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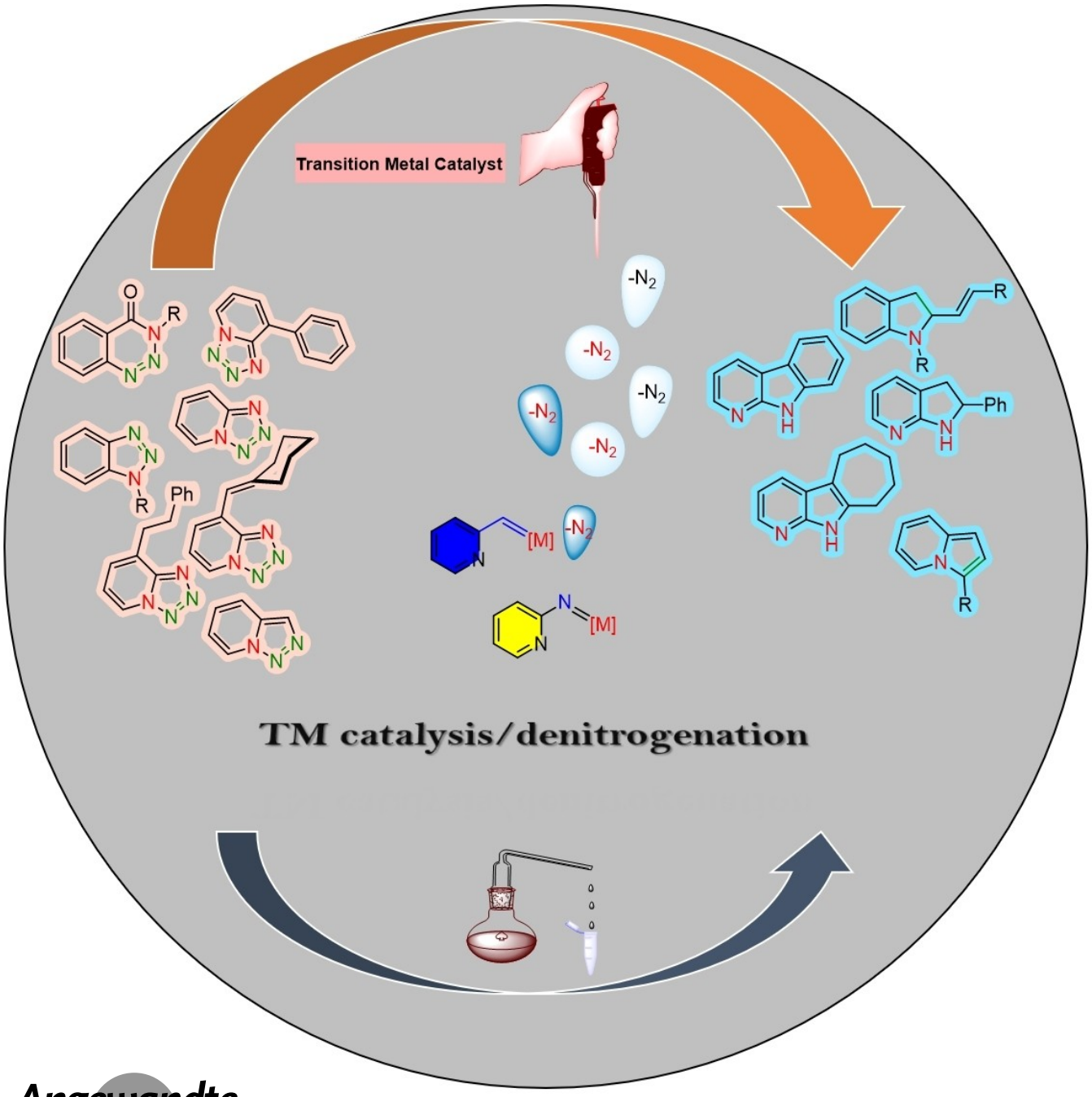
Heterocycles

Transition-Metal-Catalyzed Denitrogenative Annulation to Access High-Valued *N*-Heterocycles

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



Abstract: Over the past few years, the development of efficient methods to construct high-valued *N*-heterocyclic molecules have received massive attention owing to their extensive application in the areas of medicinal chemistry, drug discovery, natural product synthesis and so on. To access those high-valued N-heterocycles, many methods have been developed. In this context, transition-metal-catalyzed denitrogenative annulation of 1,2,3-triazoles and 1,2,3,4-tetrazoles has appeared as a powerful synthetic tool because it offers a step- and atom-economical route for the preparation of the nitrogen-rich molecules. Compared with the denitrogenative annulation of various 1,2,3-triazole frameworks, annulation of 1,2,3,4-tetrazole remains more challenging due to the inertness of the tetrazole moiety. This Review summarizes the significant achievements made in the field of denitrogenative annulation of various 1,2,3-triazoles and 1,2,3,4-tetrazoles including some pioneering examples in this area of research. We anticipate that this denitrogenative annulation reaction will find broad applications in the pharmaceutical industry, drug discovery and other fields of medicinal chemistry.

1. Introduction

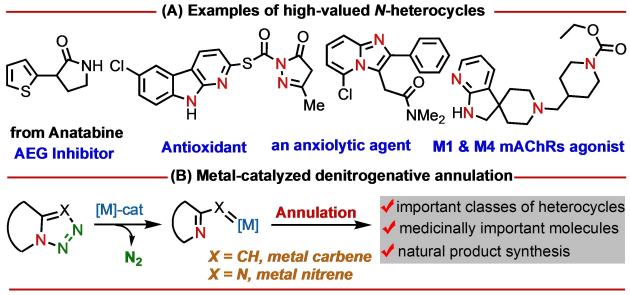
The *N*-containing heterocyclic scaffolds are important moieties found in various biologically active molecules and natural products.[1] To access those important nitrogen-rich molecules, great efforts have been made by many researchers in the last few decades to develop new and efficient synthetic routes towards the synthesis of high-valued *N*-heterocyclic scaffolds (Scheme 1). Although, numerous methods exist for the preparation of various *N*-containing heterocyclic scaffolds, there is always a need for novel, competent, and general strategies for the preparation of these important classes of *N*-heterocycles.

In this context, transition-metal-catalyzed denitrogenative annulation has emerged as an efficient method to construct high-valued nitrogen heterocycles.[2] The denitrogenative annulation has major advantages over other existing methods. It is a single step process, highly efficient, and atom-economical, and the only byproduct is environmentally benign nitrogen gas. The denitrogenative annulation approach offers a unique pathway to convert easily accessible starting materials to other important scaffolds. As a result, the development of a new concept for the denitrogenative annulation ranks among one of the most important topics in synthetic organic chemistry. In the literature, the denitrogenative annulation of 1,2,3-triazole and 1,2,3,4-tetrazole systems has been explored.[2] The main concept of this strategy is that in the presence of a metal catalyst, either a metal carbene or a nitrene is generated from the corresponding precursor via dinitrogen evolution, which is subsequently trapped by other reacting partners intermolecularly or intramolecularly, providing many important heterocycles, including medicinally important molecules or natural products.

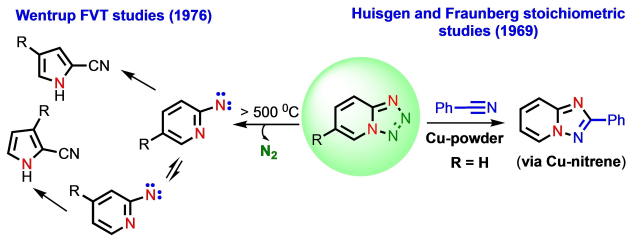
This Review will take the readers through the employment of metals in various denitrogenative transformations (1,2,3-triazoles and 1,2,3,4-tetrazoles) developed by many pioneering research groups including our group as well.

[*] Dr. S. K. Das, Dr. S. Roy, Prof. Dr. B. Chattopadhyay
Department of Biological & Synthetic Chemistry, Centre of Biomedical Research (CBMR), SGPGIMS Campus
Raebareli Road, Lucknow 226014, Uttar Pradesh (India)
E-mail: buddhadeb.c@cbmr.res.in
buddhachem12@gmail.com
Homepage: https://www.buddhacbmr.org/

In the history of denitrogenative annulation chemistry, the first such process was reported by Huisgen and von Fraunberg in the year of 1969 (Scheme 2).[3,4,5] They studied the reactivity of 1,2,3,4-tetrazole and discovered the Cu-powder-catalyzed synthesis of nitrogen heterocycles at 120 °C, which arise via a Cu-nitrene intermediate (although no experimental evidence was provided). Moving forward, in the year of 1976, Wentrup et. al reported denitrogenative thermal and photochemical nitrene–nitrene rearrangement reactions at very high temperature (>500 °C) under flash vacuum pyrolysis (Scheme 2).[6] However, despite these pioneering results, no efforts were made for the development of the denitrogenative annulation chemistry of 1,2,3,4-tetrazole. This is because of the extreme inertness of this system, which usually remains in closed tetrazolic form rather than the open azide form.[7] Only very recently, our group took on this challenge, hypothesizing that if we could capture the productive pyridyl metal-nitrene intermediate, it would open numerous novel opportunities for the discovery of smart technologies that would be extremely welcome in



Scheme 1. A) Examples of high-value *N*-heterocycles. B) Metal-catalyzed denitrogenative annulation.



Scheme 2. Early discovery of denitrogenative annulation.

the fields of medicinal chemistry, biochemistry, pharmaceutical chemistry and related areas. In this Review, along with the denitrogenative annulation of 1,2,3,4-tetrazole, we intend to discuss many important concepts of the denitrogenative annulation employing various 1,2,3-triazole systems. This Review includes transition-metal-catalyzed denitrogenative annulation of 1) pyridotriazole systems, 2) *N*-sulfonyl-1,2,3-triazoles, 3) benzotriazole systems, 4) 1,2,3-benzotriazinones, 5) 1,2,3,4-benzothiazinones, 6) monocyclic tetrazoles and 7) pyridotetrazole systems (Scheme 3).

While many methods for the denitrogenative annulation of 1,2,3-triazole systems have been developed by several pioneering research groups, in this Review, we have tried to focus on some important advances of annulation of triazoles, dividing them on the basis of heterocyclic skeletons. In the case of tetrazoles, since this is a growing field, here we have elaborated all the developed methods and applications. We believe that this overview of denitrogenative annulation methods will stir up motivate researchers all over the world and open up new paths for the preparation of complex drugs and important *N*-heterocycles through a simple one-step, mild and highly facile denitrogenation pathway.

2. Denitrogenative Annulation of 1,2,3-Triazoles

Triazole derivatives can tautomerize to their diazoimine isomers upon heating and consequently be utilized as precursors to produce α-imino metal carbenoids with suitable transition-metal catalysts (Scheme 4). The nature and position of substituents can influence the equilibrium of a pyridotriazole-diazo compound. Thus, the content of the diazo form in the reaction mixture can affect the overall reaction rate of the pyridotriazole denitrogenation.

It was proposed earlier that the lone-pair repulsive force between the Cl and N at the *peri* position of pyridotriazoles was responsible for the shift of the equilibrium to the diazo structure.[8] Bao et al.[9] performed a computational investigation of the transformation between pyridotriazole and the diazo compound. As shown in Scheme 5, the presence of a chlorine atom at C7 position of the pyridotriazole facilitates ring opening and stabilizes the diazo isomer, in contrast to the situation with $R^1 = H$. As indicated by the estimations, a 7-F-substituted substrate went through ring opening even more promptly, and the generated diazo isomer was even somewhat exergonic (Table 1). The generated metal carbenoids produced from the triazoles could go through numerous carbene involved reactions, including cyclopropanation/cyclopropenation and X–H (X = C, N, O, and so forth) bond insertion. Likewise, α-imino metal-carbenoids can react with a ton myriad of unsaturated substrates to deliver different *N*-heterocyclic compounds, for example, derivatives of pyrrole, imidazole, oxazole/oxazine, indole, azepine, furan, hydro-pyridine, quinoline, and other valuable compounds.

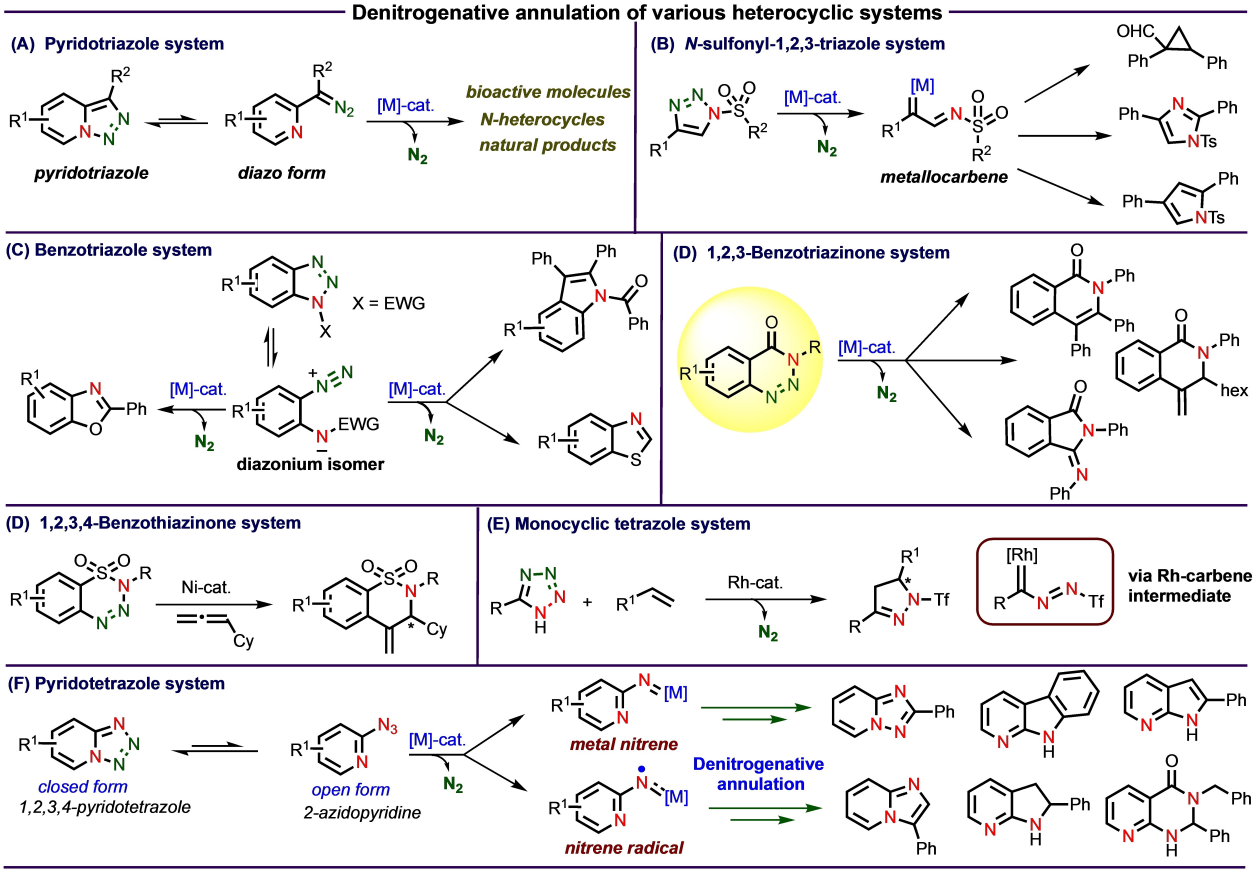
2.1. Denitrogenative Annulation of Pyridotriazole Systems via an Ionic Mechanism

In 2007, the Gevorgyan group first discovered the denitrogenation of 1,2,3-pyridotriazole using a terminal alkyne in the presence of a Rh^{II} catalyst.[10] It was found that 1,2,3-pyridotriazole with phenyl acetylene in the presence of $Rh_2(OAc)_4$ catalyst produced a mixture of the cyclopropene

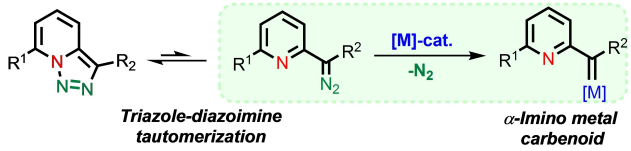
Sandip Kumar Das was born in West Bengal (India). In 2021 he obtained his PhD for research conducted under the direction of Prof. Chattopadhyay at the Centre of Biomedical Research, Lucknow (India) on transition-metal-catalyzed denitrogenative annulation for the synthesis of heterocycles. He is currently a postdoctoral researcher under the guidance of Prof. Rylan Lundgren at the University of Alberta (Canada).

Satyajit Roy was born and raised in the small city of West Bengal (India). In 2021 he obtained his PhD for research on transition-metal-catalyzed carbene and nitrene chemistry conducted under the supervision of Prof. Chattopadhyay at the Centre of Biomedical Research, Lucknow (India). He moved to USA in 2021 for postdoctoral studies under the guidance of Prof. Rudi Fasan at the University of Rochester.

