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Synthesis and Catalytic Properties of Palladium-N-Heterocyclic Carbene Complexes for cancer therapy: A comprehensive Review

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ABSTRACT

Heterocyclic compounds, characterized by cyclic structures containing heteroatoms such as nitrogen, oxygen, or sulphur, play a pivotal role in medicinal chemistry due to their diverse biological activities and applications in treating various diseases, including cancer. This research paper explores the synthesis and catalytic properties of novel palladium-N-heterocyclic carbene (NHC) complexes, specifically PEPPSI-type complexes, highlighting their effectiveness in facilitating direct arylation reactions of heterocycles. The study presents the synthesis of new imidazolinium salts and their conversion into stable palladium complexes with notable catalytic activity for arylation processes. Additionally, it examines the synthesis of spiro isoxazole-5-one derivatives and the development of iron-catalysed methodologies for generating pyrimidine and benzo carbazole derivatives, underlining the significance of iron catalysts in organic transformations. The research emphasizes the importance of optimizing reaction conditions and utilising earth-abundant catalysts to enhance the sustainability of chemical processes while achieving high yields and selectivity. Through mechanistic insights and experimental findings, this work contributes to the ongoing advancement of synthetic methodologies for producing heterocyclic compounds, which are essential in developing new therapeutic agents.

Keywords: *Heterocyclic compound, Anticancer activity, catalyst, Palladium-N- heterocyclic carbene*

1. INTRODUCTION

Cyclic organic molecules with at least one heteroatom are known as heterocyclic compounds. The most prevalent heteroatoms are nitrogen, oxygen, and sulphur, although heterocyclic rings with other heteroatoms are also well-known. A carbocyclic compound is a cyclic organic molecule with all of its carbon atoms in rings. Due to its ability to treat various diseases, heterocyclic compounds are regarded as one of the necessary kinds of organic compounds and are utilised in many biological disciplines. The primary skeleton of many biological substances, such as DNA and RNA, haemoglobin, chlorophyll, vitamins, and many more, contains heterocyclic rings. There are several heterocyclic compounds that have been utilised to cure common ailments. For example, triazine compounds have been used as anti-inflammatory drugs, urinary antiseptics, and antimicrobial herbicides. Benzimidazole derivatives have been demonstrated to possess a range of biological activities, such as antibacterial, antifungal, antiviral, and anthelmintic qualities.[1] Medicinal chemistry is a significant area of chemistry that combines chemistry with medical problems by attempting to understand common illnesses and how to treat them. Researchers worldwide have been concentrating on this area of contemporary chemistry since the separation and purification of active ingredients from the tissues of plants and animals as well as from microorganisms and their fermentation products. Medical chemistry is based on the traditional areas of chemistry, including biology, organic chemistry, and a few physics topics [2].

Sustainability depends on catalysts because they permit chemical processes to take place in more benign conditions, saving energy and lowering the amount of byproducts produced. Since the majority of industrial chemical reactions take place in the presence of a catalyst, catalysts are widely used [3]. Both homogeneous and heterogeneous catalysts are employed in the chemical process. The yields of chemical reactions can be increased by dissolving homogeneous catalysts with the reactants [4,5]. Nevertheless, there are a few fundamental issues with product contamination from ligand residues, recycling, and

separation [6,7,8,9]. Several benefits of heterogeneous catalysts include higher air and moisture stability, quick recovery, ease of recycling, robustness, and protection against ligand contamination [10,11].

With about 10 million fatalities from the disease estimated in 2020 alone, cancer is regarded as one of the worst public health issues to ever affect humanity. It was the second leading cause of death in 2020, with over 19.3 million new cases

recorded worldwide. [12,13] A complicated collection of illnesses, cancer is defined by aberrant and uncontrolled cell growth or division. It can be either benign or malignant. While malignant tumours move to remote locations throughout the body through its circulatory and lymphatic systems, benign tumours stay localised and do not invade surrounding tissues or bodily sites [14]. The most common cancer among the 36 human cancer kinds was breast cancer, which was followed by colorectal, prostate, lung, and stomach cancerThe most common cause of cancer-related fatalities is lung cancer, followed by colorectal, liver, stomach, and breast cancers [12].

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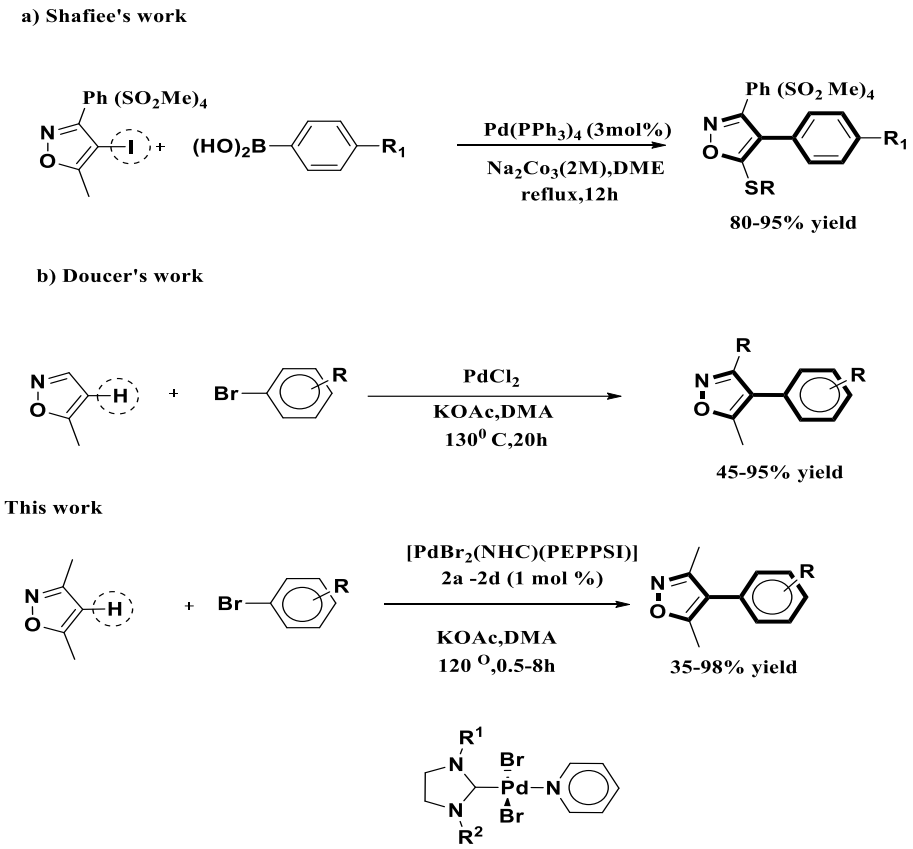
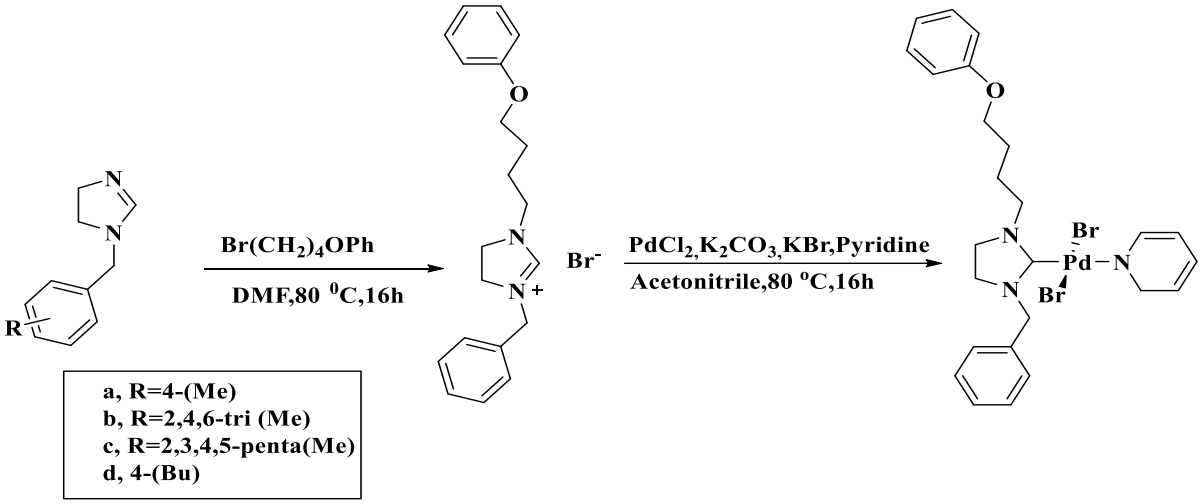
As neutral two-electron donors, N-Heterocyclic Carbenes (NHCs) are well-known for being potent Lewis bases and superior nucleophiles that bind metals more effectively than phosphines [15]. When compared to other ligand classes, NHCs' stability is one of their primary characteristics. Many stable metal-NHC complexes are formed as a result of NHC ligands' strong σ-donating but weak π-accepting capabilities. Another characteristic of NHCs is that they enable the substitution of N-substituents to produce complexes with the required steric and electronic characteristics [16]. As a result, NHCs have somewhat replaced The well-known ligands for tertiary phosphines in coordination chemistry and homogeneous catalysis. The most potent and popular catalysts in homogeneous catalysis are palladium-complexes of NHCs [17]. Pyridine Enhanced Precatalytic Preparation Stabilisation and Initiation, or PEPPSI-type palladium-NHC complexes, have shown remarkable catalytic activity towards a range of carbon-carbon and carbon-heteroatom cross coupling processes.[18] One reason for the high catalytic success of PEPPSI-type palladium complexes is the existence of a loosely bound "throwaway" pyridine ligand that facilitates the entry of the incoming substrate [19]. Many other palladium-NHC complexes of the PEPPSI type have been created to date, and their catalytic properties in the direct arylation of heterocyclomatics have been reported [20]. We have also recently created PEPPSI-type palladium complexes based on benzimidazolin-2-ylidene, which shown very strong catalytic capabilities for the direct arylation of heteroarenes with aryl halides [21]. All palladium complexes have been tested for their catalytic use in the direct C4-arylation of dimethyl isoxazole with para-, ortho-, and hetero-substituted aryl bromides when there is a 1 mol% catalyst loading present (Reaction 1).



