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Palladium Catalyzed Cascade Reactions: A Review Study

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ABSTRACT: The Tandem or domino reaction popularly known as the Cascade reaction, are the chemical processes in which numerous bonds are composed in a way without confining intermediates, altering conditions, and without any add on reagents. The very purpose of cascade sequence includes high atom economy and maximum contraction in waste produced due to various chemical procedures, plus work period needed to conduct these processes. Their effectiveness is measured out in terms of how many bonds are constructed in the final course. The d-block metal's catalyzed cascade reactions are of particular attraction for the preparation of natural materials as well as in the analogy of a few significant leading structures for the advancement of bioactive materials and are employed for the synthesis of other compounds as well. Several remarkable d-block-Catalyzed cascades reactions were evolved and noted very recently that attracted synthetic chemists all over the world, especially because of their high efficiency and variety. Palladium was considered the most significant metal catalyst in the twentieth century for the transition metal-catalyzed organic transformations including the Heck reaction, Suzuki reaction, and cross-coupling reactions. In this work, we have done a literature review of palladium catalyzed cascade reactions.

Keywords: Cascade reactions, Synthesis, Pd-catalyzed, Domino-Tandem, Annulation, Suzuki Coupling, Cyclization, Heterocycles, Negishi cross-coupling.

INTRODUCTION

Palladium is of the six-platinum group metals and possesses great catalytic activity. What makes it unique is its ground-state electronic configuration, i.e. $4d^{10}5s^{0}$, which makes this only transition block metal to combine a filled d-orbital having a vacant frontier s-orbital. Palladium(II) with d8 electron configuration is present in many organo-metallic compounds which mainly have two vacant axial coordination sites and these compounds usually exist in square planar geometry.

The unique chemical and physical properties of palladium account for its widespread use in organic synthesis, catalysis electrochemistry. In recent years palladium catalysts have found use in a sequential multistep synthesis reaction, called domino/tandem or cascade reaction. Cascade reaction is a chemical transformation that consists of at least two continuous reactions wherein the product of one reaction step is the substrate for the next sequential step. Pd-catalyst is best suited for such types of sequential reactions because it can easily coordinate with an organic moiety to form Pd(0)M (M= alkyl ring, allyl, heterocycle, etc) to form a carbo-palladium complex which either undergoes insertion or attacks another substrate molecule to form a substituted product or cyclization product. After the attack Pd(0) leaves the organic moiety and the product is formed. Pd(0) can re-enter the cycle.

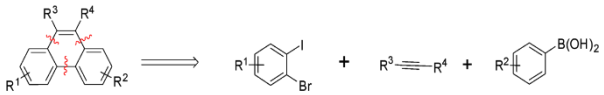
In recent years palladium-Catalyzed cascade has caught the attention of many organic chemists because of the versatile nature of Pd-catalyst and the high efficacy rate of cascade reactions are because of their atom economic nature. Here Pd-Catalyzed cascade reactions are employed for the synthesis of various bio-active compounds like quinoline, isoquinoline, indole, bicyclic dihydrofuran, ethers, fused heterocycles, and many more pharmaceutical agents via tandem allylic substitution, heck coupling, Suzuki coupling, C-H bond, activation, carbonylation, aldol condensation, and multistep annulation.

LITERATURE REVIEW

Pd-Catalyzed annulation cascade reactions

Phenanthrene synthesis. The Pd–Catalyzed three-constituent cascade reactions have been formulated for

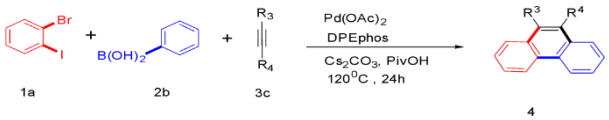
the creation of phenanthrene. Many researchers have figured out different ways of synthesis of phenanthrenes and most of these researchers primarily concentrated on the establishment of the innermost ring of phenanthrene. Nevertheless, the construction of these three new C-C bonds in one pot (scheme 1) is of valuable consideration, because it has many advantages, like convenient substrates, step economy, and many more. Consequently, it is usually recommended that phenanthrenes are synthesized via multi-component coupling (Scheme 1). Here in the systematic three-component Pd-catalyzed reaction for the construction of phenanthrene derivatives out of alkynes, o-bromoaryl iodides, and arylboronic acid.



Scheme 1: Construction of phenanthrene derivatives from three-component Pd-catalyzed reaction.

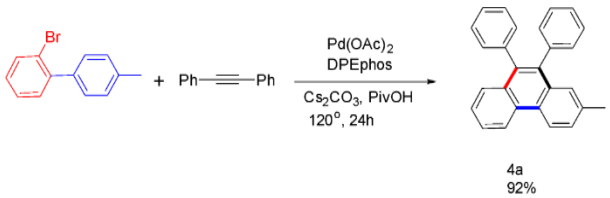
The regulated reaction arrangement by Suzuki-Miyaura coupling converts into the biaryl motif which follows in depth technique of introduction of alkynes of final annulations to offer phenanthrene derivation via C-H activations (Juan *et al.*, 2019). The optimized circumstances of the reaction were based on the ideal conversion of *o*-bromoiodobenzene, diphenylacetylene, and 4-methylphenylboronic acid.

The ideal reaction conditions employed are 1.0 equivalent o-bromoiodobenzene,1 equivalent 4-methylphenylboronic acid with 2.5 equivalent diphenyl-diacetylene, 5mol% of pd(OAc)2, 10 mol% DPEphos, 2.0 equivalent Cs_2CO_3, 1.0 equivalent of PiVOH in toluene (2ml) at 120^0 for 24h, and finally phenanthrene (4) was obtained in 92% of confined yield.



Scheme 2: Pd-Catalyzed coupling different diaryl acetylenes along with o-bromoiodobenzene and phenylboronic acid.

The evidence indicates that these transformations are guided by a controlled series of reactions involving Suzuki-Miyaura coupling, alkynes introduction, and subsequent annulations, resulting in the formation of phenanthrene derivatives through C-H activation (Juan *et al.*, 2019). This was demonstrated by carrying out the annulations of 2-bromo-4'-methyl-1,1'-biphenyl under standard conditions, leading to the product (4a) with a high yield of 92%.



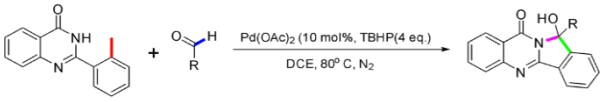
Scheme 3: Annulations reaction.

Pd-Catalyzed CDC(Cross Dehydrogenative Coupling):

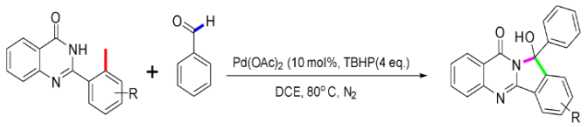
Systematic technique to synthesis of Hydroxy isoindolo[1,2-b] quinazolinone. In recent times, Cross Dehydrogenative-Coupling (CDC) reactions have emerged as important methods for C-H activation, offering an attractive alternative to traditional C-C bond-forming reactions. These reactions have become a preferred synthesis approach for selectively forming C-C bonds. In contemporary studies, aldehydes have been used in direct metal-catalyzed CDC/Annulation reactions to prepare heterocyclic compounds.

Building on the latest advancements in C-H activation reactions and organic synthesis, a palladium-catalyzed cross dehydrogenative-coupling reaction followed by intramolecular cyclization was performed using aryl-quinazolinones and aldehydes, with tert-butyl hydroperoxide (TBHP) serving as the oxidant. The aim was to produce hydroxy isoindolo[1,2-b]quinazolinone. (Minoo *et al.*, 2019). The reaction conditions were optimized using2-phenylquinazoline-4(3H)-one and benzaldehyde as substrates. The optimal reaction conditions were found to be Pd(OAc)2 (10 mol%), TBHP (4 eqv) in DCE solvent at 80°C for 16 hours under a nitrogen atmosphere.