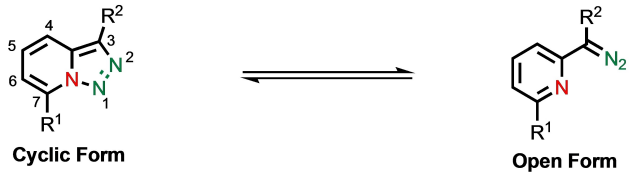
Buddhadeb Chattopadhyay obtained his B.Sc. (2001) in chemistry from the Burdwan University and M.Sc. (2003) in chemistry from Visva-Bharati University. He completed his PhD in 2009 with Professor K. C. Majumdar. He spent around six years as a postdoctoral research associate in USA at the University of Illinois at Chicago with Professor Gevorgyan and at Michigan State University with Professor Smith, III. In August 2014, he started his independent research career at the Centre of Biomedical Research (CBMR) Lucknow (India) as a Ramanujan Fellow. Currently, he is an Associate Professor of the same institute. His research interests include metal-catalyzed C–H borylation chemistry (catalyst/ligand engineering) via noncovalent interactions and radical activation chemistry via denitrogenative annulation to get high-valued N-heterocycles.



Scheme 3. Overview of the denitrogenative annulation of 1,2,3-triazole and 1,2,3,4-tetrazole.



Scheme 4. Tautomerization of triazole and the diazo form.



Scheme 5. Closed/open equilibrium of pyridotriazole.

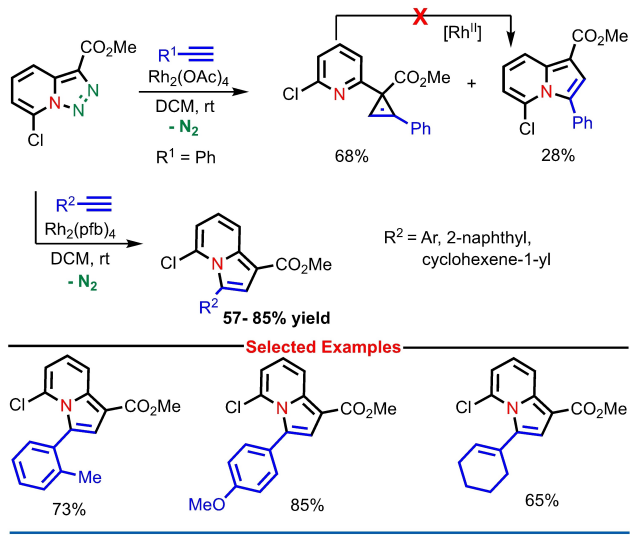
Table 1: Effect of substituents on the closed/open equilibrium of pyridotriazole.

R^1	R^2	$\Delta G^{\#}$ [kcal mol^{-1}]	$\Delta\Delta G^{\#}$ [kcal mol^{-1}]
H	$-CO_2Me$	22.3	10.9
Cl	$-CO_2Me$	17.5	2.0
F	$-CO_2Me$	15.0	−1.4

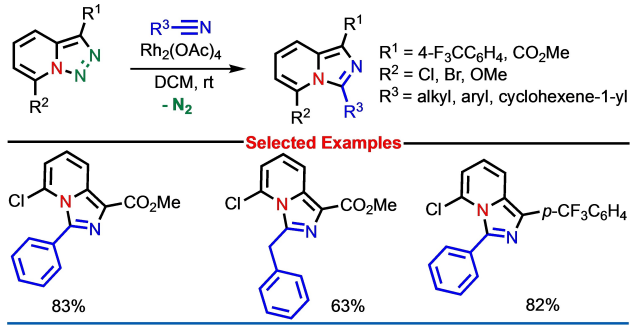
(major) and indolizine (minor) products. All the pyridotriazoles used in this work demonstrated long shelf life (were stored at room temperature for several months) and no signs of spontaneous decomposition were observed.

These two products are formed via [2+1] and [2+3] cycloaddition reactions, respectively. Experimental results excluded the possibility of an additional transformation of cyclopropene to indolizine under these reaction conditions, which led to the proposition of an independent pathway for the indolizine formation. Notably, when $[Rh_2(pfb)_4]$ was utilized as a catalyst, the selectivity of the annulation reaction was dramatically improved, prompting only indolizine in good yield. Only 7-chloro-substituted pyridotriazole underwent annulation reaction with various terminal alkynes with good to excellent yield (Scheme 6).

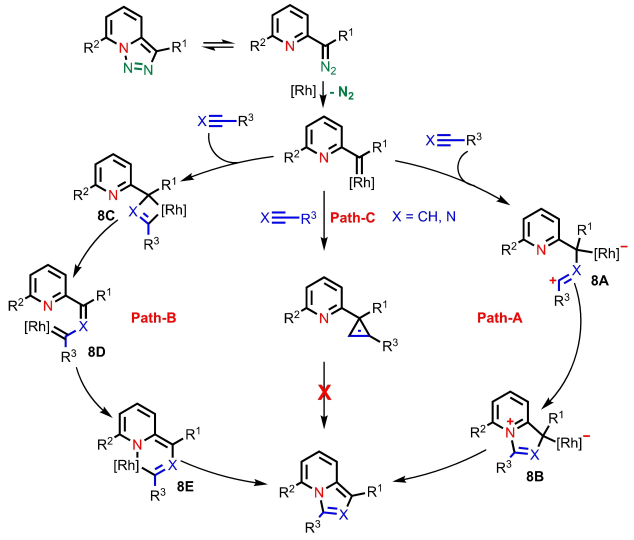
Next, the Gevorgyan group applied the annulation reaction of pyridotriazole with various nitriles to afford *N*-fused imidazopyridines (Scheme 7).[10] It was found that pyridotriazoles efficiently react with aryl, alkyl, and alkenyl nitriles in the presence of $Rh_2(OAc)_4$ to give the corresponding imidazopyridines in good to excellent yields. Pyridotriazoles bearing electron-withdrawing groups such as Cl, Br, or OMe at C7 position were only compatible under the developed reaction conditions. This Rh^{II}-catalyzed annulation reaction proceeds through the generation of the rhodium carbenoid intermediate (Scheme 8). In the case of Path-A, direct nucleophilic attack of the alkyne or nitrile at



Scheme 6. Rh^{II}-catalyzed denitrogenative annulation of pyridotriazole with alkynes.



Scheme 7. Rh^{II}-catalyzed denitrogenative annulation of pyridotriazole with nitriles.

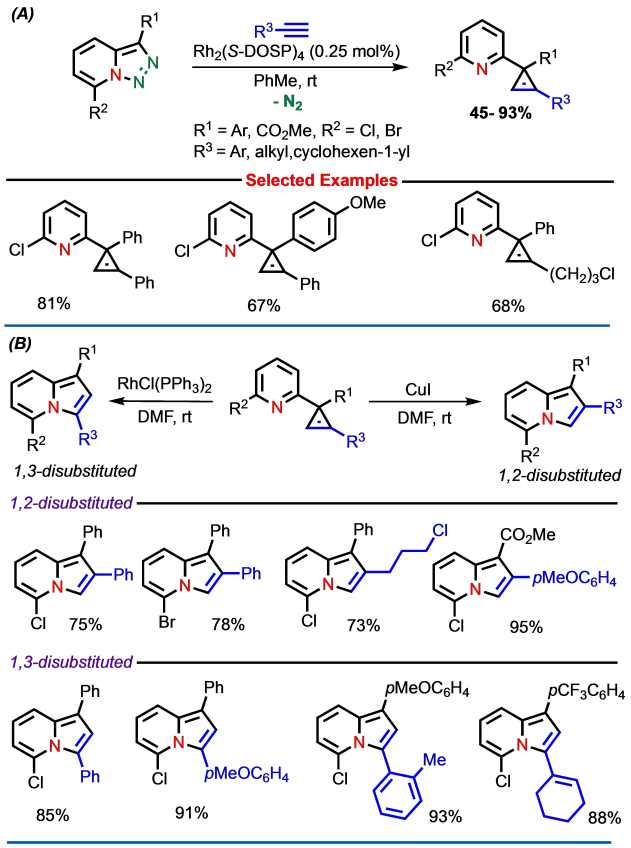


Scheme 8. Proposed mechanism of the Rh^{II}-catalyzed denitrogenative annulation of pyridotriazole.

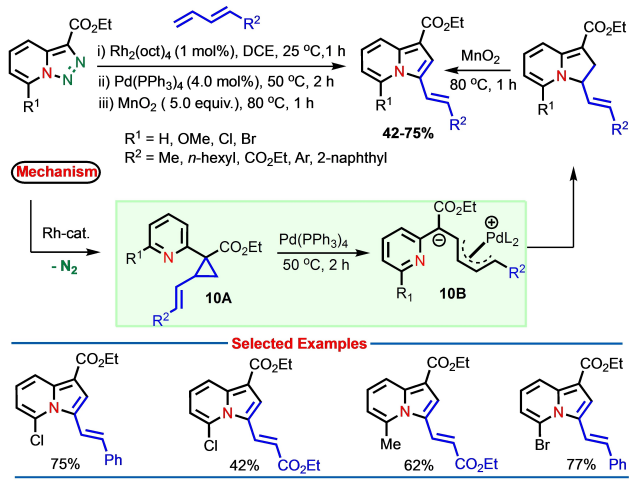
the carbene intermediate offers the intermediate ylide (**8A**) (Scheme 8), which undergoes cyclization to form either indolizine or imidazopyridine via the cyclic zwitterion intermediate (**8B**).

On the other hand, for Path-B, [2+2] cycloaddition between the carbenoid intermediate and the alkyne or nitrile resulted in the metallocyclobutane intermediate (**8C**), which undergoes a σ-bond metathesis to produce the rhodium carbene intermediate (**8D**). The rhodium carbene intermediate (**8D**) undergoes 6π electrocyclization to produce intermediate **8E**, which upon reductive elimination gives the desired annulated product either indolizine or imidazopyridine. The possibility of Path-C was discarded as the [2+1] cycloisomerized product did not undergo further cycloisomerization under the optimized reaction conditions.

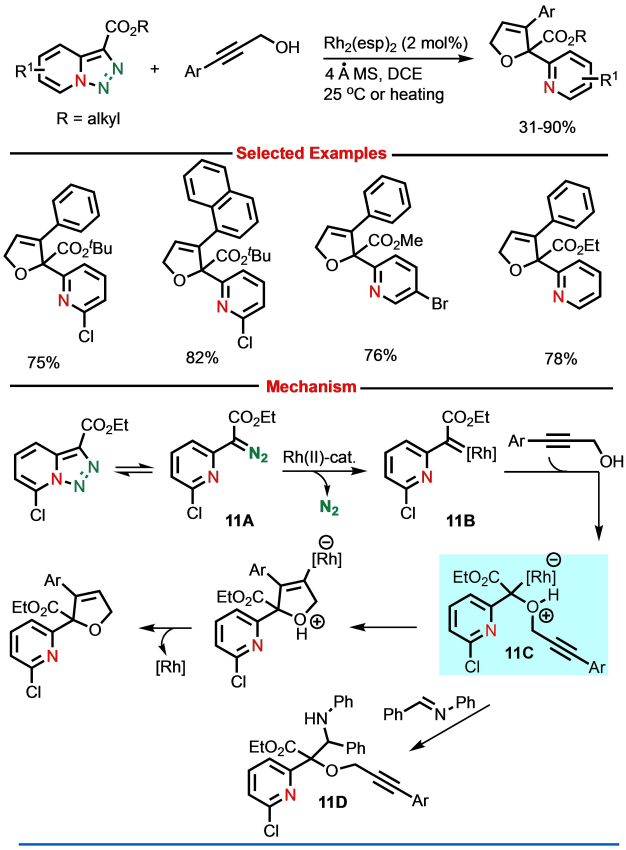
In the same year, Gevorgyan et. al reported a method for the regiodivergent synthesis of indolizine derivatives in which the authors dealt with the synthesis of *N*-fused pyrroles prepared from 3-(pyridin-2-yl)cyclopropenes (Scheme 9A, B).[11] Notably, choice of the rhodium or copper catalyst empowered the regiodivergent synthesis of the indolizine derivatives. It should be noted that just one set of regioisomers was synthesized and, in this way, the complementarity of the strategy is not ensured. The two reactions were proposed to occur through metal-carbene formation followed by cyclization and aromatization.



Scheme 9. Rh^{II}- and CuI-catalyzed regiodivergent synthesis of substituted indolizines.



Scheme 10. Rh^{II}/Pd^{0}-catalyzed one-pot synthesis of 3-alkenylindolizines from pyridotriazoles.



Scheme 11. Rh^{II}-catalyzed reaction of pyridotriazoles with aryl propargyl alcohols.

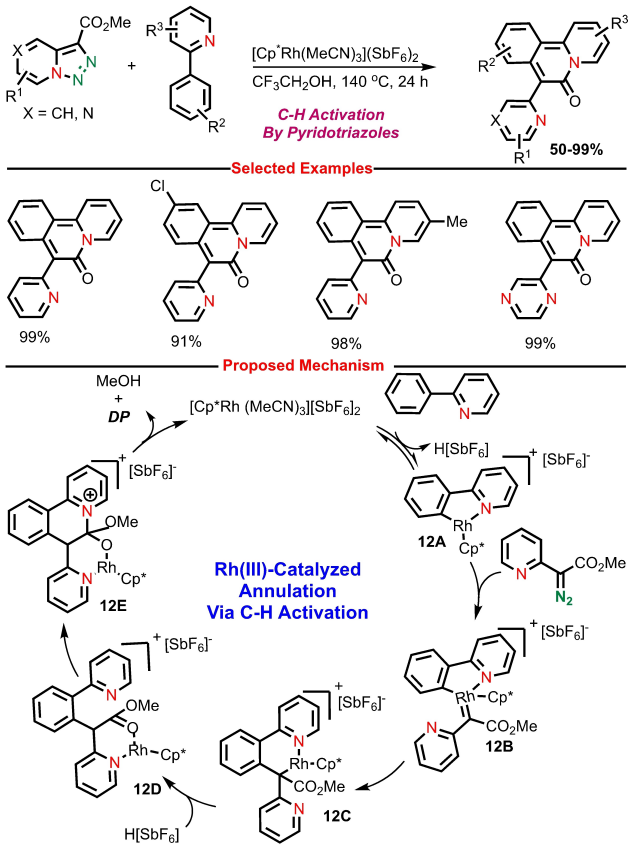
In accordance with the perceptions in furan synthesis, application of Wilkinson's rhodium catalyst to 3-(pyridin-2-yl)cyclopropanes led to indolizines by means of C1–C3 bond cleavage; in contrast, CuI worked through C2–C3 bond cleavage to give indolizines. However, no clarification on the origin of the regioselectivity was given. The two catalysts worked proficiently under mild conditions. As an impediment, only 2-halo-substituted pyridines could be utilized as they were the only substrates suitable for creating the necessary starting cyclopropenes.

Lee and co-workers demonstrated a one-pot synthesis of 3-alkenyl-substituted indolizines from 1,3-dienes and pyridotriazoles by means of successive reactions: 1) Rh-catalyzed cyclopropanation to give allyl cyclopropanes (**10A**), 2) Pd-catalyzed expansion of the cyclopropane ring to generate dihydroindolizines via intermediate **10B**, and 3) oxidation utilizing MnO_2 (Scheme 10).[12] Mechanistically, the reaction begins with the denitrogenation of the diazo form of pyridotriazole to produce Rh^{II} carbenoid. 1,3-Dienes with electron-withdrawing or electron-donating aryl substituents as well as alkyl and ester groups function excellently under the reaction conditions. Both C7-substituted and C7-unsubstituted pyridotriazoles were shown to work, but harsher conditions were required for the complete conversion of the starting materials in the case of C-7 unsubstituted pyridotriazoles.

