Denitrogenative Transformations of Pyridotriazoles and Related Compounds: Synthesis of *N*-Containing Heterocyclic Compounds and Beyond

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ABSTRACT: The high demand for new and efficient routes toward synthesis of nitrogen-containing heterocyclic scaffolds has inspired organic chemists to discover several methodologies over recent years. This perspective highlights one standout approach, which involves the use of pyridotriazoles and related compounds in denitrogenative transformations. Readily available pyridotriazoles undergo ring-chain isomerization to produce uniquely reactive α-diazoimines. Such reactivity, enabled by metal catalysts, additives, or visible light irradiation, can be applied in transannulation, insertion, cyclopropanation, and many other transformations.

1. Introduction

N-containing heterocyclic frameworks are ubiquitous in drugs, dyes, and high-performance materials.[1] Pyridines, fused pyridines, and other heterocyclic scaffolds possessing bridgehead nitrogens are important moieties present in several biologically active molecules and natural products.[2] Due to the broad and emergent applications of these families of molecules, new, efficient, and general methods for their synthesis are in constant demand. Several strategies involve the use of triazoles as nitrogen sources for synthesis of fused *N*-heterocyclic and carbocyclic compounds.[3] Those employing *N*-sulfonyl-1,2,3-triazoles have emerged in the past few years, and are summarized elsewhere.[4] This perspective will focus on denitrogenative transformations of pyridotriazoles and related compounds. This reaction class stands out as a single-step process featuring high efficiency and atom economy, as the only byproduct is molecular nitrogen.

Pyridotriazoles are essential building blocks in pharmaceutical chemistry and material science.[3b, 5] They are readily available either through the reaction of pyridine-2-yl- acetates with 4-acetamidobenzenesulfonyl azides, or the oxidative *N*–*N* coupling of in-situ generated hydrazones from ketones.[6]

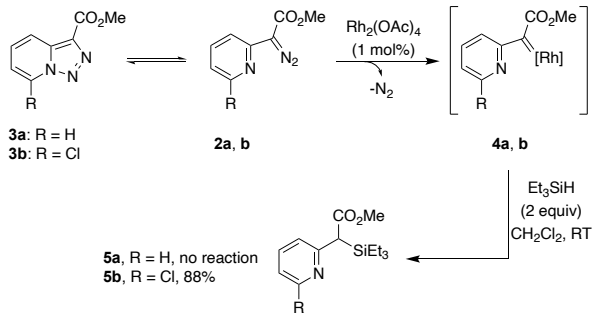
Cyclic triazoles are known to undergo ring-chain isomerization.[7] Particularly, pyridotriazole **1** in solution will undergo reversible ring-chain isomerization (Scheme 1) to produce diazo compound **2**,[8] or vice-versa.[9] The equilibrium of this isomerization can be influenced by reaction conditions, particularly by solvent and temperature. However, a crucial factor in shifting the equilibrium toward the open or closed isomer is the substitution pattern around the ring, specifically at C7.[8d] For instance, introducing a halogen atom (R^1 = Cl) at this position shifts the equilibrium to the right, likely due to the non-bonding repulsion between the lone pairs of electrons at halogen atom with those at the nitrogen atom in the *peri* position of **1** (Scheme 1).[10] Computational studies by Bao group showed that the formation of the diazo tautomer **2** occurs readily, and even slightly exothermically, when R^1 = F.[8a]

Scheme 1. Ring-Chain Isomerism of Pyridotriazoles

1 **2**

In 2007, Gevorgyan group disclosed the use of pyridotriazoles as stable precursors for rhodium carbenes.[11] It was shown that pyridotriazole **3b**, which exists in equilibrium with pyridyl diazo compound **2b** via ring-chain isomerism, reacted with rhodium catalyst to release molecular nitrogen and form rhodium carbene **4b**.[12] Formation of the latter was confirmed by its smooth Si–H insertion reaction[13] with triethylsilane to produce the corresponding product **5b** (Scheme 2). Not surprisingly under the reaction conditions, pyridotriazoles **3a** and **3b** showed completely different reactivity, as no reaction was observed with **3a**. This further illustrates the governing effect of the C7 substituent on the open-close form equilibrium between **3** and **2**.

Scheme 2. Rhodium(II)-Catalyzed Si–H Insertion



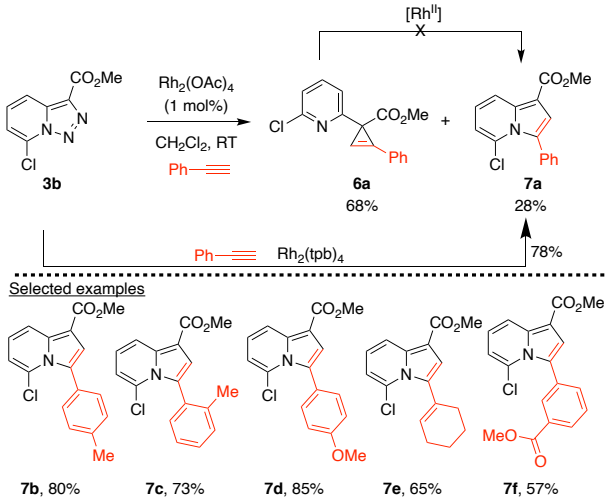
2. Transannulation of Pyridotriazoles

2.1 Rhodium-Catalyzed Transannulation

Species **4** are unique as they possess inherently electrophilic rhodium carbene moiety alpha to a nucleophilic imine group. Gevorgyan and co-workers first uncovered remarkable reactivity of these species in transannulation reaction with alkynes and nitriles toward synthesis of indolizines and imidazopyridines from readily available and inexpensive pyridotriazoles.[11]

Initially, transannulation reaction of pyridotriazole **3b** with phenyl acetylene in the presence of rhodium acetate yielded a mixture of the [2+1] and [3+2] cycloaddition products **6a** and **7a**, respectively (Scheme 3). Upon re-submission of isolated cyclopropene **6a** to the reaction no isomerization of the latter into indolizine **7a** was observed, thus pointing out on independent mechanisms for formation of **6** and **7**. Notably, employment of more electrophilic $Rh_2(pfb)_4$, led to the highly chemoselective formation of indolizine **7a** in 78% yield. Under the optimized reaction conditions, pyridotriazole **3b** reacted smoothly with different aryl alkynes and enynes to give indolizines **7** in good to excellent yields. However, the reactions with aliphatic alkynes were much less efficient.

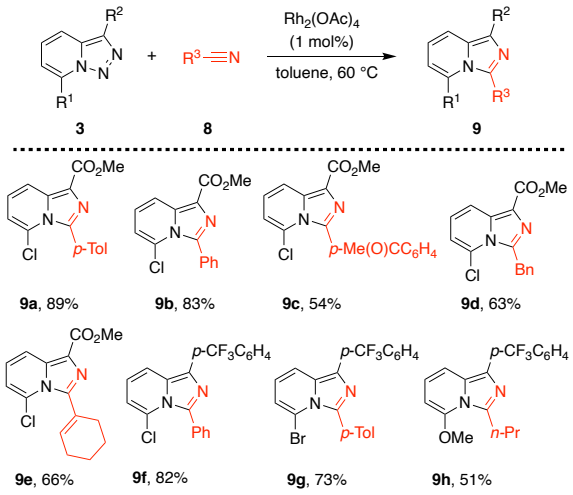
Scheme 3. Rhodium(II)-Catalyzed Transannulation with Aryl and Alkenyl Acetylenes



Next, Gevorgyan group demonstrated efficient synthesis of *N*-fused imidazopyridines through the transannulation of pyridotriazoles **3** with nitriles **8** (Scheme 4). Electronically different aryl, alkenyl, and alkyl nitriles proven to be capable reaction partners for pyridotriazoles **3** to produce the corresponding *N*-fused imidazopyridines **9** in moderate to good yields even in the presence of less electrophilic rhodium acetate catalyst. Diversely substituted pyridotriazoles such as 3-methoxycarbonyl, 3-aryl, 7-Br, and 7-OMe reacted well under these reaction conditions.

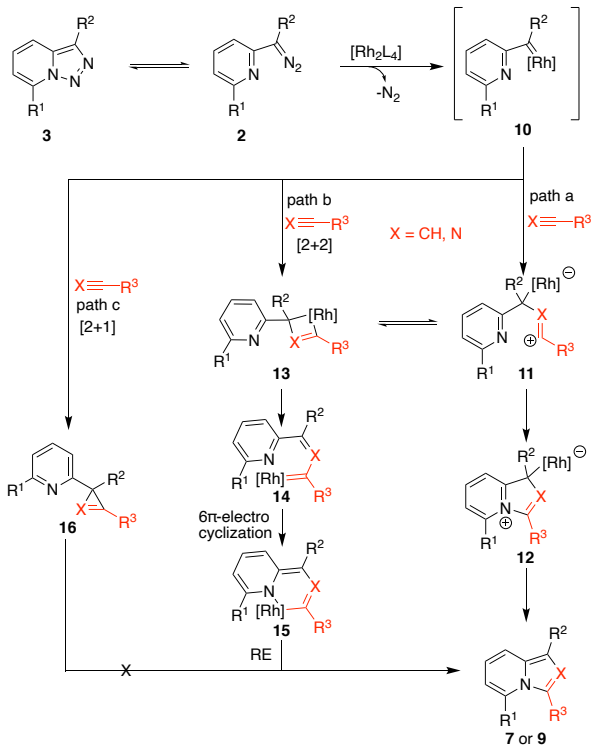
Two alternative mechanisms were proposed by the authors for this transannulation reaction (Scheme 5). According to the path a, pyridotriazole **3** reacts with rhodium catalyst via its in-situ generated open form **2** to form the rhodium carbene species **10**, followed by a direct nucleophilic attack[14] of an alkyne or nitrile to produce the intermediate ylide **11**. A subsequent cyclization leads to the corresponding products **7** or **9** via zwitterionic intermediates **12** (Scheme 5, path a). Alternatively (path b), upon [2+2] cycloaddition of rhodium carbene **10** with alkyne or nitrile, a rhodacyclobutene **13** is produced, which could also be formed from the cyclization of **11**.[15] Ring opening of rhodacyclobutene **13** would produce rhodium carbene species **14**, which, upon 6π-electrocyclization and a subsequent

Scheme 4. Rhodium(II)-Catalyzed Transannulation with Nitriles



reductive elimination, would yield the corresponding products **7** or **9**. As previously stated, even though cyclopropene **16** was observed from [2+1] cycloaddition of pyridotriazole **3** with alkynes in the presence of rhodium(II) acetate, path c could be ruled out as no isomerization **16**→**7** was observed.

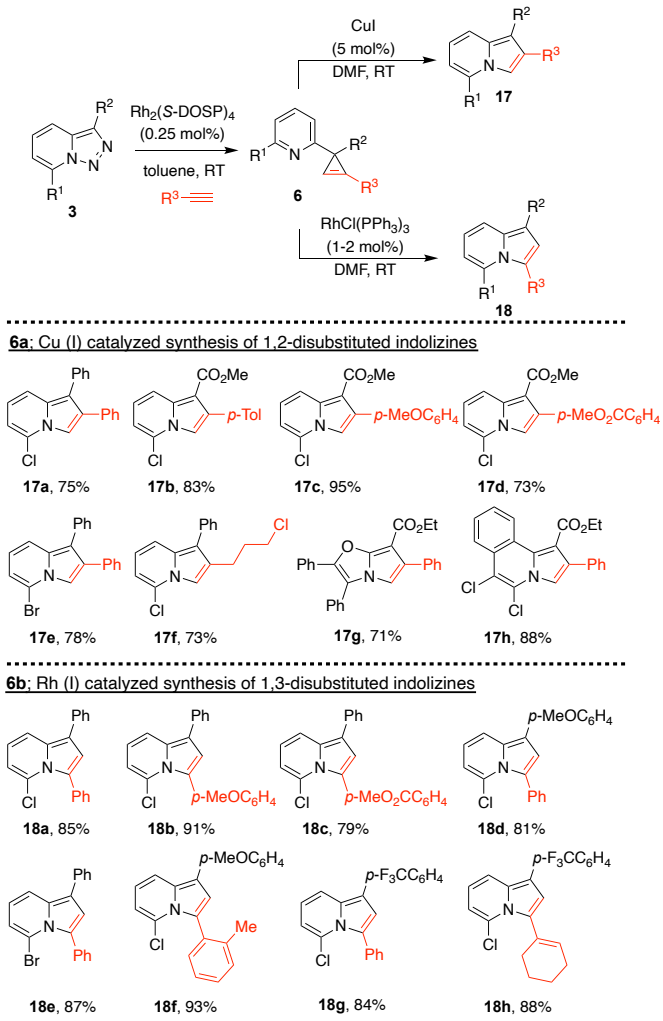
Scheme 5. Proposed Mechanism for Rhodium(II)-Catalyzed Transannulation



Next, Gevorgyan group reported a two-step method for a regiodivergent synthesis of 1,2- and 1,3-disubstituted indolizines from pyridotriazoles **3** and terminal alkynes.[16] At the first step, an efficient access to a variety of 3-iminocyclopropenes **6** was readily achieved in the presence of Rh_2(*S*-DOSP)$_4$ (Scheme 6). This intermediate could be then subjected to the copper catalyst to selectively obtain 1,2-disubstituted indolizines **17** (Scheme 6a). Alternatively, using rhodium(I) catalyst, selective formation of 1,3-disubstituted indolizines **18** could be achieved (Scheme 6b). These protocols are

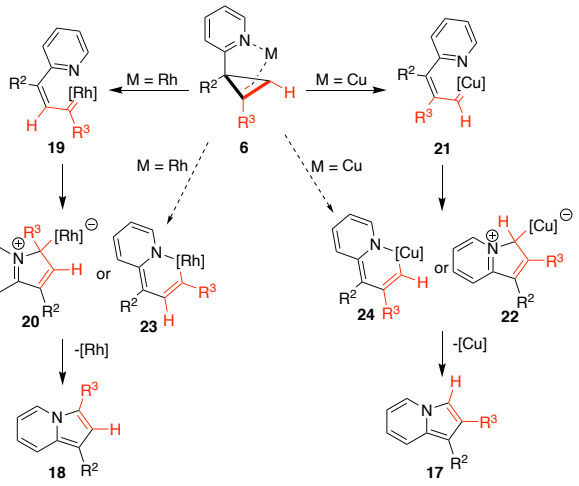
remarkably regiodivergent, as regioisomeric indolizines **17** and **18** were obtained with >99% selectivity. These protocols are quite general with respect to the electronic nature of cyclopropenes used.

