

Review

Nitrene-transfer from azides to isocyanides: Unveiling its versatility as a promising building block for the synthesis of bioactive heterocycles

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SUMMARY

Cross-coupling azide and isocyanide have recently gained recognition as ideal methods for efficiently synthesizing asymmetric carbodiimides. This reaction exhibits high reaction rates, efficiency, and favorable atom/step/redox economy. It enables the nitrene-transfer process, facilitating the formation of C-N bonds and providing a direct and cost-effective synthetic strategy for generating diverse carbodiimides. These carbodiimides are highly reactive compounds that can undergo *in-situ* transformations into various functional groups and organic compounds, including heterocycles. Developing one-pot and tandem processes in this field has significantly contributed to advancements in organic chemistry. Moreover, the demonstrated utility of these architectural motifs extends to areas such as chemical biology and medicinal chemistry, further highlighting their potential in various scientific applications.

INTRODUCTION

The nitrene-transfer reaction is of utmost importance for direct C-N bond formation or insertion of amine in various saturated and unsaturated structural frameworks for developing bioactive compounds.¹ The history of nitrenes is as old as carbenes. In 1891, Ferdinand Tiemann was the first to report the formation of nitrenes as intermediates in Lossen rearrangement.² From 1940 to the 1950s, when the click-type reaction was explored, nitrene addition to various bonds gained more attention for synthesizing amines or aziridines. Smith and Brown developed photochemical and thermal conditions for synthesizing carbazoles from azido biphenyls via cyclization.³ Other research groups led by Smolinsky,⁴ Edwards,⁵ Breslow,⁶ Lwowski,⁷ etc.,⁸ reported further advancements in this area. As nitrenes are highly reactive groups, the yield was a vital issue that was solved to some extent by Kwart and Kahn with their first-ever metal (Copper) catalyzed nitrene transfer reaction in 1967.⁹ This opened a new window for further exploration for critical players in this area.^{10–12} Building upon the historical foundations of nitrene chemistry, recent years have brought forth innovative approaches and catalytic processes, breathing new life into the field and expanding its applications.

The utility of the nitrene transfer reaction^{1,13,14} catalyzed by transition metals is well established for developing azaheterocycles. Transition metal (TM) catalysis occupies a central position in enabling the highly efficient *in situ* generation of nitrene species **A**, primarily derived from azides **B**.¹⁵ This catalytic approach facilitates a variety of noteworthy transformations, such as the formation of aziridines through their reaction with unsaturated bonds **C**, and the C-H insertion of nitrenes **D**, as illustrated in Figure 1.¹⁶ The coupling reaction between a nitrene **A** and CO **E** or an isocyanide **F** represents a beneficial approach to obtaining important synthetic intermediates, as depicted in Figure 1. The reaction of a nitrene with CO yields isocyanate **I**, considered a valuable building block in organic synthesis,^{17,18} Specifically, the reaction between a nitrene and an isocyanide leads to the formation of a carbodiimide **J**, which is widely recognized for its utility in synthesizing heterocycles and as a peptide coupling agent.^{19,20} Hence, the transfer of nitrenes to isocyanides is a promising foundation for developing novel cascade processes, capitalizing on the *in situ* formation of carbodiimides **J** as versatile building blocks. Apart from the nitrene transfer reactions, the chemist recently discovered a 'magical' technique to allow skeletal editing in the molecule. This method enables the chemist to move, insert, or replace a single atom at a time in the molecule's core. These reactions have recently emerged as a hot spot of research, which is used for late-stage skeletal modifications and streamlining the chemical synthesis.²¹ In recent work, Song and his group disclosed an unexpected synthesis of azepinone-based derivatives under metal-free conditions via a photochemical cascade reaction.²² The group was the first to explore 2-aryloxyarylnitrenes to synthesize unprotected carbazoles promoted by blue light.²³

Recently, much emphasis has been placed on forming C-N bonds via the nitrene transfer on the isocyanides toward generating carbodiimides (see the utility of carbodiimides in Figure 2). Compared to the traditional techniques available for synthesizing unsymmetrical carbodiimides, one that involves the nitrene transfer on isocyanides is popular and one of the most efficient alternatives for rapid, atom-economical, and efficient cross-coupling. These synthons are frequently used as precursors in organic synthesis and find an array of utilities in developing

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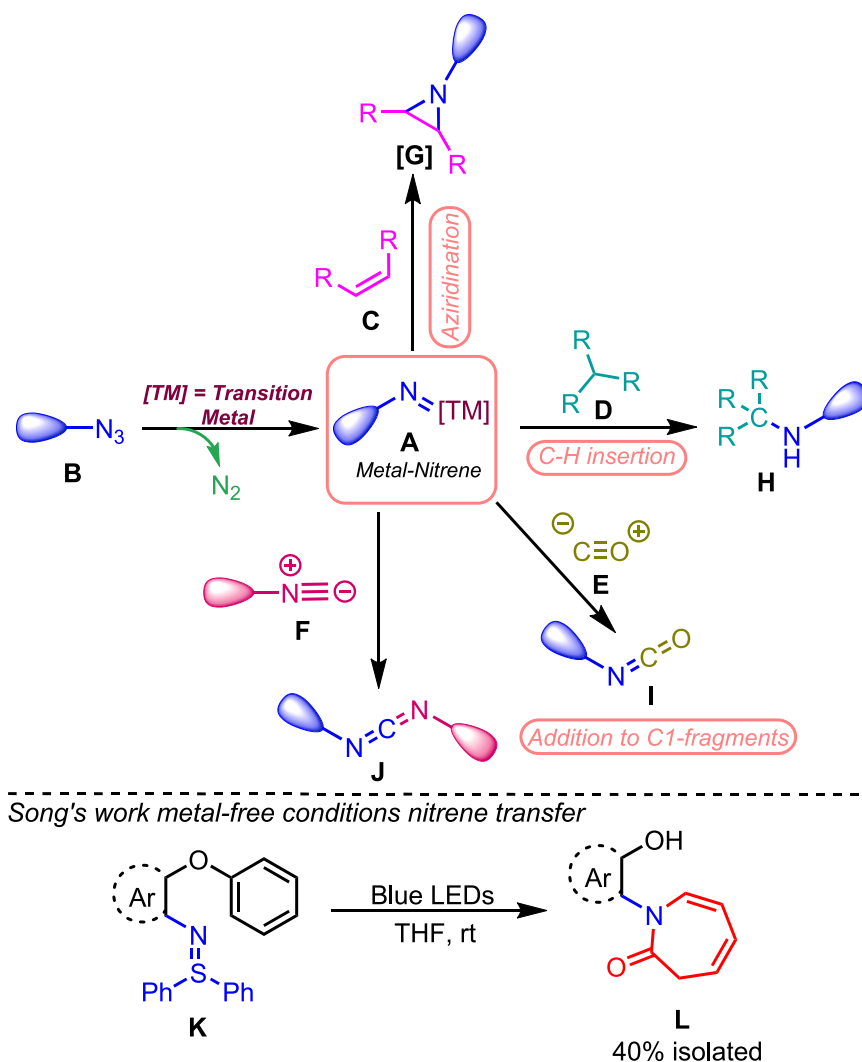


Figure 1. Overview of common transformations involving transition metal nitrene species

Nitrene transfer reactions play a crucial role in the development of azaheterocycles, with transition metal (TM) mediated catalysis being pivotal in their well-established mechanisms. The figure also highlights an exceptional case by Song et al., where they revealed an unexpected synthesis of azepinone-based derivatives. This synthesis occurred under metal-free conditions through a photochemical cascade reaction promoted by blue light, showcasing a unique instance in nitrene transfer reactions.

polymeric materials, drug synthesis, and the development of dyes and/or dehydrating agents. Xing et al. reported that chemo-selective nitrene transfers to complex natural molecules at a late stage.²⁴ The synthesis of Rapivab (BCX-1812 (RWJ-270201)), an approved anti-influenza drug, is one example that involves nitrene transfer in one of its multi-step synthetic protocols.²⁵

This review aims to delve into the significance of TMs in catalyzing nitrene-transfer reactions on isocyanides and their subsequent post-functionalization. The primary focus of this article is to offer comprehensive insights to medicinal and organic chemists regarding the transfer reaction on isocyanide, which results in the formation of diverse azaheterocycles incorporating alkynes, nitriles, alkenes, allenes, and isocyanides. This review article also covers synthetic and mechanistic applications associated with the described nitrene-transfer reactions. Examining these facets provides a valuable resource for researchers looking to explore the potential of these reactions in their work.

Stoichiometric reaction for nitrene-transfer reaction

During the late 20th century, researchers employed a range of TM complexes as catalysts in azide-isocyanide cross-coupling reactions to synthesize carbodiimides. In 2000, Royo utilized a tantalum imido complex [TaCp*Cl₂(N^tBu)] **1a** as a nitrene transfer agent, leading to the synthesis of carbodiimide **1c** (Scheme 1A) and proposing the formation of an intermediate three-membered metal-aziridine ring **1d**.²⁶ In 2002, Hillhouse utilized benzyl isocyanide **1f** and the Ni-imido complex **1e** to produce carbodiimide **1g** (Scheme 1B), suggesting a potential intermediate three-membered metal-aziridine **1h**.²⁷ Furthermore, in 2006, Warren and his team developed a protocol to generate asymmetric

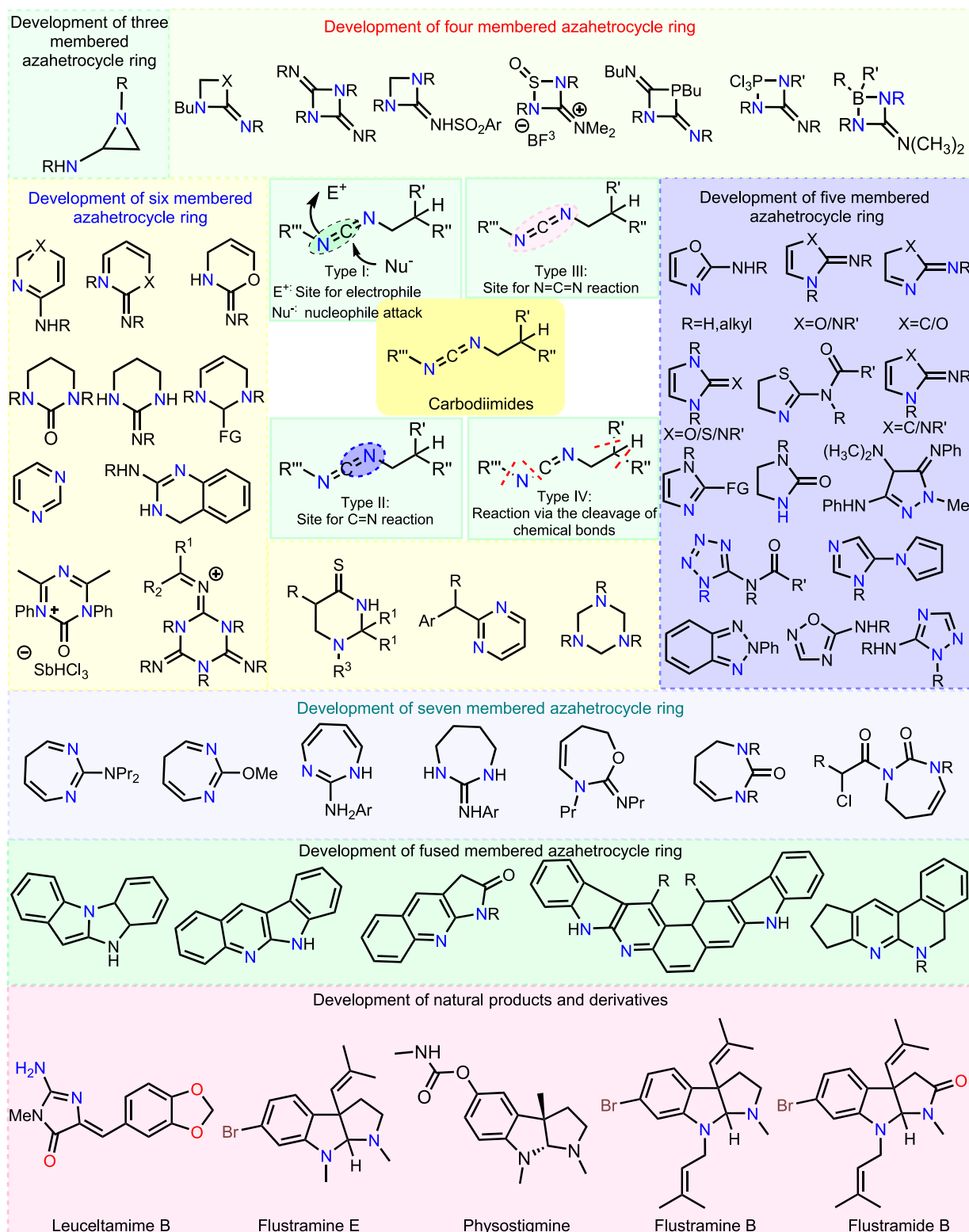
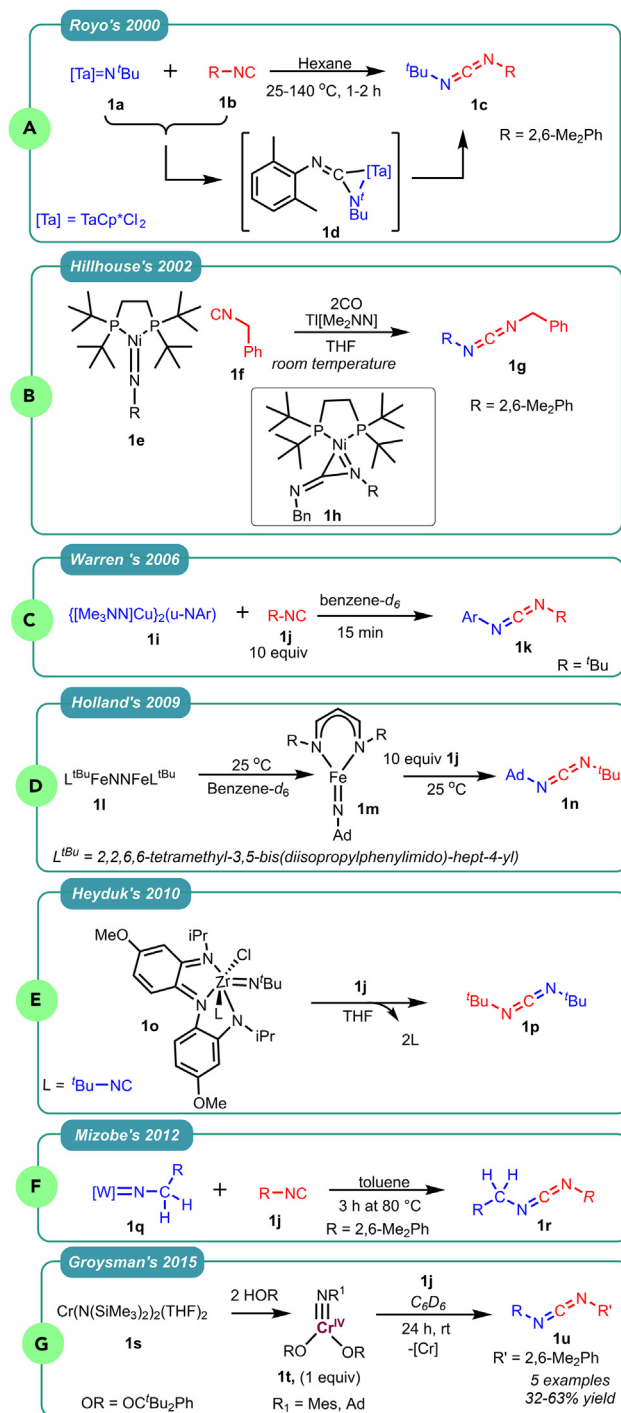


