Coinage Metal: A Unique Heterogeneous Catalyst for the synthesis of Heterocyclic Compounds

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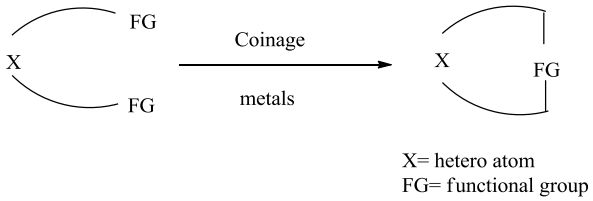
ABSTRACT

Coinage metal catalysis has become a potent tool for a variety of C-C and C-X bond formation events, frequently with intriguing molecular routes. Catalysts made of coinage metal can be used alone or in combination with other catalysts. The synthesis of heterocyclic compounds can be catalyzed by coinage metals like copper, silver, and gold. The literature contains a variety of well-established methods for synthesizing heterocycles, which has been a research objective for over a century. A new approach to synthesizing knowledge has been developed over the past few years through efficient and atom-economic routes. One of the most appealing features of the many recently developed synthetic transformations is transition metal-catalyzed reactions. In mild conditions, complex molecules can be created directly from readily available starting materials through these reactions. This section focuses on the uses of heterocycles created using coinage metal catalysis in the fields of materials science, medicine, and agrochemicals. These heterocyclic compounds' exceptional biological activity and distinctive characteristics have led to their usage in advanced material development, medicine research, and crop protection. Modern organic chemistry has been revolutionized by the use of coinage metals as catalysts in heterocycle synthesis, which allows the creation of complex structures with extraordinary efficiency and accuracy.

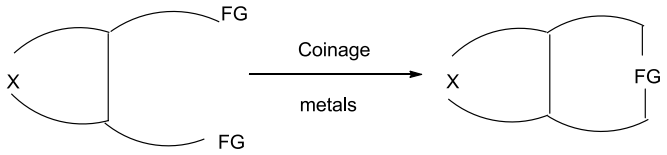
Keywords: Coinage Metal, Heterocyclic, Cross-coupling, Copper-catalyzed, Organic molecules, Imidazole.

1. Introduction

Heterocycles are rings with one or more heteroatoms within. This course will emphasize aromatic systems, whether they are completely or partially saturated [1]. A significant fraction of natural goods include heterocycles, which are essential [2]. At least one heterocyclic unit can be found in many medicines and agrochemicals[3]. For novel materials with intriguing electrical, mechanical, or biological characteristics, heterocyclic systems are crucial building blocks [4]. Heterocyclic compounds have a significant role in the fields of drugs, agriculture chemicals, medicine, materials, and synthetic tools [5]. Coinage metal catalysts are employed both as co-catalysts and as primary catalysts. Because it is made of a mixture of two metals, the term "bimetallic catalyst" was previously used to describe this kind of catalyst [6], [7]. In addition to Pd-Cu, Pd-Ag, Rh-Ag, Pt-Ag, Au-Ag, and Mn-Cu, there are also bimetallic systems such as Pd-Ag, Rh-Ag, and Pt-Ag. Since the topic of multi-metallic catalysis has already been covered in-depth, we will focus on the synthesis of heterocycles. Coinage metals are the sole catalysts in this study [3], [7]. There are several studies on the production of heterocycles using Cu, Ag, and Au catalysts[8]. In this assessment, we have tried to include a lot of current cases [7], [9]. Although it would be ideal to cover every report, it is impossible to describe every document in the text [10]. In 2020, Zhao Y, Wu F, Wei J, *et al*. Were cover the most crucial comments here; nevertheless, the references section includes references to further pertinent evaluations and publications. For instance, coinage metals can catalyze the formation of a heterocyclic ring, as shown in Scheme 1 [11], or they can assist heterocycles in closing their side rings, as shown in Scheme 2 [1]. In general, the field of heterocyclic synthesis has been transformed by the use of coinage metal catalysts, which have made it possible to develop fresh, more reliable artificial ways to important subclasses of heterocyclic compounds [12].



Scheme 1: Coinage metals can catalyze the formation of a heterocyclic ring



Scheme 2: Catalyze the side ring closure of heterocycles

2. Motivation and purpose of study for the coinage metals assisted synthesis of heterocycles

Coinage metals, in particular copper, silver, and gold, have been demonstrated to be efficient catalysts for a variety of organic processes, including those involving heterocyclic compounds [13]. It is feasible to create new and better synthetic procedures for the creation of complex heterocyclic compounds by investigating the usage of these metals in heterocyclic chemistry [14]. The possibility of creating novel medicinal medicines is another reason to research the use of coinage metals in heterocyclic chemistry [15]. Heterocyclic compounds are often utilized as medications in the pharmaceutical sector, and research is always being done to create novel heterocyclic compounds with enhanced features, such as greater bioavailability, and lower toxicity [16]. The use of coinage metals in the creation of novel therapeutics, including cancer treatments and medications for infectious illnesses and other ailments [17]. The study of the mechanism of coinage metal-catalyzed reactions in heterocyclic chemistry, considers the part ligands and other elements play in selectivity and yield control[9]. In general, the choice of a particular topic will be influenced by the study objectives and interests of the individual researcher as well as the existing level of expertise in the area [18].

3. Synthesis of heterocycles compound

The wide and significant field of organic chemistry is known as heterocyclic compound synthesis. Organic compounds that have at least one heteroatom, such as a nitrogen, oxygen, or sulfur atom, in their ring structure are known as heterocyclic compounds [19]. These substances are utilized as medications, insecticides, and colors because of the vast range of biological and pharmacological activity they have [20]. The following are some popular techniques for creating heterocyclic compounds:

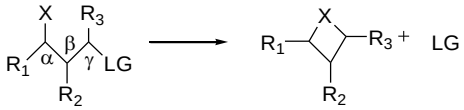
3.1. Saturated Four-Membered Heterocycle Synthesis

The relevance and prevalence of saturated four-membered rings with O, N, and S atoms in physiologically active compounds and potential therapies continue to be the driving force behind attempts to create these rings efficiently [21]. These heterocycles are synthesized using both classic and modern methods, which are discussed in this article. There are four main methods for creating four-membered heterocycles:

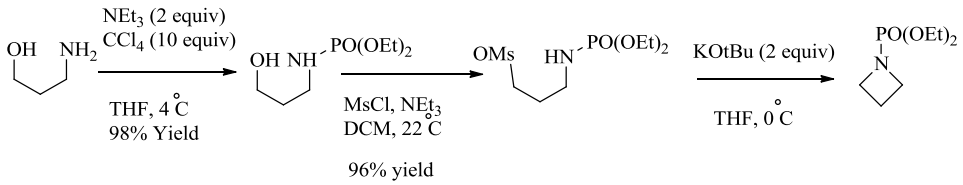
1. the formation of carbon-heteroatom bonds during cyclization,
2. the formation of carbon-carbon bonds causes cyclization,
3. explicit contractions and expansions of rings, and
4. cycloaddition.

3.1.1. Bond formation between carbon and heteroatoms in cyclization

When fundamental circumstances are present, an activated electrophilic carbon produces four-membered heterocycles when a heteroatom nucleophile displaces a leaving group(Scheme 3) [22]. This often calls for a heteroatom group, which is formed by connecting three carbon atoms and two heteroatoms. This frequently makes use of variations in heteroatom reactivity, whether a steric factor or intrinsic nucleophilicity may explain this [23]. In 2014, Sun *et al*. explained that Using 3 amino propanol, protected azetidine was prepared in three steps (Scheme 4) [24]. This technique achieved 1,3- positioning of the heteroatom nucleophile and the heteroatom- based leaving group by using 3- amino- 1- propanol as a convenient, commercially available starting material [25], [26] A phosphoramidate was initially formed by converting the amino group to diethyl phosphite, exploiting the relative nucleophilicity of the amino groups. Additional oxidation of the azetidine has been carried out by omesylation and cyclization in the presence of potassium tert-butoxide. This multi-step technique is a moderate and practical approach to store azetidine as its equivalent diethyl phosphoramidite since acid hydrolysis produces azetidine as its hydrochloride salt.

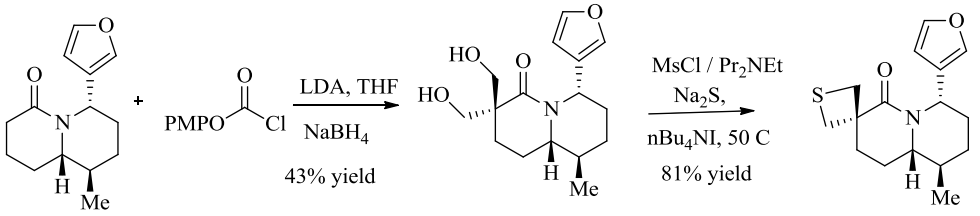


Scheme 3: General method for producing C-X bonds is used cyclization.



Scheme 4: Synthesis of azetidine with selective omesylation.

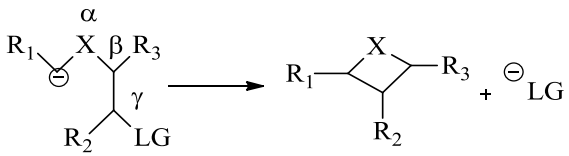
In 2017, Zakarian *et al*. investigates the nucleophilic reactivity of enolates as another method for installing relative to a heteroatom nucleophile, leaving groups at the location [27]. To get 1,3-bismesylates, a bicyclic lactam was bis acylated, then reduced, and O-sulfonated (Scheme 4) [28]. A thietane was built using sodium sulfide double nucleophilic displacement in the same way a sesquiterpene alkaloid called thionuphlutine is synthesized, which contains thiolane [17]. Thietane and thiolane nucleoside analogs were also synthesized using this double displacement technique.



Scheme 4: Using carbonyl functionalization to generate cyclization electrophiles.

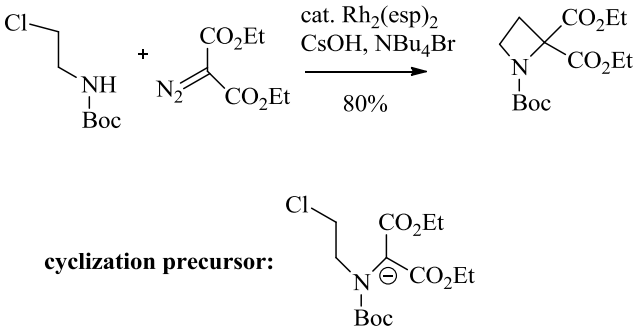
3.1.2. The formation of carbon-carbon bonds during cyclization

In the synthesis of four-membered rings, C-C bond cyclization offers various advantages over C-heteroatom cyclization (Scheme 5). The effectiveness of synthesizing heterocycles with four members with bulky C2 and C4 substituent locations is frequently constrained by steric repulsion [29]. In contrast, this restriction does not affect the creation of bonds between C2 and C3. A deprotonation-induced in-situ enolate synthesis with leaving groups is a typical method for synthesizing 4-membered rings via C-C bonds [25].



Scheme 5: A general strategy for cyclization of C-C bonds.

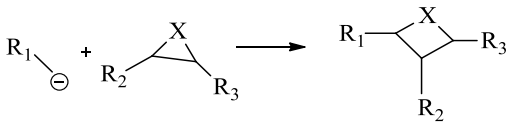
In 2019, Bull *et al.* explained that high substituted oxetanes synthesis is made possible by this 4 exotic cyclization between C2 and C3, which contrasts with the 4 exoticcyclizations shown in (Scheme 6). Unhindered locations experienced competitive lithiation, which led to undesirable Lactonization and Wittig rearrangement [2,3]. This was, however, sensitive to Michael's acceptor [26].



Scheme 6: Synthesis via cycle formation of the C-C bond.