Scheme 6. Regiodivergent Synthesis of N-fused Heterocyclic Compounds



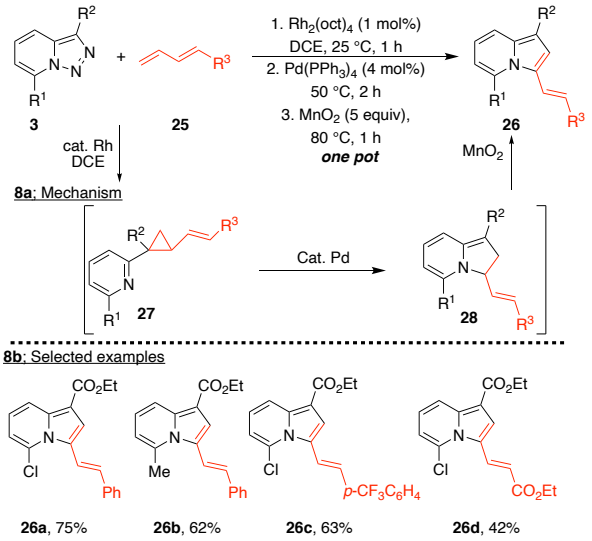
The authors proposed the following mechanisms for the regiodirvergent cycloisomerizations of cyclopropenes **6** into indolizines **17** and **18** (Scheme 7). For the rhodium-catalyzed method, upon ring opening of cyclopropene the most substituted rhodium carbene **19** forms.[17] A nucleophilic attack by the nitrogen lone pair would then lead to a zwitterionic intermediate **20**. A subsequent elimination of the rhodium would furnish the 1,3-regioisomeric product **18**. Alternatively, in the presence Cu(I), formation of the less substituted copper carbene **21**, followed by its cyclization to zwitterionic intermediate **22** occurs,[17d, 18] eventually leading to the 1,2-regioisomeric product **17**. The authors confirmed that isomeric carbenes **19** and **21** are not interconverted through the cycloaddition/cycloreversion equilibrium,[17a, 17d] since no crossover product was observed upon addition of 5 equiv. of the alkyne. Alternatively, regioisomers **17** and **18** could arise from the reductive elimination of aza-metalacyclic carbene intermediates **23** and **24**.

Scheme 7. Proposed Mechanisms for the Regiodivergent Cu(I)- and Rh(I)-Catalyzed Synthesis of Substituted Indolizines



Later, Lee group expanded the transannulation chemistry to synthesis of 3-alkenyl indolizines by employing 1,3-dienes (Scheme 8).[19] In this one-pot three-step protocol, pyridotriazoles **3** reacted with 1,3-dienes **25** in the presence of rhodium catalyst via [2+1][16] cycloaddition reaction to produce cyclopropane **27**. The latter, upon Pd-catalyzed cycloisomerization produced dihydroindolizine **28** (Scheme 8a). A subsequent oxidation with MnO_2 lead to 3-alkenyl indolizines **26**. Under these conditions, pyridotriazoles **3** reacted very well with electronically different 1,3-dienes (*E*)-**25** to produce 3-alkenyl indolizines **26** in moderate to good yields (Scheme 8b).

Scheme 8. Rh- and Pd-Catalyzed Synthesis of 3-Alkenyl Indolizines

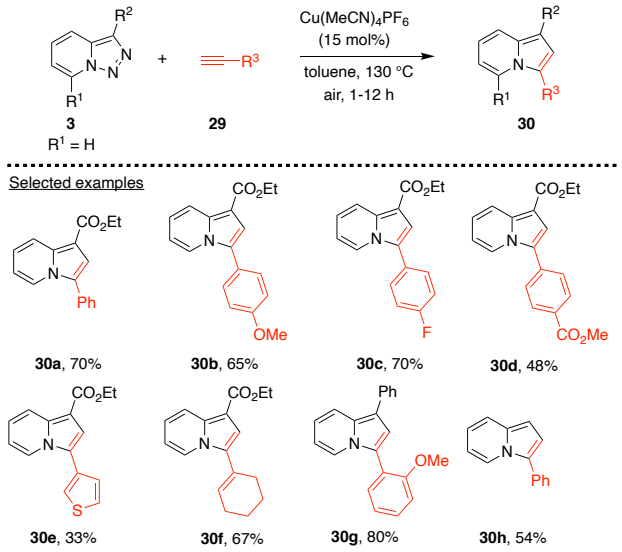


2.2 Copper-Catalyzed Transannulation

Previously developed transannulation methods relied on rhodium catalysis, which required C7-substituted pyridotriazoles as precursors for the α-imino diazo compounds.[11,16] Gevorgyan group reported a copper-catalyzed expansion of this reaction under aerobic conditions (Scheme 9).[20] This methodology does not require substitution at the C7 position, employment of electron-deficient pyridotriazoles, and use of expensive rhodium(II) catalysts. Employment of this method allowed to efficiently produce indolizines **30** with electronically diverse aryl acetylenes **29**. Aliphatic and heteroaromatic alkynes also reacted well, which was not possible under the

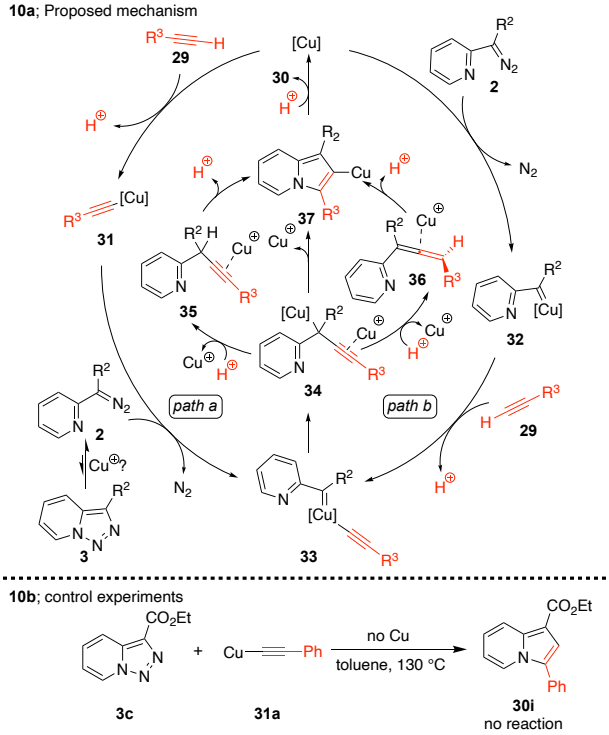
previously reported rhodium-catalyzed conditions.[11] Most notably, unsubstituted pyridotriazoles (R^1, R^2 = H) turned out to be the competent substrates for this reaction as well.

Scheme 9. Cu-Catalyzed Transannulation



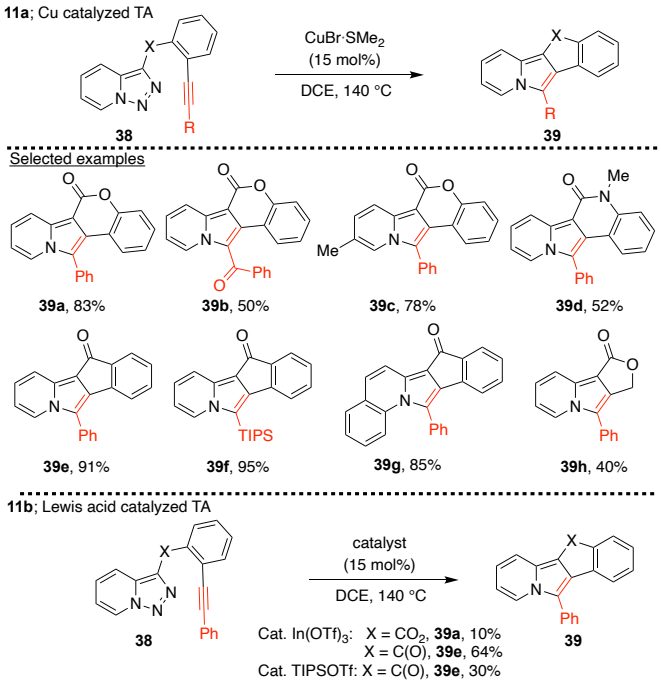
The following mechanism was proposed for the copper-catalyzed transannulation of pyridotriazoles into indolizines (Scheme 10a). First, terminal acetylene **29** reacts with the copper catalyst to generate copper acetylide **31**, which upon reaction with diazo compound **2** generates the copper-carbene complex **33** (path a). The latter could also be generated by the reaction of copper carbene **32** and alkyne **29** (path b). Next, a migratory insertion of the alkynyl group into the carbene **33** would produce intermediate **34**.[21] Generation of intermediate **37** from **34** could occur via a nucleophilic attack of the pyridine nitrogen at the triple bond, likely activated by the electrophilic copper complex.[22] On the other hand, the in-situ generated propargylic intermediate **35** or allenic intermediates **36** could also lead to the formation of **37**, protodecupration of which would deliver indolizine product **30**. Importantly, no reaction was observed when copper acetylide **31a** and pyridotriazole **3c** were subjected to the reaction conditions without copper catalyst (Scheme 10b). This suggests that electrophilic copper[22] ($Cu(MeCN)_4PF_6$) is indeed required for activation of the triple bond during the cyclization step (**34**→**37**).

Scheme 10. Proposed Mechanism for Cu-Catalyzed Transannulation of Pyridotriazoles with Alkynes



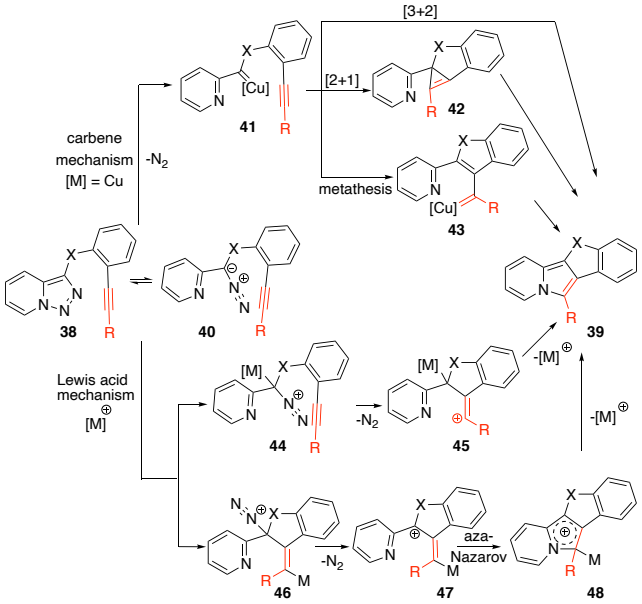
In continuation of their work on the synthesis of *N*-heterocyclic structures via transannulation chemistry, the Gevorgyan group reported assembly of diverse polycyclic frameworks via the copper-catalyzed intramolecular transannulation reaction (Scheme 11).[23] Pyridotriazoles **38** tethered with internal alkynes participate well in this intramolecular transannulation reaction to produce in a single step the corresponding tri-, tetra-, and pentacyclic fused indolizines **39** in moderate to good yields, (Scheme 11a). Interestingly, it was uncovered that this reaction can also be catalyzed by Lewis acids, such as $In(OTf)_3$ and TIPSOTf (Scheme 11b).

Scheme 11. Cu-Catalyzed Intramolecular Transannulation



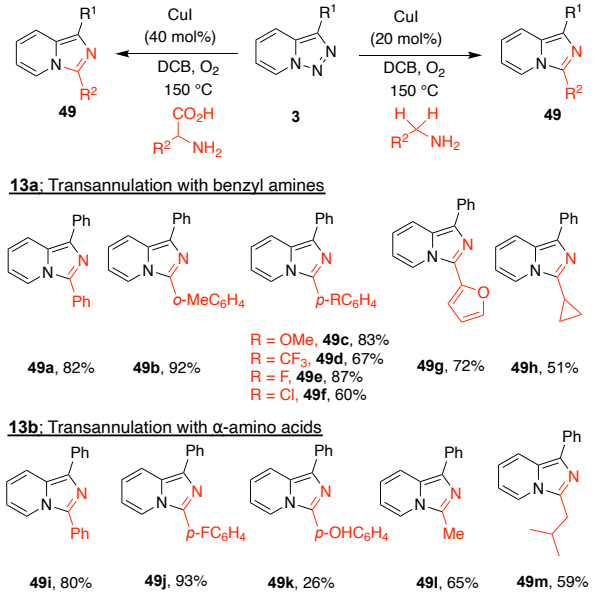
Copper-catalyzed intramolecular transannulation was proposed to proceed through the in-situ generated copper carbene intermediate **41** (Scheme 12), which upon a [3+2] cycloaddition reaction would produce indolizine **39**.[11] The latter could also be formed via a direct [2+1] cycloaddition to produce the cyclopropene intermediate **42**, followed by cycloisomerization.[16] Another pathway could involve carbene alkyne metathesis[24] of the copper carbene intermediate **43**. The Lewis acid-catalyzed version was envisioned to operate via the cationic intermediate **45**, which could be formed through the denitrogenative cyclization of a Lewis acid adduct **44**. A subsequent cyclization with the loss of the metal would produce indolizine **39**. Alternatively, a nucleophilic attack of the α-imino carbon at the Lewis acid-activated triple bond could form intermediate **46**. Extrusion of dinitrogen, followed by the aza-Nazarov-type cyclization produces **48**,[25] which upon metal loss would deliver the indolizine product **39**.

Scheme 12. Mechanism of Cu- and Lewis Acid-Catalyzed Intramolecular Transannulation



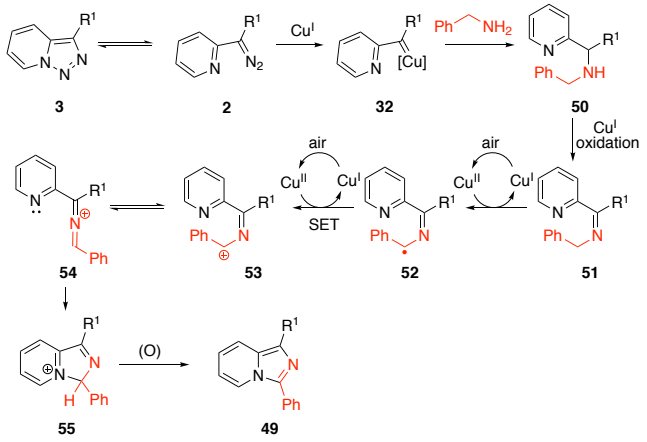
In 2016, Adimurthy and co-workers reported aerobic copper-catalyzed transannulation of pyridotriazoles with benzylamines into aza-heterocyclic compounds.[26] Pyridotriazoles **3** reacted efficiently with different substituted benzyl amines to produce the imidazopyridines **49a-h** in high yields (Scheme 13a). Heteroaromatic and cyclic amines reacted well, however no reaction was observed with aza-heterocyclic or aliphatic amines. α-Amino acids reacted smoothly with pyridotriazoles **3** in a decarboxylative manner to produce the corresponding products **49i-m** in high yields (Scheme 13b).