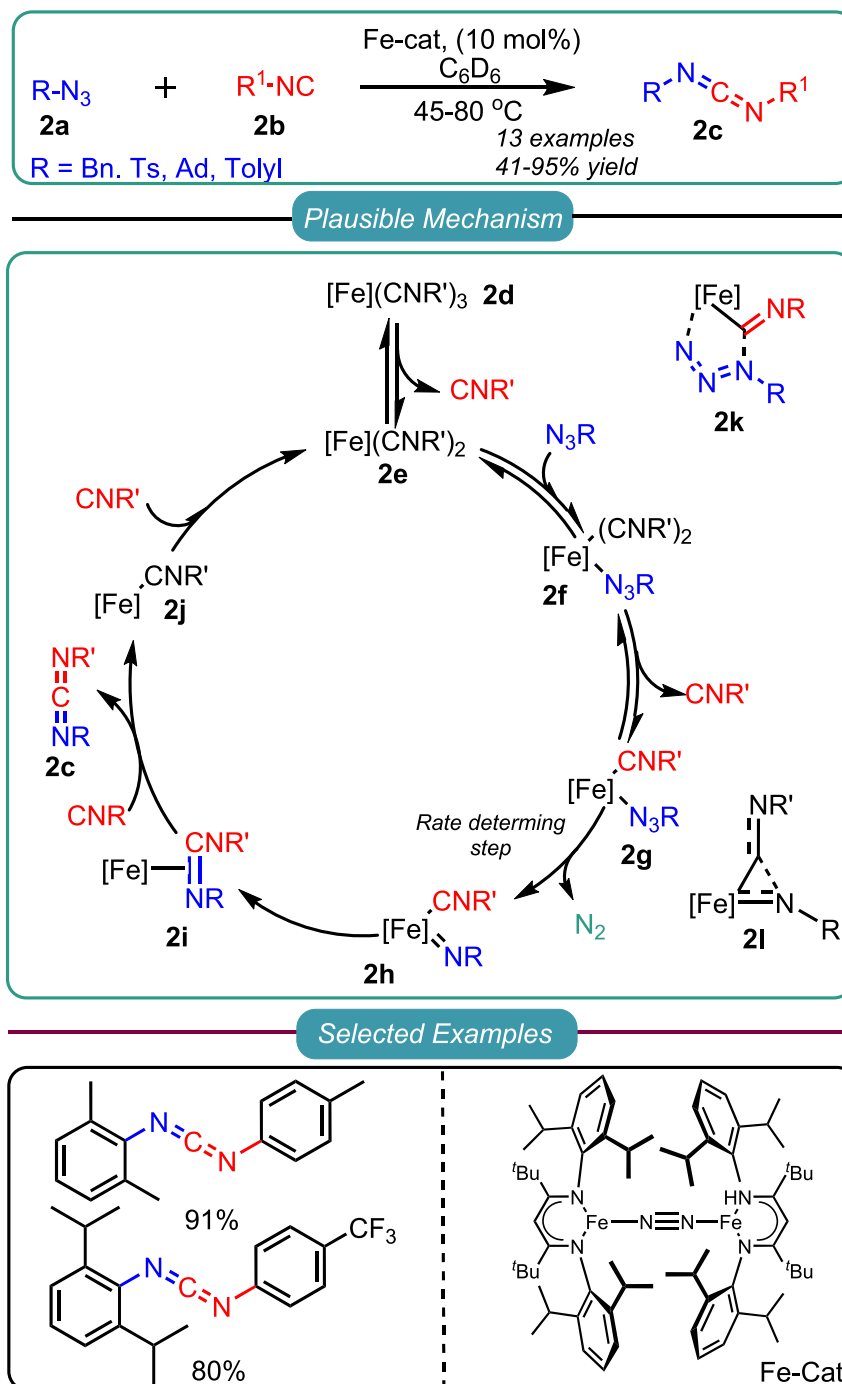
Figure 2. Reactive sites and utility of carbodiimides for the synthesis of diversified azaheterocycles

This comprehensive figure illustrates the reactive sites and synthetic utility of carbodiimides in the formation of diverse azaheterocycles, including semisynthetic analogues. This underscores their crucial importance, contributing to the expansion of chemical space for applications in organic synthesis, medicinal chemistry, and materials science.



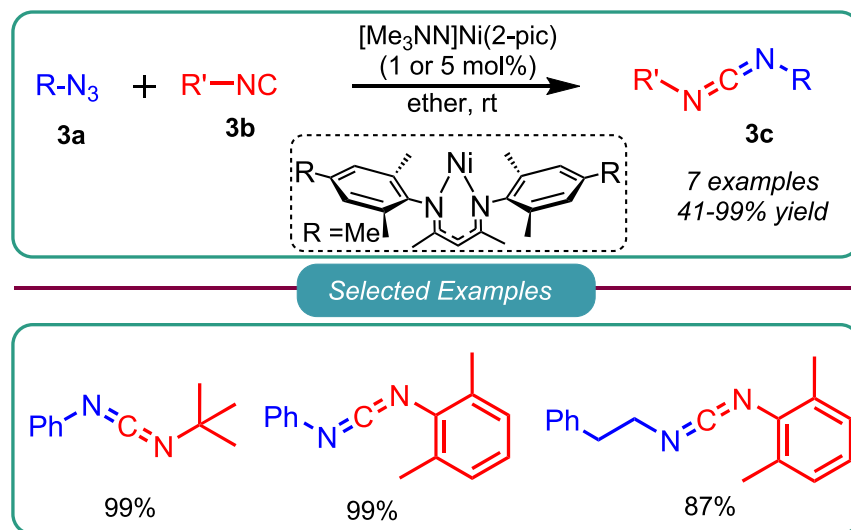
Scheme 1. Previous stoichiometric reaction for azide-isocyanide cross-coupling reaction

carbodiimides by reacting an organic azide with [Me₃NN]Cu₂(toluene) to form the dicopper nitrene [Me₃NN]Cu₂(-NAr) **1i**. They introduced CN^tBu **1j** and PMe₃ as reactants, producing carbodiimide **1k** via group transfer through aziridination (Scheme 1C).²⁸ In 2009, Holland reported the synthesis of carbodiimide **1n** through the stoichiometric reaction of isocyanide **1j** and imido-iron complex **1m** (Scheme 1D).²⁹ Similarly, in 2011, Heyduk demonstrated the nitrene-transfer catalyzed reaction of ^tbutyl isocyanide **1j** and zirconium imido complex **1o**, generated from ^tBuN₃ and [NNNCat]ZrCl₂ (L = THF), for the synthesis of symmetric carbodiimide **1p** (Scheme 1E).³⁰ In 2012, Mizobe investigated the isocyanide transfer reaction on low-valent center tungsten imido complexes **1q**. Treatment of the tungsten imido complexes with 2,6-dimethyl



Scheme 2. Holland's report on Fe-catalyzed cross-coupling reaction

phenyl isocyanide at 80°C yielded asymmetric carbodiimide **1r** in high yield (Scheme 1F).³¹ In 2015, Groysman et al. reported the nitrene transfer on isocyanides utilizing the Cr-imido complex **1t**. They explored the reactivity of trigonal-planar Cr(IV) mono-imido complexes formed by the reaction of Cr(N(SiMe₃)₂)₂(THF)₂ with azides bearing bulky substitution. These complexes reacted with various isocyanides, forming corresponding carbodiimides **1u** (Scheme 1G).³² It is important to note that all these studies involved the stoichiometric use of imido metal complexes, which limits their application in organic synthesis due to the high cost of metals. In some cases, an excess of isocyanide (up to 10 equivalents) was utilized.



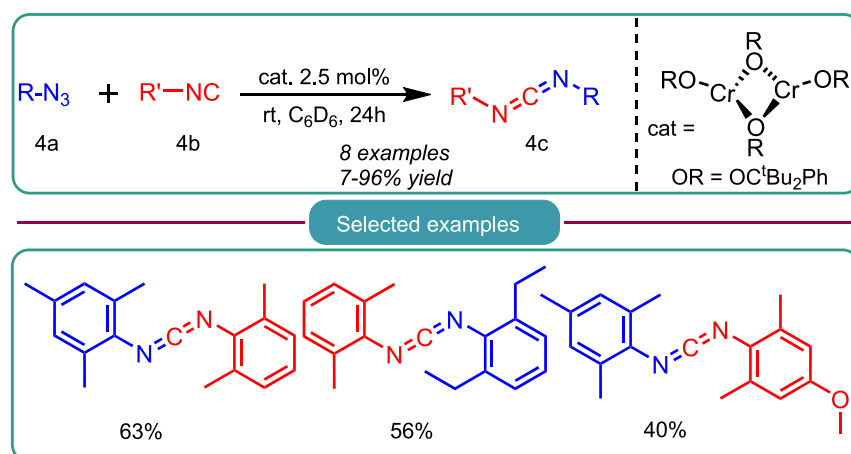
Scheme 3. Warren's work on Ni-catalyzed synthesis of asymmetric carbodiimides