By employing various types of aldehydes and 2-arylquinazolin-4(3H)-one derivatives under the optimized conditions, a wide range of hydroxy-isoindolo[1,2-b] quinazolinones were synthesized, demonstrating the scope of the process (Minoo *et al.*, 2019). Different benzaldehydes with substituents on the benzene ring, such as p-Me, p-i-Pr, p-OMe, and p-OBn, provided good yields. However, electron-deficient benzaldehydes showed lower reactivity under these conditions.

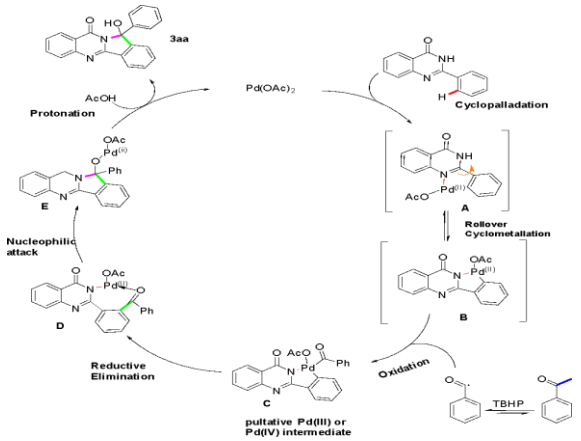


Moreover, the scope of the 2-arylquinazolin-4(3H)-one substrate was explored. Among them, para-substituted aryl quinazolinones with electron-releasing groups on the benzene rings showed favorable reactivity in the reaction and resulted in the desired product formation with good yields. On the other hand, electron-withdrawing groups like p-Cl and p-NO_2 exhibited lower reactivity in the reaction conditions (Minoo *et al.*, 2019).



The proposed mechanism is as follows: Firstly, the 2-phenylquinazolin-4(3H)-one 1(a) undergoes chelate-assisted O-selective cyclometallation with $Pd(OAc)_2$ to form a five-membered cyclopalladated intermediate (A). This intermediate then undergoes further cyclometallation to produce intermediate (B). The palladated cycle is further oxidized by an acyl radical, generated through hydrogen abstraction, leading to the formation of highly active Pd(IV) species or dimeric Pd(III) intermediate (C). Next, through reductive elimination, a new C-C bond is formed with Palladium attached to an amide nitrogen atom of phenyl-

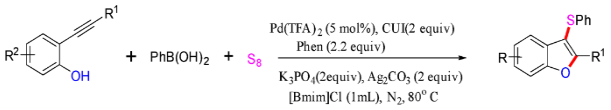
quinazoline, where intramolecular nucleophilic attack occurs, resulting in the formation of a palladium alkoxide (E). Finally, this palladium alkoxide is protonated by acetic acid, leading to the formation of the desired product (3aa) (Minoo *et al.*, 2019).



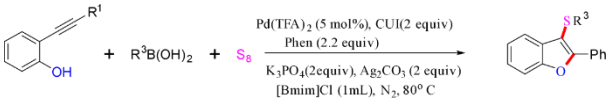
Assemblage of 3-Sulfenylindoles and 3-Sulfenylbenzofurans through Pd- catalyzed cascade annulation or aryl-thiolation. For efficient construction of C-heteroatom bond, the transition metal-catalyzed transformations have turned up as a dominant tool, hence becoming a great and versatile strategy in more recent organic synthesis chemistry, for example, C-S is one of them. Many methods have been formulated by researchers all over the world for constructing C-S bonds, but all these developments suffer some limitations. Here explored a more straightforward and efficient synthetic method for the preparation of 2-substituted 3-sulfenylbenzofurans (Jianxiao *et al.* 2016). Traditional approaches often involve the use of foul-smelling, toxic, and unstable sulphur sources, making the process less desirable from a safety and environmental perspective. Inspired by the success of Pd-catalyzed cross-coupling reactions in ionic liquids, we aimed to develop a transition metal-catalyzed cascade annulation as an ideal strategy.

This research focused on the synthesis of 3-sulfenylindoles and 3-sulfenylbenzofurans through nucleo-palladium triggering of an intermolecular cascade reaction in ionic liquids. To find the optimal conditions, here used a model system consisting of 2-(phenylethynyl) phenol, phenylboronic acid, and sulphur. After careful optimization, it is found that the best reaction conditions were achieved with Pd(TFA)2 as the catalyst (5 mol%), CuI as the co-catalyst (2 eqv), Phen as the ligand (2.1 eqv), K_3PO_4 as the base (2 eqv), Ag_2CO_3 as the additive (2 eqv), and [Bmim]Cl as the ionic liquid solvent (1 ml), under N_2 atmosphere at 80°C (Jianxiao *et al.*, 2016).

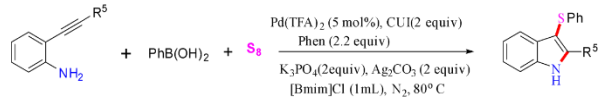
Encouraged by the success of the optimized conditions, it is then investigated the generality and substrate scope of 2-alkynylphenol derivatives. Fortunately, both electron-withdrawing groups (EWGs) and electron-donating groups (EDGs) on the phenyl ring were well-tolerated, leading to the desired products in good yields (Jianxiao *et al.*, 2016). One of the most remarkable features of this cascade annulation/aryl-thiolation reaction is its high tolerance for various functional groups, making it a versatile and valuable synthetic tool.



To further demonstrate, aryl boronic acid derivatives were introduced to check the potential of this method. Then in this reaction, the different substituent of aryl boronic acids like methyl, methoxy, halo, and nitro groups was handled well, permitting the creation of a wide variety of 3-sulfenyl benzofurans derivatives with mild yield.

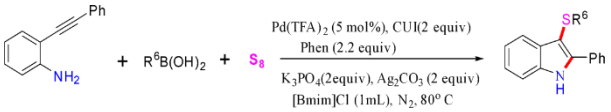


3-sulfenylindoles can be prepared by 2-alkynyl anilines with disulfide and, they could be formed by cascade annulation/aryl-thiolation of 2-(phenylethynyl) aniline derivatives with phenyl boronic acid. The nucleophilic substituents like methyl, methoxy or electrophilic substituents like Florine, Chlorine, Bromine, and Trifluoromethyl radical showed results in good yield. Moreover, the substitution site of the aromatic ring just had little effect.



Moreover, to further check the inference and extent of the above method many 2-alkynyl amines were investigated. A different number of functional groups on aryl alkynyl moieties like p-Me, p-OMe, and p-Cl were accepted under standard conditions (Jianxiao *et al.*, 2016). Under the optimized conditions, here investigated the reactivity of substrates containing three, five, and six-member ring substituted 2-alkynyl amines. Remarkably, these substrates reacted smoothly and provided the desired products in significant yields.

Additionally, explored the compatibility of different aryl-boronic acid derivatives bearing various substituents such as p-Me, p-MeO, p-F, m-F, o-F, and p-Cl. Encouragingly, these derivatives exhibited high compatibility with this current procedure, leading to the formation of the corresponding 3-sulfenylindole derivatives in good yields (Jianxiao *et al.*,2016). The ability to tolerate different substituents further highlights the versatility and usefulness of our synthetic approach.

