

Review

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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, essential building blocks in pharmaceuticals and fine chemicals. The cooperative action of two (and sometimes more) different metal catalysts enables intricate control over reaction pathways, enhancing selectivity and efficiency of *N*-heterocyclic compounds synthesis. 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.

## 1. Introduction

Catalysis plays a vital role in modern chemical synthesis, efficiently converting simple starting materials into valuable complex compounds. Bimetallic catalysis, involving 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 by-products [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 molecule synthesis [3,7].

One particularly promising area of bimetallic catalysis is the synthesis of *N*-heterocycles, essential building blocks in numerous biologically active compounds and pharmaceuticals [8]. Traditional synthetic routes for *N*-heterocycles have some drawbacks, involving multiple steps, harsh conditions, and generating 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 mono-metallic 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 atom efficiency, making the process more environmentally friendly and economically viable [3,7].

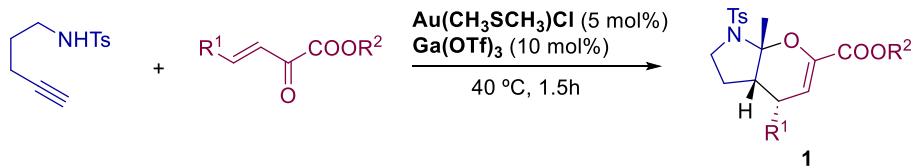
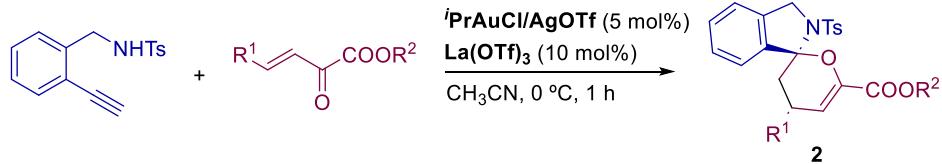
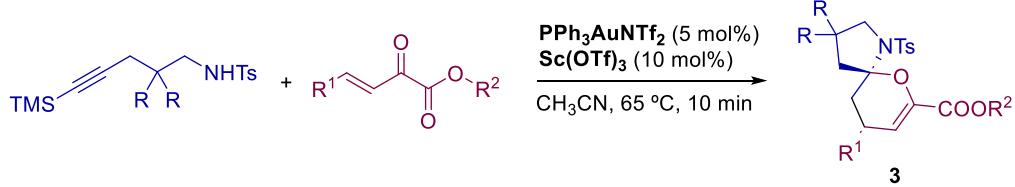
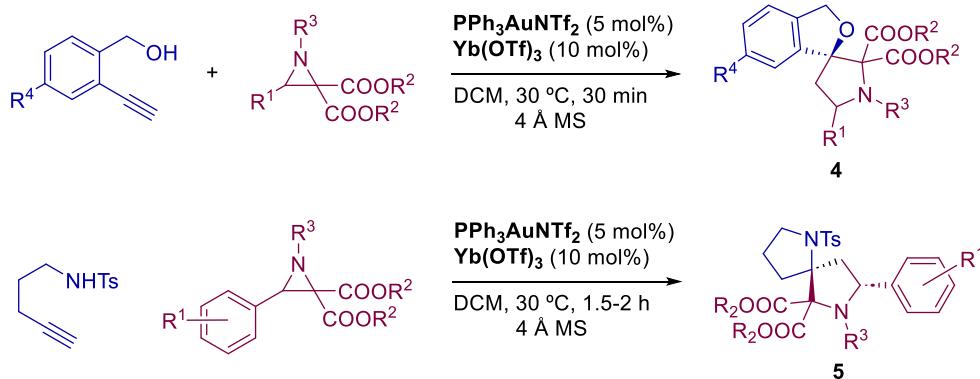
As the field continues to evolve, this review presents an overview of the recent developments concerning bimetallic sequential catalysis for the synthesis of *N*-heterocycles, which represents a promising avenue in catalysis.

## 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 [9]. In the conventional approach, *N,O*-aminals are derived either from the corresponding  $\alpha$ -amido sulfones via nucleophilic substitution, replacing the sulfonyl group with an alkoxy moiety [10–14], or from the corresponding imines by means of nucleophilic addition, introducing an alkoxy group [15–23].

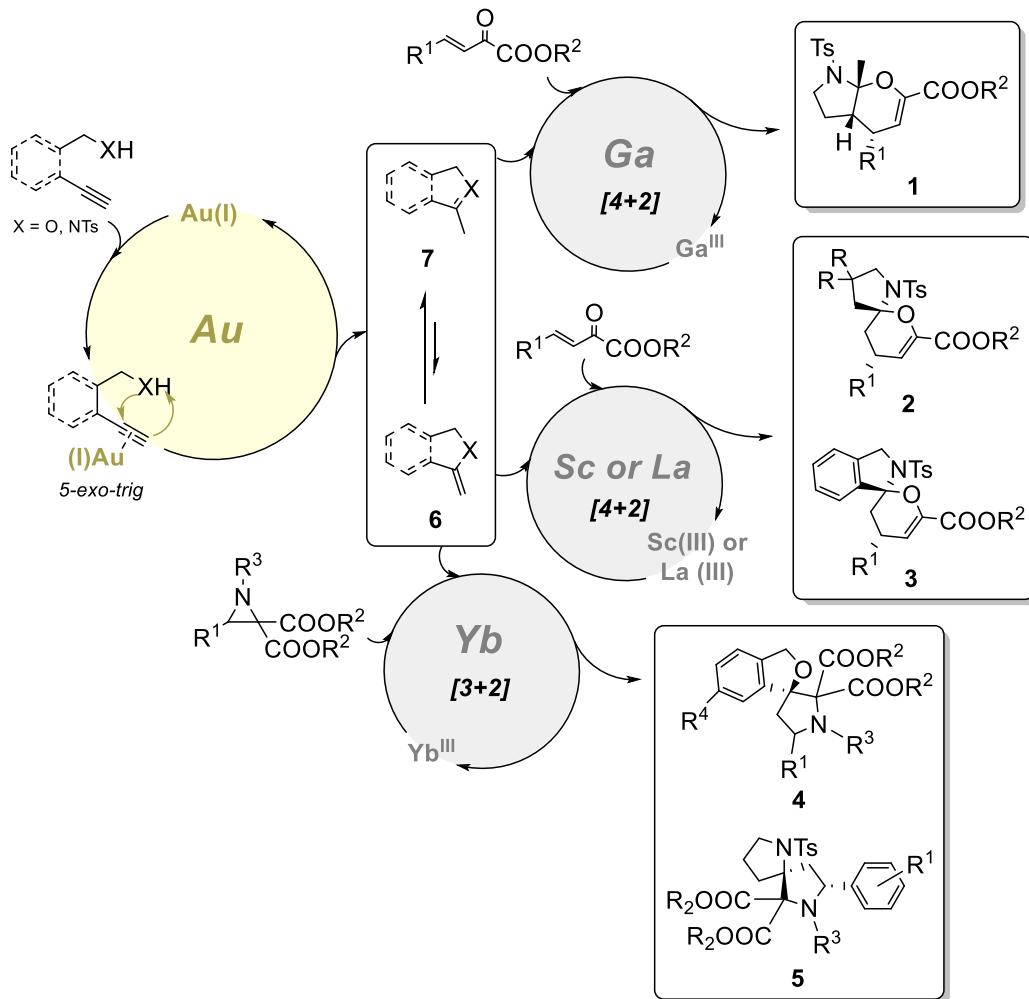
While several methods exist for synthesizing these compounds, enantioselective examples are still limited, particularly for the construction of chiral tetrasubstituted carbon centers [21]. Moreover, some of these methods do come with certain disadvantages such as the requirement of harsh reaction conditions, 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 by-products 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, where bimetallic catalysis has shown important perspectives [24].

Xu and co-workers has been actively developing synthetic processes for fused bicyclic *N,O*-aminals and spiro-*N,O*-aminals. The authors focused on bimetallic catalysis under mild conditions, utilizing Au(I) as a catalyst and a metallic Lewis acid as a co-catalyst. 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 scope and yields up to 90% (Scheme 1a) [25]. 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) [24]. 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 scope with yields 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) [26]. In this work, trimethylsilyl (TMS) was employed as a traceless controlling group to stabilize the derived enamide and inhibit its isomerization, resulting in a scope of 14 examples and yields up to 89%. Additionally, in 2016, Xu and co-workers reported the preparation of spiro-heterocycles through a Au(I)/Yb(III)-catalyzed diastereoselective [3+2] cycloaddition between aziridines and alkynyl substrates (Scheme 1d) [27]. Various *N*-protecting groups and aliphatic and aromatic alkynyl substrates were tested, resulting in a scope of substituted spiro-*N,O*-heterocycles **4** with 16 examples and yields up to 99%. Furthermore, by switching from alkynyl alcohols to alkynyl amides, a similar reaction with aziridines afforded aromatic-substituted spiro-*N,N*-heterocycles **5** with a scope of 9 examples and yields up to 80%.

a) *Org. Lett.* (2013)b) *Org. Lett.* (2014)c) *ChemComm* (2014)d) *Org. Lett.* (2016)

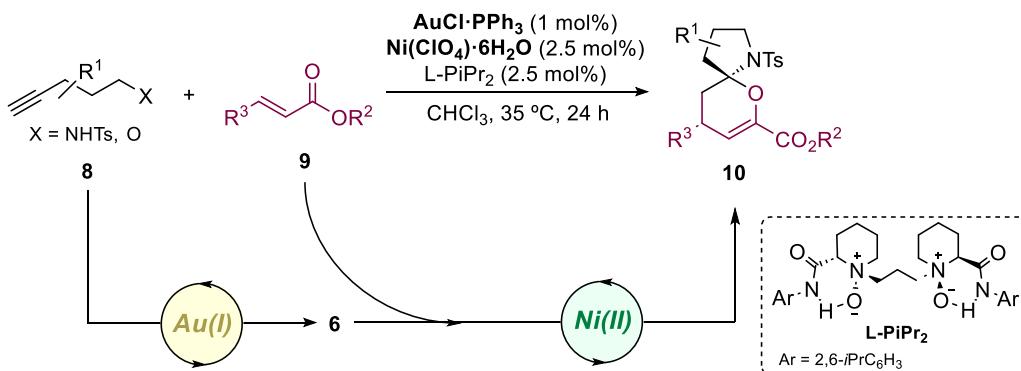
**Scheme 1.** Xu's contributions towards the bimetallic synthesis of fused bicyclic- and spiroaminals.

To gain insights into the reactions' mechanisms (Scheme 2), Xu and co-workers conducted deuteration experiments that showed that the alkynyl substrate undergoes a  $\text{Au(I)}$ -catalyzed  $5\text{-}exo$ -dig cyclization affording the 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.