EARLY REPORTS ON THE CATALYTIC REACTION FOR THE NITRENE-TO-ISOCYANIDE TRANSFER REACTION

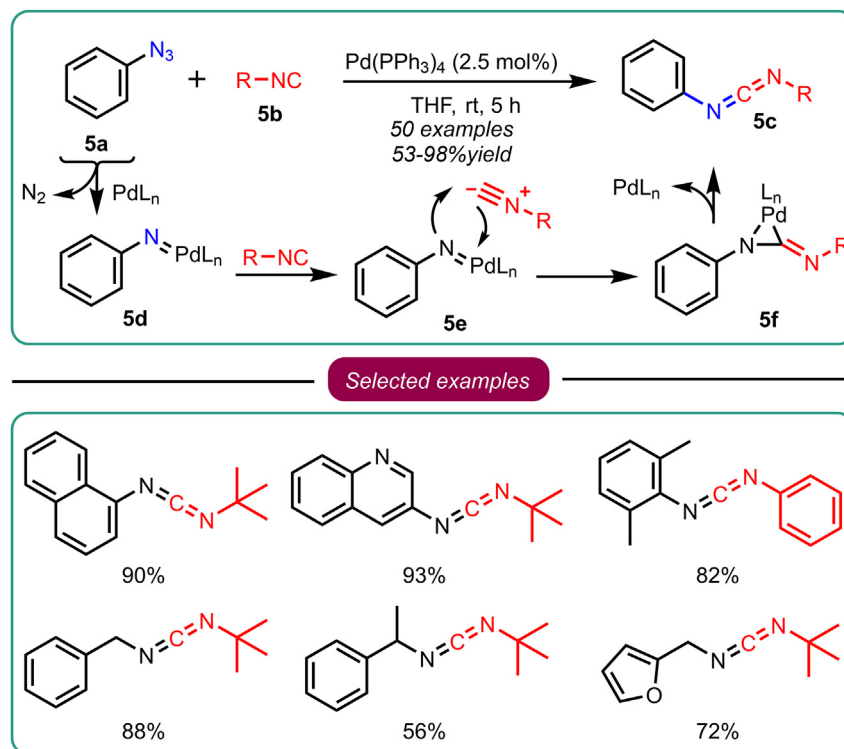
Drawing on their previous work on stoichiometric Fe-catalyzed reactions for carbodiimide synthesis, a catalytic version of the cross-coupling azide-isocyanide reaction has recently been developed. In 2013, Holland introduced a nitrene transfer approach on isocyanides using low-spin Fe(I) complexes with bulky β -diketiminato ligands to generate asymmetric carbodiimide **2c** from azides **2a** and isocyanides **2b** (Scheme 2).³³ Kinetic experiments revealed an inverse second-order dependence on the concentration of isocyanide, indicating the dissociation of two molecules before the rate-determining step. Based on these findings, a plausible mechanism was proposed and illustrated in Scheme 2. Initially, the Fe-complex coordinates with organoazides to form a coordination complex **2f**, which then interacts with isocyanide to generate complex **2g**. Subsequently, complex **2g** eliminates dinitrogen, forming imido iron complex **2h**, followed by nitrene transfer to yield carbodiimide **2c**. The author proposed the existence of two intermediate species, namely the 5-membered metallacyclic complex **2k** and the three-membered metallic-aziridine complex **2L**. However, no experimental or DFT studies were provided to support their presence.

In continuation of early attempts, Warren and the group developed a method for synthesizing asymmetric carbodiimide using a cross-coupling reaction catalyzed by Ni(I) in 2013.³⁴ Variety of aliphatic as well as aromatic azides **3a** were investigated with electron-rich partner isocyanides **3b** for their ability to produce high yields of corresponding asymmetric carbodiimides **3c**, few examples are shown in Scheme 3. However, aromatic isocyanides proceeded slowly and required a more extended period for the reaction.

In a parallel manner, a catalytic nitrene transfer reaction is employed to generate carbodiimide using the early TM chromium (Cr). Groysman et al. unveiled a low-coordination Cr(II) complex within this category. They investigated its reactivity in catalyzing nitrene transfer to isocyanide **4b** within a bis(alkoxide) ligand environment (as illustrated in Scheme 4).³⁵ Their research team explored the use of less bulky aryl



Scheme 4. Groysman's work on the Cr-catalyzed synthesis of carbodiimide



Scheme 5. Zhang's work on azide-isocyanide cross-coupling reactions for the generation of asymmetric carbodiimides

azides, which, however, did not lead to the formation of carbodiimides due to the absence of Cr(IV) imido, a crucial intermediate. Their research deduced that carbodiimide synthesis via nitrene transfer is feasible only in the presence of bulky aryl azides or aryl isocyanides. The reaction does not proceed when aliphatic azides and isocyanides (specifically, adamantyl) are employed to produce the desired carbodiimides 4c.

TRANSITION METAL CATALYZED AZIDE-ISOCYANIDE CROSS-COUPLING

Palladium-based reactions

In 2015, Zhang and the group disclosed for the first time that using palladium (0) at a catalytic amount could transform azide-isocyanide cross-coupling. This reaction was mediated via nitrene transfer, which allows the synthesis of asymmetric carbodiimides (Scheme 5).³⁶ The reaction involved aryl azide 5a and isocyanide 5b in THF as a solvent and Pd(PPh₃)₄ 2.5 mol % as a catalyst to accomplish the desired asymmetric carbodiimide 5c at room temperature in 5 h. The reaction diversity was further explored by employing different substrates that included aryl azides, inactivated benzyl, and alkyl, leading to the development of numerous asymmetric trisubstituted guanidines in a single pot with a tandem amine insertion. They proposed a 3-membered metallaziridine ring as an intermediate 5f in the nitrene transfer reaction. It is

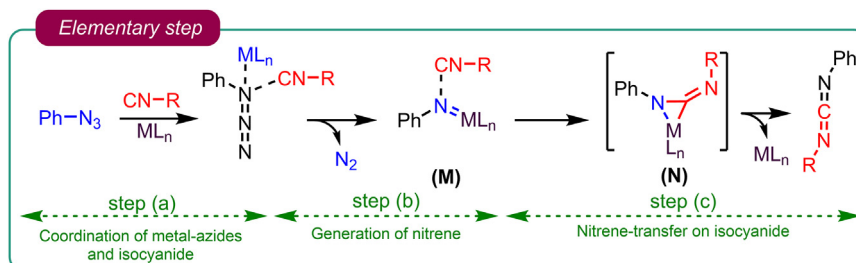
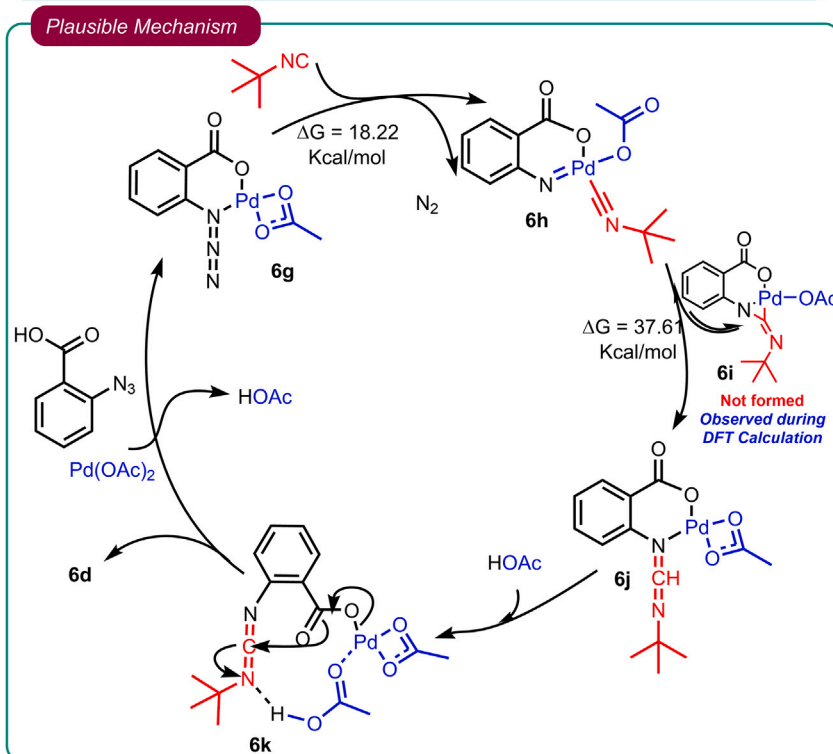
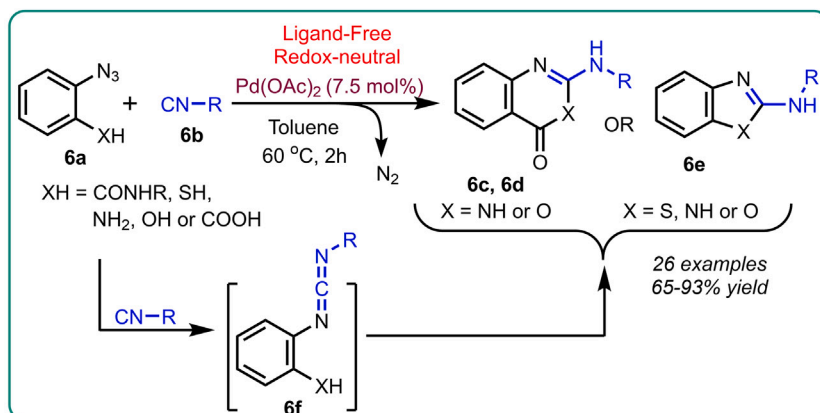


Figure 3. Elementary step involved in azide-isocyanide cross-couplings

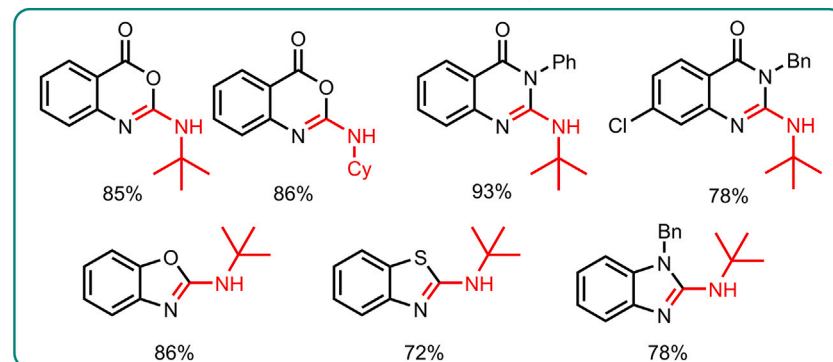
Step (a) Coordination of metal with azide and isocyanide: Involves the coordination of a metal species with azide and isocyanide molecules.

Step (b) Extrusion of dinitrogen to generate nitrenes: In this step, dinitrogen (N₂) is eliminated, leading to the formation of reactive species called nitrenes.

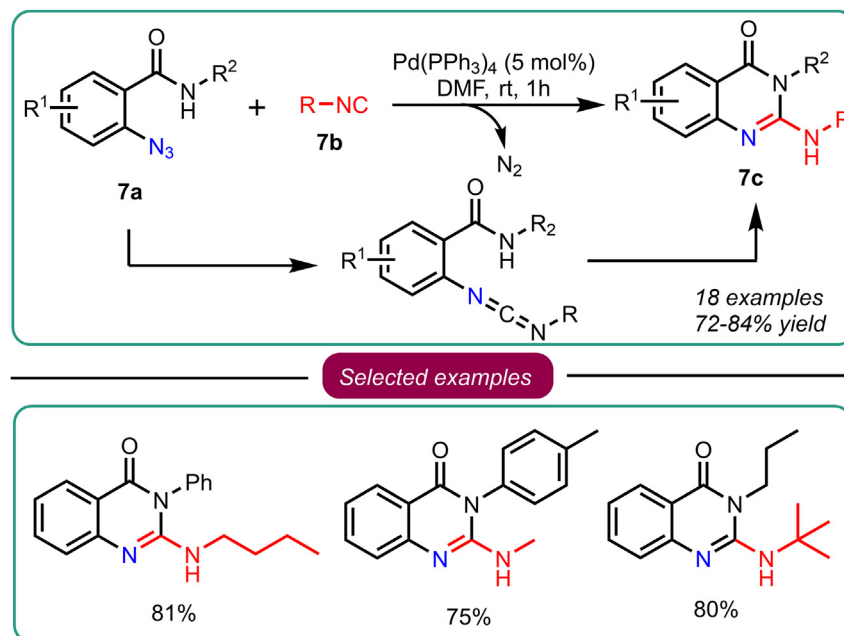
Step (c) Transfer of nitrenes onto isocyanides: Nitrenes, the reactive intermediates formed in the previous step, are transferred or react with isocyanide molecules to generate carbodiimide.