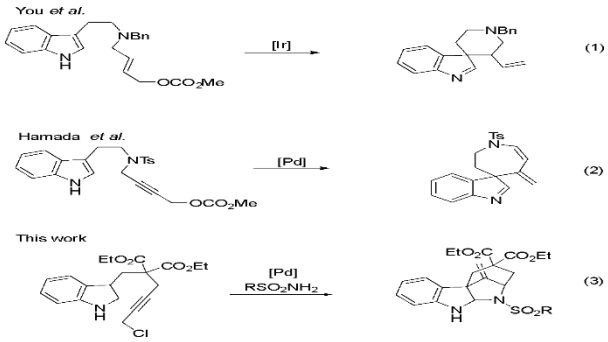


Pd-CATALYZED CYCLIZATION TANDEM-REACTION

Bi-cyclic ethers: Synthesis. The scaffolds of bi-cyclic ethers are found in many natural products. The persistent curiosity in making convenient ways to approach natural products for drug discovery, by using simple substrates by Palladium-Catalyzed cascade reaction. Reduction and oxidation processes drew much attention recently, due to

their power of transmitting reactivity by saturated parts of a molecule. In finding out the further outgrowth of Pd bi-cyclization Tandem-reaction, firstly synthesized diene- diol substrate. Initial steps resulted in the formation of chromene rather than a desired bi-cyclic product, and then employed basic catalytic network to stop chromene development (Michaelyn *et al.* 2019*).* Finally, raising the temperature up to 80° led to the construction of a required bi-cyclic product.

In finding out the scope of palladium Catalyzed bi-cyclization cascade reaction, designed a substrate p-position to phenol to evaluate electronic effects. Wherein the electron-withdrawing group resulted in low yield product and the electron-donating groups resulted in high yield product. We then synthesized other substrates (Michaelyn *et al.*, 2019). Moreover, 1,4-dienes undergo the cascade reaction to form bi-cyclic products.



To understand the mechanism of the cascade reaction, we observed that the cis-fusion in this process is a result of an equilibrium method. The initial oxidative cyclization and redox relay steps are reversible, while the pi-allyl Pd cyclization is irreversible (Michaelyn *et al.* 2019). Interestingly, the pi-allyl Pd-cyclization proceeds with an inversion of configuration compared to Pd for alkoxides.

During the redox relay process, a mixture of single bond rotamers is present, leading to the formation of a mixture of pi-allyl Pd diastereomers, which in turn gives rise to a mixture of vinyl side chain diastereomers. This redox relay approach has been successfully used to create versatile bi-cyclic ether scaffolds in a well-planned and universal manner.

Furthermore, the redox relay procedure involves Pd relocation and a break-off at an olefin to generate a pi-allyl Pd species. In the future, there is potential to control the diastereomer-selectivity of pi-allyl Pd- cyclization through the design of new catalysts. This could offer exciting opportunities for enhancing the efficiency and selectivity of the cascade reaction.

The compounds that are described here display a wide range of biological activity and are Spiro-heterocyclic. Out of these, the fused spiro-indoles are of paramount importance present in various alkaloids as well as other biologically active compounds.

Their mechanistic examination is compatible with the reversibility of cyclization and a symmetric method in which the ring fusion diastereo-selectivity is eventually imposed by the subsequent, irreversible pi allyl–pd cyclization.

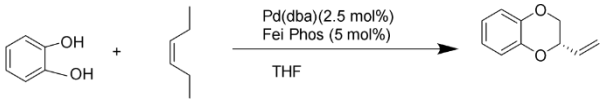
Cascade hydrosilylated reduction and Domino or Tandem allylic cyclization/substitution

Transition metal-catalyzed allylic substitution reactions are valuable tools in organic chemistry for creating alkene-substituted compounds. Among these, asymmetric allylic substitutions using chiral compounds are particularly important. Researchers are still interested in using allylic acetates with various functional molecules for these reactions. One significant type of allylic substitution is the stereoselective allylic alkylation of alcohols, which helps in making chiral ether-containing compounds. Palladium complexes with certain ligands have shown good results in constructing diverse Carbon-Oxygen bonds and chiral ethers.

Limited progress has been made in the Tandem allylic alkylation of catechol with allylic reagents to synthesize chiral 2-vinyl-2,3-dihydro-benzo [1,4]dioxanes. To address this, research has explored the use of palladium catalysts with Fei-Phos or other P-ligands to achieve the desired reaction outcome. These reactions are of great significance as they are essential for creating 1,4-benzodioxane ring systems found in natural products and potential pharmaceuticals with important biological activities. The study also investigates the impact of different phosphine ligands, organic and inorganic bases, Bronsted acids, and other additives on the asymmetric palladium-catalyzed alkylation of catechol with allylic diacetate.

To initiate the experiments, first tested the allylic substitution/cyclization reaction of benzene 1,2-diol with an allylic acetate derived from (Z)-but-2-ene-1,4-diol as a model reaction. The results revealed that most phosphine ligands resulted in poor or no yield of the product. The only palladium salt that effectively promoted the tandem allylic substitution was Pd(PPh3)4, while other palladium salts did not work as suitable catalysts.

Recent research has also investigated the impact of organic acids on the enantioselective Pd-catalyzed allylic alkylation. Although chiral organic acids did produce the desired product, the enantioselectivity was low. This suggests that organic acids can influence the catalytic efficiency of the palladium catalyst in this reaction.



In conclusion, this study determined that Fei-Phos is effective in the asymmetric palladium-catalyzed tandem allylic alkylation of 1,2-bifunctional nucleophiles. It is also investigated that various reaction parameters' influence on this reaction, including the choice of phosphine ligands, bases, acids, and other additives. With optimized conditions, they achieved promising enantioselectivity and good yields of the desired 2-vinyl-2,3-dihydro-benzo [1, 4] dioxine products. Additionally, developed a novel one-pot reaction combining allylic substitution/cyclization and cascade reduction using methyl phenylsilane, showcasing the concept of silicon-mediated organic synthesis (SiMOS). The researchers believe that modifying Fei-Phos could be a successful

strategy to enhance asymmetric palladium-catalyzed reactions.

Regio and stereo-selective of allene bi-functionalization cascade reaction via p-allyl intermediate. Here described a Pd-catalyzed allene bi-functionalization reaction that formed Ce-C, Ce-O or Ce-N bonds in one pot gives very good regio- and stereo-selectivity. The appropriate nucleophiles used are Carboxylic acids, amides, and hydroxides, and the hydroxide shift reagent was organo-boronic acid. A pi-allyl intermediatory complex was isolated, it enhanced catalytic activity and stereoselectivity (Tao *et al.*, 2017). Poly-substituted allyl compounds play a crucial role in organic synthesis and are commonly found in natural products. Transition metal-catalyzed nucleophilic allylic substitution is a rapid and efficient method for creating these valuable molecules.

While previous studies have mainly focused on allenes with electron-donating or weak electron-withdrawing groups in palladium-catalyzed reactions, those involving allenes with strong electron-withdrawing groups have received less attention *(*Tao *et al.*, 2017*).* Boronic acids, well-known for their use in Suzuki-Miyaura coupling to form carbon-carbon bonds, have been employed in this research.

This study explored a cascade reaction involving phenyl sulfonyl allene and phenyl iodide. By testing various palladium sources and bases, the researchers identified the optimal reaction conditions. To gain insights into the origin of the hydroxide nucleophiles, control experiments with water or boroxine were conducted. The cascade reaction's scope was further explored with different aryl iodides, successfully yielding the desired products in moderate to good yields. Notably, the carbon-halogen bonds on the phenyl ring remained intact, presenting opportunities for the construction of more complex molecules.

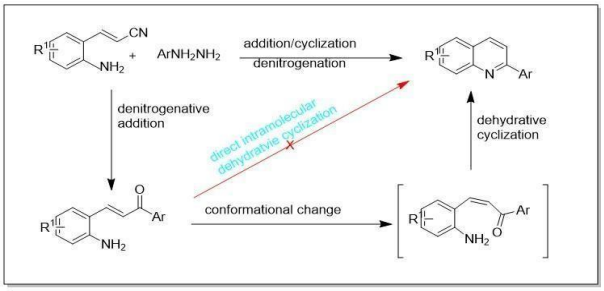
In addition to phenyl sulfonyl allene, different functional groups were examined, including phosphonate and ester. The cascade reaction yielded cyclic products, and their formation was elucidated as a result of internal nucleophilic substitution of the hydroxide group.