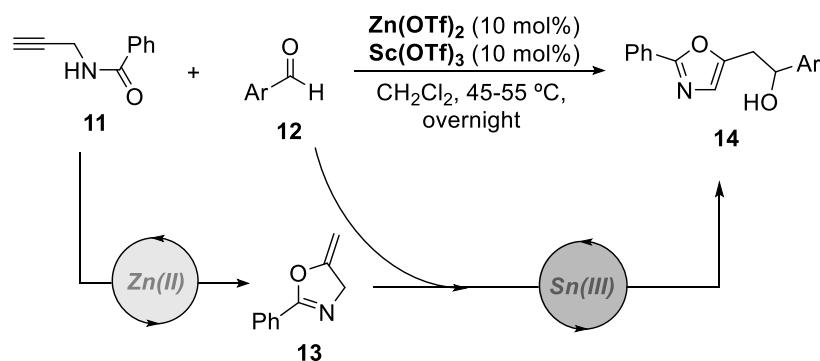
**Scheme 2.** A plausible mechanism of the Au/Lewis acid bimetallic synthesis of fused bicyclic- and spiroaminals by Xu's group.

In 2016, Li and co-workers described an innovative asymmetric cascade reaction between alkynyl amides **8** and keto esters **9**, employing a bimetallic catalytic system of achiral  $\pi$ -acid Au(I) and chiral Lewis acid  $N,N'$ -dioxide Ni(II) complex (Scheme 3) [28]. This approach enabled the synthesis of spiroaminals **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.



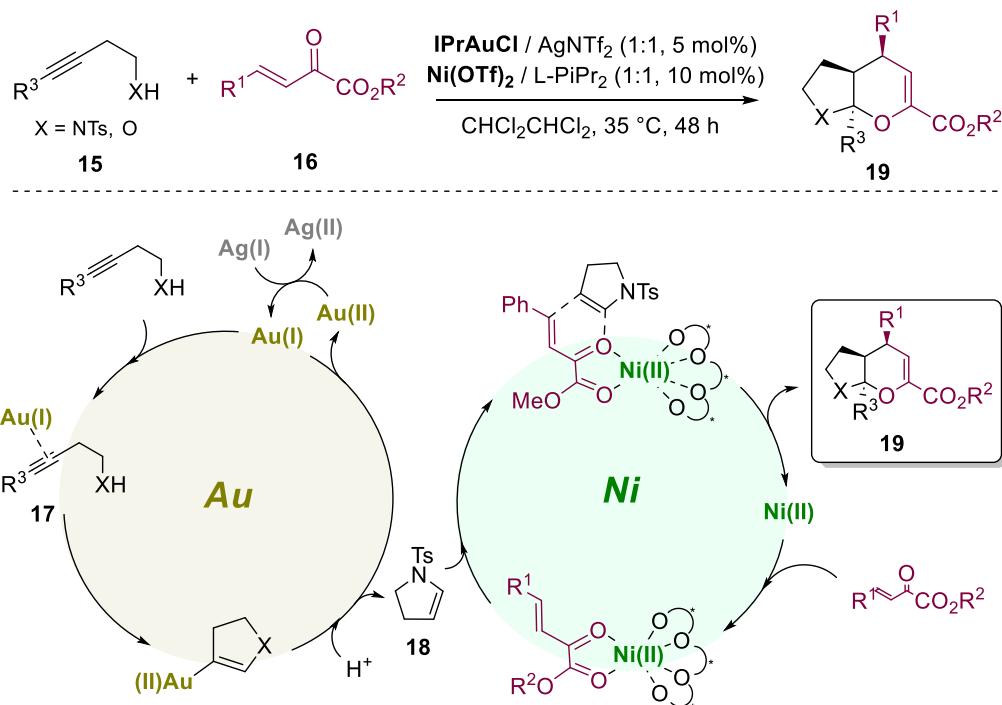
**Scheme 3.** General conditions for the preparation of spiroaminals by a Au(I)/Ni(II)-catalyzed bimetallic approach.

In 2016, another interesting bimetallic relay catalytic system was developed by the group of Xu, enabling the synthesis of oxazole derivatives from readily available *N*-(propargyl)-aryl amides and aldehydes under mild reaction conditions (Scheme 4) [29]. The system consists of  $Zn(OTf)_2$  and  $Sc(OTf)_3$ , which act as a  $\pi$  acid and a  $\sigma$  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 showed a great atom-economy and straightforwardness, possessing the potential for applications in organic synthesis and medicinal chemistry.



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

A similar work was reported by Feng's group in 2018 [30]. In this work, a similar efficient catalytic asymmetric cyclization reaction (Scheme 5) was conducted by 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,  $\beta,\gamma$ -unsaturated  $\alpha$ -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  $\beta,\gamma$ -unsaturated  $\alpha$ -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 p-gold-alkyne complex **17** and, in situ, generated the key cyclic intermediate **18**. On the other hand, chiral Lewis acid Ni(II)/L-PiPr<sub>2</sub> activated  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoester **16** reacts with **18**, giving the fused bicyclic acetal **19**.

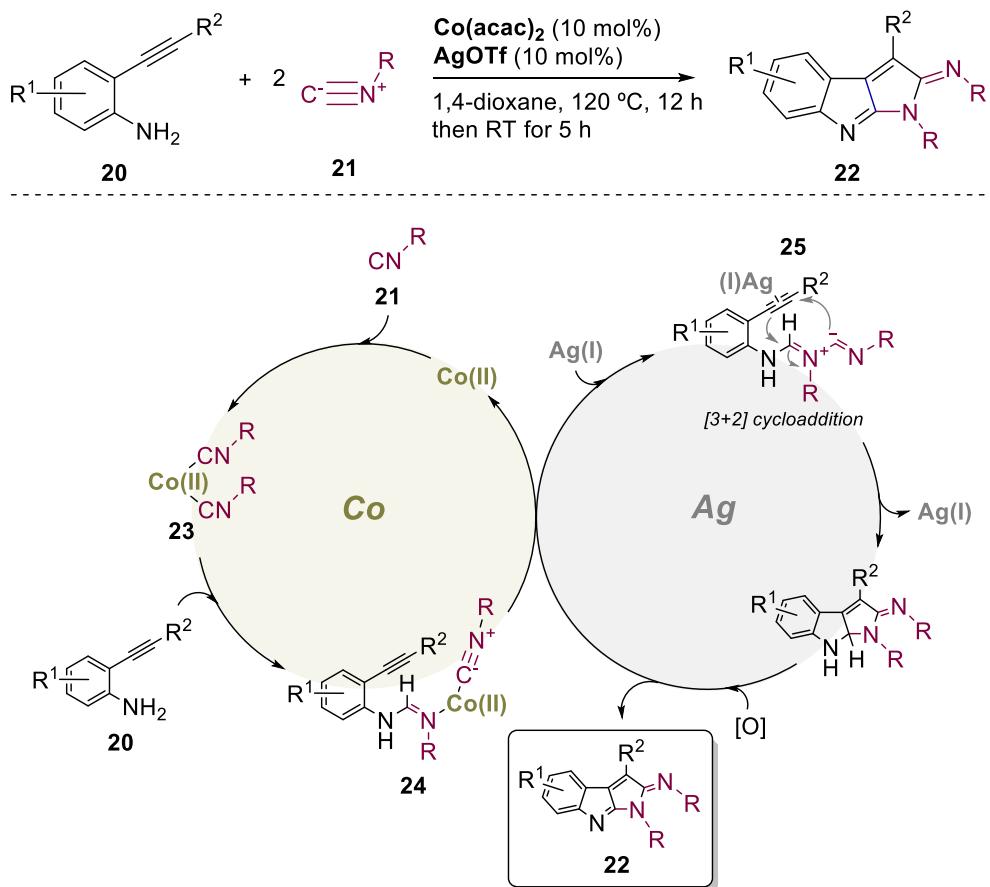


**Scheme 5.** General conditions and a plausible mechanism for the preparation of fused bicyclic acetals or aminals by a  $\text{Au(I)}/\text{Ni(II)}$ -catalyzed bimetallic approach.

### 3. Bimetallic Approaches Involving Indole Scaffolds

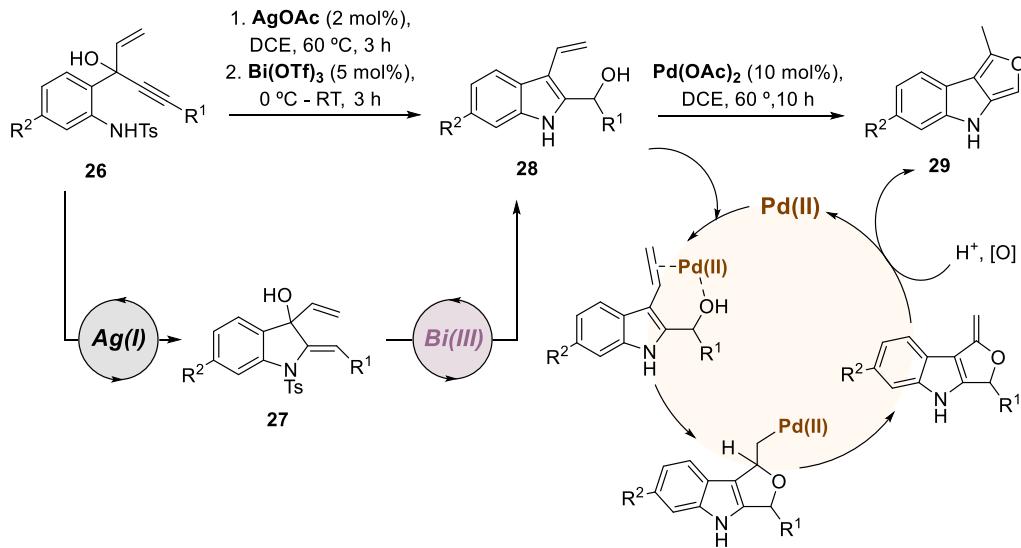
Indoles and indolines are of great importance in medicinal chemistry, pharmaceuticals, and natural product synthesis due to their involvement in various biological processes and structural significance. Several common methods for synthesizing indoles, including the Fischer indole synthesis, Bischler-Möhlau indole synthesis, Madelung indole synthesis, Reissert indole synthesis, and Buchwald-Hartwig amination, have been widely employed [31]. 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 by-products 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-*b*]indoles via catalyzed bicycloaddition reactions is a very attractive yet challenging process. Isocyanides happen to be a simple group and, taking advantage of their electrophilicity, can be inserted either by Lewis acid [32], or transition metal catalysis, undoubtedly with palladium as the most popular choice [33–35]. In contrast, Gao and co-workers, in 2015, explored the preparation of pyrrolo[2,3-*b*]indoles by an inexpensive  $\text{Co(II)}$ -enabled process (**Scheme 6**) [36]. The authors demonstrated that the combination of  $\text{Co}(\text{acac})_2$  and  $\text{AgOTf}$  promoted a bimetallic relay catalysis reaction between 2-ethynylanilines **20** and isocyanides **21**, allowing access to new densely functionalized pyrrolo[2,3-*b*]indoles **22**. Overall 26 examples were reported, in yields up to 86%. The authors suggested that the reaction pathway involves a  $\text{Co(II)}$ -catalyzed double isocyanide insertion followed by a  $\text{Ag(I)}$ -catalyzed 1,3-dipolar cycloaddition. A suitable mechanism for the formation of pyrrolo[2,3-*b*]indoles can be described by a ligand exchange, affording the 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  $\text{Co(II)}$  catalyst. The presence of  $\text{Ag(I)}$  allows an intramolecular 1,3-dipolar cycloaddition followed by dehydrogenation under air conditions, that leads to the desired thermodynamically stable pyrrolo[2,3-*b*]indole **22**.