Selected examples



Scheme 6. Sawant's work on Pd-catalyzed azide-isocyanide cross-coupling reaction



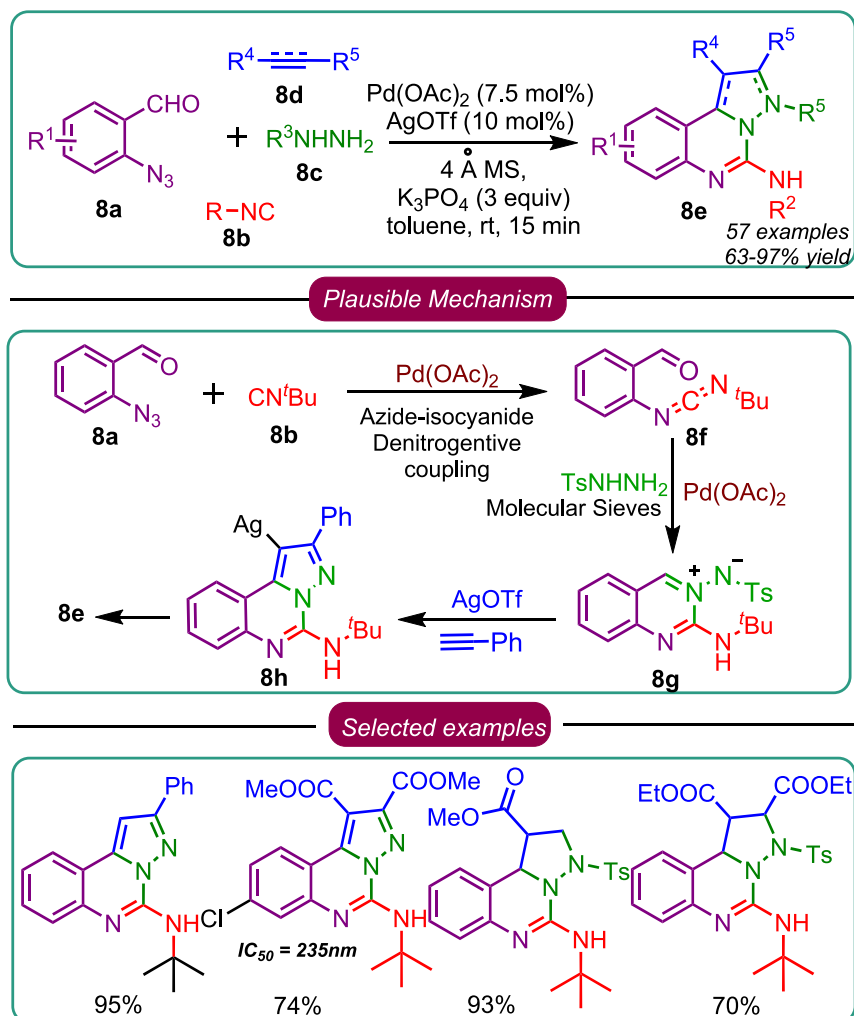
Scheme 7. Ding's work on one-pot Pd(0)-catalyzed domino synthesis of quinazolin-4(3H)-ones

important to note that most of these reports postulate the involvement of the metal nitrene-transfer reaction. However, none of these reports provided substantial evidence supporting this intermediate.

Building upon the groundwork laid by Zhang et al., Sawant et al. embarked on a comprehensive exploration of the azide-isocyanide cross-coupling reaction. Initially, they delved into deciphering the intricacies of this reaction by scrutinizing its fundamental steps. The investigation unveiled that this process unfolds through three pivotal stages: (1) the formation of a coordination complex between the metal and azide as well as isocyanide; (2) subsequent dinitrogen extrusion facilitating the generation of nitrenes; and (3) the transfer of these newly formed nitrenes onto the isocyanides (as illustrated in Figure 3). In a groundbreaking development, they devised a novel tandem Pd-catalyzed cross-coupling azide-isocyanide reaction and their post-cyclization to generate N-containing heterocycles.³⁷

Mechanistically, reaction conditions were optimized by attempting cross-coupling reactions of azide **6a** and isocyanide **6b** under various solvents, catalysts, and temperatures (Scheme 6). The optimization studies suggested the reaction proceeds with significantly high yields under the catalytic influence of Pd(OAc)₂ with toluene as a solvent and a temperature of 60°C. The reaction was diversified and tolerable for numerous substrates that could react with the azide and isocyanide, leading to the development of different azaheterocycles. This includes benzoxazinones **6c**, quinazolinones **6d**, and benzazoles **6e**. Moreover, the established protocol was efficient, rapid, ligand-free, devoid of the prerequisite of a dry condition, and obeyed all the atom/step/redox economy principles. This research concluded that the transfer of nitrene on isocyanide follows a concerted reaction path rather than a sequential one. The research team also disapproved of the formation of metallaziridine **6i** as an intermediate during the reaction. A series of control experiments and first-principles-based quantum mechanical calculations were carried out to investigate the reaction mechanism. Based on these studies, the proposed catalytic cycle of the tandem reaction commences with the coordination of Pd(OAc)₂ with 2-azidobenzoic acid **6a**, yielding compound **6g**. In the subsequent step, the conversion of **6g** into the Pd-imido intermediate **6h** occurs, where nitrogen elimination is associated with a Gibbs free energy barrier of 18.22 kcal/mol. Furthermore, chemical kinetic investigations of the tandem cross-coupling/cyclization reaction have revealed that Pd(OAc)₂ and *tert*-butyl isocyanide exhibit first-order kinetics, indicating their participation in the turnover-limiting step. First-principles-based calculations have predicted that the intermolecular nitrene-transfer reaction progresses through a three-membered transition state with an energy barrier of 37.61 kcal/mol. Carbodiimide was exclusively observed instead of the expected palladaaziridine **6i**, a surprising outcome contrary to expectations. The intrinsic reaction coordinates (IRC) and potential energy surface (PES) scan demonstrated that the metalla-aziridine intermediate **6i** is not stable; instead, a concerted path leads to the formation of **6j** without the intermediacy of **6i**. Despite a substantial energy barrier of 37.61 kcal/mol, the exceptionally high thermodynamic stability drives the nitrene-transfer reaction, making it the rate-determining step (RDS). Thus, the tandem reaction described in this study is governed by thermodynamics. In the subsequent step, acetic acid coordinates with Pd to form compound **6k**. This coordination event ejects carbodiimide from its interaction with the metal, bringing carbodiimide closer to the carboxylate of benzoate. Consequently, a 6-*exo*-dig cyclization of the carboxylate onto carbodiimide occurs, forming the thermodynamically stable product **6d** (accompanied by a favorable energy change of 23.27 kcal/mol). These mechanistic discoveries are pivotal, as the intermediate has been identified as a potent synthon for synthesizing numerous bioactive heterocycles through azide-isocyanide coupling reactions.

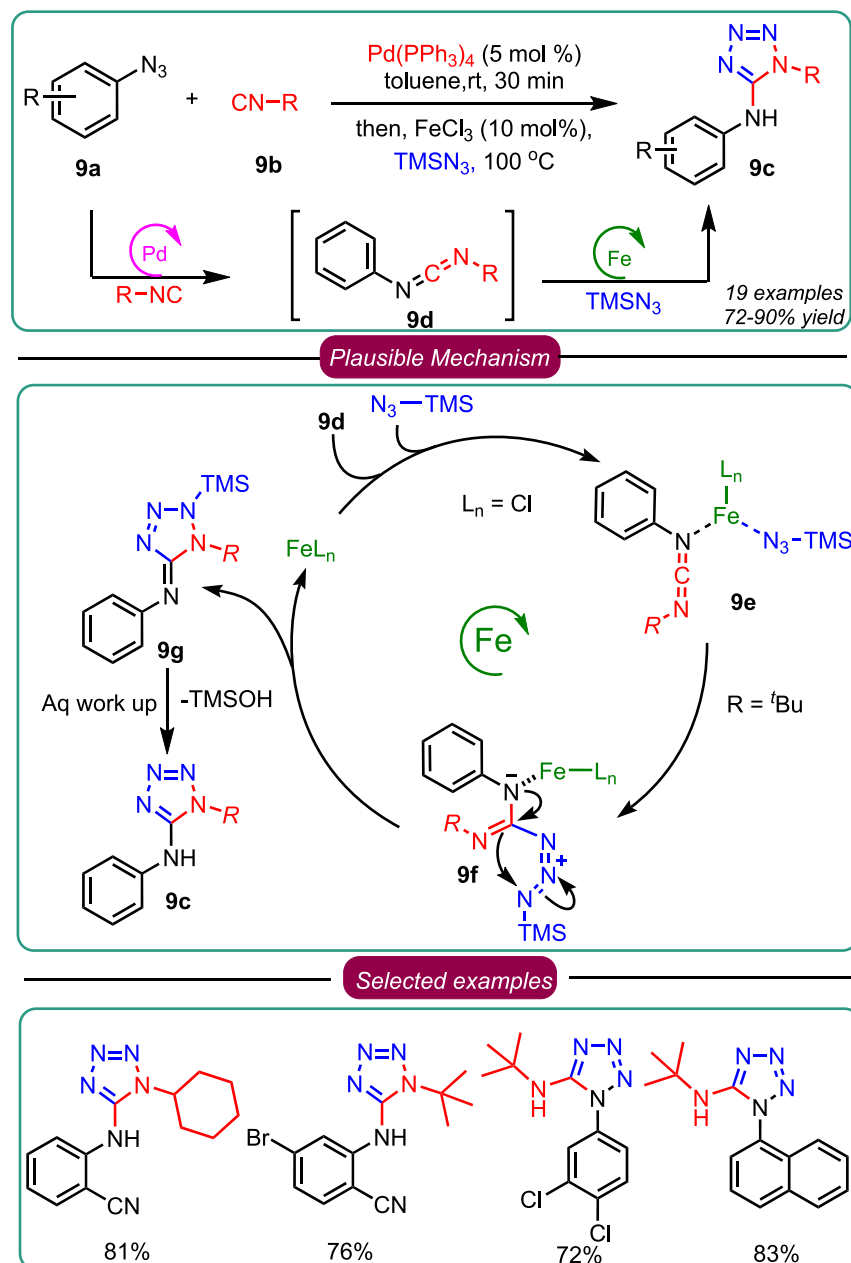
Similarly, in 2018, Ding's group reported a one-pot Pd-catalyzed domino reaction for synthesizing quinazolin-4(3H)-ones (Scheme 7).³⁸ The reaction involved Pd-catalyzed cross-coupling of 2-azidobenzamides **7a** with isocyanides **7b** at ambient temperature. The resulting coupled



Scheme 8. Sawant's work on 4-CR based on nitrene transfer on isocyanide

intermediate underwent carbodiimide-mediated cyclization, forming quinazolin-4(3H)-ones **7c**. The researchers extended their methodology to synthesize benzoimidazo[2,1-*b*]quinazolin-12(6H)-ones by employing similar reaction conditions with Cs₂CO₃ as the base and a reaction temperature of 90°C. This innovative approach offers a convenient and efficient strategy for accessing quinazolin-4(3H)-ones and benzoimidazo[2,1-*b*]quinazolin-12(6H)-ones, demonstrating the versatility of Pd-catalyzed domino reactions in the synthesis of complex heterocyclic structures.

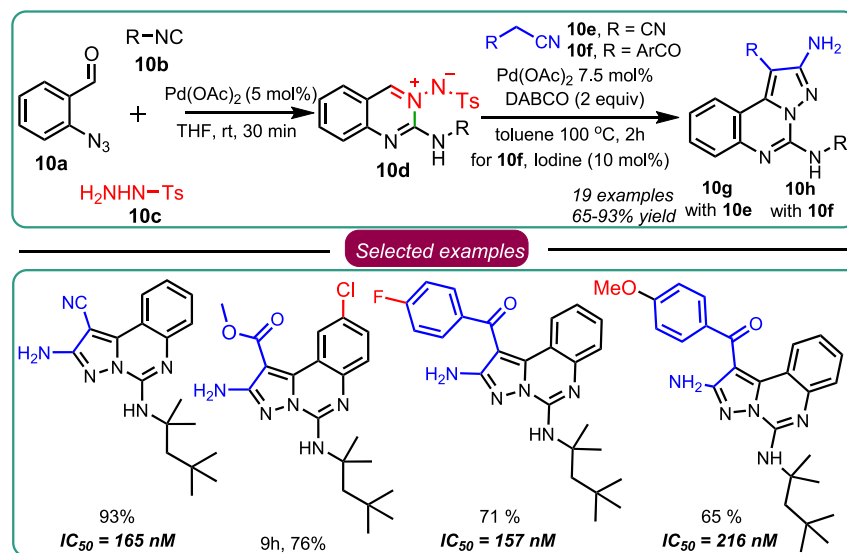
Motivated by the study, as mentioned earlier, Sawant's research group investigated the rate-determining step of nitrene transfer on isocyanide. To gain a deeper understanding, a relay catalysis strategy was employed, utilizing Pd(II)/Ag(I) as the relay catalyst. The reaction was conducted in a one-pot tricyclic mode, forming pyrazolo[1,5-*c*]quinazolines **8e** (Scheme 8). A remarkable feature of this reaction was the development of 5 new chemical bonds from the readily available precursors. The findings unveiled that the initiation of the reaction involved the azide-isocyanide cross-coupling, which generates carbodiimide **8f**. Subsequently, the condensation of tosyl hydrazide **8c** led to the formation of azomethine imine **8g**, which underwent a base-mediated direct alkylation to give rise to **8e**.³⁹ Further exploration of the substrate scope of this 4-component reaction (4-CR) revealed its extensive applicability. Alkynes, alkenes, and electron-deficient alkenes such as acrylates and acrylonitrile exhibited excellent compatibility, affording the desired product **8e** with high yields. Remarkably, the substrate scope study demonstrated the high tolerance of both electronic and steric effects, facilitating the generation of the desired products. Notably, the reaction displayed a single diastereomer in the case of alkynes, and high regioselectivity was observed across all substrates. Biological investigations on the synthesized pyrazolo[1,5-*c*]quinazolines were conducted. Compound **8e** exhibited potent inhibitory activity against kinase EGFR inhibitory activity (IC₅₀ = 235 nM) and displayed significant anticancer potential, as shown in the representative substrate scope. Furthermore, exploring the substrate scope led to the discovery that one of the molecules exhibited twice the potency of the existing drug, erlotinib. This comprehensive study showcases the significance of the developed 4-component reaction and highlights its potential for synthesizing diverse pyrazolo[1,5-*c*]quinazolines with notable biological activities.