Furthermore, this research expanded the nucleophilic scope by employing carboxylates as coupling partners. Both alkyl and aryl carboxylic acids participated effectively in the cascade reaction, leading to the formation of products with moderate to good yields. Additionally, tosyl, a nitrogen-containing nucleophile, was used to synthesize allylic amides with moderate yield.

In conclusion, this research demonstrated a palladium-catalyzed cascade reaction involving aryl iodides and functionalized allenes. The reaction showed high stereo-selectivity and efficiently produced (Z)-allylic alcohol compounds, offering valuable insights and potential applications in organic synthesis.

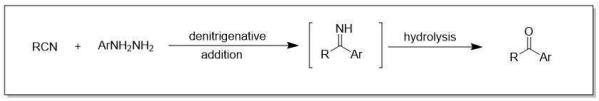
Pd-Catalyzed synthesis of heterocycles

N-Heterocycles: From the past few years, denitrogenative pd-catalyzed reaction of O-aminocinnamonitrile and aryl-hydrazines gives quinolines with decent yields is well admired (Scheme 1). Aryl hydrazines are usually the aryl source that undergoes sequential denitrogenation.



Scheme 1: Cascade reaction of *O*-amino-cinnamonitriles with aryl-hydrazines.

Nitriles are commonly used as ligands in organometallic reactions or solvents as well, because the carbon-nitrogen triple bond is stable and unreactive. In recent times, there has been a useful method developed where nitriles react with arylhydrazine to produce aryl ketones (a type of compound) or other products like quinoline and its derivatives through cyclization reactions (as shown in Scheme 2). This process has opened up a good pathway for synthesizing these compounds using transition metal catalysts.



Scheme 2: Pd-Catalyzed synthesis of aryl-ketones.

The Quinoline framework is present in structures in medicinal chemistry, therapeutic drugs, and natural products. Bioactive quinoline derivatives show potential in clinical trials to treat neurological malignancies, neck cancer, head cancer, and anti-Alzheimer's activities (Fig. 1).

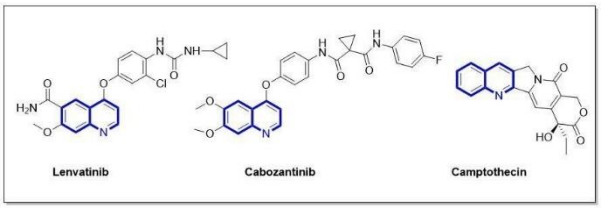
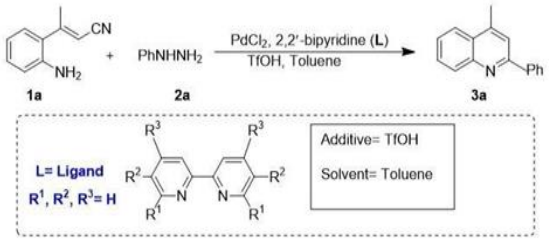


Fig. 1.

Desired quinoline derivative i.e. 2-phenylquinoline (3a) is obtained from denitrogenative addition and intramolecular cyclization of (E) 3-(2-aminophenyl)but-2-enenitrile (1a) and phenyl hydrazine (2a) (Jing *et al.*, 2020*).* It is found that out of numerous Pd-catalysts like $Pd(PPh_3)$, $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2Pd(OM)_2$, $Pd(Cf_3CO_2)$, and $Pd(Cl)_2$, among these $Pd(Cl)_2$ relayed the highest catalyst activity and gave the highest yield of 31% combination with trifluoroacetic acid (TFA) as an additive, tetrahydrofuran (THF) as solvent 2,2'-bipyridine (L) as a ligand under normal condition atmosphere (Devi *et al.*, 2023). The lowest yield of 12% was reported with combination of $Pd(OAc)_2$, TFA, 2,2'-bipyridine in THF under normal condition atmosphere. When solvent was changed to toluene, reaction yield improved to 56%. The change of Ligand to bidentate N-ligands lowered the reaction yield. When reaction took

place under O_2 atmosphere reaction yield increased drastically to 81% with TfOH as an additive and toluene as a solvent. No product was obtained either absence of Pd-catalyst or the absence of ligand. The reaction condition of the above scheme 3: 1a (0.3 mmol), 2a (0.6 mmol), Pd-catalyst (10 mol %), ligand (20 mol %), additive (2 eqv), solvent (2ml), 90°C, 24h, under O_2.



In more detail under optimized conditions, first, the cascade reaction of 1(a) with different arylhydrazines was studied, and then the cascade reaction with different O-aminocinnamonitrile was studied. The steric effect of substituents greatly influenced the reaction yield, reaction with para and meta-tolyl-hydrazine gave moderate to high yield (Jing *et al.,* 2020).

The substrate with moderate electron-withdrawing halogens afforded a moderate yield of42-76%. It turned out, the reaction output was altered when substituted O-amino-cinnamonitriles reacted with arylhydrazines. The R_1 substituted either with electron-withdrawing or electron-donating species supported corresponding products having fair yield and R_2 when substituted with ethyl, isopropyl, and phenyl gave corresponding products in 71%, 62%, and 57 % (Fig. 2).

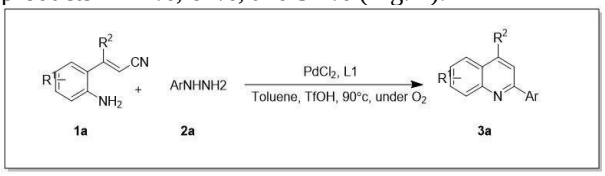
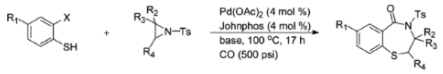


Fig. 2.

Pd-Catalyzed carboxamidation, aldol and carbonylation cascade reaction

1, 4-Benzothiazepin-5-ones- synthesis. The synthesis of 1,4-benzothiazepin-5-ones from N-Tosyl Aziridines and 2-Iodothiophenols is a valuable process. These compounds, known as 1,4-thiazepinones, have shown great potential in various biological and pharmacological applications, such as calcium channel blockers, antitumor agents, and antidepressants.

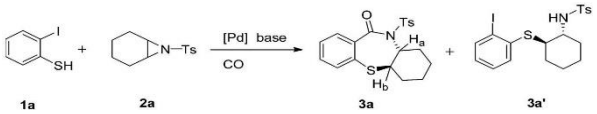
The traditional methods to make 1,4-thiazepinones have some drawbacks, like the formation of unwanted by-products and harsh reaction conditions, leading to low yields and multiple steps. To overcome these issues, researchers have developed a more efficient approach using a palladium-catalyzed cascade reaction (Fanlong *et al.,* 2011). This method allows the formation of numerous new bonds in one single step, reducing the need for additional reagents, waste generation, separation processes and energy and time consumption. Overall, this new scheme can be beneficial for synthesizing 1,4-benzothiazepin-5-ones with improved yields and selectivity.



Scheme 1(a): Ring-Opening Domino/Carboxamidation reaction of 2-Halothiophenolswith N-Tosyl Aziridines

According to experimental data, conducting the reaction under specific conditions resulted in distinct product outcomes. When using 500 psi of CO gas, 3.0 equivalents of Et_3N, 4 mol % of $Pd(OAc)_2$, and dppf at 100°C for 17 hours, the desired product 3a was not obtained in good yield. Instead, a ring-opening product called 3a' was formed with a 67% isolated yield. However, when employing (2-biphenyl) di-tert-butyl phosphine (Johnphos) as the ligand, the yield of 3a significantly improved to 93% (Fanlong *et al.,* 2010).

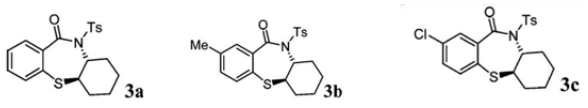
Moreover, using the Xantphos phosphine ligand with 2.0 equivalents resulted in the formation of intermediate 3a' as the main product, indicating that the ligand-to-catalyst ratio plays a crucial role in determining the reaction outcome. These findings highlight the importance of ligand choice and precise reaction conditions in achieving the desired product with high yield.