3.1.3. Ring expansion and contraction

Ring growth is being reduced from cyclic starting elements; one may commonly produce four-membered heterocycles (Scheme 7). This field has produced several transformations that enable the creation of azetidines and thietanes with several substitutions. In a convergent process, certain atoms can be added to the contraction technique [28].

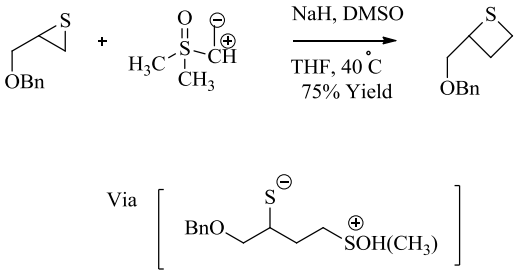


Scheme 7: General approach ring expansion.

3.1.3.1. Ring Expansion

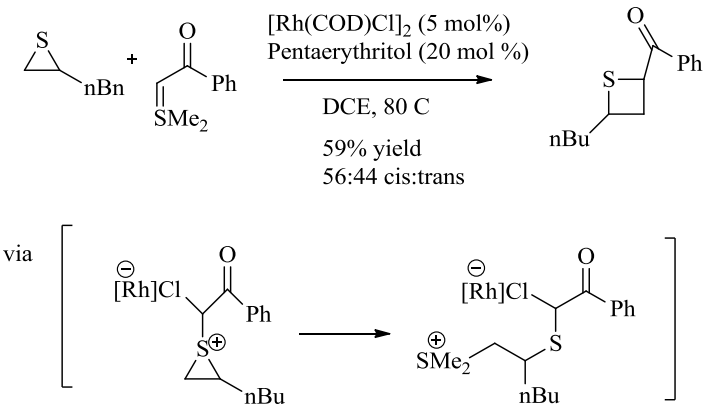
Xu *et al.* (2017) investigated that thietane and azetidine can be prepared by a one-carbon homologation due to the polarised bonds of thiiranes and aziridines and their ring stretch. To achieve the necessary 1,3 placement of the nucleophile and electrophile, this overall approach necessitates the

employment of a close-releasing group from a one-carbon source. Thietanes were made by expanding thiiranes using dimethyl-oxo-sulfonium methylide (Scheme 8) [24].



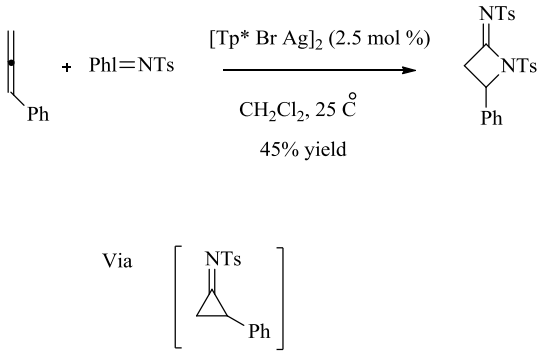
Scheme 8: Ring expansion via nucleophilic C1 insertions.

Xu *et al.*in 2019 explained with this method, it was possible to synthesize moderate to high diastereoselective in highly substituted bicyclic methylene azetidines by using the diazo-ester to increase aziridines as a source of one carbon. It was suggested that this transformation would proceed from a locally produced Rh-bound carbene to an N-based aziridine attack through aziridinium ylide production. The azetidine C2C3 bond was created by the ensuing ring-opening and ring-closing cascade that progressed to a hypothetical non-racializing C-bound Rh-enolate. As an alternative, a few 2-acyl thietanes were created by the ring expansion of thiiranes, which was catalyzed by Rh (Scheme 9) [30].



Scheme 9: Nucleophilic C1 insertions that result in ring expansions.

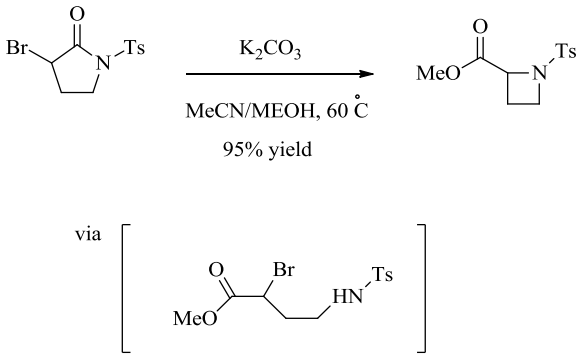
Maseras, Diaz-Requejo, and Perez 2020 investigated a kind of in-situ Ag-nitrene created using hydro-tris(pyrazolyl)borate silver dimer, which underwent selective intermediates of the unstable cyclopropylamineare formed by nitrene transfer to aryl substituted allenes. The observed azetidine compounds were made possible by later silver-mediated nitrene insertion (Scheme 10) [31].



Scheme 10: Ring expansion via N-atom insertions.

3.1.3.2. Ring extraction

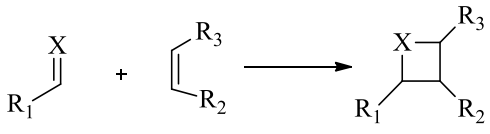
Pale & Blanc *et al.* in 2014 reported that when "bromo"-N sulfonyl pyrrolidinones are nucleophiles by alcohol or amine, azetidines containing the two positions are filled with esters or amides (Scheme 11). As a result of the pyrrolidinone amide bond, a primary nucleophilic acyl substitution was broken, resulting in the bromo group being preferentially displaced to create azetidine by the pendant sulfonamides nucleophile. The availability of substituted pyrrolidinones makes this tactic advantageous [32].



Scheme 11: Azetidine synthesis through ring contraction.

3.1.4. Cycloadditions

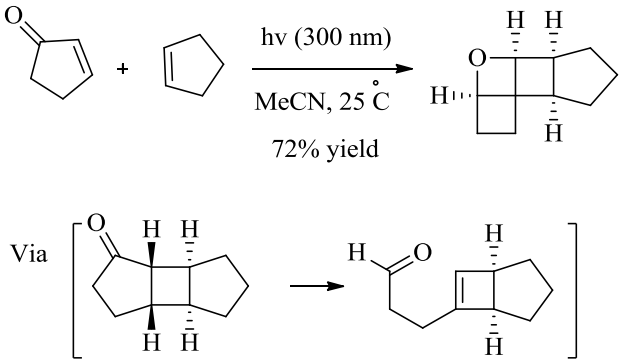
The synthesis of several functionalized heterocycles may be accomplished using cycloadditions, a significant and mechanistically varied family of reactions. Four-membered heterocycles are often created using photochemically permitted [2+2] cycloadditions, for which novel synthetic techniques are constantly being developed (Scheme 12) [33]. These techniques include the use of transition metal coordination techniques, specially formulated directly excited substances, and photosensitized substances. Both [2+2] annulations using Lewis bases as catalysts and formal [2+2] cycloadditions under heat circumstances have made significant progress [34].



Scheme 12: General strategy for [2+2] Cycloadditions.

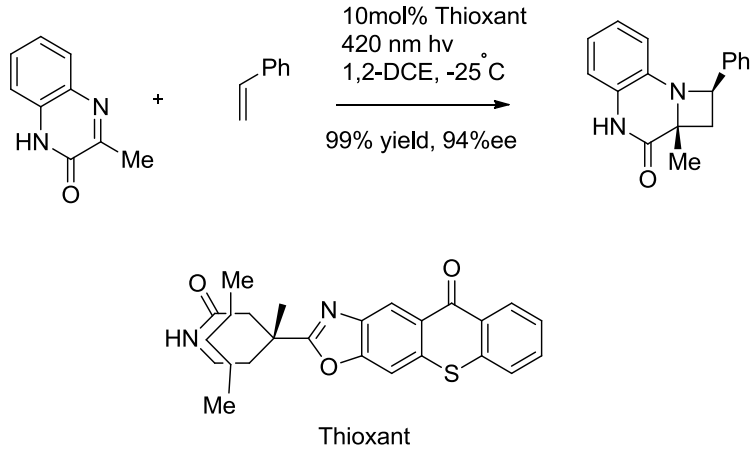
3.1.4.1. Photocycloadditions of [2+2]:

Four-membered heterocycle synthesis may be accomplished using a variety of techniques called photocycloadditions. The Paterno-Buchi reaction is the traditional [2+2] photocycloaddition that produces oxetanes by exposing an olefin and an aldehyde or ketone to UV light [21]. The alkene interacts with the excited state, which is reached by a carbonyl n-π* transition, to create the 4-membered ring[35]. There have been many other variations that might potentially synthesize azetidines, and increased interest has encouraged the discovery of other strategies. In 2018, Aitken explained about the tricyclic oxetanes were created by directly exposing light at 300 nm using cyclopentenones and alkenes (Scheme 13) [36].



Scheme 13: Direct irradiation of octane results in [2+2] photocycloadditions.

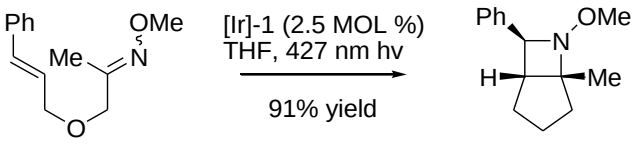
Bach *et al.* (2020) investigated the imine starting material's photochemical E/Z isomerization as one possible relaxation route from the excited state that might reduce the amount of productive cycloaddition [35]. A concerted, singlet route made possible by "stacking pre-organization" is, however, considering the stereochemistry of the alkene starting material, the mechanism that best fits the experimental results was conserved by the azetidine. A pre-organization method has been employed to produce azetidines using visible light (Scheme 14). This method involves hydrogen bonding to a photosensitizer [37].



Scheme 14: Using substrate pre-organization techniques, azetidine may generate [2+2] photocycloadditions.

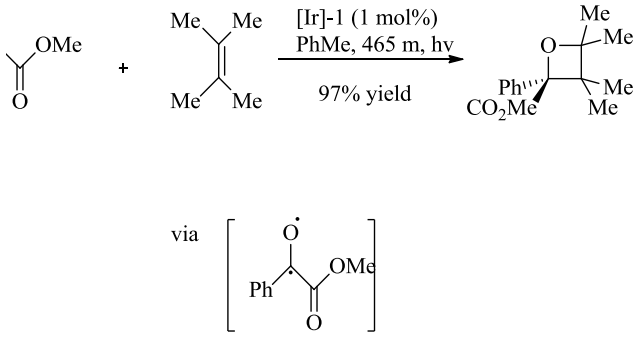
Schindler *et al.* in 2019, Mechanistic studies revealed that the formation of azetidine had been the result of [Ir]-1's initial triplet-excited state energies that were perfectly matched, which triplet

sensitized the tethered aryl alkene C=C double bonds (Scheme 15). Iridium photocatalysts have furthermore been employed as photosensitizers in the production of azetidines and oxetanes [38].



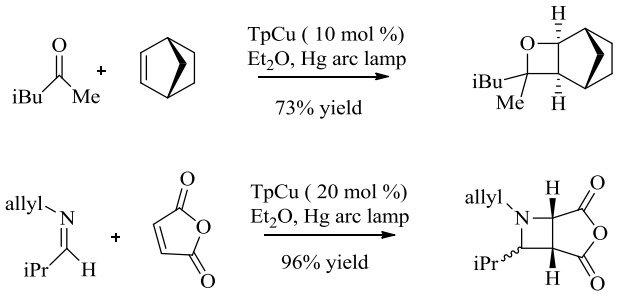
Scheme 15: Ir-based photosensitization of C=C& C=N bonds for [2+2] cycloadditions.

Yoon and Schindler *et al.* in 2020 synthesized the vinyl-substituted azetidines was made possible by extending this method to dienes [39]. Two distinct organizations simultaneously announced the achievement of the identical Ir-photocatalyst. Using visible light, transfer of triplet energy to the aryl keto ester oxo A double C=O bond and subsequent trapping by substituted alkenes produce oxetanes (Scheme 16).



Scheme 16: Ir-based photosensitization of C=O& C=N bonds for [2+2] cycloadditions.

