(D)**, Representative examples of important molecules pyridyl-bearing 1,5-disubstituted-1,2,3-triazoles and 1,2,4-pyridotriazoles. **(E)**, Previous report of metalloradical activation of 1,2,3,4-tetrazoles for intermolecular denitrogenative annulation. **(F)**, Proposed design principle for the present work of 1,3-cycloaddition (click reaction) and denitrogenative annulation with nitriles.

For the ineffectiveness of these catalysts, we reasoned that the azide coordinated Ru-catalyst is deactivated[15] by the chelation with the nitrogen atom of the pyridine ring. Next, considering our prior working hypothesis using Fe-nitrene radical intermediate (**Fe-NR-Int-1**) and the importance of the Mn-catalytic systems for various synthetic transformations,[16] we made a blueprint. The foundation of the proposed blueprint is based on two important considerations. Firstly, requirement of a similar type of porphyrin-based catalytic system that would be different from our previous design principle that would enforce the reaction through an ionic mechanism generating a metal-bound nitrene type of intermediate instead of the Fe-nitrene radical intermediate. For that reason, we considered to design Mn-based porphyrin systems. The logic behind the selection

of the porphyrin is that due to the relatively bulkiness of the metal-porphyrin system, which would prevent the additional coordination of the metal with the pyridine ring and will facilitate the reaction. Secondly, replacement of Fe to Mn system that would switch the radical activation mechanism towards the ionic mechanism.

Table 1. Screening and Optimization of the Click Reaction[a]



Entry	[M]-cat. (mol%)	Reductant (mol%)	T °C	3a/3a'/3a"	Conversion (%)
1	$Cu(OTf)_2$•C_6H_6 (20)	-	130	0/100/0	>99
2	CuI (20)	-	130	0/100/0	>99
3	Ag(OAc)/bpy (20)	-	130	25/65/10	>99
4	$RuCp(Cl)(PPh_3)_2$ (5)	-	100	0/0/0	0
5	$RuCp^*(Cl)(PPh_3)_2$ (5)	-	100	0/0/0	0
6	Mn(TPP)Cl (5)	-	130	0/0/0	0
7	Mn(TPFPP)Cl (5)	-	130	0/0/0	0
8	Mn(pc) (5)	-	130	0/0/0	0
9[b]	Fe(TPP)Cl (5)	Zn (10)	100	0/0/0	0
10	Mn(TPP)Cl (5)	Zn (10)	100	90/0/10	>99 (85)[c]
11	Mn(TPP)Cl (20)	Zn (40)	80	95/0/05	82 (73)[c]
12	Mn(TPP)Cl (20)	Zn (40)	60	100/0/0	42[d]
13	Mn(salen)Cl (5)	Zn (10)	100	0/0/0	0

[a]Reactions were conducted in 0.5 mmol scale. [b]99% annulated product was observed. [c]In parenthesis isolated yield is reported. [d]Reaction was run for 90 h.

Following this blueprint, we screened several Mn-based catalysts (**Table 1**) and some of them are Mn(TPP)Cl, Mn(TPFPP)Cl, Mn(TMPP)Cl, but all these catalysts were found to be inactive to produce the 1,5-triazoles. Moreover, salen and pthalocyanin framework-based Mn-catalysts, such as Mn(salen)Cl, Mn(pc) and $Mn(pc)SbF_6$ were also proved to be unsuccessful (see SI for details). Notably, in our earlier report, we have shown that the in situ generated Fe(II)(TPP) was effective catalyst for the denitrogenative annulation with alkyne, although click reaction was completely failed. Thus, we questioned that what would occur if we replace the Fe by the Mn in this reaction? Can we develop an active catalytic system that would follow as per our proposed blueprint to deliver the desired product? Accordingly, we performed a reaction using Zn as a reductant in presence of Mn(TPP)Cl at 100 °C. Remarkably, we got exclusively the 1,5-disubstituted triazole[17] (**3a**) along with 10% amine (**3a"**) (entry 10).[18] To suppress the amine (**3a"**), several reactions were performed changing catalyst loadings, reductant loadings and temperature (see SI for details) and we observed that the amine (**3a"**) can be suppressed in presence of 20 mol% catalyst and 40 mol% Zn at either 80 °C temperature (entry 11) that 73% isolated pure product (**3a**) and 5% (**3a"**) or 60 °C temperature (entry 12) that afforded only 40% conversion without any amine (**3a"**). Next, to verify the role of porphyrin unit, we performed a reaction in presence of Mn(salen)Cl and Zn-dust (entry 13), which gave no reaction and thus indicating the essential role of the porphyrin unit in this catalytic reaction. Importantly, since we have noticed 10% amine (**3a"**) as by-product during the course of the click reaction, the origin of the amine might be via the generation of the corresponding Mn-nitrene intermediate as proposed in the design principle (**Figure 1F**).