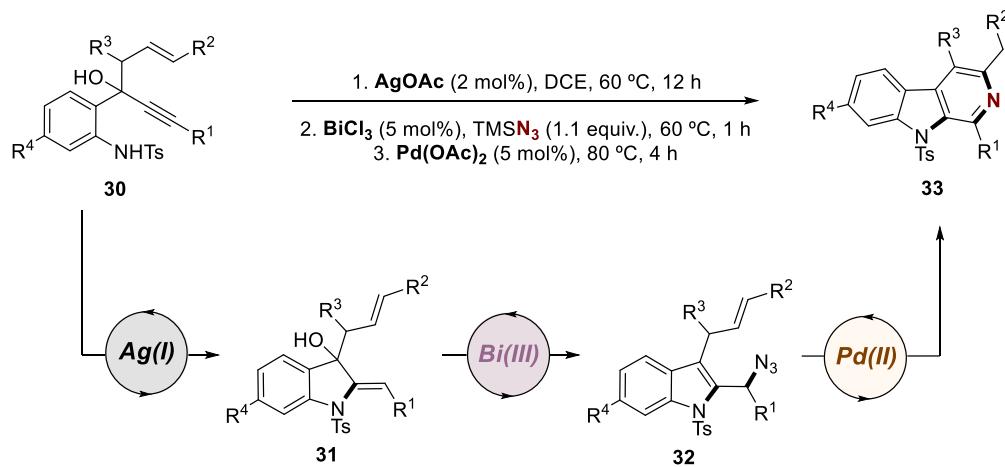
**Scheme 6.** General conditions and a plausible mechanism for the preparation of pyrrolo[2,3-β]indoles by a  $\text{Co}(\text{II})/\text{Ag}(\text{I})$ -catalyzed bimetallic approach.

In 2016, Ramasastry and co-workers 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 preparing furo[3,4-b] indoles (Scheme 7) [37]. This approach utilized a sequential  $\text{Ag}(\text{I})/\text{Bi}(\text{III})/\text{Pd}(\text{II})$  trimetallic catalysis, demonstrating its versatility with 10 examples and yields up to 57%. The preparation of cyclopenta[β]indoles was also investigated using a one-pot  $\text{Ag}(\text{I})/\text{Brønsted acid}$  catalysis from 3-(2-aminophenyl)-4-pentenyn-3-ols, although not involving a multimetallic catalytic approach. The reaction mechanism involved  $\text{Ag}(\text{I})$ -catalyzed 5-*exo*-dig cyclization of substrate 26 to generate intermediate 27, followed by  $\text{Bi}(\text{III})$ -catalyzed 1,3-allylic alcohol isomerization leading to 38. Finally, a  $\text{Pd}(\text{II})$ -catalyzed intramolecular etherification through a 5-*exo*-trig cyclization under oxidative conditions resulted in the desired furo[3,4-b]indole 29.



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

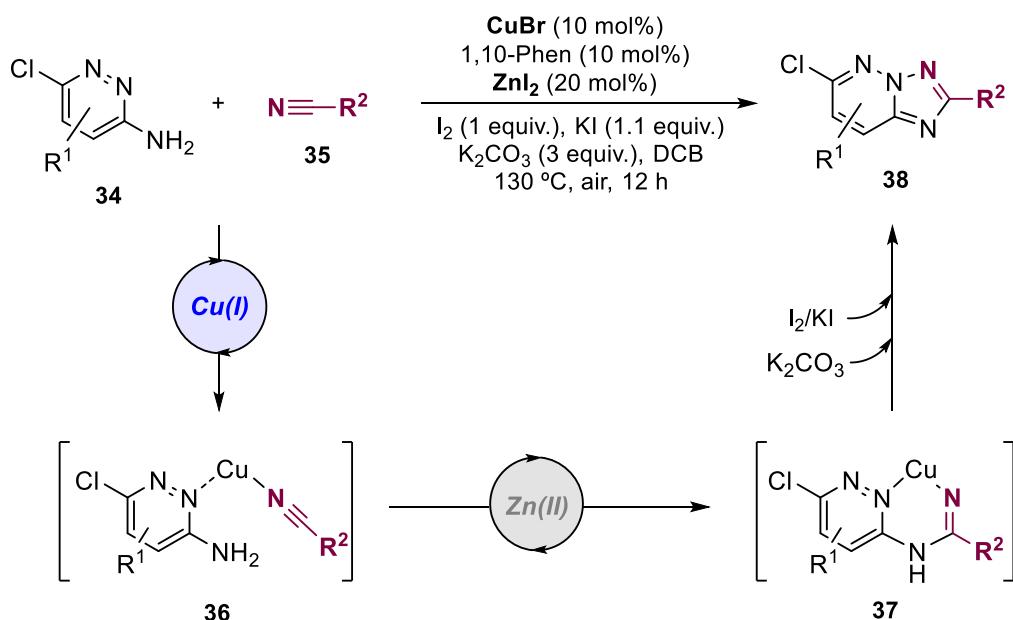
In the second work of 2016, Ramasastry and co-workers presented a similar one-pot triple-orthogonal-metal relay catalysis strategy for synthesizing 1,3-di- and 1,3,4-trisubstituted  $\beta$ -carbolines, also employing silver, bismuth, and palladium catalysts in a sequential manner (Scheme 8) [38]. The 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 a 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  $\beta$ -carbolines, offering new possibilities for the synthesis of these valuable compounds.



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

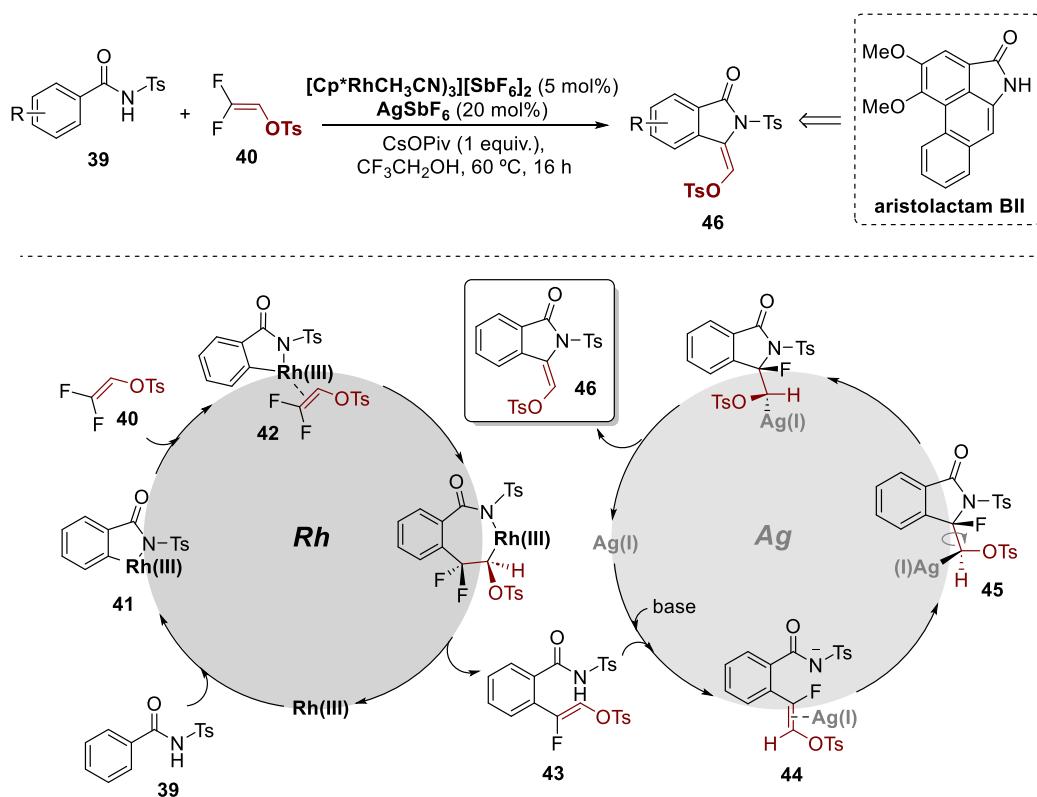
In 2017, Mu and co-workers reported a new and efficient protocol for the preparation of chlorine-containing 1,2,4-triazolo[1,5-*b*]pyridazine scaffolds (Scheme 9) [39]. The authors developed a one-pot oxidative cycloaddition reaction of 3-aminopyridazine derivatives 34 and nitriles 35, involving cooperative Cu(I) and Zn(II)-catalyzed tandem C-N addition to achieve intermediate 36 followed by

the 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**.



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

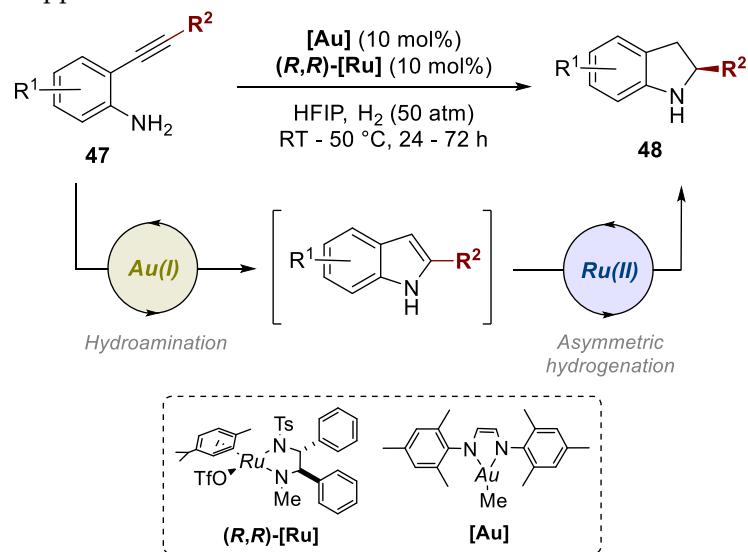
In 2017, Wang and co-workers reported the construction of 3-alkylidene isoindolinones. This was efficiently achieved through a redox-neutral bimetallic Rh(III)/Ag(I) relay catalysis between *N*-tosyl benzamides **39** and 2,2-difluorovinyl tosylate **40** (Scheme 10) [40]. The Rh(III) catalyst facilitates the C-H monofluoroalkenylation 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**, that leads to intermediate **42**, underwent a regioselective olefin insertion, followed by an anti-coplanar  $\beta$ -F elimination, resulting in the Z-type monofluoroalkenylation product **43** with notable stereoselectivity. The Ag(I) salt was suggested to act as a  $\pi$  acid, promoting the activation of the olefin (**44**) and facilitating the intramolecular cyclization reaction. Consequently, the anti-addition to the double bond induced 5-*exo* cyclization, resulting in the formation of intermediate **45**. The selective attack at the  $\alpha$ -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 anti-coplanar  $\beta$ -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 10.** General conditions and a plausible mechanism for the preparation of 3-alkylidene isoindolinones by a Rh(III)/Ag(I)-catalyzed bimetallic approach.