Scheme 9. Sawant's works on 3-CR for the synthesis of amino tetrazole

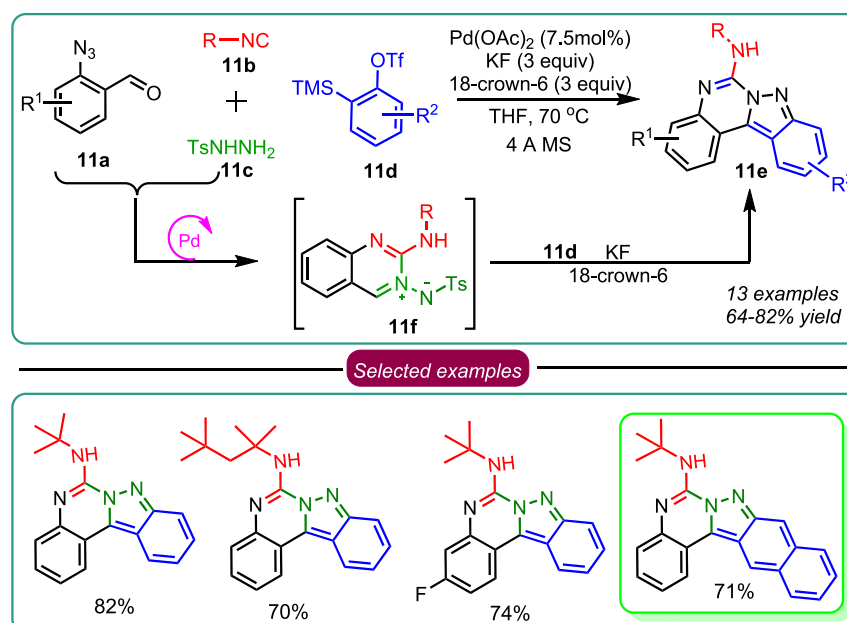
In a similar interest, Sawant's group, in the year 2018, disclosed the rapid and efficient synthesis of amino tetrazole from 3-CR. The reaction involved sequential dual Pd(0)/Fe(III) catalyzed 3-CR of aryl azides **9a**, isocyanides **9b**, and TMSN_3 in generating amino tetrazole **9c** (Scheme 9).⁴⁰ The optimization study revealed that toluene is the best solvent, and Pd and Fe are the most efficient catalysts to produce the desired product. Based on control experiments, a plausible mechanism was depicted (Scheme 9). The cycle portrays that the transformation involves the development of *in-situ* asymmetric carbodiimide via cross-coupling of azide-isocyanide denitrogenative coupling reactions catalyzed by Pd. Next, in the presence of FeCl_3 , intermediate **9d** reacts with TMSN_3 in a single pot to generate **9e** in good to excellent yield. This reaction's scope (Scheme 9) disclosed that wider varieties of aryl azide derivatives and a range of isocyanides **9b** were tolerated well to yield the related 5-amino-1H-tetrazoles **9c**. The limitation of this methodology was that aryl isocyanide failed to form a cross-coupled product with aromatic azides. Nevertheless, this methodology has tremendous potential over traditional synthetic approaches and is practical and scalable.

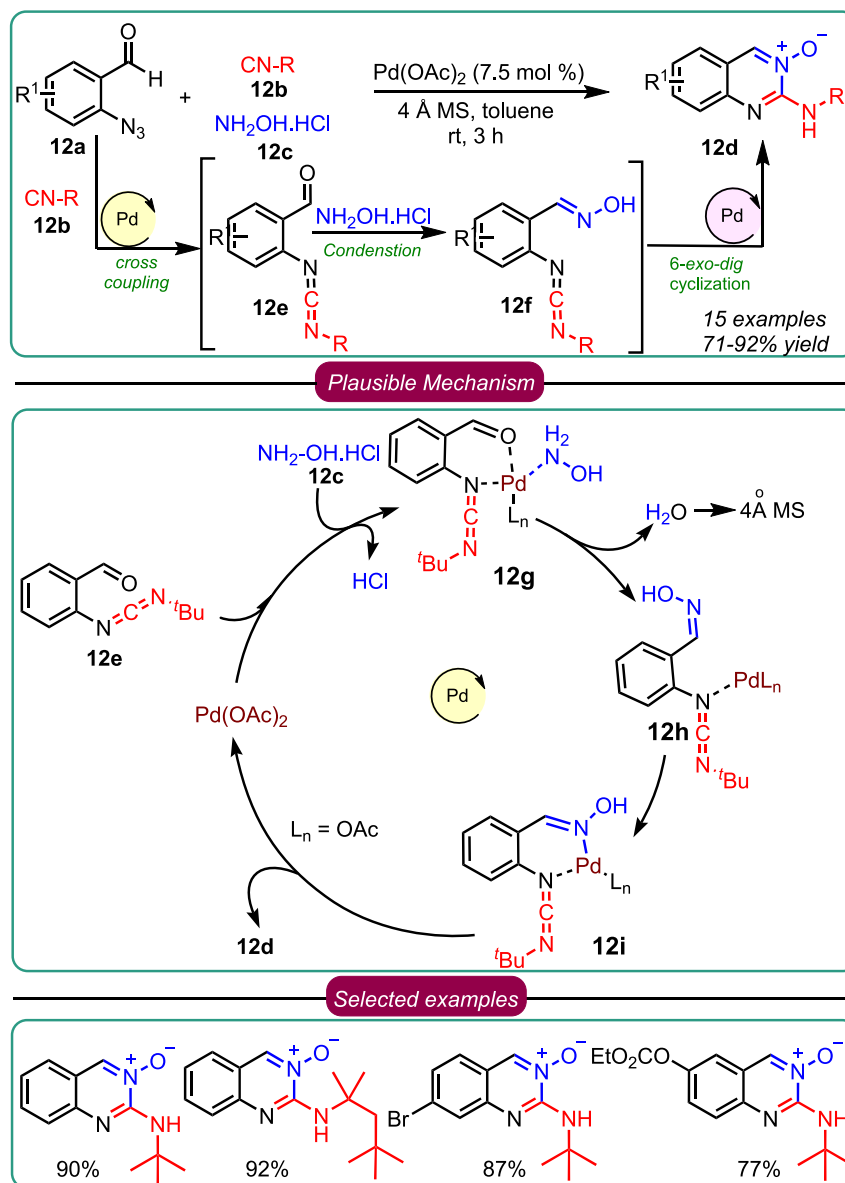
Coming ahead in exploring the competency of established 4-CR presented in Scheme 8, Sawant's research team developed nitrene-transfer reaction-based 4-CR to synthesize pyrazolo[1,5-c]quinazoline as a bioactive scaffold. The reaction was accomplished under the catalytic



influence of Pd with the most readily available starting materials, including 2-azidobenzaldehyde **10a**, isocyanide **10b**, aryl sulphonyl hydrazide **10c**, and acetonitrile **10e**, **10f**. During the reaction, they found that the desired product was not obtained upon the reaction of β -ketonitrile under optimal conditions. Further, they developed one-pot 4-CR, which typically involves the reaction of the *in situ*-produced azomethine imine **10d** and reacted with the acetonitrile derivative **10g/10h** (Scheme 10).⁴¹ All the developed molecules were explored for their anti-cancer assets. Among the synthesized leads, two molecules exhibited potent anticancer potential compared to standard kinase inhibitors (erlotinib and gefitinib) and were mechanistically found to inhibit EGFR-mediated kinase activity. The active molecules were found devoid of cardiac cell damage, a common drawback of approved EGFR inhibitors. In a nutshell, the presence of an amino group on the pyrazole ring of pyrazolo [1,5-c]quinazolines made them potent and safe inhibitors of EGFR. The present study validated the Schreiber hypothesis that chemical spacing on small molecules is vital in guiding drug discovery and development.

Next, a library of indazolo[2,3-c]quinazolines was synthesized using Pd-catalyzed single-pot sequential 4-CR based on the foundation and concept laid by previous 4-CR research. Five chemical bonds were formed during the sequential reaction of 2-azido benzaldehyde **11a**,

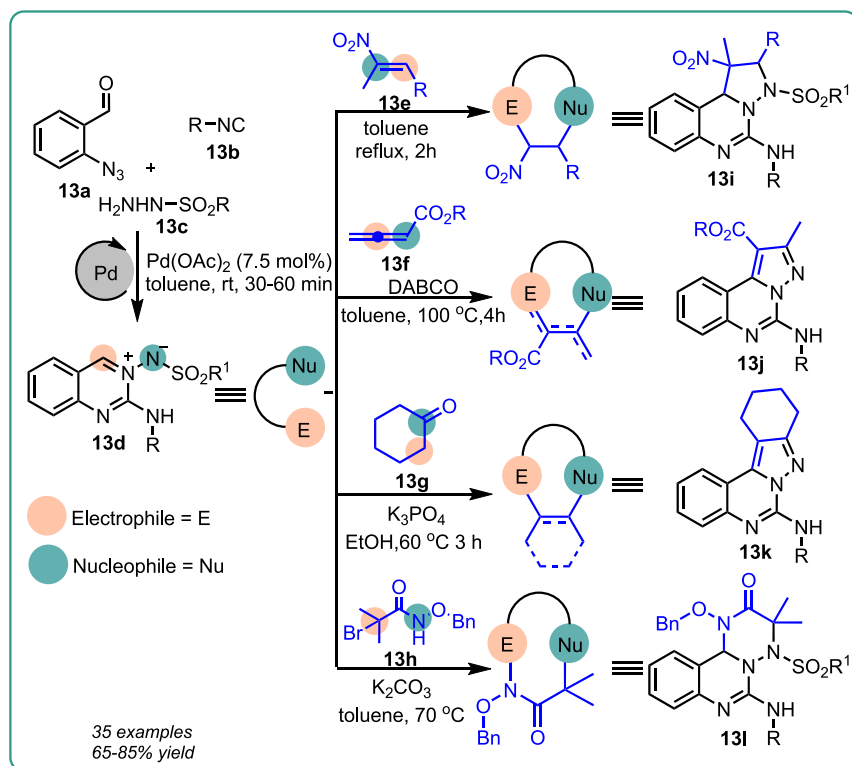




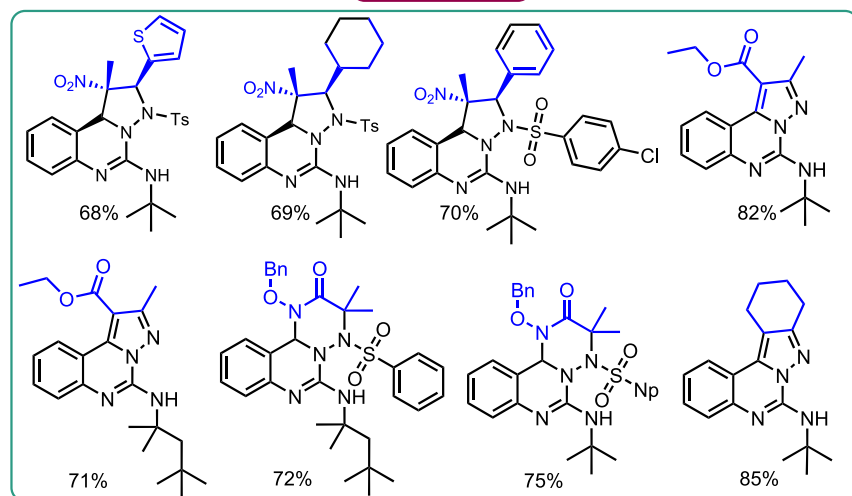
Scheme 12. Sawant's work on 3-CR for synthesizing quinazoline 3-oxides

isocyanide **11b**, aryl sulphonyl hydrazide **11c**, and aryne precursor **11d**, which also involved the concatenation of three simple steps (Scheme 11).⁴² Green fluorescence was produced under visible light by the synthesized derivative **11e**, with a quantum yield of 68%. The compound also exhibited good Stokes shifts of up to 2796 cm^{-1} in CHCl_3 and excellent photostability in DMSO for 30 min. The green dye developed produced a fluorescent effect in cancer cell mitochondria and cytoplasm with superior photo-stability and negligible cytotoxicity. The simplicity with which indazolo[2,3-*c*]quinazolines **11e** have been made available here is a fine example of the great appeal of multicomponent reactions and presents a chance for high-throughput, modulated screening for particular functional molecules.