Using these optimal reaction conditions (conditions-A, entry 10, **Table 1** and conditions-B, entry 11, **Table 1**), we then assessed the generality of the 1,3-cycloaddition (click reaction) with respect to the terminal alkynes, alkyne-bearing important biomolecules and various types of 1,2,3,4-tetrazoles and the results are summarized in **Figure 2** (for detailed discussion, see SI). To demonstrate the utility of the established method, we applied the conditions for the short synthesis of ASK1 inhibitor (**4**) in gram scale (**Figure 2B**).[19] To expand the repertoire of the Mn-catalyzed click reaction, the developed reaction was explored to include some selected and important biomolecule bearing alkynes, such as alkaloids, carbohydrates and estrones. To our delight, all of these biomolecule bearing alkynes underwent 1,3-cycloaddition (click) reactions to afford the desired products in good yields (**3ad-3ah**). Notably, the regiochemical assignments were confirmed by the 2D-NMR (see SI for details) and other spectroscopic data.[20]

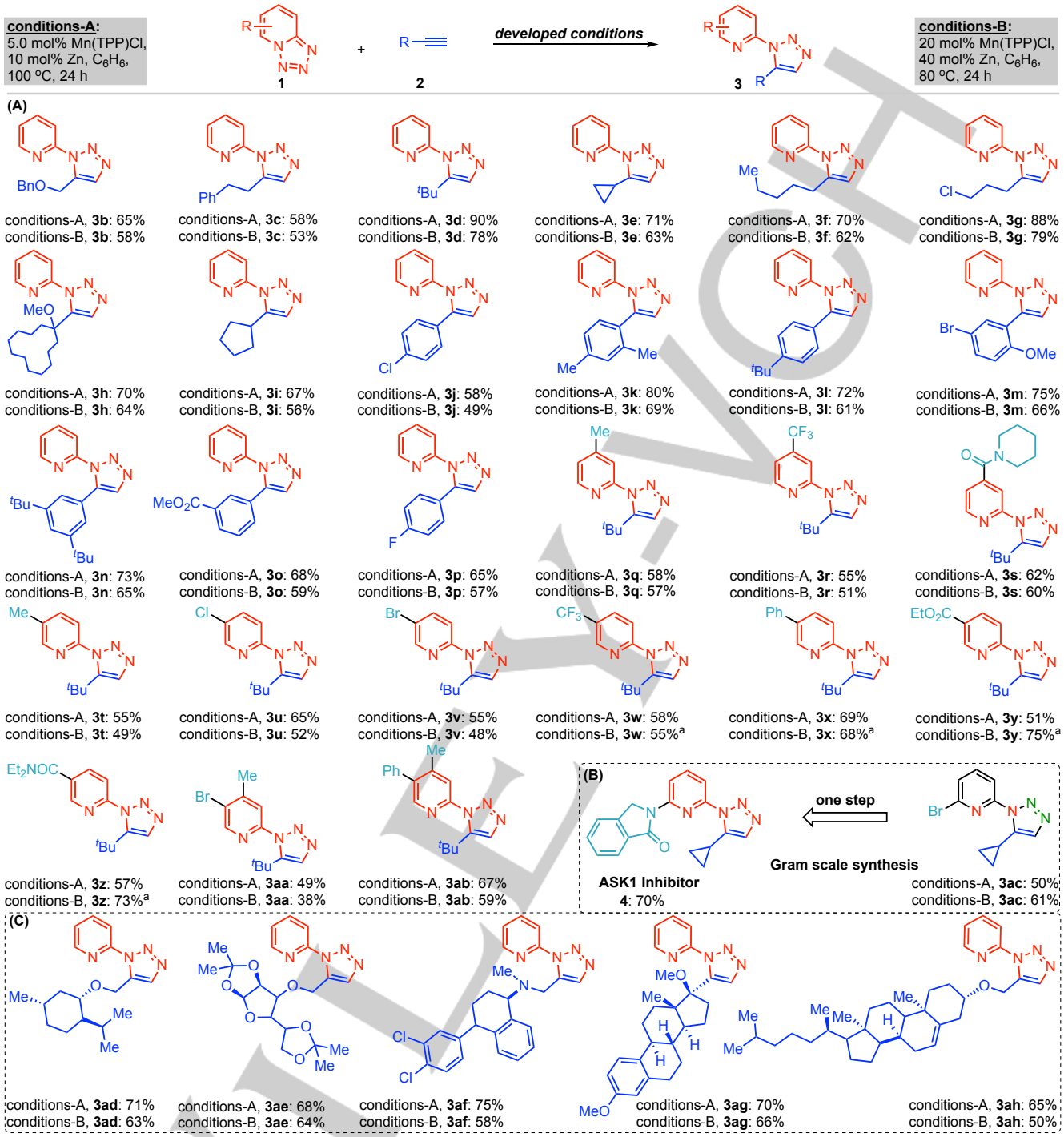
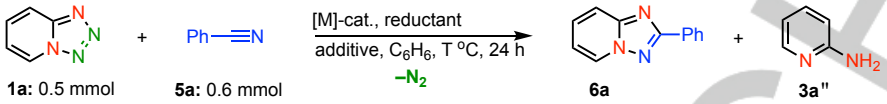