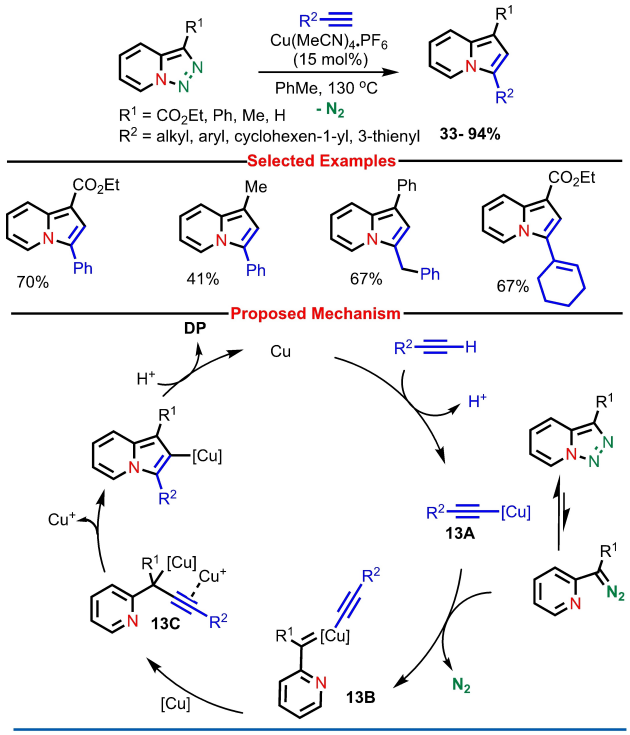
In 2019, a Rh^{II}-catalyzed intermolecular denitrogenative reaction of pyridotriazoles with aryl propargyl alcohols yielding 2,5-dihydrofuran derivatives was developed by Xu, Hu, and co-workers (Scheme 11).[13] Different aryl propargyl alcohols, particularly those with electron-withdrawing groups, gave the desired compounds with exceptional yields. The reaction was sensitive to the steric effect of an *ortho* substituent on the aryl ring of the propargylic alcohol. Unsubstituted pyridotriazoles as well as 4-, 5, 6-, and 7-substituted pyridines delivered 2,5-dihydrofurans in moderate to great yields. The reaction proceeds through the development of 1) Rh^{II} carbenoid (**11B**) from the diazo structure (**11A**), 2) oxonium ylide complex (**11C**), and finally 3) intramolecular nucleophilic attack on the alkyne moiety. Mechanistic examinations uncovered that the oxonium ylide is a key intermediate in this [4+1]-cycloaddition. This oxonium intermediate was captured effectively through a Mannich-type reaction with an outer imine to give an acyclic compound (**11D**).

In 2015, Strassert, Glorius, and co-workers reported the first Rh^{III}-catalyzed directing-group-assisted C–H bond activation of pyridotriazoles (Scheme 12).[14] The authors explored the scope of various 2-arylpyridines. Mono- or disubstituted 2-arylpyridines possessing electron-poor groups (Cl, Br, F, CF_3) or electron-rich groups (Me, OMe, NMe_2) were found to be fully compatible under these established reaction conditions and afforded the corresponding cyclized products in excellent yields. Notably, this annulation reaction is also applicable to extended π-systems under slightly modified reaction conditions (only required high catalyst loading). In addition, substituted pyridines and pyridotriazoles with different substituents successfully underwent annulation to give the desired products in high yields.

The desired product formation starts with the coordination of 2-arylpyridine to the Rh^{III} catalyst followed by a reversible C–H bond cleavage to generate the cationic five-membered rhodacycle (**12A**), which reacts with the diazo compound to generate the Rh^{III}-carbene intermediate



Scheme 12. First example of Rh^{III}-catalyzed denitrogenative C–H activation by pyridotriazoles.



Scheme 13. Cu-catalyzed denitrogenative annulation of pyridotriazoles.

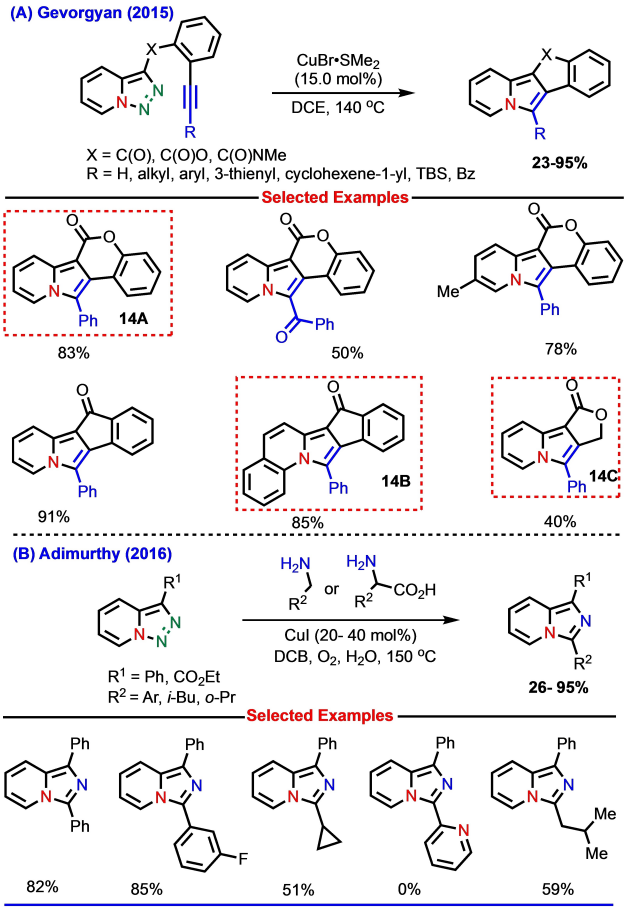
(**12B**). Subsequently, a migratory insertion leads to the six-membered rhodacycle (**12C**) which undergoes proto-demetalation to afford the insertion product **12D**. Next, nucleophilic addition to the activated carbonyl group of the ester by the pyridine *N*-atom occurs to give the intermediate **12E**, which upon elimination of alcohol yields the annulated product.

In 2015, Gevorgyan and co-workers revealed a Cu-catalyzed denitrogenative annulation reaction of pyridotriazoles with terminal alkynes for the synthesis of indolizines (Scheme 13).[15] In this work, they have overcome the shortcomings of their previously described Rh-catalyzed annulation reaction[10] by replacing Rh with a copper catalyst at high temperature. Pyridotriazoles bearing hydrogen, methyl, or a phenyl group at C3 position responded well, managing the formation of the indolizines in moderate to great yields.

The mechanism proceeds in the following way: First, the terminal alkyne in the presence of Cu-catalyst produces a copper acetylide complex (**13A**), which upon reaction with the diazo compound affords another Cu-complex (**13B**). Then, migratory insertion occurs to produce the intermediate (**13C**), which upon cyclization and proto-demetalation provides the final product. In order to verify the formation of the Cu acetylide (**13A**) in this transformation, the authors performed several control experiments. At first, they conducted a reaction between pyridotriazole (having CO_2Et at C3 position) and acetylide complex (**13A**), but it resulted in no reaction. However, the intermediate (**13A**) was formed in presence of $Cu(MeCN)_4PF_6$ and HPF_6 (aq.). This experiment suggests that the electrophilic Cu-species is essential to activate the alkyne during the cyclization. However, more detailed study is necessary to explain the mechanism of this Cu-catalyzed annulation reaction.

As an extension of their effort on the preparation of high-value *N*-heterocyclic scaffolds via denitrogenative annulation chemistry, Gevorgyan and Shi reported the first Cu-catalyzed intramolecular annulation reaction of pyridotriazoles using terminal and internal alkynes to synthesize diverse polycyclic frameworks (Scheme 14A).[16] The method affords C6-substituted fused indolizines (**14A**). Tri- (product **14C**), tetra- (e.g., product **14A**), and pentacyclic indolizines (**14B**) can be prepared in a single step in moderate to good yields. Grippingly, the reaction could also be prompted by Lewis acids, such as [TIPSOTf or $In(OTf)_3$]; however, yields were lower.

In 2016, Adimurthy and co-workers demonstrated a Cu-catalyzed synthesis of imidazo[1,5-*a*]pyridines from pyridotriazoles and benzylamines or α-amino acids (Scheme 14B).[17] Different benzylamines as well as cyclopropylmethaneamine gave the imidazo[1,5-*a*]pyridines in great yields. Aryl glycine derivatives, alanine, and leucine afforded the corresponding products in moderate to good yields. The utilization of the commercially accessible benzylamines as substrates and air as the oxidant are benefits of the reaction. The reaction presumably proceeds through 1) N–H insertion of the Cu-carbene complex which is generated from the diazo structure; 2) decarboxylation of



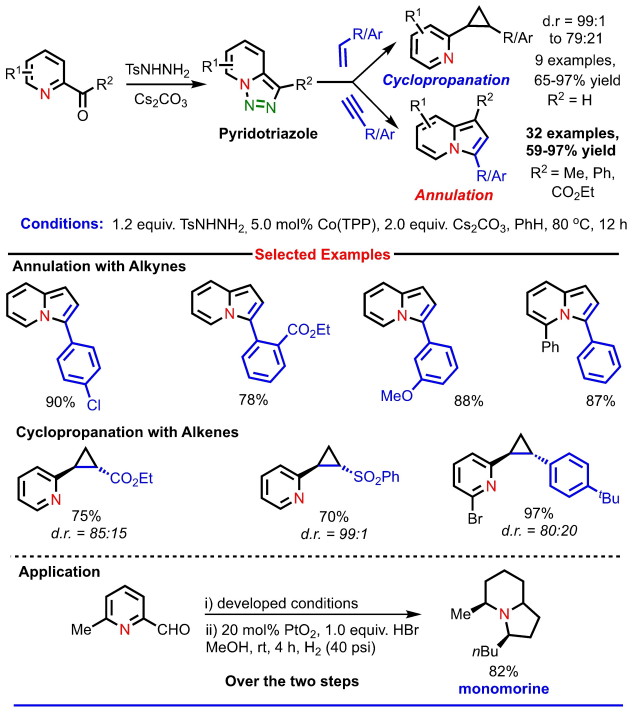
Scheme 14. Cu^{I}-catalyzed intramolecular and intermolecular annulation of pyridotriazoles.

the amino acid then occurred; and lastly 3) copper-catalyzed aerobic oxidation of the amine to the aza-allenyl cation and cyclization produced the imidazopyridine.

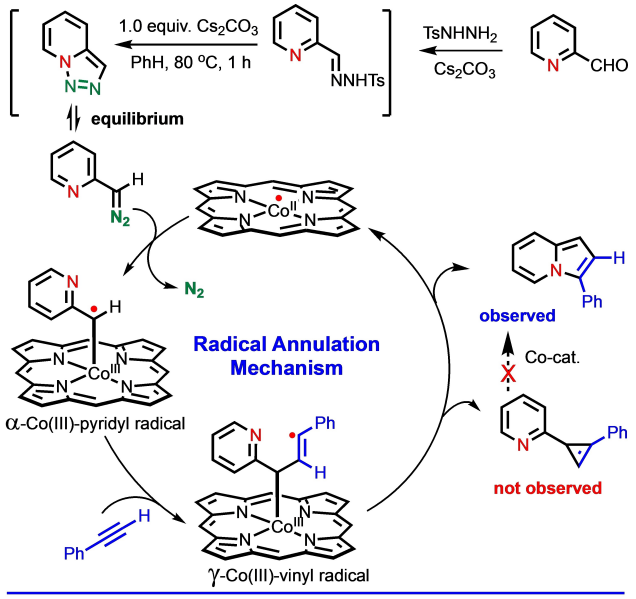
2.2. Denitrogenative Annulation of Pyridotriazole Systems via a Radical Mechanism

In 2018, for the first time, we reported a one-pot Co^{II}-based metalloradical activation approach for the denitrogenative annulation with alkynes, and cyclopropanation with alkenes that yielded indolizines and cyclopropanes, respectively with good to excellent yields (Scheme 15).[18] In this annulation reaction, we observed that bicyclic pyridotriazole is formed in situ from carbonyl compounds and tosylhydrazine via the hydrazone intermediate. It was found that the in situ generated *N*-tosylhydrazone reacted well with diverse aromatic and aliphatic alkynes to furnish indolizines in good to excellent yields. Replacing the alkynes by alkenes resulted in substituted cyclopropanes in high yields and diastereoselectivity. To demonstrate the potential utility of this radical annulation reaction, we synthesized racemic monomorine[19] in two steps.

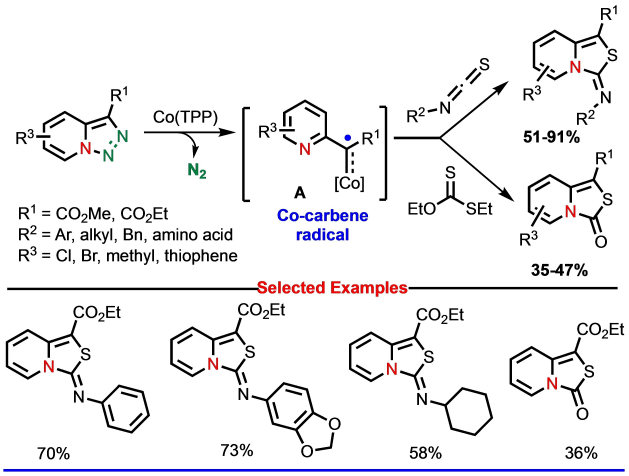
The mechanism of the radical reaction proceeds as follows (Scheme 16). At first, the in situ formed pyridotriazole, which is in equilibrium with its open 2-diazomethyl pyridine form, in the presence of the Co-catalyst, generates an α-Co^{III} pyridyl radical intermediate. Next, the α-Co^{III}-pyridyl radical intermediate upon reaction with the alkyne gives the γ-Co^{III}-vinyl radical intermediate, which after radical recombination delivers the indolizines with regeneration of the catalyst. The mechanism was supported by several control experiments. To trap the α-Co^{III}-pyridyl



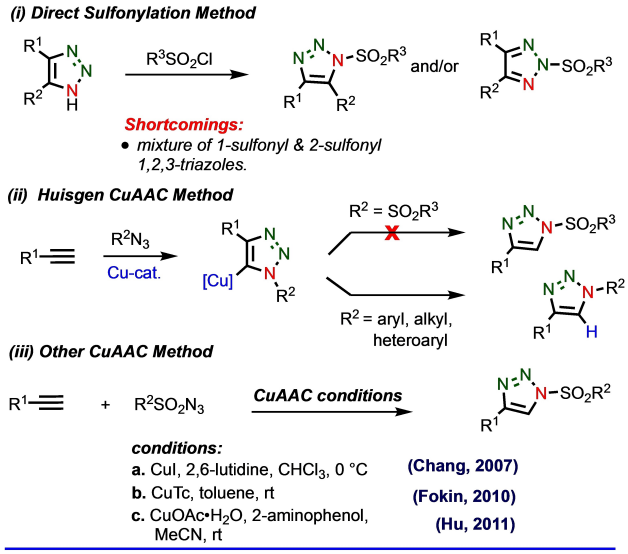
Scheme 15. Co^{II}(Por)-based metalloradical activation of 2-(diazomethyl)-pyridines.



Scheme 16. Proposed mechanism for denitrogenative radical activation.



Scheme 17. Co^{II}-catalyzed annulation of pyridotriazoles with isothiocyanates and xanthate esters.



Scheme 18. Methods for the synthesis of *N*-sulfonyl-1,2,3-triazoles.

radical intermediate, a trapping experiment was performed utilizing 3.0 equivalent of TEMPO. Fortunately, we were able to isolate the TEMPO-trapped intermediate which was separated and characterized by spectroscopic data.

Recently, an elegant method for the denitrogenative annulation reaction of pyridotriazoles with isothiocyanates and xanthate esters was developed by the Gevorgyan group (Scheme 17).[20] This method highlights the conversion of pyridotriazoles into two *N*-containing heterocyclic frameworks: 1) imino-thiazolopyridines and 2) oxo-thiazolopyridine derivatives. The authors proposed that the one-pot Co^{II}-catalyzed annulation reaction proceeds via a radical activation mechanism. The synthetic utility of the developed strategy was shown by the synthesis of amino acid derivatives and further transformations of the acquired reaction product.

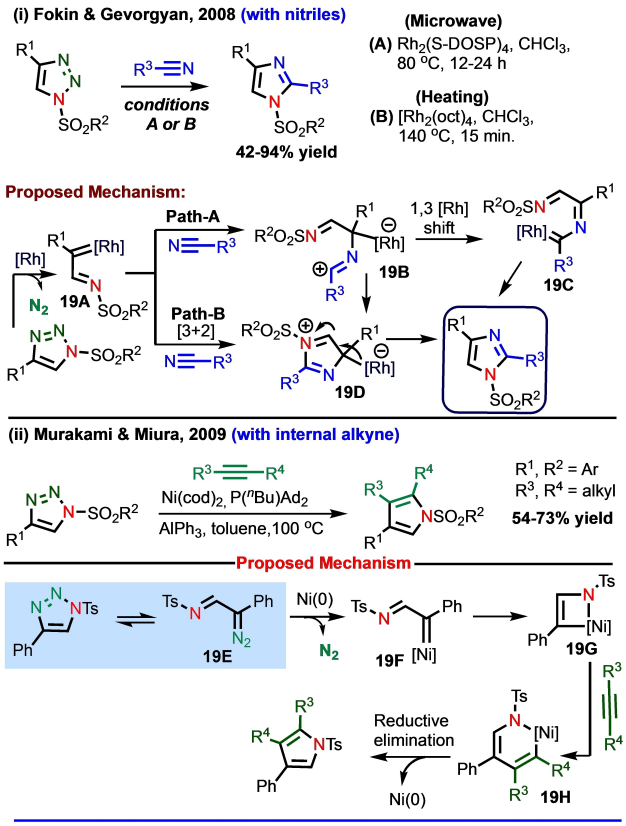
2.3. Denitrogenative Annulation of N-Sulfonyl-1,2,3-triazoles via an Ionic Mechanism

Among the most studied 1,2,3-triazole systems are the *N*-sulfonyl-1,2,3-triazoles. The conventional method to synthesize the *N*-sulfonyl-1,2,3-triazoles is the direct sulfonylation of NH-triazoles using sulfonyl chloride. However, this strategy leads to a mixture of two isomers, i.e., isomeric N2- and N1-sulfonylated triazoles (Scheme 18(i)).[21,22] Since the pioneering reports by the groups of Sharpless[23] and Meldal,[24] the Cu-catalyzed azide–alkyne cycloaddition (CuAAC) has become an ideal and efficient strategy to prepare 1,4-disubstituted 1,2,3-triazoles in high yields and excellent regioselectivities. Regrettably, this well-known CuAAC method does not produce the desired *N*-sulfonyl-1,2,3-triazoles (Scheme 18(ii)).