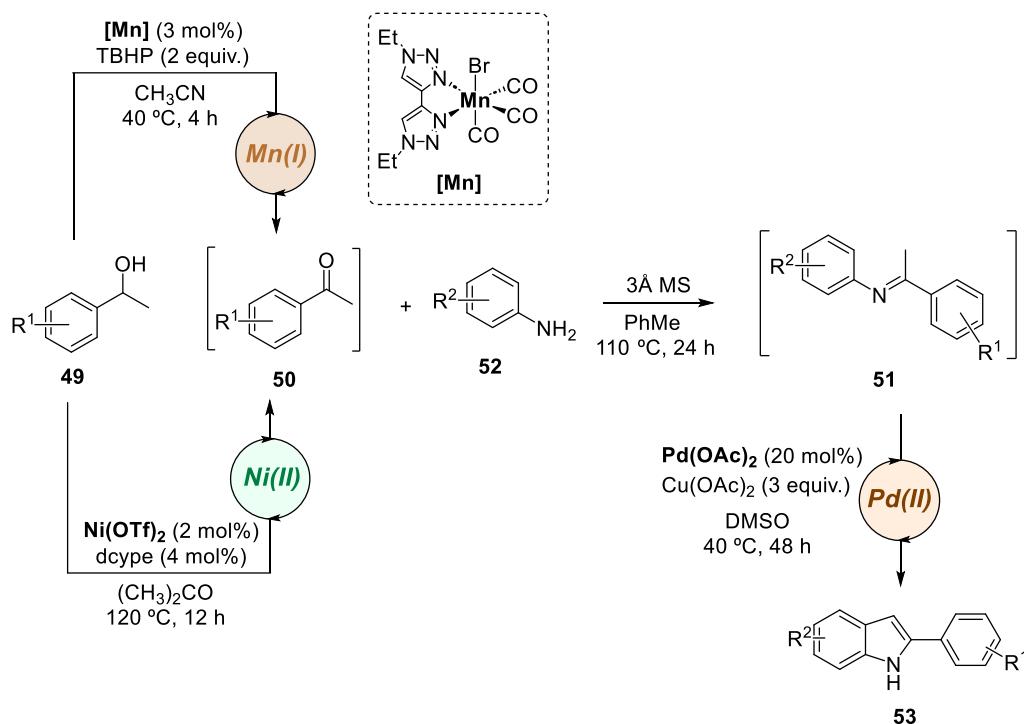
X. Feng and co-workers reported a highly efficient asymmetric cascade reaction of alkenyloxindoles with pyridines and diazoacetates via a bimetallic iron(III)/chiral  $\text{N},\text{N}'$ -dioxide-scandium(III) complex catalyst [41]. Tetrahydroindolizines were obtained with good to excellent diastereo- and enantioselectivities.

In 2019, Fan and co-workers published a one-pot cascade reaction strategy to afford functionalized indolines. This process involved a sequential Au(I)-catalyzed intramolecular hydroamination followed by a Ru(II)-catalyzed asymmetric hydrogenation of various anilino-alkynes **47** (Scheme 11) [42]. This enabled the 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 11.** General conditions for the preparation of asymmetrically-substituted indolines by a Au(I)/Ru(II)-catalyzed bimetallic approach.

Marques and co-workers have 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**, while 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 3-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.



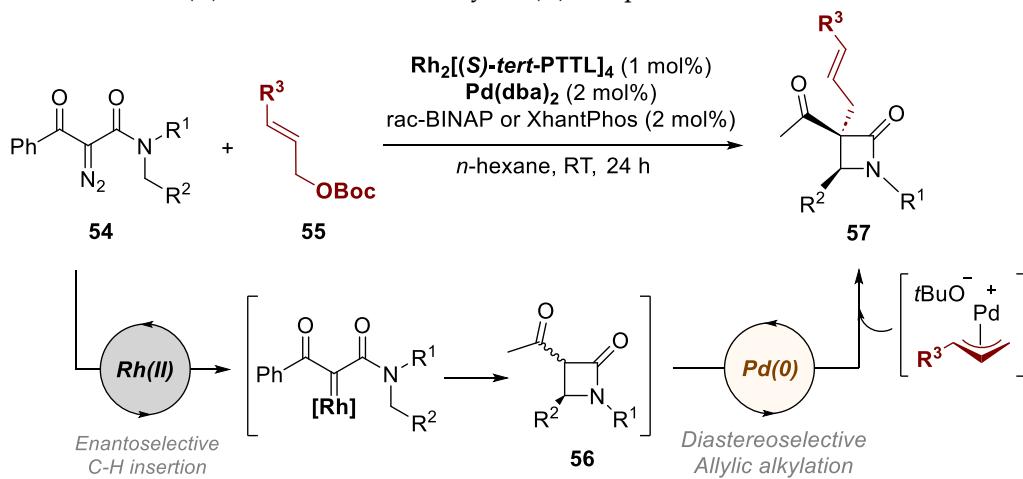
**Scheme 12.** General conditions for the preparation of 2-arylindoles by a Mn(I)/Pd(II)- or Ni(II)/Pd(II)-catalyzed bimetallic approaches.

#### 4. Bimetallic Approaches Involving Lactam Scaffolds

The  $\beta$ -lactam is the common core structure of clinically used drugs such as penicillin, cephalosporin, and monocyclic antibiotics such as aztreonam [43–46]. Development of novel methods to access new  $\beta$ -lactams is important in further studies of this heterocyclic system, including structure-activity relationships and the discovery of new antibiotics, and is thus important in global health problems. Synthetic methods that construct the  $\beta$ -lactam ring have been developing exorbitantly over the last century from almost every imaginable set of synthons. Yet, there is still a necessity for innovation and improvement in the field, even within each category of well-established reactions [47]. Despite all of the synthetic methods to date for obtaining achiral or racemic lactams, asymmetric methodologies remain largely limited to chiral auxiliary-based systems [48]. This review presents below two examples of asymmetric bimetallic catalytic approaches to afford substituted  $\beta$ -lactams.

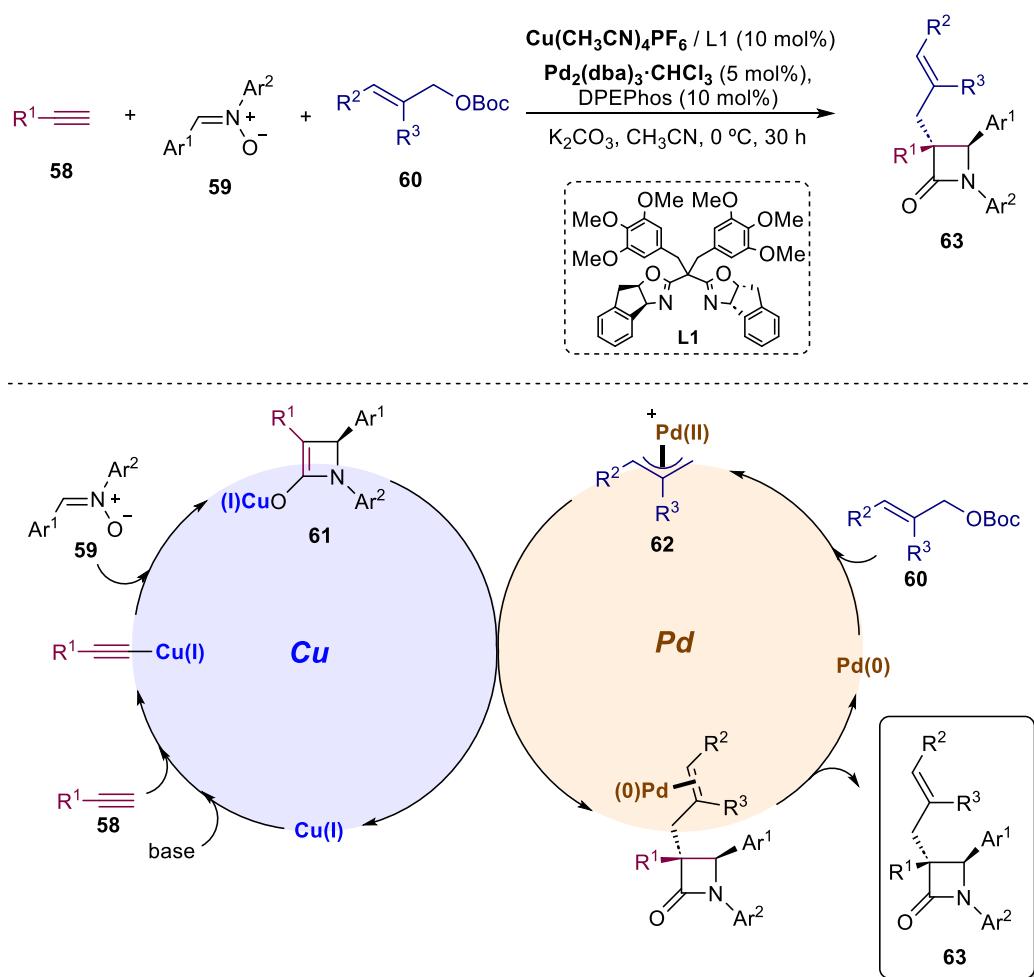
In 2018, Lee and co-workers developed a novel asymmetric dual Rh(II)/Pd(0) relay catalysis for synthesizing  $\alpha$ -quaternary allylated chiral  $\beta$ -lactams, by reacting *N*-benzyl  $\alpha$ -diazoamides **54** and allyl *tert*-butyl carbonates **55**. (Scheme 13) [49]. The experiments conducted in this work supported a relay reaction with the formation of  $\beta$ -lactam intermediate **56** that resulted on the desired  $\alpha$ -

quaternary allylated chiral  $\beta$ -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 provided a wide scope, achieving yields up to 99% and with 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  $\pi$ -allyl Pd(II) complexes.



**Scheme 13.** General conditions and plausible mechanism for the preparation of allylated chiral  $\beta$ -lactams by a Rh(II)/Pd(0)-catalyzed bimetallic approach.

Xu and co-workers have successfully disclosed a groundbreaking asymmetric multicomponent reaction: the interrupted Kinugasa allylic alkylation (Scheme 14) [50]. This methodology synergistically merges a copper-catalyzed Kinugasa system with a palladium-catalyzed allylic alkylation. This remarkable reaction enables the synthesis of  $\alpha$ -quaternary chiral  $\beta$ -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 stereocontrolled allylic substitution between **61** and **62** leads to the desired  $\alpha$ -quaternary chiral  $\beta$ -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  $\alpha$ -quaternary chiral  $\beta$ -lactams, thus 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 [51].



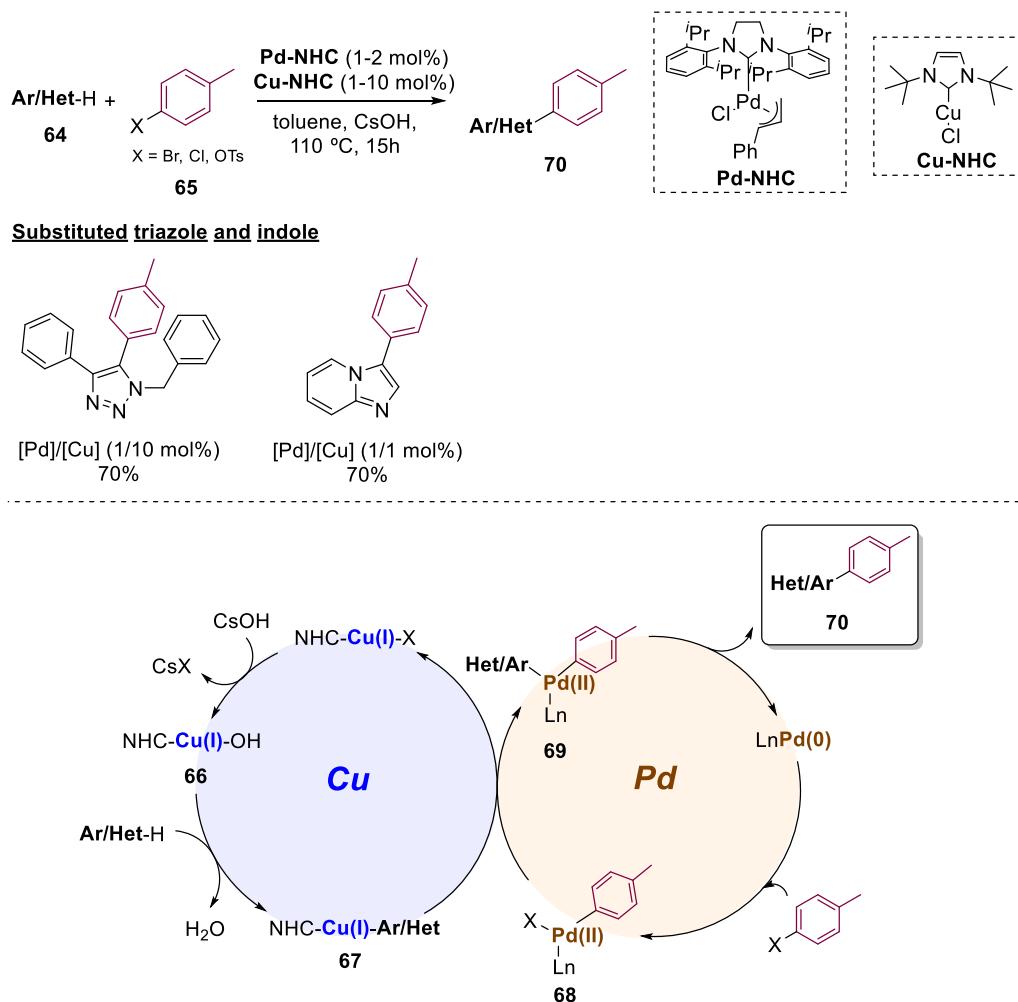
**Scheme 14.** General conditions and plausible mechanism for the preparation of  $\alpha$ -quaternary chiral  $\beta$ -lactams by a Cu(I)/Pd(0)-catalyzed bimetallic approach.

##### 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 [52]. The wide range of bioactivity displayed by these *N*-heterocycles has stimulated the development of many synthetic strategies.

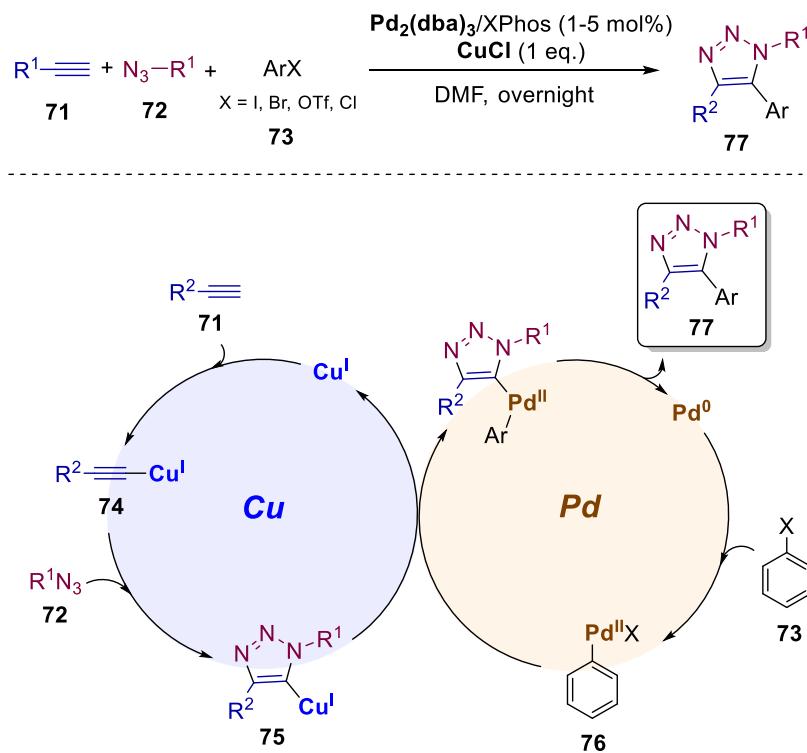
In comparison to the more established cross-coupling reactions, C–H activation is becoming a hot topic in all areas of chemistry, dismissing the pre-functionalization of both coupling partners [53]. Considering the inferior reactivity of arenes, when compared to aryl halides, their selective and direct arylation remains a challenge. These issues can be addressed by the presence of directing groups on the arene substrate, however, may provide 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 co-workers developed a process that promotes the construction of C–C bonds through an intermolecular direct arylation, that eliminated the need for directing groups (Scheme 15) [54]. The scope of this reaction included the functionalization of *N*-heterocycles, respectively, 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 a scope constituted by 20 examples and yields of up to 98%. The authors performed mechanistic studies that allowed them to propose a catalytic cycle, firstly 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<sub>2</sub>O. 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, thus completing the catalytic cycle.



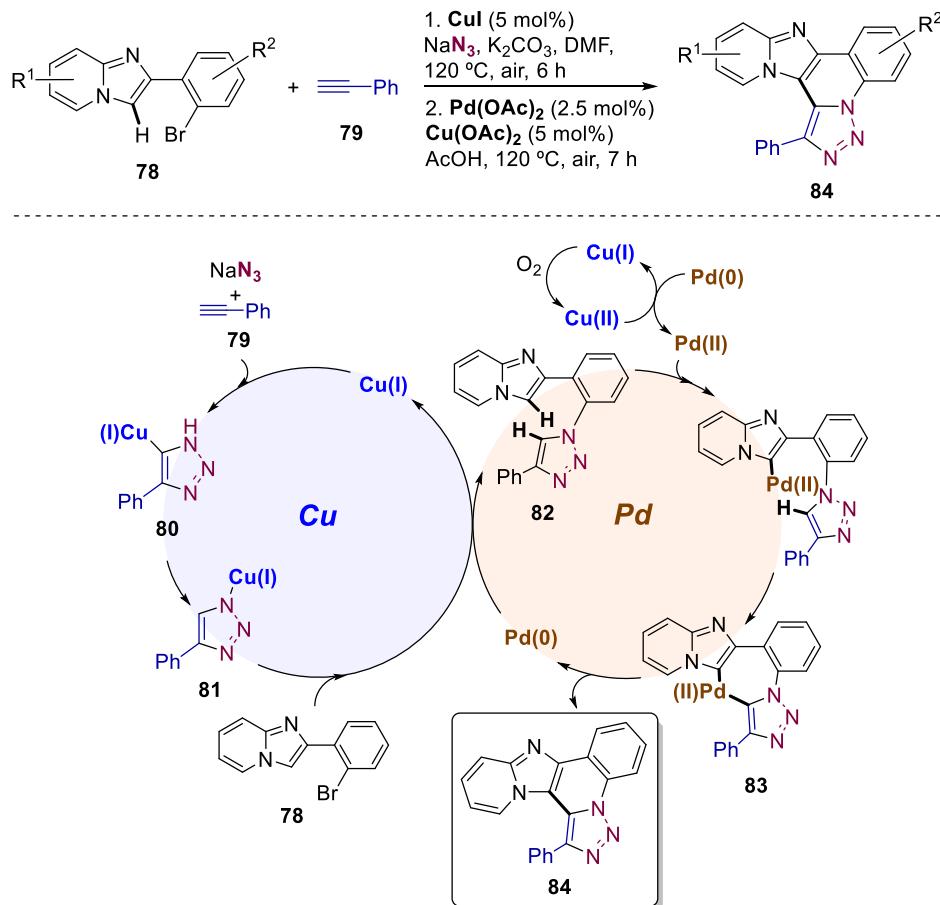
**Scheme 15.** General conditions and plausible mechanism for the preparation of functionalized N-heterocycles, including triazole and indole scaffolds by a Cu(I)/Pd(II)-catalyzed bimetallic approach.

A crucial limitation of the famous click reaction remains the difficulty to obtain 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 [55]. Nevertheless, in 2015, Xu and coworkers successfully synthesized 1,4,5-trisubstituted 1,2,3-triazoles by relying on a Cu/Pd transmetalation relay catalysis, a modular synthesis that afforded trisubstituted triazoles from the reaction between alkynyl substrates **71** with azides **72** and aryl halides **73** (Scheme 16) [56]. This reaction makes it possible to freely install three different substituents onto the triazole ring in one step, with a total of 33 examples with yields 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 regenerate the Pd(0) catalyst.



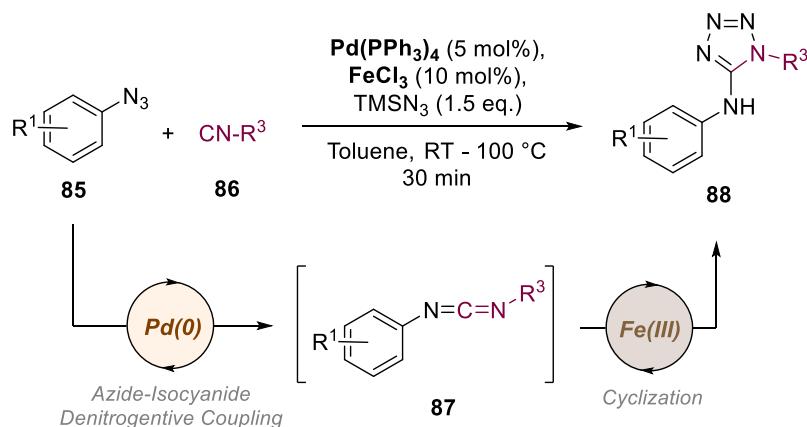
**Scheme 16.** General conditions and plausible mechanism for the preparation of 1,4,5-trisubstituted 1,2,3-triazoles by a Cu(I)/Pd(0)-catalyzed bimetallic approach.

Imidazo[1,2-a]pyridine constitutes a valuable skeleton for a variety of pharmaceuticals [57,58]. Hence, different strategies for the preparation of these scaffolds have been implemented [59–61]. Although there is already a report bearing a Cu-catalyzed process to obtain 1,2,3-triazole-fused imidazo[1,2-a]pyridines, it relies on brominated imidazo[1,2-a]pyridines as substrates [62]. To optimize the atom economy and environmental aspects of this process, Fan and co-workers reported, in 2016, an efficient one-pot synthesis of 1,2,3-triazole/quinoline-fused imidazo[1,2-a]pyridines starting from 2-(2-bromophenyl)imidazo[1,2-a]pyridines **78**, alkynes **79**, and sodium azide (Scheme 17) [63]. 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 built a scope of different alkynes and 2-(2-bromophenyl)imidazo[1,2-a]pyridines with a total of 24 examples and yields up to 74%. Fan suggested that the mechanism started with a Cu(I)-catalyzed azide–alkyne cycloaddition to afford intermediate **80**. **81** is then formed by a copper-hydrogen exchange. C–N coupling between **78** and **81** results in the formation of the key intermediate **82**. In the second phase of this cascade process, aromatic palladation of **82** by a sequence of C–H bond cleavage yields the seven-membered palladacycle **83**. Finally, reductive elimination affords the final 1,2,3-triazole/quinoline-fused imidazo[1,2-a]pyridine **84** and Pd(0) is re-oxidized into Pd(II) by Cu(II)/atmospheric O<sub>2</sub>.



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

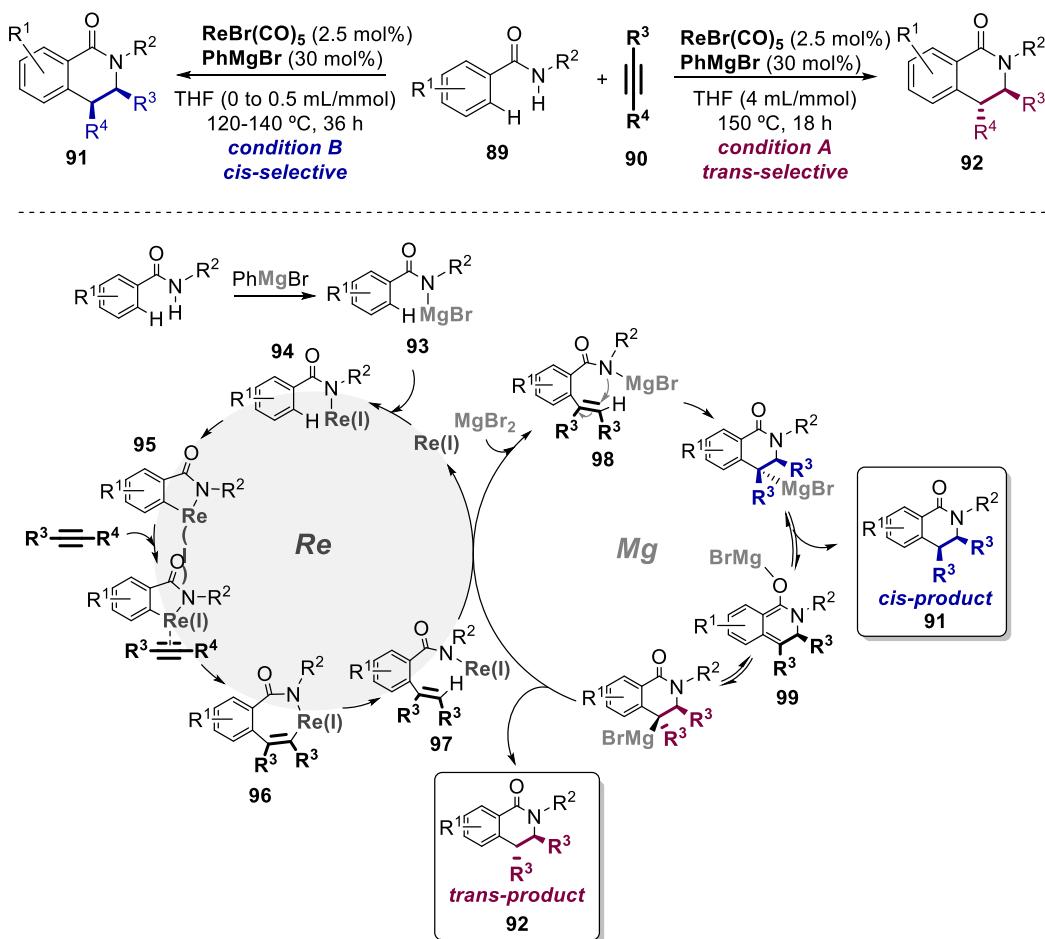
In 2018, Sawant and colleagues developed a fast and efficient method to produce aminotetrazoles (Scheme 18) [64]. The authors used aryl azides **85**, isocyanides **86**, and  $\text{TMSN}_3$  in a sequential  $\text{Pd}(0)/\text{Fe}(\text{III})$  catalyzed reaction. The process involved a  $\text{Pd}$ -catalyzed reaction to generate carbodiimide **87** *in situ*, which then reacts with  $\text{TMSN}_3$  in the presence of  $\text{FeCl}_3$ , all in one pot, and finally yields the respective aminotetrazole **88**. This approach has advantages over traditional methods that use toxic  $\text{Hg}$  and  $\text{Pb}$  salts in large amounts. With the optimized conditions in hand, they 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  $\text{TMS-N}_3$  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 pose steric hindrance. Alkyl-, cycloalkyl-, and aryl-substituted isocyanides reacted successfully under the optimized conditions, obtaining a scope with 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 18.** General conditions and plausible mechanism for the preparation of aminotetrazoles by a  $\text{Pd}(0)/\text{Fe}(III)$ -catalyzed bimetallic approach.

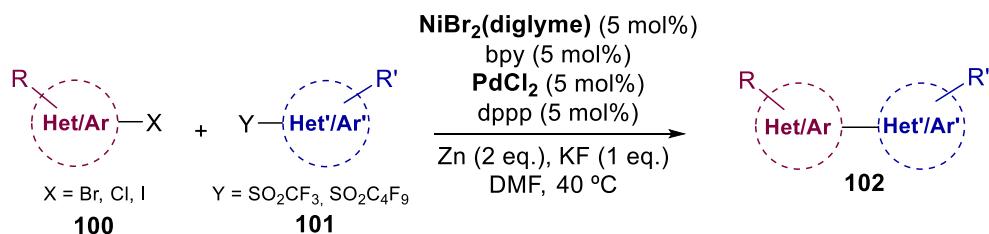
## 6. Bimetallic Approaches Involving Pyridine, Pyrimidine, and Related Scaffolds

Isoquinolinones can be prepared via metal-catalyzed C-H activation [65–67]. 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 this limitation, in 2013, Wang and co-workers disclosed the first redox-neutral  $\text{Re}^I/\text{Mg}^{II}$  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) [68]. This was accessed in a simply by subtle tuning of reaction conditions, which adds further values to this bimetallic catalyst system. The scope for the formation of both *cis*- and *trans*-disubstituted scaffolds involved a total of 44 examples, affording yields up 90% and isomer ratios up to 36:1 and 16:1, respectively. Mechanistic experiments were conducted and allowed the authors to formulate a plausible reaction mechanism. With the aid of  $\text{PhMgBr}$ , 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 seven-membered rhenacycle **96**, which further leads to intermediate **97** upon protonation. Transmetalation results into a new amido-magnesium intermediate **98** which undergoes an intramolecular nucleophilic addition/cyclization generating the *cis* product, or further leading to the *trans* product via intermediate **99**. Protonation of these species affords the final products and regenerates the amido-magnesium **93**, thus closing the entire  $\text{Re}/\text{Mg}$  bimetallic tandem catalytic cycles.

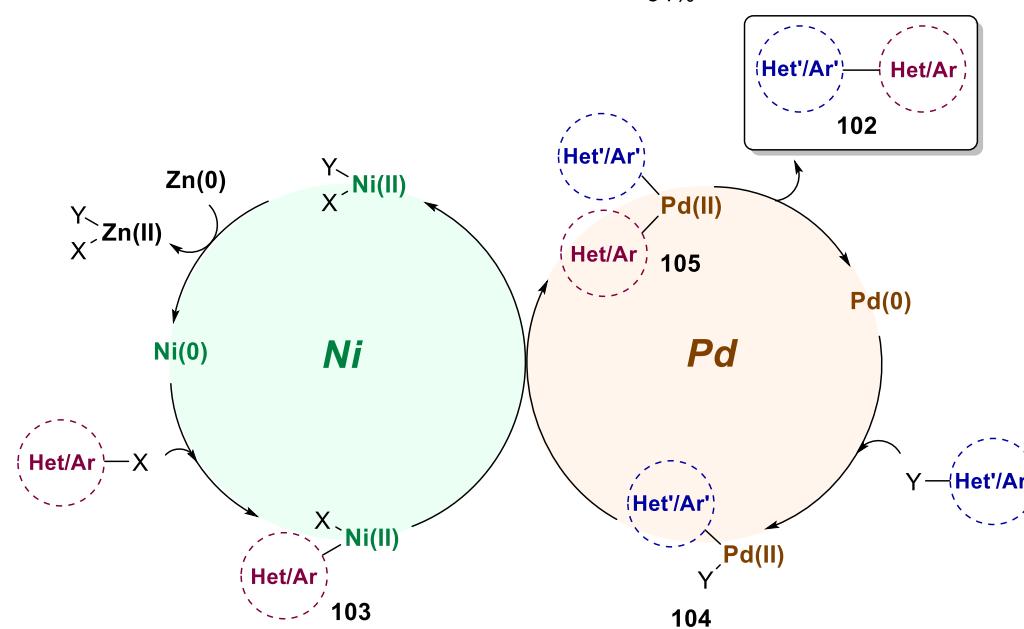
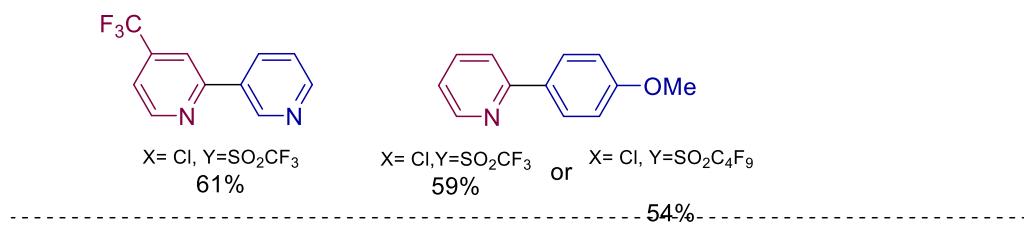


**Scheme 19.** General conditions and plausible mechanism for the preparation of cis- and trans-3,4-dihydroisoquinolinones by a Re(I)/Mg-catalyzed bimetallic approach.