Figure 2. Substrates Scope for the 1,3-Cycloaddition Reaction. (**A**), General scope of the reaction with different tetrazoles and alkynes. Reactions were conducted using conditions-A and conditions-B with 0.5 mmol tetrazoles (**1**) and 2.0 equiv. alkynes (**2**); [a]Reaction temperature is 60 °C. (**B**)**,** ASK1 inhibitor (**4**) was prepared in gram scale from **3ac**. (**C**)**,** Bioactive molecule-bearing alkynes were tested with tetrazole for the 1,3-cycloaddition reaction.

After developing a new catalytic system for the 1,3-cycloaddition (click) reaction using Mn-porphyrin catalyst, we then became interested to develop the denitrogenative annulation between tetrazole and nitrile, which was failed under our previously developed electrocyclization[10] and radical activation mechanism.[13] Thus, we wondered whether our newly developed Mn-catalyzed reaction conditions could solve this long-standing problem or not. For that, we choose tetrazole (**1a**) and benzonitrile (**5a**) as the model substrates. As per our design principle (**Figure 1F**), we anticipated that the metal-bound complex (**Mn-MBC-1**) would generate the Mn-nitrene complex (**Mn-N-Int-1**) if a reaction was performed between tetrazole (**1a**) and benzonitrile (**5a**) upon loss of the dinitrogen molecule.

Accordingly we performed a denitrogenative annulation reaction using Mn(TPP)Cl (5.0 mol%) and reductant Zn-dust (10.0 mol%) in benzene solvent at 100 °C (**Table 2**, entry 5), but to our surprise, we did not see any product in the crude reaction mixture. Increasing the reaction temperature from 100 °C to 140 °C, we saw minor amount of desired product along with the reduced amine product (entry 6). Conducting annulation using Mn(TPFPP)Cl at 100 °C resulted in no reaction (entry 7).

Table 2. Screening and Optimization of the Denitrogenative Annulation Reaction[a]



1a: 0.5 mmol **5a:** 0.6 mmol **6a** **3a"**

Entry	[M]-cat. (mol%)	Reductant (mol%)	Additive (mol%)	T °C	6a/3a"
1	$[Cp^*IrCl_2]_2$ (5)	-	-	130	0/0
2	$[Cp^*IrCl_2]_2$ (5)	-	$AgSbF_6$ (20)	130	0/0
3	Fe(TPP)Cl (5)	Zn (10)	-	100	0/5
4	Mn(TPP)Cl (5)	-		100	0/0
5	Mn(TPP)Cl (5)	Zn (10)	-	100	0/10
6	Mn(TPP)Cl (5)	Zn (10)	-	140	23/20
7	Mn(TPFPP)Cl (5)	Zn (10)	-	100	0/10
8	Mn(TPP)Cl (5)	Zn (10)	$InCl_3$ (5)	100	0/15
9	Mn(TPP)Cl (5)	Zn (10)	$In(OTf)_3$ (5)	100	0/15
10	Mn(TPP)Cl (5)	Zn (10)	$AgBF_4$ (5)	100	0/12
11	Mn(TPP)Cl (5)	Zn (10)	$AgSbF_6$ (5)	100	0/10
12	Mn(TPP)Cl (5)	Zn (10)	$AgNTf_2$ (5)	100	0/10
13	Mn(TPP)Cl (5)	Zn (10)	CuI (5)	100	95(92)[b]/5
14	-	-	CuI (5)	100	0/0
15	-	-	Cu-powder (20)	100	0/0
16[c]	-	-	Cu-powder (100)	120	65/0
17	Mn(TPP)Cl (5)	Zn (10)	Cu-powder (5)	100	0/10
18[d]	Mn(TPP)Cl (20)	Zn (40)	CuI (5)	80	77(62)[b]/7