Subsequently, in 2019, the Sawant group embarked on an expedition to develop diversely functionalized quinazoline 3-oxides **12d** (Scheme 12) through a novel synthetic process involving 2-azido benzaldehydes **12a**, isocyanides **12b**, and hydroxylamine hydrochloride **12c** in a one-pot three-component reaction.⁴³ The reaction was catalyzed by Pd(II) and facilitated the formation of three new chemical bonds in a regioselective manner. They further explored the versatility of this reaction by varying the substrates and employing different reaction conditions. The reaction exhibited a broad substrate scope and excellent tolerance toward many functional groups, enabling the synthesis of desired products in shorter reaction times with good yields. Mechanistic investigations shed light on the reaction pathways. It was found that the reaction proceeded through three major individual pathways. First, denitrogenative coupling of azide derivatives with the isocyanide occurred, followed by condensation with hydroxylamine to produce complex **12g**. Lastly, **12h** catalyzed by Pd(II), cyclization occurred in a 6-



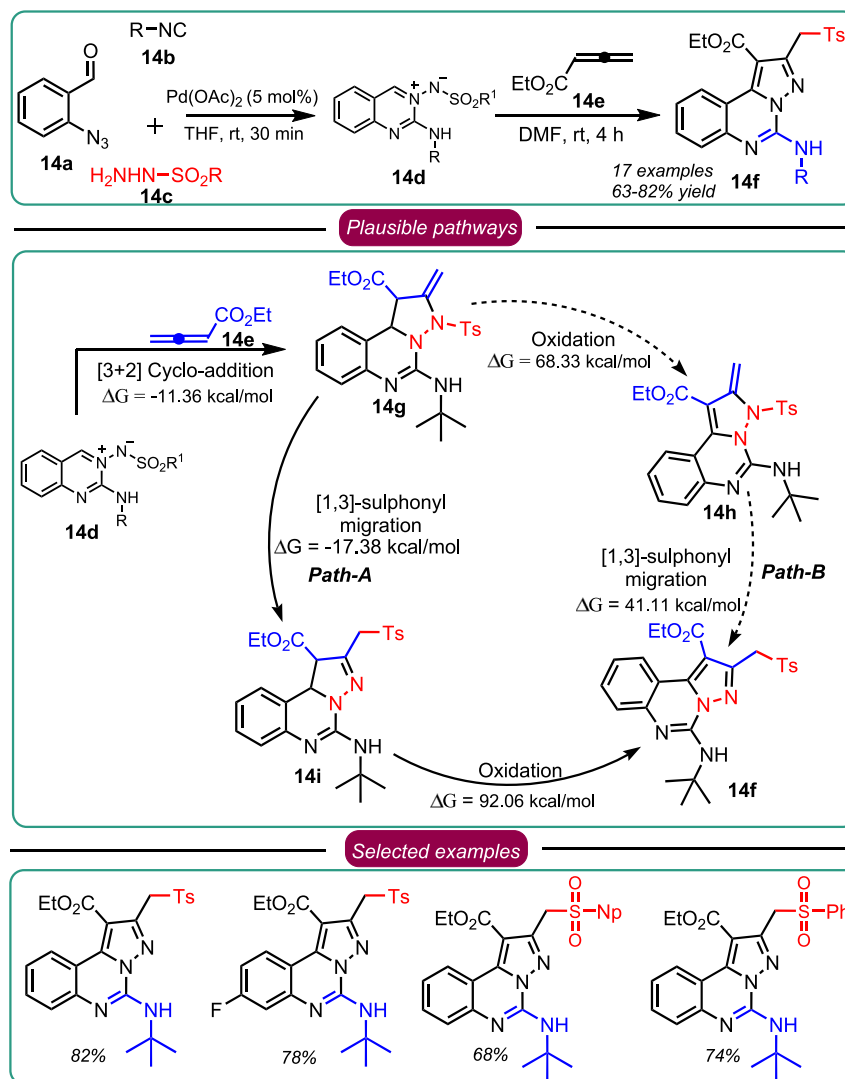
Selected examples



Scheme 13. Sawant's work on diversity-oriented synthesis based on 4-CR using different dipolarophiles to generate complex poly-heterocycles

exo-dig manner with hydrazones on the carbodiimide scaffold, which generated the desired quinazoline 3-oxides. This innovative approach provided the utility for a one-pot, three-component reaction via auto-tandem Pd(II) catalysis, offering a novel method to access quinazoline 3-oxides **12d** from readily available substrates with high efficiency and a simple protocol.

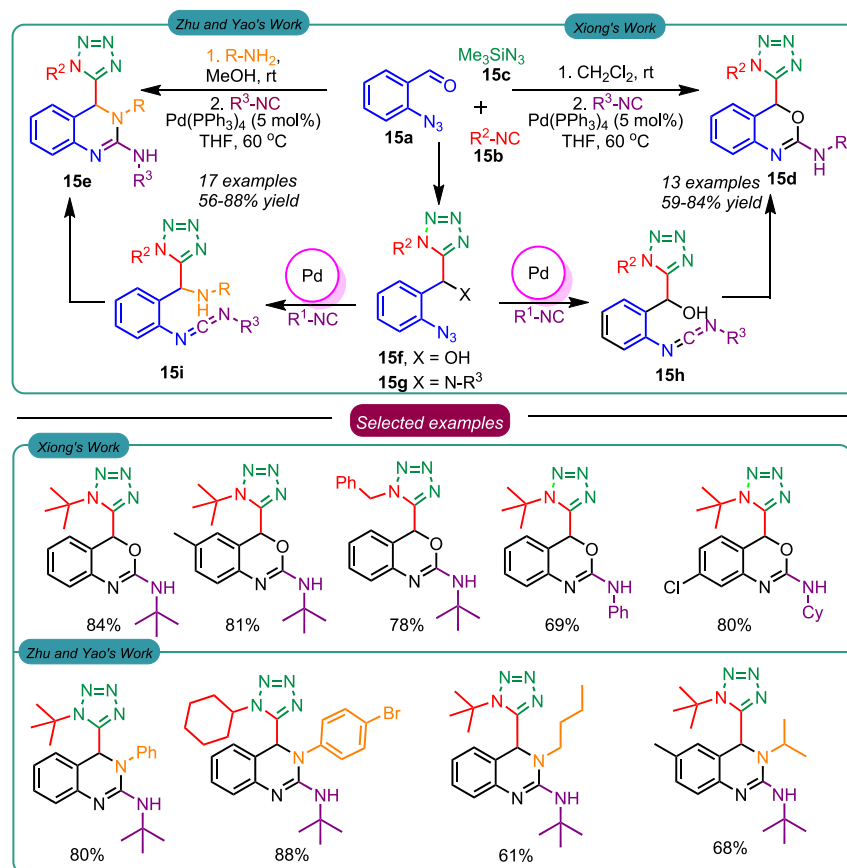
A comprehensive literature search uncovered the significance of azomethine imine as a versatile building block for synthesizing poly-heterocycles. Motivated by this, Sawant's research group developed a one-pot, three-component reaction for synthesizing azomethine imines, employing an auto-tandem Pd(II) catalysis approach (Scheme 13).⁴⁴ Encouraged by this result, they envisaged that skeletally diverse compound collections could be generated from the azomethine imine. Incorporating various dipolarophiles through diversity-oriented synthesis enables the generation of a skeletally diverse molecule, facilitating the synthesis of complex heterocycles with potential medicinal applications. To initiate this endeavor, they focused on creating a compound collection centered around azomethine imine. The group accomplished this by reacting 2-azido benzaldehyde **13a**, alkyl isocyanide **13b**, and aryl sulfonyl hydrazide **13c** in toluene as the solvent. Pd(OAc)₂ was the



Scheme 14. Sawant et al., work on the synthesis of unprecedented [1,3]-sulfonyl migration

catalyst, while 4 Å molecular sieves were employed. The reaction mixture was stirred at room temperature for 30 min, forming azomethine imine **13d** in good to excellent yields. Further, azomethine imine **13d** was reacted with reagents possessing orthogonal functionality such as nitroolefins, allenates, cyclic ketone, and α -halo hydroxamates **13e-13h** to produce diverse and complex molecules **13i-13l** respectively (Scheme 13). Incorporating various dipolarophiles into the skeleton of a molecule through diversity-oriented synthesis was found beneficial in the production of complex heterocycles for medicinal use. The optimal 4-CR protocol facilitated a significant degree of step/atom economy. Excellent regio- and stereoselectivity, as well as functional group tolerance, were observed in the reaction. A collection of compounds with diverse and intricate molecular architectures could play a crucial role in future drug discovery and development.

Based on dedicated research efforts, Sawant et al. revealed a novel one-pot synthesis of aryl sulfonyl methyl-substituted pyrazolo[1,5-*c*]quinazolines **14f** from azomethine imine **14d** and allenate **14e**. Mechanistic investigations have uncovered an unexpected regioselective sulfonyl migration during the cycloaddition of N-sulfonyl azomethine imine **14d** with allenates **14e**, leading to the formation of compound **14f** (Scheme 14).⁴⁵ 1,3-sulfonyl migration was further explored using DFT studies in addition to the controlled experiments. The coupling reaction involves oxidative aromatization, which is thermodynamically favored and concerned with the lower activation energy. Energy-wise, mechanistic research indicates that the transition from **14d** to **14f** is highly favorable and may occur via two pathways: (1) [1,3]-sulfonyl migration followed by oxidation (Path-A) and (2) oxidation followed by [1,3]-sulfonyl migration (Path-B). [1,3]-Sulfonyl migration can be considered a [1,3]-sigmatropic shift. The first pathway includes a concerted [1,3]-sigmatropic shift, allowing the sulfonyl migration with a shallow energy barrier accomplished by a diminished steric cloud in the second step. In controlled experiments, detosylated compound **13j** was isolated as a significant product when toluene was used as a solvent. Along Path-B, the oxidation step and migration of ArSO₂ occur with an energy



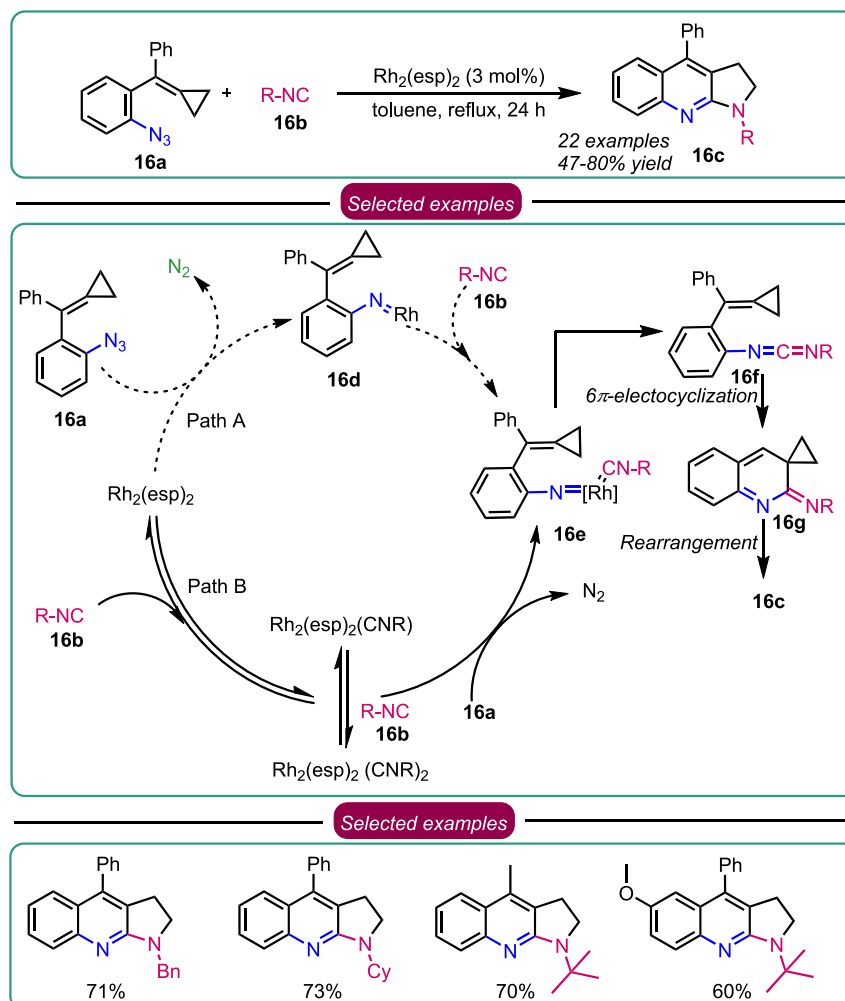
Scheme 15. Azide-isocyanide cross-coupling reaction-based synthesis of tetrazole-containing heterocyclic scaffolds

gain of 68.3 and 41.1 kcal/mol respectively. This is a spontaneous process, as the transition state for the migration could not be traced along the reaction path. Path-B is probably more favorable because it involves two barrierless reactions, whereas Path-A involves activation energy in the [1,3]-sulfonyl migration step. In a nutshell, DMF was the best solvent for conversion, completely suppressing the side product **13j** formation. Thus, it was concluded that an optimized methodology with high product yields could be achieved by stirring the mixture of **14d** and **14e** in DMF for 4 h at room temperature. The findings thus opened up new avenues for forecasting [1–3]-sulfonyl migration involving two or more components, leading to the synthesis of diverse bioactive compounds.