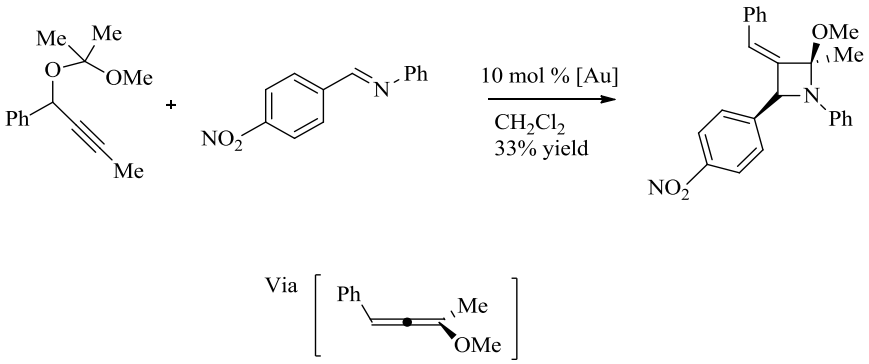
In 2019 and 2021, Schmidt *et al.* reported that an exchange of charges between two transition metals method was also used to activate alkenes for [2+2] photocycloadditions (Scheme 17) [40]. In solution, an active chromophore is formed by coordinatively capturing the Cu(I) center with the Norbornene. The creation of oxetane spirocyclic and other 2,2,3,4-tetrasubstituted oxetanes was supported by spectroscopic investigation of metal-to-ligand charge transfer (MLCT) between Cu(I)alkene and ligands [25]. Wider-ranged cyclic strained alkene partners for azetidines, including maleic anhydride and maleimide, were created by a similar application of imines [41].



Scheme 17: Photocycloadditions [2+2] through C=C bond activation in MLCT.

3.1.4.2. Thermal [2+2] cycloaddition:

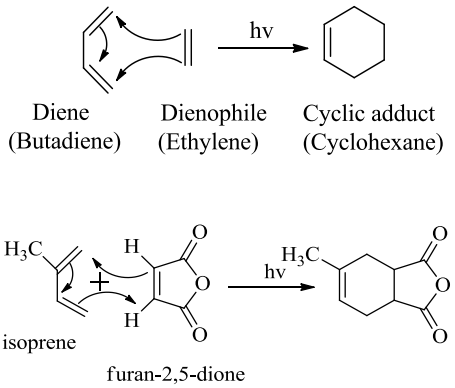
An electrophilic C=X partner is intermolecularly added, the ring is closed, and the reaction is eliminated freeing the organo-catalyst and generating the 4-membered heterocycle product. Fiksdahl *et al.*, in 2020 explained that instead of accessing benzylidene azetidines, propargyl ethers have been activated by Au(I) in the presence of imines (Scheme 18) [42]. Coordination-mediated alkyne activation caused the acetone elimination process produces an electron-rich allene, which then undergoes a thermal [2+2] cycloaddition with an imine.



Scheme 18: Lewis's acid-catalyzed [2+2] cycloaddition produces azetidine.

3.1.4.3. Ring-closing reactions

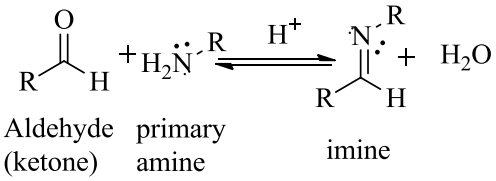
In a ring-closing reaction, a new ring is created in a molecule. For instance, a cyclohexene ring can be created through the interaction between a diene and a dienophile in a Diels-Alder reaction (Scheme 19) [43]. Numerous heterocyclic compounds can be produced using this method.



Scheme 19: Diels Alder reaction:

3.1.4.4. Cyclization processes

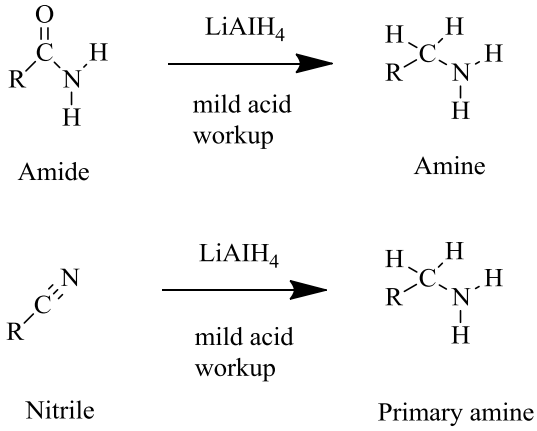
In cyclization reactions, a ring can form in a molecule without the aid of a diene or a dienophile (Scheme 20). For instance, a condensation reaction between a ketone and a primary amine can result in the formation of a cyclic imine (Schiff base) [44].



Scheme 20: Synthesis of imines from aldehydes and ketones.

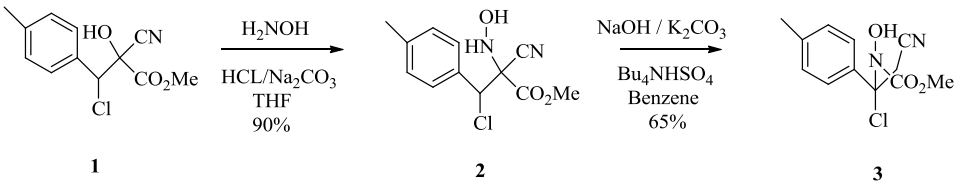
3.1.4.5. Reduction reactions

Reduction reactions add electrons to a molecule, frequently with the help of a reducing agent like lithium aluminum hydride (LiAlH4). For instance, it is possible to convert a nitro group into an amine, which can then be cyclized to create a heterocyclic ring (Scheme 21) [45].



Scheme 21: Synthesis of LiAlH4 will open at the least substituted carbon and it will reduce alkyl halides to alkanes.

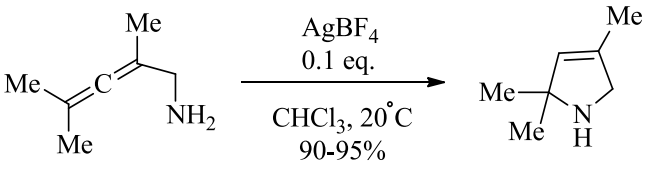
Aziridine derivatives are employed as affinity probes, which are identified compounds that specifically react with relevant biological molecules for detection and testing investigations [46]. They are also used in medicine to cure cancer. The most popular category of naturally occurring compounds that include the aziridine ring is the mitomycin family of antitumor antibiotics [47]. Heterocyclic compounds, the focus of heterocyclic chemistry, make up around 65 percent of organic chemistry. Ring-closing reactions using properly substituted amines can also produce aziridines. For instance, under phase-transfer circumstances, hydroxylamine derivatives are used to transform halohydrins **(1)** into N-hydroxy aziridines **(3)**. Next, the intermediate halo amino esters **(2)** undergo an intramolecular S_N2 reaction that is base-catalyzed (Scheme 22) [48].



Scheme 22: Synthesis of Aziridine derivatives.

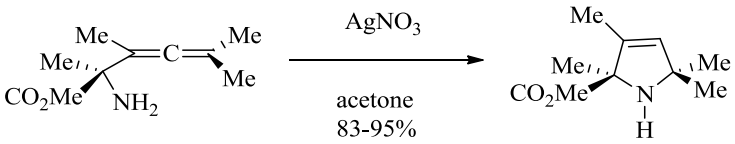
4. N-heteroatom contained five-membered heterocycles synthesis of the influence of silver

When the substituent was near the allene moiety, trans-2,3-pyrrolidines could be produced with high diastereomer selectivity [49]. Nevertheless, now required 1 equivalent of Ag salt for the reaction (Scheme 23). Aallenic amines were converted into 3-pyrrolines in a catalytic quantity of AgBF4 at room temperature, according to Claessen and colleagues' ground-breaking study [50]. Only 3% of the pyrroles were found. To add a metal cation to Alene's p-bond in a face-selective manner that required interacting with the nitrogen atom and the X-residue that would later be added to the heterocyclic ring, allenic amine interacted with silver (I). This interaction produced a silver (I)/p-complex [51].

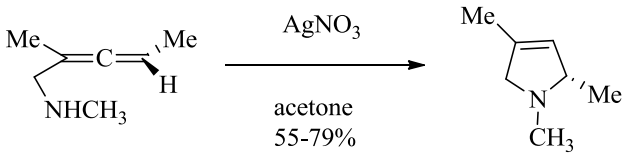


Scheme 23: Synthesis of 2,2,4-trimethyl-2,5-dihydro-1H-pyrrole.

The α-amino allenes used to make the pyrrolines (Scheme 24 and 25) had a high degree of diastereomeric purity (about 95%). It was decided that the syn configuration would be the main one [52].

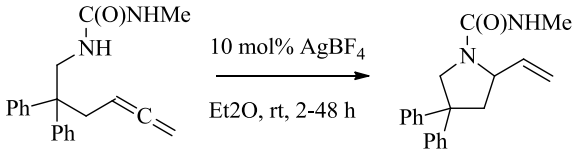


Scheme 24: Synthesis of (R)-methyl 2,3,5,5-tetramethyl-2,5-dihydro-1H-pyrrole-2-carboxylate.



Scheme 25: Synthesis of (S)-1,2,4-trimethyl-2,5-dihydro-1H-pyrrole.

By using gold (I)-catalyzed intramolecular AHA of allenes, Toste *et al.*, in 2007 were reported to produce chiral piperidines and pyrrolidines in outstanding enantioselectivities and yields. The same group expanded this procedure in 2010 to produce pyrazolidines and isoxazolidines of pharmacological significance by the intramolecular assault of hydrazine and hydroxylamines (Scheme 26) [53].

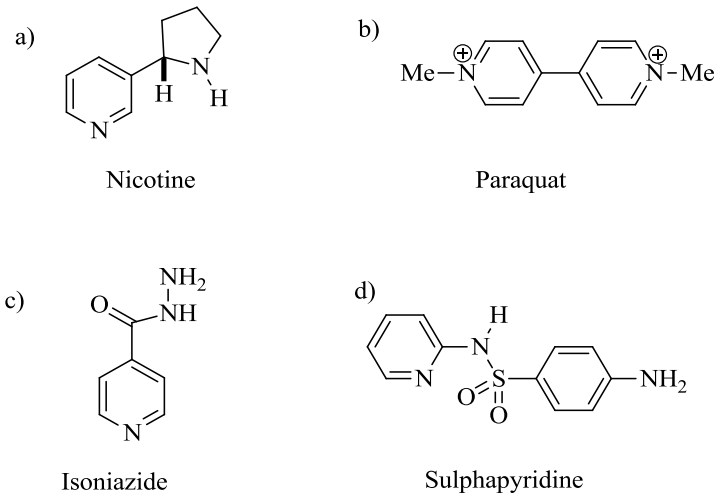


Scheme 26: Synthesis of N-methyl-4,4-diphenyl-2-vinylpyrrolidine-1-carboxamide.

5. Bioactivity of pyridines in heterocycles

A significant portion of medical chemistry involves heterocyclic molecules, and many of the medications now on the market include heterocyclic rings. Pyridine, a six-membered heterocyclic molecule, has a wide range of uses in agrochemicals and pharmaceuticals as a solvent, reagent, and precursor. New antiviral medications must be developed medically due to the rise in drug resistance. The pyridine scaffold as well as its derivatives of it display a wide spectrum of biological effects, such as anti-microbial, antiviral, antioxidant, anti-diabetic, anti-cancer, anti-malarial, analgesic, and anti-inflammatory in nature properties [54]. Some of the examples are shown in Scheme 27. Nicotine is a

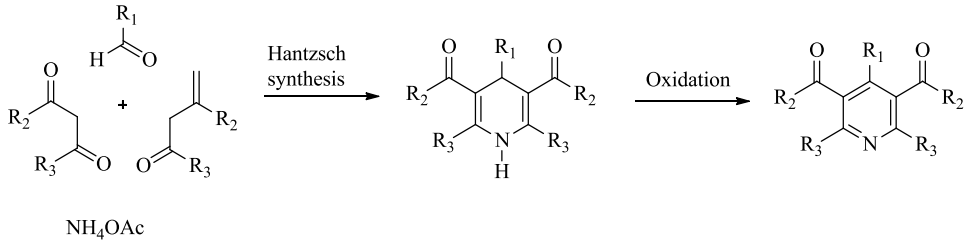
harmful and addictive component of tobacco that is pharmacologically active [55]. One of the first herbicides ever created, paraquat is poisonous and non-selective [56]. One of the first antibiotics, sulphapyridine, is a sulfonamide anti-bacterial agent [57]. Although isoniazid is still used to treat TB, there is a serious and developing issue with resistance [58].