Scheme 13. Cu(I)-Catalyzed Transannulation with Benzylamines and α-Amino acids



It was proposed that in the presence of copper catalyst, the carbene intermediate **32** forms (Scheme 14).[20, 23] A migratory insertion of the latter with the N–H bond of benzylamine generates pyridine **50**. The following consecutive single electron transfer events would produce benzylic cation **53**,[27] which exists in equilibrium with azaallene **54**. A subsequent cyclization-oxidation would furnish imidazopyridine **49**.

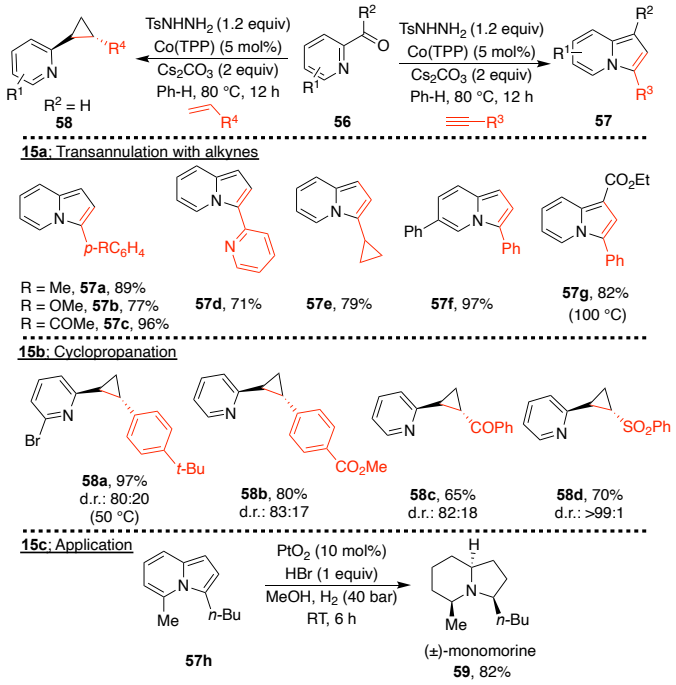
Scheme 14. Proposed Mechanism of Cu(I)-Catalyzed Transannulation with Benzylamines and α-Amino acids



2.3 Cobalt-Catalyzed Transannulation

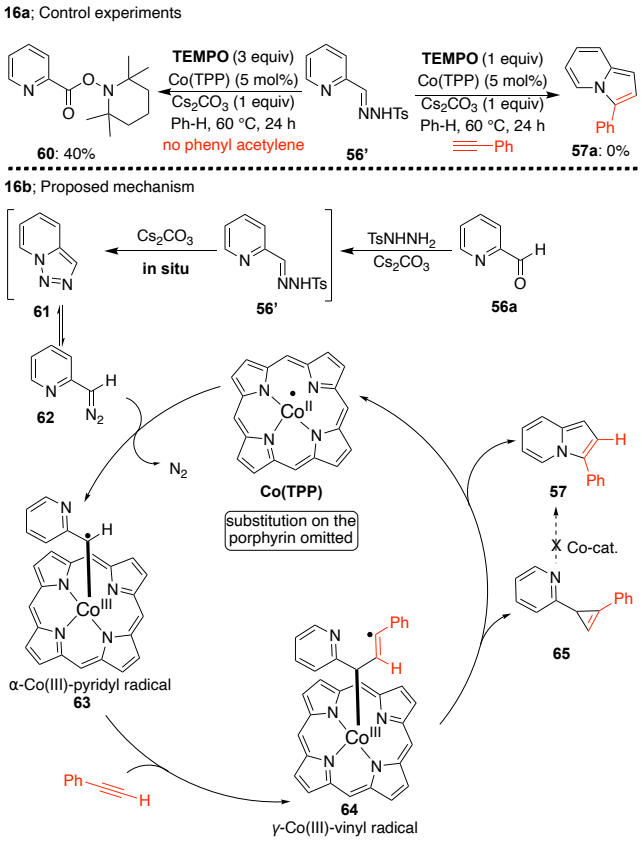
Recently, Chattopadhyay group reported a cobalt(II)-catalyzed radical transannulation and cyclopropanation reactions.[28] Employment of pyridotriazoles or 2-(diazomethyl)pyridines in the presence of Co(TPP) catalyst and alkyne partners resulted in the synthesis of *N*-containing heterocycles (Scheme 15). The in-situ generated *N*-tosylhydrazones underwent transannulation with various substituted aryl, heteroaryl, and alkyl alkynes in the presence of Co(TPP) to produce the indolizines **57** in good to excellent yields (Scheme 15a). In a similar fashion, the use of alkenes in place of alkynes provided substituted cyclopropanes **58** in high yields and good diastereoselectivity (Scheme 15b). The potential application of this radical transannulation was demonstrated in two-step synthesis of (±)-monomorine **59** (Scheme 15c).

Scheme 15. Co(II)-Catalyzed Transannulation and Cyclopropanation



Control experiments showed TEMPO-trapping products **60** in the absence of alkyne, and a complete shut down if the reaction in the presence of phenylacetylene (Scheme 16a). Based on these data, the following radical mechanism was proposed (Scheme 16b). The produced in-situ *N*-tosylhydrazone **56'** upon exposure to the base produces pyridotriazole **61**, which exist in equilibrium with α-imino diazo compounds **62**. The latter would be converted into the α-Co^{III}-pyridyl radical intermediate **63** in the presence of Co^{II}(TPP) catalyst.[29] A radical addition to phenylacetylene would produce γ-Co^{III}-vinyl radical intermediate **64**. A subsequent cyclization would produce indolizine **57**. Alternatively, formation of indolizine could result from the ring expansion of cyclopropene intermediate **65**, obtained via radical recombination process. However, based on the fact that this intermediate was never observed in the reaction mixtures, the authors ruled out this pathway.

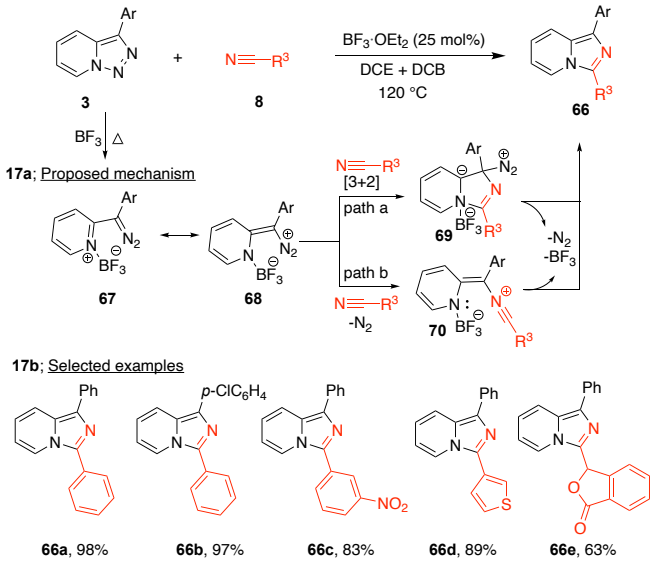
Scheme 16. Proposed Mechanism of Co(II)-Catalyzed Radical Transannulation



2.4 Lewis Acid-Catalyzed Transannulation

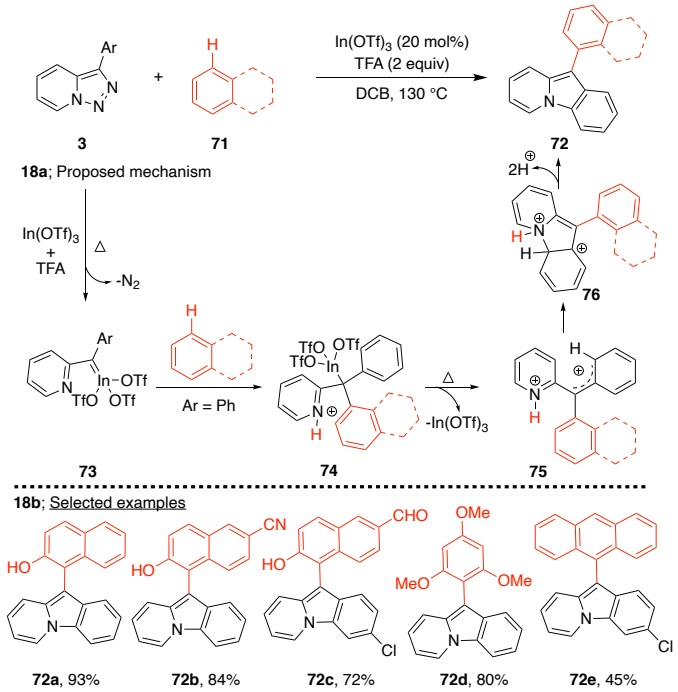
The Adimurthy group reported a general metal-free transannulation reaction of pyridotriazoles for synthesis of imidazopyridines.[30] The authors utilized $BF_3{\cdot}OEt_2$ as a Lewis acid catalyst, and pyridotriazoles **3** as precursors for α-imino diazo compounds **4** (Scheme 17). It is believed that coordination of $BF_3{\cdot}OEt_2$ to pyridine nitrogen atom stabilizes the open forms of pyridotriazole **67** and its vinyl diazonium form **68**. In one scenario, a direct [3+2] cycloaddition (path a) of benzonitrile generates intermediate **69**, which upon elimination of dinitrogen and BF_3 produces imidazopyridine **66** (Scheme 17a). Alternatively, an intramolecular nucleophilic addition of intermediate **70** and a subsequent elimination of BF_3 delivers the product (path b). Pyridotriazoles reacted well with electron-donating, withdrawing, and neutral aromatic and heteroaromatic nitriles. Notably, aliphatic nitriles are also competent substrates for this transformation (Scheme 17b).

Scheme 17. BF_3·OEt_2-Catalyzed Transannulation



Later, the same group extended this protocol for reactions of electron-rich arenes. Thus, transannulation of pyridotriazoles was successful in the presence of catalytic amounts of $In(OTf)_3$ and trifluoroacetic acid as an additive.[31] A somewhat unusual mechanism was proposed by the authors, that involved indium-carbene intermediate **73**, which was generated from $In(OTf)_3$ and pyridotriazoles **3** (Scheme 18a). Next, insertion of electron-rich arenes onto the indium-carbene[32] leads to the metallated aza-Nazarov type intermediate **74**.[25a, 33] Upon elimination of $In(OTf)_3$ under acidic conditions, the biscationic intermediate **75** is produced.[33-34] It was reasoned that at high temperature, the phenyl ring in this sterically congested intermediate would come close to the pyridine ring to generate intermediate **76** via C–H amination. The pyridoindole **72** is produced upon a subsequent proton loss. DFT calculations supported the proposed mechanism.

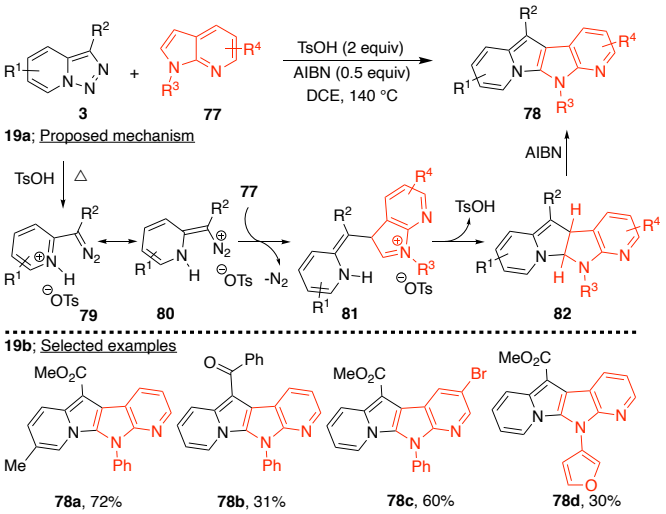
Scheme 18. $In(OTf)_3$-Catalyzed Transannulation



2.4 Brønsted Acid-Mediated Transannulation

Xu and Dong proposed an unusual synthesis of pyridoindoloindolizines through a Brønsted acid-mediated transannulation.[35] It is likely that TsOH stabilizes diazo-diazonium intermediates **79**↔**80**, which upon nucleophilic attack of 7-azaindole (**77**) produce intermediate **81** (Scheme 19a). A subsequent cyclization with the loss of TsOH generates **82**. An oxidation with AIBN completes synthesis of pyridoindoloindolizine **78**. As exemplified in the Scheme 19b, this Brønsted Acid-mediated transannulation is quite general with respect to pyridotriazole and pyridoindole components used.

Scheme 19. PTSA-mediated Transannulation

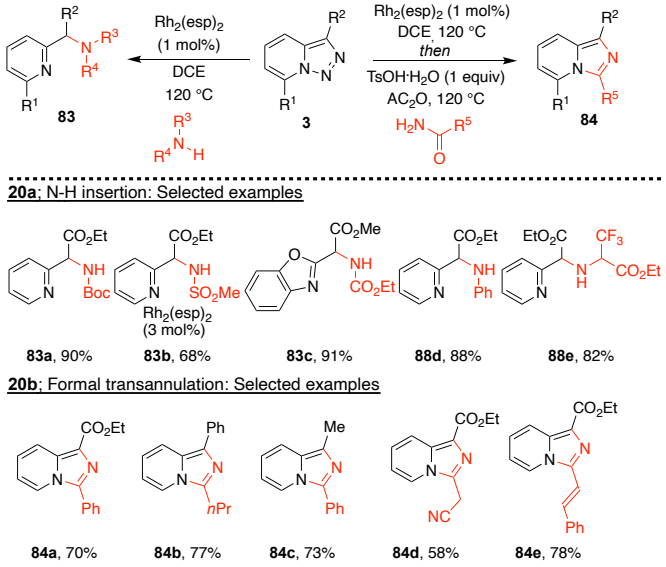


3. Pyridotriazole Insertion

3.1 Rhodium-Catalyzed N–H Insertion

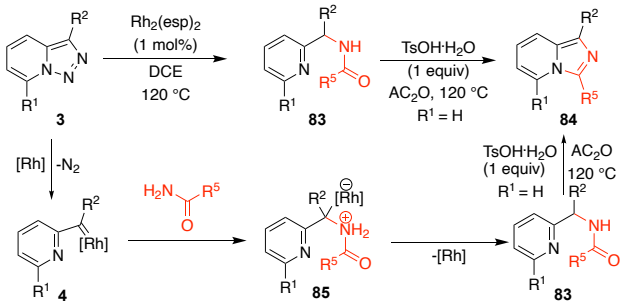
In 2014, Gevorgyan group reported the rhodium-catalyzed *N*–H insertion reactions of pyridotriazoles.[36] Various 2-picolylamine derivatives **83** were obtained from the corresponding pyridotriazoles and NH-containing amides, anilines, amines and enamines in the presence of $Rh_2(esp)_2$ catalyst (Scheme 20a). After developing the *N*–H insertion reaction with various amides, a formal transannulation using a combination of Brønsted acid with rhodium-catalyst was accomplished. This one-pot protocol allows for efficient synthesis of a wide variety of imidazopyridines possessing alkyl-, aryl-, benzyl, and alkenyl substituents at the C3 position of heterocycle (Scheme 20b).