In 2020, Xiong et al. presented their work on the synthesis of 4H-3,1-benzoxazine derivatives using a sequential one-pot, a three-component reaction catalyzed by Pd.⁴⁶ Initially, the passerine-azide adduct **15f** was formed through a three-component reaction involving 2-azidobenzaldehydes **15a**, trimethylsilyl azide **15c**, and isocyanides **15b**. Subsequently, the passerine-azide adduct **15f** underwent a tandem palladium-catalyzed transformation to generate the carbodiimide intermediate **15h** through an azide-isocyanide cross-coupling process. The **15h** was further found to undergo cyclization via 6-exo-dig cyclization (Scheme 15) to afford the desired 4H-3,1-benzoxazine derivatives **15d**. In a similar context, Zhu and Yao et al. in 2022 developed the synthetic access route to develop 4-tetrazolyl-3,4-dihydroquinazolines **15e** catalyzed by the Pd in one-pot sequential reaction that included the cross-coupling of Ugi-azide with the isocyanide.⁴⁷ In this Ugi-azide reaction, 4 reactants were involved, including 2-azidobenzaldehydes **15a**, amines, trimethylsilyl azide **15c**, and isocyanides **15b** that yielded the azide-Ugi adduct **15g**. Upon reaction with isocyanides, the adduct yielded 4-tetrazolyl-3,4-dihydroquinazoline derivatives **15e** (Scheme 15). The derivative of the **15e** series was found to possess anticancer potential against breast cancer cells and may possess numerous applications in anticancer drug discovery.

Rhodium-based reaction

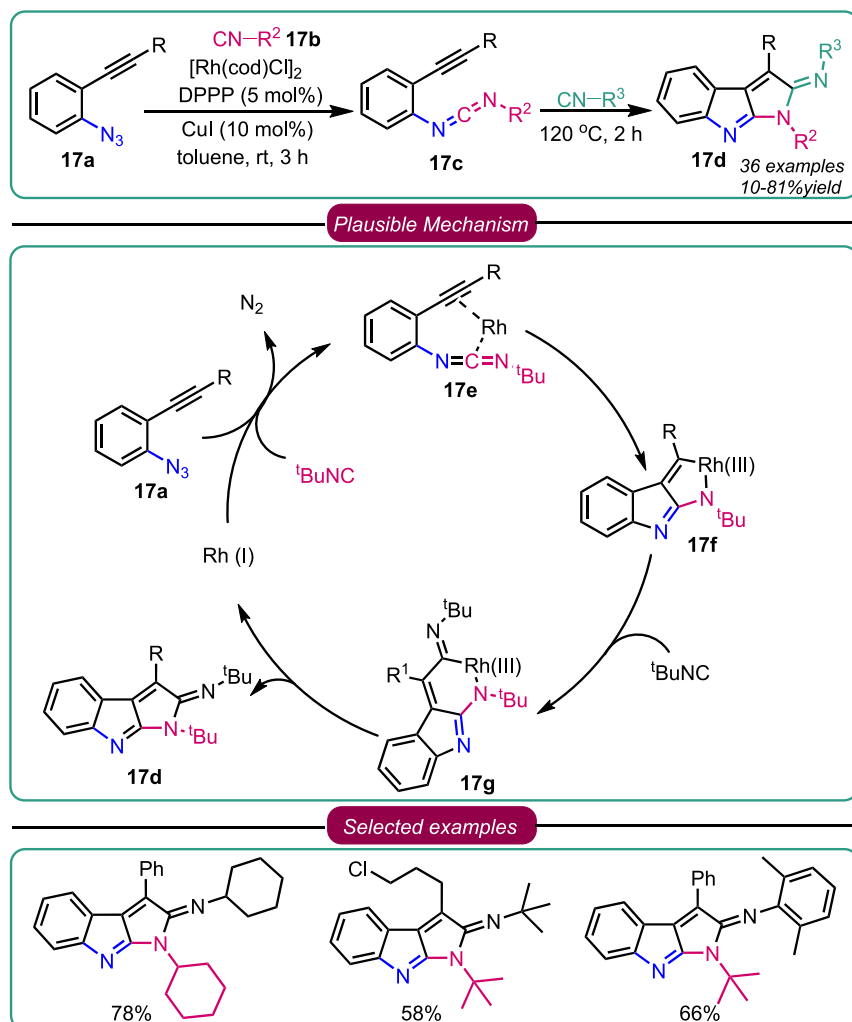
Based on their previous report, Shi et al. designed azide-tethered methylenecyclopropanes (MCPs) **16a**, which proceeded via an intermolecular cyclization that involved the reaction of isonitriles **16b** by a Rh(II) complex via carbodiimide intermediates **16f** to afford the pyrrole-fused quinoline skeletons **16c** (Scheme 16).⁴⁸ Initially, the reaction condition was investigated, and Shi's group found Rh₂(esp)₂ was the catalyst and toluene was the solvent. Next, examining the substrate scope electronic parameter on the aromatic ring did not alter the outcome of the product. ^tBuNC was found to be best toward the reactivity to test the other substrate. Based on control experiments, two plausible paths were depicted. In path A, the extrusion of nitrogen generates the Rh-nitrene complex **16d**, followed by the formation of complex isocyanide



Scheme 16. Shi's reports on the synthesis of pyrrolo[2,3-*b*]quinolines

16e. Alternatively, another proposed path of this reaction (path B) involves the reaction of the $\text{Rh}_2(\text{esp})_2$ with $^t\text{BuNC}$, allowing the formation of an unstable intermediate, $\text{Rh}_2(\text{esp})_2(\text{CN}^t\text{Bu})_2$, that further decomposes readily to yield stable $\text{Rh}_2(\text{esp})_2(\text{CN}^t\text{Bu})$. Path A is more favorable because of its stability and Rh-nitrene intermediate formation. After the renaissance of the rhodium catalyst, nitrene was transferred to isocyanide to generate carbodiimide **16f**. A sequential 6 π -electrocyclization affords the intermediate **16g**, which then undergoes a thermally induced rearrangement to yield the product **16c**. In addition, synthetic applications of these compounds for constructing structurally new and diversified bioactive heterocycles were explored.

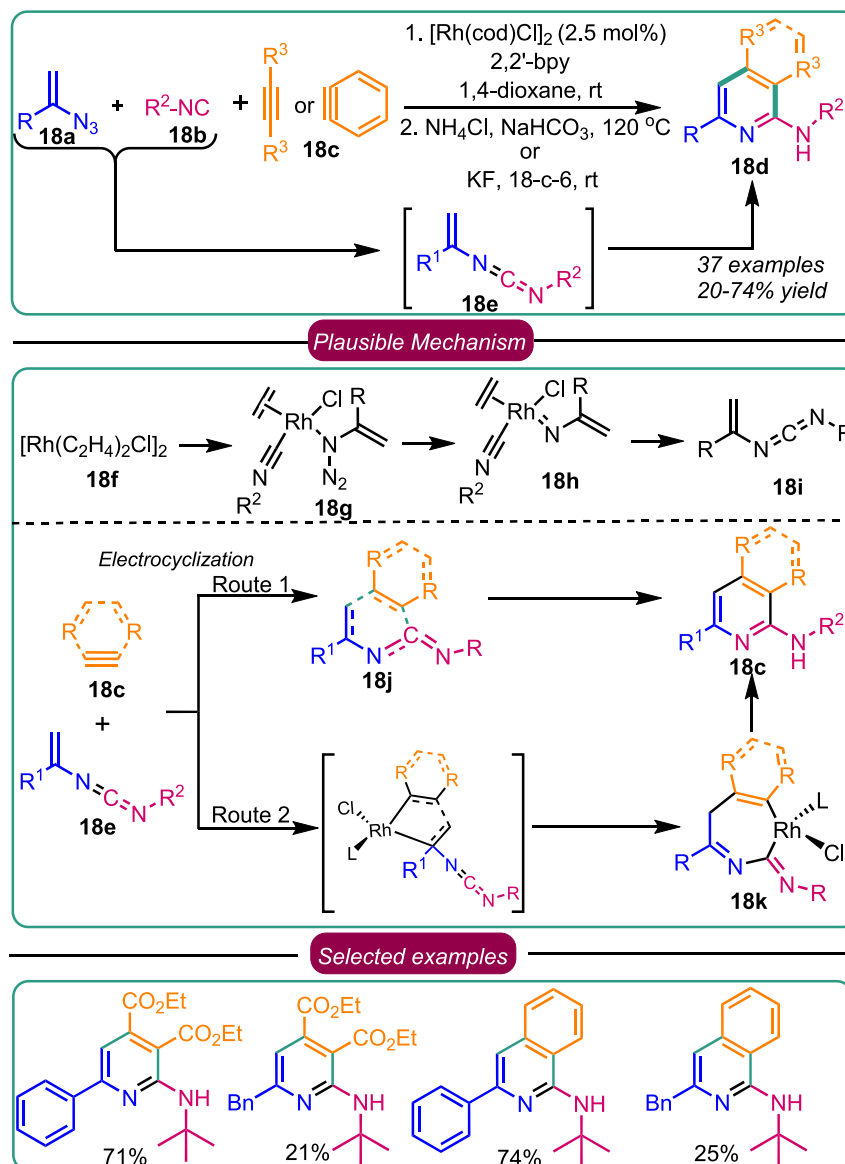
In 2016, building upon the concept of nitrene transfer to isocyanides, Zhang et al. introduced a straightforward methodology for synthesizing pyrrolo[2,3-*b*]indole scaffold **17d**. This reaction relied on rhodium (I) as a catalyst, enabling the self-relay reaction of tandem nitrene transformations. The alkyne-azides **17a** underwent aza-Pauson-Khand cyclization with ligand isonitrile **17b**, possessing both electron-donating and electron-withdrawing groups, sequentially forming a poly-fused heterocycle system (Scheme 17).⁴⁹ During the optimization of the reaction conditions, $[\text{Rh}(\text{cod})\text{Cl}]_2$ was identified as the catalyst, with 1,3-bis(diphenylphosphine)propane (DPPP) serving as the ligand. The inclusion of CuI as an additive and toluene as the solvent further enhanced the reaction efficiency. Diversified electron-donating and electron-withdrawing groups on the aromatic ring of intermediate 1-azido-2-(phenylethynyl)benzenes **17a** were tolerated, resulting in high yields of the desired product **17d**. Additionally, various isonitriles were found to provide excellent results (Scheme 17). The mechanistic insights suggest two plausible routes for forming pyrrolo[2,3-*b*]indoles. The first route involves the cross-coupling reaction of azides **17a** with isonitriles **17b**, catalyzed by Rh(I). The second route involves an aza-Pauson-Khand cyclization mechanism. Initially, nitrene transfer to the isocyanide leads to the formation of alkynyl carbodiimide intermediate **17c** through the expulsion of nitrogen. Complexation of **17e** with Rh(I), followed by oxidative cyclometallation, results in the formation of a rhodacycle species **17f**. Subsequent isonitrile insertion into the Rh-C bond of species **17f** generates complex **17g**, which, upon reductive elimination, affords the pyrrolo[2,3-*b*]indole derivatives **17d** while regenerating the active rhodium (I) catalyst.