Scheme 1(b): On improving the reaction conditions for the reaction between 2-iodothiophenol and 7-tosyl-7-azabicyclo[4.1.0] heptane.

Under improved reaction conditions, the N-tosyl aziridine of cyclohexene was reacted with 2-iodothiophenol, 4-methyl-2-iodothiophenol, and 4-chloro-2-iodothiophenol. The corresponding 1,4-thiazepinone compounds 3a-c were obtained with good yields of 93%, 95%, and 94%, respectively (Fanlong *et al.,* 2010).

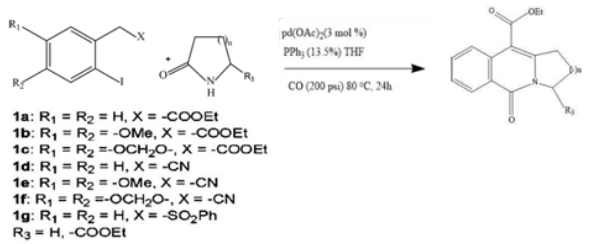
These results demonstrate that the reaction is versatile and can tolerate different substituents on the phenyl group of the thiophenol, regardless of whether they are electron-donating (e.g., methyl) or electron-withdrawing (e.g., chlorine) groups. The ability to incorporate various substituents expands the potential for synthesizing diverse and functionalized thiazepinone compounds.



The synthesis of 1,4-benzothiazepin-5-one compounds using a one-pot palladium-catalyzed tandem ring-opening/carboxamidation reaction is very exciting. This method offers a flexible, practical, and straightforward way to create these sulphur-containing compounds, which could have valuable applications in various fields (John *et al.,* 2011).

Synthesis of Isoquinolinone. Isoquinolinone is a heterocyclic aromatic organic compound. Isoquinolinone has a great importance in synthetic as

well as biological (medicinal) importance. Isoquinolinone is a heterocyclic aromatic organic compound. However, this method gives low product yield. But unlike others it is seen that one-pot domino N-amidoacylation/aldol-type condensation processes show otherwise results. Gagan Chouhan and Howard Alper reported a novel pd-catalyzed cascade carboxamidation/aldol condensation reaction of 1, 2 and CO to quick access to various ring-fused isoquinolinone, under optimized reaction condition gives 95% yield and K_2CO_3 as base with THF as solvent at 80°C. After achieving proper condition for the reaction, they further explored and found out that along with six-seven membered ring lactams, 2-piperidone and caprolactam gave fused Isoquinolinone in a fair yield (Gagan *et al.*, 2008).



Scheme 2a: The pd-catalyzed carboxamidation/aldol condensation, using active methylene compounds 1 and lactams 2.

Upon applying the palladium-catalyzed carboxamidation and aldol condensation cascade reaction to an electron-rich substrate in combination with lactam 2-pyrrolidone, the researchers observed exclusive formation of the carboxamidation product. However, by using a stronger base such as Cs_2CO_3, achieved the desired product in a high yield of 90% (Gagan *et al.*, 2008). This method demonstrates great potential for molecular manipulation, which could prove valuable in pharmaceutical and medicinal research activities.

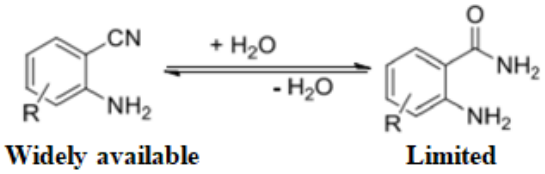
Through a series of experiments, the studies successfully identified the optimal conditions for the cascade reaction. It is found that using 1.5 mol % of Pd(OAc)2 at 100 psi CO pressure for a reaction time of 4 hours yielded the most favorable results (Gagan *et al.*, 2009). Additionally, PdCl2(PPh3)2 was identified as the most effective palladium catalyst, providing almost complete conversion to the desired product 5b. Further investigations involving various active methylene compounds resulted in the synthesis of a diverse array of ring-fused oxazolo-isoquinolinones and pyrazolo-isoquinolinones in the presence of Pd(OAc)2.

The obtained products from these cascade reactions contained different functional groups, allowing for additional modifications and molecular manipulations of these intriguing nitrogen-containing heterocycles. This versatile methodology opens exciting possibilities for creating a broader range of diverse and functional compounds with potential applications in various fields.

Carbonylation reaction

Quinazolinones synthesis using 2-Amino-benzonitriles and Aryl Bromides. 2-aryl quinazolin4(3H)-ones (quinazolinones) considered valuable group of compounds showing various biological activities, including anticancer, antiviral, anti-inflammatory, and antimicrobial properties. The conventional methods for their synthesis involve reacting 2-aminobenzamide with acyl chlorides or benzyl alcohols, however, due to limited availability of 2-aminobenzamide derivatives restricts the variety of products (Li *et al.*, 2014).

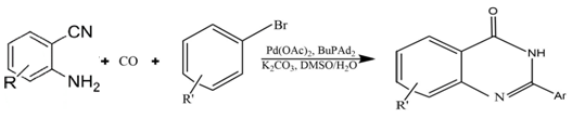
A more efficient approach using palladium-catalyzed carbonylation to synthesize quinazolinones using aryl bromides and 2-aminobenzamide could be a better solution. However, there are minimal variations possible on the 2-aminobenzamide part, which limits the range of products that can be obtained. An attractive substitute to 2-aminobenzamide is 2-aminobenzonitrile also its derivatives are broadly available.



Scheme 4(a): Functional Group Transformations.

Carbonylation reactions are useful for preparing compounds with carbonyl groups, allowing the carbon chain of the parent molecules to be extended and ready for further modifications. In the study, they tested different bases and found that using 2.5 mmol of K_2CO_3 resulted in 85% of 2-phenylquinazolin-4(3H)-ones with complete conversion of the starting material.

The researchers used K_2CO_3 as a cost-effective base in an aqueous solution with a palladium catalyst to produce various quinazolinones in good yields. Under the best reaction conditions [Pd(OAc)2 (2 mol%), BuPAd2 (6 mol%), K_2CO_3 (2.5 mmol), DMSO/H_2O (v/v=1:1; 2 mL), CO (10 bar), 120°C, 16 h], successfully obtained quinazolinones with different substituents, such as methyl, methoxy, Fluoro, and Chloro groups, from their corresponding parent substrates in yields ranging from 55% to 87% (Khan *et al.*, 2015).



Scheme 4 (b): Carbonylative Synthesis of Quinazolinones using 2-Aminobenzonitriles.

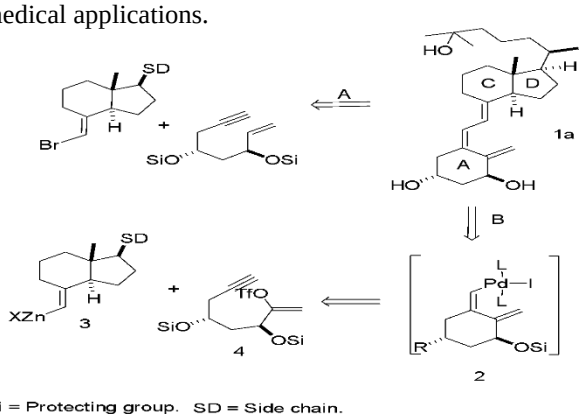
PALLADIUM-CATALYZED CROSS COUPLINGCASCADEREACTION

Negishi Cross-Coupling Cascade. Calcitriol (1α,25-(OH)2-D3) is a biologically active form of vitamin D3 with crucial roles in regulating mineral metabolism. Its therapeutic potential has garnered significant interest among researchers, particularly in treating conditions like osteo-dystrophy, renal failure, rickets, osteoporosis, and psoriasis. Additionally, its analogues are being explored for their ability to influence cell differentiation, inhibit cell growth, and regulate cell death (apoptosis), making them promising candidates for cancer treatment and other diseases involving abnormal cell proliferation.