Reaction 1: 2-Ylidene-based Palladium-PEP-PSI Catalyst

By reacting imidazoline with 4-phenoxybutyl bromide and a substituted benzyl group attached to a nitrogen atom, four new imidazolinium salts (1a–1d) were synthesized as carbene precursors. These salts were obtained in yields ranging from 67% to 80% after 16 hours of reaction in dimethylformamide (DMF) at 80 °C.



Reaction 2 illustrates the normal process for imidazolinium salts and the PEP-PSI-type palladium complexes that correspond to them.

Four novel palladium-PEPPSI complexes (2a-2c) based on imidazolidin-2-ylidene were created by reacting imidazolinium salts (1a-1d) with pyridine and $PdCl_2$ in the presence of potassium bromide. Because of their great moisture and air stability against air, light, and moisture, the palladium complexes may be kept for months at room temperature without clearly losing their catalytic activity. A variety of spectroscopic and analytical methods, including 1 H NMR, 13C NMR, FTIR, and elemental analysis, were used to characterise each palladium complex. Lastly, the reaction time was reduced to 0.5–8 hours in the current study by using a catalyst loading of 1 mol%. In addition, 3,5-dimethylisoxazole was effectively arylated at the C4 position, yielding positive outcomes when compared to other research of a similar kind [22–26]. For the past twenty years, researchers have used a range of methods in the literature to examine how the spatial and electronic effects affect the catalytic activity of NHC ligands [19,27,28]. However, there is still very little knowledge about how these influences affect catalytic activity. Our preference in this investigation was for saturated imidazolidin-2-ylidene ligands with sterically bulky benzyl substituents and 4-phenoxybutyl with O-donor.

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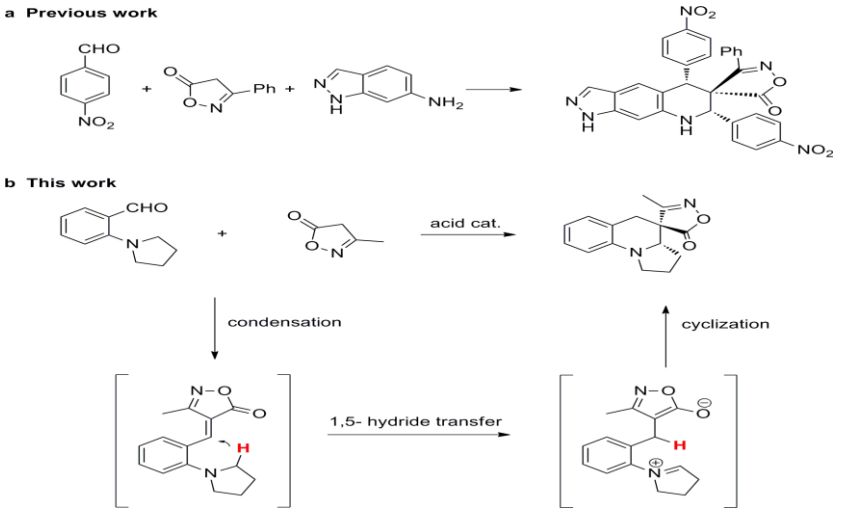
Only a few methods for dealing with spiro isoxazole-5-ones have been devised thus far, beginning with isoxazole-5-one derivatives.[28] As far as we are aware, just one work describes the synthesis of a spiroisoxazol-5-one tetrahydroquinoline skeleton via condensation and addition processes (Reaction 3).



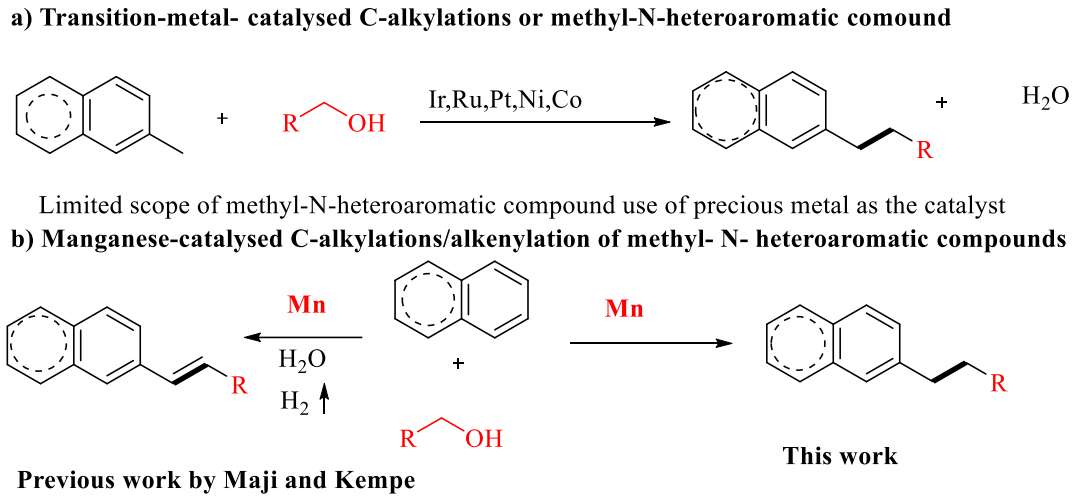
Reaction: 3 Preparation of spiro [isoxazolone-tetrahydroquinoline] derivatives.

We describe a novel, effective approach for building the spiro isoxazole-5-one tetrahydroquinoline skeleton that combines Knoevenagel condensation, intramolecular 1,5-hydride shift, and cyclization sequence. In the last few years, this internal redox process has produced a large number of new heterocycle molecules. [29–31] Using this approach, our group recently reported an effective stereoselective synthesis of spiropyrazolone tetrahydroquinolines catalysed by Lewis acid.[32] We were inspired by these endeavours to create new spiro isoxazole-5-one derivatives in a straightforward, effective, and stereoselective format. This one-pot reaction sequence, which includes an intramolecular 1,5-hydride shift/6-endo cyclization process after an intermolecular Knoe evangel condensation, yields spiro isoxazole-5-one tetrahydroquinolines in good to high yields with good to excellent Dia stereoselectivities (Scheme 3b). Initially, 3-methylisoxazol-5(4H)-one and 2-(pyrrolidine-1-yl) benzaldehyde were chosen as model substrates for reaction condition optimization. We used EtOH as a solvent to screen the catalysts. To our delight, the reaction was able to smoothly generate the product in 80 % yield with 91:9 dr after 17 hours when zinc chloride was used as a catalyst. Next, with zinc chloride as the Lewis acid catalyst, diverse solvents were evaluated.