Scheme 27: Bioactivity pyridines of heterocycles.

5.1. Synthesis of pyridines

The most significant heterocycles are pyridines, which are widely present in natural goods, medicines, agrochemicals, additives, flavors & perfumes. They act as catalysts, building components, and ligands in coordination chemistry as well as in organic synthesis [59]. This is the reason why the synthesis of pyridines continues to be a hot issue. One of the most common ways to make pyridines is by oxidizing the equivalent 1,4-dihydropyridines, which may be made using the traditional Hantzsch 1,4-dihydropyridine synthesis (Scheme 28) [60].



Scheme 28: Synthesis of Hantzsch of 1,4-dihydropyridines

There have been many techniques established over time to facilitate the 1,4-dihydropyridines' oxidative aromatization that employs at least stoichiometric concentrations of an inorganic oxidant.

6. Challenges in heterocyclic reactions

The creation of effective and trustworthy synthetic procedures depends on the identification of issues in heterocyclic reactions. Typical issues that can occur in heterocyclic reactions

6.1. **Low yield**: Incomplete responses or unintended side effects may cause low yields. Low yields can also be caused by the reactants' or products' poor solubility [61].

6.2. **Problems with selectivity**: Heterocyclic compounds frequently have several reactive sites, which can lead to low selectivity. Selectivity might be compromised by unwanted side effects or competing reactions [62].

6.3. **Stability of reactant or product**: Some heterocyclic compounds have the potential to decompose or undergo unfavorable reactions. Poor selectivity or yields may come from this. Some heterocyclic compounds may be toxic or hazardous, which could cause problems with safety during synthesis or use. To guarantee safe and efficient usage, careful handling and relevant safety precautions are required [63].

6.4. **Scalability:** Due to challenges in maintaining reaction conditions and restricting side reactions, scaling up heterocyclic reactions can be difficult [64].

To ensure effective and dependable synthesis of heterocyclic compounds, it is critical to create processes that are scalable and resilient. In general, rigorous examination of the reaction conditions, reactants, and products is necessary for the detection of issues in heterocyclic reactions [65]. It is feasible to create effective and dependable synthetic methods for the synthesis of heterocyclic molecules by addressing these problems. The limitations of heterocyclic compounds can restrict their use in some circumstances. These negative aspects include.

7. Drawbacks of heterocyclic

Some heterocyclic compounds have the potential to be toxic and dangerous to human health. For instance, several heterocyclic substances have been connected to mutagenicity, cancer, and other health issues.

7.1. **Environmental impact:** Some heterocyclic substances have the potential to persist in the environment and harm ecosystems. For instance, it has been shown that certain heterocyclic chemicals are hazardous to aquatic creatures and can build up in the food chain [66].

7.2. **Cost and accessibility:** The usage of several heterocyclic compounds may be constrained by their expensive synthesis and constrained accessibility [67].

7.3. **Reactivity:** Because some heterocyclic compounds are unstable and extremely reactive, it might be challenging to handle and use them in some situations [68].

Some heterocyclic compounds can be difficult to dissolve in water, and because of their weak solubility in water and other solvents, several heterocyclic compounds may have limited uses. Overall, despite the widespread use of heterocyclic compounds in many fields and their abundance of useful properties, their drawbacks must be carefully considered and managed to ensure their safe and efficient use.

8. Coinage metals get around these by recognizing heterocyclic reactions

8.1. **Gaining yield:** By catalyzing the synthesis of the intended product and reducing side reactions, coin metals can boost the yield of heterocyclic processes. For instance, it has been demonstrated that reactions of heterocyclic compounds catalyzed by gold improve yields of sophisticated heterocyclic molecules [69].

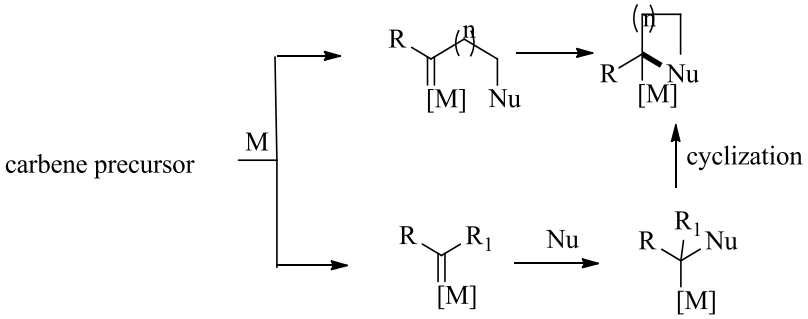
8.2. **Enhancing selectivity:** By guiding the reaction towards the desired product, coin metals can enhance the selectivity of heterocyclic reactions. By cooperating with certain functional groups in the reactant, for instance, copper-catalyzed reactions of heterocyclic compounds might enhance the selectivity of the reaction [70].

8.3. **Enhancing stability:** By binding to certain functional groups and stabilizing the intermediate or product, coin metals can increase the stability of heterocyclic compounds. By combining with functional groups, for instance, silver-catalyzed reactions of heterocyclic compounds can stabilize the intermediate [71].

Improving scalability: By offering effective and stable reaction conditions, coin metal catalysts can improve the scalability of heterocyclic processes. For instance, it has been demonstrated that gold-catalyzed reactions of heterocyclic compounds are scalable and effective, enabling the mass synthesis of complex heterocyclic molecules. Overall, the yield, selectivity, stability, and scalability of heterocyclic reactions may be improved by using coin metals as catalysts by resolving some of the identification issues that might occur during the processes [72].

9. Metal carbenes are produced during the heterocyclic synthesis process by establishing new carbon-heteroatom bonds

Coinage-carbene complexes, which belong to the class of electrophilic Fisher carbenes and can be used to synthesize linear or cyclic frameworks, have been more vital during the past 15 years. The evaluation of chemo-, region-, and enantio-selective processes that emerged from their application frequently met the criteria for creating safe and environmentally sound procedures [73]. The establishment of innovative, simple, and effective procedures to produce these reactive intermediates is also important for the development of these compounds [74]. These approaches are primarily used in the field of heterocyclic chemistry when new C-C bonds are formed utilizing the carbine carbon atom and when the heteroatom is embedded as an outsider in a side chain [1]. Rare examples exist where a carbine interacts with a heteroatom nucleophile to produce carbon-heteroatom bonds. However, if properly developed, this kind of reaction could offer a beautiful substitute for the usual syntheses of heterocycles. Due to these factors, decided to report on the current state of the coinage metal carbine reaction to create heterocycles via creation [75]. The creation of the metal carbine complex from appropriate precursors and a nucleophilic heteroatom afterward joining the electrophilic carbon atom of the carbene is the general mechanism for the reactions discussed. This process matches up with the cyclization step if it proceeds intramolecular [76].



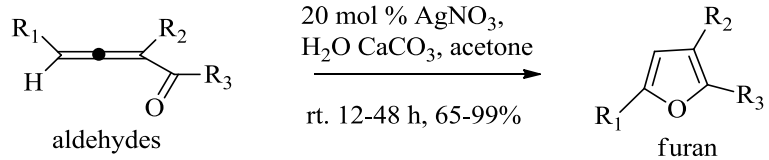
Scheme 29: The interaction of coinage metal carbenes to create new carbon-heteroatom linkages, leading to the synthesis of heterocycles.

Controlling the selectivity of highly reactive intermediates is an important objective in organic chemistry. Carbenes produced by nitrogen extrusion from diazo compounds, either thermally or

photochemically, typically lack control and result in complicated product combinations. However, the metal-catalyzed breakdown of diazo compounds produces highly selective "carbenoids" that can produce reactions with high selectivity (Scheme 29) [77].

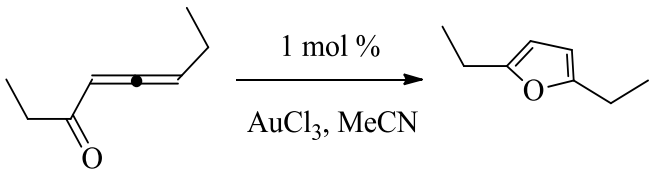
10. Using tethered nucleophiles to cyclize unsaturated C-C bonds

The synthesis of several substituted furans and pyrroles is relatively easily accomplished through the cyclization of alkenyl carbonyls, alkenyl, imines, and epoxides. In organic synthesis, tethered nucleophiles are frequently used to convert unsaturated C-C bonds into cyclic molecules. Using a linker or "tether" molecule, a nucleophile that is attached to an unsaturated C-C bond, such as an alkene or alkyne, is used in this method [78]. An appropriate nucleophile can perform a cyclization process to create a new bond with the unsaturated carbon atom when it is placed near the unsaturated C-C bond. Consequently, a cyclic molecule is created, which has several uses in the synthesis of organic compounds. The Heck process, which uses an aryl or vinyl halide as a substrate and a tethered alkene as a nucleophile, is an illustration of a tethered nucleophile cyclization reaction [79]. The production of a new C-C bond and the release of the halide leaving group are the results of the reaction, which is normally catalyzed by a palladium catalyst and happens through a coordinated process. Another illustration is the ring-closing metathesis reaction, which uses a metal catalyst, such as ruthenium or molybdenum, to speed up the process and a tethered alkene or alkyne as a nucleophile [80]. The production of a new C-C bond and the release of the catalyst occur as a result of this reaction's progression through a cyclic transition state. Tethered nucleophiles are an effective method for creating cyclic compounds from unsaturated C-C bonds. These reactions have several uses in the synthesis of organic compounds, including the creation of materials, drugs, and natural products (Scheme 30) [81].



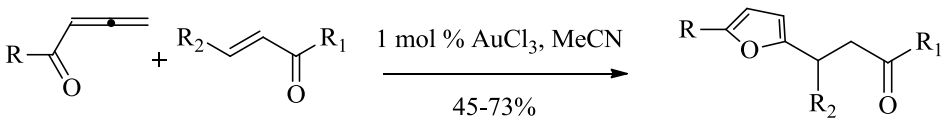
Scheme 30: Disclosed a method for the cyclization of aldehydes by Ag (I) to produce furans.

According to Marshall et al., there is a method for synthesizing furans involving alkenyl ketones or aldehydes being cyclized by Ag (I). This group was the first to demonstrate how effective this kind of cyclization is for producing furans with multiple substituents (Scheme 31) [82].



Scheme 31: Furan was produced by the cyclization of alkenyl ketone when catalytic quantities of $AuCl_3$ were present.

Given their belief in the transitional nature, the authors provide two possibilities for the development. When the $AuCl_3$ reacts with the enones (Scheme 32), then it can create new C-C bonds by merely exchanging an electrophilic aromatic with a C-C bond at the furan's 5-position [83].



Scheme 32: To produce C-2 substituted ketones, the process was expanded to include one-pot cyclization with R-unsaturated ketones.

