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Review

Bimetallic (or Multimetallic) Synthesis of *N*-Heterocycles

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Abstract: Bimetallic (or multimetallic) catalysis has emerged as a powerful tool in modern chemical synthesis, offering improved reaction control and versatility. This review focuses on the recent developments in bimetallic sequential catalysis for the synthesis of nitrogen heterocycles, which are essential building blocks in pharmaceuticals and fine chemicals. The cooperative action of two (sometimes more) different metal catalysts enables intricate control over reaction pathways, enhancing the selectivity and efficiency of the synthesis of *N*-heterocyclic compounds. By activating less reactive substrates, this multimetal catalytic strategy opens new synthetic possibilities for challenging compounds. The use of catalytic materials in bimetallic systems reduces waste and improves atom efficiency, aligning with green chemistry principles. With a diverse range of metal combinations and reaction conditions, bimetallic catalysis provides access to a broad array of *N*-heterocyclic compounds with various functionalities. This paper highlights the significant progress made in the past decade in this topic, emphasizing the promising potential of bimetallic catalysis in drug discovery and the fine chemical industries.

Keywords: bimetallic catalysis; multimetallic catalysis; sequential catalysis; *N*-heterocycles; transition metals; green chemistry

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1. Introduction

Catalysis plays a vital role in modern chemical synthesis, efficiently converting simple starting materials into valuable complex compounds. Bimetallic catalysis, which involves two different metal species working together synergistically, has emerged as a powerful tool for various chemical reactions [1–4]. Sequential bimetallic catalysis represents a cutting-edge approach, enabling the synthesis of valuable compounds with higher efficiency, selectivity, and atom economy. It opens new synthetic possibilities for more complex compounds by activating and transforming substrates that may be unreactive or challenging for a single-metal catalyst, aligning with green chemistry principles and reducing the formation of unwanted byproducts [5].

Pioneering studies on transition-metal-catalyzed cross-coupling reactions, such as Suzuki, Heck, and Negishi reactions, laid the foundation for bimetallic catalysis by demonstrating selective coupling of different organic fragments [6]. Early investigations into tandem catalysis, performing consecutive reactions without intermediate isolation, inspired the concept of sequential bimetallic catalysis for increased efficiency and shorter reaction times. The cooperative action of two metal catalysts to activate a substrate showcased the potential of combining multiple metals for improved reactivity and selectivity. Cascade reactions, where bond-forming events occur in a one-pot manner, influenced the design of sequential bimetallic catalysis, promoting multiple cyclical reactions for complex molecular synthesis [3,7].

One particularly promising area of bimetallic catalysis is the synthesis of *N*-heterocycles, which are essential building blocks in numerous biologically active compounds and pharmaceuticals [8]. Traditional synthetic routes for *N*-heterocycles have some drawbacks, such as the involvement of multiple steps, harsh conditions, and the generation of significant waste. Therefore, bimetallic catalysis offers several key advantages in *N*-heterocycle synthesis. In particular, the use of two different metal catalysts in tandem allows for intricate control over the reaction pathways, enhancing selectivity and improving yields of the desired *N*-heterocyclic products. This is particularly important in complex molecules, where traditional methods may lead to competing side reactions.

Moreover, bimetallic catalysis facilitates the activation of less reactive substrates, enabling the synthesis of *N*-heterocycles that were previously challenging or unattainable through monometallic catalysis. This expands the synthetic toolbox, providing access to a broader range of *N*-heterocyclic structures. In addition, the efficient use of bimetallic catalysis reduces waste and increases atomic efficiency, making the process more environmentally friendly and economically viable [3,7]. However, the practical application of dual catalysis in organic synthesis is still limited by factors such as the compatibility between catalysts (including ligand exchange, acid–base interactions, and redox processes) and the matching of reaction kinetics [9].

As the field continues to evolve, this review presents an overview of the recent developments concerning bimetallic sequential catalysis for the synthesis of *N*-heterocycles, which represents a promising avenue in catalysis.

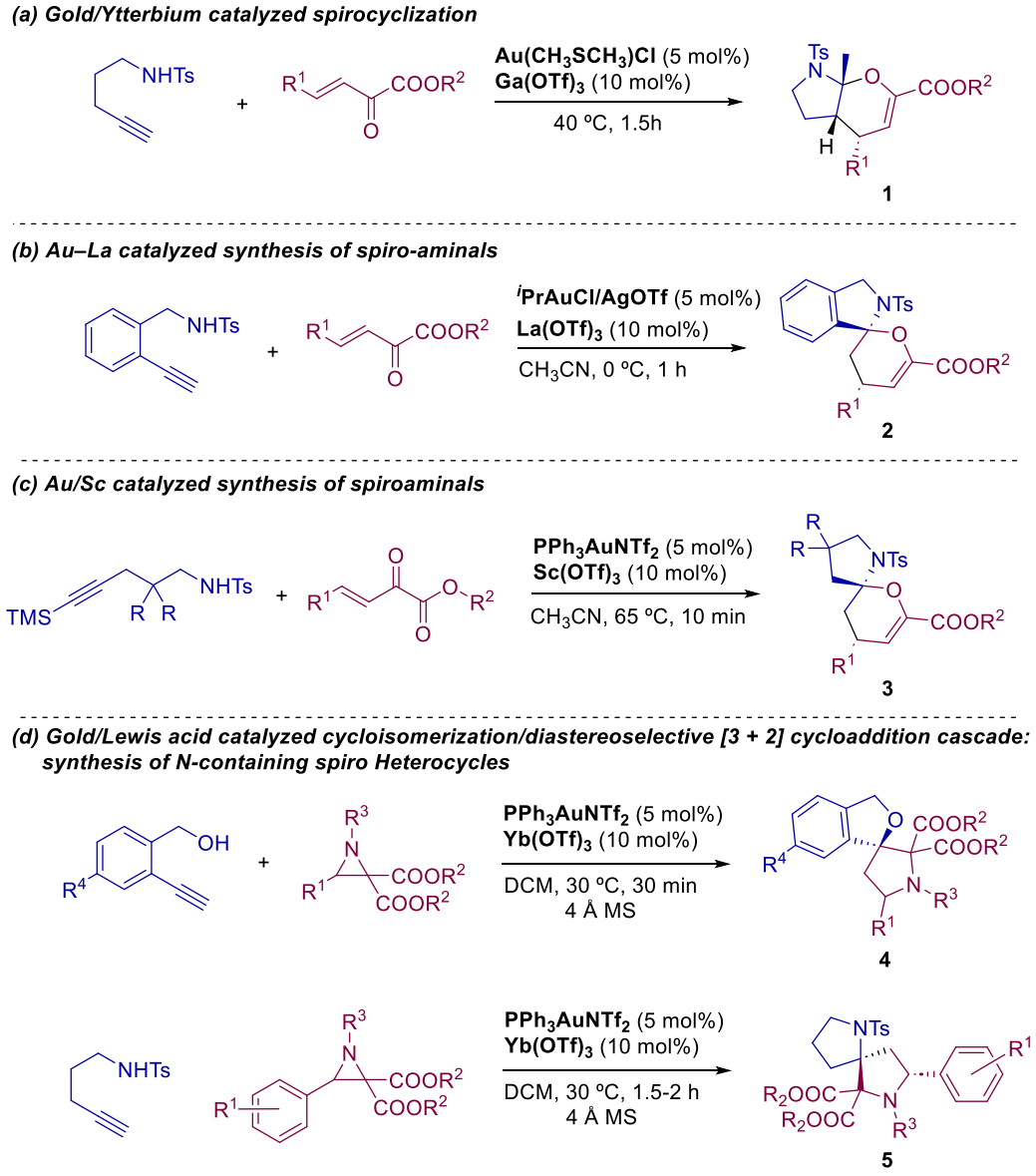
2. Bimetallic Approaches to *N,O*-Aminals and Related Spiro-*N,O*-Heterocycles

N,O-aminals are an interesting class of substituted molecules bearing a geminally *N,O*-substituted (stereogenic) carbon center and have been recently recognized as an important class of building blocks in organic synthesis [10]. In the conventional approach, *N,O*-aminals are derived either from the corresponding α-amido sulfones via nucleophilic substitution, replacing the sulfonyl group with an alkoxy moiety [11–15], or from the corresponding imines by means of nucleophilic addition, introducing an alkoxy group [16–24].

While several methods exist for the synthesis of these compounds, enantioselective examples are still limited, particularly for the construction of chiral tetrasubstituted carbon centers [22]. Moreover, some of these methods do come with certain disadvantages, such as the requirement for harsh reaction conditions, such as the use of strong acids or high temperatures, which may lead to side reactions or limited substrate compatibility. Additionally, the formation of unwanted byproducts and the potential for racemization can pose challenges, particularly in the synthesis of chiral *N,O*-aminals. Despite these drawbacks, researchers continue to explore new strategies to overcome these limitations and develop more sustainable and selective routes for *N,O*-aminal synthesis, with bimetallic catalysis showing important potential [25].

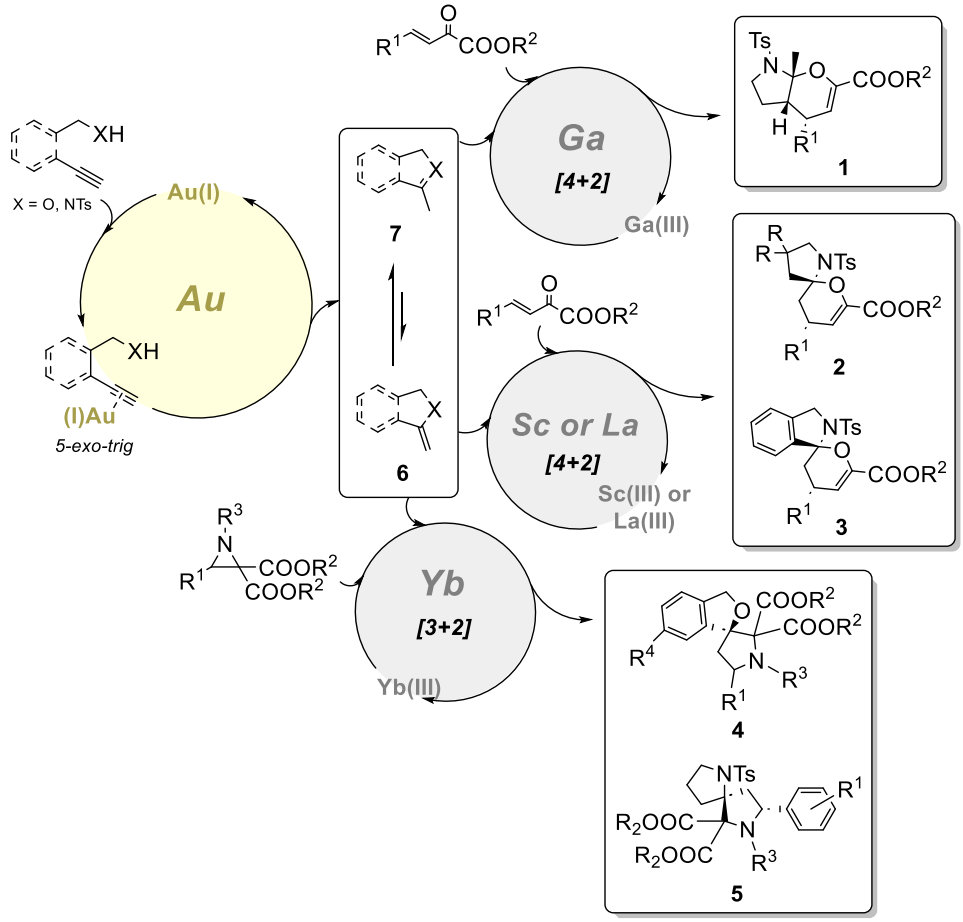
Xu and coworkers have been actively developing synthetic processes for fused bicyclic *N,O*-aminals and spiro-*N,O*-aminals. The authors have focused on bimetallic catalysis under mild conditions, utilizing Au(I) as a catalyst and a metallic Lewis acid as a cocatalyst. In 2013, the group successfully achieved the synthesis of aromatic and allyl-substituted fused bicyclic aminals (**1**) through a Au(I)/Ga(III)-catalyzed [4+2] cycloaddition cascade reaction, with 13 examples and yields of up to 90% (Scheme 1a) [26]. Subsequently, in 2014, the same group disclosed the synthesis of spiro-*N,O*-aminals (**2**) by employing a Au(I)/La(III)-catalyzed [4+2] cycloaddition bimetallic approach (Scheme 1b) [25]. To prevent inward isomerization of the generated enamide, a fused aromatic ring was introduced in the same alkyne amine, enabling the reaction with activated electrophiles and yielding spirocyclic products in 12 examples, with yields of up to 90%. In the same year, Xu's group successfully synthesized aromatic and allyl-substituted spiro aminals (**3**) using a bimetallic Au(I)/Sc(III)-catalyzed [4+2] cycloaddition process (Scheme 1c) [27]. In this work, trimethylsilyl (TMS) was employed as a traceless controlling group to stabilize the derived enamide and inhibit its isomerization, resulting in 14 examples and yields of

up to 89%. Additionally, in 2016, Xu and coworkers reported the preparation of spiro heterocycles through a Au(I)/Yb(III)-catalyzed diastereoselective [3+2] cycloaddition between aziridines and alkynyl substrates (Scheme 1d) [28]. Various *N*-protecting groups and aliphatic and aromatic alkynyl substrates were tested, resulting in diverse substituted spiro-*N*,*O*-heterocycles (**4**), with 16 examples and yields of up to 99%. Furthermore, by switching from alkynyl alcohols to alkynyl amides, a similar reaction with aziridines afforded aromatically substituted spiro-*N*,*N*-heterocycles (**5**), with nine examples and yields of up to 80%.



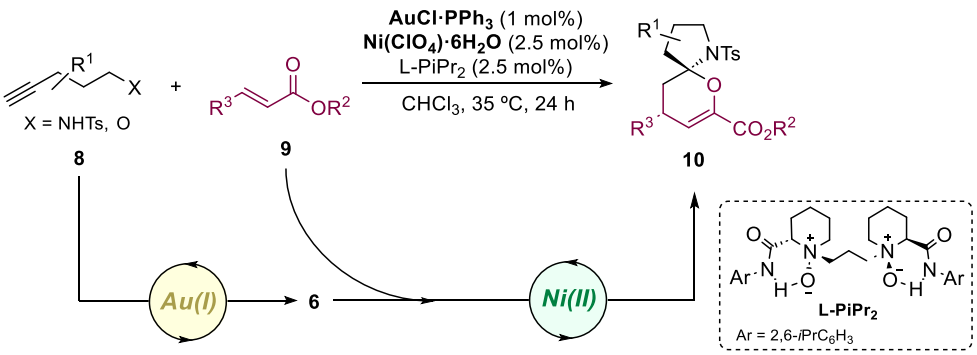
Scheme 1. (**a**–**d**) Xu's contributions to the bimetallic synthesis of fused bicyclic and spiro aminals.

To gain insights into the reactions' mechanisms (Scheme 2), Xu and coworkers conducted deuteration experiments that showed that the alkynyl substrate undergoes a Au(I)-catalyzed 5-*exo-dig* cyclization, affording enamide **6**, followed by isomerization into another enamide (**7**). Although **7** is more stable, depending on the reaction conditions and the type or loading of the Lewis acid, either spiro or fused aminals can be afforded by a [4+2] cycloaddition. Thus, the Lewis acid activates the electrophile and generates the final product. When in contact with aziridines, enamide **6** can also undergo a Lewis-acid-catalyzed [3+2] cycloaddition.



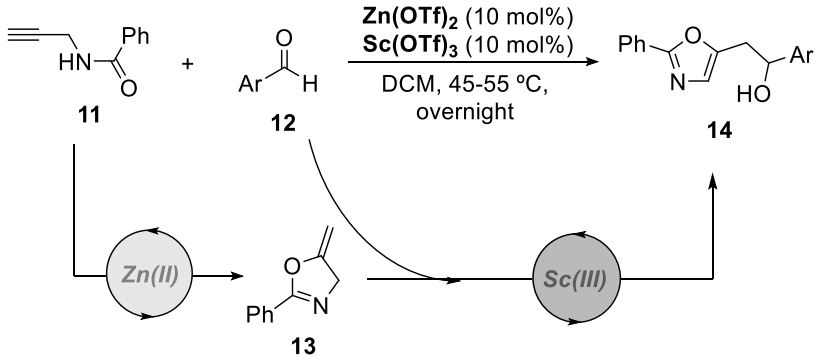
Scheme 2. A plausible mechanism of the Au/Lewis acid bimetallic synthesis of fused bicyclic and spiro aminals proposed by Xu's group.

In 2016, Li and coworkers described an innovative asymmetric cascade reaction between alkynyl amides (**8**) and keto esters (**9**), employing a bimetallic catalytic system of achiral π-acid Au(I) and a chiral Lewis acid *N*,*N*′-dioxide Ni(II) complex (Scheme 3) [29]. This approach enabled the synthesis of spiro aminals (**10**) with high yields (up to 99%), excellent enantioselectivity (over 99% ee), and moderate to high diastereoselectivity (19:1 d.r.) under mild reaction conditions. The bimetallic catalytic system facilitated the sequential activation of the carbonyl and alkyne moieties, with the *N*,*N*′-dioxide ligand playing a crucial role.



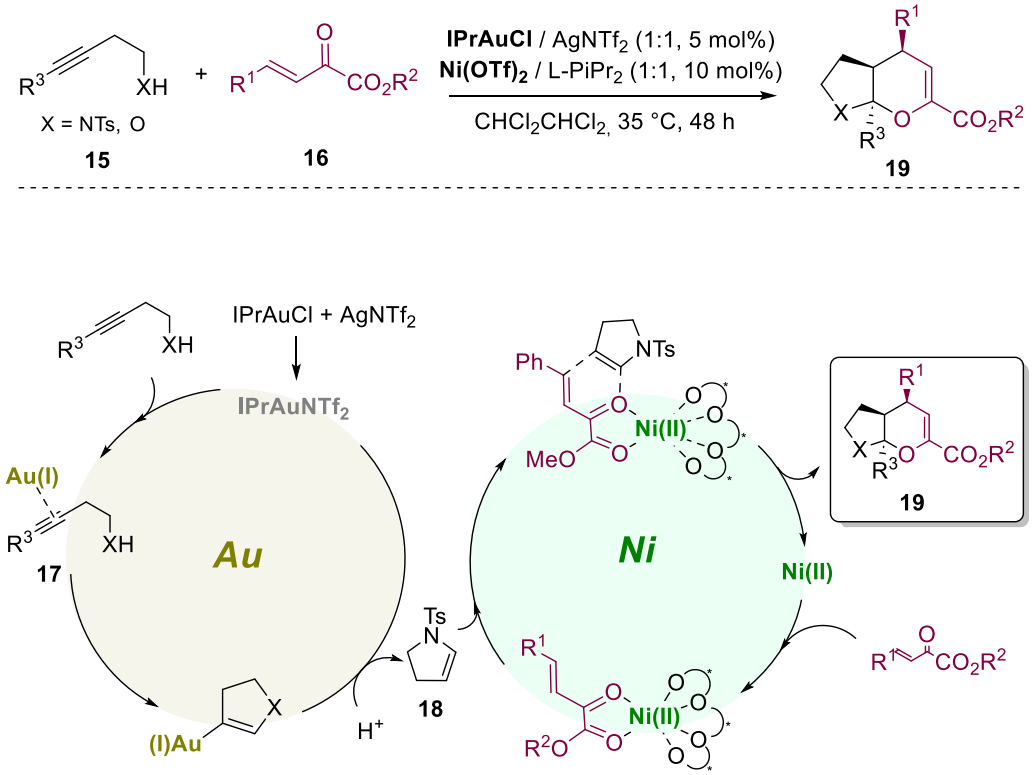
Scheme 3. General conditions for the preparation of spiro aminals using a Au(I)/Ni(II)-bimetallic catalyzed approach.

In 2016, another interesting bimetallic relay catalytic system was developed by Xu's group, enabling the synthesis of oxazole derivatives from readily available *N*-(propargyl)-aryl amides and aldehydes under mild reaction conditions (Scheme 4) [30]. The authors demonstrated that both $Zn(OTf)_2$ and $Sc(OTf)_3$ catalysts are necessary to achieve the final product. Control experiments demonstrated that in the absence of $Sc(OTf)_3$, the product was obtained in a 16% yield, along with the oxazoline intermediate (**13**) (41%), while in the absence of $Zn(OTf)_2$, only trace amounts to product were detected. The system consists of $Zn(OTf)_2$ and $Sc(OTf)_3$, which act as a π acid and a σ acid, respectively. The reaction proceeds through a cascade of reactions, beginning with an intramolecular 5-*exo-dig* cyclization of alkynyl amide **11** catalyzed by $Zn(OTf)_2$. Simultaneously, $Sc(OTf)_3$ coordinates with the carbonyl group of the aldehyde (**12**), promoting the subsequent carbonyl–ene reaction with the oxazoline intermediate (**13**), yielding the desired oxazole product (**14**). This method was straightforward, with considerable atomic economy, possessing the potential for applications in organic synthesis and medicinal chemistry.



Scheme 4. General conditions for the preparation of oxazoles using a Zn(II)/Sc(III)-bimetallic catalyzed approach.

A similar work was reported by Feng's group in 2018 [31]. In this work, a similar efficient catalytic asymmetric cyclization reaction (Scheme 5) was conducted using a bimetallic system that involved an achiral Au(I) catalyst and the same chiral *N*,*N*′-dioxide ligand/Ni(II) catalyst. This reaction also involved the cyclization of alkyl amides or alcohols (**15**) with β,γ-unsaturated α-ketoesters (**16**), leading to the formation of fused bicyclic *N*,*O*-acetals or *O*,*O*-acetals. The researchers employed a 5-*endo-dig* cyclization process based on Baldwin's rules, resulting in a cycloalkene intermediate capable of reacting with β,γ-unsaturated α-ketoesters to form the desired fused bicyclic products through an inverse electron-demand hetero-Diels–Alder (IEDHDA) reaction. The optimal conditions for the reaction were determined, yielding products with good yields (77–99%) and excellent enantioselectivities (96–99% ee). The reaction tolerated various substrates, including those with 2-naphthyl and heteroaromatic groups. The substrate scope was expanded to alkynyl alcohols and alkynyl amines, yielding the desired fused bicyclic *N*,*O*-acetals with excellent yield and enantioselectivity. Based on control experiments, a reaction mechanism is proposed: initially, the gold catalyst coordinates with the alkynyl substrate (**15**) to form a π–gold–alkyne complex (**17**) and generated the key cyclic intermediate (**18**) in situ. On the other hand, chiral Lewis acid Ni(II)/L-$PiPr_2$-activated β,γ-unsaturated α-ketoester (**16**) reacts with **18**, affording fused bicyclic acetal **19**.

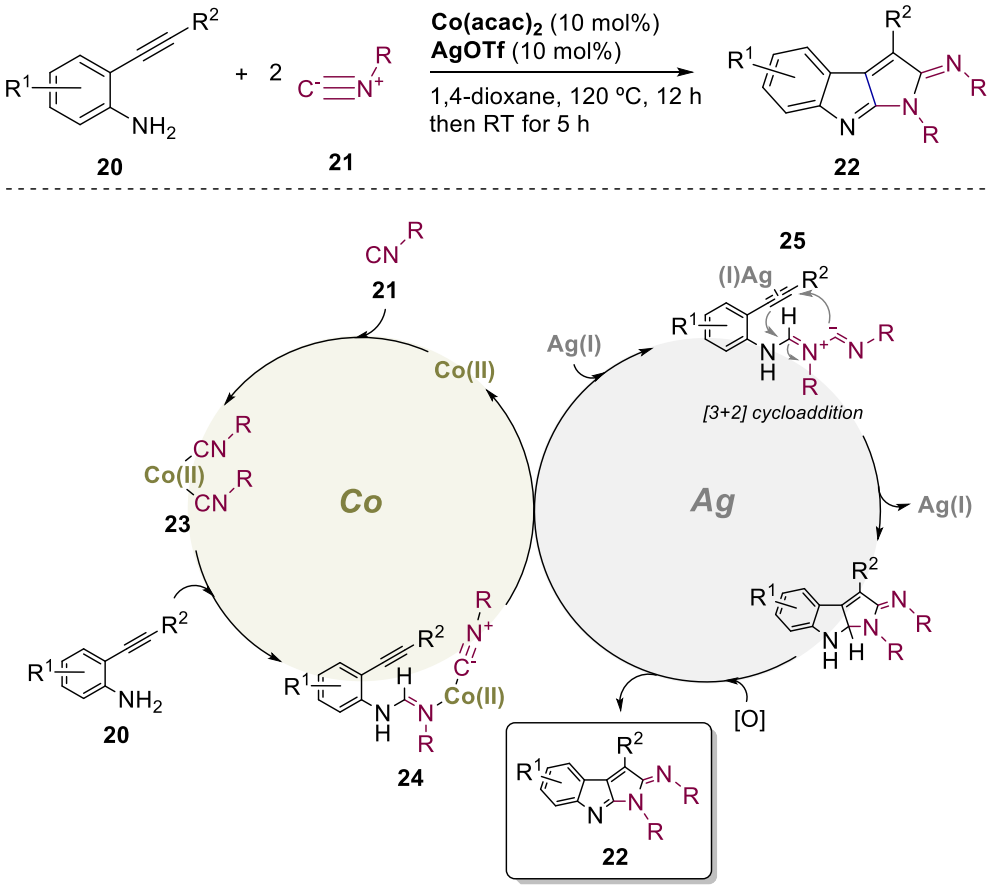


Scheme 5. General conditions and a plausible mechanism for the preparation of fused bicyclic acetals or aminals using a Au(I)/Ni(II)-bimetallic catalyzed approach.

3. Bimetallic Approaches Involving Indole Scaffolds

Indoles and indolines are of great importance in medicinal chemistry, pharmaceuticals, and natural product synthesis due to their involvement in various biological processes and their structural significance. Several common methods for synthesizing indoles, including Fischer indole synthesis, Bischler–Möhlau indole synthesis, Madelung indole synthesis, Reissert indole synthesis, and Buchwald–Hartwig amination, have been widely employed [32]. However, some traditional routes suffer from drawbacks such as harsh reaction conditions, multistep processes, limited substrate scope, and regioselectivity issues, which can lead to the formation of unwanted byproducts or the need for expensive catalysts. Thus, bimetallic catalytic routes that involve the formation of an indole intermediate or product has emerged as a desirable approach.

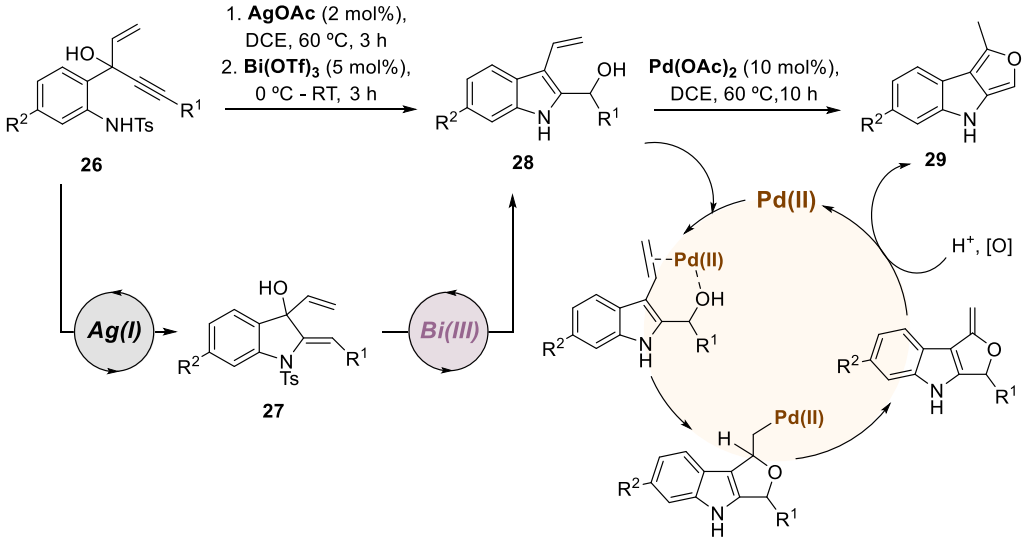
The direct formation of pyrrolo [2,3-β]indoles via catalyzed bicycloaddition reactions is a very attractive yet challenging process. Isocyanides can be inserted either with a Lewis acid [33] or via transition metal catalysis, undoubtedly with palladium as the most popular choice [34–36]. In contrast, in 2015, Gao and coworkers explored the preparation of pyrrolo [2,3-β]indoles using an inexpensive Co(II)-enabled process (Scheme 6) [37]. The authors demonstrated that the combination of $Co(acac)_2$ and AgOTf promoted a bimetallic relay catalysis reaction between 2-ethynylanilines (**20**) and isocyanides (**21**), allowing access to new densely functionalized pyrrolo [2,3-β]indoles (**22**). Overall, 26 examples were reported, with yields of up to 86%. The authors suggested that the reaction pathway involves a Co(II)-catalyzed double isocyanide insertion followed by a Ag(I)-catalyzed 1,3-dipolar cycloaddition. A suitable mechanism for the formation of pyrrolo [2,3-β]indoles can be described by a ligand exchange, affording intermediate complex **23**, which activates the electrophile isocyanides, a key step in this process. It then undergoes an N–H insertion to obtain the enyne-imine species (**24**) detected using GC-MS. Then, a second migratory insertion affords the 1,3-dipole (**25**) and regenerates the Co(II) catalyst. The presence of Ag(I) allows for intramolecular 1,3-dipolar cycloaddition followed by dehydrogenation under air conditions, which leads to the desired thermodynamically stable pyrrolo [2,3-β]indole (**22**).



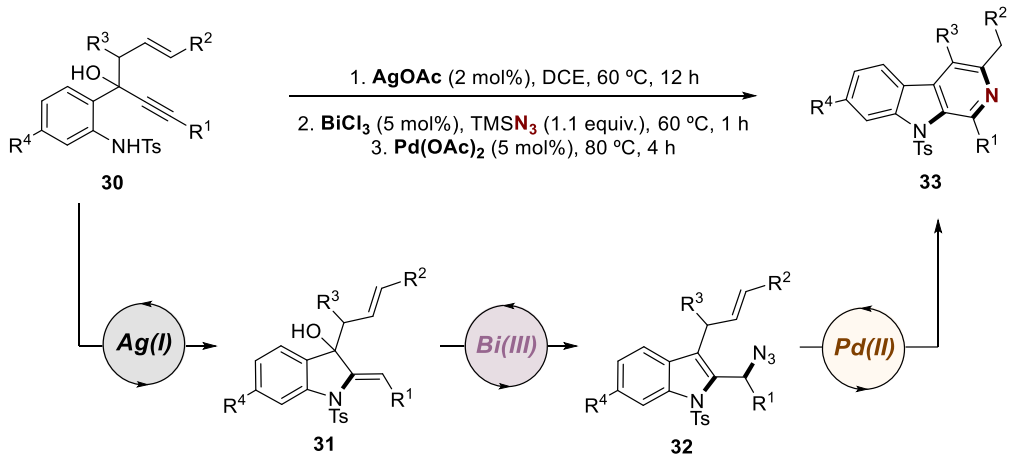
Scheme 6. General conditions and a plausible mechanism for the preparation of pyrrolo [2,3-β]indoles using a Co(II)/Ag(I)-bimetallic catalyzed approach.

In 2016, Ramasastry and coworkers published two research works involving indole synthesis and subsequent transformation through a trimetallic catalytic system. In the first study, the authors reported a successful three-orthogonal metal relay catalytic system for the preparation furo [3,4-β] indoles (Scheme 7) [38]. This approach involves sequential Ag(I)/Bi(III)/Pd(II) trimetallic catalysis, demonstrating its versatility with 10 examples and yields of up to 57%. The preparation of cyclopenta[β]indoles was also investigated using a one-pot Ag(I)/Brønsted acid catalysis from 3-(2-aminophenyl)-4-pentenyn-3-ols, although not involving a multimetallic catalytic approach. The reaction mechanism involved Ag(I)-catalyzed 5-*exo-dig* cyclization of substrate **26** to generate intermediate **27**, followed by Bi(III)-catalyzed 1,3-allylic alcohol isomerization, leading to **38**. Finally, a Pd(II)-catalyzed intramolecular etherification through a 5-*exo-trig* cyclization under oxidative conditions resulted in the desired furo [3,4-β]indole (**29**).

In a second work published in 2016, Ramasastry and coworkers presented a similar one-pot triple-orthogonal metal relay catalysis strategy for the synthesis of 1,3-di- and 1,3,4-trisubstituted *β*-carbolines, also employing silver, bismuth, and palladium catalysts in a sequential manner (Scheme 8) [39]. The synthetic pathway included intramolecular hydroamination, Friedel–Crafts-type dehydrative azidation, and a unique annulation step, leading to the formation of the pyridine ring. Starting from **30**, they achieved indoline intermediate **31** through a Ag(I)-catalyzed 5-*exo-dig* cyclization and protodemetalation. A subsequent Bi(III)-promoted cascade reaction involving 1,3-allylic alcohol isomerization and nucleophilic azidation led to the formation of azide **32**. This intermediate underwent Pd(II)-mediated aziridine formation, followed by deprotonation, ring opening of the aziridine, and aromatization, resulting in the desired substituted *N*-heterocycle (**33**). This innovative approach provided access to a diverse range of distinct *β*-carbolines, offering new possibilities for the synthesis of these valuable compounds.



Scheme 7. General conditions and a plausible mechanism for the preparation of furo [3,4-β]indoles using a Ag(I)/Bi(III)/Pd(II)-catalyzed trimetallic approach.

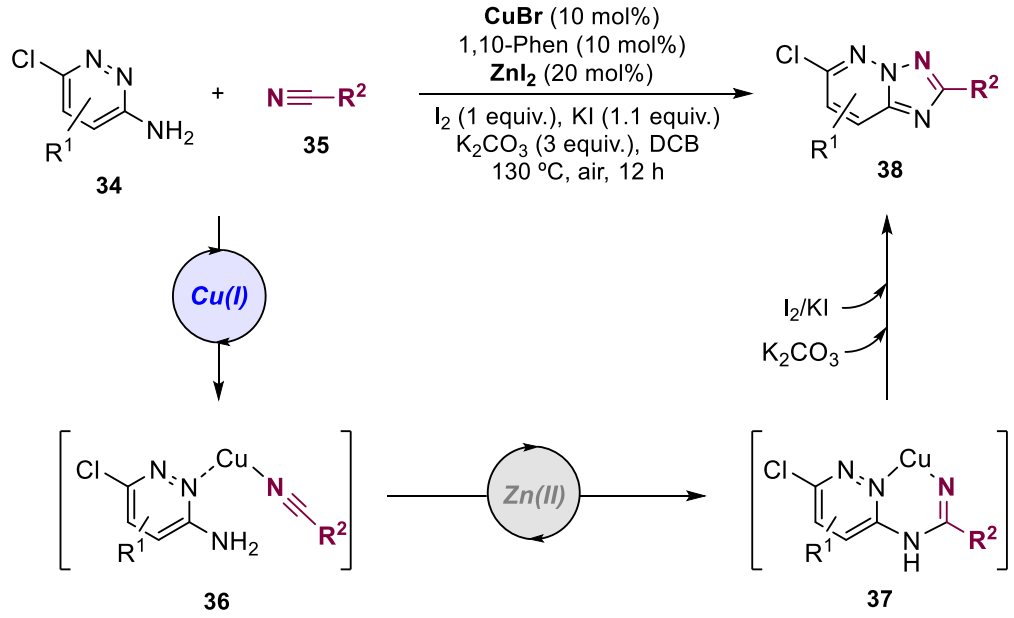


Scheme 8. General conditions and a plausible mechanism for the preparation of 1,3-di- and 1,3,4-trisubstituted *β*-carbolines using a Ag(I)/Bi(III)/Pd(II)-catalyzed trimetallic approach.

In 2017, Mu and coworkers reported a new and efficient protocol for the preparation of chlorine-containing 1,2,4-triazolo [1,5-*b*]pyridazine scaffolds (Scheme 9) [40]. The authors developed a one-pot oxidative cycloaddition reaction of 3-aminopyridazine derivatives (**34**) and nitriles (**35**) involving cooperative Cu(I) and Zn(II)-catalyzed tandem C-N addition to achieve intermediate **36** followed by amidine **37**. Then, a I_2/KI-mediated intramolecular oxidative N−N bond formation affords the final 1,2,4-triazolo [1,5-*b*] pyridazine derivatives (**38**).

In 2017, Wang and coworkers reported the construction of 3-alkylidene isoindolinones. This was efficiently achieved through a redox-neutral bimetallic Rh(III)/Ag(I) relay catalysis between *N*-tosyl benzamides (**39**) and 2,2-difluorovinyl tosylate (**40**) (Scheme 10) [41]. The Rh(III) catalyst facilitates the C−H monofluoroalkylation reaction, while the Ag(I) salt acts as an activator for the subsequent cyclization step. According to the authors, the mechanism starts with the Rh(III)-catalyzed C−H activation in *N*-tosylbenzamide (**39**), assisted by the NTs group, generating intermediate **41**. The subsequent coordination of **40**, which leads to intermediate **42**, underwent a regioselective olefin insertion, followed by an anticoplanar β-F elimination, resulting in the *Z*-type monofluoroalkylation product (**43**) with notable stereoselectivity. The Ag(I) salt was suggested to act as a π acid, promoting the activation of the olefin (**44**) and facilitating the intramolecular cyclization reaction.

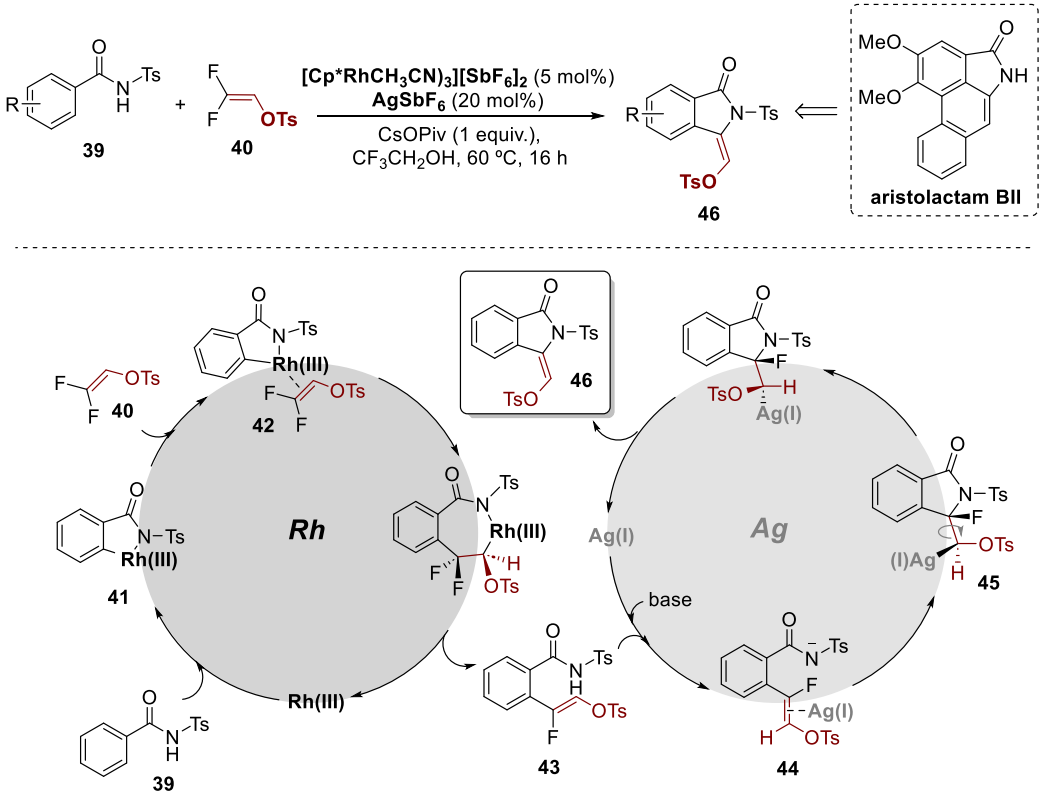
Consequently, the antiaddition to the double bond induced 5-*exo* cyclization, resulting in the formation of intermediate **45**. The selective attack at the α position of the fluorine atom was attributed to the low-lying LUMO with a significant coefficient at this position. Finally, a stereospecific formation of the *E*-type 3-alkylidene isoindolinone product (**46**) was achieved through an anticoplanar β-F elimination process. The methodology described in this study was used to rapidly synthesize aristolactam BII, a natural product with potential pharmaceutical applications. The results demonstrate the potential of difluorovinyl tosylate and Rh(III)/Ag(I) relay catalysis for the efficient synthesis of a variety of biologically active compounds.



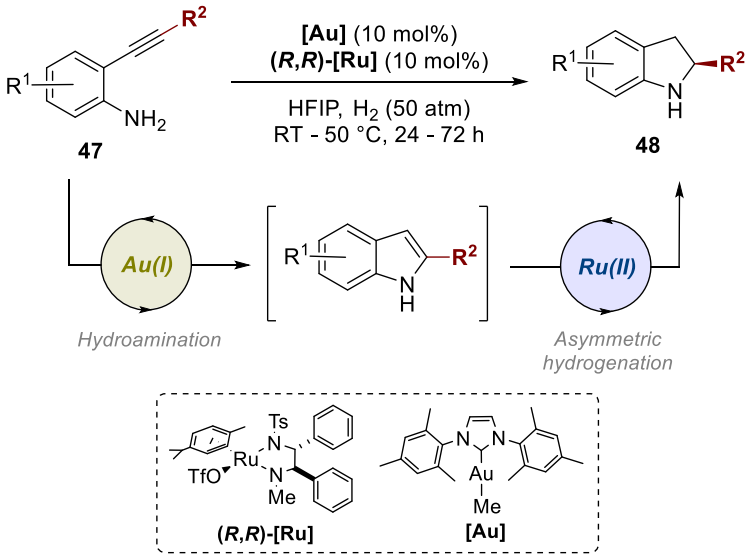
Scheme 9. General conditions and a plausible mechanism for the preparation of 1,2,4-triazolo [1,5-b] pyridazines using a Cu(I)/Zn(II)- bimetallic catalyzed approach.

X. Feng and coworkers reported a highly efficient asymmetric cascade reaction of alkenyloxindoles with pyridines and diazoacetates via a bimetallic iron(III)/chiral *N*,*N*′-dioxide–scandium(III) complex catalyst [42]. Tetrahydroindolizines were obtained with good to excellent diastereo- and enantioselectivities.

In 2019, Fan and coworkers published a one-pot cascade reaction strategy to afford functionalized indolines. This process involves sequential Au(I)-catalyzed intramolecular hydroamination followed by Ru(II)-catalyzed asymmetric hydrogenation of various anilino-alkynes (**47**) (Scheme 11) [43]. This enabled access to chiral indolines (**48**). Optimal reaction conditions were determined, and the reactions proceeded smoothly, achieving full conversions, with high yields (up to 98%) and moderate to excellent enantioselectivities (up to 97% ee). This work was also extended to chiral 1,2,3,4-tetrahydroquinolines, although only requiring one ruthenium catalyst and not a bimetallic approach.



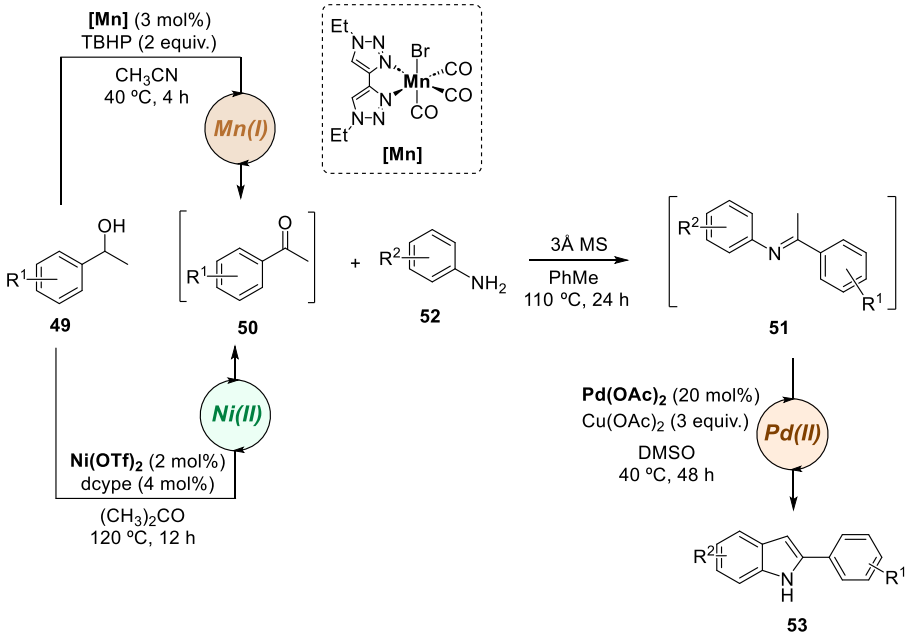
Scheme 10. General conditions and a plausible mechanism for the preparation of 3-alkylidene isoindolinones using a Rh(III)/Ag(I)-bimetallic catalyzed approach.



Scheme 11. General conditions for the preparation of asymmetrically substituted indolines using a Au(I)/Ru(II)-bimetallic catalyzed approach.

Marques and coworkers recently disclosed a novel one-pot bimetallic catalytic approach for the synthesis of indole derivatives using secondary alcohols and anilines as starting materials (Scheme 12) [8]. A commercially available nickel catalyst combined with a simple phosphine was investigated for the dehydrogenation of alcohol (**49**); a phosphine-free manganese complex was also synthesized to achieve this oxidation step. Both systems were studied to obtain the desired ketone (**50**), which was subsequently converted to an imine (**51**) through condensation with an aniline (**52**), followed by an in situ palladium-

catalyzed oxidative cyclization. This system achieved several 2-arylindoles (**53**), with a three-step synthetic pathway and overall yields of up to 45%. This process had the advantage of avoiding the isolation of sensitive intermediates and presented a sustainable pathway for the preparation of functionalized indoles.



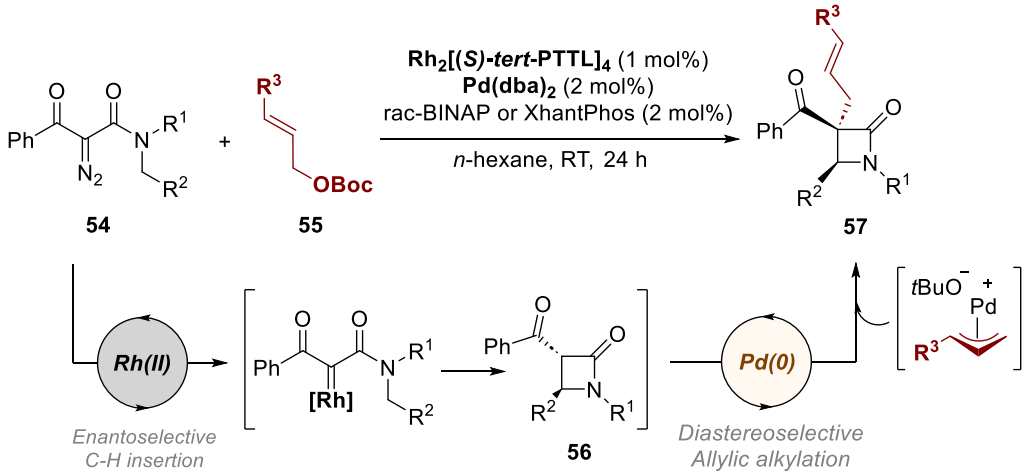
Scheme 12. General conditions for the preparation of 2-arylindoles using Mn(I)/Pd(II)- or Ni(II)/Pd(II)-bimetallic catalyzed approaches.

4. Bimetallic Approaches Involving Lactam Scaffolds

β-lactam is the common core structure of clinically used drugs such as penicillin and cephalosporin and monocyclic antibiotics such as aztreonam [44–47]. The development of novel methods to access new β-lactams is important for the drug discovery process, such as the discovery of new antibiotics, which are important with respect to global health problems. Synthetic methods to construct the β-lactam ring have been developed over the last century from almost every imaginable set of synthons. However, further innovation and improvement in the field are necessary, even within each category of well-established reactions [48]. Despite the variety synthetic methods proposed to date to obtain achiral or racemic lactams, asymmetric methodologies remain largely limited to chiral auxiliary-based systems [49]. This review presents two examples of asymmetric bimetallic catalytic approaches to afford substituted β-lactams.

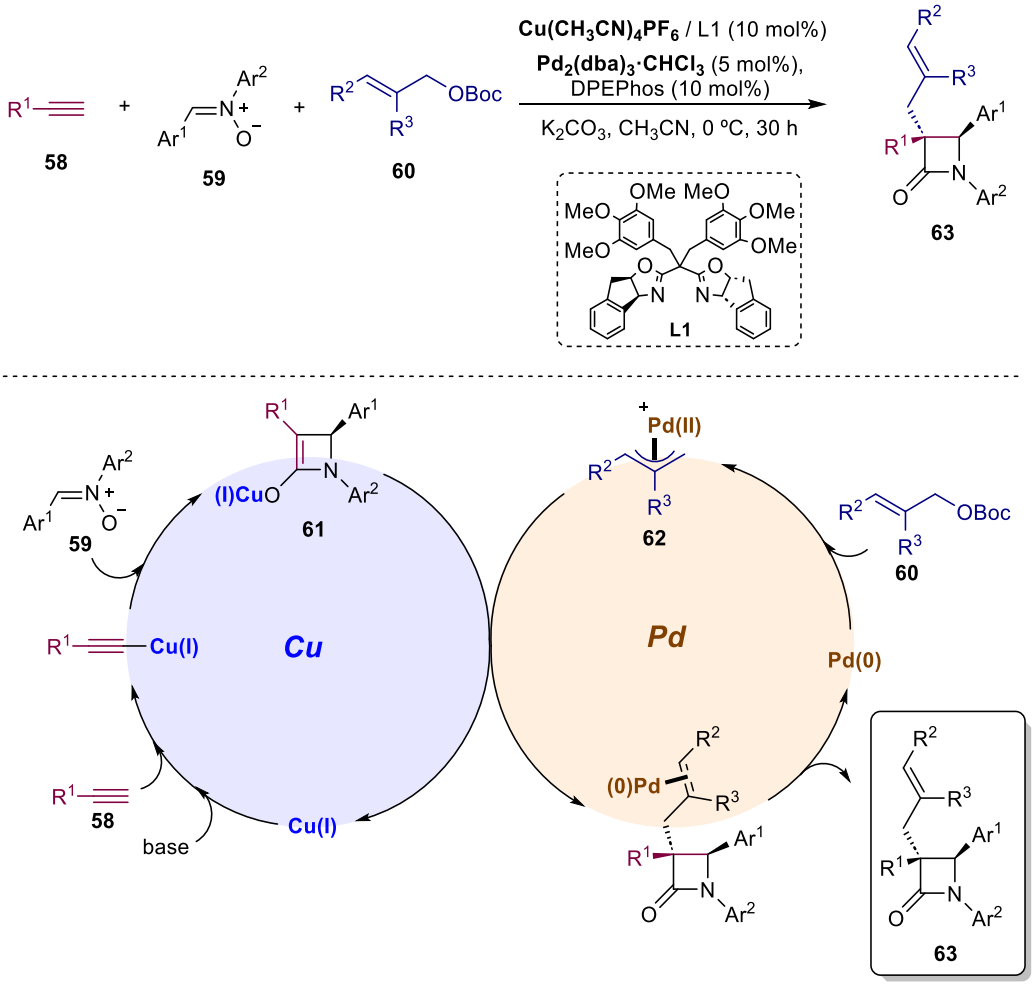
In 2018, Lee and coworkers developed a novel asymmetric dual-Rh(II)/Pd(0) relay catalysis method for the synthesis of α-quaternary allylated chiral β-lactams by reacting *N*-benzyl α-diazoamides (**54**) and allyl *tert*-butyl carbonates (**55**). (Scheme 13) [50]. The experiments conducted in this work supported a relay reaction with the formation of β-lactam intermediate (**56**) that resulted in the desired α-quaternary allylated chiral β-lactams (**57**). Optimization showed that nonhalogenated and nonpolar solvents yielded superior results compared to halogenated solvents. Different electron-donating and -withdrawing groups on the phenyl ring were well-tolerated. The position of substituents on the aromatic ring affected the reaction, with ortho substituents exhibiting reduced reactivity due to steric hindrance. Heteroaromatic rings and naphthyl rings demonstrated favorable performance. This method was found to be versatile, with yields of up to 99% and good diastereomeric ratios (up to >91:1 dr) and enantioselectivities (up to 98% ee). Furthermore, by varying the allylic substrates, given the widespread availability of the diazo compounds and allyl carbonates, this asymmetric dual-relay catalysis strategy may be a cornerstone for many

new reactions exploiting multimetallic transformations of Rh(II) carbenoids and π-allyl Pd(II) complexes.



Scheme 13. General conditions and plausible mechanism for the preparation of allylated chiral β-lactams using a Rh(II)/Pd(0)-bimetallic catalyzed approach.

Xu and coworkers successfully disclosed a groundbreaking asymmetric multicomponent reaction: interrupted Kinugasa allylic alkylation (Scheme 14) [51]. This methodology synergistically merges a copper-catalyzed Kinugasa system with a palladium-catalyzed allylic alkylation. This remarkable reaction enables the synthesis of α-quaternary chiral β-lactams from simple and readily available alkynes (**58**), nitrones (**59**), and allylic carbonates (**60**), with high yield (up to 87%) and excellent stereoselectivity (up to 96:4 er). The most plausible mechanism can be initiated with the cycloaddition of Cu(I) acetylide and nitrones; a pivotal chiral four-membered enolate Cu(I) intermediate (**61**) is formed. Simultaneously, the palladium catalyst reacts with the allylic electrophile, resulting in the creation of an allylic palladium intermediate (**62**). Subsequent stereo-controlled allylic substitution between **61** and **62** leads to the desired α-quaternary chiral β-lactams (**63**), while concurrently regenerating both the Cu(I) and Pd(0) catalysts. This one-pot approach is distinguished by a well-programmed reaction sequence, highly efficient formation of multiple bonds in asymmetric multicomponent reactions, and the construction of medicinally important α-quaternary chiral β-lactams, anticipating its utility in the synthesis of other biologically attractive molecules. Furthermore, in 2023, the same research group reported a novel bimetallic system, substituting the palladium with an iridium catalyst capable of accomplishing the synthesis of the same type of compounds [52].



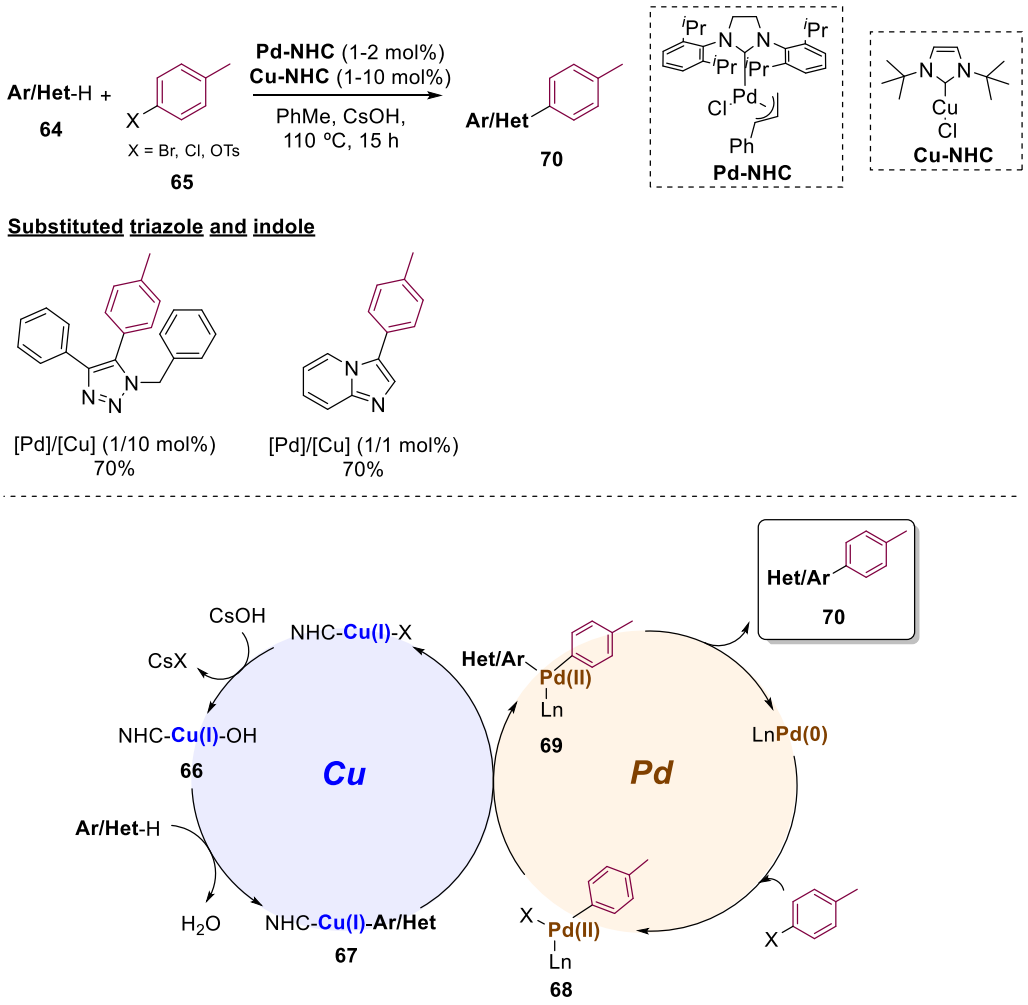
Scheme 14. General conditions and plausible mechanism for the preparation of α-quaternary chiral β-lactams using a Cu(I)/Pd(0)-bimetallic catalyzed approach.

5. Bimetallic Approaches Involving Triazole and Tetrazole Scaffolds

Triazoles and their derivatives are important *N*-heterocyclic scaffolds in medicinal chemistry, presenting significant biological properties, such as antimicrobial, antiviral, antitubercular, anticancer, antioxidant, and anti-inflammatory activities, among others [53]. The wide range of bioactivity displayed by these *N*-heterocycles has stimulated the development of many synthetic strategies.

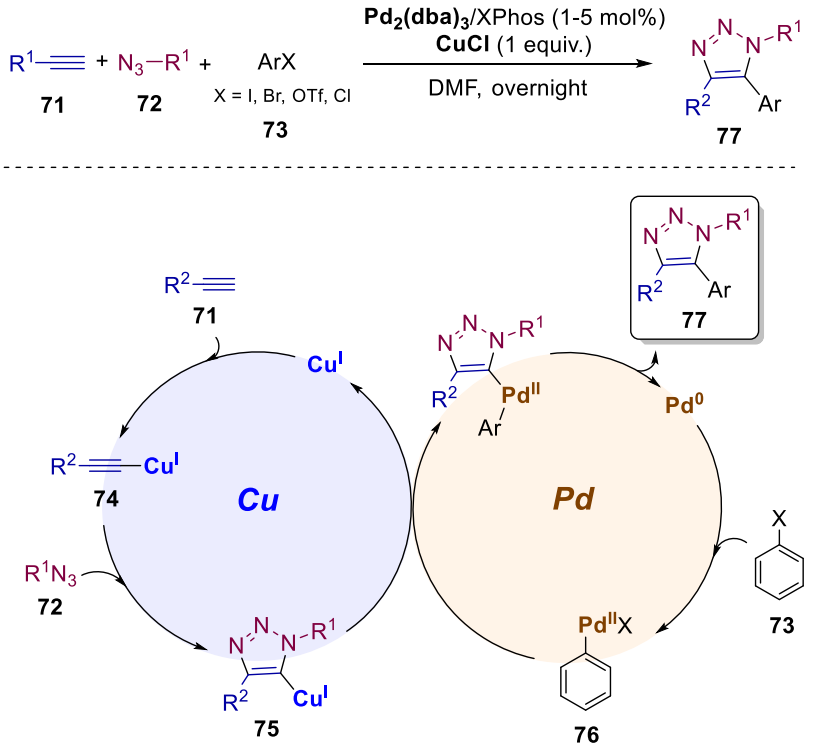
C−H activation is a hot topic in all areas of chemistry, and in comparison to the well-established cross-coupling reactions, it removes the need for prefunctionalization of both coupling partners [54]. Considering the inferior reactivity of arenes when compared to aryl halides, their selective and direct arylation remains a challenge. These issues can be addressed by the presence of directing groups on the arene substrate; however, this may result in a limited scope, since the directing group strictly facilitates the activation in the *ortho*-positioned C–H bond. In this context, in 2014, Cazin and coworkers developed a process that promotes the construction of C–C bonds through an intermolecular direct arylation, which eliminated the need for directing groups (Scheme 15) [55]. The scope of this reaction included the functionalization of *N*-heterocycles, triazole, and indole rings. The authors reported a novel Cu/Pd bimetallic catalytic system to promote C−H activation from arenes or heteroarenes (**64**) using aryl halides (**65**). Both Pd and Cu complexes were composed of imidazole-based ligands (Pd/Cu-NHC), with 20 examples and yields of up to 98%. The authors performed mechanistic studies that allowed them to propose a catalytic cycle, first including the formation of the hydroxide [Cu(OH)(NHC)] (**66**) by transmetalation involving CsOH. Then, an acid–base reaction promoted the C–H activation

of the heteroaryl, producing **67** and H_2O. The transmetalation between **67** and the Pd(II) catalyst (**68**) leads to the regeneration of the Cu(I) catalyst and the Pd(II) intermediate (**69**). Finally, product **70** is released after reductive elimination, and the Pd(0) catalyst is regenerated, completing the catalytic cycle.



Scheme 15. General conditions and plausible mechanism for the preparation of functionalized N-heterocycles, including triazole and indole scaffolds, using a Cu(I)/Pd(0)-bimetallic catalyzed approach.

A crucial limitation of the famous click reaction remains the difficulty of obtaining fully substituted 1,2,3-triazoles from internal alkynes as substrates, owing to the increased energy barrier and difficulty in regiocontrol, particularly for intermolecular reactions [56]. Nevertheless, in 2015, Xu and coworkers successfully synthesized 1,4,5-trisubstituted 1,2,3-triazoles by relying on Cu/Pd transmetalation relay catalysis, a modular synthesis method that afforded trisubstituted triazoles from the reaction between alkynyl substrates (**71**) with azides (**72**) and aryl halides (**73**) (Scheme 16) [57]. This reaction makes it possible to freely install three different substituents onto the triazole ring in one step, with a total of 33 examples and yields of up to 98%. The most plausible mechanism starts with the cycloaddition of Cu(I) acetylide (**74**) with azide and generates cuprate−triazole intermediate **75**. Simultaneously, oxidative addition of aryl halide to Pd(0) catalyst forms the palladium intermediate (**76**). The transmetalation reaction between **75** and **76**, followed by reductive elimination, produced the target trisubstituted triazole (**77**) and regenerated the Pd(0) catalyst.

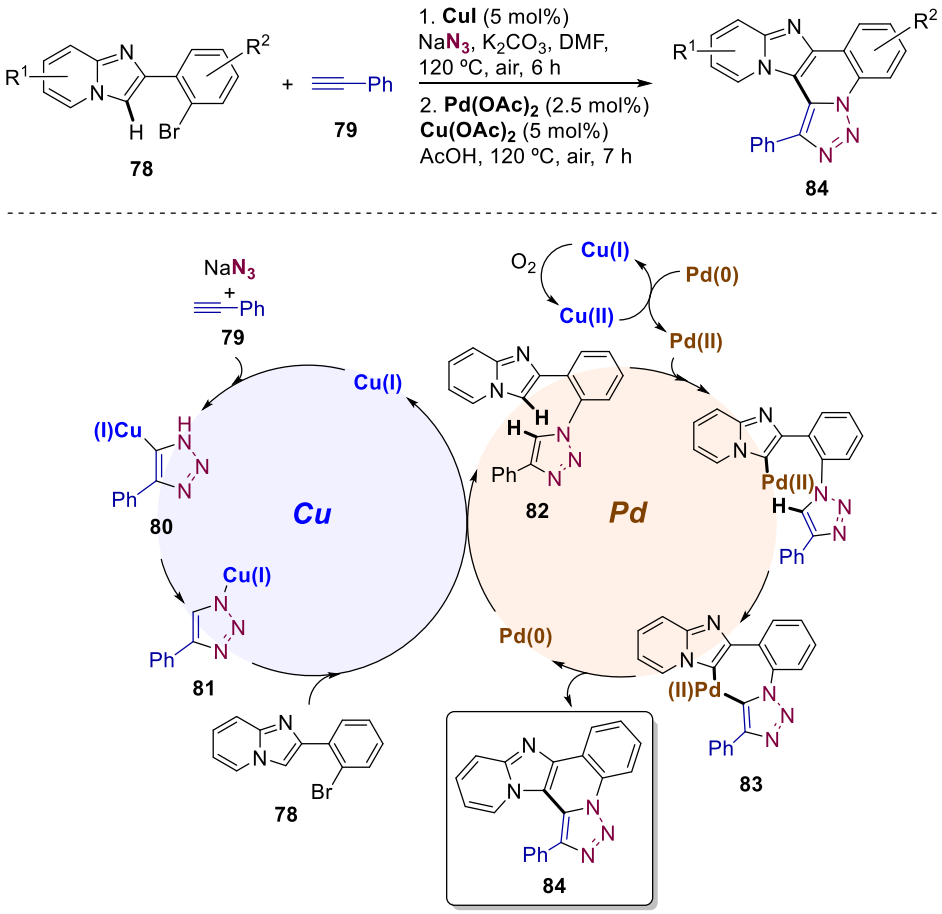


Scheme 16. General conditions and plausible mechanism for the preparation of 1,4,5-trisubstituted 1,2,3-triazoles using a Cu(I)/Pd(0)-bimetallic catalyzed approach.

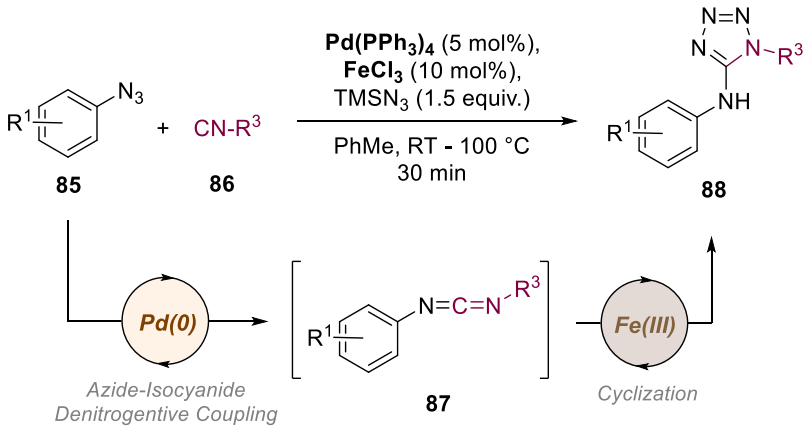
Imidazo [1,2-α]pyridine constitutes a valuable skeleton for a variety of pharmaceuticals [58,59]. Hence, different strategies for the preparation of these scaffolds have been implemented [60–62]. Although there is already a report bearing a Cu-catalyzed process to obtain 1,2,3-triazole-fused imidazo [1,2-α]pyridines, it relies on brominated imidazo [1,2-α]pyridines as substrates [63]. To optimize the atomic economy and environmental aspects of this process, in 2016, Fan and coworkers reported an efficient one-pot synthesis of 1,2,3-triazole/quinoline-fused imidazo [1,2-α]pyridines starting from 2-(2-bromophenyl)imidazo [1,2-α]pyridines (**78**), alkynes (**79**), and sodium azide (Scheme 17) [64]. This involved a cascade one-pot bimetallic Cu/Pd relay-catalyzed process combining azide–alkyne cycloaddition, C−N coupling, and cross-dehydrogenative C−C coupling. They obtained different alkynes and 2-(2-bromophenyl)imidazo [1,2-α]pyridines, with a total of 24 examples and yields of up to 74%. Fan suggested that the mechanism started with a Cu(I)-catalyzed azide−alkyne cycloaddition to afford intermediate **80**. Then, **81** forms as a result of a copper–hydrogen exchange. C−N coupling between **78** and **81** results in the formation of key intermediate **82**. In the second phase of this cascade process, aromatic palladation of **82** by a sequence of C−H bond cleavage yields a seven-membered palladacycle (**83**). Finally, reductive elimination affords the final 1,2,3-triazole/quinoline-fused imidazo [1,2-α]pyridine (**84**), and Pd(0) is re-oxidized into Pd(II) by Cu(II)/atmospheric O_2.

In 2018, Sawant and colleagues developed a fast and efficient method to produce aminotetrazoles (Scheme 18) [65]. The authors used aryl azides (**85**), isocyanides (**86**), and $TMSN_3$ in a sequential Pd(0)/Fe(III)-catalyzed reaction. The process involved a Pd-catalyzed reaction to generate carbodiimide (**87**) in situ, which then reacted with $TMSN_3$ in the presence of $FeCl_3$, all in one pot, yielding the respective aminotetrazole (**88**). This approach has advantages over traditional methods that use toxic Hg and Pb salts in large amounts. With the optimized conditions in hand, the authors investigated the reaction's versatility, showing various aryl azides with different substituents, including electron-donating and electron-withdrawing groups, which reacted well with different isocyanides and TMS-N_3 to produce the corresponding 5-amino-1*H*-tetrazoles. Substituents at all three positions of the aryl azides were well-tolerated—even *ortho* substituents that usually

represent steric hindrances. Alkyl-, cycloalkyl-, and aryl-substituted isocyanides reacted successfully under the optimized conditions, obtaining 19 examples and yields of up to 90%, although aryl isocyanides with electron-donating groups and aliphatic azides did not react under the standard conditions.



Scheme 17. General conditions and plausible mechanism for the preparation of 1,2,3-triazole/quinoline-fused imidazo [1,2-α]pyridines using a Cu(I)/Pd(II)-bimetallic catalyzed approach.

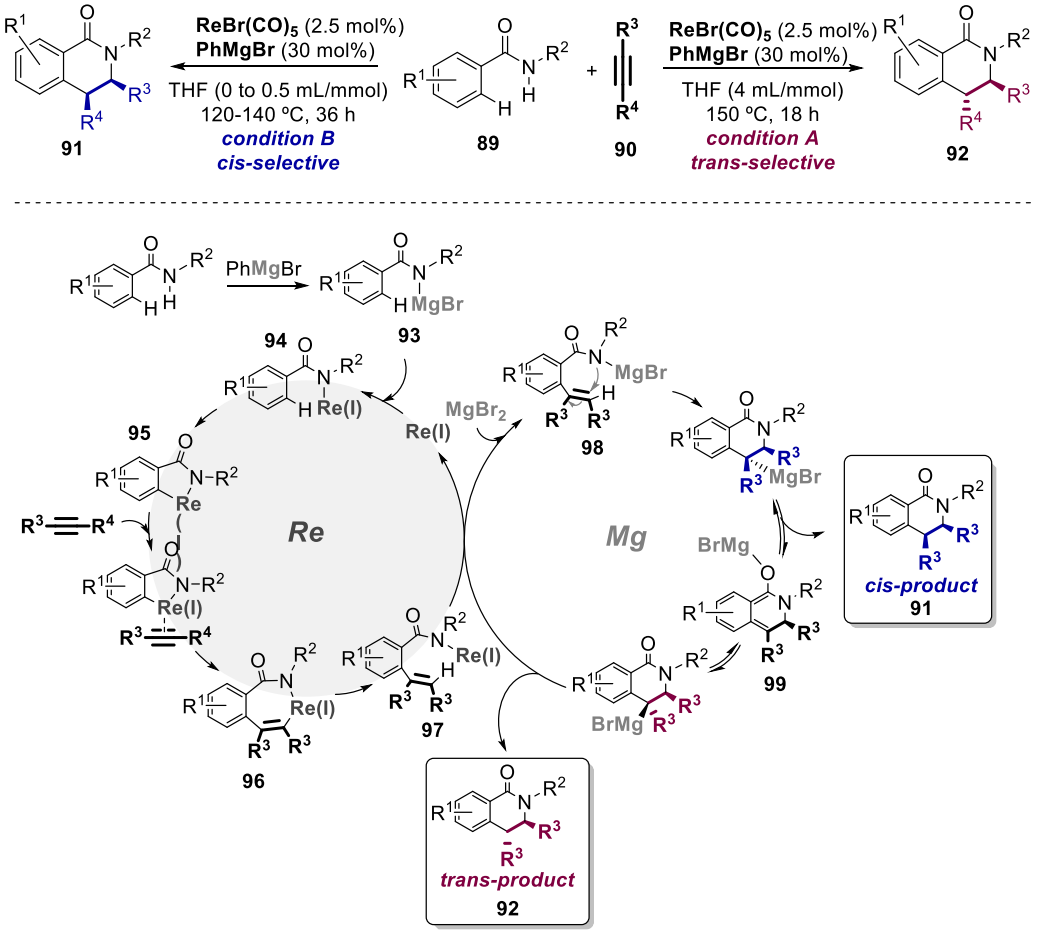


Scheme 18. General conditions and plausible mechanism for the preparation of aminotetrazoles using a Pd(0)/Fe(III)-bimetallic catalyzed approach.

6. Bimetallic Approaches Involving Pyridine, Pyrimidine, and Related Scaffolds

Isoquinolinones can be prepared via metal-catalyzed C−H activation [66–68]. However, this process bears the requirement of internal/external oxidants, and in the case of

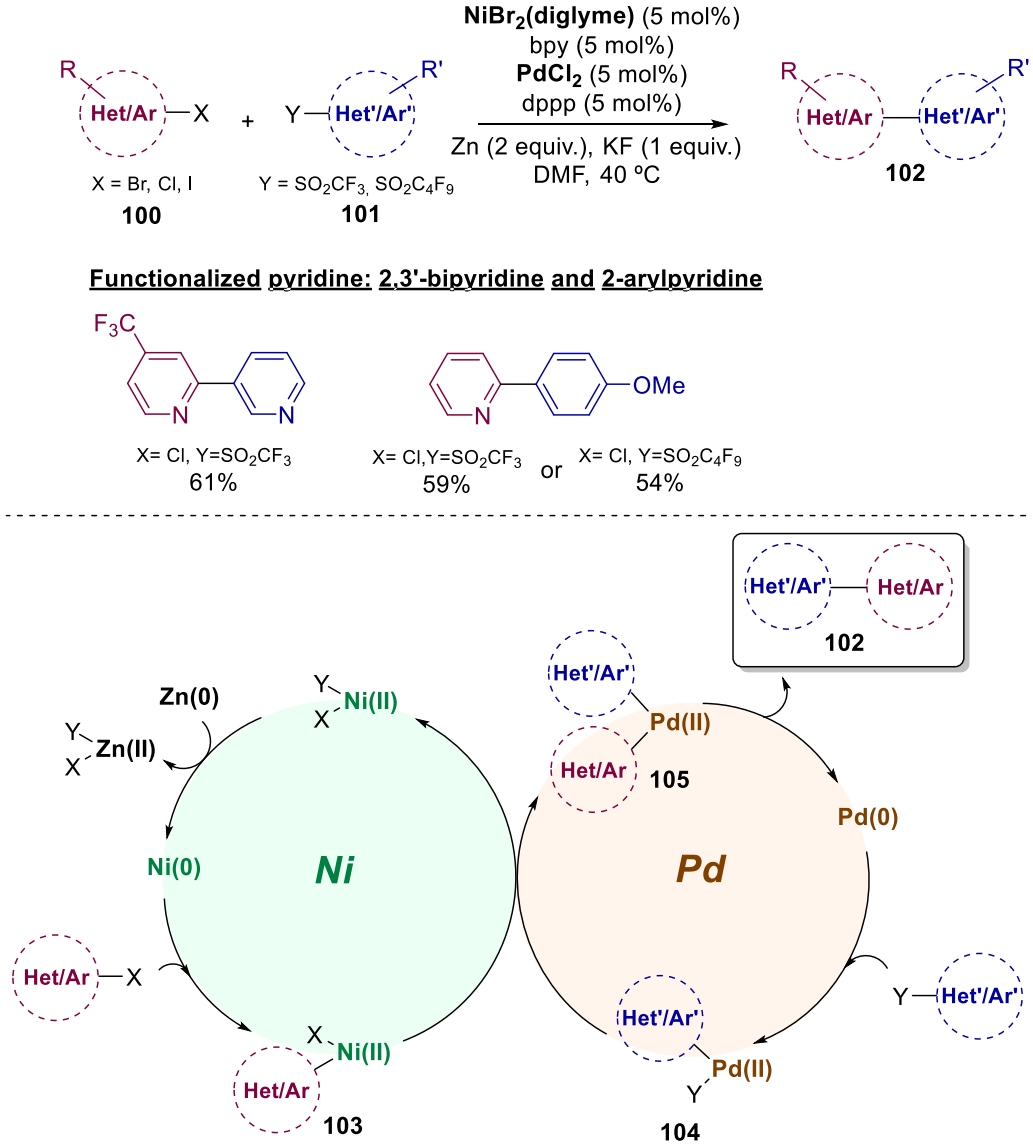
3,4-disubstituted isoquinolinones, poor diastereoselectivity is encountered. To overcome these limitations, in 2013, Wang and coworkers disclosed the first redox-neutral Re^{I}/Mg^{II}-cocatalyzed [4+2] annulation of benzamides (**89**) and alkynes (**90**) via C−H/N−H functionalization to afford both cis- and trans-3,4-dihydroisoquinolinones (**91** and **92**, respectively) in a highly diastereoselective fashion (Scheme 19) [69]. This was achieved by subtle tuning of reaction conditions, adding further values to this bimetallic catalyst system. Both cis- and trans-disubstituted scaffolds were formed in a total of 44 examples, with yields of up 90% and isomer ratios of up to 36:1 and 16:1, respectively. Mechanistic experiments were conducted, which allowed the authors to formulate a plausible reaction mechanism. With the aid of PhMgBr, via amido-magnesium (**93**), amido-rhenium (**94**) is initially formed, which then undergoes a deprotonative cyclorhenation, affording rhenacycle **95**. The ensuing coordination and insertion of an alkyne gives rise to a seven-membered rhenacycle (**96**), which further leads to intermediate **97** upon protonation. Transmetalation results in a new amido-magnesium intermediate (**98**), which undergoes an intramolecular nucleophilic addition/cyclization, generating the cis product or leading to the trans product via intermediate **99**. Protonation of these species affords the final products and regenerates the amido-magnesium (**93**), ending all Re/Mg bimetallic tandem catalytic cycles.



Scheme 19. General conditions and plausible mechanism for the preparation of *cis*- and *trans*-3,4-dihydroisoquinolinones using a Re(I)/Mg-bimetallic catalyzed approach.

Cross-Ullmann couplings are amongst the most common procedures to obtain biaryls. Nevertheless, a crucial challenge of cross-Ullmann reactions remains the achievement of selectivity for the heterocoupling product over the homocoupling [70]. Un 2015, Ackerman and coworkers developed a method to couple aryl halides (**100**) with aryl triflates (**101**), affording heterocoupled bi(hetero)aryls (**102**) through a Ni/Pd bimetallic catalyzed cross-

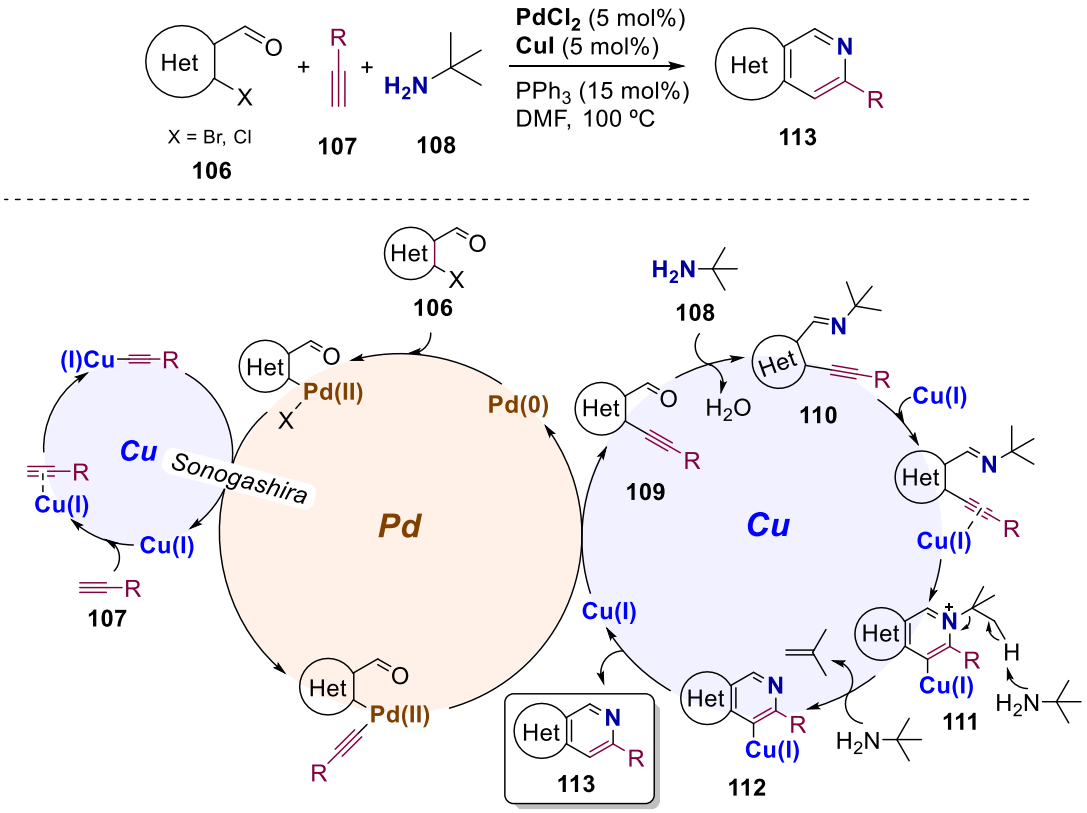
Ullmann coupling (Scheme 20) [71]. The selectivity was envisioned by the orthogonal reactivity of the two catalysts and the relative stability of the two arylmetal intermediates. Initially, each catalyst formed less than a 5% yield of the cross-coupled product. However, a total of 20 examples were described, achieving yields of up to 94%. This new method can obtain biaryls; heteroaryls; dienes; and, specifically, *N*-heterocycles by functionalization of the pyridine ring, affording 2,3′-bipyridine and 2-arylpyridine. The authors suggest that the mechanism of this cross-Ullmann reaction undergoes a bimetallic approach, where the Ni catalyst reacts preferentially with aryl bromides to form a transient, reactive intermediate (**103**), while the Pd catalyst reacts preferentially with aryl triflates to afford a persistent intermediate (**104**). When each of the two catalysts activates only one of the two substrates, transmetalation occurs from nickel to palladium (**105**), which affords the final product by reductive elimination, regenerating the Pd(0) catalyst. A Ni(0) catalyst is reobtained with the help of a Zn(0) reductant.



Scheme 20. General conditions and plausible mechanism for the preparation of heterocoupled bi(hetero)aryls using a Ni(0)/Pd(0)- bimetallic catalyzed approach.

Copper-catalyzed electrophilic cyclization is highly attractive due to its low cost, easy availability, and high tolerance towards diverse functional groups. Nevertheless, relatively few synthetic studies have been conducted on Cu-catalyzed three-component

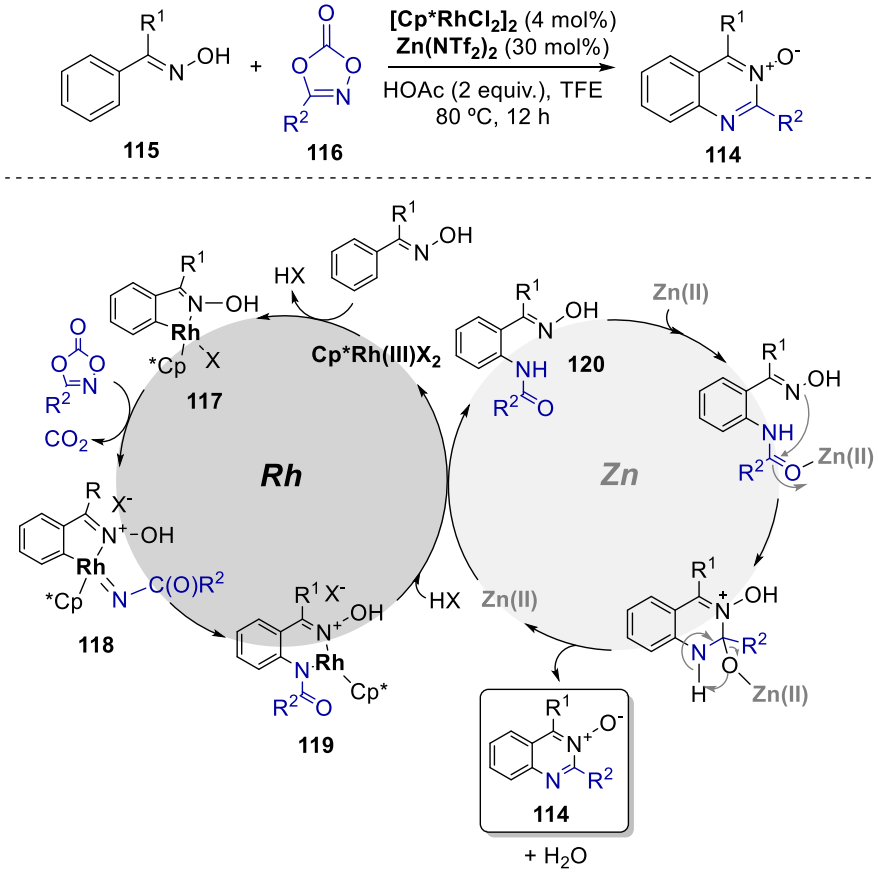
tandem reactions for the synthesis of polyheterocycles. Moreover, there has been no report showing the dual behavior of a Cu(I) catalyst, as well as *tert*-butylamine, for the synthesis of polyheterocycles. In 2016, Verma's group reported the synthesis of heterocyclic scaffolds starting from substrates (**106**) and alkynyls (**107**) via Pd(II)/Cu(I)-catalyzed Sonogashira coupling followed by a Cu(I)-catalyzed *6-endo-dig* cyclization, with *tert*-butylamine (**108**) as a nitrogen source (Scheme 21) [72]. Naphthyridines, isoquinolines, and benzothieno- and benzofuropyridines were prepared, with a total of 33 examples and yields of up to 83%. To provide insights into the mechanism, an array of preliminary control experiments was performed, revealing the dual role of Cu: to enhance the rate of Sonogashira coupling and to assist in electrophilic cyclization. The catalytic system involves the formation of C–C and C–N bonds via Sonogashira coupling and electrophilic cyclization, respectively. The authors suggest that initially, the ortho-halo aldehyde reacts with terminal alkynes under Sonogashira coupling conditions, generating the *ortho*-alkynyl aldehyde intermediate (**109**). The latter reacts with *tert*-butylamine and leads to the formation of imine 110. π-Complexation between 110 and Cu(I) facilitates the electrophilic cyclization and affords **111**. The presence of a *tert*-butyl group enhances the formation of intermediate **112** by the elimination of an isobutylene fragment. Finally, protodemetalation yields the desired cyclized pyridine-containing heterocycle (**113**).



Scheme 21. General conditions and plausible mechanism for the preparation of polyheterocycles using a Cu(I)/Pd(0)-bimetallic catalyzed approach.

The preparation of *N*-oxides of azacycles via direct C−H activation of arenes remains a highly underexplored challenge, with only a few reports on the synthesis of *N*-oxides of isoquinoline [73,74]. For this reason, in 2016, Li and coworkers prepared quinazoline-*N*-oxides **114** by a single-step C−H activation approach via a Rh(III)/Zn(II)-bimetallic catalyzed process. They selected simple substrates, such as ketoximes (**115**) and 1,4,2-dioxazol-5-ones (**116**) (Scheme 22) [75]. This annulation system proceeded with high efficiency under mild conditions, with H_2O and CO_2 as the coproducts, obviating any need for oxidants. A total of 32 examples of both oximes and dioxazolones was obtained

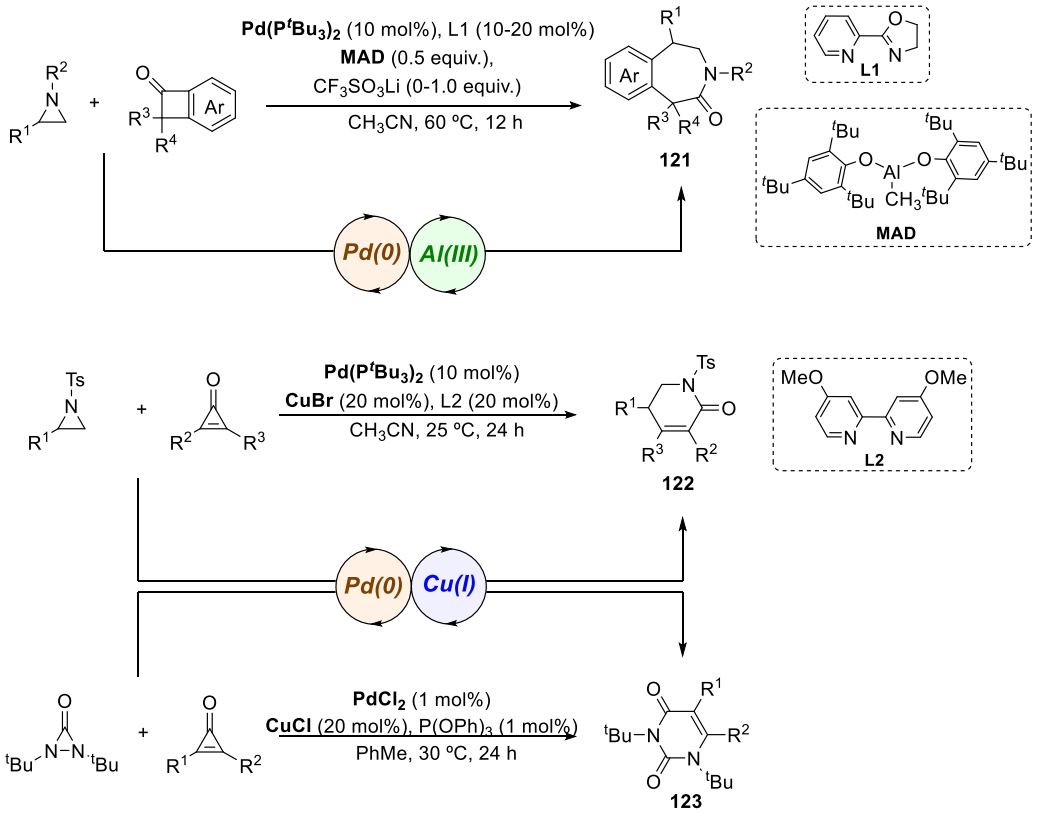
in yields of up to 95%. Preliminary mechanistic studies were constructed to gain insight into the mechanism of this annulation reaction, and the authors concluded that Rh(III) participated in the C−H activation–amidation of the ketoximes and Zn(II) in the cyclization. The authors suggested that, first, an active rhodium catalyst (Cp^*RhX_2, where X = NTf_2 or OAc) is generated from the anion exchange between $[RhCp^*Cl_2]_2$ and $ZnNTf_2$ or HOAc. Next, the oxime reagent undergoes a cyclometallation to afford the rhodacyclic intermediate (**117**) and an acid via a concerted metalation−deprotonation mechanism. Coordination of dioxazolone is followed by decarboxylation with CO_2 elimination, yielding a nitrenoid species (**118**), and subsequent migratory insertion of the Rh-aryl bond produces the amidate (**119**). Protonolysis of the latter releases the amidated intermediate (**120**) and regenerates the Rh(III) complex. Zn(II) then catalyzes the cyclization and condensation of **120**, furnishing the final quinazoline *N*-oxide (**114**).



Scheme 22. General conditions and plausible mechanism of the preparation of quinazoline *N*-oxides using a Rh(III)/Zn(II)-bimetallic catalyzed approach.

In 2021, Zhao and coworkers developed a general ring expansion strategy that enables the efficient and scalable synthesis of diverse *N*-heterocycles (Scheme 23), such as 3-benzazepinones (**121**) (up to 90% yield), dihydropyrimidinones (**122**) (up to 91% yield), and uracils (**123**) (up to 98% yield) [76]. The designed concept is based on the use of synergistic bimetallic catalysis to promote a formal cross-dimerization reaction between three-membered aza-heterocycles and three- and four-membered ring ketones. The authors presented a novel methodology that combines strain-release-induced oxidative C−C bond cleavage and C−N bond cleavage, effectively expanding the scope for stereospecific *N*-heterocycle synthesis. In this route, the palladium complex serves as the main catalyst for the reactions, although aluminum and copper, which function as Lewis acids, are also highlighted as critical components in this pathway. This approach provides a versatile and reliable method for the synthesis of 3-benzazepinones, dihydropyrimidinones, and uracils,

showcasing its flexibility and significant potential in the synthesis of complex molecules through transition-metal-catalyzed formal cross dimerization of cyclic compounds.

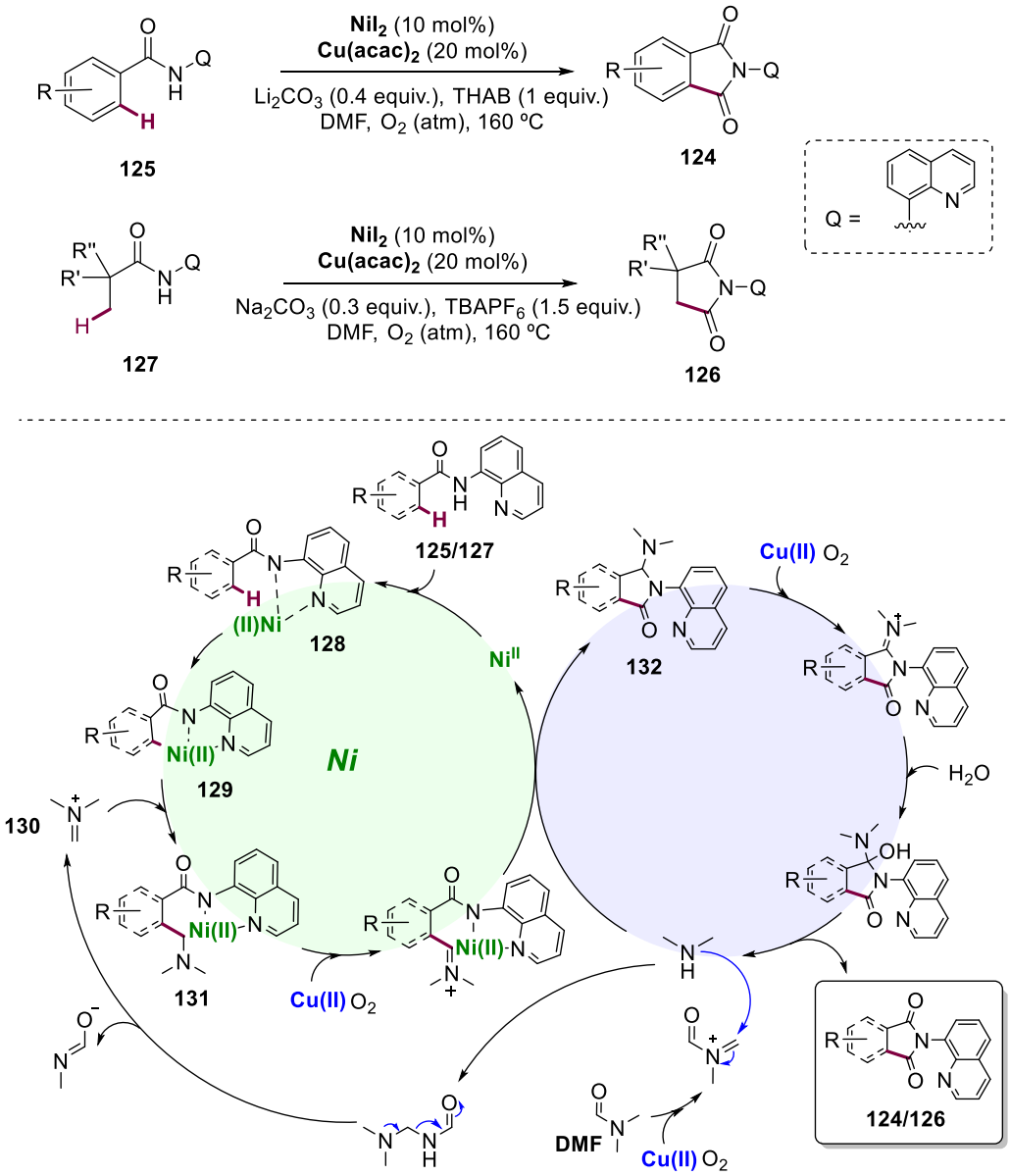


Scheme 23. General conditions for the preparation of 3-benzazepinones using a Pd(0)/Al(III)-bimetallic catalyzed approach and dihydropyrimidinones and uracils using a Pd(0)/Cu(I)-bimetallic catalyzed approach.

7. Bimetallic Approaches Involving Other *N*-Heterocyclic Scaffolds

Within the metal-catalyzed C−H functionalization reaction class, direct carbonylation has attracted considerable attention in recent years due to the prevalent presence of the carbonyl group in organic molecules. The direct carbonylation of C(sp^3)−H bonds has been demonstrated by transition-metal-catalyzed processes, although mainly relying on the use of toxic CO gas at high pressure [77–79]. To overcome this limitation, in 2015, Ge and coworkers described the direct carbonylation of aromatic sp^2 and unactivated sp^3 C−H bonds of amides via a Ni/Co bimetallic catalysis with *N*,*N*-dimethylformamide (DMF) as the carbonyl source (Scheme 24) [80]. The reactions were performed under atmospheric O_2, and the substrates were constituted by a bidentate directing group (Q). The authors provided aryl-substituted phthalimides (**124**) from aromatic amides (**125**), achieving yields of up to 90% under optimized conditions, as well as 3,3′-disubstituted succinimides (**126**) from aliphatic amides (**127**), with yields of up to 81%. Preliminary control experiments elucidated that both nickel and copper catalysts are required for this process, suggesting that this reaction is performed via synergistic catalysis. The authors suggested that the process starts with the coordination of amide **125/127** to Ni(II) via a ligand exchange under basic conditions, forming complex **128**. Then, cyclometalation of **128** occurs via either sp^2 or sp^3 C−H bond activation to generate intermediate **129**, keeping in mind that sp^2 C−H bond cleavage is a reversible step, while sp^3 is irreversible. Electrophile **130** is then inserted into the catalytic cycle, generated in situ from DMF. This results in decarboxylation or an elimination process via Cu(II)/O_2. These intermediates react through a nucleophilic addition and sequential decarbonylation. The nucleophilic addition of the intermediate **C** to the iminium ion intermediate (**130**) provides **131**. Oxidation of the latter followed by

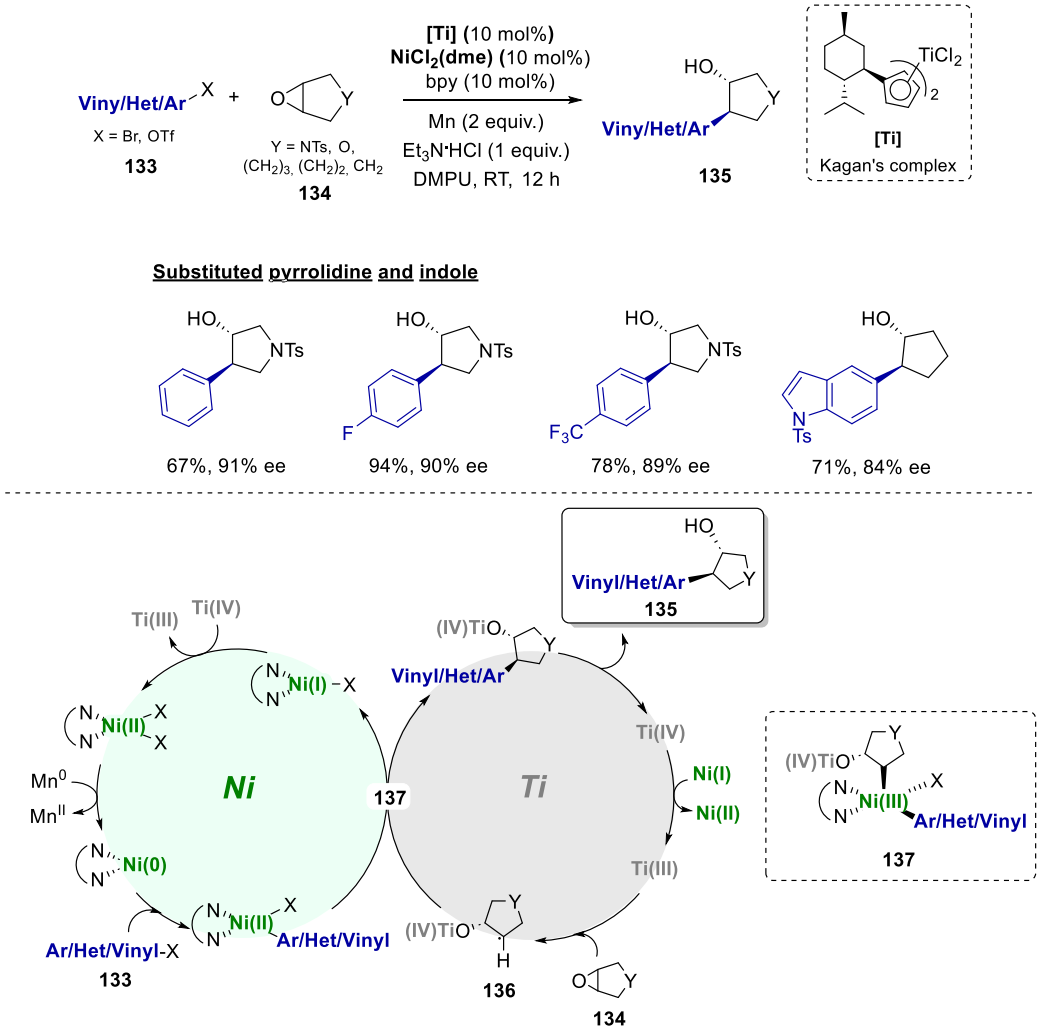
intramolecular nucleophilic addition gives rise to intermediate **132**, which then produces product **124** or **126** via oxidation by Cu(II) and hydrolysis.



Scheme 24. General conditions and plausible mechanism of the preparation of phthalimides and 3,3′-disubstituted succinimides using a Ni(II)/Cu(I)-bimetallic catalyzed approach.

The enantioselective coupling of aryl and vinyl nucleophiles with meso-epoxides is considered to be highly challenging, with the best results to date resorting to aryl lithium reagents and chiral ligands [81,82]. In this context, in 2015, Zhao and Weix reported an enantioselective cross-electrophile coupling of aryl halides (**133**) with *meso*-epoxides (**134**) to form *trans*-β-arylcycloalkanols (**135**) from a novel bimetallic Ni(II)/Ti(III) catalytic system (Scheme 25) [83]. The reaction was catalyzed by a combination of (bpy)$NiCl_2$ and a chiral titanocene under reducing conditions. Different titanocenes were tested, and the one first reported by Cesarotti and coworkers [84] showed the highest yield and enantioselectivity. This enantioselective coupling of aryl, heteroaryl, or vinyl halides with *meso*-epoxides (28 examples) also included examples of the functionalization of pyrrolidine scaffolds and one example for indole, with yields of up to 94% and enantiomeric excesses of up to 91% ee. The authors suggested that the coupling mechanism (Scheme 25) was initiated by the enantioselective formation of a β-titanoxy carbon radical from the meso-epoxide

(**136**), followed by the oxidative addition of a β-titanoxy carbon radical to an arylnickel(II) intermediate, forming a diorganonickel(III) species (**137**), and the reductive elimination of the product (**135**). Finally, the reduction of both catalysts closes the catalytic cycle.



Scheme 25. General conditions and plausible mechanism of the preparation of *trans*-β-arylcycloalkanols using a Ni(0)/Ti(III)-bimetallic catalyzed approach.

8. Conclusions

Bimetallic catalysis offers the potential for synergistic effects and dual activation of reactants, leading to enhanced reactivity and selectivity. By employing two different metal catalysts in a sequential or concurrent manner, researchers have unlocked new synthetic pathways and achieved more efficient and selective transformations. In recent years, bimetallic catalysis has shown promising results in various organic transformations.

The diversity of metal combinations and reaction conditions available in bimetallic catalysis offers a versatile platform to access a wide array of *N*-heterocyclic compounds with diverse functionalities. This benefits not only the pharmaceutical industry, where these compounds play a crucial role in drug discovery, but also fine chemical industries, where *N*-heterocycles serve as important intermediates in the synthesis of various key chemicals.

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Conflicts of Interest: The authors declare no conflict of interest.

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