Maji et al.

In a groundbreaking study, *Kempe et al*. used a homogeneous P, N-ligated iridium(I) catalyst to describe the C-alkylation of methyl pyrimidine and methyl pyrazine derivatives (Scheme 4a).[33] Then, employing Ir, Ru, and Pt catalysts, the group of Obera,[34] Lang,[35]

Oe,[36] and Shimizu [37] reported C-alkylation of methyl quinolines and methyl quinoxalines. Using nickel and cobalt catalysts, Banerjee et al. [38] and Kundu et al. [39], respectively, were able to C-alkylate the derivatives of methyl pyrazine, methyl quinoline, and methyl quinoxaline. Manganese(I)-complex activity in catalytic organic transformations has recently been investigated by us and others.[40], [41] Interestingly, manganese is found in many biological systems, is non-toxic, and is the third most prevalent transition metal in the crust of the earth.[42]The manganese(I)-complex Mn-1,2 catalysed C-alkenylation of methyl N-heteroarenes via acceptor less dehydrogenation catalysis was created independently by Kempe et al.(Scheme 4b) and us [43].



Scheme 4 Diversification of commonly accessible methyl-N-heteroarenes using feedstock alcohols, catalysed by transition metals. N heterocycles are synthesized via iron-catalysed intramolecular and intermolecular cyclization processes.

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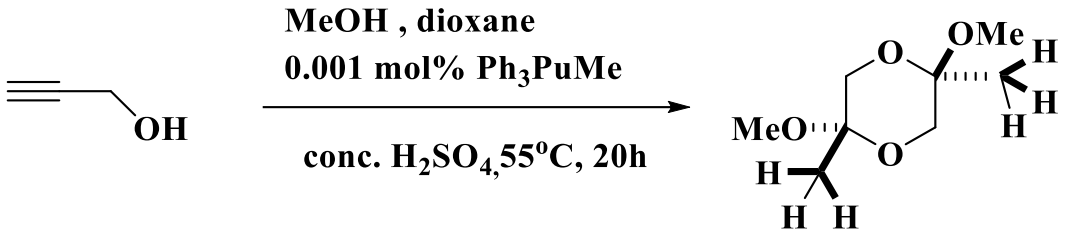
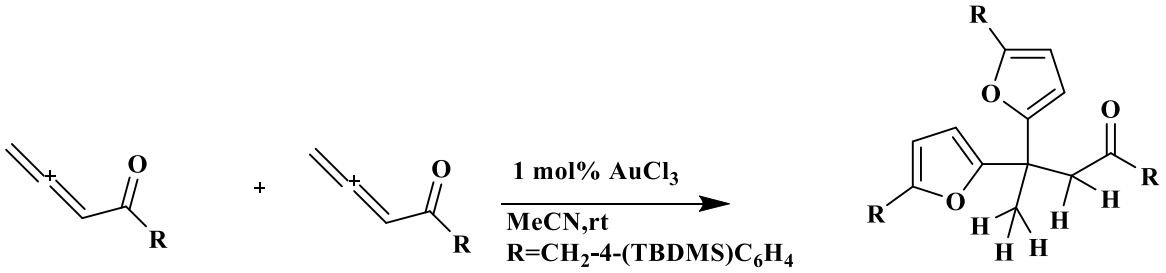
They found that the synthesis of tetrahydropyridines by intramolecular hydro-amination of alkynes was significantly better than the analogous palladium-catalysed processes.[44] One The synthesis of Spiro cycle 6 was the first instance of a hydroxy group being added to an activated alkene by a gold catalyst.[45] Here, a second cyclisation yields the spiro-annulated tetrahydrofuran following the previous synthesis of the fused furan 5. The production of unsaturated nitrogen heterocycles was made possible by many publications on gold-catalysed hydroaminations of unactivated alkenes that surfaced in 2006.[46] There have been documented extensions of this approach.[47] Although more intricate rearrangements have previously been documented, a subsequent ring expansion or deletion is shown in this particular instance.[48] Simple propargyl alcohol cyclisation is a stunning and early example of this reaction mode; the reaction's turnover number of 100,000 is noteworthy (Scheme 5).[49]



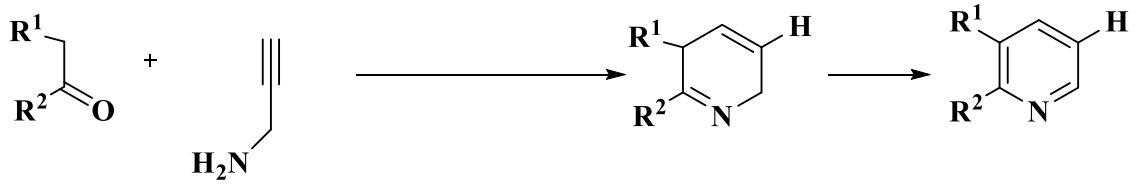
Scheme 5: Diastereoselective synthesis of a bis-ketal cyclic repeat.

The product is produced by two intermolecular alcohol-to-enol ether addition processes, as well as intramolecular and intermolecular alcohol-to-alkyne additions. The final addition is extremely diastereoselective for the trans-product. Similar combinations for cycloisomerization/hydroarylation processes have been noted for allenic substrates (Scheme 6).[45]



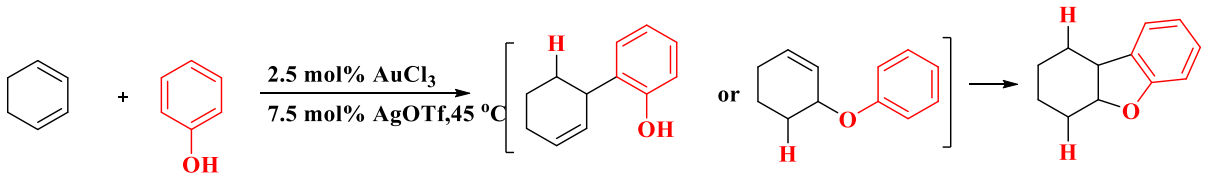
Scheme 6: Allenyl ketone trimerization.

An imine-formation and cyclization/dehydrogenation procedure are combined in a single pot to create a novel pyridine synthesis that yields 11 directly (Scheme 7).[50]



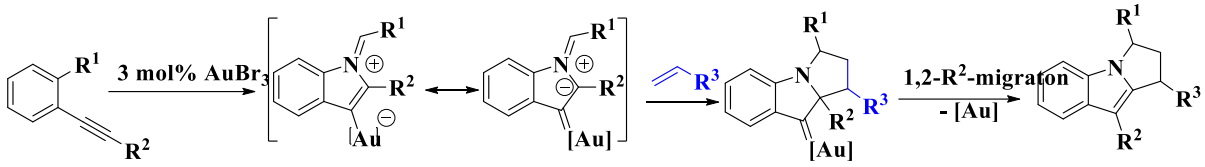
Scheme 7 Arcadi pyridine synthesis

Two very basic components, cyclohexadiene and phenol, were easily converted into a non-aromatic, unrelated dihydrobenzo furan derivative 12 (Scheme 8). Whether the hydroaryloxylation or hydroarylation phase is the first step is uncertain.[51]



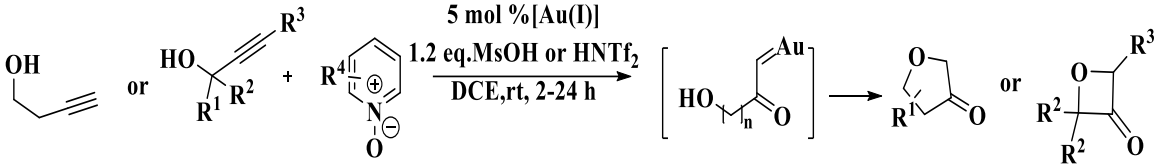
Scheme 8 Cancellation sequence

A series of reactions that produce 1,3-dipolar structures as intermediates is another extremely adaptable cancellation sequence. A good illustration is provided in (Scheme 9).[52] The intermediate 13, which may be expressed as a 1,3-dipole following the intramolecular nucleophilic assault, does, in fact, intercept an olefin as a dipolarophile. The result of a one,two-shift and the removal of the gold catalyst is product.