11. Significance of heterocyclic and instances in which they have been utilized as medications

Heteroatoms are a highly prevalent component of many excipients and active medicinal ingredients, regardless of whether they are isostatically substituted carbons. Heterocyclic scaffolds are widely used in privileged structures [84]. According to statistics, heterocycles are present in more than 85% of all chemical compounds that have physiological activity [85]. This finding emphasizes the critical role heterocycles play in the creation of modern medications. Physiologically, hydrogen bonds are altered by heterocycles [86]. The development of synthetic techniques like several functionalized heterocycles may be quickly accessed by metal-catalyzed cross- and hetero-coupling procedures., is related to the rising prevalence of different heterocycles in pharmaceuticals [87]. The structures of numerous heterocyclic lead compounds, on the other hand, were first simplified and then modified by medicinal chemists after they were isolated from natural resources. As a result, heterocycles are crucial for medicinal chemists because they enable the expansion of the chemical space that can contain drugs and the advancement of more successful drug development initiatives. The creation, discovery, design, identification, and synthesis of physiologically active substances are all aspects of medicinal chemistry, which is a chemical-based field that also involves components of living creatures, healthcare, and pharmacological sciences. As a result, the study of their metabolism is important [88].

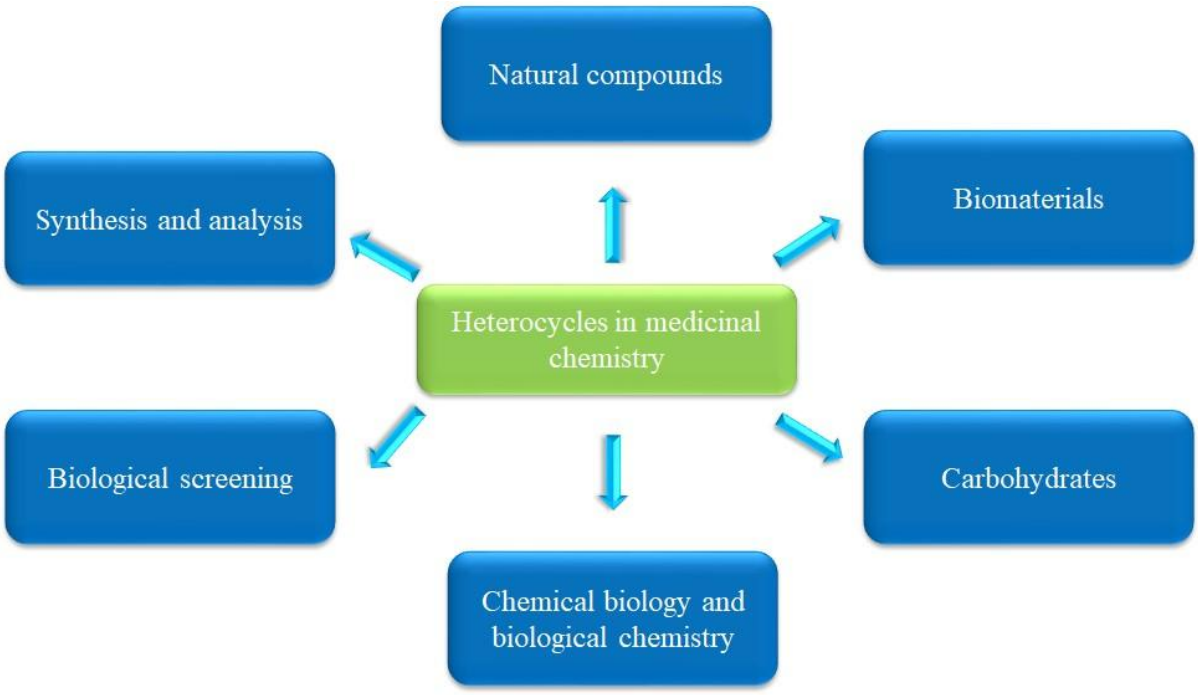


Figure 1: Heterocycles used in medicinal chemistry

Most synthetic heterocyclic compounds are used as drugs for hypnotic, anticonvulsant, antineoplastic, disinfecting, antiviral, and tumor-fighting purposes, among other things [89]. In pharmacopeias, a

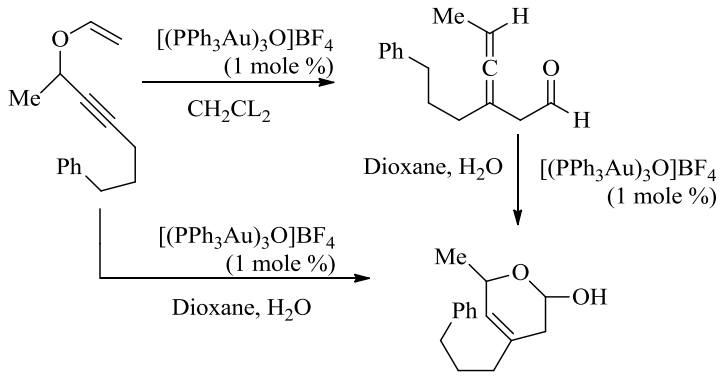
dependable enormous number of heterocyclic drugs are included. The ring structures' size and kind, along with the persuading substituent clusters of the mother stage, forcefully illustrated their physical characteristics [87]. Heterocyclic mixtures have a very dynamic activity as antiviral, antibacterial, pain-relieving, ant-parasitic, and antitumor medicines, among other different therapeutic applications [89]. The extent of this brief review does not adequately apply. The alkaloids are the largest collection of heterocyclic mixtures that occur often and have extensive natural action [90]. Heterocyclic substances, some of the massive natural are acting as precursors through chalcone subordinates. According to medical chemistry, the bulk of chalcone heterocyclic compounds principally functions as significant anti-bacterial and anti-parasitic medicines [91]. Organic compounds known as chalcones have two aromatic rings joined by a three-carbon. They are widely distributed across the plant world and have been shown to possess some biological properties, such as antioxidant, anti-inflammatory, and antibacterial properties. The opposite is true for heterocyclic chalcones [92], which are chalcone derivatives in which one or both of the aromatic rings have been replaced by a heterocyclic ring. These compounds could result in the development of novel drugs with improved pharmacological properties [93]. The presence of heterocyclic rings in chalcone structures can result in improved biological activity overall, making them intriguing candidates for the development of new drugs. Depending on how the nitrogen atoms are substituted, S-triazines can arise in a variety of ways. Three nitrogen atoms are symmetrically positioned in the common S-triazine 1,3,5-triazine [94]. This substance, also known as cyanuric triazine, is often used in the manufacturing of a variety of substances, such as herbicides, dyes, and flame retardants. The biological characteristics of S-triazines have also been investigated, and they have the potential to be potent antiviral, antibacterial, and anticancer drugs. For example, it has been demonstrated that some S-triazines inhibit the DNA replication of cancer cells, whilst other S-triazines have been discovered to limit viral enzyme activity. By choosing s-triazine as the primary center of the incorporated compounds, we were able to orchestrate a few compounds on the s-triazine moieties, which are notable anti-threatening development and anti-tumor specialists and have undergone enormous amounts of assessment work [95]. Triazole is a type of heterocyclic chemical that is significant, and triazole-centered molecules are sufficient authors have incorporated compounds with a triazole central that have wonderful biological development as our main center because there are many efficient medications on the market [96].

12. Future perspective of coinage metal synthesis of heterocycles

To synthesize heterocyclic molecules, coinage metals, including copper, silver, and gold have been used as catalysts. Particularly when new and more efficient catalytic systems are involved, there has been an increase in interest in employing these metals to synthesize complex heterocyclic structures in recent years. One of the main advantages of using coinage metals as catalysts is that they are more environmentally friendly because they are less poisonous than other transition metals [97]. High selectivity and catalytic activity in these metals may potentially lead to more efficient and targeted synthesis routes. Future heterocycle synthesis is expected to use coinage metals increasingly frequently, particularly in asymmetric synthesis and cascade reactions. Many heterocyclic compounds, including pyrazoles [98], pyridines [99], and pyrimidines [100], have been successfully synthesized by cycloaddition reactions that were made possible by silver. Oxazoles, thiazoles, and pyrazines are just a few of the heterocyclic structures that have been created utilizing gold-catalyzed processes [101]. Another topic for future research is the development of new ligands that can enhance the reactivity and selectivity of coinage metal catalysts. As a result, new synthetic methods for the extremely efficient and selective production of complex heterocyclic compounds may be developed [102].

12.1. The gold-catalyzed reaction of heterocyclic compounds

A potent tool for the synthesis of a vast array of organic molecules has emerged: heterocyclic compound reactions catalyzed by gold [103]. High selectivity, accommodating reaction conditions, and the capacity to activate substrates that would not otherwise react are just a few benefits of using gold as a catalyst in organic processes[104]. The intramolecular hydroamination reaction is one instance of a gold-catalyzed reaction of heterocyclic compounds. In this reaction, an amine group is added to a heterocyclic molecule across a carbon-carbon double bond, producing a cyclic product [105]. Gold catalysts can activate the carbon-carbon double bond and make it easier for the amine group to be added nucleophilically (Scheme 33). Another illustration is the gold-catalyzed cyclization of alkynes with heterocyclic substances, such as pyridines and pyrimidines, to create aromatic molecules. Natural products like alkaloids and terpenoids have also been synthesized using gold-catalyzed processes [106]. For instance, the pyrrole-ringed natural product stemofoline has been synthesized using gold-catalyzed processes. With several potential uses in the synthesis of natural products, medicines, and materials, gold-catalyzed reactions of heterocyclic compounds have grown to be a significant field of research in organic synthesis [107].



Scheme 33: Gold-catalysed reaction of heterocyclic compounds.

12.2. The silver-catalyzed reaction of heterocyclic compounds

The synthesis of several organic molecules has also been widely investigated and developed using silver-catalyzed reactions of heterocyclic compounds. Due to their low toxicity, great stability, and wide application to a variety of organic processes, silver catalysts are appealing [108]. Alkynes may be cyclized with heterocyclic compounds to create aromatic compounds, which is an illustration of a silver-catalyzed reaction of heterocyclic compounds [109]. The silver catalyst activates the alkyne in this reaction, which is subsequently subjected to cyclization with the heterocyclic molecule [110]. Numerous natural products and medicines have been synthesized using this reaction. Another illustration is the cross-coupling of heterocyclic compounds with aryl halides under the influence of silver to produce diaryl compounds. The silver catalyst activates the aryl halide in this reaction, which is subsequently cross-coupled with the heterocyclic molecule [111]. A variety of diaryl compounds, including some with potential uses in medical chemistry, have been synthesized using this process. The synthesis of heterocyclic compounds has also been carried out using silver-catalyzed processes. For instance, pyrazoles, pyrimidines, and triazoles have all been created using silver-catalyzed cycloaddition processes. Overall, the synthesis of natural products, drugs, and materials using silver-catalyzed reactions of heterocyclic compounds has grown into a significant area of research in organic synthesis [112].

13. The most recent developments in coinage metal nanostructures and bio-applications

Coinage metal nanostructures have notable qualities, including catalytic, optical, electrical, and chemical characteristics that depend on size and form [113]. Each of these characteristics has stimulated intensive research into the development and production of metal nanostructures used in coinage and their potential applications [114]. The development of coinage metals like Cu, Ag, and Au, as well as their bimetallic nanostructures, most notably when utilizing solution-based methods, is summarized in this study for these reasons. It encompasses a range of synthetic techniques, such as traditional procedures and more contemporary techniques, that have been used to enhance functionality by carefully regulating the size, shape, and composition of coinage metal nanostructures [97]. It also emphasizes how these coinage metal nanostructures may be used for electrochemical sensing, surface-enhanced Raman scattering (SERS), and antibacterial characteristics for bio-applications [115]. Because they have a much wider range of applications and much smaller feature sizes than their bulk counterparts, metal nanostructures are attracting a lot of attention. A high surface area to volume ratio has the benefit of increasing the percentage of surface atoms, which might boost the material's reactivity [116]. Due to their unique size- and shape-dependent characteristics, they consequently show considerable potential for widespread commercial applications in the sectors of electronics, information storage, medical devices, as well as environmental and energy technologies. When light waves collide with metallic surfaces, conductive electrons or surface Plasmon collectively oscillate, giving rise to the peculiar optical properties of these coinage nanostructures. The synthesis, characterization, properties, and applications of bimetallic Au-Ag nanostructures will all require more study [117].