In 2007, for the first time, Chang et. al[25] discovered that Cu^{I}-catalyzed effective and selective conversion of sulfonyl azides and terminal alkynes into 4-substituted *N*-sulfonyl-1,2,3-triazoles (Scheme 18(ii)). They used a stoichiometric amount of a bulky base (2,6-dimethylpyridine). Subsequently in 2010, Fokin and co-worker[26] reported an improved cycloaddition reaction of terminal alkynes and sulfonyl azide in the presence of CuTc catalyst to prepare sulfonyl triazoles (Scheme 18(ii)). After that, in 2011, Hu established a Cu^{I}-catalytic system to access *N*-sulfonyl-1,2,3-triazoles.[27] They found that combination of copper(II) acetate monohydrate and 2-aminophenol (ligand as well as reductant) in the presence of a terminal alkyne and sulfonyl azide produced 4-substituted *N*-sulfonyl-1,2,3-triazoles in a short time period with high yield and selectivity (Scheme 18(iii)).

In recent years, *N*-sulfonyl azides have come to light as stable and expedient imino-carbene precursors and this opened up a new path in metal carbene chemistry. *N*-Sulfonyl-1,2,3-triazole remains in Dimorth-type equilibrium[28] with α-diazo imine, which produces the more electrophilic metal-carbene intermediate in the presence of metal catalyst. Due to the high electrophilicity, the resulting metallocarbenes undergo various important synthetic transformations with many nucleophiles such as nitriles, alkynes, alkenes, and carbonyl compounds to access high-value nitrogen-containing heterocycles.

In 2008, Fokin and Gevorgyan demonstrated a Rh-catalyzed denitrogenative annulation reaction of *N*-sulfonyl triazoles with various nitriles to afford numerous *N*-sulfonyl imidazoles (Scheme 19(i)).[29] The authors established two different protocols such as microwave conditions and traditional heating conditions to achieve this annulation reaction. It was found that both sets of conditions are competent to afford annulated product, albeit the heating conditions require longer reaction time to reach completion. The developed method was equally applicable with various nitriles and triazoles. Preliminary screening of several rhodium salts revealed that electron-rich $Rh_2(oct)_4$ and $Rh_2(S\text{-}DOSP)_4$ are preferrable to the electron-deficient dirhodium(II) tetrakis(trifluoroacetate) or dirhodium(II) tetrakis(heptafluorobutanoate) catalysts.



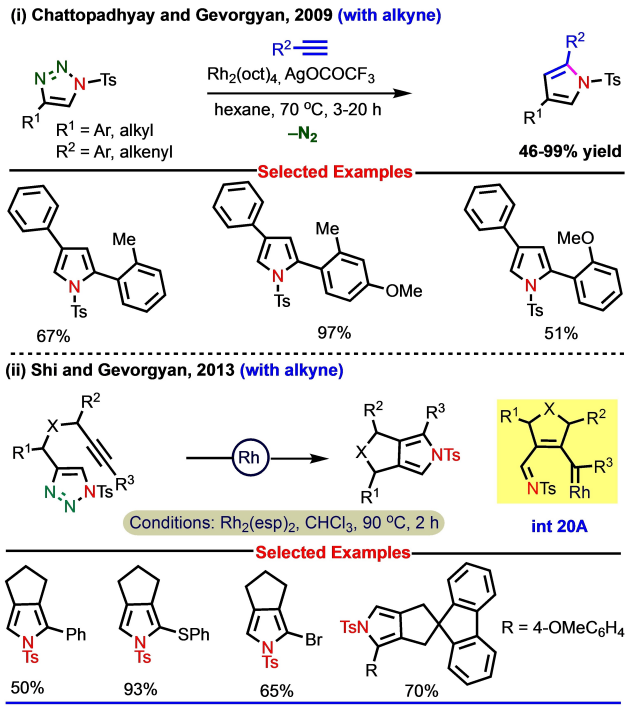
Scheme 19. Denitrogenative annulation of *N*-sulfonyl-1,2,3-triazoles with nitriles and internal alkynes.

It should be mentioned that terminal alkynes are not compatible under these employed reaction conditions. The authors proposed a mechanism for this Rh-catalyzed annulation reaction (Scheme 19) that is quite similar to that reported by Helquist, Akermark, and co-workers.[30] As shown in path-A, nucleophilic attack of nitrile on the rhodium carbenoid intermediate (**19A**) results in ylide (**19B**), which upon cyclization gives the zwitterionic intermediate (**19D**) and finally loss of metal furnishes the desired imidazole. Alternatively, ylide (**19B**) undergoes [1,3]-Rh shift to produce intermediate (**19C**) and subsequent cyclization followed by reductive elimination produces desired imidazole. Notably, direct product formation from intermediate (**19A**) via [3+2] cycloaddition with nitrile (Path-B) cannot be disregarded.

In 2009, Murakami et al. discovered an elegant method for the denitrogenative annulation reaction of *N*-sulfonyl-1,2,3-triazoles with internal alkynes using [Ni(cod)$_2$] as the catalyst and P(^{n}Bu)Ad$_2$ as an electron-rich bulky phosphine ligand to furnish substituted pyrroles (Scheme 19(ii)).[31] The authors also used AlPh$_3$ as a Lewis acid to execute this annulation reaction with internal alkynes. Under the optimized reaction conditions, symmetrical alkynes produced corresponding annulated products with moderate yields, but unsymmetrical alkynes gave a mixture of isomers. However, terminal alkynes were ineffective because of self-oligomerization. From the previous report, it is noticeable that terminal alkyne did not participate in the annulation reaction with monocyclic triazoles. Mechanistically, in the first step, the chain form (**19E**) in the presence of Ni-catalyst produces nickel carbenoid (**19F**), which cyclizes to azanickel cycle (**19G**) and subsequent insertion of internal alkyne into the Ni–C bond produces intermediate (**19H**). Finally, the desired pyrrole is formed after reductive elimination of Ni^0 from the six-membered nickelacycle (**19H**). The function of the Lewis acid in this annulation reaction may be to support the ring–chain tautomerization or to expedite the reductive elimination of Ni from (**19H**).

In 2009, Gevorgyan et al. discovered the annulation of *N*-sulfonyl-1,2,3-tosyl triazoles with terminal alkynes using a binary rhodium/silver catalyst system (Scheme 20(i)).[32] A number of C4-substituted triazoles and electron-rich terminal alkynes are fully compatible under these reaction conditions, and the desired pyrrole products were obtained in good yields. However, electron-poor terminal alkynes resulted in no reaction. Meanwhile, in 2013, Shi and Gevorgyan disclosed a rhodium-catalyzed intramolecular annulation of alkyne-tethered *N*-sulfonyl-1,2,3-triazoles to produce fused pyrroles (Scheme 20(ii)).[33] They synthesized several substituted pyrroles from corresponding triazole precursors in good yields. The authors stated that this annulation reaction proceeds via **int 20A**, which is formed from the alkyne-tethered triazole through rhodium-carbene-alkyne metathesis.

Like the denitrogenative annulation of *N*-sulfonyl triazoles with alkynes and nitriles, annulation reactions with alkene and keto compounds were also studied and resulted in structurally diverse motifs and heterocycles. An enantio-



Scheme 20. Denitrogenative annulation of *N*-sulfonyl-1,2,3-triazoles with terminal and internal alkynes.

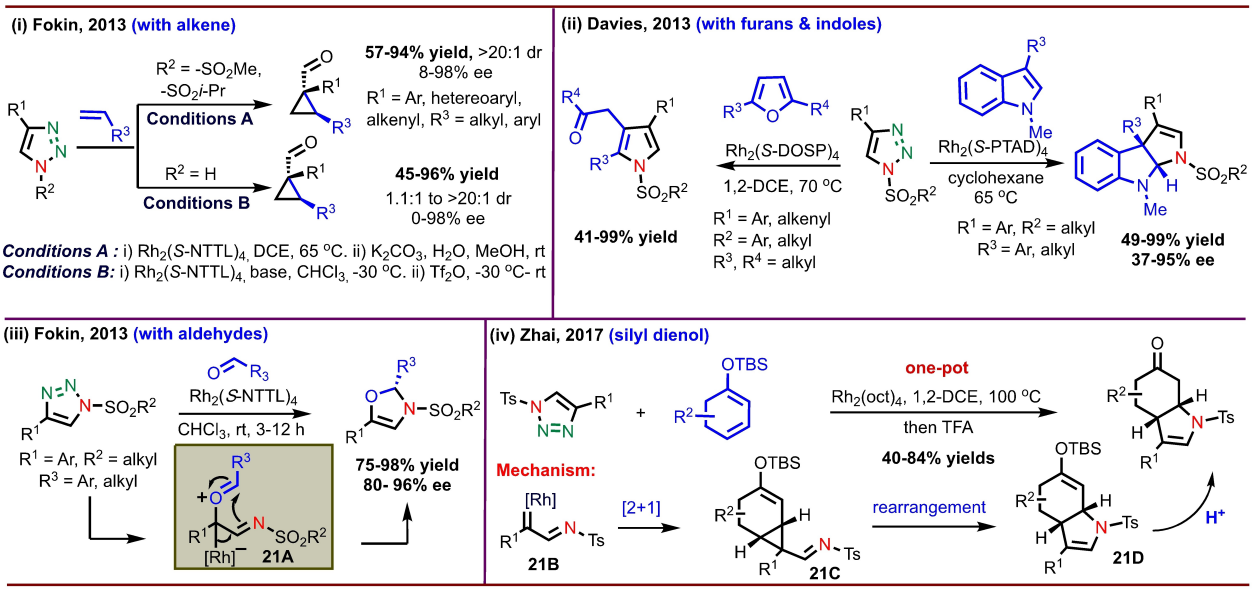
selective cyclopropanation reaction between alkenes and *N*-sulfonyl triazoles in the presence of a chiral Rh^{II}-catalyst was first reported by Fokin and co-workers in 2009 (Scheme 21 (i)).[34] They found that various 4-substituted *N*-sulfonyl triazoles react with styrene derivatives at 65 °C in DCE solvent in the presence of Rh_2(*S*-NTTL)$_4$ catalyst and yield the corresponding cyclopropane carboxaldimines, which on further treatment with K_2CO_3 in wet methanol produced stable cyclopropanecarboxaldehyde derivatives in excellent yield and enantiomeric excess. Employing this developed protocol, they synthesized a wide number of electronically and sterically varied chiral cyclopropane carboxaldehydes from readily available triazoles and alkenes.

Subsequently, in 2010, the same research group reported an elegant method to generate a reactive rhodium-azavinyl carbene from stable and readily accessible NH-triazole by installing a highly electron-deficient triflate group onto the triazole nitrogen atom (Scheme 21 (i), Conditions B).[35] They prepared *N*-triflyltriazoles in the reaction medium from *N*-sulfonyl triazoles, Tf_2O and 2,6-*tert*-butyl-4-methylpyridine. Various alkenes reacted smoothly with *N*-triflyl triazoles in the presence of Rh_2(*S*-NTTL)$_4$ in $CHCl_3$ solvent and afforded the desired cyclopropane carboxaldehydes in excellent yield and enantiomeric excess.

In 2013, the Davies group reported a Rh^{II}-catalyzed annulation reaction of *N*-sulfonyl triazoles with 2,5-disubstituted furans to furnish highly effective trisubstituted pyrroles (Scheme 21 (ii)).[36] Steric and electronic effects had negligible impact on the potency of the reaction, but in the case of unsymmetrically substituted furans, a mixture of isomers was observed. Though most Rh^{II}-carboxylate catalysts showed good reactivity, Rh_2(*S*-DOSP)$_4$ was found to be the superior catalyst. To expand the scope of the denitrogenative annulation reaction, in the same year the Davies group established an enantioselective [3+2] cycloaddition reaction[37] between sulfonyltriazoles and C3-substituted indoles in the presence of a Rh^{II}-catalyst to produce pyrroloindoline skeleton (Scheme 21 (ii)). It was found that when the annulation reaction was conducted in a nonpolar hydrocarbon solvent with Rh_2(*S*-PTAD)$_4$ catalyst, both conversion and enantioinduction were excellent. Various aryl-substituted pyrroloindolines featuring electron-donating and electron-withdrawing groups were synthesized in high yields and also with an excellent level of enantioselectivity. Substrates featuring a bulky sulfonyl group or a bulky substituent at the nitrogen atom of indole were unable to afford the pyrroloindolines, which indicated that reaction was sensitive towards steric bulk.

In 2013, the Fokin group disclosed a denitrogenative reaction[38] of azavinyl carbenes derived from the triazole with aldehydes in the presence of Rh^{II}-catalyst to produce 4-oxazoline derivatives (Scheme 21 (iii)). In the first step, the Rh^{II}-carbenoid and the aldehyde furnish the ylide intermediate (**21A**). Subsequently, an intramolecular cyclization occurs with the adjacent sulfonyl imine to produce the desired oxazoline in excellent yields and a high level of enantioselectivity. It was found that the developed Rh^{II}-catalyzed method is equally applicable with many aryl and alkyl aldehydes.

In 2017, Li, Zhai, and co-workers showed that cyclic silyl dienol ethers could be used as annulating precursors.[39] They reported a Rh-catalyzed [3+2]-cycloaddition reaction between *N*-sulfonyl triazoles and cyclic silyl dienol ethers to prepare functionalized hydroindolones (Scheme 21 (iv)). Mechanistically, in the first stop, the *N*-sulfonyl-1,2,3-triazole reacts with the Rh-catalyst to produce an α-iminocarbene intermediate (**21B**). This reactive carbene intermediate is trapped by the cyclic silyl dienol ether and results in a cyclopropyl imine (**21C**). Finally, a ring-opening intramolecular aza-Michael addition and subsequent hydrolysis affords the desired bicyclic hydroindolone (**21D**). This

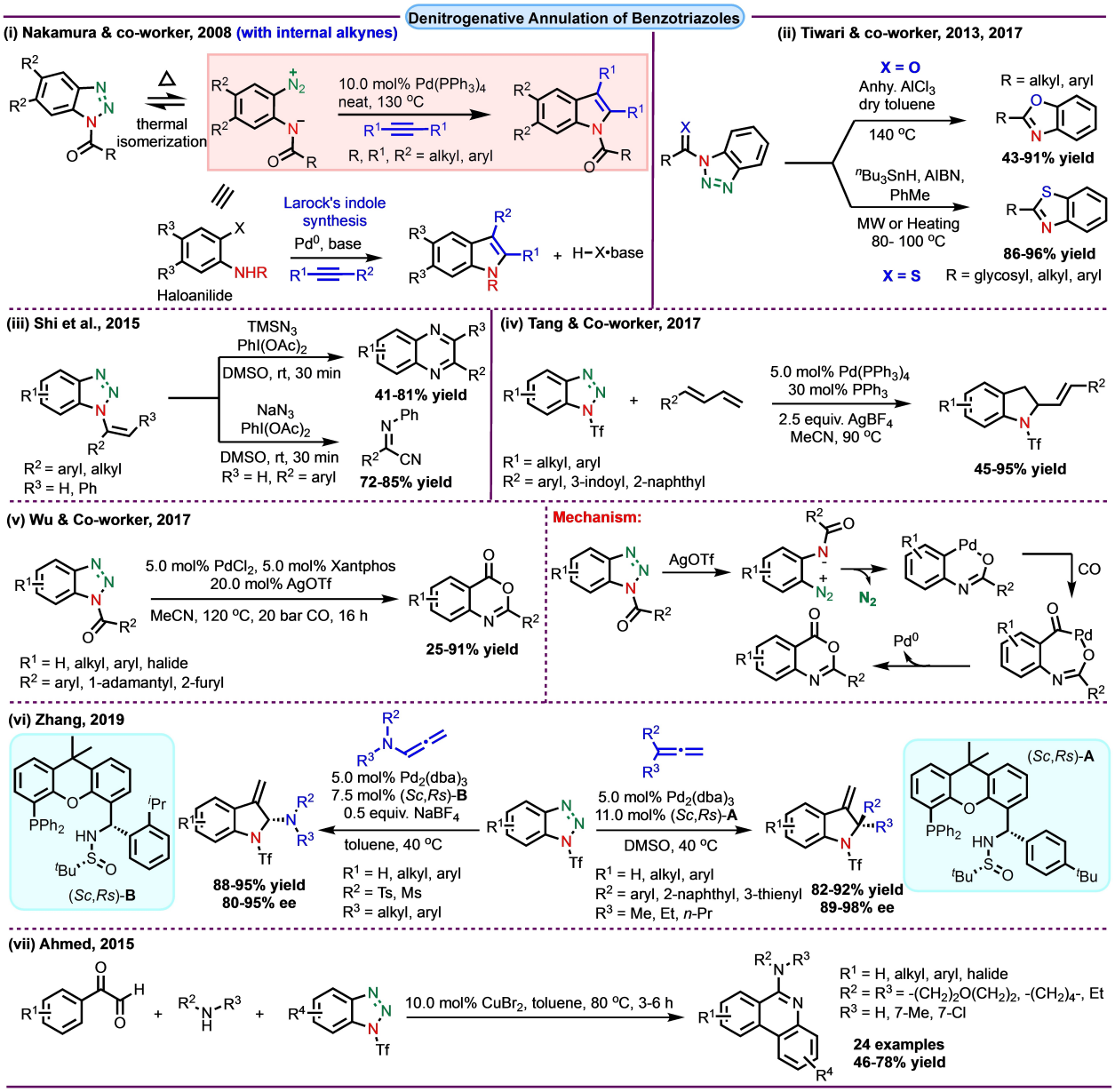


Scheme 21. Denitrogenative annulation of *N*-sulfonyl-1,2,3-triazoles with alkenes and carbonyl compounds.

annulation method produced a library of polysubstituted hydroindolones with good yield and excellent diastereoselectivity.