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 hetero-coupling product over the homo-coupling [69]. For this matter, in 2015, Ackerman and co-workers developed a method to couple aryl halides **100** with aryl triflates **101** and affording hetero-coupled bi(hetero)aryls **102** by directly by a Ni/Pd bimetallic-catalyzed cross-Ullmann (Scheme 20) [70]. 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. Yet, 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, thus regenerating the Pd<sup>0</sup> catalyst. Ni<sup>0</sup> catalyst is reobtained with the help of a Zn<sup>0</sup> reductant.



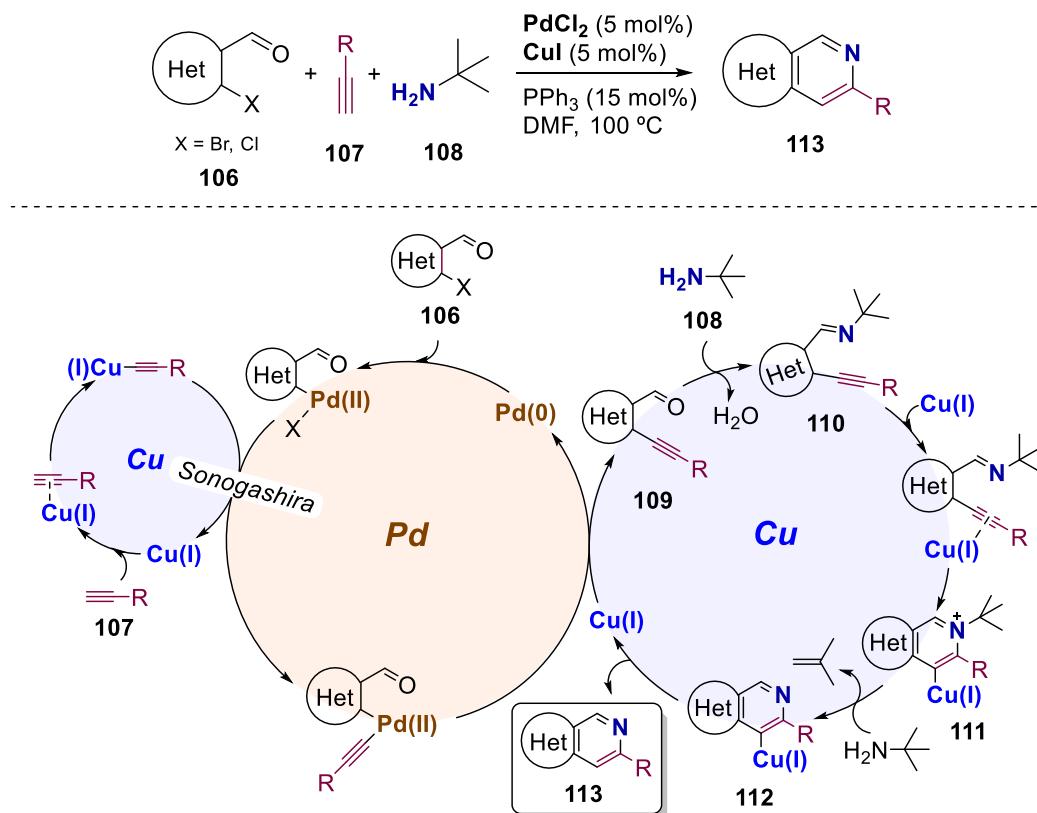
#### Functionalized pyridine: 2,3'-bipyridine and 2-arylpypyridine



**Scheme 20.** General conditions and plausible mechanism for the preparation of hetero-coupled bi(hetero)aryls by a Ni(II)/Pd(II)-catalyzed bimetallic approach.

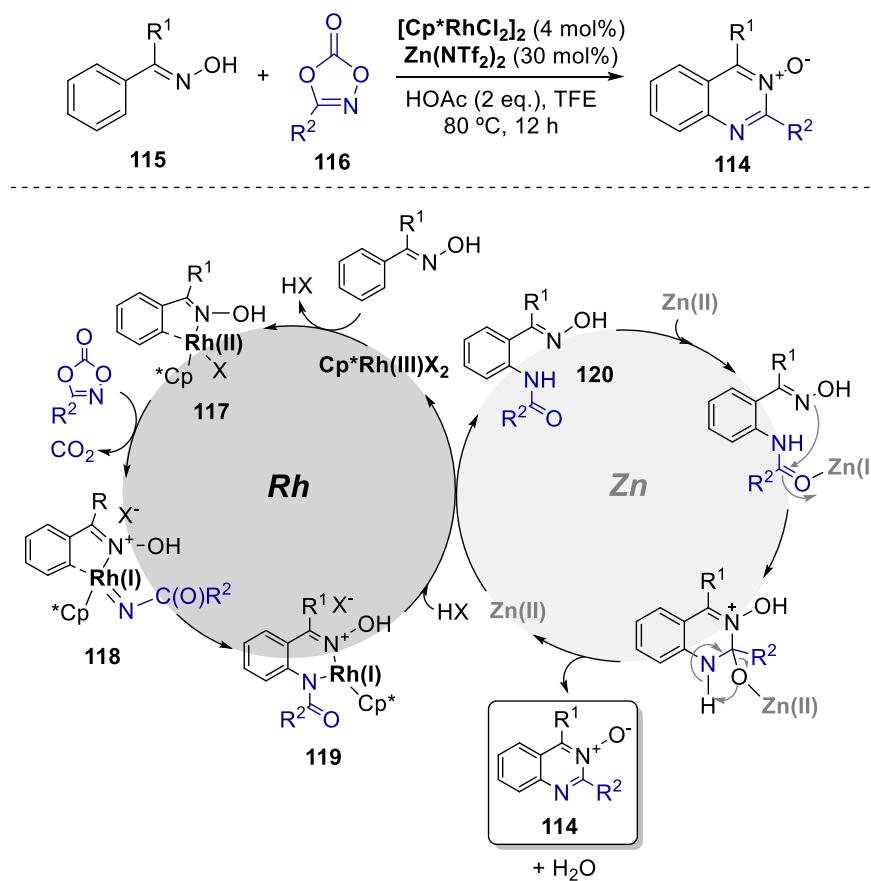
Copper-catalyzed electrophilic cyclization is highly attractive due to its low cost, easy availability, and high tolerance towards diverse functional groups. Nevertheless, there are relatively few synthetic studies on the Cu-catalyzed three component tandem reaction for the synthesis of polyheterocycles. Moreover, there has been no report which shows the dual behaviour of a Cu(I) catalyst, as well as *tert*-butylamine, for the synthesis of polyheterocycles. For this matter, 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-endocyclic* cyclization, with *tert*-butylamine **108** as a nitrogen source (Scheme 21) [71]. The scope of this process included the preparation of naphthyridines, isoquinolines, benzothieno- and benzofuropyrpyridines with a total of 33 examples and yields up to 83%. To give insights into the mechanism, an array of preliminary control experiments was performed and revealed the dual role of Cu: to enhance the rate of Sonogashira coupling and to assist 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**.  $\pi$ -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**.



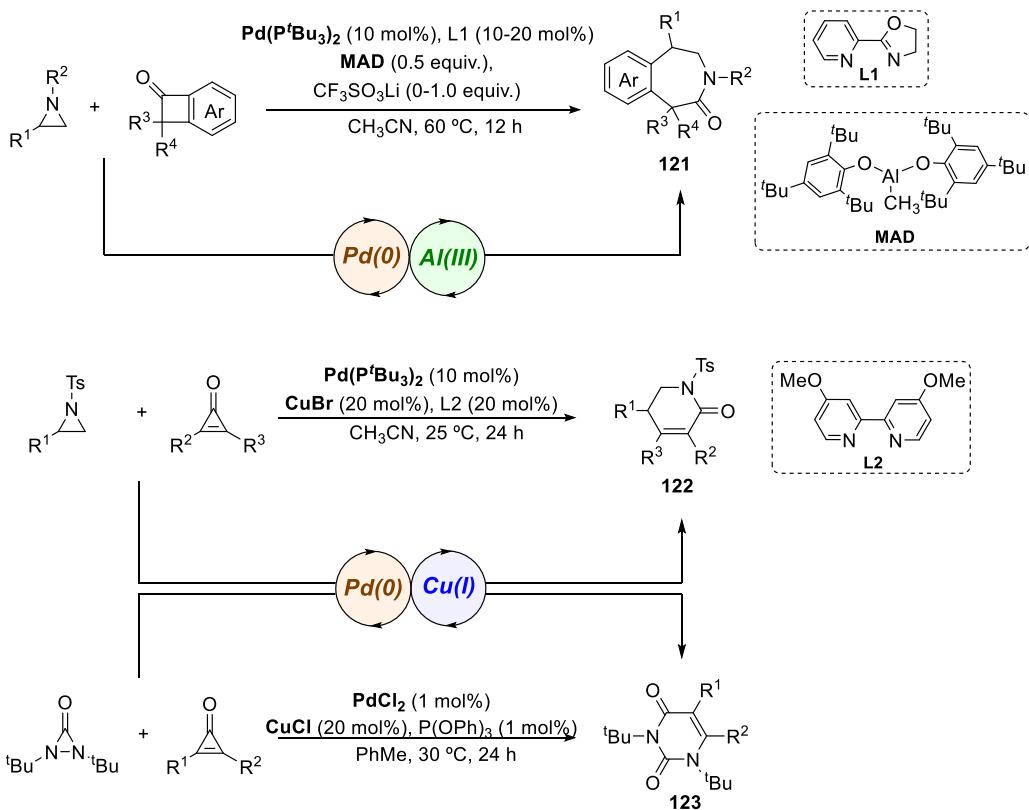
**Scheme 21.** General conditions and plausible mechanism for the preparation of polyheterocycles by a Cu(I)/Pd(II)-catalyzed bimetallic approach.

Until nowadays, the preparation of *N*-oxides of azacycles via direct C–H activation of arenes remains a challenge and highly underexplored, with only a few reports on the synthesis of *N*-oxides of isoquinoline [72,73]. For this reason, in 2016, Li and co-workers prepared quinazoline-*N*-oxides **114** via a single-step C–H activation approach by 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) [74]. This annulation system proceeded with high efficiency under mild conditions with H<sub>2</sub>O and CO<sub>2</sub> 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 concluded that Rh(III) participated in the C–H activation-amidation of the ketoximes and Zn(II) in the cyclization. The authors suggest that, first, an active rhodium catalyst Cp<sup>\*</sup>RhX<sub>2</sub> (where X = NTf<sub>2</sub> or OAc) is generated from the anion exchange between [RhCp<sup>\*</sup>Cl<sub>2</sub>]<sub>2</sub> and ZnNTf<sub>2</sub> or HOAc. Next, the oxime reagent undergoes a cyclometalation to afford the rhodacyclic intermediate **117** and an acid via a concerted metalation–deprotonation mechanism. Coordination of dioxazolone is followed by a decarboxylation with CO<sub>2</sub> 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) will then catalyze 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 by a Rh(III)/Zn(II)-catalyzed bimetallic approach.