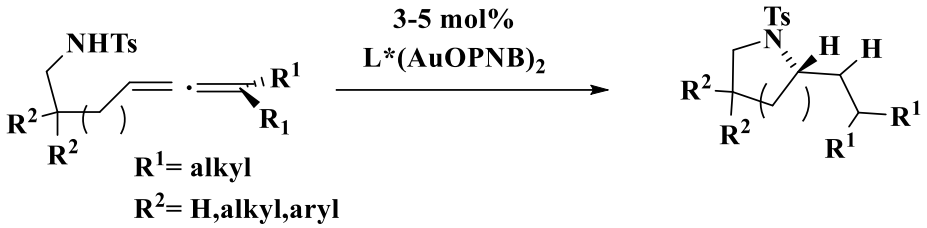
Scheme 9 Cancellation by 1,3-dipolar intermediates.

The movement of oxygen atoms from chemicals such as pyridine-N-oxide is another contemporary subject. In Scheme 10, the pyridine ring serves as a loosing group after the inter-molecular nucleophile. Following the oxygen transfer, the intramolecular nucleophile and gold carbenoid react to produce heterocyclic ketones.[53] Even rings with four members may be synthesised when propargylic alcohols are used.[54]



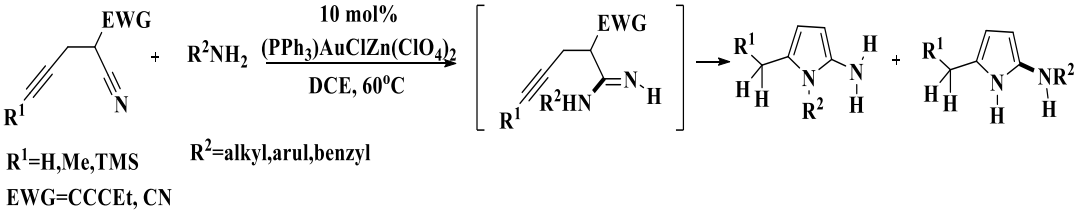
Scheme 10 Oxidative cyclisation's

Stiff tricyclic cage-like structures might also be built using the concepts of intramolecular and intermolecular nucleophilic addition participation.[55] Although Ito and Hayashi's pioneering work on the catalytic asymmetric aldol reaction of aldehydes with isocyanoacetate for the synthesis of oxazoline systems laid the foundation, the synthesis of enantiomerically pure heterocycles from achiral starting materials has only been 'rediscovered' in recent years, a quarter of a century later.Alleles 24 may be enantioselectivity hydroaminated intramolecularly using chiral Di nuclear gold(I)-phosphine complexes (Scheme 11).[56]



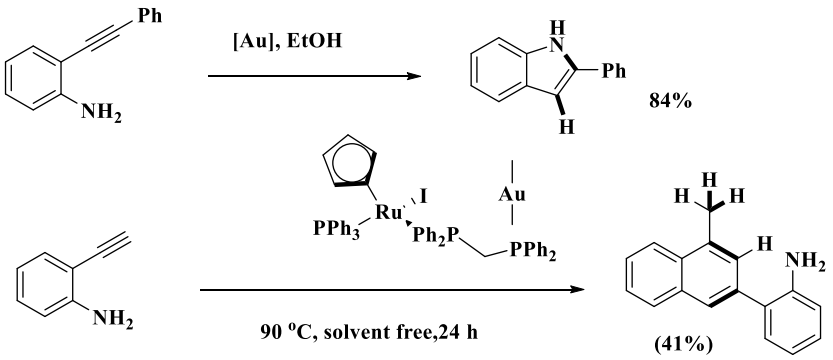
Scheme 11 Enantiomerically pure tetrahydropyrroles from achiral allenes.

Furthermore, exceptional chiral induction was also created by applying chiral counter-ions to the metal core without the presence of any chiral ligands.[57] Using a catalyst system that contains Zink $(ClO_4)_2$ for the nitrile amination process and the PPh3AuCl promoted cyclization step, 4-pentynenitriles undergo a tandem-hydroamination-annulation process in the presence of amine nucleophiles to yield aminopyridines (Scheme 12).[58] The amidine's cyclisation is not chemo-selective; frequently, the two possible constitutional isomers are seen.



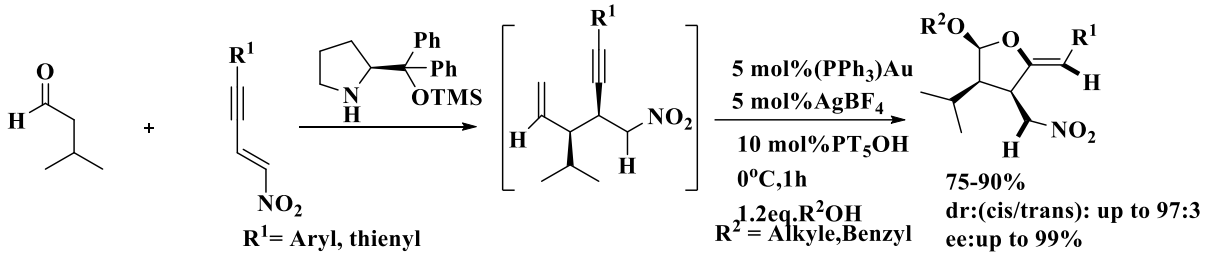
Scheme 12 Pyrroles by a combined of Au (I) and Zn(II) catalysts

Ethynyl aniline dimerised to the quinoline derivative using the heterobimetallic catalyst. Reactivity was not observed in control experiments using PPh3AuI or the monomeric ruthenium complex.



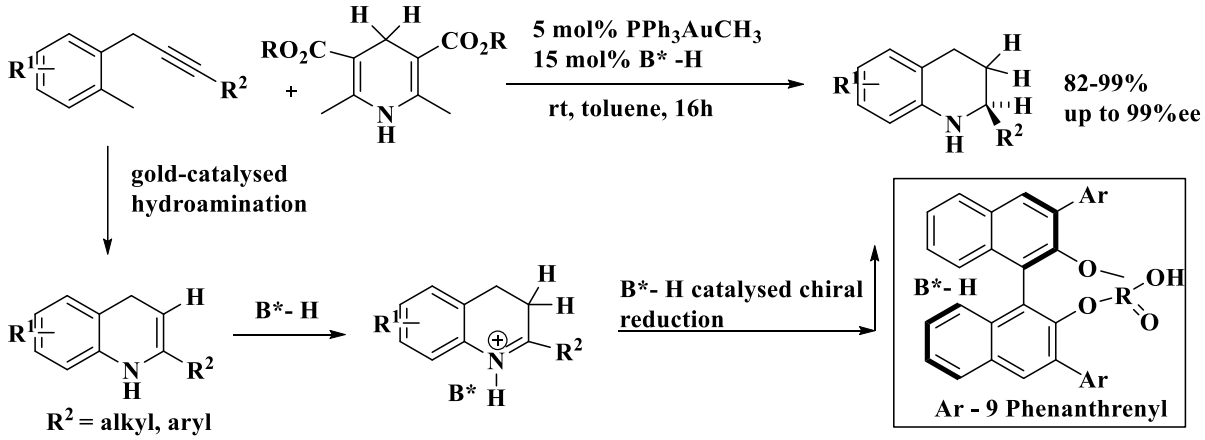
Scheme 13 New pathway with a dinuclear heterobimetallic compound

Gold catalysis and organocatalytic together provide a novel avenue for creating complex heterocyclic structures from basic building blocks. Krause and colleagues provide a fantastic and realistic illustration of this tactic. They discussed a Au-catalysed cyclization process after an organo-catalysed Michael addition of aldehydes to nitroolefins (Scheme 14).[59]



Scheme 14 Combined organo and gold catalysis.

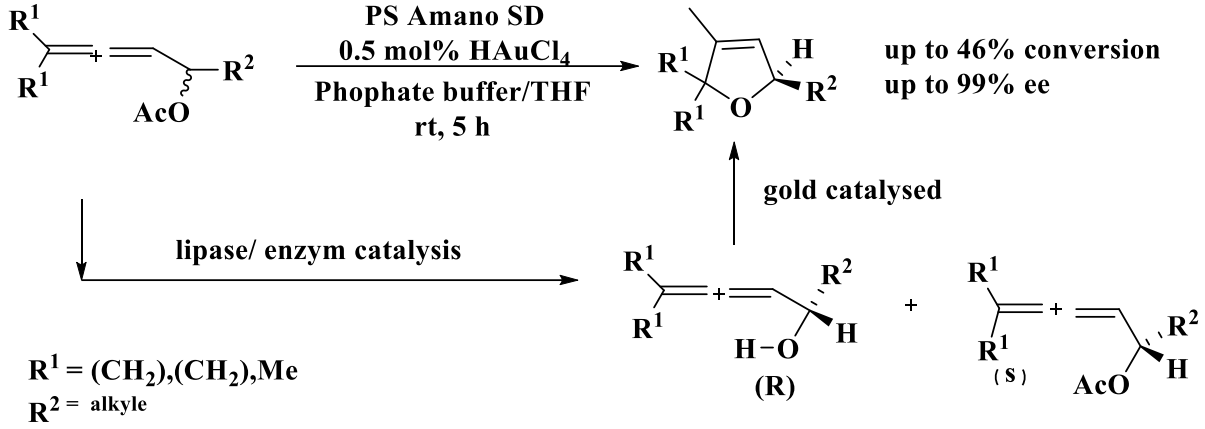
Au-catalysed cycloisomerization of the substrate (Scheme 15) and the ensuing utilising Hantsch ester and a chiral phosphoric acid are two examples of how the sequence of gold catalysis and organocatalytic may be reversed.[60]



Scheme 15 Combined gold and organocatalyst.

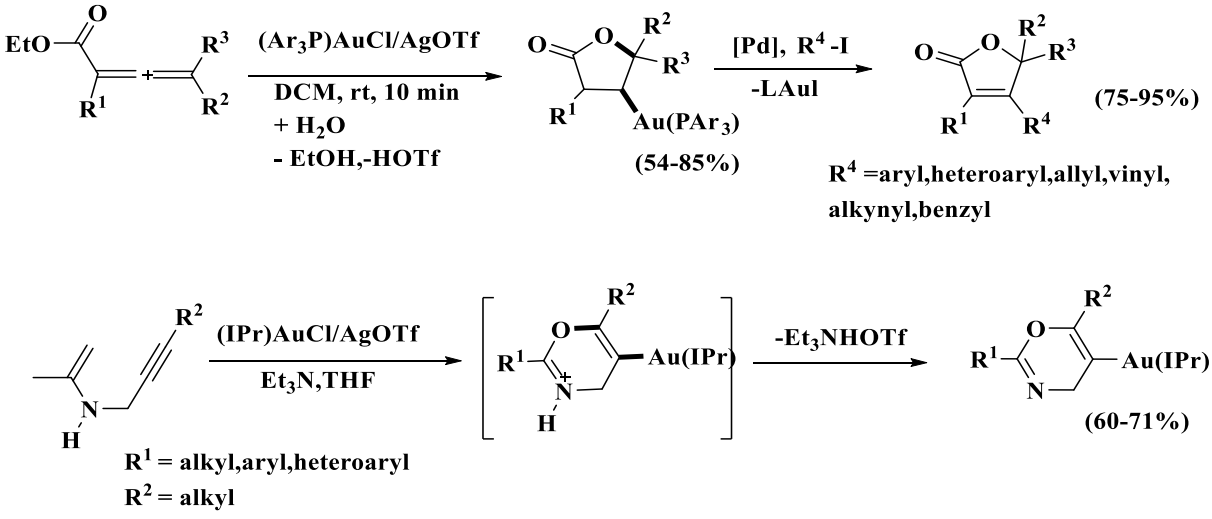
Gold catalysts and enzymes may also be coupled. For example, lipase and racemic allenic acetate 30 were mixed, and when the enzyme releases the enantiomerically pure alcohol, the Au-catalyst causes the cyclisation to the enantiomerically pure

dihydrofuran derivative (Scheme16).[61]



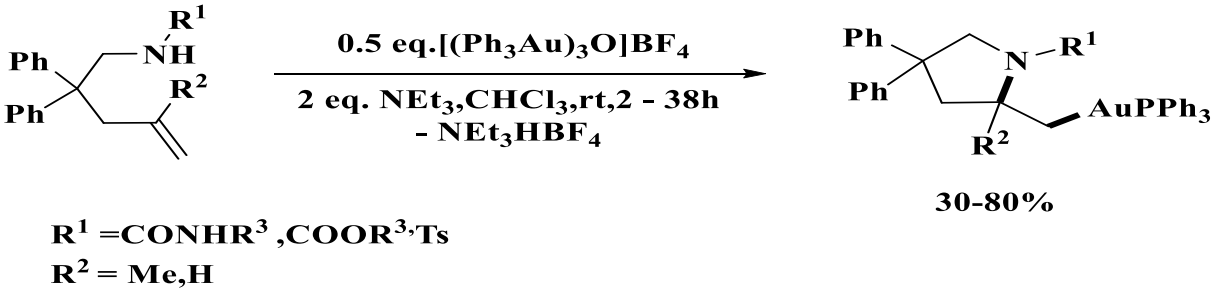
Scheme 16 Enzyme and gold catalysis.

Heterocyclic organogold compounds were proposed as important intermediates in several mechanistic theories, The extremely sluggish cyclisation of allenic esters using gold(I) catalysts produced the first contribution in this field (Scheme 17). It is possible to isolate vinyl gold (I) phosphane complexes using stoichiometric quantities of phosphane gold(I) complexes.[62] A base that prevents the proto-demetallation phase, which closes the catalytic cycle, is necessary in this situation.



Scheme 17 Initial production of viable heterocyclic gold intermediates and their reactions.

It was recently possible to apply the idea of stabilising the organogold(I) intermediate with simple triethylamine [62,63] to alkyl gold compounds that are produced in within-molecule hydroamination processes (Scheme 18).



Scheme 18 Growth of triethylamine's application in the production of reliable heterocyclic alkyl gold (I) intermediates

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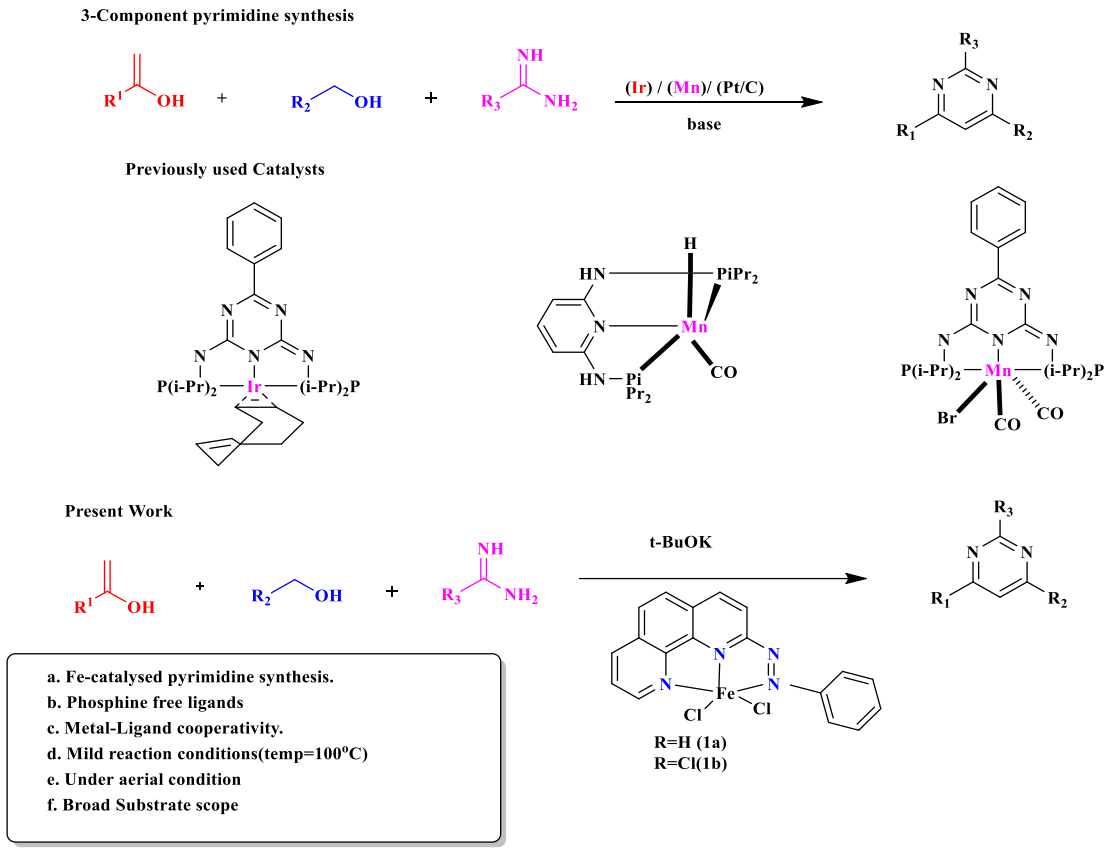
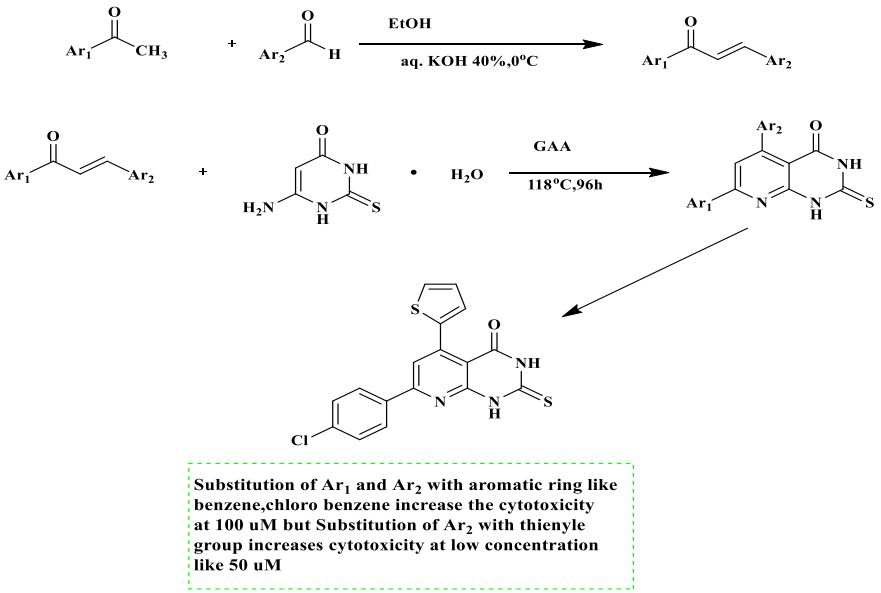
Recently, we demonstrated the catalytic dehydrogenation of alcohols at 75°C in the presence of air, using well-defined iron(II) complexes, [FeLa/bCl2] (1a, 1b), with redox-active 2-arylazo-(1,10-phenanthroline) ligands, La/b (where La = 2-(phenyldiazenyl)-1,10-phenanthroline and Lb = 2-((4-chlorophenyl)diazenyl)-1,10-phenanthroline) as catalysts. (Scheme 1).[64] Mechanistic studies showed that the 2-aryl azo-(1,10-phenanthroline) moiety and iron work together to dehydrogenate alcohols. A hydrogen atom transfer mechanism is used by the iron-stabilised azo-anion radical to steal the alcohol's hydrogen atom, creating a ketyl radical intermediate that, when subjected to a quick one-electron oxidation, yields the required carbonyls. .[65] It was feasible to accomplish the dehydrogenation reaction at 75°C by avoiding the energetically taxing Fe-centered two-electron Fe (II)/Fe(IV) redox events through the active engagement of the azo-anion radical ligand. We decided to investigate the multicomponent dehydrogenative coupling of primary and secondary alcohols with amidines to create pyrimidines to broaden the scope of the iron-catalysed dehydrogenation of alcohols. [66,67,68,69] At 100°C and air, catalyst 1b produced a range of 2,4,6 trisubstituted pyrimidines in moderate to good isolated yields, demonstrating encouraging activity.

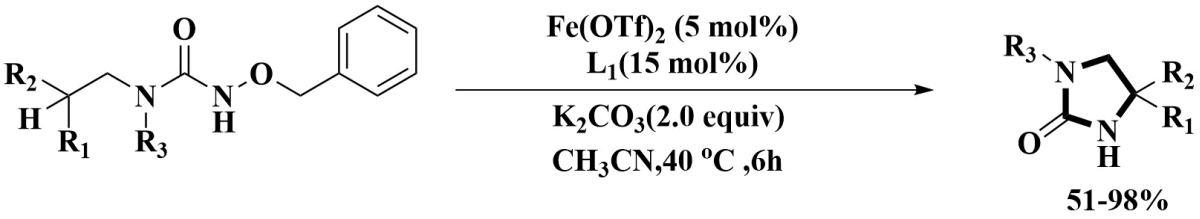


The fundamental structural component of pyrimidine analogues is the pyrimidine ring, which functions as an antimetabolite, disrupts nucleotide synthesis, competes with ATP, and influences DNA and RNA synthesis. A group of new pyrido [2,3-d] pyrimidine derivatives were created and synthesised in 2023 by Myriagkou et al. as powerful anticancer drugs. The novel pyrimidine derivatives were created chemically by condensing of 4-amino-6-hydroxy-2-mercaptopyrimidine a monohydrate by using a suitable α, β-unsaturated ketone in the presence of glacial acetic acid.. The cancer cell lines, A-549 and HaCaT, were subjected to cytotoxicity and cell viability tests. The MTT experiment showed that none of the compounds were viable against the HaCaT cell line at a dose of 100 µM. At a dose of 50 µM, (Scheme 3) demonstrated the most powerful cytotoxic among the investigated compounds, while all of them showed strong cytotoxicity against the A-549 cell line at 100 µM [70].



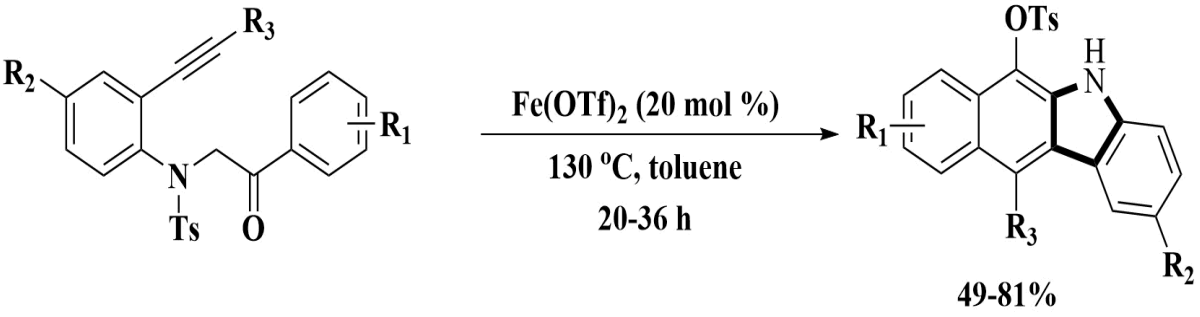
Scheme 20 Production of 2,3-dihydropyrido-5,7-dimethyl-2-thioxo[2,3-d] Utilizing pyrimidin-4(1H)-one as an anticancer drug [71]

Iron-catalysed chemical transformations through intra- and intermolecular processes, such as C-H activation, oxidation, coupling, cyclisation, etc., are the main topic of this study, which covers the literature up to 2021. Zhong et al. produced in situ between molecules amidations of N-benzoyloxyureas using bipyridine and Fe-catalyst [Fe (OTf)2] without the usage of external oxidants. Utilising N-benzoyloxylurea as a substrate and 10 mol% FeCl2 as a catalyst, cyclic urea was produced at 40 °C for 6 hours while ligands such as acetonitrile, bipyridine and K2CO3 as a base were present. The electron-rich groups and a range of substituents, such as halogens at the phenyl group's Para position, were well tolerated in good to high yields.[72]



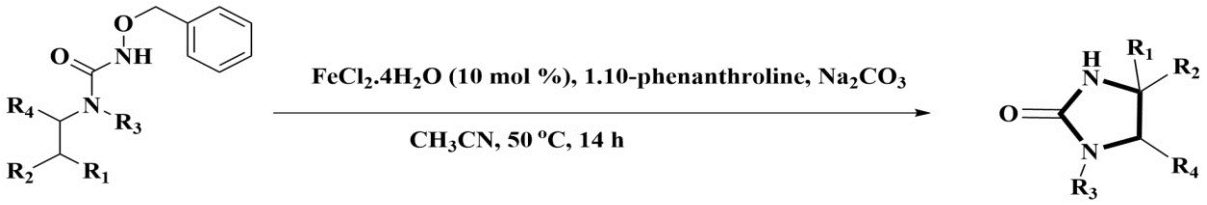
Scheme 21 Using an iron catalyst to facilitate the intramolecular amidation of N-benzoyloxyureast.

Using an aroyl substrate catalysed by 20 mol% Fe (OTf)2 at 130 C, the corresponding benzo[b]carbazoles (4) were created. With aroyl moieties in R1 (electron-donating), R2 substituted chloro, fluoro, and methyl, and R3 containing both electron-rich and poor groups in reasonable yields, the reaction proceeded smoothly for a broad variety of 5H-benzo[b]carbazoles (Scheme22).[73]



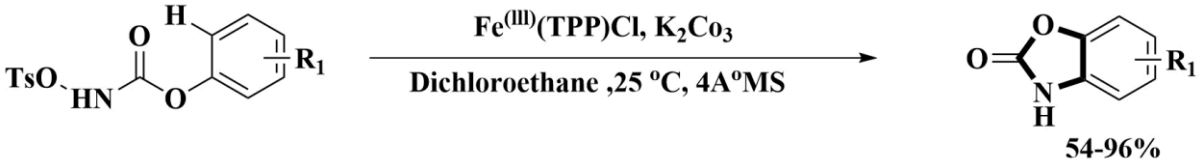
Scheme 22 Iron-catalysed synthesis of benzocarbazoles by using aroyl substrates

Using iron catalysts such as iron(II) chloride tetrahydrate (0.02 mmol), 1,10-o-phenanthroline, MeCN, and Na2CO3 at 50 C for 14 hours, The reaction conditions for synthesizing imidazolidin-2-one involved the use of N-benzoyloxyureas as the starting material. Both electron-rich and electron-poor substituents were successfully added to the para-position of the phenyl group. The propargylic and approximately two-thirds of the aliphatic C(sp3)-H bonds underwent amination, resulting in the desired 2-imidazolidones with yields between 68% and 95% (Scheme23).[74]



Scheme 23 Iron catalysed synthesis of imidazoline-2-ones.

An Fe Accelerator, such as Fe (TPP)Cl (2 mol%), was used to synthesise benzoxazoles utilising ntosyloxyarylcarbamates as the substrate for 6–12 hours at 25 C. Various substrates, including alkoxy, and halogen groups, were well tolerated by N-tosyloxyarylcarbamates. Electron-donating substituents (Methyl, alkoxy) produced excellent yields, while electron-poor substituents produced lower yields, as demonstrated by the electronic impact on 4-substituted carbamate (Scheme 24).[75]



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The utilisation of both homogeneous and heterogeneous catalysts is one of the notable advancements in the oxidative coupling of styrenes [76] and ketones in recent years. In some situations, pursuing the change also requires the presence of a co-catalyst. [77, 78]

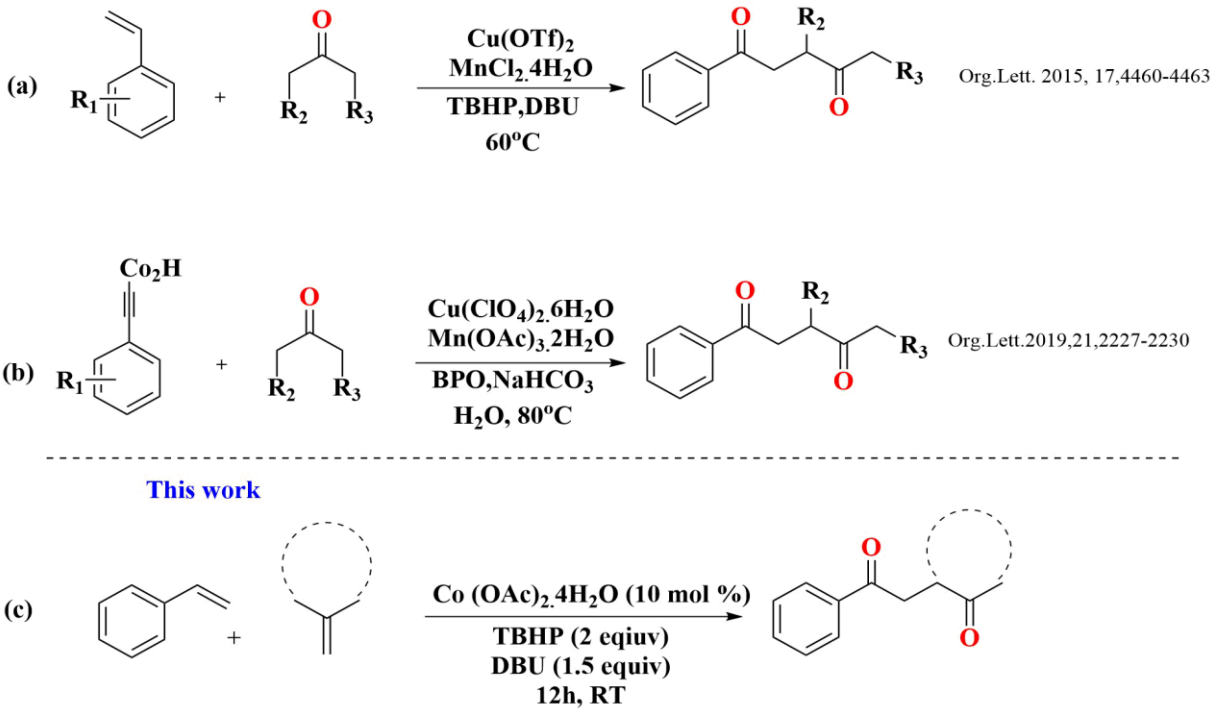
We found a method for forming 1,4-dicarbonyls from the previous report [79] that requires α-bromo ketone to be presynthesized and purified before being used in the conversion. This method involves a radical addition of α-bromo ketone to vinyl arene through C-Br bond activation at very high temperatures and very long times. Another process utilised the dual catalysed oxidative coupling of ketone and styrene (Scheme 25a), where a manganese co-catalyst was necessary to increase the yield of the desired product because the costly copper triflate salt alone only generated a trace of the product. It was also shown that 1,4-Dicarbonyl compounds may be produced by decarboxylative oxyalkylation of alkynyl carboxylic acid with ketone at 80 °C with a dual catalyst (copper/manganese) [78] (Scheme25b).

In addition to these methods, vinyl arene may also be converted into a 1,4-dicarbonyl molecule by employing β-diketones as the starting material and a photo redox catalyst [80]; however, this approach necessitates the use of presynthesized and purified starting materials. To create the desired 1,4-dicarbonyl product, the majority of the aforementioned processes require a certain temperature, an inert environment, presynthesized starting materials, co-catalysts, or intricate ligand templates.

Consequently, we have developed a technique (Scheme 25c) based on cheap, earth-abundant cobalt salt as part of our continued interest in the development of Co-based catalysts in organic transformations [81].By oxidatively combining styrene and ketone in a moderate environment with an aerobic atmosphere, 1,4-dicarbonyl molecules were created using this efficient, sustainable, and one-pot synthetic process. One of the biggest benefits is that the reaction can be conducted at room temperature with and yields a sizable amount of the intended product using unavoidable post modifications, particularly for heterocyclic compounds with five or six members that are highly biologically significant.[82] Two hydrogen atom transfer (HAT) processes are involved in the reaction, as shown by the combined experimental and theoretical investigations. The base stimulates the second HAT mechanism, while the Co (II) catalyst causes the first. This approach is appealing and more demanding since it uses inexpensive to synthesise industrially significant γ-diketones in high yields and convert them into a variety of heterocyclic compounds that are valuable both synthetically and physiologically

Pevious reports

Dual catalyst (Cu/Mn) used for synthesis of 1,4-diketone



In order to maximise the reaction conditions, we started our inquiry by using acetone as the source of the carbonyl group and styrene as the model aryl alkene. We discovered that Cu and Mn catalysts [77,78] by alone is insufficient for the subsequent transformation; nevertheless, they are all efficient when co-catalysts are present and the reaction conditions are severe. Using styrene and acetone as model substrates, we tried the reaction and successfully obtained the desired 1,4-dicarbonyl product in 60% yield with a catalyst of 10%, a radical generator, 4 equiv of tert-butyl hydroperoxide (TBHP) as the oxidant, and 1.5 equiv of 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) as a base at 80 °C (Scheme 26, Table 1, entry 1). It's interesting to note that switching from DBU to benzimidazole as the base produced the Required product in a low yield (30%) (Scheme 26 Table 1, entry 2). After screening a number of other bases, we found that while a trace of the Required product was obtained in the presence of the nitrogen-containing organic base 1-methylimidazole (Scheme 26 ,Table 1, entry 3), the Required product was not formed in the presence of other nitrogen-containing organic bases such as imidazole, trimethylamine, piperidine, oxazole, 1,2,4-triazole, and N,N diisopropylethylamine; only the starting material remained (Scheme 26 ,Table 1, entries 4–9).

Scheme 26. Modification of the Reaction Field

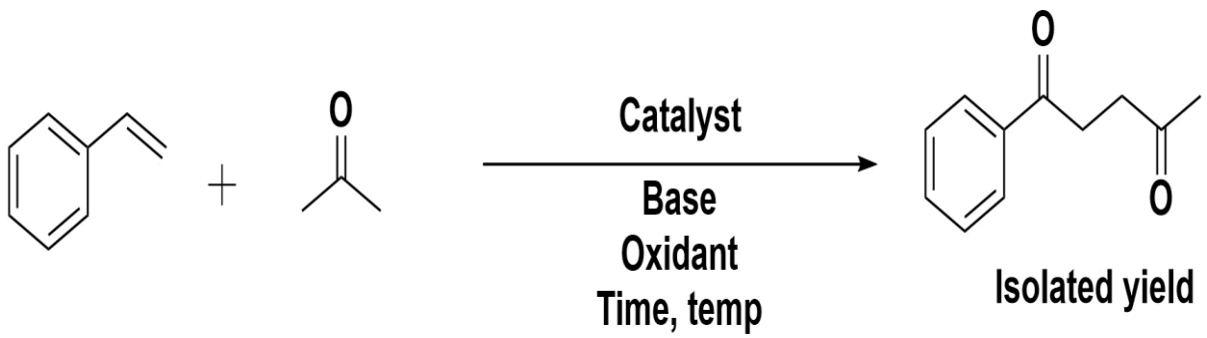


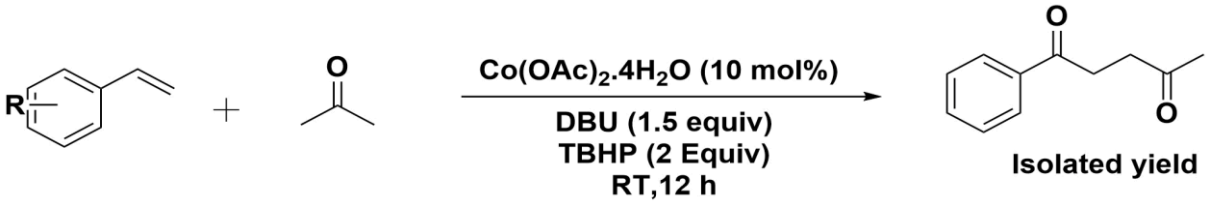
Table:1 Modification of the Reaction Field *a*, *b*

Entry	Catalyst (mol%)	Oxidant(equiv)	Base (equiv)	Time	Temp	% Yield
1	Co $(OAc)_2.4H_2O$ (10)	TBHP (4)	DBU (1.5)	12 h	80°C	60
2	Co $(OAc)_2.4H_2O$ (10)	TBHP (4)	Benzimidazole (1.5)	12 h	80°C	30
3	Co $(OAc)_2.4H_2O$ (10)	TBHP (4)	1-methylimidazole (1.5)	12 h	80°C	50
4	Co $(OAc)_2.4H_2O$ (10)	TBHP (4)	Imidazole (1.5)	12 h	80°C	ND
5	Co $(OAc)_2.4H_2O$ (10)	TBHP (4)	Triethyl amine (1.5)	12 h	80°C	ND
6	Co $(OAc)_2.4H_2O$ (10)	TBHP (4)	Piperidine (1.5)	12 h	80°C	ND
7	Co $(OAc)_2.4H_2O$ (10)	TBHP (4)	Oxazole (1.5)	12 h	80°C	ND
8	Co $(OAc)_2.4H_2O$ (10)	TBHP (4)	1,2,4-trizole (1.5)	12 h	80°C	ND
9	Co $(OAc)_2.4H_2O$ (10)	TBHP (4)	DIPEA (1.5)	12 h	80°C	ND

a Catalytic condition: 1a (1 equiv), 2a (0.5 mL), DBU (1.5 equiv), TBHP (70 wt. % in water, 2 equiv), catalyst (10 mol %), room temperature (RT), 12 h. ND = not detected. DTBP = di-*tert*-butyl peroxide. TBPB = *tert*-butyl per benzoate. DDQ = 2,3-dichloro-5,6-dicyano-1,4- benzoquinone. *b* Isolated yield based on column chromatography.

After the ideal circumstances were established, more aryl alkenes and ketones were added to the substrate scope. Initially, a number of styrene derivatives with electron-donating and electron-withdrawing groups were investigated for their ability to react with acetone (Scheme 27). We also used β-substituted styrene [(E)-stilbene)] with acetone to broaden the substrate scope, and we were able to generate the required product in good yield (62%) (Scheme 27).[77] Furthermore, no product was generated in the presence of -NO2, -CN, -NMe2, and -NH2 groups, possibly because of their potent mesomeric action (+R/−R), which may cause conjugation to disturb the electronic environment of the terminal alkene of vinyl arenes.[83]

Scheme 27. Substrate Scope of the Reaction with Various Aryl Alkenes.



***a* Reaction conditions: 1a−1l (1 mmol), 27a (0.5 mL), DBU (1.5 equiv), TBHP (70 wt. % in water, 2 equiv), Co (OAc)2·4H2O (10 mol %), room temperature, 12 h. *b* Isolated yield after column chromatography.**

2. CONCLUSION

In conclusion, the synthesis and catalytic properties of novel palladium-N-heterocyclic carbene (NHC) complexes, particularly PEPPSI-type palladium-NHC complexes, have shown remarkable potential in medicinal chemistry. These complexes have demonstrated strong catalytic capabilities for the direct arylation of heterocyclic compounds, offering promising prospects for treating various diseases, including cancer. The use of sustainable catalysts, such as PEPPSI-type palladium-NHC complexes, represents a significant advancement in the field of medicinal chemistry, providing a more benign and energy-saving approach to chemical processes. The development of these complexes holds great promise for the future of medicinal chemistry and the treatment of diseases like cancer.

3. ACKNOWLEDGEMENT

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Abbreviations: TBHP= tert-butyl hydroperoxide, DBU= 1,8-diazabicyclo [5.4.0] undec-7-ene, RT= room temperature, ND = not detected, DTBP = di-tert-butyl peroxide, TBPB = tert-butylperbenzoate,DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone,DMF= dimethylformamide, NHC= novel palladium-N-heterocyclic carbene

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