Scheme 20. Rhodium-Catalyzed N–H Insertion



The authors proposed that rhodium carbenes **4** formed from the in-situ generated α-imino diazo compounds, react with amides to form an ylide intermediate **85** (Scheme 21). Regeneration of the rhodium catalyst produces 2-picolylamines **83.** An acid-assisted intramolecular dehydrative condensation furnishes imidazopyridine product **84**.

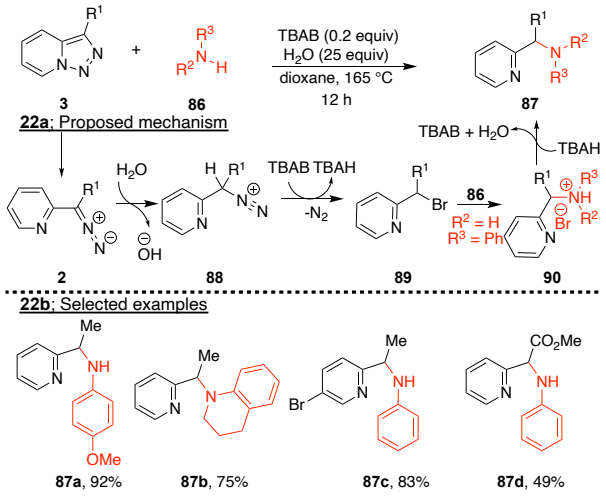
Scheme 21. Rhodium-Catalyzed N–H Insertion Mechanism



3.2 Metal-Free C(sp³)–N Bond Formation

Recently, Alami and Hamze reported interesting metal-free C(sp³)–N bond formation of pyridotriazoles with weakly nucleophilic aniline derivatives (Scheme 22a).[37] Based on control experiments, it was proposed that first water reacts with α-imino diazo compounds **2** to produce diazonium intermediate **88**. Next, the nucleophilic substitution by bromine from TBAB (tetrabutylammonium bromide) produces benzyl bromide **89**, which upon alkylation of amine and a subsequent dehydrobromination delivers the reaction product **87**. Different pyridotriazoles reacted well under these conditions with diversely substituted anilines to produce the pyridyl alkyl amines **87** in good to excellent yields (Scheme 22b).

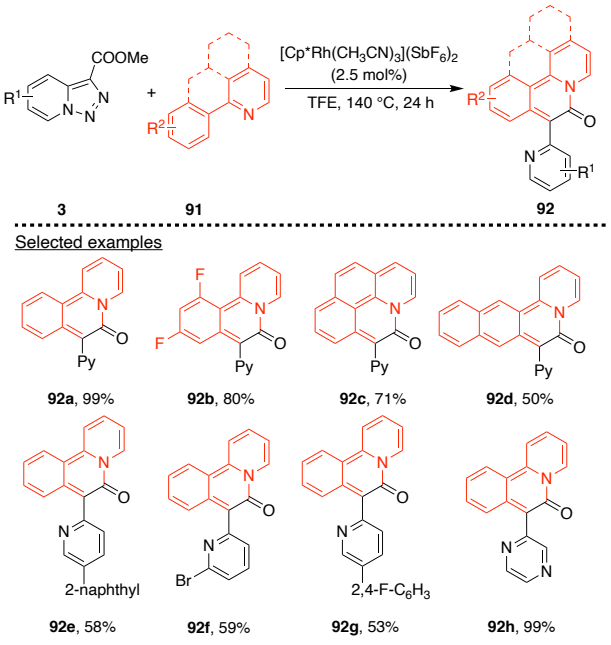
Scheme 22. Metal-Free C(sp³)–N Bond Formation



3.3 Rhodium(III)-Catalyzed C–H Insertion

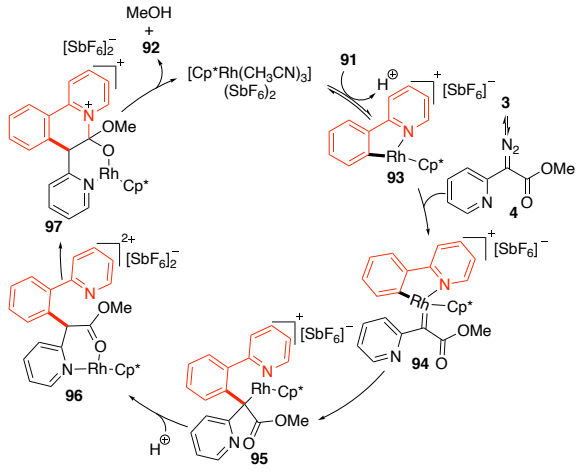
In 2015, Strassert and Glorius reported rhodium(III)-catalyzed directing group-assisted C–H activation of pyridine derivatives **91** followed by reaction with pyridotriazoles **3** toward synthesis of fused fluorescent scaffolds **92**(Scheme 23).[38] In this protocol, the pyridine moiety plays a dual role, by acting as a directing group in the C–H activation step, as well as a nucleophile at the cyclization step. The fluorescent properties of the obtained molecules and their complexes with metal salts were studied.

Scheme 23. Rhodium (III)-Catalyzed C–H Insertion



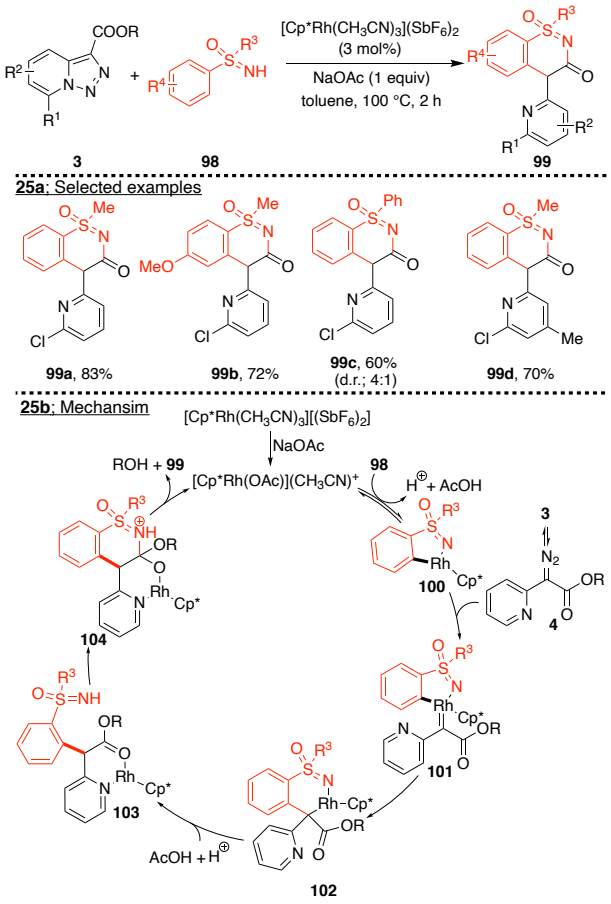
The proposed mechanism starts with the reversible coordination of cationic rhodium with 2-phenyl pyridine **91** to produce via C–H activation a cationic rhodacycle **93** (Scheme 24). Next, it reacts with the diazo compound **4**, which upon release of dinitrogen produces carbene intermediate **94.** A migratory insertion of pyridyl carbene leads to **95**, which undergoes protoderhodation to afford **96**. A nucleophilic addition of pyridine at the activated carbonyl group of the ester produces **97**. A subsequent elimination of alcohol and the catalyst yields the reaction product **92**.

Scheme 24. Proposed Mechanism of Rhodium(III)-Catalyzed C–H Insertion



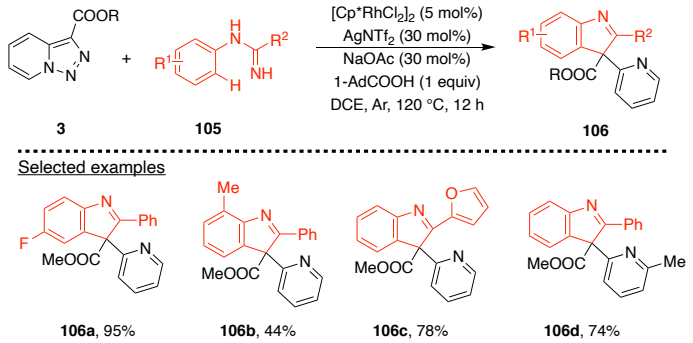
Later, the Lee group reported related sulfoximine-directed C–H functionalization method,[39] which provides expeditious access to 1,2-benzothiazines from the corresponding sulfoximines and pyridotriazoles in the presence of Rh(III) catalyst and sodium acetate (Scheme 25a). Mechanistically, this reaction (Scheme 25b) follows similar path with that of the above mentioned method (Scheme 24). A variety of 1,2-benzothiazines were efficiently synthesized via this domino C–H activation/cyclization/elimination protocol from readily available sulfoximines and pyridotriazoles.

Scheme 25. Rhodium (III)-Catalyzed C–H Insertion with Sulfoximines

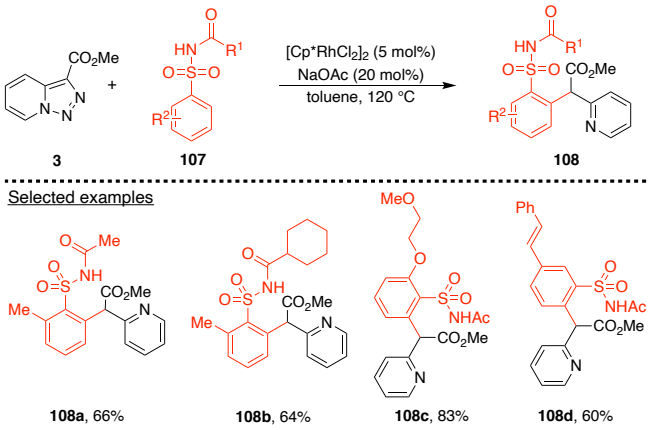


The Dong group expanded this chemistry to the Rh(III)-catalyzed C–H activation of *N*-phenylbenzimidamides, followed by a subsequent coupling with pyridotriazoles/cyclization to access the corresponding 3H-indoles **106** (Scheme 26).[41] Recently, Xu group reported that *N*-acetyl substituted sulfonamide **107** derivatives under similar conditions produce the C–H insertion product **108** exclusively (Scheme 27).[42]

Scheme 26. Rhodium (III)-Catalyzed C–H Insertion with *N*-Phenylbenzimidamides



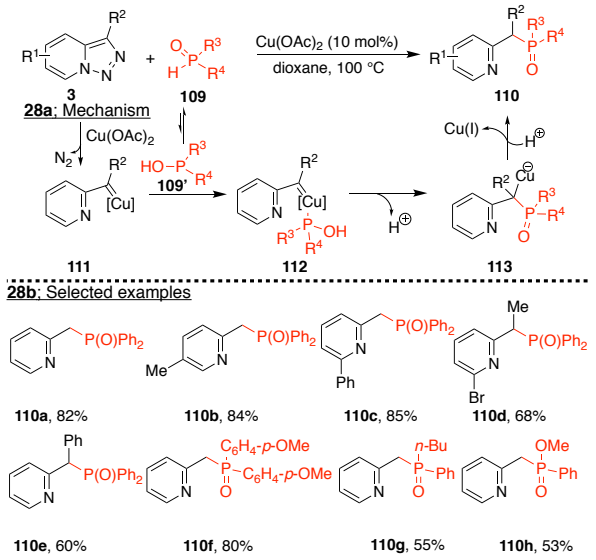
Scheme 27. Rhodium (III)-Catalyzed C–H Insertion with *N*-Acetyl Substituted Sulfonamides



3.4 Copper-Catalyzed P(O)–H Insertion

In 2018, Shen group reported denitrogenative synthesis of phosphorylated picolyl derivatives via the C–P bond formation.[43] As proposed in Scheme 28a, the formed copper carbene **111** reacts with **109'**, the P–OH tautomer of **109** (P(O)–H) to produce **112**, which after 1,2-phosphorous migration (**113**) and protodecupration delivers the reaction products **110**. Under these conditions, various H-phosphonates, H-phosphinates, and H-phosphine oxides reacted well with pyridotriazoles to efficiently produce 2-picolylphosphoryl derivatives (Scheme 28b).

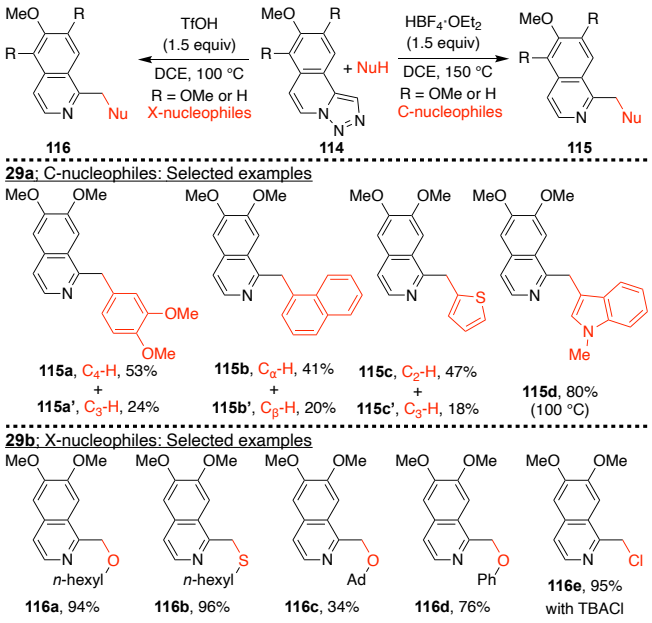
Scheme 28. Copper(II)-Catalyzed P(O)–H Insertion



3.4 Metal-Free Nucleophile Insertion Reactions

Very recently, Dehaen reported an acid-mediated metal-free insertion reaction of methoxylated triazoloisoquinolines into weakly nucleophilic Nu–H bonds.[44] This method operates via an acid-mediated denitrogenative ring-opening of triazoloisoquinoline **114**, followed by the trapping with weak nucleophiles (Scheme 29). C-nucleophiles, arenes and heteroarenes such as veratrole, naphthalene, and thiophene in the presence of $HBF_4{\cdot}OEt_2$ produced mixtures of regioisomers (**115a-c**). Conversely, reaction with *N*-methyl-indole produced a single regioisomer (**115d**) exclusively (Scheme 29a) in the presence of triflic acid TfOH. Unlike their nonpolar counterparts, polar nucleophiles, such as amines, alcohols, and thiols smoothly reacted in the presence of triflic acid TfOH under slightly modified conditions to give the corresponding products **116a-e** in good yields (Scheme 29b). The authors commented on importance of a methoxy substituent at the isoquinoline moiety, which is crucial for a facile ring opening step.