Scheme 17. Zhang's work on Rh-catalyzed synthesis of pyrrolo[2,3-b]indoles

In 2018, Zhang et al. developed a coupling reaction for the formation of diversified azaheterocycles **18d** via the $\text{Rh}(\text{I})$ -catalyzed reaction of vinyl azides **18a** with isonitriles **18b** and alkynes/benzynes **18c** (Scheme 18).⁵⁰ Initially, azide moiety and isonitrile form active vinyl carbodiimide intermediates **18e** through the involvement of Rh -nitrene species. This was supported by using control experiments and DFT calculations. The process initiated with the $\text{Rh}(\text{I})$ dimer catalyst (**18f**) undergoing dissociation into a monomeric active catalyst, which coordinated with the isonitrile and vinyl azide to generate the Rh -complex **18g**. In a subsequent step, species **18h** released N_2 , creating nitrene intermediate **18i** through an exergonic transition state with an energy of 25.6 kcal/mol. The nitrene moiety of **18i** then engaged in a coupling reaction with the isonitrile, forming the vinyl carbodiimide. Ultimately, a ligand exchange event yielded the free vinyl carbodiimide, accompanied by a decrease in Gibbs energy ($\Delta G = 21.3$ kcal/mol). This observation supports that the coupling step necessitated the involvement of a Rh -nitrene intermediate. Following the successful formation of the vinyl carbodiimide, intermediate **18e** engaged in a tandem cyclization process with unsaturated compounds, including alkynes and benzynes **18c**. A comprehensive exploration of this synthetic route unveiled two distinct pathways: direct electrocyclicization and oxidative cyclization reductive elimination, both facilitated by $\text{Rh}(\text{I})$, ultimately yielding the desired azaheterocycles **18d**. Further investigation into the substrate scope revealed that electronic influences had a negligible impact and did not compromise the desired product's outcome. Remarkably, alkyne and benzyne substrates exhibited robust reactivity, resulting in the desired products with excellent yields.

In 2019, Zhang et al. developed another Rh -catalyzed reaction to develop 2*H*-pyrrol-2-imine **19d** (Scheme 19) in high yields. The mechanistically mediated reaction involves the cross-coupling of azide with isocyanide.⁵¹ The reaction presents broader substrate tolerance, possessing diversified functionality and electronic surroundings. Mechanistically, the *in situ* generated $\text{Rh}(\text{I})$ complex **19e** initiates the reaction from vinyl azide **19a** with isocyanide **19b** to generate vinyl carbodiimide intermediate **19f** via nitrene transfer on isocyanide, which consequently undergoes thermal cyclization with the second isocyanide **19c** to yield the desired product, 2*H*-pyrrol-2-imine **19d**. During the

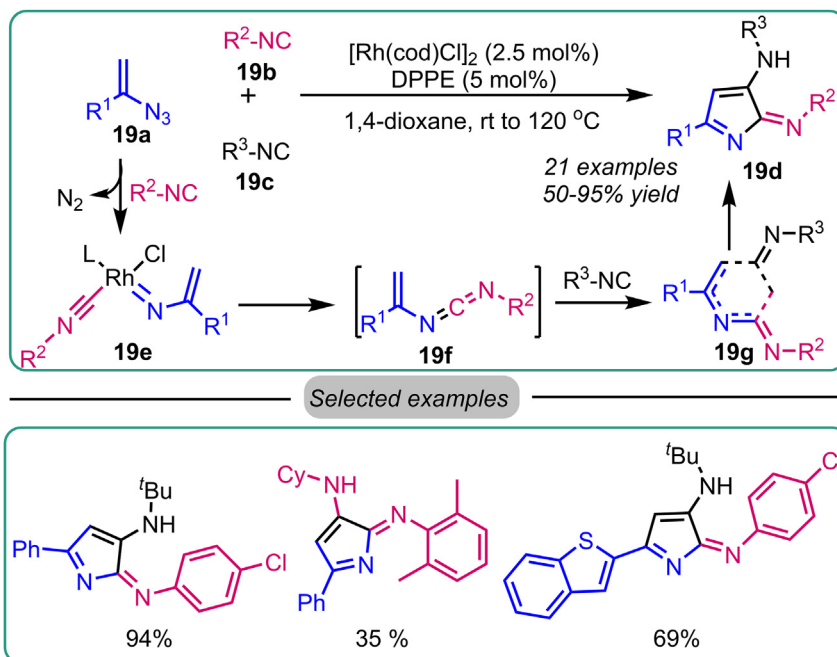


Scheme 18. Zhang's work on Rh-catalyzed synthesis of azaheterocycles

evaluation of the substrate scope, electron-donating aryl isocyanides participated well, whereas electron-withdrawing aryl isocyanides produced moderate yields, providing access to 2*H*-Pyrrol-2-imine. The second isocyanide was an aliphatic, and aromatic isocyanide participated well in producing the proposed product with good yields (Scheme 18).

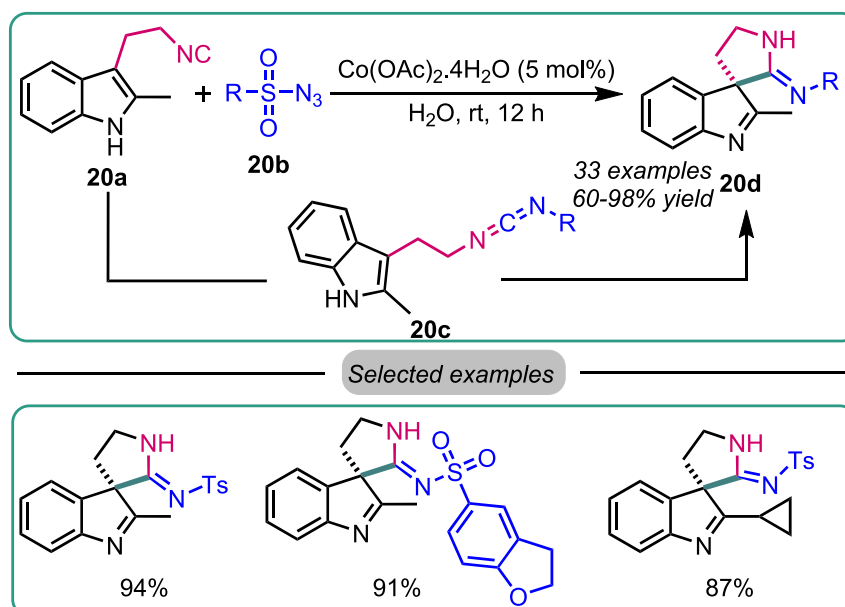
Cobalt-based reaction

In 2021, Ji et al. reported the synthesis of spiroindolenine **20d** through a Co-catalyzed cross-coupling reaction of tryptamine-derived isocyanides **20a** with sulfonyl azides **20b** (Scheme 20).⁵² The reaction was carried out in pure water at room temperature for 12 h using an aqueous system that proved to be highly efficient. The recyclability of the cobalt catalyst was also investigated, revealing that the same aqueous system could be used with the catalyst for approximately 10 cycles without a significant decrease in catalytic efficiency in mediating the cross-coupling reaction. The plausible mechanism proposed involves cross-coupling the azide derivative with the isocyanide derivative under the catalytic influence of cobalt, leading to the generation of a Co(III)-nitrene intermediate. This intermediate was further converted to the carbodiimide intermediate **20c** upon nitrogen (N_2) release. Subsequently, the nucleophilic C3 position of the indole undergoes spiro cyclization, followed by an isomerization process, ultimately yielding the desired product **20d**.

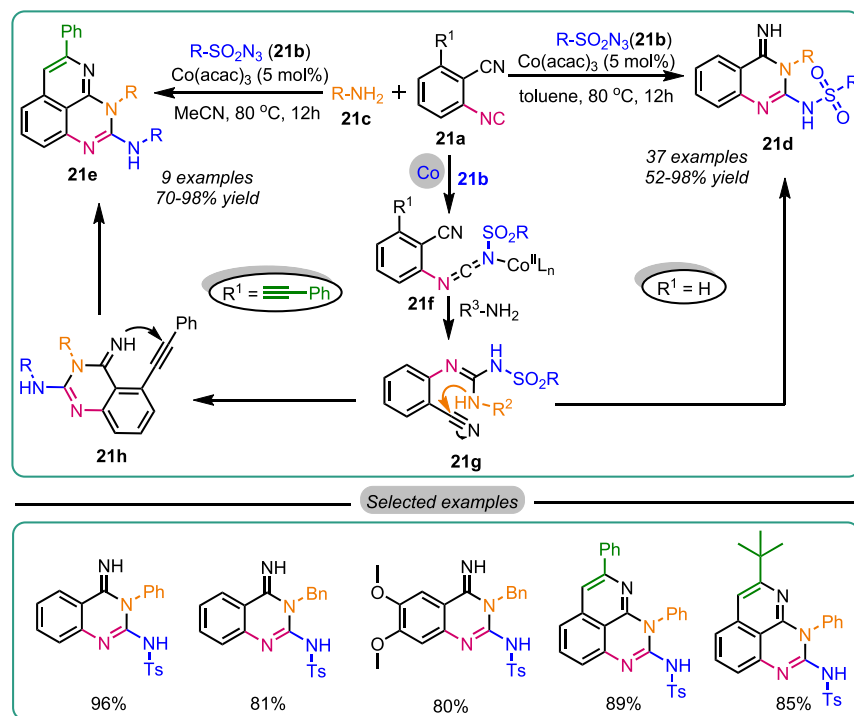


Scheme 19. Zhang's work on Rh-catalyzed synthesis of 2H-Pyrrol-2-imine

The same research group developed a Co-catalyzed, highly efficient, and cost-effective method for synthesizing various quinazoline derivatives. The methodology involved a three-component reaction comprising 2-isocyanobenzonitriles **21a**, sulfonyl azides **21b**, and amines **21c** under Co-catalysts' influence. This approach led to the formation of two distinct heterocycles: quinazoline-4(*H*)-imines **21d** and pyrido [2,3,4-*de*]-quinazolines **21e** (using alkyne) in good to excellent yields, exhibiting a broad substrate scope (Scheme 21).⁵³ Through control experiments, a plausible mechanism was proposed. The reaction initiates with the Co-catalysts, facilitating the utilization of azide and isocyanide to form the carbodiimide intermediate **21f**. Subsequently, the nucleophilic addition of an amine to the carbodiimide leads to the formation of the guanidine product **21g**. The nitrogen atom from the amine further attacks the cyano group, resulting in the desired product



Scheme 20. Ji's work on Co-catalyzed synthesis of spiroindolenine via nitrene-transfer reaction



Scheme 21. Co-catalyzed synthesis of quinazolin-4(H)-imines and pyrido[2,3,4-de]-quinazolines

21d. Additionally, intermediate **21h** undergoes intramolecular cross-coupling to form a C-N bond, particularly in the alkyne and iminyl groups in the alkyne substituent, ultimately affording fused quinazolines **21e**.

CONCLUSION

In summary, the cross-coupling reaction of azides with isocyanides through nitrene transfer is a robust, efficient, and adaptable method for synthesizing diverse carbodiimides. The evolution of TM complexes, notably employing stable metals like Pd, Rh, and Co, has considerably broadened the scope and practicality of this approach. Additionally, the conversion of carbodiimides into valuable compounds via relay transition-metal-catalyzed cascade reactions has yielded a plethora of unique structures, enriching the utility of the azide-isocyanide coupling technique.

While significant strides have been made, these strategies remain necessary for simplification and cost-effectiveness. Exploring earth-abundant metals such as Fe, Ni, and Cu for cascade reactions, with cobalt being a notable exception, presents an exciting avenue for further research. Investigating the compatibility and feasibility of heterogeneously catalyzed cascade reactions holds promise. Furthermore, the future of this field is likely to witness innovative approaches, including electrochemical or visible-light-induced models, aligning with the principles of green and sustainable chemistry.

Looking forward, the organic chemistry community is poised to discover an increasing array of consequential consecutive reactions. These discoveries will enrich the arsenal of synthetic methodologies and redefine the limits of chemical synthesis. As researchers delve deeper into unexplored realms, the horizon of possibilities in chemical synthesis is boundless, promising a future of even more sophisticated and environmentally conscious approaches.

Note: The alphanumeric designations (**1b**, **1f**, **1j**, **2b**, **3b**, **4b**, **5b**, **6b**, **7b**, **8b**, **9b**, **10b**, **11b**, **12b**, **13b**, **14b**, **15b**, **16b**, **17b**, **18b**, **19b**, **19c**, **20a**, and **21a**) exclusively represent the isocyanides in the manuscript. However, these represented isocyanides may vary in their derivatization or functional groups, a distinction that is clearly delineated within the manuscript.

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AUTHOR CONTRIBUTIONS

D.M.S., G.J., and A.J.A. collected the references. A.J.A. and G.J. conceived the project and prepared this manuscript. A.J.A. and D.M.S. overall supervised the project.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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