Efficient approaches to synthesize calcitriol involve convergent methodologies, wherein a preformed ring-A fragment is attached to a cyclohexane-1,2-diol (CD) fragment. Various routes for obtaining this ring-A fragment have been reported. Notably, a successful method involves a Pd(0)-catalyzed alkylation-cyclization reaction, starting from an acyclic unit and a vinyl bromide (referred to as route A in Scheme 1) (Clara *et al.*, 2005).

Furthermore, researchers have developed an alternative approach (route B in Scheme 1) using a one-pot Pd-catalyzed tandem cyclization-Negishi coupling process, which involves an intermediate alkenyl zinc compound (3) and a vinyl triflate (4) to construct the triene unit. (Clara *et al.*, 2005). These innovative synthetic routes open up new possibilities for the production of calcitriol and its analogues, potentially leading to advancements in disease treatment and research.

These methods have proven effective in synthesizing calcitriol and its analogues for further study and potential medical applications.



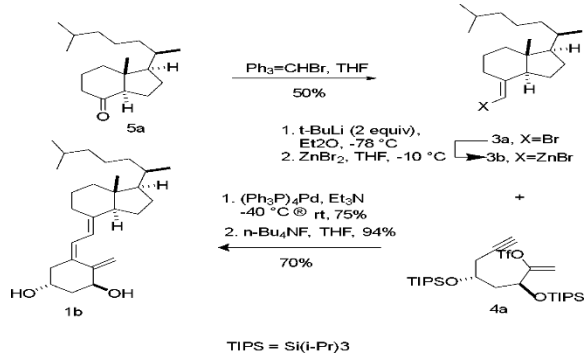
Si = Protecting group. SD = Side chain.

Scheme 1 (A) Trost approach and X (B) new retro-synthetic analysis of 1α-25.

Based on the previous work's results, this research envisioned a new method to synthesize the triene system of calcitriol and its 1-hydroxylated analogues. This method involved a palladium-catalyzed cascade reaction, starting with vinyl triflate 4, after that cross-coupling with an alkenyl zinc derivative.

Calcidiol (1b) is chosen as the initial target to test the feasibility of this new synthetic approach, and prepared the necessary starting material, bromo olefin 3a, from Grundmann's ketone (5a) following Trost's procedure. Vinyl triflate 4a, obtained with 45% yield from l-carvone (Clara *et al.*, 2005).

The cascade reaction was carried out by combining vinyl triflate 4a, Et_3N, and small quantity of tetrakis (triphenylphosphine) palladium(0) with the organo zinc derivative 3b in THF at low temperature (Maestro *et al.*, 2007). After the completion, the desired calcidiol (1b) is obtained with 75% yield from 3a after purification. This method shows promise for the efficient synthesis of calcitriol and its analogues using a convergent strategy.

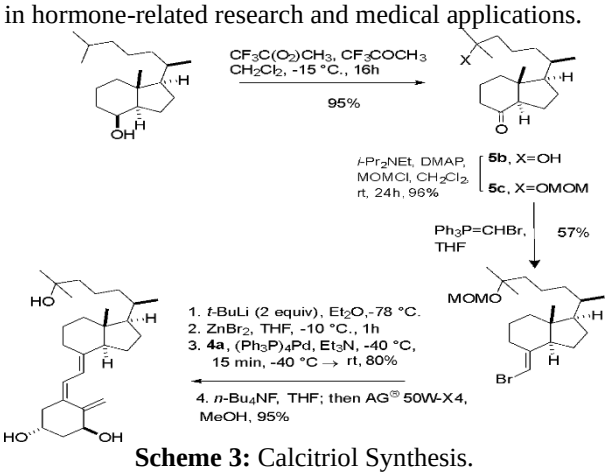


Scheme (2): Calcidiol (1b): A convergent synthesis.

A newly developed strategy to synthesize the natural hormone calcitriol (1α-25-(OH)2-D3), as depicted in Scheme 3.

To initiate the synthesis, here first degraded commercially available vitamin D3 using a known procedure, involving ozone treatment and sodium borohydride, which yielded alcohol 6 in an 84% yield, Surprisingly, when alcohol 6 was treated with methyl-(trifluoromethyl) dioxirane, directly obtained 25-hydroxy Grundmann's ketone (5b) in a high yield of 95%, without any noticeable change in the configuration at C-14.

Proceeding further, protected compound 5b by converting it into the methoxymethyl ether and then conducted bromo olefination to obtain alkenyl bromide3c (in 57% yield, two steps). Subsequently, bromo olefin 3c was transformed into the corresponding organo zinc derivative, which was then reacted with vinyl triflate 4a. By utilizing the palladium-catalyzed cascade reaction and subsequent deprotection steps, successfully obtained the desired hormone calcitriol (1α-25-(OH)2-D3) in a 76% yield (three steps from 3c) or 41% yield (six steps from alcohol 6) (Clara *et al.*, 2005). Importantly, the compound synthesized through this new method exhibited identical spectral data to the material obtained from a different route, confirming its authenticity and purity. This newly developed strategy provides an efficient and reliable approach to synthesize calcitriol, which holds great potential for advancements in hormone-related research and medical applications.



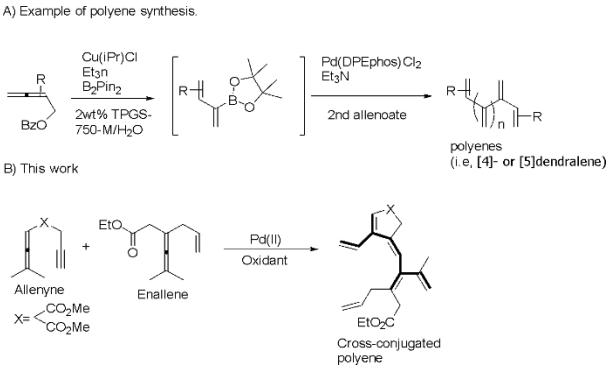
Scheme 3: Calcitriol Synthesis.

Cross-Conjugated Polyene synthesis via Pd-Catalyzed oxidative C-C Bond founding Cascade Reactions of Allenes

In the field of organic chemistry, achieving selective formation of unsaturated molecular frameworks by controlled carbon-carbon (C-C) bond formations poses a significant challenge. Cascade reactions, particularly transition-metal-catalyzed cyclization of allenes, have emerged as efficient and environmentally friendly approaches for synthesizing polyunsaturated molecules. However, the preparation of higher cross-conjugated polyenes in a single step remains limited.

Several esteemed researchers, including Hopf, Sherburn, Shimizu, and the Lipshutz group, have been actively working on acyclic cross-conjugated polyenes. Notably, the Lipshutz group recently made a significant breakthrough by developing a novel tandem borylation/Suzuki-Miyaura reaction for synthesizing cross-conjugated polyenes, including [4]- and [5] dendralene (Scheme 1A). This innovative method opens exciting possibilities for the efficient production of these complex polyenes with specific structural features, representing a promising advancement in the field of organic synthesis.

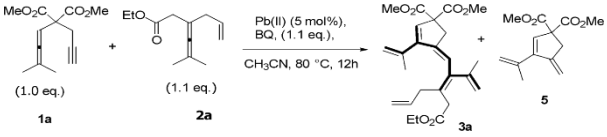
Scheme1: Polyene Synthesis and Proposed study for this Work



In the past decade, some dedicated research group has been focused on exploring palladium(II)-catalyzed oxidative carbo-cyclization reactions of allenes, leading to the synthesis of various [3] dendralenes through C-C bond formation. Despite these advancements, there has been a lack of reported intermolecular cascade reactions between allenes for the one-pot synthesis of cross-conjugated polyenes. As a result, the researchers took on the challenge of investigating palladium(II)-catalyzed oxidative coupling and carbo-cyclization reactions of enallenes with allenynes to produce polyenes (Scheme 1).