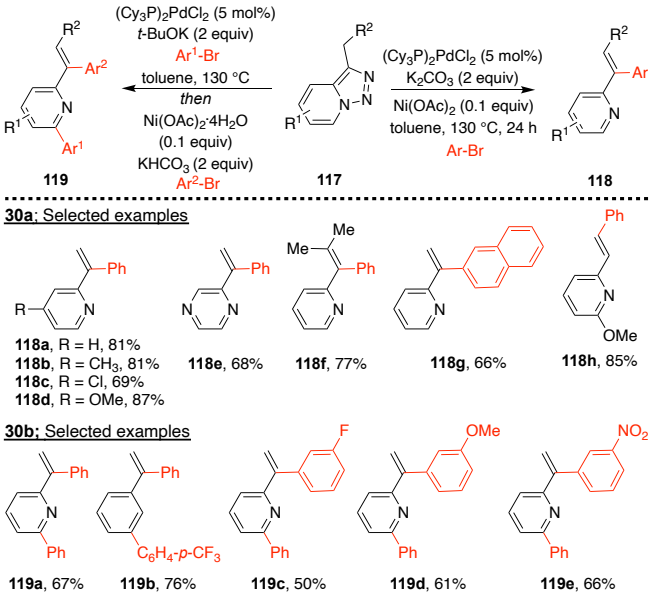
Scheme 29. Acid-Mediated Nucleophilic Insertions



4. Miscellaneous Reactions of Pyridotriazoles

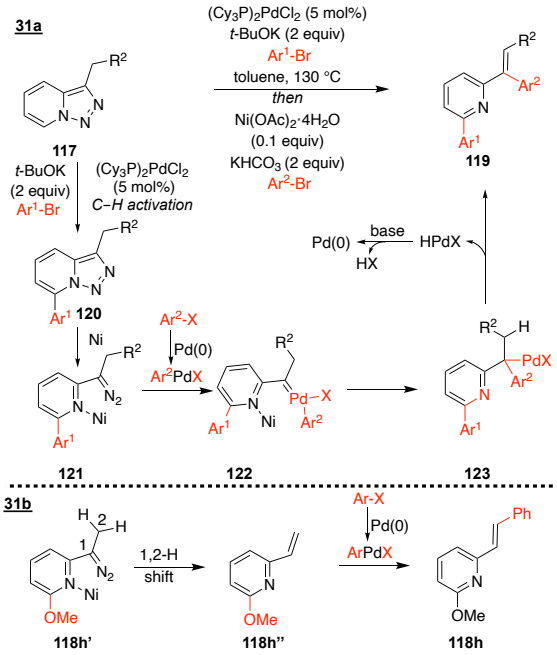
Hong reported the palladium-catalyzed arylation of alkyl-substituted pyridotriazoles with aryl bromides.[46] Interestingly, two different products were obtained from the same starting material, depending on the choice of the base used (Scheme 30). In the presence of potassium carbonate, the reaction leads to the C3-arylation products **118** mostly possessing an exo-methylene fragment. However, under modified semi-one pot conditions employing potassium *tert*-butoxide, C3 and C7-arylation products **119** were produced in high yields (Scheme 30b).

Scheme 30. Palladium-Catalyzed Arylation



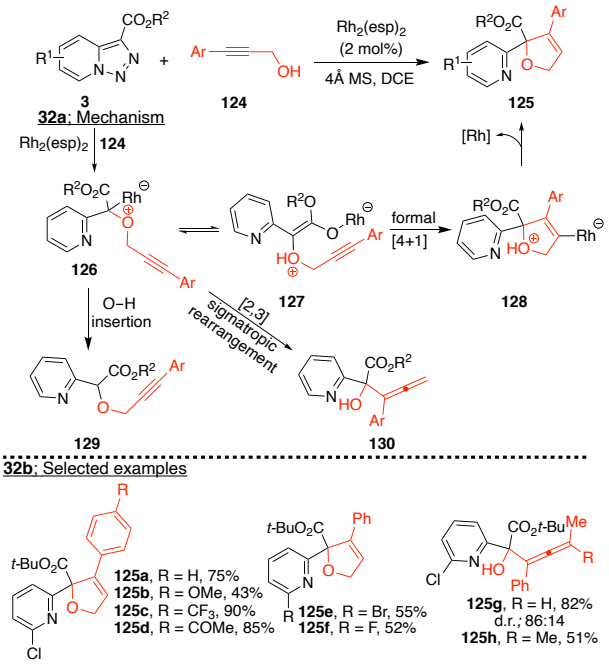
Based on the control experiments, the authors proposed the following mechanism (Scheme 31a). Initially, the ^{t}BuOK-promoted palladium-catalyzed C–H arylation of pyridotriazole occurs at the C7-position to produce **120**. Next, the nickel salt enables ring-opening of pyridotriazoles and stabilizes the diazo compounds through the coordination with the pyridine nitrogen atom (**121**). The palladium carbene complex **122** is subsequently formed from the reaction of intermediate **121** with Pd(II), which is generated via the oxidative addition with aryl halides. Then, **122** undergoes aryl migratory insertion, followed by the β-hydride elimination to give the exocyclic double bond containing compounds **119**. The endocyclic product **118h** originates from the 1,2-hydride shift of C7-methoxy diazo compound **118h'**, without the need for palladium catalysis, to afford the pyridyl styrene derivative (**118h''**). Finally, Heck reaction leads to the corresponding product **118h** (Scheme 31b).

Scheme 31. Proposed Mechanism for Palladium-Catalyzed Arylation



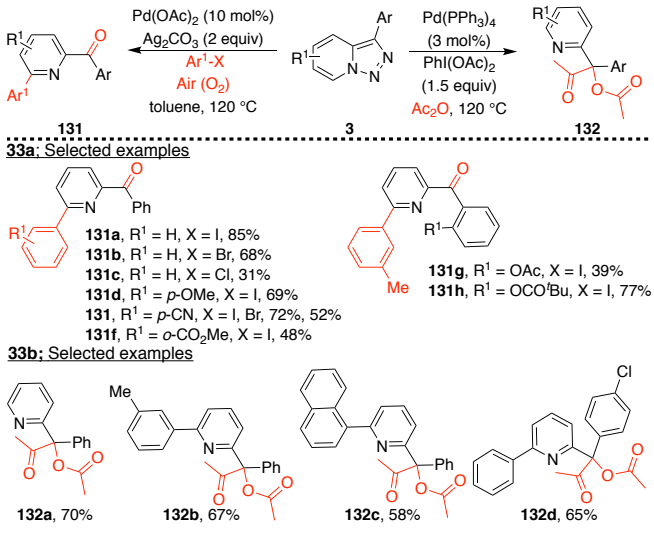
Xu and Hu reported a formal [4+1] cycloaddition of pyridotriazoles with propargyl alcohols for synthesis of pyridyl-substituted 2,5-dihydrofuran derivatives **125** (Scheme 32).[47] In this reaction, propargyl alcohol **124** reacts with rhodium carbene to form the oxonium ylide **126**, which is in equilibrium with rhodium enolate **127**. The following intramolecular nucleophilic addition of the C-enolate at the triple bond of alkyne in the 5-*endo-dig* fashion produces zwitterion **128**, which upon protoderhodation delivers the reaction product **125** (Scheme 32a). Moderate to high yields of pyridyl substituted 2,5-dihydrofurans were obtained using this method (Scheme 32b). In the case of secondary and tertiary alcohols, the reaction led to the formation of allene products **125g-h**, which was explained via [2,3]-sigmatropic rearrangement from the oxonium ylide **126**. Notably, $Rh_2(esp)_2$ was the only selective catalyst toward dihydrofurans **125**. Employment of other rhodium sources, such as $Rh_2(OAc)_4$, $Rh_2(oct)_4$, as well as copper and palladium catalysts, led to mixtures of O–H insertion (**129**), [2,3]-sigmatropic rearrangement (**130**), and formal [4+1] cycloaddition products (**125**).

Scheme 32. Rh-Catalyzed [4+1] Cycloadditions



Adimurthy reported oxidation of pyridotriazoles into arylated benzoyl pyridines **131**,[48] which was achieved through palladium-catalyzed C–H arylation, and silver-mediated aerobic oxidation of readily available pyridotriazoles and haloarenes (Scheme 33a). Iodoarenes produced higher yields compared to their bromo-and chloro- counterparts (**131a-c**). Later, the same group reported the acetoxylative version of this reaction using acetic anhydride as a solvent.[49] Interestingly, both the acetyl and acetoxy groups of acetic anhydride were incorporated in the molecule to form the 2-oxo-1-phenyl-1-(pyridin-2-yl)propyl acetate **132**. Aryl- and naphthyl-substituted pyridotriazoles smoothly underwent this reaction to produce **132** in good yields (Scheme 33b).

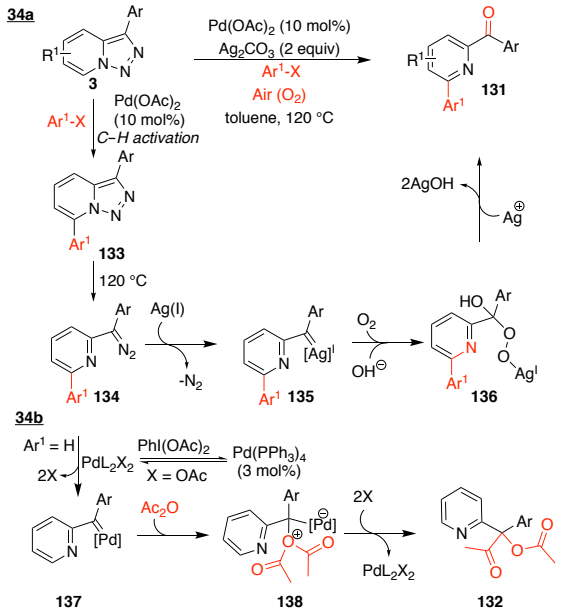
Scheme 33. Pd-Catalyzed Aerobic Oxidation



Product formation was proposed to occur via following sequence (Scheme 34a). Upon initial Pd-catalyzed directed C–H arylation, the diazo compound **134** is formed, which is converted to silver carbene **135**. The latter upon oxidation (**136**) produces 6-aryl 2-benzoyl pyridines **131**. The acetylacetoxylation reaction was proposed to occur via the formation of palladium carbene **137** (Scheme 34b).

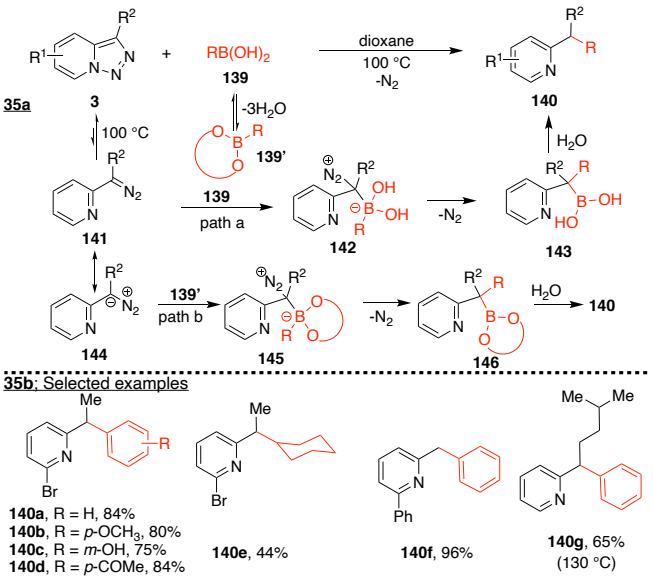
The following reaction with acetic anhydride would generate the ylide intermediate **138**, which presumably via acyl group migration and reductive elimination of palladium-catalyst produces **132**. Similarly to Hong's method described above,[46] the pyridotriazole moiety plays a dual role both as a directing group for the C–H functionalization and as a carbene precursor. The Driver group also reported conversion of pyridotriazoles into picolyl alcohol derivatives under heating with HCl or AcOH.[50]

Scheme 34. Pd-Catalyzed Oxidation Mechanism



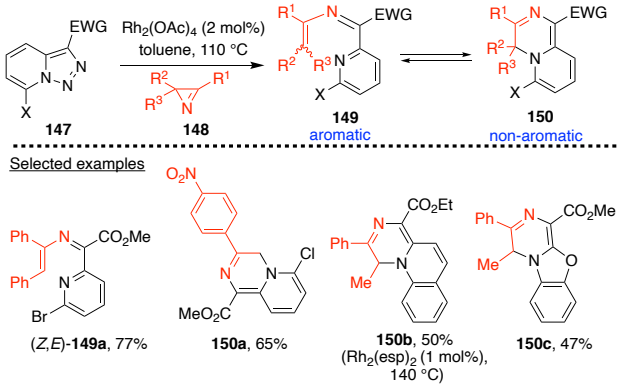
Shen reported the metal-free method for C–C bond formation of pyridotriazoles with boronic acids toward substituted picolines (Scheme 35a).[51] α-Diazopyridine **141**, generated from pyridotriazole upon heating reacts either with boronic acid **139** (path a), or in-situ generated boroxine **139'** (path b). Upon nucleophilic addition of **141** or **144** at the boron species, zwitterionic borates **142** or **145** are formed. A subsequent denitrogenative 1,2-R shift (**143**, **146**), followed by protodeboration deliver the reaction product **140**. Commercially available aryl and alkyl boronic acids reacted well with pyridotriazoles under these metal-free conditions to efficiently produce secondary and tertiary substituted picolines.

Scheme 35. Metal-Free C–C Bond Formation



Very recently, Rostovskii group disclosed an interesting rhodium-catalyzed reaction of pyridotriazoles **147** with azirines **148** to afford 1-(2-pyridyl)-2-azabuta-1,3-dienes **150** (Scheme 36).[52] First, the thermally generated rhodium carbene reacts with azirine **148** to form diazatriene **149**, which upon reversible 1,6-electrocyclization delivers non-aromatic pyridopyrazine **150**. This protocol was found to be efficient for synthesis of 1*H*-pyrazino[1,2-*a*]quinoline and 4*H*-benzo[4,5]oxazolo[3,2-*a*]pyrazine **150b-c**. The configuration of the C=C bond of the diazatriene **149** was found to be an important thermodynamic factor for the position of the equilibrium between **149** and **150**.