2.4. Denitrogenative Annulation of Benzotriazole Systems

Like other triazole systems, the denitrogenative annulation of benzotriazole skeletons has gained considerable growth to generate various benzoheterocycles including indoles, benzothiazoles, benzoxazoles, and quinoxalines. In 2008, Nakamura et al. invented a denitrogenative [3+2] cycloaddition reaction of *N*-aroylbenzotriazoles with internal alkynes[40] using a Pd-catalyst to construct 1,2,3-trisubstituted indoles (Scheme 22 (i)). As *N*-aroylbenzotriazoles remain in equilibrium between the open and closed forms, the authors envisioned that the diazonium isomer could act as a synthetic equivalent of the haloanilide that is used in indole synthesis reported by Larock and co-workers.[41] This method is more atom-economical than the well-known Larock indole synthesis because it produces only dinitrogen gas instead of the HX-base adduct produced in Larock's synthesis. Other solvents and palladium catalysts were found to be less effective in this reaction under the developed conditions. The electronic nature of the aryl carbonyl group on the triazole nitrogen atom significantly affected the reaction outcomes. For example, substrates possessing electron-withdrawing groups at the carbonyl functionality react better than those with electron-rich groups. Although various symmetrical alkynes are compatible under these



Scheme 22. Denitrogenative annulation of benzotriazole systems.

reaction conditions, unsymmetrical alkynes showed varied regioselectivity. Notably, this Pd^0-catalyzed annulation reaction is inefficient for terminal alkynes.

In 2013, Tiwari and co-worker reported an intramolecular radical denitrogenative cyclization reaction of benzotriazole rings to access a series of 2-substituted benzothiazoles in good yields under microwave or heating conditions (Scheme 22(ii)).[42] For this transformation, they used a mixture of a benzotriazolemethanethione, $^nBu_3SnH$ as a stannane reagent, and azobisisobutyronitrile (AIBN) as an initiator. Next, the same group reported a $AlCl_3$-catalyzed ring-opening reaction of *N*-aroylbenzotriazole systems for the preparation of benzoxazoles (Scheme 22(ii)).[43] The product yield ranged from 43–91 %. It should be noted that benzylic *N*-acyltriazole substrates produced only the traditional Friedel–Crafts product (ketone) under the developed conditions.

In 2015, Shi and co-workers disclosed an efficient intermolecular radical addition reaction using *N*-vinyl-substituted benzotriazoles and azides in the presence of hypervalent iodine as oxidant (Scheme 22(iii)).[44] A number of quinoxalines could be constructed under neutral conditions in 41–81 % yield. The use of NaN_3 instead of $TMSN_3$ in 0.033 (M) DMSO solvent resulted in only imine nitriles in 72–85 % yield. Azide radical addition and denitrogenative annulation led to the formation of the quinoxaline derivatives. Moreover, the formation of imine nitriles could be explained by considering base-mediated azide denitrogenation and subsequent radical-promoted triazole ring-opening.

In 2017, a palladium-catalyzed denitrogenative cycloaddition reaction of triflate-protected benzotriazoles with simple 1,3-dienes to access 2-vinyl indolines was reported by Tang and co-workers (Scheme 22(iv)).[45] The desired product 2-vinyl indolines form via three key steps: 1) alkene insertion, 2) nucleophilic attack, and 3) reductive elimination. DFT calculation studies revealed that 1,3-dienes suffered intramolecular *N*-allylation.

The same year, Wu and co-workers disclosed a denitrogenative carbonylation reaction of *N*-acylbenzotriazoles using silver and palladium co-catalysts under CO pressure (20 bar) in acetonitrile solvent at 120 °C (Scheme 22(v)).[46] Under the established conditions, electron-rich or electron-deficient aryl, 2-heterocyclic, and 1-adamantyl-substituted benzotriazoles afforded the anticipated benzoxazinone products in 25–91 % yield. In the first step of the reaction mechanism, a N–N bond is cleaved in the presence of AgOTf to generate an arenediazonium intermediate, which undergoes oxidative addition with the Pd^0-catalyst to deliver an organopalladium complex. Subsequently, CO inserts into the C–Pd bond and generates a seven-membered-ring intermediate, which undergoes reductive elimination to produce the final product.

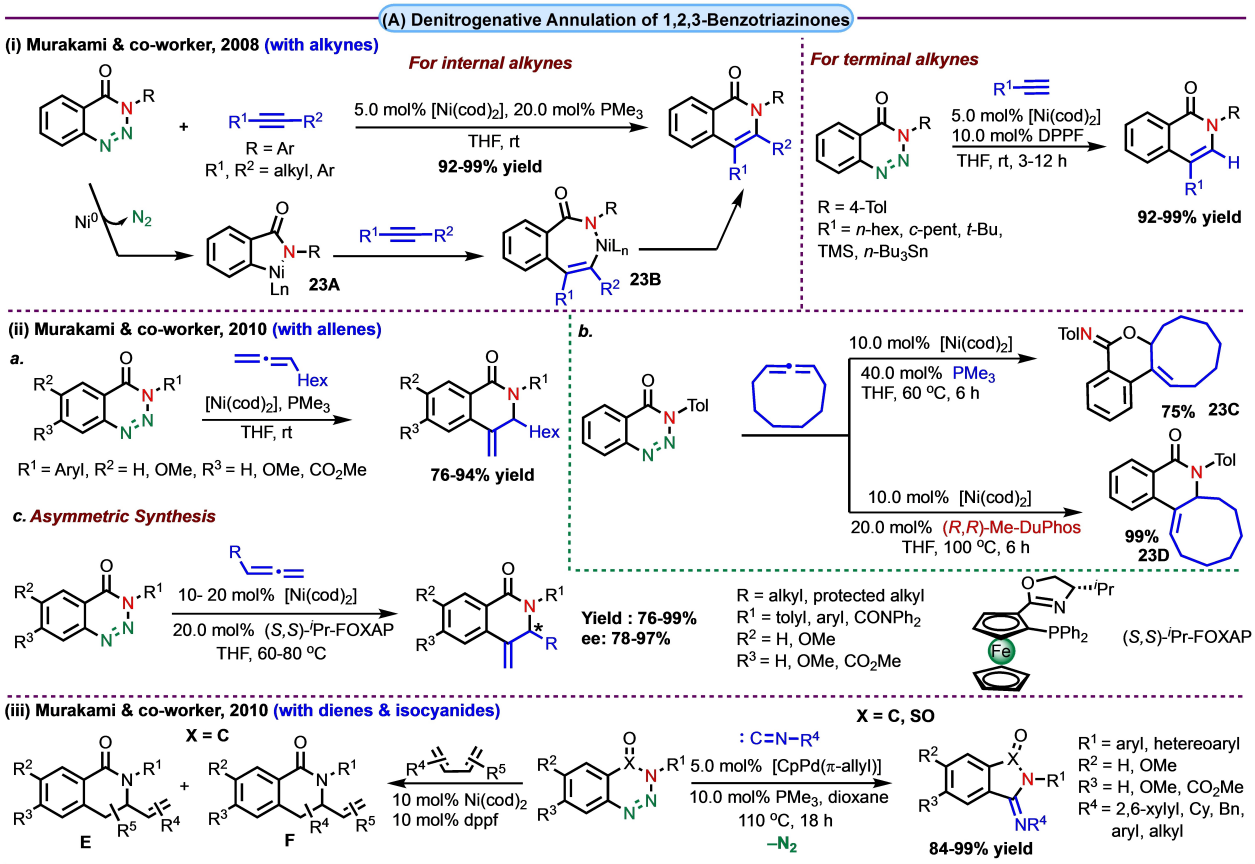
Recently, Zhang et. al[47] published the first report of a Pd-catalyzed enantioselective denitrogenative annulation reaction of benzotriazoles with allenes (Scheme 22(vi)). The authors found that their newly developed ligand (Sc,Rs)-**A** with $Pd_2(dba)_3$ catalyst in DMSO solvent at 40 °C furnished the expected 3-methyleneindolines with a quaternary stereogenic center in good yield with high regioselectivity and excellent enantioselectivity. They further extended their developed strategy for the preparation of 2-*N*-substituted 3-methyleneindolines. They used *N*-allenamides as the cycloaddition partners and (*Sc,Rs*)-**B** as a chiral ligand. The yield of the corresponding indoline products ranged from 88–95 %. Various sensitive functional groups are compatible under these established reaction conditions.

In 2015, Ahmed and co-workers[48] described an efficient Cu-catalyzed decarbonylative cyclization reaction of benzotriazole systems, 2-oxoaldehydes, and secondary amines to synthesize 6-aminophenanthridines (Scheme 22(vii)). In addition to various secondary amines, a wide range of *m*- and *p*-substituted 2-oxoaldehydes smoothly participate in the Cu-mediated denitrogenative reaction followed by decarbonylative cyclization. The authors mentioned that subjecting monosubstituted benzotriazoles under these developed conditions resulted in two 6-aminophenanthridine isomers. This annulation strategy renders a simple protocol for the construction of 6-aminophenanthridines from commercially accessible inexpensive starting materials.

2.5. Denitrogenative Annulation of 1,2,3-Benzotriazinones

In 2008, Murakami and co-workers[49] disclosed a Ni-catalyzed denitrogenative annulation of 1,2,3-benzotriazinones with internal alkynes to prepare isoquinolones (Scheme 23(i)). Mechanistically, in the first step Ni^0 inserts into the N–N bond of the 1,2,3-benzotriazinone, which after N_2 evolution generates the azanickelacycle (**23A**). The alkyne then inserts into the Ni–C bond of the azanickelacycle (**23A**) and forms seven-membered nickelacycle intermediate (**23B**). Lastly, reductive elimination of intermediate gives the anticipated isoquinolone and regenerates the Ni^0 catalyst (Scheme 23). The scope of this Ni-catalyzed reaction was very general with respect to symmetrical and unsymmetrical internal alkynes, and produced the expected isoquinolones in high yields (92–99 %). It was found that unsymmetrical internal alkynes showed different regioselectivity. Pleasingly, terminal alkynes furnished reasonable yields and regioselectivities under the slightly modified reactions. The authors stated that substrates with electron-donating or electron-withdrawing aryl substituents at the nitrogen atom of 1,2,3-benzotriazinones efficiently underwent annulation reactions at room temperature, while methyl- and benzyl-substituted 1,2,3-benzotriazinones needed elevated reaction temperature.

In 2010, Murakami and co-workers discovered an elegant method[50] for the denitrogenative annulation of 1,2,3-benzotriazinones with allenes using Ni-catalyst (Scheme 23(ii)). They reported that the reaction of benzotriazinones with allenes in the presence of a catalytic amount of $Ni(cod)_2$ and PMe_3 afforded isoquinolones as a major isomer. Substrates with either electron-poor and electron-rich substitutions on the N-atom of the benzotriazinone ring reacted well under these optimized reaction conditions. Possibly, sterics is the governing factor that determines the regioselectivity of this transformation. The authors also explored the scope of the 1,3-disubstituted allene, which



Scheme 23. Denitrogenative annulation of 1,2,3-benzotriazinones.

showed an exciting result (Scheme 23 (ii), b). Here, product formation depends on the type of phosphine ligand used in the reaction medium. When the reaction was conducted THF solvent with phosphine ligand PMe_3, the imino ester (**23C**) was produced. In contrast, use of the bidentate phosphine ligand (*R,R*)-Me-duphos in toluene at 100 °C afforded **23D** as the major product in 99 % yield. The authors also investigated the asymmetric synthesis of substituted isoquinolones. Chiral bidentate phosphine ligands such as (*R,R*)-Me-duphos and (*S,S,R,R*)-tangphos exhibited good enantioselectivity.

Remarkably, high regio- and enantioselectivity was obtained when the chiral phosphinooxazoline ligand (*S,S*)-^{i}Pr-foxap was used. To extend the developed methodology, the same research group established a denitrogenative annulation strategy using benzotriazinone with 1,3-dienes (Scheme 23 (iii)).[51] For this transformation, the authors used 10 mol % [Ni(cod)$_2$], 10 mol % dppf, and THF solvent at 60 °C. Under the employed reaction conditions, differently substituted benzotriazinones produced various *N*-protected isoquinolones (**23F**) with high yields in the presence of symmetrical 1,3-dienes; however, *N*-benzyl-substituted benzotriazinone yielded a lower amount of product. It was found that substrates with either electron-donating or electron-withdrawing groups present in the benzene ring of benzotriazinones were also effective in the reaction. Gratifyingly, unsymmetrical dienes led to the desired isoquinolones (**23F**) as major regioisomers over **23E**. The mechanism of this Ni-catalyzed annulation reaction was reported to be quite similar to that of the reported nickel-catalyzed annulation of benzotriazinones with allenes. It is worth mentioning that besides several 1,3-dienes, the authors also examined various activated alkenes with benzotriazinones in the presence of [Ni(cod)$_2$] and P(^{n}Bu)$_3$. Electron-poor alkenes such as methyl acrylate, acrylonitrile, acrylamide, and pyridine-bearing alkene were fully compatible under these optimized conditions and produced dehydroisoquinolinones in excellent yield. Notably, electron-rich and electrons-neutral alkenes are ineffective towards annulation.

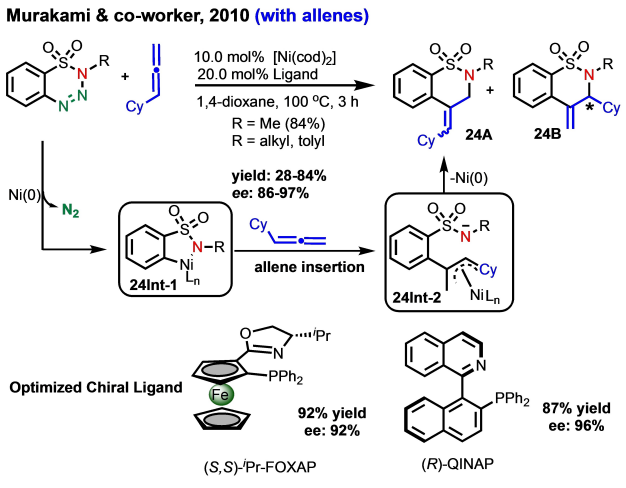
In 2011, the Murakami group introduced isocyanide in the annulation reaction.[52] They developed a reaction of 1,2,3-benzotriazinone (and benzothiatriazine dioxide) with isocyanides using a catalytic amount of palladium catalyst and phosphine ligand to afford the corresponding 3-(imino)isoindolin-1-ones and 3-(imino)thiaisoindoline 1,1-dioxides, respectively, in high yield (Scheme 23 (iii)). Various isocyanides including aryl, benzyl, cyclohexyl, and even aliphatic isocyanides were well tolerated, affording the desired annulated product in high yields. However, *N*-alkyl-substituted triazinones exhibited no reactivity.

2.6. Denitrogenative Annulation of 1,2,3,4-Benzothiazinones

In 2010, Murakami and co-workers devised a Ni-catalyzed enantioselective annulation reaction[53] of 1,2,3,4-benzothiazinones with a monosubstituted allene to synthesize 1,2,3,4-benzothiazine-1,1(2*H*)-dioxide derivatives (**24A**) and (**24B**) (Scheme 24). For this enantioselective transformation, the authors employed [Ni(cod)$_2$] as the catalyst. They screened many chiral C2-symmetric bidentate phosphine ligands such as (*S*)-binap, (*S,S,R,R'*)-tangphos, and (*R,R*)-Me-duphos, which were not suitable for this reaction. Remarkably, the yields and enantiopurity were both enhanced when an unsymmetrical bidentate *P,N*-type ligand, such as (*S,S*)-^{i}Pr-foxap, was introduced. In particular, (*R*)-quinap provided the best enantioselectivity. Substrates with a variety of substituents present at the N-atom of the 1,2,3,4-benzothiatriazine-1,2(2*H*)-dioxide were tested and afforded major regioisomer (**24A**) with good enantioselectivity. When R = ^{t}Bu in the triazole, another isomer (**24B**) was major due to steric hindrance. The *p*-tolyl-substituted substrate (R = *p*-tolyl) did not work well under these developed conditions.