14. The current state of metals used for coins

Even though their principal applications have changed from being used in currencies, copper, silver, and gold are still in great demand and are still frequently employed. For many contemporary uses, such as industrial machinery, plumbing, and electrical wiring, copper is a crucial metal. In addition, it is utilized in electronics, transportation, and construction materials [118]. Although silver is still used to make coins, it is now primarily used in manufacturing, especially in the creation of electronic parts, solar panels, and medical devices. Silverware and jewelry are some items that utilize it [119]. In addition to its continued usage as coinage and as a store of wealth, gold is also employed in industry, notably in the fields of electronics and medicine [120]. Jewelry and ornamental arts also employ it[121]. These metals' prices are subject to volatility and are affected by several variables, including supply and demand, general economic conditions, and geopolitical developments [75]. Copper, silver, and gold prices have been in a great deal of flux recently, reflecting the turbulence and uncertainty in world markets. Overall, coinage metals continue to be significant and valuable materials with a variety of uses, and their status will likely change in response to shifting economic and technological circumstances [122].

15. Conclusion

In conclusion, the use of coinage metals in heterocyclic chemistry presents a great opportunity for the creation of fresh and effective synthetic processes for the synthesis of sophisticated heterocyclic compounds. It has been demonstrated that copper, silver, and gold are efficient catalysts for a variety of organic processes, including those involving heterocyclic compounds. In comparison to conventional catalysts, these metals have a variety of benefits, such as excellent selectivity, minimal toxicity, and the capacity to function in benign environments. The synthesis of natural products, drugs, and other physiologically active chemicals has already advanced significantly as a result of the employment of coinage metals in heterocyclic chemistry. In addition, understanding the mechanism of coinage metal-catalyzed reactions in heterocyclic chemistry has given researchers important new

information on the variables that affect selectivity and yield. Despite these achievements, the study of coinage metals and heterocyclic chemistry still faces numerous obstacles. The creation of fresh ligands and catalysts that can increase the selectivity and effectiveness of these reactions is a significant problem. The improvement of response conditions to reduce waste and boost sustainability is another difficulty. All things considered, further research into the use of coinage metals in heterocyclic chemistry has the potential to create novel synthetic processes as well as new therapeutics and other physiologically active chemicals.

Reference

[1] N. T. Patil and Y. Yamamoto, "Coinage metal-assisted synthesis of heterocycles," *Chemical Reviews*, vol. 108, no. 8. 2008. doi: 10.1021/cr050041j.

[2] F. S. Geitner, M. A. Giebel, A. Pöthig, and T. F. Fässler, "N-Heterocyclic Carbene Coinage Metal Complexes of the Germanium-Rich Metalloid Clusters [Ge9R3]− and [Ge9RI2] 2− with R= Si (i Pr) 3 and RI= Si (TMS) 3," *Molecules*, vol. 22, no. 7, p. 1204, 2017.

[3] T. Zhang, J. Zhong, and Z. Wu, "Recent advances in catalytic conversion of carbon dioxide to propiolic acids over coinage-metal-based catalysts," *J. Energy Chem.*, vol. 59, pp. 572–580, 2021.

[4] B. H. Lipshutz and Y. Yamamoto, "Introduction: coinage metals in organic synthesis," *Chem. Rev.*, vol. 108, no. 8, pp. 2793–2795, 2008.

[5] B. D. Ellis *et al.*, "An oxetane-based polyketide surrogate to probe substrate binding in a polyketide synthase," *J. Am. Chem. Soc.*, vol. 140, no. 15, pp. 4961–4964, 2018.

[6] H. Choo, X. Chen, V. Yadav, J. Wang, R. F. Schinazi, and C. K. Chu, "Synthesis and anti-HIV activity of D-and L-thietanose nucleosides," *J. Med. Chem.*, vol. 49, no. 5, pp. 1635–1647, 2006.

[7] A. J. Jordan, G. Lalic, and J. P. Sadighi, "Coinage metal hydrides: synthesis, characterization, and reactivity," *Chem. Rev.*, vol. 116, no. 15, pp. 8318–8372, 2016.

[8] F. A. Khaliullin, Y. V Shabalina, A. V Samorodov, F. K. Kamilov, G. A. Timirkhanova, and D. Z. Murataev, "Synthesis and antiaggregant activity of 2-[3-Methyl-1-Ethylxanthinyl-8-Thio] acetic acid salts containing a thietane ring," *Pharm. Chem. J.*, vol. 52, pp. 52–56, 2018.

[9] R. Melot and V. Michelet, "Coinage Metal-Catalyzed Asymmetric Reactions of ortho-Alkynylaryl and Heteroaryl Aldehydes and Ketones," *Molecules*, vol. 27, no. 20, p. 6970, 2022.

[10] N. T. Patil and Y. Yamamoto, "ChemInform Abstract: Coinage Metal Assisted Synthesis of Heterocycles," *ChemInform*, vol. 39, no. 48, 2008, doi: 10.1002/chin.200848261.

[11] Y. Zhao *et al.*, "Designer Gold-Framed Palladium Nanocubes for Plasmon-Enhanced Electrocatalytic Oxidation of Ethanol," *Chem. - A Eur. J.*, vol. 28, no. 32, 2022, doi: 10.1002/chem.202200494.

[12] B. Yin and Z. Luo, "Coinage metal clusters: From superatom chemistry to genetic materials," *Coordination Chemistry Reviews*, vol. 429. 2021. doi: 10.1016/j.ccr.2020.213643.

[13] E. López, O. Bernardo, and L. A. López, "Coinage metal-catalyzed carbo- and heterocyclizations involving alkenyl carbene intermediates as C3 synthons," *Tetrahedron Lett.*, vol. 109, p. 154156, 2022, doi: 10.1016/j.tetlet.2022.154156.

[14] C. A. Malapit and A. R. Howell, "Recent applications of oxetanes in the synthesis of heterocyclic compounds," *J. Org. Chem.*, vol. 80, no. 17, pp. 8489–8495, 2015.

[15] S. Cacchi, "The Chemistry of Heterocycles," *Synthesis (Stuttg).*, vol. 2004, no. 14, 2004, doi: 10.1055/s-2004-834452.

[16] S. W. Kim, W. Zhang, and M. J. Krische, "Catalytic enantioselective carbonyl allylation and propargylation via alcohol-mediated hydrogen transfer: merging the chemistry of grignard and sabatier," *Acc. Chem. Res.*, vol. 50, no. 9, pp. 2371–2380, 2017.

[17] N. Nishizono, Y. Akama, M. Agata, M. Sugo, Y. Yamaguchi, and K. Oda, "Synthesis of thietane nucleoside with an anomeric hydroxymethyl group," *Tetrahedron*, vol. 67, no. 2, pp. 358–363, 2011.

[18] J. Jampilek, "Heterocycles in medicinal chemistry," *Molecules*, vol. 24, no. 21. 2019. doi: 10.3390/molecules24213839.

[19] S. S. Tawfik, S. Zarechian, and A. A. Farahat, "Synthesis and anti-influenza activity of five member heterocycles containing compounds: A mini review," *Arkivoc*, vol. 2021, no. 9. 2021. doi: 10.24820/ARK.5550190.P011.602.

[20] J. E. Sánchez-Velandia, H. G. Baldoví, A. Y. Sidorenko, J. A. Becerra, and F. Martínez O, "Synthesis of heterocycles compounds from condensation of limonene with aldehydes using heteropolyacids supported on metal oxides," *Mol. Catal.*, vol. 528, 2022, doi: 10.1016/j.mcat.2022.112511.

[21] A. D. Richardson, M. R. Becker, and C. S. Schindler, "Synthesis of azetidines by aza Paternò–Büchi reactions," *Chem. Sci.*, vol. 11, no. 29, pp. 7553–7561, 2020.

[22] Y. Guo, W. Lee, and M. J. Krische, "Enantioselective Synthesis of Oxetanes Bearing All- Carbon Quaternary Stereocenters via Iridium- Catalyzed C− C Bond- Forming Transfer Hydrogenation," *Chem. Eur. J.*, vol. 23, no. 11, pp. 2557–2559, 2017.

[23] P. Mukherjee, M. Pettersson, J. K. Dutra, L. Xie, and C. W. Am Ende, "Trifluoromethyl Oxetanes: Synthesis and Evaluation as a tert- Butyl Isostere," *ChemMedChem*, vol. 12, no. 19, pp. 1574–1577, 2017.

[24] J. Sun, S. S. Gong, and Q. Sun, "A Novel Strategy for the Synthesis of Azetidine," in *Advanced Materials Research*, 2014, vol. 830, pp. 135–138.

[25] K. P. Malarney, K. C. Shekhar, and V. A. Schmidt, "Recent strategies used in the synthesis of saturated four-membered heterocycles," *Org. Biomol. Chem.*, vol. 19, no. 39, pp. 8425–8441, 2021.

[26] M. Serhan *et al.*, "Recent Strategies Used in the Synthesis of Saturated Four- Membered Heterocycles," *AIChE Annu. Meet. Conf. Proc.*, vol. 19, pp. 8425–8441, 2021, doi: 10.1039/x0xx00000x.

[27] J. J. Lacharity, J. Fournier, P. Lu, A. K. Mailyan, A. T. Herrmann, and A. Zakarian, "Total synthesis of unsymmetrically oxidized nuphar thioalkaloids via copper-catalyzed thiolane assembly," *J. Am. Chem. Soc.*, vol. 139, no. 38, pp. 13272–13275, 2017.

[28] T. W. Reidl and L. L. Anderson, "Divergent Functionalizations of Azetidines and Unsaturated Azetidines," *Asian J. Org. Chem.*, vol. 8, no. 7, pp. 931–945, 2019.

[29] A. S. K. Hashmi, L. Schwarz, J. Choi, and T. M. Frost, "A new gold- catalyzed C− C bond formation," *Angew. Chemie Int. Ed.*, vol. 39, no. 13, pp. 2285–2288, 2000.

[30] J. Dong, H. Du, and J. Xu, "Synthesis of Functionalized Thietanes via Electrophilic Carbenoid-Induced Ring Expansion of Thiiranes with Sulfonium Acylmethylides as Carbene Precursors," *J. Org. Chem.*, vol. 84, no. 17, pp. 10724–10739, 2019.

[31] M. R. Rodriguez, M. Besora, F. Molina, F. Maseras, M. M. Díaz-Requejo, and P. J. Perez, "Intermolecular allene functionalization by silver-nitrene catalysis," *J. Am. Chem. Soc.*, vol.

142, no. 30, pp. 13062–13071, 2020.

[32] N. Kern, A.-S. Felten, J.-M. Weibel, P. Pale, and A. Blanc, "Robust synthesis of N-sulfonylazetidine building blocks via ring contraction of α-bromo N-sulfonylpyrrolidinones," *Org. Lett.*, vol. 16, no. 23, pp. 6104–6107, 2014.

[33] P. Quadrelli and M. Moiola, "Cycloaddition reactions for antiviral compounds," *Mod. Appl. Cycloaddit. Chem.*, no. January, pp. 1–83, 2019, doi: 10.1016/B978-0-12-815273-7.00001-0.

[34] N. M. Shoup, "Lewis Base Promoted Annulations of Allenoates with 1,4-Naphthoquinones," University of Denve, 2019.

[35] X. Li, J. Großkopf, C. Jandl, and T. Bach, "Enantioselective, visible light mediated aza Paternò–Büchi reactions of quinoxalinones," *Angew. Chemie*, vol. 133, no. 5, pp. 2716–2720, 2021.

[36] J. Buendia *et al.*, "Preparation of Cyclobutene Acetals and Tricyclic Oxetanes through Photochemical Tandem and Cascade Reactions," *Angew. Chemie Int. Ed.*, vol. 57, no. 22, pp. 6592–6596, 2018.