Scheme 36. Rh-Catalyzed Dearomative Cyclization



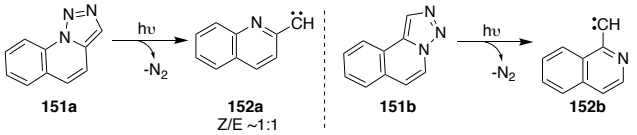
5. Photolysis of Pyridotriazoles

5.1 UV-Mediated Decomposition of Pyridotriazoles

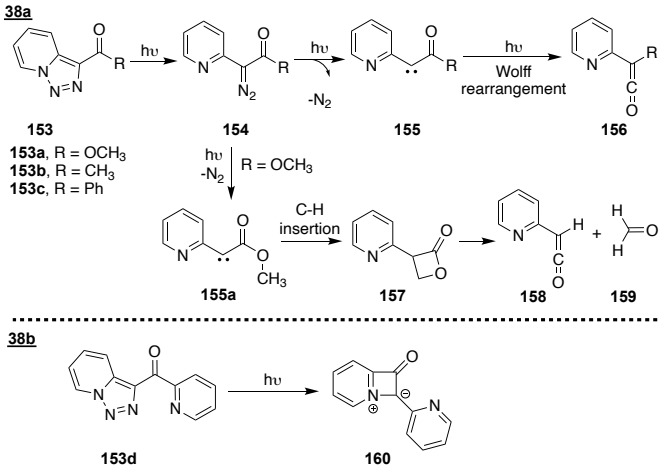
Formation of carbenes **152** under the UV photodecomposition of quinoline- and isoquinoline-based pyridotriazoles **151** was reported by Wentrup group in 1986 (Scheme 37).[53] Later, Tomioka applied UV-irradiation for the matrix photolysis of 3-methoxy carbonyl-1,2,3-pyridotriazoles into ketenes **156** (Scheme 38).[54] The formation of ketenes was explained by the ring opening of pyridotriazoles **153a** upon light irradiation (> 300 nm) to form the diazo compound **154**, and then carbene **155**, which underwent Wolff rearrangement[55] into ketene **156** (Scheme 37). Later, Wentrup group observed similar ketene and other side products from light irradiation of pyridotriazoles **153b, c** (Scheme 38a).[56] However, in the case

of ester derivative **153a**, ketene **158** was observed as the major product, likely through an intramolecular C–H insertion of OCH_3 via singlet carbene intermediate **155a** followed by fragmentation of the formed propiolactone **157** into ketene **158** and formaldehyde **159**. The latter observation was supported by DFT calculations.[57] Tidwell group reported formation of the ylide **160** upon photolysis of 3-pyridyl substituted pyridotriazoles[58] (Scheme 38b).

Scheme 37. Photolysis of Quinoline Triazoles

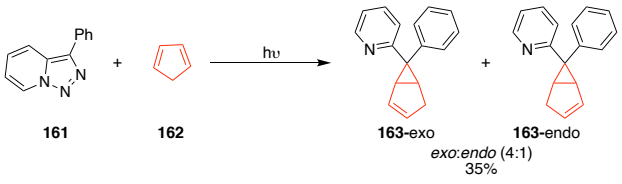


Scheme 38. Photolysis of 3-Substituted Pyridotriazoles



Zimmerman group utilized the UV-generated carbene intermediate from pyridotriazole **161** for cyclopropanation of cyclopentadiene **162**,[59] which was employed as solvent to give a mixture of *exo*- and *endo* products **163** in moderate yield (Scheme 39). All these photolysis reactions described above were carried out under UVC and UVB irradiations.

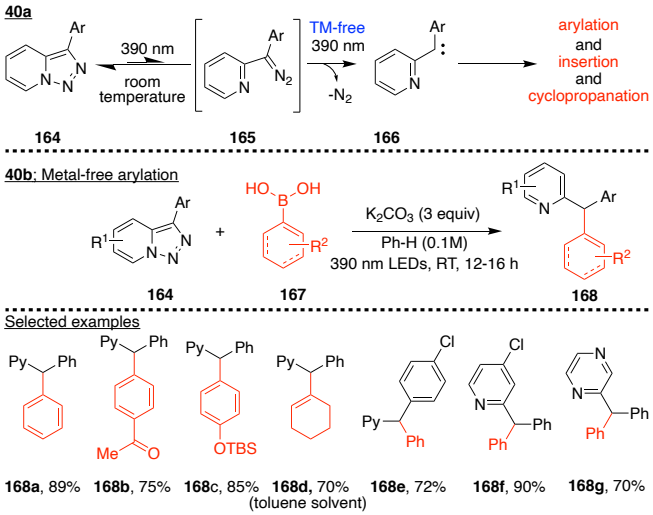
Scheme 39. Cyclopropanation of Pyridotriazoles



5.2 Visible Light-Induced Transformations of Unactivated Pyridotriazoles

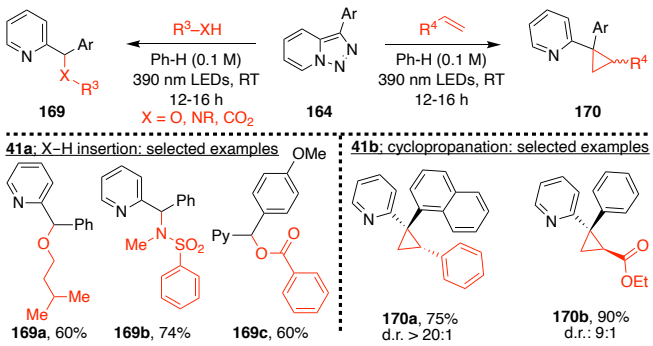
Recently, Gevorgyan group reported UVA light-induced denitrogenative transformations of unactivated pyridotriazoles at room temperature,[60] which were inspired by the observed sufficient absorption of pyridotriazoles at 390 nm (Scheme 40). Upon irradiation at 390 nm, 3-aryl pyridotriazoles **164** underwent ring-chain isomerization to produce α-diazoimines **165**, which upon loss of dinitrogen were converted into carbene species **166**.[61] The latter was efficiently utilized in several synthetic transformations. Thus, under these metal-free conditions, arylation of pyridotriazoles with boronic acids in the presence of K_2CO_3 was accomplished.[62] Different 3-aryl pyridotriazoles **164** reacted smoothly with a number of aryl and alkenyl boronic acids **167** to deliver triarylmethanes **168** in good to excellent yields at room temperature (Scheme 40b).

Scheme 40. Visible Light-Induced Transformations of Unactivated Pyridotriazoles



In addition to arylation reactions, 3-aryl pyridotriazoles underwent other visible light-induced transformations, such as X–H (O–H, N–H and CO_2–H) insertion reactions of alcohols, amines and carboxylic acids without any additives or catalysts, to produce heteroatom substituted benzylpyridine derivatives **169** (Scheme 41a). Furthermore, 3-aryl substituted pyridotriazoles also reacted with a variety of alkenes deliver the corresponding [2+1] cyclopropanation products **170** (Scheme 41b). Employment of this method for synthesis of biologically important molecules has been demonstrated. This method, however, is limited to C-3 aryl-substituted pyridotriazoles, which have adequate absorption at 390 nm. Other derivatives, such as 3-methyl pyridotriazoles, which are transparent in that area, did not react under these conditions at all. Overall, this method allows for efficiant formation of a broad spectrum of compounds from pyridotriazoles at room temperature in regular glassware without utilizing transition metals, Lewis acids, or harsh reaction conditions.

Scheme 41. Visible Light-Induced X–H Insertion and Cyclopropanation of Unactivated Pyridotriazoles

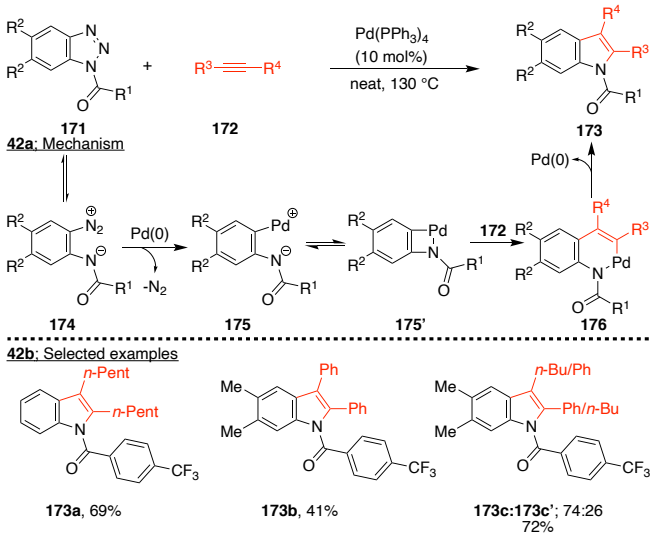


6. Synthesis of Indoles from Benzotriazoles

In 2009, Nakamura group reported the palladium-catalyzed denitrogenative synthesis of polysubstituted indoles from *N*-aroyl-1,2,3-

benzotriazoles and internal alkynes (Scheme 42).[63] 2-Iminobenzenediazonium species **174**, formed under thermal decomposition of benzotriazoles **171**,[64] experiences oxidative addition with palladium into intermediates **175**/**175'**(Scheme 42b). A subsequent migratory insertion of internal alkyne **172** leads to palladacycle **176**, and after reductive elimination delivers indole **173**. High reaction temperature (130° C) was mandatory to induce ring opening of the benzotriazoles. Both the electron-withdrawing group on the *N*1-atom and the slightly electron-donating group at R^2 helped stabilizing the in-situ generated 2-iminobenzenediazonium species **174**. A variety of benzotriazoles and internal alkynes smoothly reacted under these conditions to deliver the polysubstituted indoles **173** in moderate to good yields (Scheme 42b). Expectedly, in the case of unsymmetrical internal alkynes, a mixture of regioisomers **173c** was observed. Terminal alkynes such as phenyl acetylene yielded only traces amount of product, and *N*-acetyl substituted benzotriazole did not react at all. Very recently, Tang published a review on this topic.[65]

Scheme 42. Pd-Catalyzed Synthesis of Polysubstituted Indoles



Conclusions

In this perspective, we have described the recent developments on denitrogenative transformations of pyridotriazoles. Suitably substituted pyridotriazoles undergo ring-chain isomerization to generate the α-diazoimines. The latter can then be trapped or stabilized by transition metal catalysts, or Lewis and Brønsted Acids, to generate the more reactive carbene species, which display diverse reactivity. Pyridotriazoles are surrogates of 1C and (aza)-3C synthons for transannulation, cyclopropanation, insertion followed by rearrangement, and other miscellaneous reactions with suitable nucleophiles, for synthesis of variety of *N*-containing heterocyclic compounds and beyond. Pyridine-containing biologically important heterocyclic cores can now easily be accessed from the corresponding pyridotriazoles in a one-pot fashion without loss of efficiency, which is a considerable improvement over existing methods. Pyridotriazoles are readily available from pyridyl ketones or aldehydes and hydrazines, as well as from other precursors.

Regardless of a substantial progress made, this chemistry still has room for further development. Some drawbacks include the requirement to utilize activated pyridotriazoles or harsh reaction conditions to induce the ring-opening and generate the reactive α-diazoimines. Recently, these limitations have been partially overcome by using visible light irradiation conditions at room temperature without any additives. In addition, stereoselective denitrogenative transformations of pyridotriazoles and related compounds are hugely underdeveloped. We are hopeful that this methodology once fully developed, will find its broad applications in synthetic and medicinal chemistry.

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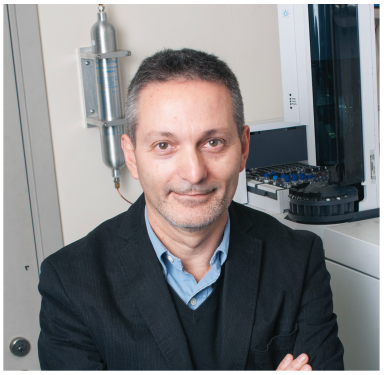
Biography

Dongari Yadagiri was born in Telangana, India. He received his Ph.D in 2016 from Indian Institute of Technology (IIT) Madras, India with Dr. P. Anbarasan. In 2017, he joined the Gevorgyan group at the University of Illinois at Chicago as a post-doctoral fellow. Later, he moved to the University of Texas at Dallas along with his advisor. Here, his work is focused on the development of selective methods for C(sp^3)–H functionalizations via photoexcited Pd catalysis, radical chemistry, and light-induced transformation of pyridyl carbenes.

Mónica Rivas was born and raised in Bogotá, Colombia. She received her B.S. from the University of Central Florida. In 2017, she joined the Gevorgyan group at the University of Illinois at Chicago as a PhD student, and later at the University of Texas at Dallas. Her work has focused on the development of mild and selective C(sp^3)–H functionalization methods.



Vladimir Gevorgyan received his PhD from the Latvian Institute of Organic Synthesis. After two years of postdoctoral research (1992–1994, JSPS- and Ciba-Geigy International Postdoctoral Fellowships) at Tohoku University, Japan, and a visiting professorship (1995) at CNR, Bologna, Italy, he joined the faculty at Tohoku University (Assistant Professor, 1996; Associate Professor, 1997–1999). In 1999, Vladimir Gevorgyan moved to USA to join UIC (Associate Professor, 1999; Professor, 2003; LAS Distinguished Professor, 2012). In 2019, he joined the University of Texas at Dallas to become a Robert. A. Welch Distinguished Chair in Chemistry. Vladimir also holds a Professor position at the University of Texas Southwestern Medical Center. His group is interested in the development of novel synthetic methodology, particularly toward biologically relevant molecules.

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REFERENCES

(1) (a) Kalaria, P. N.; Karad, S. C.; Raval, D. K. A Review on Diverse Heterocyclic Compounds as the Privileged Scaffolds in Antimalarial Drug Discovery. *Eur. J. Med. Chem.* **2018**, *158*, 917-936; (b) Katritzky, A. R.; Rees, C. W., *Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds*. 1st ed.; Pergamon: Oxford; New York, 1984; (c) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., *Comprehensive Heterocyclic Chemistry II: A Review of the Literature 1982-1995: The Structure, Reactions, Synthesis, and Uses of Heterocyclic Compounds*. 1st ed.; Pergamon: Oxford ; New York, 1996; (d) Ataf, A. A.; Shahzad, A.; Gul, Z.; Rasool, N.; Badshah, A.; Lal, B.; Khan, E. A Review on the Medicinal Importance of Pyridine Derivatives. *J. Drug Des. Med. Chem.* **2015**, *1*, 1-11.