[a]Reactions were conducted in 0.5 mmol scale. [b]In parenthesis isolated yield is reported. [c]The reaction was run for 3 h. [d]Reaction was run for 36 h.

Thus, we realized that perhaps benzonitrile is not that much reactive relative to the alkyne, as we seen in the denitrogenative annulation between tetrazole and alkyne. In order to activate the nitrile, we decided to see the effects of additives in the same reaction conditions. Hence, the reactions were performed using various additives such as $InCl_3$, $In(OTf)_3$ and different Ag-salts ($AgBF_4$, $AgSbF_6$, $AgNTf_2$) however, no reaction occurred (entries 8-12). Remarkably, when we used 5.0 mol% CuI as an additive in our annulation reaction, we observed 95% product conversion (**6a**, 92% isolated yield, entry 13) based on crude GC-MS

analysis along with 5% reduced product 2-amino pyridine (**3a**"). In this context, it deserves mentioning that a reaction between 1,2,3,4-tetrazole (**1a**) and benzonitrile (**5a**) was reported[8c] in presence of the Cu-powder catalyst, which afforded the product (**6a**) in 62% yield (**Figure 3**). The reaction likely underwent via a Cu-nitrene intermediate. Thus, we were curious whether our annulation reaction would occur in presence of CuI only or not. Accordingly, we performed few reactions without Mn(TPP)Cl and found that use of CuI catalyst (entry 14) was not effective for the reaction (see SI for details).

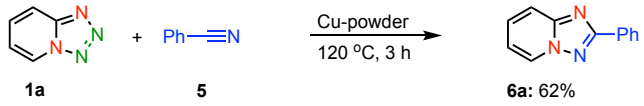


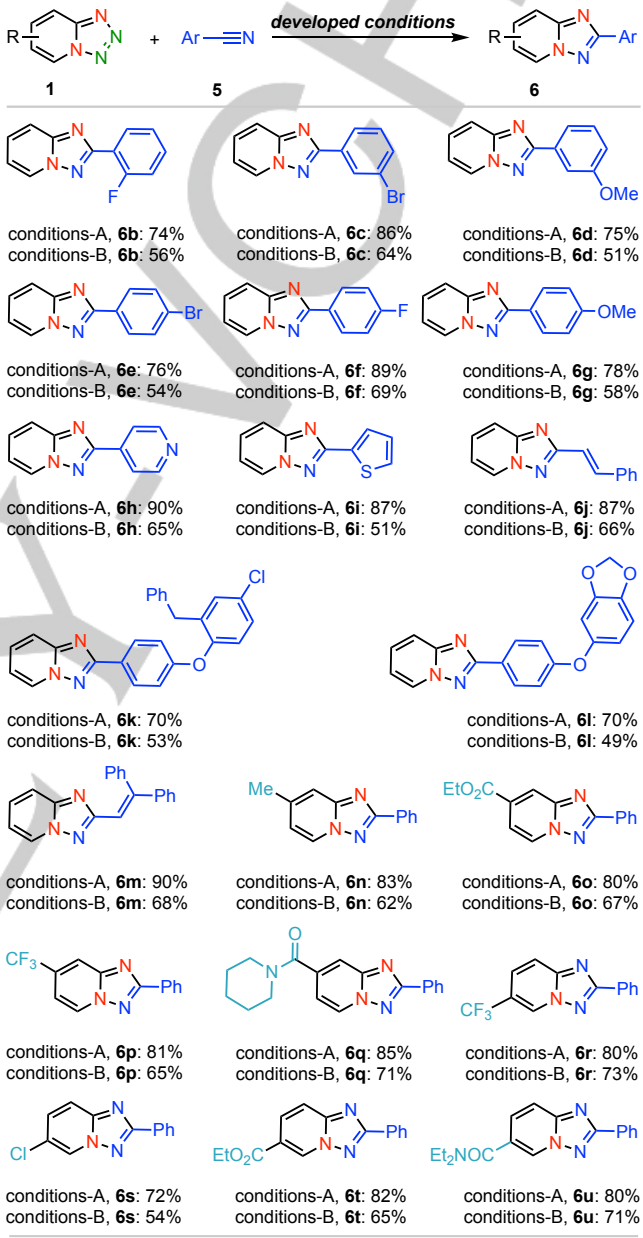
Figure 3. Fraunberg and Huisgen's Report in 1969.