The mechanism of this annulation reaction is considered to consist of 1) oxidative addition of nickel(0) into the N–N bond of 1,2,3,4-benzothiazinone, 2) formation of the five-membered-ring aza-nickelacycle (**24Int-1**) after the elimination of dinitrogen from the benzothiazinone, 3) allene insertion to form (**24Int-2**), and 4) allylic amidation reaction at the more-substituted carbon to deliver the product and regenerate the nickel (0) catalyst.

Numerous substituted allenes underwent the denitrogenative annulation reaction in the presence of [Ni(cod)$_2$] to generate 1,2,3,4-benzothiazine-1,1(2*H*)-dioxide derivatives (**24A**) and (**24B**) in high yields and good enantioselectivities. It was observed that allenes bearing siloxy, benzyloxy, and *N*-phthalimidoyl groups at the alkyl chains also worked well, although enantiopurity were found to be slightly lower.



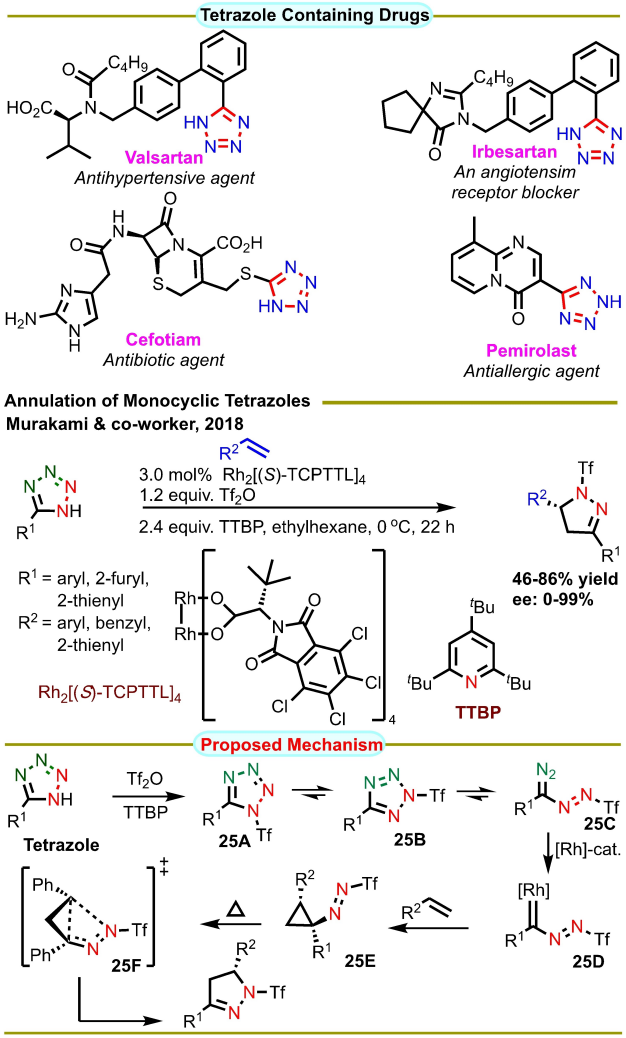
Scheme 24. Denitrogenative annulation of 1,2,3,4-benzothiazinones.

3. Denitrogenative Annulation of 1,2,3,4-Tetrazoles

Tetrazoles are a class of doubly unsaturated five-membered heterocycles. The heterocycle has four nitrogen atoms and one carbon atom. Remarkably, tetrazoles are stable heterocycles with the maximum number of nitrogen atoms; in contrast, pentazoles are extremely explosive compounds even at low temperature. In 1885, Swedish chemist J. A. Bladin for the first time discovered a tetrazole derivative at the University of Upsala.[54] Bladin noticed that the reaction between dicyanophenylhydrazine and nitrous acid formed a new compound with the chemical formula of $C_8H_5N_5$ which was later known as "tetrazole". Tetrazoles can be classified into four categories—unsubstituted, mono-, di- and trisubstituted—depending on the number of substituents. Tetrazole motifs are an integral part of many heterocyclic scaffolds with a wide range of applications in organic chemistry, the photographic industry, explosives, biochemistry, pharmacology, and in particular, medicinal chemistry. More intriguingly, tetrazoles are also used as an environmentally benevolent module in gas generators with a high burn rate and relative stability as they have a high number of nitrogen atoms. It is worth mentioning that the utility of tetrazoles in medicinal chemistry is amazing. According to the drug data bank report,[55] tetrazole-bearing derivatives possess antiviral, antiallergic, cytostatic, hypertensive, antimicrobial, nootropic, and many other biological activities (Scheme 25).

3.1. Denitrogenative Annulation of Monocyclic 1,2,3,4-Tetrazoles via a Metal Carbene

In 2018, Murakami and co-workers demonstrated an elegant enantioselective denitrogenative annulation method of the in situ triflate protected 5-substituted 1*H*-tetrazoles with styrenes using rhodium as a catalyst to produce pyrazolines (Scheme 25) via a metal carbene intermediate.[56] To improve the yield and enantioselectivity, a variety of chiral Rh-catalysts were evaluated and finally the best result was obtained using Rh$_2$[(*S*)-TCPTTL]$_4$ as a catalyst for this annulation reaction with 84% yield and 96% ee. Interestingly, the nonpolar solvent ethyl cyclohexane was more suitable than other solvents, e.g., chloroform, toluene, and cyclohexane. Various styrenes and substituted tetrazoles were tested. The reaction of alkyl-substituted tetrazoles with styrenes was unsuccessful due to the decomposition of the corresponding nitrile imines, which infrequently react with alkenes. The reaction mechanism of this annulation reaction is summarized in Scheme 25: 1) In the first step, tetrazole in the presence of triflic anhydride tetrazole produces an isomeric mixture of tetrazoles (**25A**) and (**25B**), which remain in equilibrium. Then, N_2-triflylated tetrazole (**25B**) participates in ring–chain isomerization to furnish a stable α-diazo diazene (**25C**). 2) Then, dinitrogen is released from intermediate (**25C**) irreversibly with the help of the Rh-catalyst to furnish a Rh^{II} carbenoid species (**25D**). After that, the carbenoid species (**25D**) undergoes an asymmetric cyclopropanation reaction with styrene to afford the *E*-



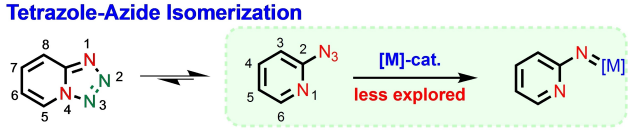
Scheme 25. Tetrazole-bearing drugs and annulation of monocyclic tetrazoles.

cyclopropyldiazene (**25E**). 3) The cyclopropyldiazene (**25E**) takes part in a ring-expansion reaction to form 2-pyrazoline via TS **25F**.

3.2. Ir-Catalyzed Denitrogenative Annulation of Pyridotetrazoles

Among various tetrazoles, pyridotetrazole (a surrogate of azide) is highly important as it has an important pyridyl unit. Pyridotetrazoles are known to undergo ring–chain isomerization. In particular, pyridotetrazole is known to undergo reversible tetrazole–azide isomerization (Scheme 26) to produce an open azide or vice versa. Tetrazole–azide isomerization is governed by reaction conditions particularly by substituents, solvent, and temperature.[57]

As discussed in the Section 2, over the past decades, there has been significant growth in the development of denitrogenative annulation reaction of 1,2,3-triazole skeletons to construct valued cyclic compounds, especially *N*-

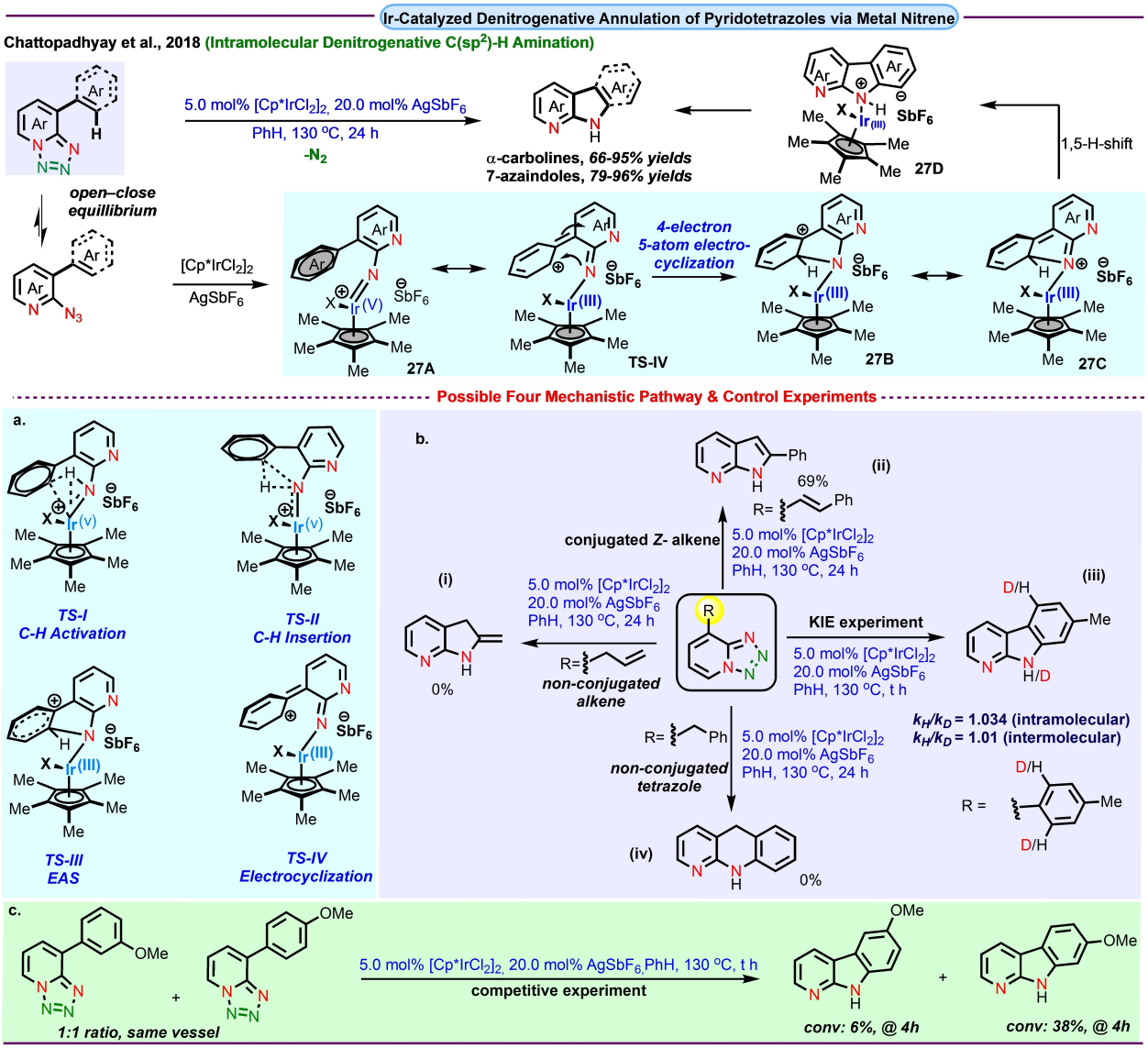


Scheme 26. Tetrazole-azide isomerization.

heterocycles. However, denitrogenative annulation of pyridotetrazole via metal nitrene remains a big challenge due to the extreme inertness of the tetrazole moiety. Like 1,2,3-triazoles, the key factor for the development of denitrogenative annulation of 1,2,3,4-tetrazoles should be 1) the ring opening of 1,2,3,4-tetrazoles in the presence of metal catalyst followed by N_2 elimination and 2) subsequent diverse transformations, which enable the rapid synthesis of various heterocycles in a single step.

Considering all these challenges, in 2018, for the first time our group reported the development of a method[58] to access *N*-pyridyl metal nitrenes from pyridotetrazoles using a Cp^*Ir^{III} cation, affording several privileged scaffolds such as aza-carbazoles, aza-indoles, and other high-value nitrogen heterocycles (Scheme 27 top). Despite the attention given to the reactivity of tetrazolopyridines by Wentrup and co-workers[6] for 40 years ago, this is the first report of productively capturing an *N*-pyridyl nitrene from a tetrazolopyridine, 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. The scope of this denitrogenative annulation strategy is broad with a good level of functional group tolerance. Tetrazoles that have different electronic environment at the reaction site as well as steric environment also work well under these optimized reaction conditions. The developed reaction was also effectively applied for the preparation of two privileged bioactive molecules i.e., neocryptolepin and an important molecule which exhibited cytotoxicity against the HL-60 cell line. Interestingly, apart from aryl substituents at the C-8 position of tetrazole, substrates that bear an alkene group at the C-8 position also react productively and eventually yielded 7-azaindole derivatives. *(Caution: Although, tetrazoles are very stable at room temperature for several months, the tetrazole preparation step was done very carefully in a fume hood for safety reasons).* To illustrate the formation of denitrogenative cyclized product, we proposed four different reaction mechanism and transition state structures: C–H activation via **TS-I**, C–H insertion via **TS-II**, electrophilic aromatic substitution (EAS) via **TS-III**, and electrocyclization via **TS-IV** (Scheme 27a)

Systematic control experiments supported the involvement of **TS-IV** i.e., the electrocyclization pathway. In the electrocyclization mechanism, in the first step, the sterically favored iridium nitrene intermediate (**27A**) is formed from tetrazole with the help of the in situ generated Cp^*Ir^{III} cation. After that, **TS-IV** (originating from **27A**) undergoes four-electron/five-atom electrocyclization to form a C–N bond (**27C**). Then, the corresponding resonance structure, **27B**, undergoes 1,5-H shift which results in intermediate



Scheme 27. Ir-catalyzed denitrogenative annulation of 1,2,3,4-tetrazoles.

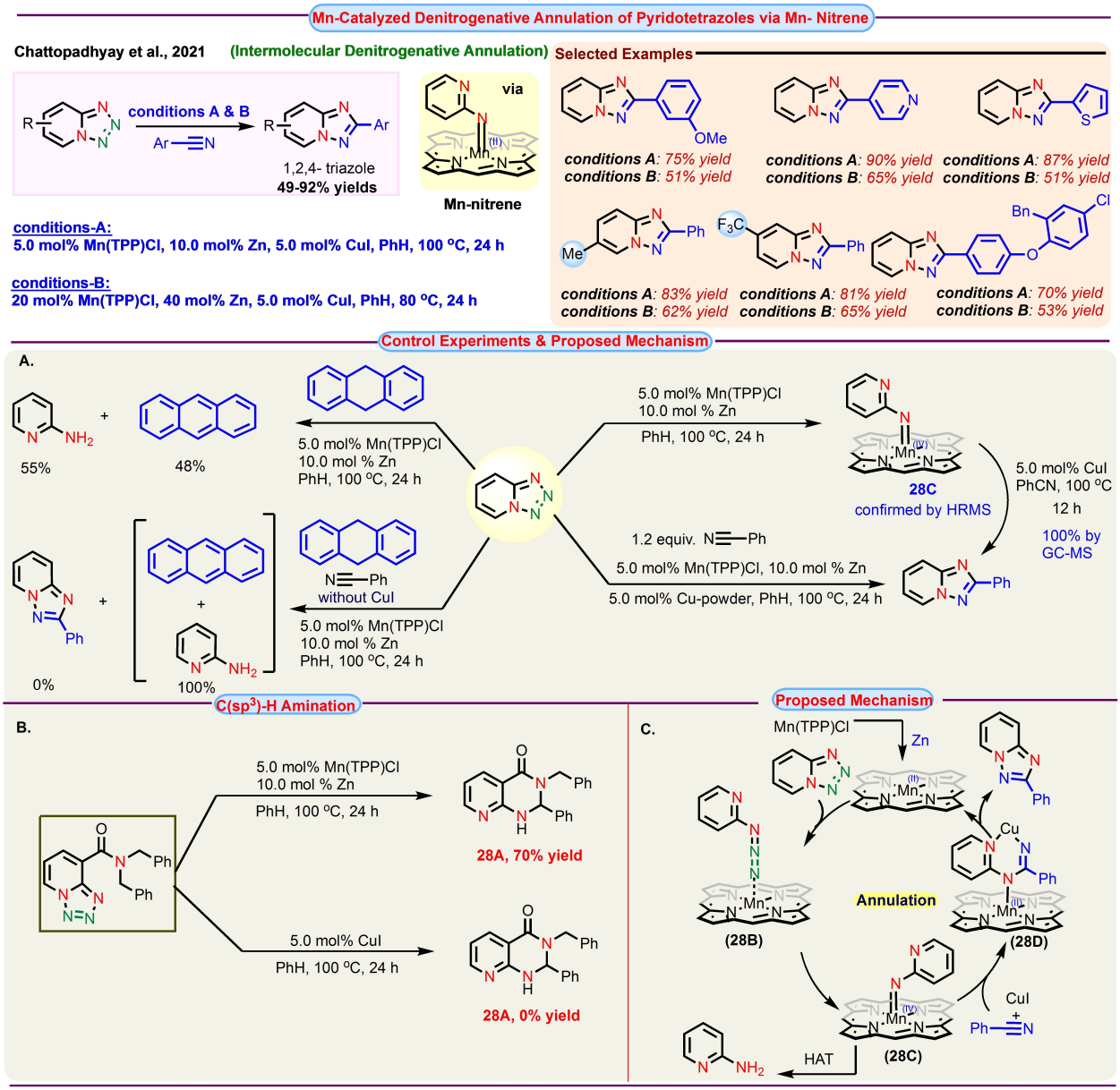
27D. Finally, from intermediate **27D**, the desired aminated product forms and the catalytic cycle is completed.