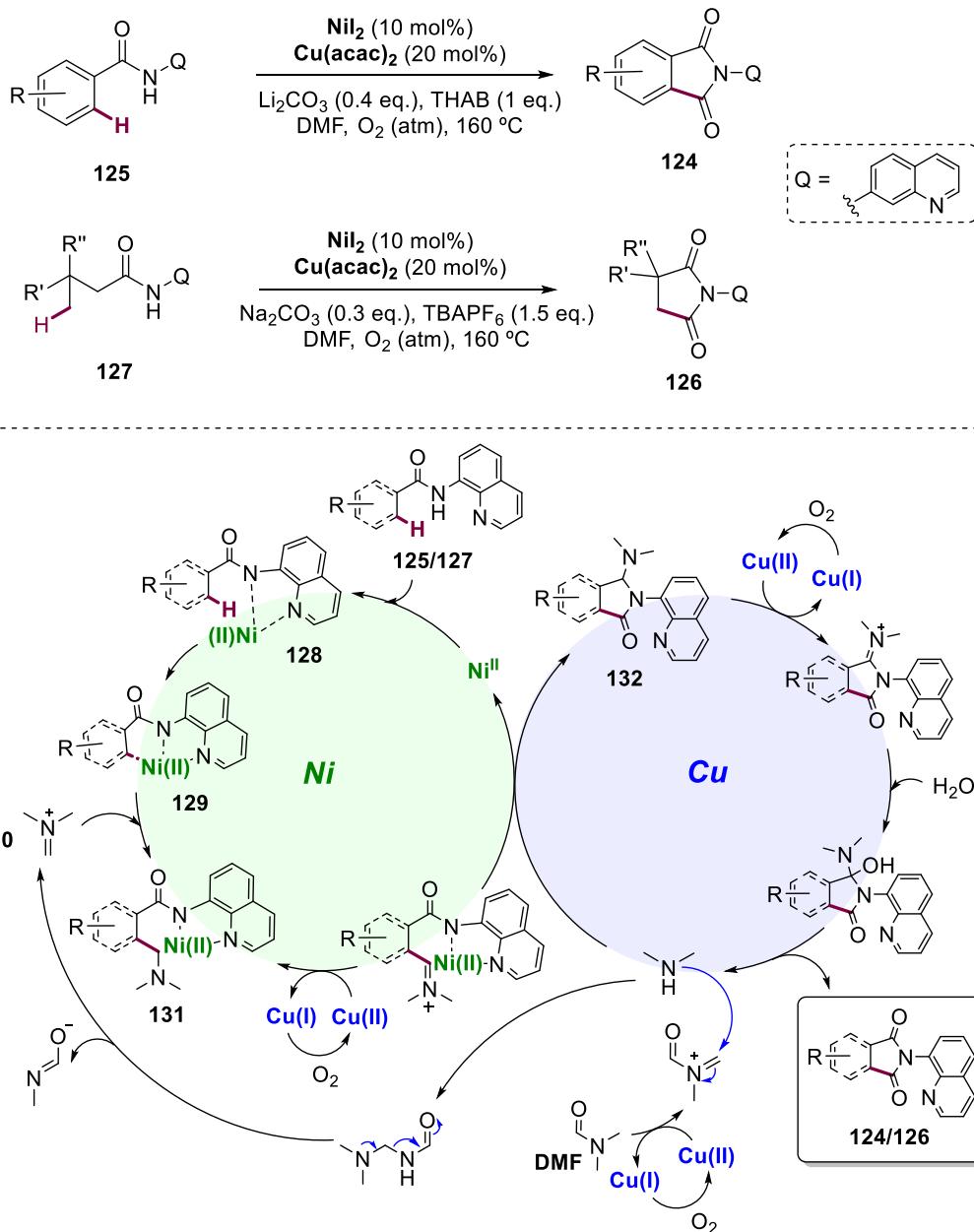
In 2021, Zhao and co-workers developed a general ring expansion strategy that enables the efficient and scalable synthesis of diverse *N*-heterocycles (Scheme 23), such as 3-benzazepinones **121** (up to 90% yield), dihydropyridinones **122** (up to 91% yield) and uracils **123** (up to 98% yield) [75]. 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 present 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 or 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, dihydropyridinones 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 by a Pd(0)/Al(III)-catalyzed bimetallic approach and dihydropyridinones and uracils by a Pd(0)/Cu(I)-catalyzed bimetallic approach.

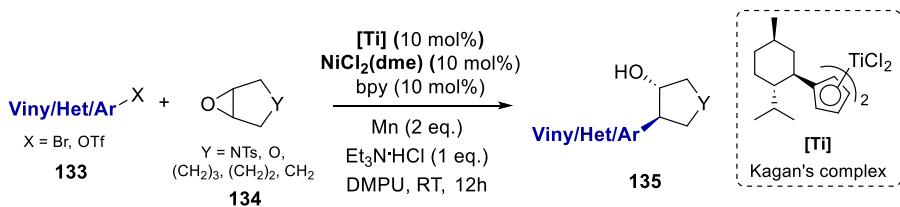
## 7. Bimetallic Approaches Involving Other N-heterocyclic Scaffolds

Within the metal-catalyzed C–H functionalization reaction's 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<sup>3</sup>)–H bonds has been demonstrated by transition metal-catalyzed processes, however, mainly rely on the use of toxic CO gas at high pressure [76–78]. To overcome this limitation, Ge and co-workers described, in 2015, the direct carbonylation of aromatic sp<sup>2</sup> and unactivated sp<sup>3</sup> C–H bonds of amides via a Ni/Co bimetallic catalysis with *N,N*-dimethylformamide (DMF) as the carbonyl source (Scheme 24) [79]. The reactions are performed under atmospheric O<sub>2</sub> and the substrates are constituted by a bidentate directing group (Q). The authors provided a scope of aryl-substituted phthalimides **124**, from aromatic amides **125** achieving yields up to 90% with the optimized conditions, as well as 3,3'-disubstituted succinimides **126**, from aliphatic amides **127**, with yields 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<sup>2</sup> or sp<sup>3</sup> C–H bond activation to generate the intermediate **129**, keeping in mind that sp<sup>2</sup> C–H bond cleavage is a reversible step while sp<sup>3</sup> is irreversible. Electrophile **130** is then inserted into the catalytic cycle, generated in situ from DMF. This suffers decarboxylation or an elimination process via Cu(II)/O<sub>2</sub>. 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 the intermediate **132** which then produces the product **124** or **126** via oxidation by Cu(II) and hydrolysis.

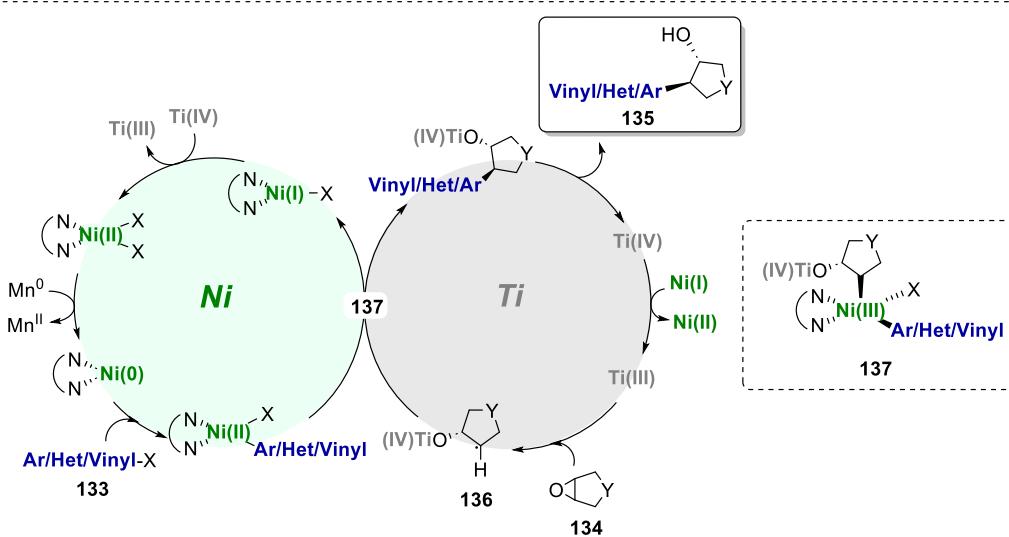
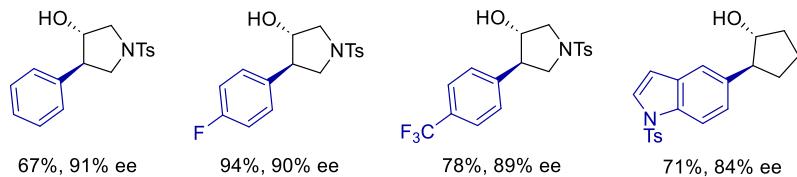


**Scheme 24.** General conditions and plausible mechanism of the preparation of phthalimides and 3,3'-disubstituted succinimides by a Ni(II)/Cu(I)-catalyzed bimetallic approach.

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 [80,81]. 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*- $\beta$ -arylcycloalkanols 135, from a novel bimetallic Ni(II)/Ti(III) catalytic system (Scheme 25) [82]. The reaction was catalyzed by a combination of (bpy) $\text{NiCl}_2$  and a chiral titanocene under reducing conditions. Different titanocenes were tested, and the one first reported by Cesarotti and co-workers [83] showed the highest yield and enantioselectivity. This combination enantioselectively coupled aryl, heteroaryl, or vinyl halides with *meso*-epoxides with a scope constituted by 28 examples. It also included examples on the functionalization of pyrrolidine scaffolds and one example for indole, with yields up to 94% and enantiomeric excesses up to 91% ee. These authors suggested that the coupling mechanism (Scheme 25) would be initiated by the enantioselective formation of a  $\beta$ -titanoxyl carbon radical from the *meso*-epoxide (136). Then, the oxidative addition of a  $\beta$ -titanoxyl carbon radical to an arynickel(II) intermediate would form a diorganonickel(III) species (137), and the reductive elimination of the product (135). Finally, the reduction of both catalysts closes the catalytic cycle.



## Substituted pyrrolidine and indole



**Scheme 25.** General conditions and plausible mechanism of the preparation of *trans*- $\beta$ -arylcycloalkanols by a Ni(II)/Ti(IV)-catalyzed bimetallic approach.

## 8. Conclusion

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 the fine chemical industries, where *N*-heterocycles serve as important intermediates in the synthesis of various key chemicals.

**Author Contributions:** All authors have read and agreed to the published version of the manuscript." Please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

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**Data Availability Statement:** Does not apply

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

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