Inspiring by Fraunberg and Huisgen's reaction, we also were curious to see the effect of the reaction using catalytic amount of Cu-powder and performed a reaction using 20 mol% Cu-powder (entry 15) at 100 °C, which resulted in no reaction. Repeating the same reaction using 100 mol% Cu-powder at 120 °C, it afforded 65% desired product based on GC/MS analysis (entry 16). Moreover, to see the effect of catalytic amount of Cu-powder instead of the catalytic amount of CuI for our developed reaction conditions (as described in entry 13), accordingly we performed a reaction (entry 17). To our surprise, the reaction did not occur to give even a trace amount of the desired product, which clearly indicates the different reactivity of the Cu-powder and CuI in the same reaction. To this end, we studied the same reaction varying catalyst loading, reductant loading and temperature. After extensive optimizations (see SI for details) we found that employment of 20 mol% Mn(TPP)Cl, 40 mol% Zn and 5 mol% CuI at lower temperature (80 °C) gave the desired product 77% conversion that was isolated in 62% pure product (entry 18).

We next examined the scope of this reaction with respect to various nitriles using our developed reaction conditions (conditions-A, entry 13, **Table 2** and conditions-B, entry 18, **Table 2**). We found that different substituted nitriles (such as halogen, pyridine, thiophene) were well tolerated under the developed conditions. Moreover, bioactive phenol-derived nitriles (**5k-5l**) also participates in our annulation reaction. On the other hand, conjugated nitriles (**5j, 5m**) also produced annulated product in excellent yields.[21] Next, we tested our annulation reaction with various substituted tetrazoles. As shown in **Table 3**, tetrazole with different substituents (such as methyl, amide, ester, trifluoromethyl and chloro) were found to be compatible as well.

To understand the mechanism of Mn(II)-catalyzed click reaction and denitrogenative annulation, we performed several control experiments (**Figure 4**). First, we carried out a deuterium labelling experiment, which resulted in almost complete preservation of the *d*-atom in the desired click product (**Figure 4A, eq. 1**). This experiment indicates that our click reaction does not follow the traditional metal acetylide complex formation (which is common for Cu-catalyzed click reaction[22]). Since we observed minor amount of the competitive amine by-product (2-aminopyridine) in the click reaction, we hypothesized that the denitrogenative annulation might proceed by the in situ generation of the Mn-nitrene complex (**Figure 4B**, **Mn-N-Int-1**), which takes protons from either the reaction solvent or reacting substrate through a HAT mechanism.[16d]

Table 3. Substrates Scope of Denitrogenative Annulation[a]



[a]Reactions were conducted in 0.5 mmol scale using conditions-A and conditions-B. Isolated yields are reported. **conditions-A**: 5 mol% Mn(TPP)Cl, 10 mol% Zn, 5 mol% CuI, C_6H_6, 100 °C, 24 h, **conditions-B**: 20 mol% Mn(TPP)Cl, 40 mol% Zn, 5 mol% CuI, C_6H_6, 80 °C, 36 h.