To support this aforementioned electrocyclization pathway, a series of control experiments were performed (Scheme 27b,c). For instance, amination with a non-conjugated alkene (Scheme 27b, (i)), conjugated *Z*-alkene ((ii)) as well as a KIE experiment (intermolecular and intramolecular, (iii)) eliminated the option of C–H activation (through **TS-I**) and the insertion mechanism (through **TS-II**). Subsequently, reaction with a non-conjugated tetrazole (Scheme 27b, (iv)) resulted in 0% product conversion, indicating that continuous conjugation is required for this amination .

Furthermore, a competition experiment (Scheme 27c) with *meta*- and *para*-substituted methoxy tetrazoles (in same vessel) led to 38% conversion of the *meta*-substituted tetrazole and 6% conversion of the *para*-OMe tetrazole, which provided evidence for the participation of electrocyclization (**TS-IV**).

3.3. Mn-Catalyzed Denitrogenative Annulation of Pyridotetrazoles

In continuation of our metal nitrene studies, very recently we developed a denitrogenative annulation reaction between tetrazole and nitrile (Scheme 28) using Mn-porphyrin-based catalytic systems.[59] Initially we did not get the desired annulated product; however, in the presence of CuI as a cocatalyst, we observed complete conversion to the desired annulated product. Since the reaction was conducted at elevated temperature, we performed the reaction at a lower temperature using a slightly higher catalyst loading; these conditions were found to give comparable results in terms of the conversion to the desired product. Later, the



Scheme 28. Mn-catalyzed denitrogenative annulation of pyridotetrazoles.

substrate scope was tested using these two sets of reaction conditions (Scheme 28 top, conditions A and B). It was observed that different tetrazoles reacted well under these conditions with diversely substituted aromatic nitriles to produce 1,2,4-triazolo pyridines in good to excellent yields.

Next, we became interested in the detailed reaction mechanism of this Mn-catalyzed annulation. At this stage, since the complete reaction mechanism was not very clear to us, to get some ideas, we conducted some mechanistic studies (Scheme 28A,B). We first performed an experiment between 1,2,3,4-tetrazole and 9,10-dihydroanthracene under the employed reaction conditions. The reaction produced 48 % anthracene and 55 % reduced 2-amino pyridine, which supported the option of the formation of a Mn-nitrene intermediate. We then conducted another reaction between tetrazole, benzonitrile, and 9,10-dihydroanthracene excluding CuI. This reaction did not afford even a trace amount of the annulation product but rather a mixture of anthracene and 2-aminopyridine, which supported the formation of the Mn-nitrene complex (**28C**) and also demonstrated the role of CuI (which mainly activates the benzonitrile for the annulation). As we used CuI as a cocatalyst to accelerate the annulation process, the formation of Cu-nitrene is possible. To test this hypothesis, we executed a control experiment with Cu-catalyst; however, it resulted in no product formation. This experiment implied that Cu-nitrene is not the probable intermediate for this transformation. Finally, when we analyzed the reaction mixture of 1,2,3,4-tetrazole, Mn(TPP)Cl catalyst, and Zn dust in the absence of CuI, we were able to detect the corresponding Mn-nitrene

intermediate by HRMS. To get further support for the generation of the Mn-nitrene intermediate (**28C**), we designed a C8-substituted tetrazole bearing a dibenzyl amide unit. Here our idea was that if the Mn-nitrene is formed during the course of the annulation reaction, we should get the corresponding C(sp^3)–H aminated product. Surprisingly, we isolated the corresponding aminated product (**28A**) in 70 % yield. Notably, when the same experiment was conducted using CuI catalyst, it led to no reaction. Thus, based on the experimental evidence, a mechanism was proposed (Scheme 28C). In the first step, the in situ generated Mn^{II}TPP coordinates with the terminal nitrogen of the tetrazole to produce an azide-bound Mn-porphyrin complex (**28B**). From complex (**28B**), by nitrogen evolution, manganese-nitrene intermediate (**28C**) is formed which in the presence of benzonitrile and CuI gives the amidine complex (**28D**). Finally, amidine complex after cyclization produces the annulated product.

3.4. Denitrogenative Annulation of 1,2,3,4-Tetrazole via a Metalloradical Mechanism

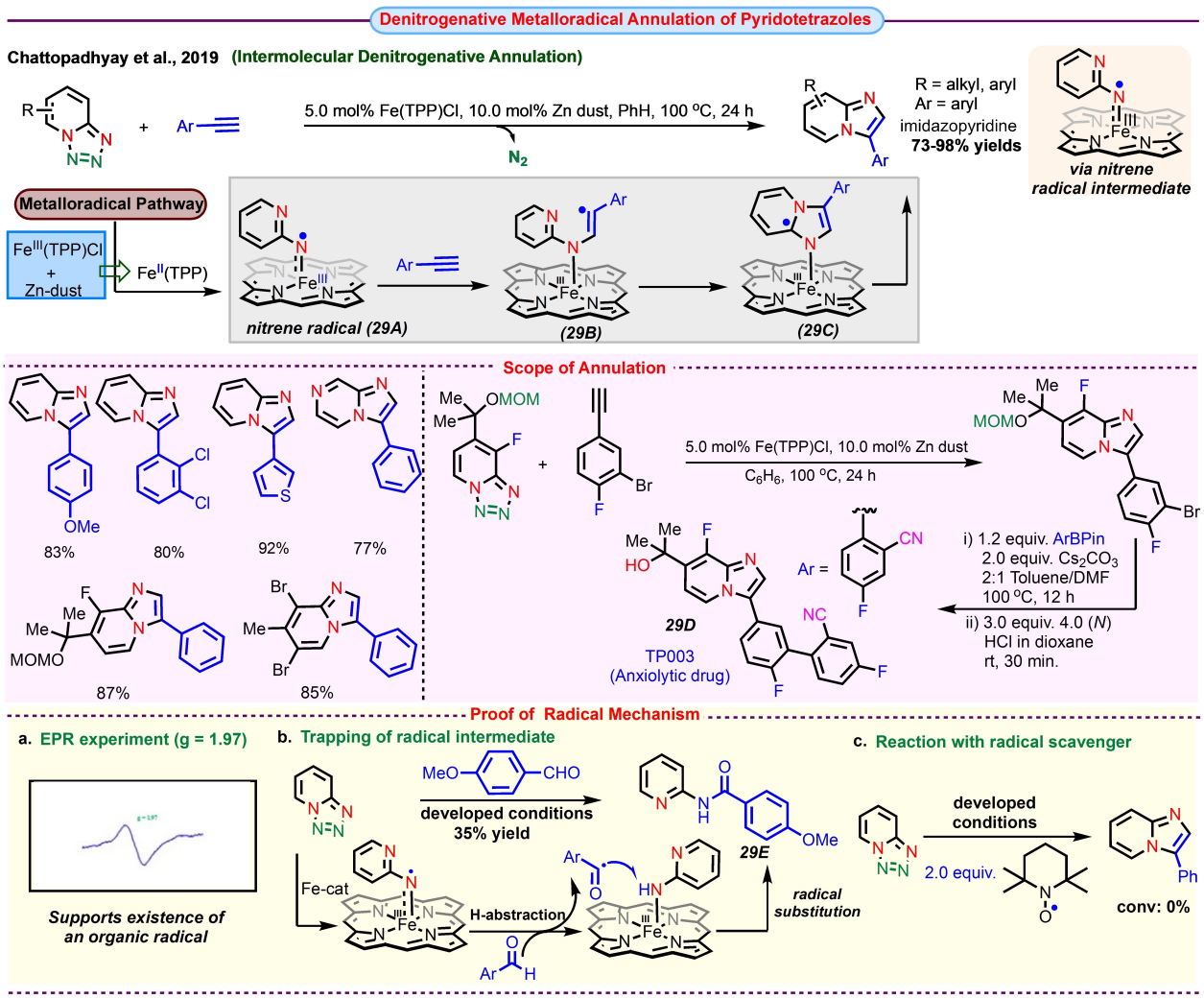
3.4.1. Intermolecular Denitrogenative Annulation

The concept of metalloradical activation for radical cyclization has attracted mounting research interest over the last few decades and has become a well-known tool in organic synthesis. Indeed, metalloradicals have remarkable synthetic utility in many research fields including in the preparation of complex molecules. In comparison to ionic reactions, metalloradical reactions have many synthetic advantages. For instance, 1) radical reactions are very fast; 2) they work under mild and neutral conditions in a broad spectrum of solvents; and 3) they show wide range of functional group tolerance. In this context, the groups of Zhang and de Bruin contributed a lot to develop numerous synthetic transformations such as radical C–C bond formation, radical C–H amination, aziridation, and many more based on Co^{II}-metalloradical chemistry.[60] However, metalloradical activation of 1,2,3,4-tetrazole is a major challenge due to the extreme inertness of the tetrazole.

Intermolecular denitrogenative annulation of 1,2,3,4-tetrazoles with terminal alkynes is quite challenging. One of the major obstacles is the competing 1,3-dipolar cycloaddition (click reaction). It has been observed that in the presence of metal catalyst 2-azidopyridine reacts quickly with terminal alkynes to produce the cycloaddition product. Thus, achieving other types of synthetic transformation particularly annulation overcoming the competitive click reaction is a formidable task. Accepting this challenge, in 2018, we reported a denitrogenative intermolecular annulation between 1,2,3,4-tetrazole (an azide surrogate) and an alkyne proceeding via an Fe^{II}-based metalloradical activation mechanism (Scheme 29).[61] This developed strategy requires 5.0 mol % Fe(TPP)Cl, 10 mol % Zn-dust (reducing agent), PhH solvent, and heating to 100 °C. Under the optimized reaction conditions, numerous substituted tetrazoles and a variety of terminal alkynes reacted smoothly to afford a number of imidazopyridines with excellent yields. It is noted that aliphatic alkynes are not effective for this reaction. The utility of our developed reaction was showcased by synthesizing the anxiolytic drug TP003[62] (**29D**) in just two steps. To explain for the formation of the annulated product, we proposed a radical activation mechanism. In the first step of this mechanism, Fe^{III}(TPP)Cl is reduced to the active catalyst Fe^{II}TPP in the presence of Zn-dust. Then, active catalyst Fe^{II}TPP aid in generating a nitrene radical from the corresponding tetrazole upon nitrogen evolution. After that, nitrene radical intermediate (**29A**) is trapped by the terminal alkyne, giving γ-Fe^{III}-vinyl radical intermediate (**29B**). Subsequently, by radical addition, a new β-Fe^{III} alkyl radical intermediate (**29C**) is generated, which experiences β-radical scission to break the N–Fe bond and form a C=N bond, affording the product and completing the catalytic cycle. To validate this proposed radical mechanism, we executed various control experiments. For example, we studied the EPR spectra which corroborated the presence of an organic radical (found *g* value 1.97) in the reaction. Next, we attempted to trap the radical intermediate using benzaldehyde in the annulation reaction conditions.[63] Delightfully, we were able to isolate the trapped product (**29E**) with 35 % isolated yield. This experiment supported the presence of a nitrene radical intermediate. However, the result of a radical-scavenging experiment using TEMPO also supported the radical pathway.

3.4.2. Intramolecular Denitrogenative C(sp^3)–H Amination

In early 2020, we applied our understanding of tetrazole reactivity towards an intramolecular denitrogenative C-(sp^3)–H amination reaction of 1,2,3,4-tetrazoles bearing inert primary, secondary, and tertiary centers using iron-based catalytic systems.[64] Along with seminal reports by Breslow[65] in the field of nitrenoid chemistry, the Betley[66] and White[67] groups also reported some elegant methods using iron and manganese catalysis. Bearing in mind the major challenges associated with the activation of inert C(sp^3)–H bonds (high bond dissociation energy and the lack of a suitably available HOMO or LUMO to interact with transition metals), we devised an Fe-based catalyst that empowered the preparation of a number of complex nitrogen heterocycles with high levels of selectivity and functional group tolerance (Scheme 30). This method offers two important *N*-heterocycles, 7-azaindoline and pyrido-pyrimidones, which are difficult to prepare using the previously reported conventional methods due to the presence of an additional nitrogen atom. After systematic screening, we found that our previously established Fe-based reaction conditions with slight modification afforded the desired C(sp^3)–H aminated product quantitatively. The scope of this amination reaction was attractive. Along with several electronically diverse C–H bonds, tetrazoles featuring an amide group with various C–H bonds at C8-position could be aminated to make high-value *N*-heterocycles with different ring sizes. It has been observed that this catalytic amination follows an unprecedented metalloradical activa-



Scheme 29. Fe-catalyzed intermolecular denitrogenative annulation of pyridotetrazoles.

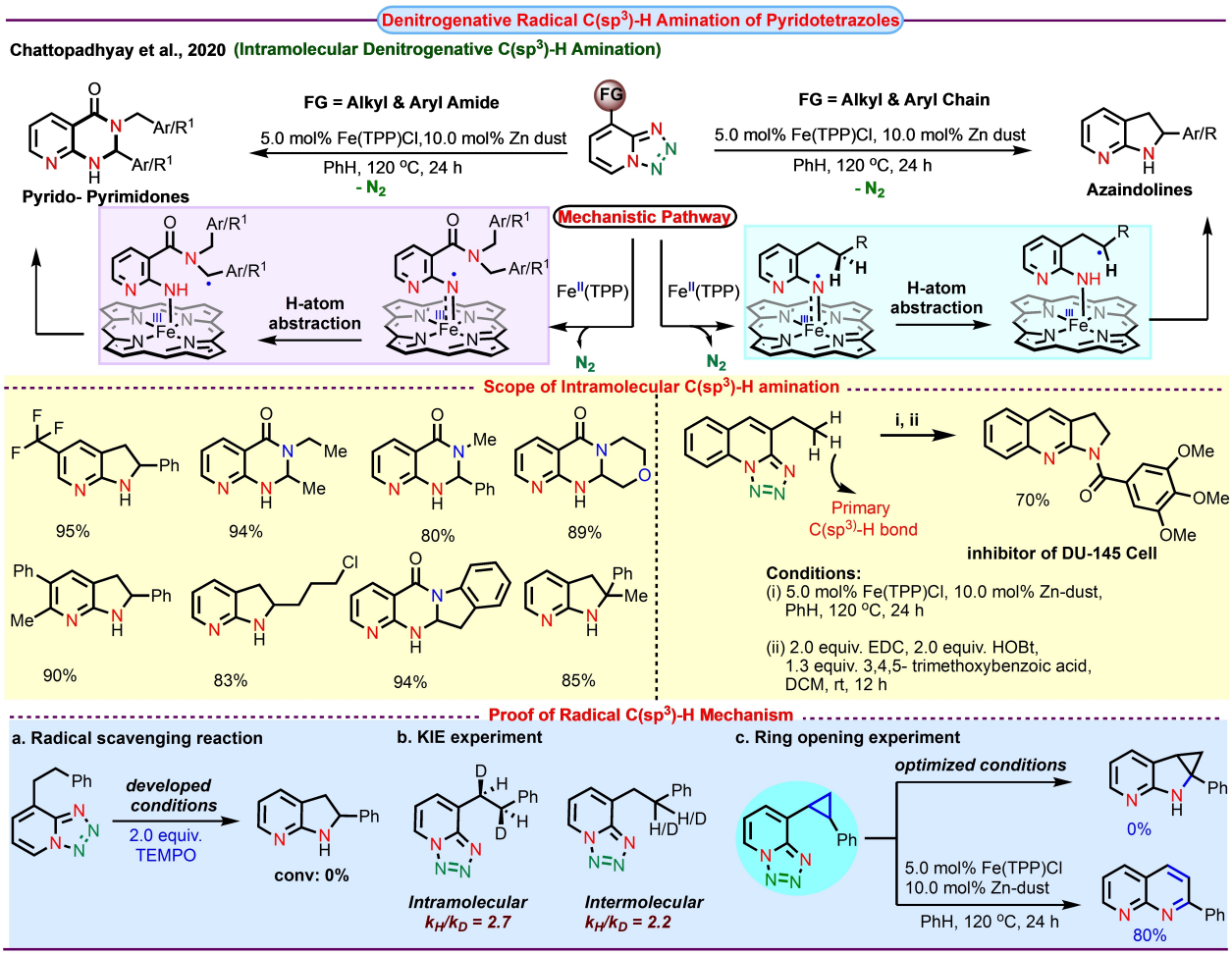
tion mechanism. In the first step of this mechanism, intramolecular H-atom abstraction occurs via the nitrene radical. Then radical substitution from the corresponding intermediate produces the desired aminated product and the catalytic cycle is completed.