(2) (a) Nikonov, I. L.; Kopchuk, D. S.; Kovalev, I. S.; Zyryanov, G. V.; Khasanov, A. F.; Slepukhin, P. A.; Rusinov, V. L.; Chupakhin, O. N. Benzyne-Mediated Rearrangement of 3-(2-Pyridyl)-1,2,4-triazines into 10-(1H-1,2,3-Triazol-1-yl)pyrido[1,2-a]indoles. *Tetrahedron Lett.* **2013**, *54*, 6427-6429; (b) Rogness, D. C.; Markina, N. A.; Waldo, J. P.; Larock, R. C. Synthesis of Pyrido[1,2-a]indole Malonates and Amines Through Aryne Annulation. *J. Org. Chem.* **2012**, *77*, 2743-55; (c) Michael, J. P., Simple Indolizidine and Quinolizidine Alkaloids. In *The Alkaloids: Chemistry and Biology*, Academic Press: 2001; Vol. 55, pp 91-258; (d) Sharma, V.; Kumar, V. Indolizine: a Biologically Active Moiety. *Med. Chem. Res.* **2014**, *23*, 3593-3606; (e) V. R. Vemula, S. V., C. K. Bairi Indolizine Derivatives: Recent Advances and Potential Pharmacological Activities. *Int. J. Pharm. Sci. Rev. Res.* **2011**, *11*, 159-163; (f) Michael, J. P. Indolizidine and Quinolizidine Alkaloids. *Nat. Prod. Rep.* **2008**, *25*, 139-165; (g) Michael, J. P. Indolizidine and Quinolizidine Alkaloids. *Nat. Prod. Rep.* **2007**, *24*, 191-222; (h) Michael, J. P. Quinoline, Quinazoline and Acridone Alkaloids. *Nat. Prod. Rep.* **2002**, *19*, 742-760; (i) Sadowski, B.; Klajn, J.; Gryko, D. T. Recent Advances in the Synthesis of Indolizines and Their π-Expanded Analogues. *Org. Biomol. Chem.* **2016**, *14*, 7804-7828; (j) Kim, B. Y.; Ahn, J. B.; Lee, H. W.; Kang, S. K.; Lee, J. H.; Shin, J. S.; Ahn, S. K.; Hong, C. I.; Yoon, S. S. Synthesis and Biological Activity of Novel Substituted Pyridines and Purines Containing 2,4-Thiazolidinedione. *Eur. J. Med. Chem.* **2004**, *39*, 433-447; (k) Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., *Comprehensive Heterocyclic Chemistry III*. 1st ed.; Elsevier: Amsterdam; New York, 2008.

(3) (a) Li, C.-G.; Xu, G.-Q.; Xu, P.-F. Synthesis of Quinazolinone Derivatives Via a Visible-Light Photocatalyzed Denitrogenation Rearrangement Process. *J. Photochem. Photobiol. A* **2018**, *355*, 25-31; (b) Jones, G. The Chemistry of the Triazolopyridines: An Update. *Adv. Heterocycl. Chem* **2002**, *83*, 1-70.

(4) (a) Chattopadhyay, B.; Gevorgyan, V. Transition-Metal-Catalyzed Denitrogenative Transannulation: Converting Triazoles into Other Heterocyclic Systems. *Angew. Chem., Int. Ed.* **2012**, *51*, 862-872; (b) Gulevich, A. V.; Gevorgyan, V. Versatile Reactivity of Rhodium-Iminocarbenes Derived from *N*-Sulfonyl Triazoles. *Angew. Chem., Int. Ed.* **2013**, *52*, 1371-1373; (c) Davies, H. M.; Alford, J. S. Reactions of Metallocarbenes Derived from *N*-Sulfonyl-1,2,3-triazoles. *Chem. Soc. Rev.* **2014**, *43*, 5151-62; (d) Anbarasan, P.; Yadagiri, D.; Rajasekar, S. Recent Advances in Transition-Metal-Catalyzed Denitrogenative Transformations of 1,2,3-Triazoles and Related Compounds. *Synthesis* **2014**, *46*, 3004-3023; (e) Hockey, S. C.; Henderson, L. C. Rhodium(II) Azavinyl Carbenes and Their Recent Application to Organic Synthesis. *Aust. J. Chem.* **2015**, *68*, 1796-1800; (f) Tang, Y.; Wang, Y.; Lei, X. Rhodium-Azavinylcarbene: A Versatile Synthon-Enabling Divergent Synthesis of Nitrogen Heterocycles. *Synlett* **2015**, *26*, 2051-2059. (g) Jiang, Y.; Sun, R.; Tang, X. Y.; Shi, M. Recent Advances in the Synthesis of Heterocycles and Related Substances Based on α-Imino Rhodium Carbene Complexes Derived from *N*-Sulfonyl-1,2,3-triazoles. *Chem. Eur. J.* **2016**, *22*, 17910-17924; (h) Jia, M.; Ma, S., New Approaches to the Synthesis of Metal Carbenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 9134-66.

(5) (a) Adam, R.; Alom, S.; Abarca, B.; Ballesteros, R. Reactivity of [1,2,3]Triazolo[1,5-a]pyridines as 1,3-Dipoles. *Tetrahedron* **2016**, *72*, 8436-8441; (b) Abarca, B.; Ballesteros, R.; Blanco, F.; Bouillon, A.; Collot, V.; Domínguez, J.-R.; Lancelot, J.-C.; Rault, S. Synthesis of Novel Triazolopyridylboronic Acids and Esters. Study of Potential Application to Suzuki-Type Reactions. *Tetrahedron* **2004**, *60*, 4887-4893; (c) Abboud, K. A.; Palenik, R. C.; Palenik, G. J. Reactions of Seven Coordinate Complexes. Synthesis, Structure, and Copper Complex of The Novel Ligand 3-Methyltriazolo(1,5-A)6-acetylsemicarbazonepyridine. *Inorg. Chim. Acta* **2004**, *357*, 321-324; (d) Abarca, B.; Ballesteros, R.; Ballesteros-Garrido, R.; Colobert, F.; Leroux, F. R. Triazolopyridines. Part 26: The Preparation of Novel [1,2,3]Triazolo[1,5-a]pyridine Sulfoxides. *Tetrahedron* **2008**, *64*, 3794-3801; (e) Abarca, B.; Ballesteros, R.; Chadlaoui, M. Triazolopyridines. Part 24: New Polynitrogenated Potential Helicating Ligands. *Tetrahedron* **2004**, *60*, 5785-5792; (f) Jones, G.; Abarca, B. The Chemistry of the [1,2,3]Triazolo[1,5-a]pyridines: An Update. *Adva. Het. Chem.* **2010**, 195-252; (g) Abarca, B.; Ballesteros, R.; Chadlaoui, M.; de Arellano, C. R.; Real, J. A. [(Pyridylcarbonyl)pyridyl]triazolopyridines, Useful Ligands for the Construction of Polynuclear Coordination Compounds – Synthesis, Crystal Structure and Magnetic Properties of a Novel Tetranuclear Copper(II) Cubane. *Eur. J. Inorg. Chem.* **2007**, 4574-4578.

(6) Hirayama, T.; Ueda, S.; Okada, T.; Tsurue, N.; Okuda, K.; Nagasawa, H. Facile One-Pot Synthesis of [1, 2, 3]Triazolo[1, 5-a]Pyridines from 2-Acylpyridines by Copper(II)-Catalyzed Oxidative *N*–*N* Bond Formation. *Chem. Eur. J.* **2014**, *20*, 4156-62, and references therein.

(7) (a) Abarca, B.; Ballesteros-Garrido, R., 1,2,3-Triazoles Fused to Aromatic Rings. In *Chemistry of 1,2,3-triazoles*, Dehaen, W.; Bakulev, V. A., Eds. Springer International Publishing: Cham, 2015; Vol. 40, pp 325-378; (b) Abarca-González, B. The Chemistry of [1,2,3]Triazolo[1,5- a]pyridines. *J. Enzym. Inhib. Med. Chem.* **2002**, *17*, 359-367, and references therein.

(8) (a) Wang, C.; Zhou, Y.; Bao, X. Mechanistic Insights into the Rh-Catalyzed Transannulation of Pyridotriazole with Phenylacetylene and Benzonitrile: A DFT Study. *J. Org. Chem.* **2017**, *82*, 3751-3759; (b) L'Abbé, G.; Godts, F.; Toppet, S. Diazoimine–Triazole Equilibrium in Fused 1,2,3-Triazolo[1,5-a]pyrimidines. *J. Chem. Soc., Chem. Commun.* **1985**, 589-590; (c) L'Abbé, G.; Godts, F.; Toppet, S. On the Equilibrium Position of Bis[1,2,3] Triazolopyrimidines (A Revision). *Bull. Soc. Chim. Belg.* **1986**, *95*, 679-680; (d) L'Abbé, G. Molecular Rearrangements of 1h-1,2,3-Triazoles and 1,2,3-Thiadiazoles. *Bull. Soc. Chim. Belg.* **1990**, *99*, 281-291; (e) Regitz, M.; Arnold, B.; Danion, D.; Schubert, H.; Fusser, G. α-Diazoimine in der Heterocyclensynthese. *Bull. Soc. Chim. Belg.* **1981**, *90*, 615-631; (f) Aylward, N.;

Winter, H.-W.; Eckhardt, U.; Wentrup, C. Triazoloazine-Diazomethylazine Valence Isomerization. [1,2,3]Triazolo[1,5-a]pyridines and 2-Diazomethylpyridines. *J. Org. Chem.* **2016**, *81*, 667-672.

(9) Regitz, M. New Methods of Preparative Organic Chemistry. Transfer of Diazo Groups. *Angew. Chem., Int. Ed.* **1967**, *6*, 733-749.

(10) Abarca, B.; Ballesteros, R.; Mojarred, F.; Jones, G.; Mouat, D. J. Triazolopyridines. Part 7. Preparation of Bromo-triazolopyridines and -Triazoloisoquinolines. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1865-1868.

(11) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. Rh-Catalyzed Transannulation of Pyridotriazoles with Alkynes and Nitriles. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757-4759.

(12) Davies, H. M. L.; Townsend, R. J. Catalytic Asymmetric Cyclopropanation of Heteroaryldiazoacetates. *J. Org. Chem.* **2001**, *66*, 6595-6603.

(13) Bagheri, V.; Doyle, M. P.; Taunton, J.; Claxton, E. E. A New and General Synthesis of α-Silyl Carbonyl Compounds by Silicon-Hydrogen Insertion from Transition Metal-Catalyzed Reactions of Diazo Esters and Diazo Ketones. *J. Org. Chem.* **1988**, *53*, 6158-6160.

(14) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. Ligand Effects on Dirhodium(II) Carbene Reactivities. Highly Effective Switching Between Competitive Carbenoid Transformations. *J. Am. Chem. Soc.* **1993**, *115*, 8669-8680.

(15) Hoye, T. R.; Dinsmore, C. J.; Johnson, D. S.; Korkowski, P. F. Alkyne Insertion Reactions of Metal-Carbenes Derived from Enynyl-α-Diazoketones [$R'CN_2COCR_2CH_2C{\equiv}C(CH_2)_{n-2}CH{=}CH_2$]. *J. Org. Chem.* **1990**, *55*, 4518-4520.

(16) Chuprakov, S.; Gevorgyan, V. Regiodivergent Metal-Catalyzed Rearrangement of 3-Iminocyclopropenes into *N*-Fused Heterocycles. *Org. Lett.* **2007**, *9*, 4463-4466.

(17) (a) Cho, S. H.; Liebeskind, L. S. Practical Organic Synthesis with Strained Ring Molecules. Rhodium Catalyzed Carbonylation of Cyclopropenecarboxylate Esters and Cyclopropenyl Ketones to α-Pyrones and of Vinylcyclopropenes to Phenols. *J. Org. Chem.* **1987**, *52*, 2631-2634; (b) Padwa, A.; Kassir, J. M.; Xu, S. L. Cyclization Reactions of Rhodium Carbene Complexes. Effect of Composition and Oxidation State of the Metal. *J. Org. Chem.* **1997**, *62*, 1642-1652; (c) Padwa, A.; Kassir, J. M.; Xu, S. L. Rhodium-Catalyzed Ring-Opening Reaction of Cyclopropenes. Control of Regioselectivity by the Oxidation State of the Metal. *J. Org. Chem.* **1991**, *56*, 6971-6972; (d) Müller, P.; Pautex, N.; Doyle, M. P.; Bagheri, V. Rh(II)-Catalyzed Isomerizations of Cyclopropenes Evidence for Rh(II)-Complexed Vinylcarbene Intermediates. *Helv. Chim. Acta* **1990**, *73*, 1233-1241.

(18) (a) Müller, P.; Gränicher, C. Selectivity in Rhodium(II)-Catalyzed Rearrangements of Cycloprop-2-ene-1-carboxylates. *Helv. Chim. Acta* **1995**, *78*, 129-144; (b) Müller, P.; Gränicher, C. Structural Effects on the RhII-Catalyzed Rearrangement of Cyclopropenes. *Helv. Chim. Acta* **1993**, *76*, 521-534.

(19) Kim, H.; Kim, S.; Kim, J.; Son, J.-Y.; Baek, Y.; Um, K.; Lee, P. H. One-Pot Synthesis of Indolizines via Sequential Rhodium-Catalyzed [2+1]-Cyclopropanation, Palladium-Catalyzed Ring Expansion, and Oxidation Reactions from Pyridotriazoles and 1,3-Dienes. *Org. Lett.* **2017**, *19*, 5677-5680.

(20) Helan, V.; Gulevich, A. V.; Gevorgyan, V. Cu-Catalyzed Transannulation Reaction of Pyridotriazoles with Terminal Alkynes Under Aerobic Conditions: Efficient Synthesis of Indolizines. *Chem. Sci.* **2015**, *6*, 1928-1931.

(21) Xia, Y.; Zhang, Y.; Wang, J. Catalytic Cascade Reactions Involving Metal Carbene Migratory Insertion. *ACS Catal.* **2013**, *3*, 2586-2598, and references therein.

(22) Worrell, B. T.; Malik, J. A.; Fokin, V. V. Direct Evidence of a Dinuclear Copper Intermediate in Cu(I)-Catalyzed Azide-Alkyne Cycloadditions. *Science* **2013**, *340*, 457-460.

(23) Shi, Y.; Gevorgyan, V. Cu-Catalyzed Transannulation Reaction of Pyridotriazoles: General Access to Fused Polycyclic Indolizines. *Chem. Commun.* **2015**, *51*, 17166-17169.

(24) Shi, Y.; Gevorgyan, V. Intramolecular Transannulation of Alkynyl Triazoles via Alkyne-Carbene Metathesis Step: Access to Fused Pyrroles. *Org. Lett.* **2013**, *15*, 5394-5396.