However, we cannot completely overrule the formation of the Cu-nitrene intermediate (**Figure 4B**, **Cu-N-Int-1**), as proposed by the Fraunberg and Huisgen, since our reaction also involves the employment of catalytic amount of CuI. Thus, to get the detailed information whether the denitrogenative annulation undergoes via either a Mn-nitrene intermediate or a Cu-nitrene

intermediate (**Figure 4B**), we conducted several experiments. First, we carried out a control experiment between 1,2,3,4-tetrazole (**1a**) and 9,10-dihydroanthracene (**7**) under the developed reaction conditions assuming that if the annulation reaction undergoes via the Mn-nitrene formation, then we would be able to see the formation of the corresponding oxidized product, such as anthracene (**8**) along with the amine product by the HAT mechanism (**Figure 4A, eq. 2**). To our delight, analyzing the crude reaction mixture by the GC/MS analysis, we observed the formation of 48% oxidized product (**8**, anthracene) and 55% 2-aminopyridine (**3a"**), which indicates the possibility for the generation of the Mn-nitrene intermediate. We then performed another control experiment between tetrazole (**1a**) and benzonitrile (**5a**) in presence of 9,10-dihydroanthracene (**7**) without CuI under the developed conditions (**Figure 4A, eq. 3**) and noticed that while the reaction did not produce even a trace amount of the annulation product (**6a**), it resulted a mixture of anthracene (**8**) and 2-aminopyridine (**3a"**), which again indicates the generation of the Mn-nitrene complex (**Mn-N-Int-1**) and revealing the important role of the CuI to activate the benzonitrile for the denitrogenative annulation.

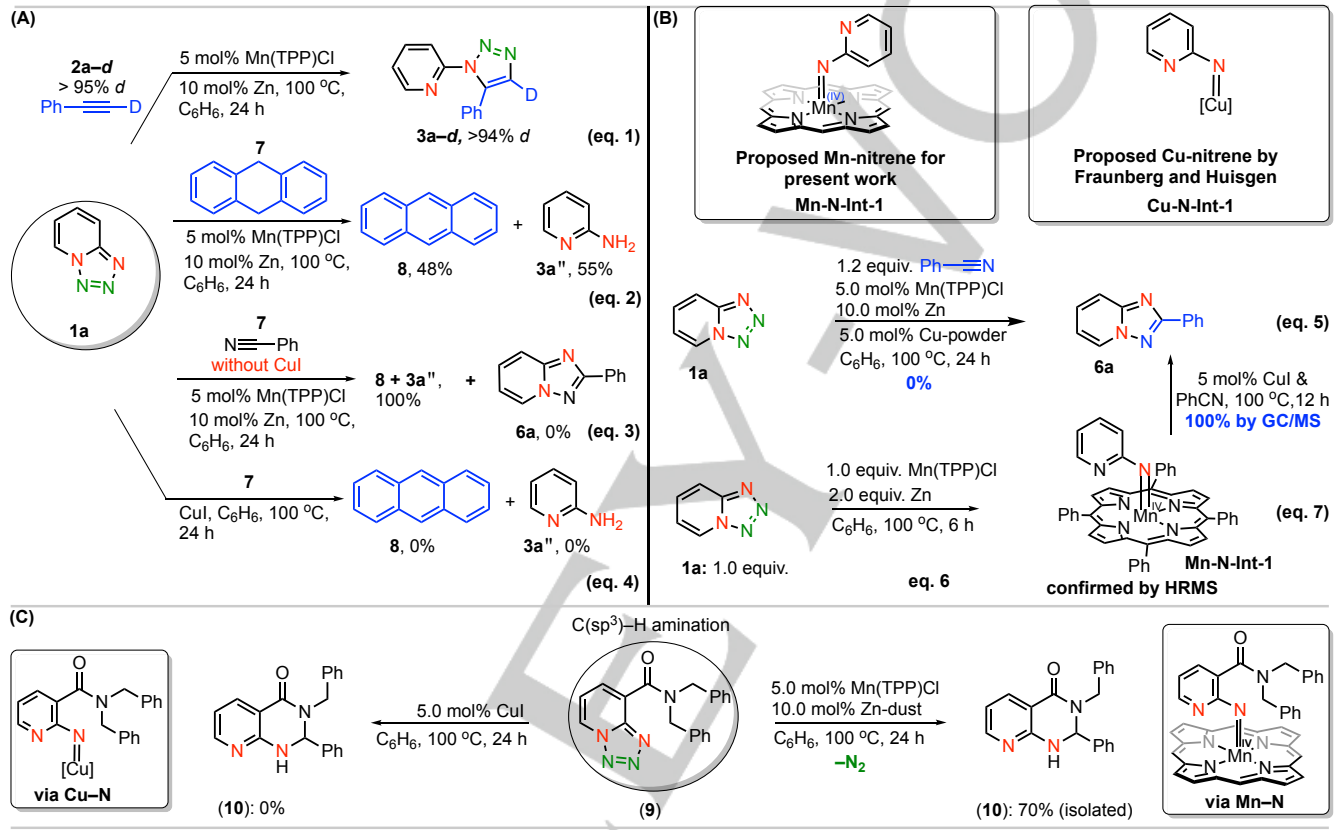


Figure 4. Detailed Mechanistic Studies and Control Experiments

Moreover, another control experiment was performed between the 1,2,3,4-tetrazole (**1a**) and 9,10-dihydroanthracene (**7**) in presence of only catalytic amount of CuI assuming that if the annulation reaction undergoes via the Cu-nitrene generation, then it would also produce the corresponding oxidized product anthracene (**8**) and amine product by the HAT mechanism (**Figure 4A, eq. 4**). However, no reaction occurred that was confirmed by the GC/MS and ^{1}H-NMR data, which is eliminating the possibility for the generation of the Cu-nitrene intermediate.

To get additional confirmation for the annulation mechanism via Mn-nitrene intermediate and the reactivity of the catalytic amount of CuI versus Cu-powder, we performed a reaction using our developed conditions in presence of Cu-powder without CuI (**Figure 4B, eq. 5**) that resulted in no reaction, which tells us two important points, such as, (i) the reaction does proceeds via a Cu-nitrene intermediate and (ii) the essential role of CuI to activate the nitrile for the annulation. Finally, the generation of the Mn–nitrene intermediate (**Mn-N-Int-1**) was confirmed by the HRMS experiment (See SI for details) by the reaction of 1,2,3,4-tetrazole (**1a**), Mn(TPP)Cl and Zn without the presence of CuI (**eq. 6**). Moreover, when a mixture of benzonitrile and CuI in benzene solution was treated with the (**Mn-N-Int-1**) intermediate[23] derived from 1,2,3,4-tetrazole, Mn(TPP)Cl and Zn, the reaction gave 100% conversion within 12 h, again supporting the proposed hypothesis (**eq. 7**). Furthermore, in order to extend the scope of the developed Mn-nitrene concept, we designed a substrate (**9**) for the C(sp^3)–H bond amination[24] and performed the reaction using our developed conditions, which gave the C(sp^3)–H aminated product in 70% yield that also follows a Mn-nitrene intermediate (**Figure 4C**). In sharp contrast, the same reaction does not occur in presence of catalytic amount of CuI.

Thus, based on these experimental evidences, we proposed a possible mechanism for the 1,3-cycloaddition (click) and

annulation reaction (**Figure 5**). Initially, Mn(TPP)Cl reduced to Mn(TPP) in presence of a catalytic amount of Zn-dust through a single electron transfer to form the active catalyst Mn^{II}(TPP) which was confirmed by the UV-visible spectroscopy (See SI for details). Then Mn^{II}(TPP) coordinates with the terminal nitrogen atom of the tetrazole to form intermediate (**B**).

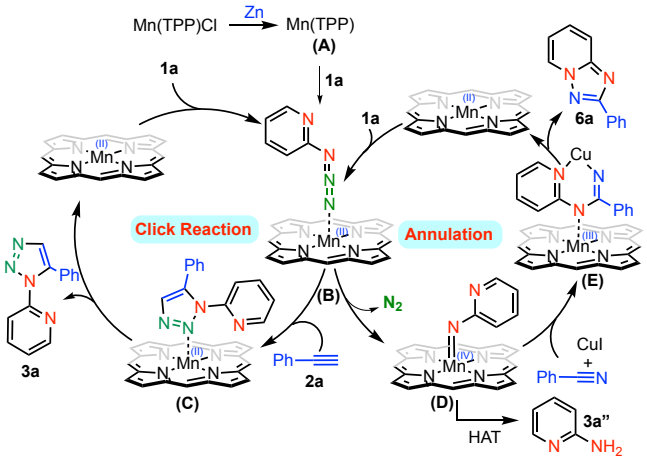


Figure 5. Proposed Reaction Mechanism

In case of 1,3-cycloaddition (click) reaction, intermediate (**B**) then readily undergoes cycloaddition reaction in presence of phenyl acetylene (**2a**) generating the intermediate (**C**), which then release the click product (**3a**) with the regeneration of the catalytic cycle. For the annulation reaction, by the loss of nitrogen gas, the metal-bound azide complex (**B**) forms the metal nitrene intermediate (**D**). Then copper first promotes a nucleophilic attack of Mn-N intermediate (**D**) on the nitrile providing the amidine[25] type of intermediate (**E**). Subsequent Cu-induced oxidative ring closure and reduction of Cu-species affords the triazolopyridine (**6a**) with the regeneration of the catalytic cycle. Notably, the formation of the competitive minor amount of side product formed may be due to the hydrogen atom transfer from either reacting substrate or reaction solvent.