Mechanistic studies (radical-scavenging experiment, KIE measurement intermolecularly as well as intramolecularly, and ring-opening experiment) helped to show that C–H amination likely occurs by a radical mechanism and C–H bond breaking occurs probably during the turnover-limiting step. Applying this strategy, one important molecule that acts as an inhibitor of DU-145 cell[68] was synthesized with good isolated yield.

3.4.3. Denitrogenative Radical Rearrangement of Pyridotetrazoles

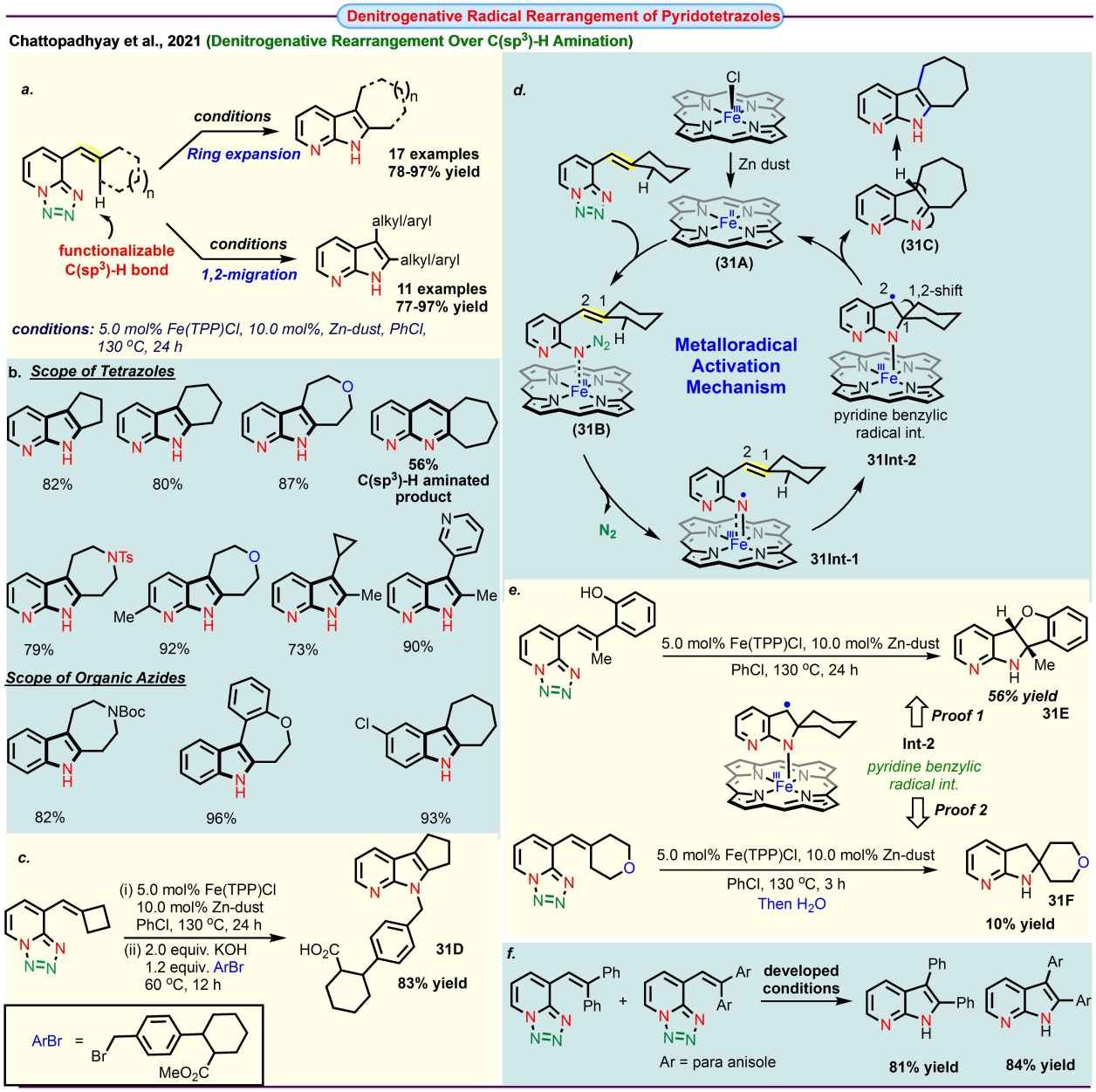
In 2021, our group expanded the scope of the denitrogenative annulation of 1,2,3,4-tetrazoles towards the denitrogenative rearrangement over C(sp^3)–H amination (Scheme 31).[69] The rearrangement chemistry of diazo precursors and organic azides was previously thoroughly studied by Murakami,[70] Fokin,[71] Driver,[72] and Shi[73] using Rh-catalysis. However, the rearrangement of 1,2,3,4-tetrazoles in the presence of base metal complexes was completely unknown. In order to develop a suitable method, we designed a substrate in which a disubstituted alkene along with a functionalizable C(sp^3)–H bond (for example, methylene cyclohexane) is present at C8 position of tetrazole. In this substrate, there is the possibility of molecular rearrangement via either a ring expansion or 1,2-migration.

Next, we devised a plan that facilitated the rearrangement over the competitive C(sp^3)–H amination. The plan is based on following assumptions: 1) Tetrazole should have a flexible methylene cycloalkane (such as cyclohexane) unit; 2) The cyclohexane unit will remain in stable chair-conformation so that the functionalizable C(sp^3)–H bonds will not be close enough to the reacting radical center to be accessible for the C(sp^3)–H amination; 3) Due to the geometric constrains, the pendent C=C bond will be in close vicinity to the reacting radical center, which after reaction



Scheme 30. Fe-catalyzed intramolecular denitrogenative radical C(sp^3)–H amination of pyridotetrazoles.

affords the rearrangement products rather than the C-(sp^3)–H aminated products. To test this plan, we screened various catalysts and found that 5.0 mol % Fe(TPP)Cl along with 10 mol % Zn-dust in PhCl solvent at 130 °C produced the desired rearrangement product. This is the optimal conditions. This developed method was very controllable with a wide range of substrates and produced both the ring-expansion and 1,2-migration products in good to excellent yields. Using organic azides (*considering the explosive nature of organic azides, we synthesized all the organic azides very carefully in the fume hood*[74]) under our developed conditions, we obtained indole product. The formation of 1,8-napthyridine was observed when C(sp^3)–H amination dominates over the rearrangement reaction. The case of exclusive C(sp^3)–H amination can be explained by considering the geometric constraints of the bicyclic or tricyclic systems, which do not allow the pendent C=C bond to be closer to the radical center; instead, the radical center abstracts the bridgehead hydrogen atom and generates a stable tertiary carbon radical center. Adding on, this established strategy was employed in the synthesis of a cardiovascular agent[75] (**31D**). Next, based on various control experiments (radical-trapping experiment, Hammett plot, ring-opening experiment), we proposed a metalloradical activation mechanism. Initially, Fe^{III}(TPP)Cl is converted into the active catalytic species Fe^{II}(TPP). Then, the metal-bound tetrazole complex (**31B**) furnishes an α-Fe^{III}-nitrene intermediate (**31Int-I**) by N_2 elimination. After that, the nitrene radical (**31Int-1**) is trapped by the pendent C=C bond to yield a pyridine benzylic radical intermediate (**31Int-2**). Next, 1,2-migration (resulting in intermediate **31C**) is followed by 1,3-H shift to provide the desired product and regenerate the catalyst. To support the formation of the pyridine benzylic radical, we conducted two vital experiments. The first is a cascade radical cyclization (in which H-atom abstraction occurs from *ortho*-substituted –OH group) which furnished cyclized product **31E** in 56 % yield) and the second is a stoichiometric reaction, which was quenched with water, affording a spiro-cyclized product **31F** in 10 % yield. Lastly, to check whether the 1,2-migration step is concerted or occurs stepwise, we conducted one crossover experiment that resulted in two types of products, confirming that 1,2-migration occurs in a concerted fashion.



Scheme 31. Fe-based denitrogenative radical rearrangement of pyridotetrazoles.

4. Conclusion

The field of transition-metal-catalyzed denitrogenative annulation has achieved pronounced advances for the construction of various high-value *N*-heterocyclic compounds (summarized in Table 2). The C–C bond and C–N bond can be shaped in a simple one-pot pathway. Realizing the standing of this strategy, the transition-metal-catalyzed denitrogenative annulation has grown in leaps and bounds in the last decade, thanks to contributions from scientific researchers all over the world. Many researchers have applied this protocol in multistep syntheses of nitrogen-rich molecules. Despite the rapid progress of this field, the requirement precious noble metal catalysts such as Rh-catalysts remains an inherent obstacle, albeit base metal catalysts such as Co and Fe have resolved this complication. Although at a first glance, it may seem the field is well developed, significant growth still awaits, paving the way of synthetic organic chemistry to newer avenues.

Acknowledgements

This work was supported by CSIR–EMR-II grant (02/0396/21/EMR-II). SR and SKD thank CSIR for their SRF. We also thank CBMR for research facilities.

Table 2: Different triazole and tetrazole skeletons used for denitrogenative annulation in the presence of various transition-metal catalysts.

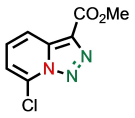
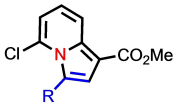
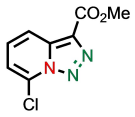
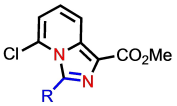
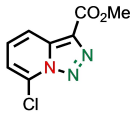
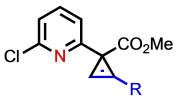
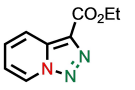
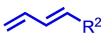
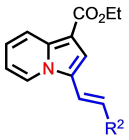
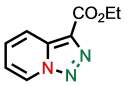
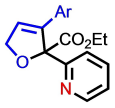
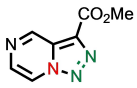
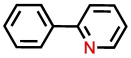
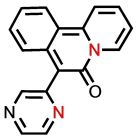
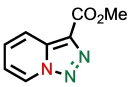
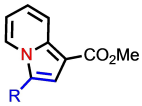
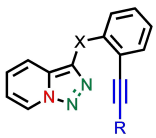
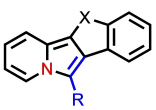
Substrate	Type of Reaction	Catalyst	Annulated Product	Reference
	Intermolecular Annulation 	$Rh_2(pfb)_4$		[10]
	Intermolecular Annulation 	$Rh_2(pfb)_4$		[10]
	Intermolecular Annulation	$Rh_2(S\text{-}DOSP)_4$		[11]
	Intermolecular Annulation 	$Rh_2(Oct)_4$ $Pd(PPh_3)_4$ MnO_2		[12]
	Intermolecular Annulation 	$Rh_2(esp)_2$ (2 mol%)		[13]
	Intermolecular Annulation 	$[Cp^*Rh(MeCN)_3](SbF_6)_2$		[14]
	Intermolecular Annulation 	$Cu(MeCN)_4{\bullet}PF_6$		[15]
	Intramolecular Annulation	$CuBr{\bullet}SMe_2$		[16]

Table 2: (Continued)

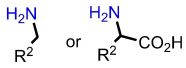
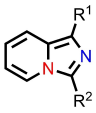
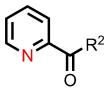
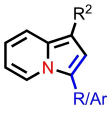
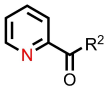
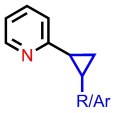
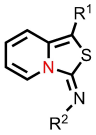
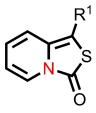
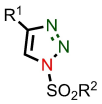
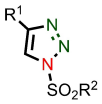
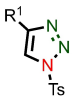
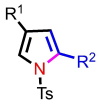
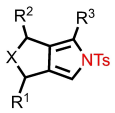
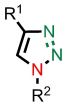
Substrate	Type of Reaction	Catalyst	Annulated Product	Reference
	Intermolecular Annulation 	CuI		[17]
	Intermolecular Annulation 	Co(TPP)		[18]
	Intermolecular Annulation 	Co(TPP)		[18]
	Intermolecular Annulation 	Co(TPP)		[20]
	Intermolecular Annulation 	Co(TPP)		[20]
	Intermolecular Annulation 	Rh_2(S-DOSP)$_4$		[29]
	Intermolecular Annulation 	Ni(cod)$_2$, P(nBu)Ad$_2$		[31]
	Intermolecular Annulation 	Rh_2(oct)$_4$, AgOCOCF$_3$		[32]
	Intermolecular Annulation	Rh_2(esp)$_2$		[33]
	Intermolecular Annulation 	Rh_2(*S*-NTTL)$_4$		[34, 35]

Table 2: (Continued)

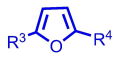
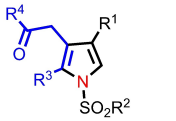
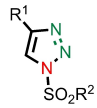
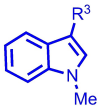
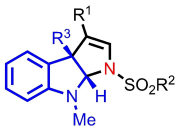
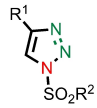
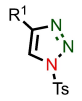
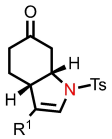
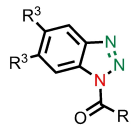
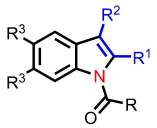
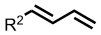
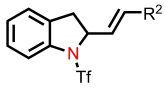
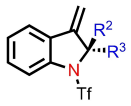
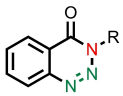
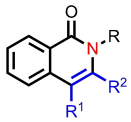
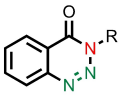
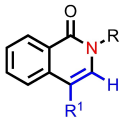
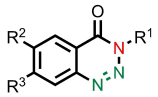
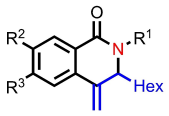
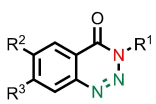
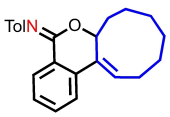
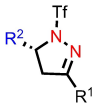
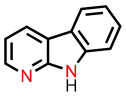
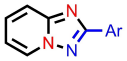
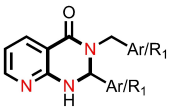
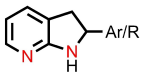
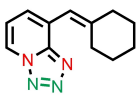
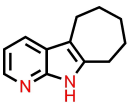
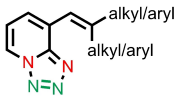
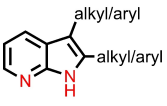
Substrate	Type of Reaction	Catalyst	Annulated Product	Reference
	Intermolecular Annulation 	$Rh_2(S\text{-DOSP})_4$		[36]
	Intermolecular Annulation 	$Rh_2(S\text{-PTAD})_4$		[37]
	Intermolecular Annulation	$Rh_2(S\text{-NTTL})_4$		[38]
	Intermolecular Annulation 	$Rh_2(oct)_4$		[39]
	Intermolecular Annulation	$Pd(PPh_3)_4$		[40]
	Intermolecular Annulation 	$Pd(PPh_3)_4$		[45]
	Intermolecular Annulation 	$Pd_2(dba)_3$		[47]
	Intermolecular Annulation	$[Ni(cod)_2]$		[49]
	Intermolecular Annulation	$[Ni(cod)_2]$		[49]
	Intermolecular Annulation 	$[Ni(cod)_2]$, PMe_3		[50]
	Intermolecular Annulation 	$[Ni(cod)_2]$		[50]

Table 2: (Continued)

Substrate	Type of Reaction	Catalyst	Annulated Product	Reference
	Intermolecular Annulation 	$Rh_2[(S)\text{-TCPTTL}]_4$		[56]
	Intramolecular Annulation	$[Cp^*IrCl_2]_2$, $AgSbF_6$		[58]
	Intermolecular Annulation 	Mn(TPP)Cl, Zn CuI		[59]
	Intermolecular Annulation 	Fe(TPP)Cl, Zn		[61]
	Intramolecular Annulation	Fe(TPP)Cl, Zn		[64]
	Intramolecular Annulation	Fe(TPP)Cl, Zn		[64]
	Intramolecular Annulation	Fe(TPP)Cl, Zn		[69]
	Intramolecular Annulation	Fe(TPP)Cl, Zn		[69]

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Denitrogenative Annulation · Synthetic Methods · Transition Metal Catalysts · Tetrazoles · Triazoles

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