(25) (a) Karthikeyan, I.; Arunprasath, D.; Sekar, G. An Efficient Synthesis of Pyrido[1,2-a]indoles Through Aza-Nazarov Type Cyclization. *Chem. Commun.* **2015**, *51*, 1701-1704; (b) Naredla, R. R.; Zheng, C.; Nilsson Lill, S. O.; Klumpp, D. A. Charge Delocalization and Enhanced Acidity in Tricationic Superelectrophiles. *J. Am. Chem. Soc.* **2011**, *133*, 13169-13175.

(26) Joshi, A.; Chandra Mohan, D.; Adimurthy, S. Copper-Catalyzed Denitrogenative Transannulation Reaction of Pyridotriazoles: Synthesis of Imidazo[1,5-a]pyridines with Amines and Amino Acids. *Org. Lett.* **2016**, *18*, 464-467.

(27) (a) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. Aerobic Copper-Catalyzed Organic Reactions. *Chem. Rev.* **2013**, *113*, 6234-6458; (b) Zhou, N.; Xie, T.; Liu, L.; Xie, Z. Cu/Mn Co-Oxidized Cyclization for the Synthesis of Highly Substituted Pyrrole Derivatives from Amino Acid Esters: A Strategy for the Biomimetic Syntheses of Lycogarubin C and Chromopyrrolic Acid. *J. Org. Chem.* **2014**, *79*, 6061-6068.

(28) Roy, S.; Das, S. K.; Chattopadhyay, B. Cobalt(II)-Based Metalloradical Activation of 2-(Diazomethyl)pyridines for Radical Transannulation and Cyclopropanation. *Angew. Chem., Int. Ed.* **2018**, *57*, 2238-2243.

(29) (a) Lu, H.; Dzik, W. I.; Xu, X.; Wojtas, L.; de Bruin, B.; Zhang, X. P. Experimental Evidence for Cobalt(III)-Carbene Radicals: Key Intermediates in Cobalt(II)-Based Metalloradical Cyclopropanation. *J. Am. Chem. Soc.* **2011**, *133*, 8518-8521; (b) Wang, Y.; Wen, X.; Cui, X.; Wojtas, L.; Zhang, X. P. Asymmetric Radical Cyclopropanation of Alkenes with In Situ-Generated Donor-Substituted Diazo Reagents Via Co(II)-Based Metalloradical Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 1049-1052; (c) Dzik, W. I.; Xu, X.; Zhang, X. P.; Reek, J. N. H.; de Bruin, B. 'Carbene Radicals' in CoII(por)-Catalyzed Olefin Cyclopropanation. *J. Am. Chem. Soc.* **2010**, *132*, 10891-10902.

(30) Joshi, A.; Mohan, D. C.; Adimurthy, S. Lewis Acid-Catalyzed Denitrogenative Transannulation of Pyridotriazoles with Nitriles: Synthesis of Imidazopyridines. *J. Org. Chem.* **2016**, *81*, 9461-9469.

(31) Rawat, D.; Ravi, C.; Joshi, A.; Suresh, E.; Jana, K.; Ganguly, B.; Adimurthy, S. Indium-Catalyzed Denitrogenative Transannulation of Pyridotriazoles: Synthesis of Pyrido[1,2-a]indoles. *Org. Lett.* **2019**, *21*, 2043-2047.

(32) (a) Yadagiri, D.; Anbarasan, P. Rhodium Catalyzed Direct Arylation of *a*-Diazoimines. *Org. Lett.* **2014**, *16*, 2510-2513; (b) Shin, S.; Park, Y.; Kim, C.-E.; Son, J.-Y.; Lee, P. H. Synthesis of 2-Alkoxyaryl-2-aryl Enamines Via Tandem Copper-Catalyzed Cycloaddition and Rhodium-Catalyzed Alkoxyarylation from Alkynes, N-Sulfonyl Azides, and Aryl Ethers. *J. Org. Chem.* **2015**, *80*, 5859-5869.

(33) Karthikeyan, I.; Sekar, G. Iron-Catalyzed C–H Bond Functionalization for the Exclusive Synthesis of Pyrido[1,2-a]indoles or Triarylmethanols. *Eur. J. Org. Chem.* **2014**, 8055-8063.

(34) Yanada, R.; Hashimoto, K.; Tokizane, R.; Miwa, Y.; Minami, H.; Yanada, K.; Ishikura, M.; Takemoto, Y. Indium(III)-Catalyzed Tandem Reaction with Alkynylbenzaldehydes and Alkynylanilines to Heteroaromatic Compounds. *J. Org. Chem.* **2008**, *73*, 5135-5138.

(35) Zhang, G.-T.; Zhang, J.; Xu, Y.-J.; Dong, L. Metal-Free [3+2] Tandem Cyclization Synthesis of Unique 11H-Pyrido[3′,2′:4,5]pyrrolo[3,2-b]indolizine from 7-Azaindoles and Pyridotriazoles. *Eur. J. Org. Chem.* **2018**, 4197-4201.

(36) Shi, Y.; Gulevich, A. V.; Gevorgyan, V. Rhodium-Catalyzed NH Insertion of Pyridyl Carbenes Derived from Pyridotriazoles: A General and Efficient Approach to 2-Picolylamines and Imidazo[1,5-a]pyridines. *Angew. Chem., Int. Ed.* **2014**, *53*, 14191-14195.

(37) Lamaa, D.; Lin, H.-P.; Bzeih, T.; Retailleau, P.; Alami, M.; Hamze, A. TBAB-Catalyzed Csp^3–N Bond Formation by Coupling Pyridotriazoles with Anilines: A New Route to (2-Pyridyl)alkylamines. *Eur. J. Org. Chem.* **2019**, 2602-2611.

(38) Kim, J. H.; Gensch, T.; Zhao, D.; Stegemann, L.; Strassert, C. A.; Glorius, F. Rh(III)-Catalyzed C–H Activation with Pyridotriazoles: Direct Access to Fluorophores for Metal-Ion Detection. *Angew. Chem., Int. Ed.* **2015**, *54*, 10975-10979.

(39) Jeon, W. H.; Son, J. Y.; Kim, J. E.; Lee, P. H. Synthesis of 1,2-Benzothiazines by a Rhodium-Catalyzed Domino C–H Activation/Cyclization/Elimination Process from S-Aryl Sulfoximines and Pyridotriazoles. *Org. Lett.* **2016**, *18*, 3498-501.

(40) Dong, W.; Wang, L.; Parthasarathy, K.; Pan, F.; Bolm, C. Rhodium-Catalyzed Oxidative Annulation of Sulfoximines and Alkynes as an

Approach to 1,2-Benzothiazines. *Angew. Chem., Int. Ed.* **2013**, *52*, 11573-11576.

(41) Xu, H.-B.; Zhu, Y.-Y.; Dong, L. Specific Synthesis of 3H-Indole Derivatives Via Rh(III)-Catalyzed Cascade Annulation Between *N*-Phenylbenzimidamides and Pyridotriazoles. *J. Org. Chem.* **2019**, *84*, 16286-16292.

(42) Dong, Y.; Chen, J.; Cui, Y.; Bao, L.; Xu, H. Cp*RhIII-Catalyzed Sulfonamide-Directed Ortho Arene C–H Carbenoid Functionalization with Pyridotriazoles. *Org. Lett.* **2020**, *22*, 772-775.

(43) Shen, R.; Dong, C.; Yang, J.; Han, L. B. Copper(II) Acetate-Catalyzed Synthesis of Phosphorylated Pyridines Via Denitrogenative C–P Coupling Between Pyridotriazoles and P(O)H Compounds. *Adv. Synth. Catal.* **2018**, *360*, 4252-4258.

(44) Opsomer, T.; Van Hoof, M.; D'Angelo, A.; Dehaen, W. 1,2,3-Triazole-Mediated Synthesis of 1-Methyleneisoquinolines: A Three-Step Synthesis of Papaverine and Analogues. *Org. Lett.* **2020**, *22*, 3596-3600.

(45) Chiassai, L.; Adam, R.; Drechslerová, M.; Ballesteros, R.; Abarca, B. Approaches for the Introduction of Fluorinated Substituents Into [1,2,3]Triazolo[1,5-a]pyridines. *J. Fluorine Chem.* **2014**, *164*, 44-50.

(46) Moon, Y.; Kwon, S.; Kang, D.; Im, H.; Hong, S. Palladium-Catalyzed Divergent Arylation with Triazolopyridines: One-Pot Synthesis of 6-Aryl-2-*a*-styrylpyridines. *Adv. Synth. Catal.* **2016**, *358*, 958-964.

(47) Lv, X.; Yang, H.; Shi, T.; Xing, D.; Xu, X.; Hu, W. Rhodium(II)-Catalyzed Formal [4+1]-Cycloaddition of Pyridotriazoles and Propargyl Alcohols: Synthesis of 2,5-Dihydrofurans. *Adv. Synth. Catal.* **2019**, *361*, 1265-1270.

(48) Joshi, A.; Semwal, R.; Suresh, E.; Adimurthy, S. Pd-Catalyzed Regioselective Synthesis of 2,6-Disubstituted Pyridines Through Denitrogenation of Pyridotriazoles and 3,8-Diarylation of Imidazo[1,2-a]pyridines. *Chem. Commun.* **2019**, *55*, 10888-10891.

(49) Rawat, D.; Kumar, R.; Adimurthy, S. Pd-Catalyzed *ortho*-Selective C–H Acyloxylation and Hydroxylation of Pyridotriazoles. *Eur. J. Org. Chem.* **2019**, 7874-7879.

(50) Liu, S.; Sawicki, J.; Driver, T. G. Ni-Catalyzed Alkenylation of Triazolopyridines: Synthesis of 2,6-Disubstituted Pyridines. *Org. Lett.* **2012**, *14*, 3744-3747.

(51) Dong, C.; Wang, X.; Pei, Z.; Shen, R. Metal-Free Denitrogenative C–C Couplings of Pyridotriazoles with Boronic Acids to Afford α-Secondary and α-Tertiary Pyridines. *Org. Lett.* **2019**, *21*, 4148-4152.

(52) Filippov, I. P.; Novikov, M. S.; Khlebnikov, A. F.; Rostovskii, N. V. Pseudopericyclic Dearomative 1,6-Cyclization of 1-(2-Pyridyl)-2-azabuta-1,3-dienes: Synthesis and Ring-Chain Valence Equilibria of 4H-Pyrido[1,2-a]pyrazines. *Eur. J. Org. Chem.* **2020**, 2904-2913.

(53) Kuzaj, M.; Lüerssen, H.; Wentrup, C. ESR Observation of Thermally Produced Triplet Nitrenes and Photochemically Produced Triplet Cycloheptatrienylidenes. *Angew. Chem., Int. Ed.* **1986**, *25*, 480-482.

(54) Tomioka, H.; Ichikawa, N.; Komatsu, K. Photochemistry of 2-(Methoxycarbonyl)phenyl Azide Studied by Matrix-Isolation Spectroscopy. A New Slippery Energy Surface for Phenylnitrene. *J. Am. Chem. Soc.* **1993**, *115*, 8621-8626.

(55) Kirmse, W. 100 Years of the Wolff Rearrangement. *Eur. J. Org. Chem.* **2002**, *2002*, 2193-2256, and references therein.

(56) (a) Plüg, C.; Kuhn, A.; Wentrup, C. Quinolizine-2,4-diones by Reversible Dimerisation 2-Pyridylketenes. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1366-1368; (b) Kuhn, A.; Plüg, C.; Wentrup, C. Direct Observation of a Carbene-Pyridine Ylide by Matrix IR Spectroscopy. Rearrangements of 2-Pyridylacylcarbenes. *J. Am. Chem. Soc.* **2000**, *122*, 1945-1948.

(57) Andersen, H. G.; Bednarek, P.; Wentrup, C. Methoxy(2-pyridyl)ketene. *J. Phys. Org. Chem.* **2003**, *16*, 519-524.

(58) Fu, N.; Allen, A. D.; Kobayashi, S.; Sequeira, P. A.; Shang, M.; Tidwell, T. T.; Mishima, M. Observable Azacyclobutenone Ylides with Antiaromatic Character from 2-Diazoacetyl-azaaromatics. *J. Am. Chem. Soc.* **2007**, *129*, 6210-6215.

(59) Zimmerman, H. E.; Ignatchenko, A. Control of the Stereochemistry of Kinetic Protonation: Intramolecular Proton Delivery. *J. Org. Chem.* **1999**, *64*, 6635-6645.

(60) Zhang, Z.; Yadagiri, D.; Gevorgyan, V. Light-Induced Metal-Free Transformations of Unactivated Pyridotriazoles. *Chem. Sci.* **2019**, *10*, 8399-8404.

(61) (a) Jurberg, I. D.; Davies, H. M. L. Blue Light-Promoted Photolysis of Aryldiazoacetates. *Chem. Sci.* **2018**, *9*, 5112-5118; (b) Ciszewski, Ł. W.; Rybicka-Jasińska, K.; Gryko, D. Recent Developments in Photochemical Reactions of Diazo Compounds. *Org. Biomol. Chem.* **2019**, *17*, 432-448; (c) Hommelsheim, R.; Guo, Y.; Yang, Z.; Empel, C.; Koenigs, R. M. Blue-Light-Induced Carbene-Transfer Reactions of Diazoalkanes. *Angew. Chem., Int. Ed.* **2019**, *58*, 1203-1207; (d) Xiao, T.; Mei, M.; He, Y.; Zhou, L. Blue Light-Promoted Cross-Coupling of Aryldiazoacetates and Diazocarbonyl Compounds. *Chem. Commun.* **2018**, *54*, 8865-8868.

(62) Selander, N.; Worrell, B. T.; Chuprakov, S.; Velaparthi, S.; Fokin, V. V. Arylation of Rhodium(II) Azavinyl Carbenes with Boronic Acids. *J. Am. Chem. Soc.* **2012**, *134*, 14670-14673.

(63) Nakamura, I.; Nemoto, T.; Shiraiwa, N.; Terada, M. Palladium-Catalyzed Indolization of *N*-Aroylbenzotriazoles with Disubstituted Alkynes. *Org. Lett.* **2009**, *11*, 1055-1058.

(64) (a) Katritzky, A. R.; Yang, B.; Jiang, J.; Steel, P. J. Ring-Opening Rearrangements of 2-(Benzotriazol-1-yl) Enamines and a Novel Synthesis of 2,4-Diarylquinazoline. *J. Org. Chem.* **1995**, *60*, 246-249; (b) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. Properties and Synthetic Utility of *N*-Substituted Benzotriazoles. *Chem. Rev.* **1998**, *98*, 409-548, and references therein.

(65) Wang, Y.; Wang, Z.; Tang, Y. Renaissance of Ring-Opening Chemistry of Benzotriazoles: New Wine in an Old Bottle. *Chem. Rec.* **2020**, 10.1002/tcr.201900088.

Graphical Abstract: