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Advances in Selected Heterocyclization Methods

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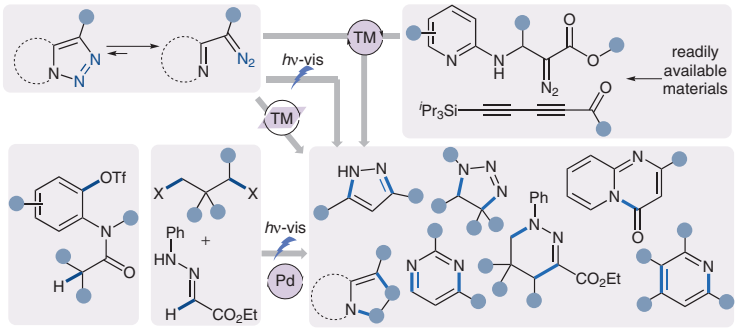

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Abstract This Account summarizes efforts in our group toward synthesis of heterocycles in the past decade. Selected examples of transannulative heterocyclizations, intermediate construction of reactive compounds *en route* to these important motifs, and newer developments of a radical approach are outlined.

Key words transannulative heterocyclization, heterocycles, radical heterocyclization, transition-metal-catalyzed heterocyclization.

1 Introduction

Synthesis of heterocycles is of critical importance to the development of pharmaceuticals and functional materials. Discovery and improvement of chemical transformations to this end have remained highly significant and continued to grow over the years. This Account updates our group's continued efforts in this endeavor, which has spanned advancement of transition-metal (TM)-catalyzed synthesis of heterocycles by migratory cascades, carbene formation, and other transformations to produce a diverse array of heterocyclic scaffolds. We have previously summarized some of this work.[2] In the recent decade, advances in these strategies have seen new development in transannulative heterocyclizations and employment of diazo or alkynone intermediates as heterocycle precursors. More recently, radical strategies have emerged to synthesize these compounds under mild conditions. This Account will cover these new developments.

2 Transannulative Heterocyclization

In 1909, Dimroth disclosed that nitrogen atoms within the ring of triazoles could rearrange via ring–chain isomerization to become exocyclic nitrogen atoms.[3] A similar phenomenon was encountered by Huisgen and von Fraunberg in 1969, who showed that this type of isomerization, in the presence of copper, could lead to loss of dinitrogen and annulation under harsh conditions.[4] In the late 2000s, Gevorgyan developed this ring–chain isomerization phenomenon into a practical strategy toward heterocycle synthesis,[6a-d, gevorgyan] paving the way for transannulative heterocyclization chemistry.[5, anbarasan] These key discoveries are illustrated in Scheme 1.[6] It was found that *N*-sulfonyltriazole[6d,7] **1** and pyridotriazoles[2b,f,8] **2** are convenient carbene precursors, existing in equilibrium with diazo form **3**, which can be trapped by transition metal to produce intermediate **4**. In the case of pyridotriazole **2**, the open-chain isomer is favored when an activating group vicinal to the nitrogen atom at the *peri* position is present,[9] which enabled the first Rh-catalyzed transannulation of pyridotriazoles toward imidazo[1,5-*a*]pyridines[10] **5**.[6a]

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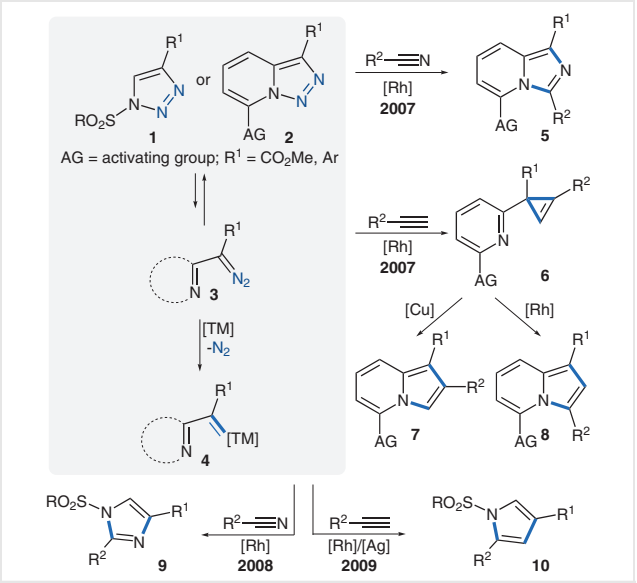


Scheme 1 Key discoveries in transition-metal-catalyzed transannulative heterocyclization

The same group disclosed that, by changing the catalyst, cyclopropenation instead of transannulation was observed, producing **6**. Subsequent regiodivergent cyclopropene rearrangement afforded 1,2- or 1,3-disubstituted indolizines **7** and **8**, respectively.[6b] The following year, another key contribution in this area was reported by Gevorgyan and Fokin, employing triazoles **1** in a Rh-catalyzed transannulation strategy with nitriles toward imidazoles **9**.[6c] Employment of silver co-catalyst enabled the analogous transformation to synthesize pyrroles **10**.[6d]

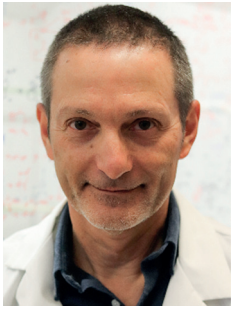
2.1 Rhodium-Catalyzed Transannulative Heterocyclization

The above-outlined key discoveries in TM-catalyzed transannulative heterocyclizations from stable triazole compounds opened new opportunities for synthesis that are being explored to this day.[2f] One such avenue focused on overcoming the substrate specificity of the reaction, which limited the types of heterocycles and substitution patterns accessible by this transformation.

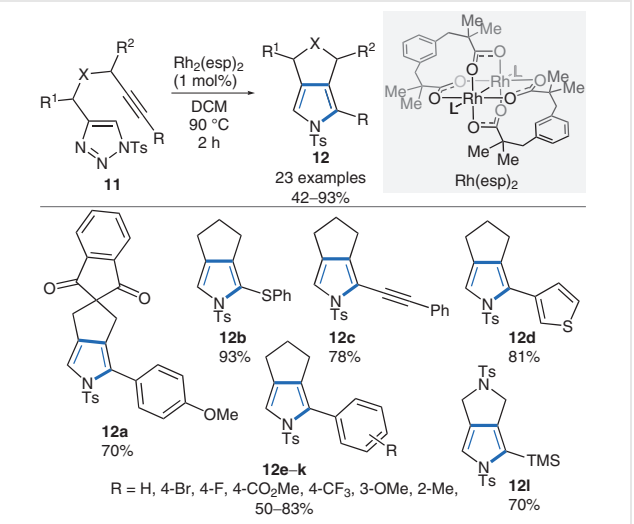
For instance, while the intermolecular transannulation reaction to synthesize pyrroles was achieved employing terminal alkynes, the requisite ylide intermediacy prohibited using internal alkynes toward fused diversely substituted pyrroles in an intramolecular fashion.[6d] This limitation was resolved by using a carbene–alkyne metathesis mechanism enabling the efficient and generalizable fused pyrrole **12** synthesis using tethered internal alkynes **11** (Scheme 2).[11]

Biographical Sketches

Mónica Rivas received her BSc in chemistry from the University of Central Florida in 2014. In 2017, she joined the Gevorgyan group at the University of Illinois at Chicago, and later at The University of Texas at Dallas as a Ruth L. Kirschtein NIH Pre-doctoral Fellow, working in collaboration with the University of Texas Southwestern Medical Center. Her PhD work focused on the development of mild methods for alkyl radical generation and their application in positron emission tomography molecular imaging probe synthesis. In 2022, Mónica joined the Mapp Lab at the University of Michigan as a May-Walt Life Sciences Postdoctoral Fellow to study allosteric modulation of dynamic protein–protein interactions.

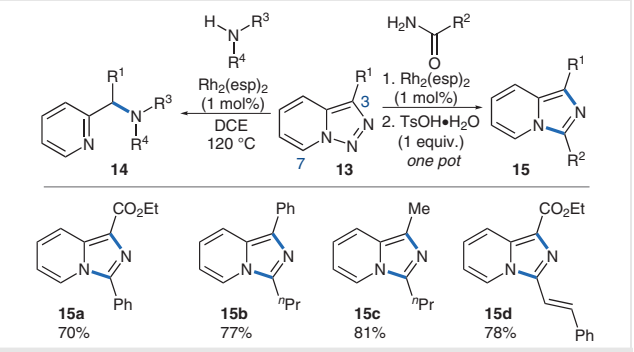


Vladimir Gevorgyan received his PhD from the Latvian Institute of Organic Synthesis. After two years of postdoctoral research (1992–1994, JSPS- and CibaGeigy International Postdoctoral Fellowships) at Tohoku University, Japan and a visiting professorship (1995) at CNR, Bologna, Italy, he joined the faculty at Tohoku University (Assistant Professor, 1996; Associate Professor, 1997–1999). In 1999, Vladimir Gevorgyan moved to the United States to join the University of Illinois at Chicago (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.



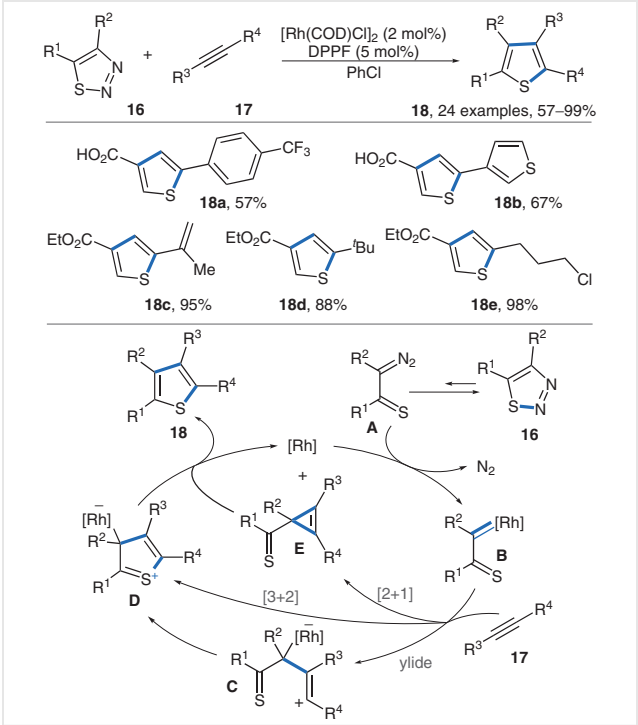
Scheme 2 Intramolecular transannulation of alkynyl triazoles via alkyne–carbene metathesis

Further development of this transformation involved the expansion of scope of pyridotriazoles to diversify the substitution pattern around the target heterocycles. To this end, unactivated pyridotriazoles **13** were employed to synthesize 2-pycolylamines **14** and imidazo[1,5-*a*]pyridines using a Rh-based catalytic system. This methodology avoided the use of activating groups at the 3- and 7-positions to afford compounds **15** in good yields (Scheme 3).[12]



Scheme 3 Synthesis of 2-picolylamines and imidazo[1,5-*a*]pyridines by Rh-catalyzed N–H insertion of pyridyl carbenes derived from pyridotriazoles

Denitrogenative transannulation strategies toward heterocycle synthesis were further expanded by Gevorgyan to include 1,2,3-thiadiazole substrates **16** toward diversely substituted thiophenes **18** (Scheme 4).[13] Ring–chain isomerization of **16** to **A**, followed by denitrogenation yields metallocarbene **B**. Formation of ylide intermediate **C** and cycloisomerization or [3+2] cycloaddition with internal alkyne **17** could yield zwitterion **D**. Alternatively, [2+1] cycloaddition with **17** could afford cyclopropene **E**, capable of ring expansion and catalyst release to yield thiophene **18**.

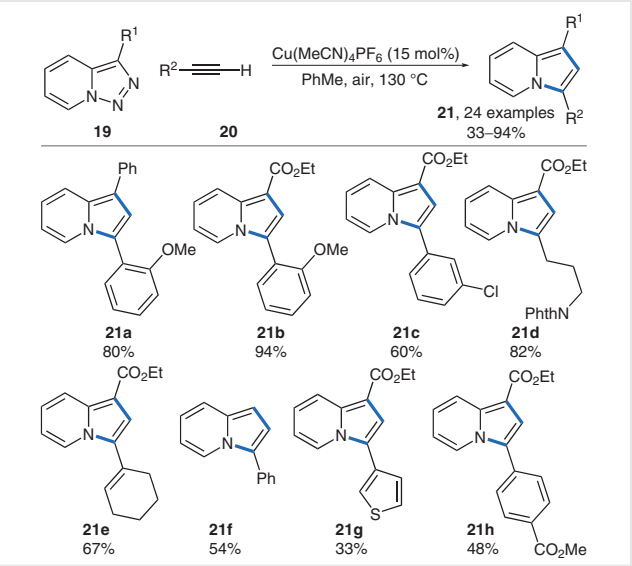


Scheme 4 Modular synthesis of multisubstituted thiophenes from 1,2,3-dithiazoles *via* rhodium thiavinyl carbene

In 2017, Lee developed a sequential Rh-catalyzed [2+1] cyclopropanation, followed by Pd-catalyzed ring expansion and manganese oxide oxidation in one pot, to produce indolizines.[14] More recently, Hu and Xu reported a denitrogenative [4+1] cycloaddition reaction between pyridotriazoles and propargylic alcohols to produce 1,2-dihydrofurans.[15] Rostovskii also employed a rhodium-based catalytic system in a denitrogenative dearomative 1,6-cyclization of pyridines and aziridines to synthesize *H*-pyrido[1,2-*a*]pyrazines.[16]

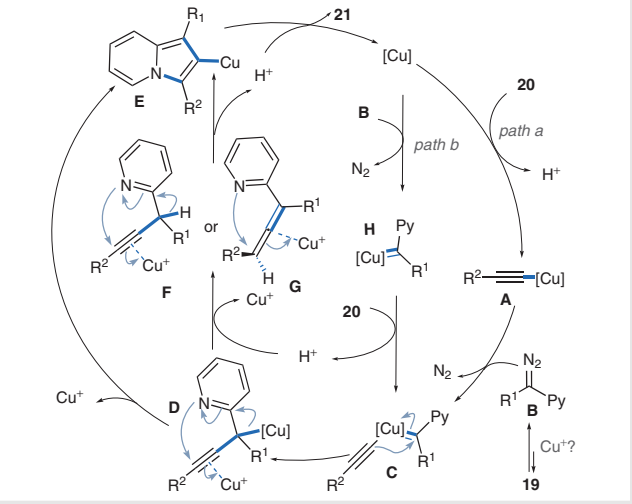
2.2 Copper-Catalyzed Transannulative Heterocyclization

Aiming at developing a transannulation strategy that was generalizable to pyridotriazole substrates not bearing an activating group, Gevorgyan discovered that the desired transformation toward diversely substituted indolizines **21** could be achieved under aerobic copper-catalyzed conditions (Scheme 5).[17] For the first time, electronically distinct pyridotriazoles and terminal acetylenes bearing aryl (**21a–c**), heteroaryl (**21g**), or alkyl groups (**21d,e**) could undergo transannulation under conditions featuring inexpensive copper catalyst. Furthermore, even unsubstituted pyridotriazoles were efficient precursors for indolizine **21f**.



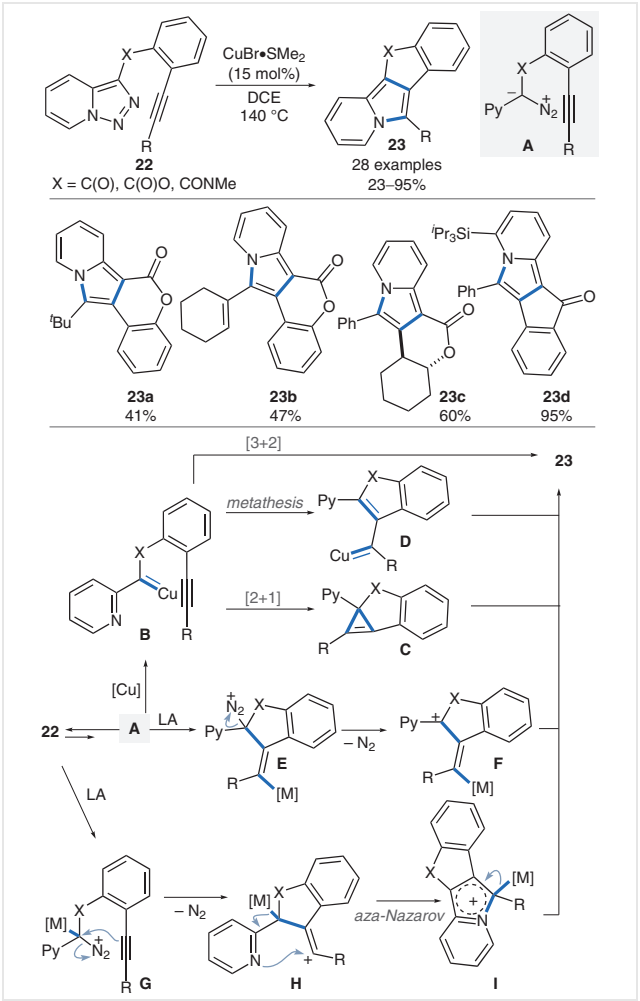
Scheme 5 Cu-catalyzed transannulation reaction of pyridotriazoles with terminal alkynes under aerobic conditions: efficient synthesis of indolizines

The proposed mechanism for this reaction involves the initial formation of copper acetylide **A**, which reacts with chain isomer, diazo compound **B**, to generate copper carbene intermediate **C** (path a, Scheme 6). Alternatively, this intermediate could be formed from the reaction of copper carbene **H** with alkyne substrate (path b). Alkyne migratory insertion (**C** → **D**) and nucleophilic attack by pyridine at the electrophilic copper-activated alkyne could produce intermediate **E**. Otherwise, the *in situ* generated intermediates **F** or **G** could also lead to **E**. Protodecupration of the latter then yields product **21** and regenerates the copper catalyst.



Scheme 6 Proposed mechanism for the Cu-catalyzed transannulation reaction of pyridotriazoles with terminal alkynes

The intramolecular version of this reaction was tackled next to synthesize the corresponding tri-, tetra-, and pentacyclic-fused indolizines **23** (Scheme 7).[18]



Scheme 7 Copper-catalyzed transannulation of pyridotriazoles toward fused polycyclic indolizines

Pyridotriazoles **22**, tethered at the 3-position with alkyl and aryl alkynes, undergo Dimroth-type isomerization toward intermediate **A**. Denitrogenation in the presence of copper catalyst produces metallocarbene **B**, capable of intramolecular [3+2] cycloaddition to directly produce **23**. Alternatively, cyclopropene **C** could be formed via [2+1] cycloaddition, followed by its subsequent cycloisomerization to yield indolizine **23**. Product could also be formed from intermediate **D**, resulting from carbene–alkyne metathesis. During reaction development, it was found that Lewis acid (LA) could also catalyze this reaction in the absence of copper catalyst. The proposed intermediate **E**, formed upon LA coordination with alkyne, could induce denitrogenation to generate cationic intermediate **F**, which upon cascade cyclization would produce **23**. Alternative coordination by LA

at C3 of pyridotriazole **G** could engender the intramolecular cyclization–denitrogenation step to produce cationic intermediate **H**. A subsequent aza-Nazarov cyclization would produce indolizine **23**. It is worth noting that, due to the importance of these heterocyclic scaffolds, methods to synthesize diversely substituted subunits are highly significant. This has been achieved by engaging mechanistically distinct protocols, like cycloisomerizations of alkynylpyridines[19] and skipped propargyl imines,[20] as well as cascade reactions including two-component organocopper-mediated S_N2' substitution cascade reaction.[21]

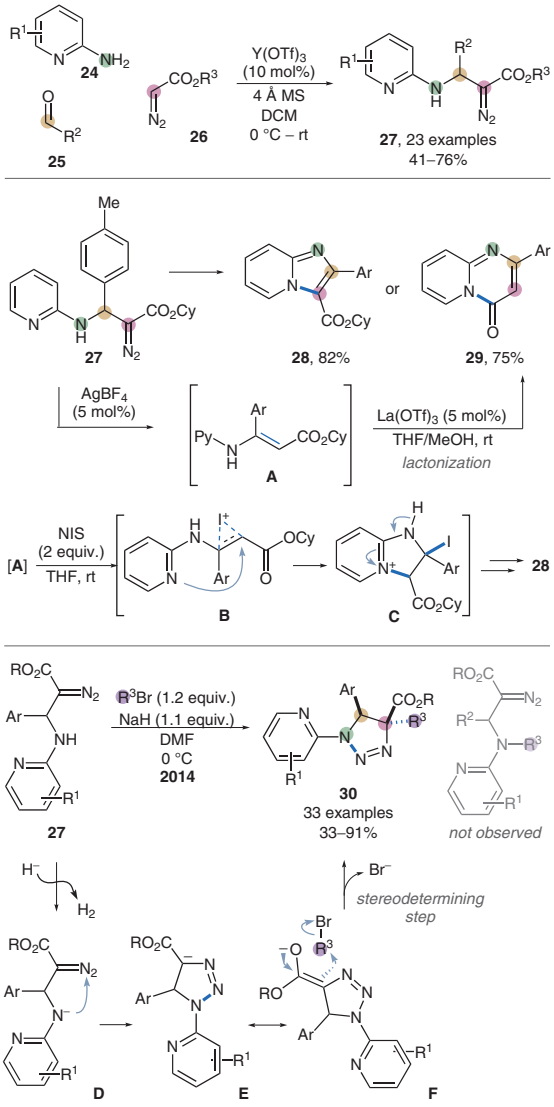
Aerobic copper-catalyzed reactions represent a vast area of research, of which only a few examples are highlighted in this Account.[22] Our group's multifocal interests in reaction development span beyond employment of copper–carbene mechanistic manifolds. For example, C–H oxygenation employing aerobic copper catalysis afforded chromenone scaffolds in good to excellent yields.[23] The reaction was further developed to work without Cu catalyst, using potassium persulfate and in some cases a catalytic amount of silver nitrate. In a collaborative extension of the group's efforts in developing multicomponent coupling reactions,[24] a batch and continuous-flow copper-catalyzed A^3 reaction toward imidazo[1,2-*b*]thiazoles was reported in 2017.[25]

3 Synthesis of Heterocycles from Reactive Precursors

As mentioned above, heterocyclic molecules can be synthesized using stable precursors, like pyridotriazoles. These methods must rely on pushing the equilibrium forward toward the ring-opened diazo intermediates, which are the main players in this transformation. Thus, methods to prepare key precursors to synthesize diverse heterocyclic scaffolds are in high demand. For example, employment of furans, featuring low energy of aromaticity as substrates for synthesis of high-value indoles, was reported under a one-pot protocol with broader functional group tolerance compared to that for the previously reported two-step methods.[26] Other important precursors, such as silacycles, were investigated in prior work.[27] In 2018, a palladium-catalyzed method for the synthesis of pyrido[1,2-*a*]indoles by mild, base-induced conditions was reported, employing aryl- and cyano-substituted *ortho*-picolylbromoarenes as precursors.[28]

3.1 Synthesis of Heterocycles from Diazo Compounds

Gevorgyan reported the pyridine-group-assisted addition of diazo compounds to imines in the 3-component coupling reaction of 2-aminopyridines **24**, aldehydes **25**, and diazo compounds **26** (Scheme 8).[29] Employment of the resulting α-diazoesters **27** in LA-catalyzed denitrogenative desaturation and lactonization afforded pyrimidinone **29**. The report also featured *N*-iodosuccinimide-mediated synthesis of imidazo[1,2-*a*]pyridine **28**. The reaction involves the *in situ* formation of iodonium **B** from intermediate **A**, which, upon subsequent nucleophilic attack, deprotonation, and HI elimination, produces **28**.



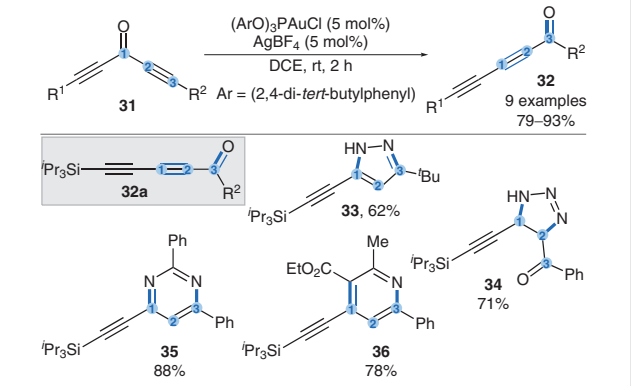
Scheme 8 Pyridine-assisted three-component coupling toward diazo compounds and their application in the synthesis of heterocycles

Shortly after, the same group reported the use of the diazo scaffold **27** in a diastereoselective cyclization to produce triazolines **30**.[30] The reaction begins with deprotonation of amine **27** to form anion **D**. A nucleophilic attack results in cyclized intermediate **E**, a resonance form of enolate **F**, which undergoes stereoselective alkylation to yield a single diastereomer of **30**. The diazo-containing scaffold **27** that

serves as a precursor for these transformations was found to be active as a lipid–protein interaction inhibitor in a recent biochemical study.[31]

3.2 Synthesis of Heterocycles from Alkynones

In continuation of Gevorgyan's extensive work on development of chemical reactions involving migrations,[2d,19a,32] the group published gold-catalyzed 1,3-transposition of ynones **31** into diynenones **32** (Scheme 9).[33] Synthesized diynenone **32a** was subjected to a variety of conditions to produce heterocycles bearing the alkyne functionality: addition of hydrazine, cycloaddition with sodium azide, reaction with benzamidine hydrochloride, and condensation with ethyl acetoacetate and ammonium acetate to efficiently produce pyrazole **33**, triazole **34**, pyrimidine **35**, and pyridine **36**, respectively.



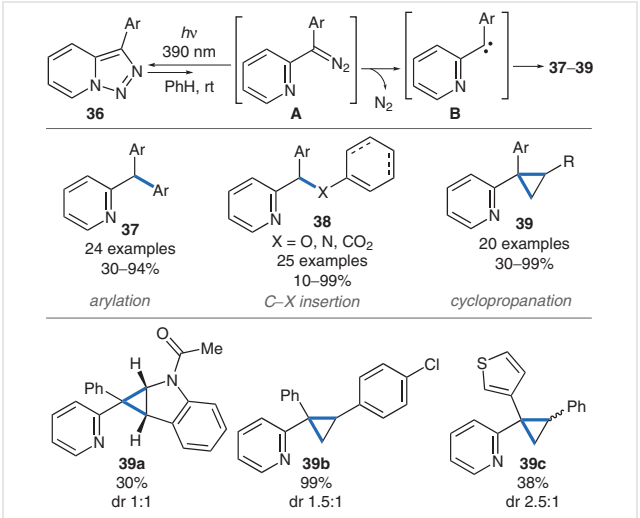
Scheme 9 Gold-catalyzed 1,3-transposition of ynones and heterocyclization

4 Radical Heterocyclization

Recent decades have brought a resurgence of radical strategies as mild, generalizable, and complementary approaches to classical two-electron methods. Thus, radical-based method development toward synthesis of heterocycles has thus become an active area of research.[34]

4.1 Light-Induced Radical Heterocyclization

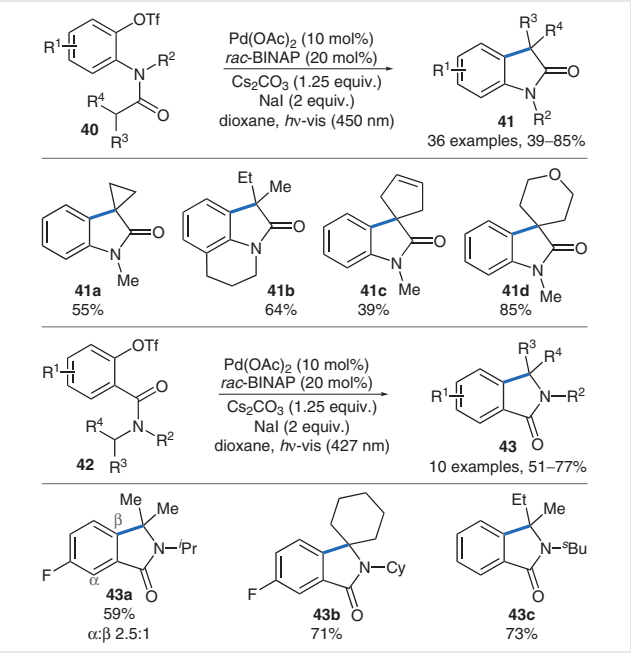
As described above, the ring–chain isomerization equilibrium of pyridotriazoles can be pushed forward under mild conditions if there is an activating group, or under harsh conditions in the case of unactivated substrates.[2f] Expansion of this reaction toward a mild, TM-free protocol could enable the Gevorgyan group to access the corresponding carbene **B** upon nitrogen loss (Scheme 10). Investigation of the UV/Vis absorption spectra led to the discovery that 3-arylpyridotriazoles undergo isomerization and denitrogenation under visible light to produce free carbene **B**.[35] This intermediate was utilized in various transformations, including arylation in the presence of boronic acids **37**, and C–X bond insertion with alcohols, anilines, amides, sulfonamides, and carboxylic acids **38**. Cyclopropanation with various alkenes afforded compounds **39** in moderate to excellent yields.



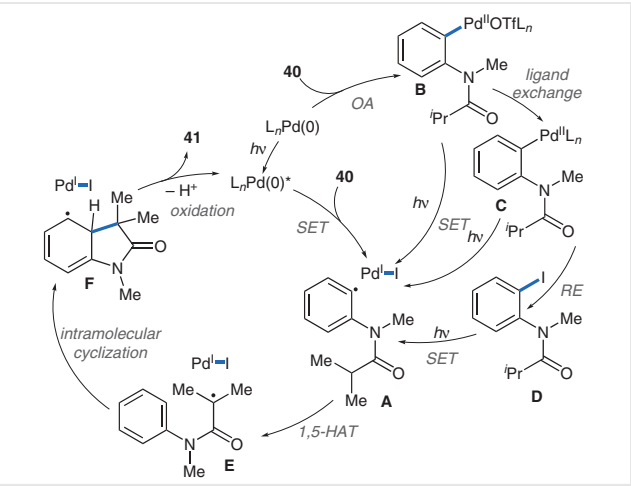
Scheme 10 Light-induced metal-free transformations of unactivated pyridotriazoles

Photoinduced TM-catalyzed radical reactions have also been employed toward the synthesis of heterocycles. In recent years, Gevorgyan reported the use of photoexcited palladium catalytic system to generate aryl,[36] vinyl,[37] and alkyl[38] radicals.[39] This catalytic system enabled the C–O bond cleavage of aryl triflates toward oxindoles **41** and isoindolin-1-ones **43** (Scheme 11).[40]

The proposed mechanism involves generating hybrid palladium radical species **A**, which could occur by photoexcitation of *in situ* formed Pd(0) followed by single-electron transfer (SET) with the substrate (Scheme 12). Alternatively, oxidative addition (OA) between **40** and Pd(0) could yield intermediate **B**, which can undergo ligand exchange (**C**), followed by a reductive elimination to produce **D**. Potentially, intermediates **B**–**D** could undergo SET and homolysis to generate **A**. A subsequent 1,5-hydrogen atom transfer (HAT) between aryl radical and tertiary C–H then produces transposed alkyl radical **E**, which is posed for intramolecular cyclization (**F**) and oxidation to afford product and regenerate the catalyst.

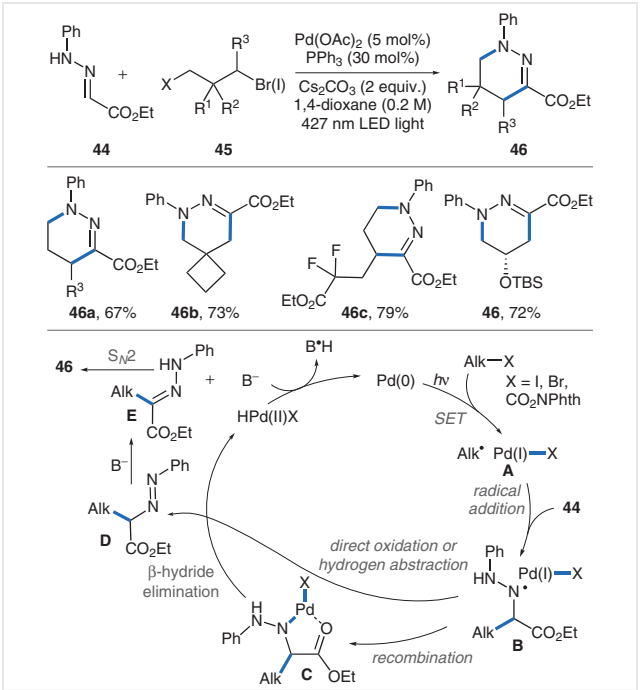


Scheme 11 Visible-light-induced palladium-catalyzed generation of aryl radicals from aryl triflates toward oxindoles and isoindolin-1-ones



Scheme 12 Proposed mechanism for oxindole synthesis

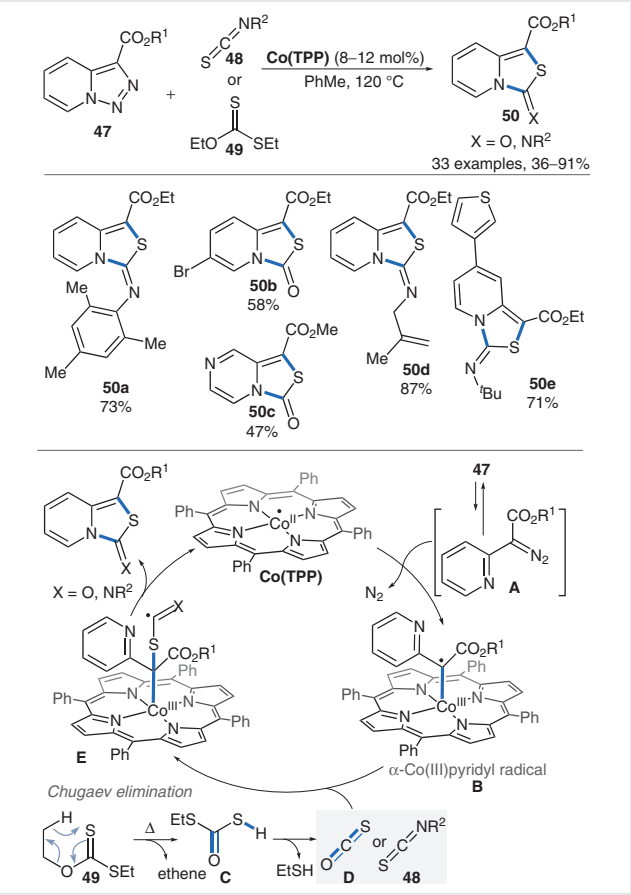
Further elaboration of the Pd(0/II/I) manifold to include the alkyl-Heck-type coupling between alkyl radicals and *N*-containing olefins resulted in the synthesis of pyridazines **46** in one pot (Scheme 13).[41] The mechanism of the reaction starts with the SET between photoexcited palladium complex and alkyl halide or redox active ester to produce nucleophilic hybrid alkyl palladium radical **A**, capable of radical addition to hydrazone **44** producing the nitrogen-centered radical **B**. The latter, either upon direct oxidation or recombination (**C**) followed by β-hydride elimination, could yield alkylated diazene **D**, which under basic conditions is tautomerized to hydrazone **E**. Importantly, this product can be isolated exclusively as the *E*-isomer, which is highly challenging to access by other methods. When substrates containing a pendant leaving group are employed (**45**), nucleophilic substitution yields the desired pyridopyrazines **46** in moderate to high yields.



Scheme 13 Synthesis of *E*-hydrazones and pyridopyrazines

4.2 Light-Free Radical Heterocyclization

Metalloradicals can serve as radical carbene equivalents, thus providing an alternate reactivity trend to use in new reaction development. In 2018, Chattoppadhyay reported the cobalt porphyrin catalyzed denitrogenative transannulation reaction of pyridotriazoles and alkynes to produce indolizines.[42] More recently, Gevorgyan reported employment of pyridotriazoles **47** and isothiocyanates **48** or xanthate esters **49** to afford the corresponding thiazoloheterocycles **50** (Scheme 14).[43] The proposed reaction mechanism involves Co porphyrin metalloradical reaction with chain isomer **A** to produce upon denitrogenation an electrophilic α-Co(III)pyridyl radical **B**. The latter undergoes radical addition to either the isothiocyanate **48** or to the carbonyl sulfide **D**, a product of the *in situ* Chugaev elimination of xanthate ester, to produce radical intermediate **E**. Terminal radical cyclization regenerates the catalyst and yields reaction product **50**. Further developments of metalloradical chemistry toward heterocycle synthesis has been extensively reported and updated.[8c,5,32]



Scheme 14 Co-catalyzed transannulation of pyridotriazoles with isothiocyanates and xanthate esters

5 Conclusion

The discovery of denitrogenative transformations toward synthesis of heterocycles provided a new avenue toward monocyclic and fused heterocyclic scaffolds. This area has grown and evolved toward the end of the last decade to include radical approaches as versatile and complementary protocols, which inherently enable efficient transformations under room temperature and/or visible-light-induced conditions.

New methods for assembly of heterocycles have evolved into a vast and highly active area of research. Nonetheless, the remaining long-standing challenges still include the need for more general and mild transformations with improved atom economy, high regio-, enantio-, and diastereoselectivity, and employment of inexpensive catalysts.

Conflict of Interest

The authors declare no conflict of interest.

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