[37] V. Light-mediated, "1- and 2-Azetines via Visible Light-Mediated [2+2]-Cycloadditions of Alkynes and Oximes," *J. Am. Chem. Soc.*, vol. 143, no. 39, pp. 16235–16242, 2021, doi: https://doi.org/10.1021/jacs.1c07523.

[38] L. D. Elliott, S. Kayal, M. W. George, and K. Booker-Milburn, "Rational design of triplet sensitizers for the transfer of excited state photochemistry from UV to visible," *J. Am. Chem. Soc.*, vol. 142, no. 35, pp. 14947–14956, 2020, doi: 10.1021/jacs.0c05069.

[39] L. Zong and C. H. Tan, "Phase-Transfer and Ion-Pairing Catalysis of Pentanidiums and Bisguanidiniums," *Acc. Chem. Res.*, vol. 50, no. 4, 2017, doi: 10.1021/acs.accounts.6b00604.

[40] M. R. Becker, E. R. Wearing, and C. S. Schindler, "Synthesis of azetidines via visible-lightmediated intermolecular [2+ 2] photocycloadditions. Nat. Chem. 12, 898–905." 2020.

[41] D. M. Flores and V. A. Schmidt, "Intermolecular 2+ 2 Carbonyl–Olefin Photocycloadditions Enabled by Cu (I)–Norbornene MLCT," *J. Am. Chem. Soc.*, vol. 141, no. 22, pp. 8741–8745, 2019.

[42] H.-S. M. Siah, H. F. Jónsson, and A. Fiksdahl, "Au (I)-catalyzed cycloaddition pathways of non-terminal propargyl substrates," *Synth. Commun.*, vol. 50, no. 12, pp. 1758–1773, 2020.

[43] S. Kotha and M. Meshram, "Application of Claisen Rearrangement and Olefin Metathesis in Organic Synthesis," *Chemistry - An Asian Journal*, vol. 13, no. 14. 2018. doi: 10.1002/asia.201800613.

[44] E. G. E. Hawkins, "Reactions of organic peroxides. Part XIV. Amino-peroxides from carbonyl compounds, primary amines, and hydrogen peroxide or hydroperoxide," *J. Chem. Soc. C Org.*, no. 20, 1969, doi: 10.1039/j39690002686.

[45] F. Berrée, A. M. Debache, Y. Marsac, B. Collet, P. Girard-Le Bleiz, and B. Carboni, "Stereoselective synthesis of 2-hydroxymorpholines and aminodiols via a three-component boro-Mannich reaction," *Tetrahedron*, vol. 62, no. 17, 2006, doi: 10.1016/j.tet.2006.02.023.

[46] R. Fan *et al.*, "An aryne triggered ring-opening fluorination of cyclic thioethers with potassium fluoride," *Chem. Commun.*, vol. 54, no. 51, pp. 7081–7084, 2018.

[47] J. C. Andrez, "Mitomycins syntheses: A recent update," *Beilstein J. Org. Chem.*, vol. 5, 2009, doi: 10.3762/bjoc.5.33.

[48] A. Kowalczyk, A. M. Pieczonka, M. Rachwalski, S. Lésniak, and P. Staczek, "Synthesis and evaluation of biological activities of aziridine derivatives of urea and thiourea," *Molecules*,

vol. 23, no. 1, 2018, doi: 10.3390/molecules23010045.

[49] Z. Li, X. Ding, and C. He, "Nitrene transfer reactions catalyzed by gold complexes," *J. Org. Chem.*, vol. 71, no. 16, pp. 5876–5880, 2006.

[50] J. S. Prasad and L. S. Liebeskind, "Silver Mediated Cyclizations of 4-Allenyl-and 4-(2-Propynyl) azetidinones. A Stereoselective Synthesis of 3-Substituted Δ1-Carbapenems Via N-C3 Closure.," *Tetrahedron Lett.*, vol. 29, no. 34, pp. 4253–4256, 1988.

[51] M. Alvarez-Corral, M. Munoz-Dorado, and I. Rodriguez-Garcia, "Silver-mediated synthesis of heterocycles," *Chem. Rev.*, vol. 108, no. 8, pp. 3174–3198, 2008.

[52] A. Horváth, J. Benner, and J. E. Bäckvall, "Enantiocontrolled synthesis of 3-pyrrolines from α-amino allenes," *European J. Org. Chem.*, no. 15, pp. 3240–3243, 2004, doi: 10.1002/ejoc.200400211.

[53] J. L. Vicario, D. Badía, and L. Carrillo, "Organocatalytic enantioselective Michael and hetero-Michael reactions," *Synthesis*, no. 14. 2007. doi: 10.1055/s-2007-983747.

[54] M. Marinescu and C. V. Popa, "Pyridine Compounds with Antimicrobial and Antiviral Activities," *Int. J. Mol. Sci.*, vol. 23, no. 10, 2022, doi: 10.3390/ijms23105659.

[55] N. L. Benowitz, "Pharmacology of nicotine: Addiction, smoking-induced disease, and therapeutics," *Annu. Rev. Pharmacol. Toxicol.*, vol. 49, pp. 57–71, 2009, doi: 10.1146/annurev.pharmtox.48.113006.094742.

[56] M. Delirrad, M. Majidi, and B. Boushehri, "Clinical features and prognosis of paraquat poisoning: A review of 41 cases," *Int. J. Clin. Exp. Med.*, vol. 8, no. 5, pp. 8122–8128, 2015.

[57] A. Ovung and J. Bhattacharyya, "Sulfonamide drugs: structure, antibacterial property, toxicity, and biophysical interactions," *Biophys. Rev.*, vol. 13, no. 2, pp. 259–272, 2021, doi: 10.1007/s12551-021-00795-9.

[58] S. Dorman and A. Gupta, "Treatment of Isoniazid-Resistant Pulmonary Tuberculosis," *Handb. Tuberc.*, vol. 3536, pp. 35–90, 2017, doi: 10.1007/978-3-319-26273-4_3.

[59] H. T. Abdel-Mohsen, J. Conrad, and U. Beifuss, "ChemInform Abstract: Laccase-Catalyzed Oxidation of Hantzsch 1,4-Dihydropyridines to Pyridines and a New One-Pot Synthesis of Pyridines.," *ChemInform*, vol. 44, no. 7, 2013, doi: 10.1002/chin.201307127.

[60] H. T. Abdel-Mohsen, J. Conrad, and U. Beifuss, "Laccase-catalyzed oxidation of Hantzsch 1,4-dihydropyridines to pyridines and a new one pot synthesis of pyridines," *Green Chem.*, vol. 14, no. 10, 2012, doi: 10.1039/c2gc35950b.

[61] R. Pagadala, V. Kasi, N. G. Shabalala, and S. B. Jonnalagadda, "Ultrasound-assisted multicomponent synthesis of heterocycles in water – A review," *Arabian Journal of Chemistry*, vol. 15, no. 1. 2022. doi: 10.1016/j.arabjc.2021.103544.

[62] M. Jóźwiak, A. Filipowska, F. Fiorino, and M. Struga, "Anticancer activities of fatty acids and their heterocyclic derivatives," *Eur. J. Pharmacol.*, vol. 871, 2020, doi: 10.1016/j.ejphar.2020.172937.

[63] M. M. Heravi and V. Zadsirjan, "Prescribed drugs containing nitrogen heterocycles: an overview," *RSC Adv.*, vol. 10, no. 72, pp. 44247–44311, 2020, doi: 10.1039/d0ra09198g.

[64] J. H. Kang *et al.*, "Scalable Subsecond Synthesis of Drug Scaffolds via Aryllithium Intermediates by Numbered-up 3D-Printed Metal Microreactors," *ACS Cent. Sci.*, vol. 8, no. 1, pp. 43–50, 2022, doi: 10.1021/acscentsci.1c00972.

[65] C. J. Taylor *et al.*, "A Brief Introduction to Chemical Reaction Optimization," *Chem. Rev.*, vol. 123, no. 6, pp. 3089–3126, 2022, doi: 10.1021/acs.chemrev.2c00798.

[66] H. Rüdel, W. Körner, T. Letzel, M. Neumann, K. Nödler, and T. Reemtsma, "Persistent, mobile and toxic substances in the environment: a spotlight on current research and regulatory activities," *Environ. Sci. Eur.*, vol. 32, no. 1, 2020, doi: 10.1186/s12302-019-0286-x.

[67] K. Dayanand and and R. W. R. Olivia E. Atherton1, Jennifer L. Tackett2, Emilio Ferrer1, "Synthesis of Constrained Heterocycles Employing Two Post-Ugi Cyclization Methods for Rapid Library Generation with In Cellulo Activity," *Physiol. Behav.*, vol. 176, no. 5, pp. 139–148, 2018, doi: 10.1002/slct.201702179.Synthesis.

[68] H. S. Fernandes, C. S. Silva Teixeira, S. F. Sousa, and N. M. F. S. A. Cerqueira, "Formation of unstable and very reactive chemical species catalyzed by metalloenzymes: A mechanistic overview," *Molecules*, vol. 24, no. 13, 2019, doi: 10.3390/molecules24132462.

[69] J. F. Campos and S. Berteina-raboin, "Greener synthesis of nitrogen-containing heterocycles in water, PEG, and bio-based solvents," *Catalysts*, vol. 10, no. 4, p. 429, 2020, doi: 10.3390/catal10040429.

[70] M. B. Gawande *et al.*, "Cu and Cu-Based Nanoparticles: Synthesis and Applications in Catalysis," *Chem. Rev.*, vol. 116, no. 6, pp. 3722–3811, 2016, doi: 10.1021/acs.chemrev.5b00482.

[71] H. Cong *et al.*, "Silver Nanoparticle-Catalyzed Diels - Alder Cycloadditions of 2 ′ - Hydroxychalcones," *J. Am. Chem. Soc.*, vol. 132, no. 21, pp. 7514–7518, 2010, doi: https://doi.org/10.1021/ja102482b.

[72] L. Liu and A. Corma, "Metal Catalysts for Heterogeneous Catalysis: From Single Atoms to Nanoclusters and Nanoparticles," *Chem. Rev.*, vol. 118, no. 10, pp. 4981–5079, 2018, doi: 10.1021/acs.chemrev.7b00776.

[73] P. H. Lanoë, B. Najjari, F. Hallez, G. Gontard, and H. Amouri, "N-heterocyclic carbene coinage metal complexes containing naphthalimide chromophore: Design, structure, and photophysical properties," *Inorganics*, vol. 5, no. 3, 2017, doi: 10.3390/inorganics5030058.

[74] L.-J. Yang, S. Li, S. Wang, J. Nie, and J.-A. Ma, "Nucleophilic lewis base dependent addition reactions of allenoates with trifluoromethylated cyclic ketimines," *J. Org. Chem.*, vol. 79, no. 8, pp. 3547–3558, 2014.

[75] I. Tolbatov *et al.*, "Reactivity of antitumor coinage metal-based N-heterocyclic carbene complexes with cysteine and selenocysteine protein sites," *J. Inorg. Biochem.*, vol. 223, p. 111533, 2021.

[76] S. Nayak and S. L. Gaonkar, "Coinage Metal N-Heterocyclic Carbene Complexes: Recent Synthetic Strategies and Medicinal Applications," *ChemMedChem*, vol. 16, no. 9. 2021. doi: 10.1002/cmdc.202000836.

[77] X. Zhang, Z. Liu, P. Sivaguru, and X. Bi, "Silver carbenoids derived from diazo compounds: A historical perspective on challenges and opportunities," *Chem Catal.*, vol. 1, no. 3, pp. 599–630, 2021, doi: 10.1016/j.checat.2021.05.001.

[78] F. L. Hong and L. W. Ye, "Transition metal-catalyzed tandem reactions of ynamides for divergent N-heterocycle synthesis," *Acc. Chem. Res.*, vol. 53, no. 9, 2020, doi: 10.1021/acs.accounts.0c00417.

[79] M. Rashighi and J. E. Harris, "The Heck process, which uses an aryl or vinyl halide as a substrate and a tethered alkene as a nucleophile, is an illustration of a tethered nucleophile cyclization reaction," *Physiol. Behav.*, vol. 176, no. 3, pp. 139–148, 2017, doi: 10.1053/j.gastro.2016.08.014.CagY.

[80] H. Villar, M. Frings, and C. Bolm, "Ring closing enyne metathesis: A powerful tool for the synthesis of heterocycles," *Chem. Soc. Rev.*, vol. 36, no. 1, pp. 55–66, 2007, doi:

10.1039/b508899m.

[81] F. P. Guengerich and F. K. Yoshimoto, "Formation and Cleavage of C-C Bonds by Enzymatic Oxidation-Reduction Reactions," *Chem. Rev.*, vol. 118, no. 14, pp. 6573–6655, 2018, doi: 10.1021/acs.chemrev.8b00031.

[82] M. D'Auria and R. Racioppi, "Oxetane synthesis through the Paternò-Büchi reaction," *Molecules*, vol. 18, no. 9, pp. 11384–11428, 2013, doi: 10.3390/molecules180911384.

[83] T. Jin and Y. Yamamoto, "Gold-catalyzed intramolecular carbocyclization of alkynyl ketones leading to highly substituted cyclic enones," *Org. Lett.*, vol. 9, no. 25, pp. 5259–5262, 2007, doi: 10.1021/ol702455v.

[84] T. A. Khattab and M. Rehan, "A review on synthesis of nitrogen-containing heterocyclic dyes for textile fibers - Part 1: five and six-membered heterocycles," *Egyptian Journal of Chemistry*, vol. 61, no. 5. 2018. doi: 10.21608/ejchem.2018.4130.1362.

[85] M. M. Díaz-Requejo and P. J. Perez, "Coinage metal catalyzed C− H bond functionalization of hydrocarbons," *Chem. Rev.*, vol. 108, no. 8, pp. 3379–3394, 2008.

[86] A. D'Amato, M. Sirignano, S. Russo, R. Troiano, A. Mariconda, and P. Longo, "Recent Advances in N-Heterocyclic Carbene Coinage Metal Complexes in A3-Coupling and Carboxylation Reaction," *Catalysts*, vol. 13, no. 5, p. 811, 2023.

[87] P. K. Shukla, A. Verma, and P. Mishra, "Significance of nitrogen heterocyclic nuclei in the search of pharmacological active compounds," *New Perspect. Agric. Hum. Heal.*, no. March, 2017.

[88] D. A. Dias, S. Urban, and U. Roessner, "A Historical overview of natural products in drug discovery," *Metabolites*, vol. 2, no. 2, pp. 303–336, 2012, doi: 10.3390/metabo2020303.

[89] C. Satheeshkumar, J.-Y. Park, D.-C. Jeong, S. G. Song, J. Lee, and C. Song, "Synthesis and electronic properties of N-heterocyclic carbene-containing conducting polymers with coinage metals," *RSC Adv.*, vol. 5, no. 75, pp. 60892–60897, 2015.

[90] A. M. Polgar, F. Weigend, A. Zhang, M. J. Stillman, and J. F. Corrigan, "AN-heterocyclic carbene-stabilized coinage metal-chalcogenide framework with tunable optical properties," *J. Am. Chem. Soc.*, vol. 139, no. 40, pp. 14045–14048, 2017.

[91] N. A. A. Elkanzi, H. Hrichi, R. A. Alolayan, W. Derafa, F. M. Zahou, and R. B. Bakr, "Synthesis of Chalcones Derivatives and Their Biological Activities: A Review," *ACS Omega*, vol. 7, no. 32. 2022. doi: 10.1021/acsomega.2c01779.

[92] D. J. Fu *et al.*, "Design and antiproliferative activity of N-heterocycle-chalcone derivatives," *J. Chem. Res.*, vol. 40, no. 10, 2016, doi: 10.3184/174751916X14740355883191.

[93] N. Shankaraiah *et al.*, "Synthesis of different heterocycles-linked chalcone conjugates as cytotoxic agents and tubulin polymerization inhibitors," *Bioorganic Med. Chem.*, vol. 25, no. 17, 2017, doi: 10.1016/j.bmc.2017.07.031.

[94] B. K. Çavuşoğlu, Ö. Atlı, G. Görmüş, Y. Özkay, and Z. A. Kaplancıklı, "Synthesis and Evaluation of Heterocycles Based Chalcone Derivatives as Antiproliferative Agents," *Anticancer. Agents Med. Chem.*, vol. 18, no. 7, 2018, doi: 10.2174/1871520618666180105163657.

[95] C. Matthee, G. Terre'Blanche, L. J. Legoabe, and H. D. Janse van Rensburg, "Exploration of chalcones and related heterocycle compounds as ligands of adenosine receptors: therapeutics development," *Molecular Diversity*, vol. 26, no. 3. 2022. doi: 10.1007/s11030-021-10257-9.

[96] B. Ardiansah, "Chalcones bearing N, O, and S-heterocycles: Recent notes on their biological significances," *J. Appl. Pharm. Sci.*, vol. 9, no. 8, 2019, doi: 10.7324/JAPS.2019.90816.

[97] S. Y. Tee and E. Ye, "Recent advancements in coinage metal nanostructures and bio-applications," *Materials Advances*, vol. 2, no. 5. 2021. doi: 10.1039/d0ma00829j.

[98] K. Karrouchi *et al.*, "Synthesis and pharmacological activities of Pyrazole derivatives: A review," *Molecules*, vol. 23, no. 1, p. 134, 2018, doi: 10.3390/molecules23010134.

[99] B. Heller and M. Hapke, "The fascinating construction of pyridine ring systems by transition metal-catalysed [2 + 2 + 2] cycloaddition reactions," *Chem. Soc. Rev.*, vol. 36, no. 7, pp. 1085–1094, 2007, doi: 10.1039/b607877j.

[100] C. M. Glinkerman, D. L. Boger, L. Jolla, and U. States, "Cycloadditions of 1,2,3-Triazines Bearing C5-Electron Donating Substituents: Robust Pyrimidine Synthesis," *Org. Lett.*, vol. 17, no. 16, pp. 4002–4005, 2016, doi: 10.1021/acs.orglett.5b01870.Cycloadditions.

[101] C. N. Muniz, J. Schaab, A. Razgoniaev, P. I. Djurovich, and M. E. Thompson, "π-Extended Ligands in Two-Coordinate Coinage Metal Complexes," *J. Am. Chem. Soc.*, vol. 144, no. 39, pp. 17916–17928, 2022.

[102] L. McEwan, M. Julius, S. Roberts, and J. C. Q. Fletcher, "A review of the use of gold catalysts in selective hydrogenation reactions," *Gold Bulletin*, vol. 43, no. 4. 2010. doi: 10.1007/bf03214999.

[103] Y. Liu, M. Liu, S. Guo, H. Tu, Y. Zhou, and H. Gao, "Gold-catalyzed highly efficient access to 3 (2H)-furanones from 2-oxo-3-butynoates and related compounds," *Org. Lett.*, vol. 8, no. 16, pp. 3445–3448, 2006.

[104] N. Kaur, "Gold and silver assisted synthesis of five-membered oxygen and nitrogen containing heterocycles," *Synth. Commun.*, vol. 49, no. 12, pp. 1459–1485, 2019.

[105] Q. Wang and M. Shi, "Synthesis of Cyclic and Heterocyclic Compounds via Gold-Catalyzed Reactions," *Synlett*, vol. 28, no. 17, 2017, doi: 10.1055/s-0036-1590827.

[106] N. Kaur, "Applications of palladium dibenzylideneacetone as catalyst in the synthesis of five-membered N-heterocycles," *Synth. Commun.*, vol. 49, no. 10, pp. 1205–1230, 2019.

[107] G. Meera, K. R. Rohit, G. S. S. Treesa, and G. Anilkumar, "Advances and Prospects in Gold-Catalyzed C−H Activation," *Asian Journal of Organic Chemistry*, vol. 9, no. 2. 2020. doi: 10.1002/ajoc.202000020.

[108] Z. Li, D. A. Capretto, and C. He, "Silver-mediated oxidation reactions: Recent advances and new prospects," *ChemInform*, vol. 41, no. 27, p. i, 2010.

[109] F. Paquin, J. Rivnay, A. Salleo, N. Stingelin, and C. Silva, "Silver-Catalysed Reactions of Alkynes: Recent Advances," *J. Mater. Chem. C*, vol. 3, pp. 10715–10722, 2015, doi: 10.1039/b000000x.

[110] G. Abbiati and E. Rossi, "Critical Surveys Covering the Year 2006 Organometallic Compounds in Organic Synthesis," *ChemInform*, vol. 41, no. 22, p. i, 2010.

[111] M. Harmata, *Silver in Organic Chemistry*. 2010. doi: 10.1002/9780470597521.

[112] K. Sekine and T. Yamada, "Silver-catalyzed carboxylation," *Chemical Society Reviews*, vol. 45, no. 16. 2016. doi: 10.1039/c5cs00895f.

[113] A. P. Taylor, R. P. Robinson, Y. M. Fobian, D. C. Blakemore, L. H. Jones, and O. Fadeyi, "Modern advances in heterocyclic chemistry in drug discovery," *Org. Biomol. Chem.*, vol. 14, no. 28, pp. 6611–6637, 2016.

[114] S. Zhan, J. Jiang, Z. Zeng, Y. Wang, and H. Cui, "DNA-templated coinage metal nanostructures and their applications in bioanalysis and biomedicine," *Coordination Chemistry Reviews*, vol. 455. 2022. doi: 10.1016/j.ccr.2021.214381.

[115] S. A. Patil *et al.*, "N-heterocyclic carbene metal complexes as bio-organometallic antimicrobial and anticancer drugs," *Future Med. Chem.*, vol. 7, no. 10, pp. 1305–1333, 2015.

[116] G. Pasparakis, "Recent developments in the use of gold and silver nanoparticles in biomedicine," *Wiley Interdiscip. Rev. Nanomedicine Nanobiotechnology*, vol. 14, no. 5, pp. 1–22, 2022, doi: 10.1002/wnan.1817.

[117] P. Wipt and K. M. George, "Plasmonics in Biology and Plasmon-Controlled Fluorescence Joseph," *Bone*, vol. 23, no. 1, pp. 1–7, 2008, doi: 10.1007/s11468-005-9002-3.Plasmonics.

[118] A. Mohajerani *et al.*, "Nanoparticles in construction materials and other applications, and implications of nanoparticle use," *Materials (Basel).*, vol. 12, no. 19, pp. 1–25, 2019, doi: 10.3390/ma12193052.

[119] S. Budagumpi, R. S. Keri, G. Achar, and K. N. Brinda, "Coinage Metal Complexes of Chiral N-Heterocyclic Carbene Ligands: Syntheses and Applications in Asymmetric Catalysis," *Advanced Synthesis and Catalysis*, vol. 362, no. 5. 2020. doi: 10.1002/adsc.201900859.

[120] S. Fernández-Fariña *et al.*, "Two synthetic approaches to coinage metal (i) mesocates: electrochemical versus chemical synthesis," *Inorg. Chem.*, vol. 61, no. 35, pp. 14121–14130, 2022.

[121] A. Schottenhammer, "Major 'International' Currencies of China and Japan: The Use of Copper Coins, Silver Ingots and Paper Money," in *Palgrave Series in Indian Ocean World Studies*, 2019. doi: 10.1007/978-3-030-20973-5_2.

[122] M. G. Abramzon, I. A. Saprykina, A. V. Chugaev, N. N. Presnyakova, and E. Y. Tereshchenko, "Chemical and Pb-Isotopic Characteristics of Metal of Silver Coins of the Bosporus and Ionia Dated from the 5th to 1st centuries BC," *Nanobiotechnology Reports*, vol. 16, no. 5, 2021, doi: 10.1134/S2635167621050025.