Conclusion

In conclusion, we have developed a Mn-porphyrin based catalytic method that enables to access two different classes of nitrogen heterocycles, such as pyridyl-substituted 1,5-disubstituted 1,2,3-triazoles via 1,3-cycloaddition (click reaction) and 1,2,4-triazolo-pyridines via denitrogenative annulation. While the click reaction undergoes directly via the Mn-bound complex, denitrogenative annulation proceeds through the Mn-N complex. Further investigations are underway to get the full details of the Mn-nitrene intermediate. The method is compatible for a wide range of substrates for both the reactions. We believe that the method would be useful for pharmaceutical industries, drug discovery and other fields of medicinal chemistry.

Acknowledgements

This work was supported by SERB-CRG grant (CRG/2018/000133), SERB-STAR AWARD grant (STR/2019/000045) and SERB-SUPRA grant (SPR/2019/000158). HK, SKD and SR thank CSIR for their SRF. We also thank CBMR for research facilities.

Funding Sources

The authors have filled a patent based on this work (patent application number: 202011021740).

Keywords: denitrogenative annulation • Mn-nitrene • 1,3-cycloaddition • catalysis • click reaction

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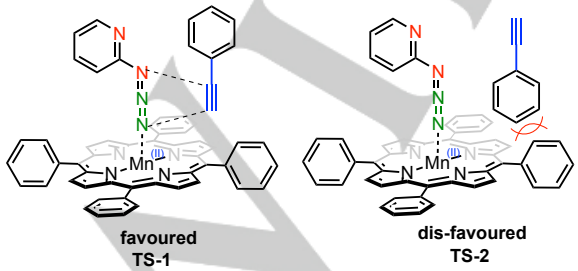
[17] We hypothesized that the origin of 1,5-selectivity over 1,4-isomer is due to the following particular orientation between the azide and alkyne that minimizes the steric interaction between alkyne and the bulky TPP ligand as shown in the following **TSs**.

origin of 1,5-selectivity **origin of 1,4-selectivity**



favoured TS-1 **dis-favoured TS-2**

For terminal coordination with azide nitrogen and metal catalyst, see: a) M. G. Fickes, W. M. Davis, C. C. Cummins, *J. Am. Chem. Soc.***1995**, *117*, 6384-6385. b) H. V. R. Dias, S. A. Polach, S.-K. Goh, D. F. Archibong, D. S. Marynick, *Inorg. Chem.* **2000**, *39*, 3894-3901.

[18] In all cases for the click reaction, 2.0 equivalent of alkynes were employed. Lowering the amount of alkyne, we observed slightly less conversion of the click product.

[19] Notably, the preparation of ASK1 inhibitor (**4**) was reported earlier from the same starting material via two-step method using pyrophoric reagent (Et_2Zn) followed by Pd-catalyzed cross-coupling reaction that resulted in 31% yield of the product. However, our developed cycloaddition reaction conditions followed by the modified cross-coupling method afforded 70% isolated yield of the desired product. For the previous report in details, see, reference, 12a.

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[23] The Mn-nitrene intermediate was confirmed by the HRMS, however, failed to isolate this intermediate due to stability issue.

[24] An iron-catalyzed method for the strong aliphatic C(sp^3)–H bond amination of suitably designed 1,2,3,4-tetrazole substrate has been developed. For details, see: S. K. Das, S. Roy, H. Khatua, B. Chattopadhyay, *J. Am. Chem. Soc.* **2020**, *142*, doi.org/10.1021/jacs.0c07810.

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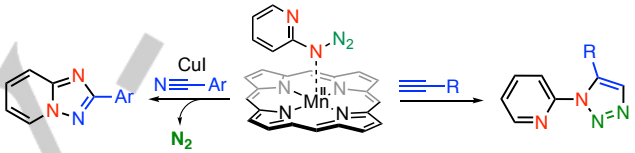
Graphical Abstract

Denitrogenative Annulation **1,3-Cycloaddition (Click Reaction)**



21 examples **Metal-bound Complex** **34 examples**

Dual Reactivity