In the initial experimental investigations, the research observed that upon treating 1a and 1.1 equivalents of 2a with 5 mol% of Pd(OAc)2 and 1.1 equivalents of benzoquinone (BQ) in dichloroethane (DCE) at 80 °C, they obtained a 64% NMR yield of the desired dendralene derivative 3a with specific regio- and stereo-configuration. Alongside this product, they also obtained 6% of a cyclo-isomerization product 5 (Scheme 2).

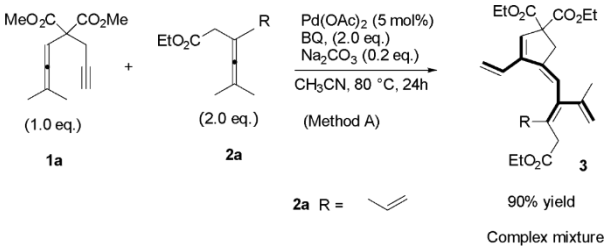
Scheme 2: Reaction optimization



Following the initial results, the research systematically investigated the impact of solvent and palladium(II) catalyst in the reaction. Various solvents were screened with Pd(OAc)2 as the catalyst, and it was found that CH3CN provided the best results, yielding product 3a in 75% yield without forming side product 5. Among the tested palladium catalysts, Pd(OAc)2 showed the highest efficiency, producing 3a in a 60% yield.

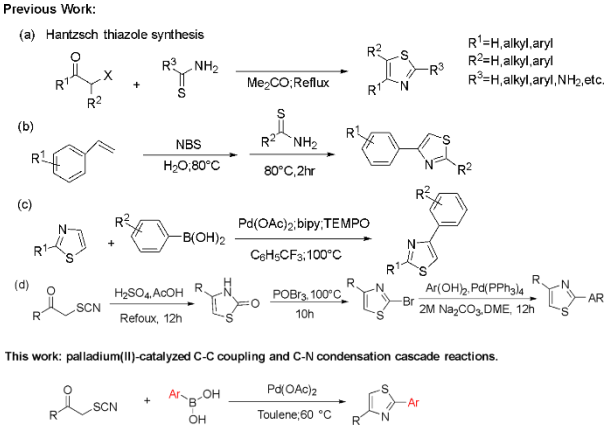
Further optimizations were conducted, and it was discovered that by treating 1a with 1.5 equivalents of 2a using 5 mol% of Pd(OAc)2 and 1.5 equivalents of BQ, the yield of 3a improved to 80%. Subsequently, by increasing the reaction time and employing 2.0 equivalents of 2a with 5 mol% of Pd(OAc)2 and 2.0 equivalents of BQ in CH3CN at 80°C for 24 hours, product 3a was obtained in a significantly improved yield of 94% (Method A, Scheme 3) (Veluru *et al.*, 2020). These optimized conditions provided a more efficient and higher-yielding synthesis of the desired product.

Scheme 3: Comparative Experiment



2,4-disubstituted thiazole cascade via ligand-free palladium (ll) catalyzed C(sp)-C(sp^2) coupling.

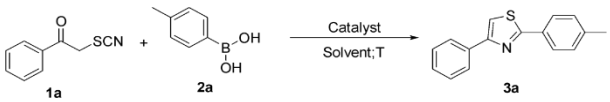
Scheme 1: Synthetic techniques of 2, 4-disubstitutedthiazoles.



Drawing inspiration from previous research, a new method was developed to synthesize 2,4-disubstituted thiazoles. The treatment of compounds 1a and 2a was investigated with Pd(OAc)2 as a catalyst at a temperature of 40 °C in toluene, resulting in the formation of the main product 3a (as shown in Scheme 2) (Zi-Juan *et al.*, 2020).When the reaction temperature was increased to 60 °C, the yield of the product improved to 79%.

However, further increasing the temperature led to a decrease in yield (Yunzhou *et al.*, 2021).

In an effort to further enhance the yields, different Pd catalysts were tested, but none showed better performance than Pd(OAc)2. Additionally, various solvents, such as DMF, MeCN, EtOH, and DMSO, were evaluated, and toluene was found to be the best choice for achieving the highest yield for the reaction (Scheme 2 provides the reaction conditions for 3a).



SUZUKI COUPLING

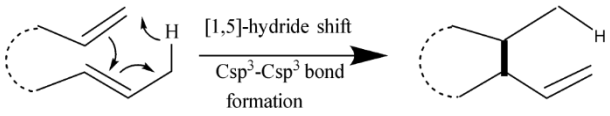
Pd-Catalyzed metallo-ene Cascade/Suzuki Coupling of Allenamides

A novel reaction called "Cascade-metallo-ene/Suzuki coupling reactions of allenamides catalyzed via palladium" has been discovered. This reaction allows the synthesis of various polyfunctional 2,3-dihydropyrrole derivatives with good yields. These polyfunctional pyrroles are highly desirable in biological, pharmaceutical, and organic chemistry fields.

Transition metal-catalyzed cyclization reactions, such as those involving nickel or palladium, are powerful and cost-effective strategies in organic synthesis. In this process, allenamides play a unique role as building blocks, making it possible to create nitrogen-containing heterocyclic compounds. Recently, Pd-catalyzed cyclization Heck reaction of allenamides was also developed, which helps in constructing 1,2,3,4-tetrahydropyridene derivatives.

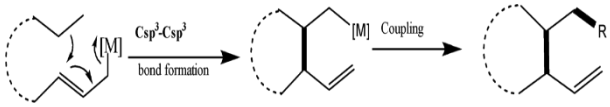
The cascade metallo-ene/Suzuki coupling reaction of allenamides offers a promising alternative to the traditional-ene reaction, which is similar to the Diels-Alder reaction but has limitations due to its higher activation energy. This new reaction allows for better yields and increased versatility in the synthesis of polyfunctional pyrroles.

TRADITIONALENE REACTION

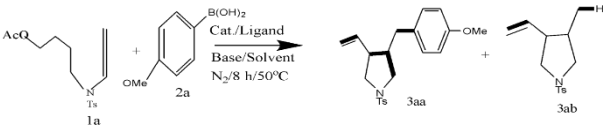


Nowadays, there is a keen interest in catalytic enantioselective metallo-ene processes, which has sparked more attention towards metallo-ene reactions. In this reaction, (1,5) hydride shift occurs, leading to the formation of a new Csp3-Csp3 bond. This process generates a transient alkyl metal intermediate, which then gives rise to a new intermediate (referred to as intermediate 1). This newly formed intermediate can be further modified through coupling reactions, allowing for the introduction of different functional groups.

METALLOENE REACTION

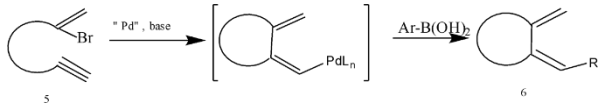


It started by studying cascade reactions using allenamines (1a) and (4-methoxyphenyl) boric acid (2a). The reaction was carried out with 10 mol% of Pd(PPh3)4 and 2.0 eqv. of potassium carbonate in toluene at 50°C in a nitrogen atmosphere. The desired 2,3-dihydropyrrole derivatives 3aa were obtained, but the yield was only 45%. As a result, we explored the use of different solvents for improving the yield of the product.

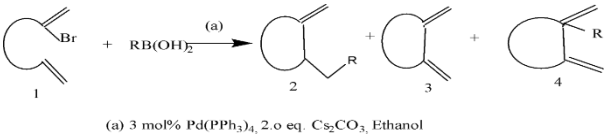


Palladium-catalyzed cascade coupling cyclization reactions of 2-bromo-1,6-enynes with organoboronic acids

A recent report described a process that involves a combination of palladium-catalyzed cyclization and Suzuki coupling. One of the N-Sulfonyl oxygens in the substrates was found to be crucial in stabilizing the alkyl palladium intermediate, preventing beta-elimination reactions and ensuring the success of the reaction (Lei *et al.*, 2015).

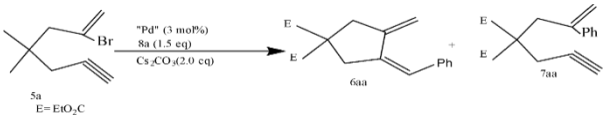


As part of ongoing research on Pd-catalyzed carbo-cyclization of enynes or dienes, recent studies have reported the use of many 2-bromo-1,6-dienes, with organo-boronic acid as given in below reaction's limitation is that beta-elimination of the alkyl palladium intermediate unless they trapped rapidly. So, there is still needed to find a way of successful cyclo-alkylation. For thisuse palladium catalyzed instead of alkyl palladium intermediate for successful one pot cyclization-coupling.

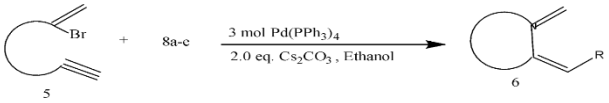


(a) 3 mol% $Pd(PPh_3)_4$, 2.0 eq. Cs_2CO_3, Ethanol

Started with 2-propargyl-2-(2-bromo-allyl)-malonic acid, diethyl ester as a substrate and palladium as catalyst and varying solvents. In this reaction, formation of two products one is cyclized product and second one is direct coupling product as given below.

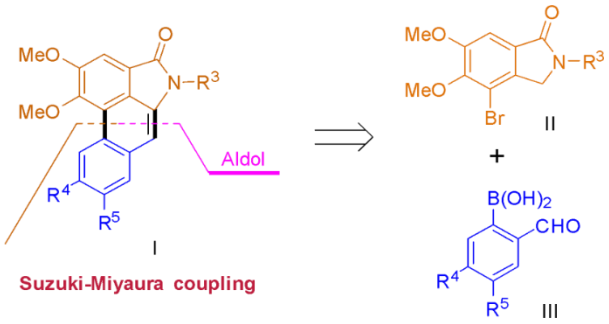


The importance of mineral bases in Suzuki-type cross-coupling reactions is widely acknowledged, although its exact role is still a subject of ongoing discussion. In the cascade cycloalylation reactions of 2-bromo-1,6-enynes with various organoboronic acids, alkenylpalladium intermediates were generated through an intermolecular Heck reaction of 2-bromo-1,6-enynes. These intermediates were subsequently subjected to cross-coupling with different organoboronic acids, leading to the desired products in high yields (Chang, *et al.*, 2003).



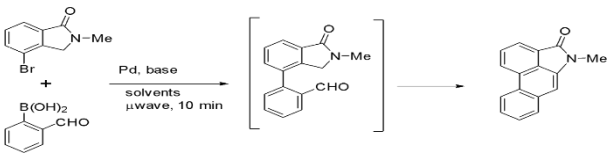
Synthesis of aristolactams via a one-pot Suzuki-Miyaura Coupling/Aldol Condensation Cascade Reaction. Aristolactams are important alkaloids found in various plant species, including Aristolochiaceae. Many efforts have been made to synthesize aristolactams, and pioneering studies by Castedo explored benzene cycloaddition of enamides, among other methods.

The novel synthetic approach involves a crucial discovery, which is the ability to synthesize phenanthrene lactam (i) by subjecting 4-bromoisoindolin-1-one (ii) to a cascade reaction with 2-formylarylboronic acid (iii). This cascade process combines Suzuki-Miyaura coupling and aldol-type condensation reactions, leading to the formation of the desired phenanthrene lactam compound (i). This innovative strategy opens up new possibilities for the efficient synthesis of this valuable compound (Joa *et al.*, 2008).

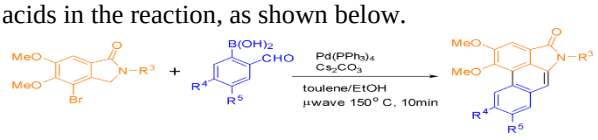


To begin this study, a direct one-pot cascade reaction using 4-bromoisoindolin-1-one and 2-formylphenylboronic acid was conducted under standard Suzuki-Miyaura coupling conditions. During this investigation, researchers tested different palladium catalysts to determine their effectiveness in generating phenanthrene lactam.

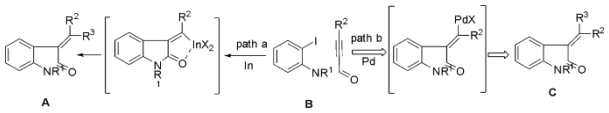
Interestingly, among the various palladium catalysts employed, Pd(PPh3)4 was found to be the most efficient catalyst for facilitating the synthesis of phenanthrene lactam (Joa *et al.*, 2008). Its superior performance in the reaction suggests its potential as a key catalyst for this cascade process.



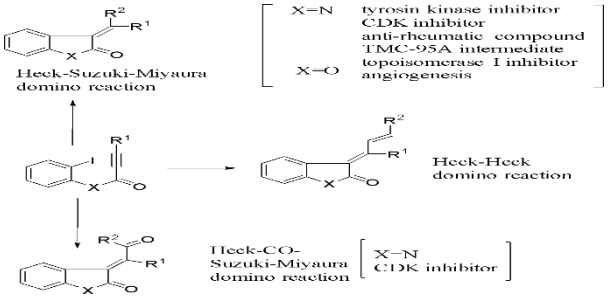
After successfully preparing Isoindolin-1-ones through multiple step reactions, we proceeded to investigate the direct synthesis of aristolactam analogues. In this process, we utilized various 2-formylphenylboronic acids in the reaction, as shown below.



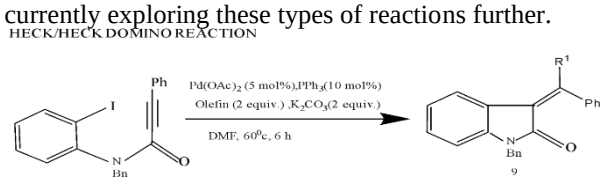
Pd-catalyzed stereo-selective synthesis of 3-Alkylideneoxindoles. Oxindoles are significant compounds found in natural indole alkaloids, with potential as pharmaceutical candidates and biochemical intermediates. Among these, 3-alkyldenoxindoles have gained attention for their biological activity and synthetic applications. Recently, a new and dynamic method is introduced for the stereo-selective synthesis of (E)-, Z-, and disubstituted 3-alkyldeneoxindoles. This involved a subtractive radical cyclization reaction of compound (B) using Indium metal (Reiko *et al.*, 2005). Additionally, we developed a domino reaction triggered by an intra-molecular Heck reaction, enabling synthesis of polycyclic compounds in one single step.



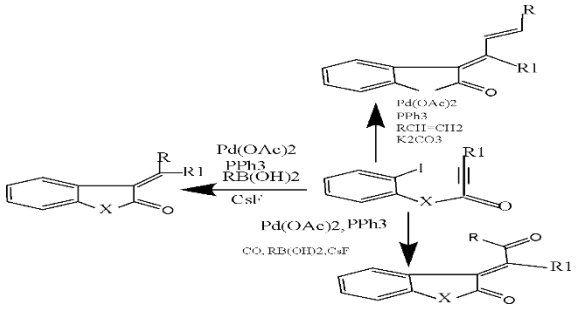
Recently, Cossy's group described a Heck-Suzuki-Miyaura domino reaction for synthesizing (E)-3-alkylideneoxindoles. In another recent study, Muller tried a Heck domino reaction to produce derivatives of 3-alkyldeneoxindoles *(*Reiko *et al.*, 2005). Both of these methods offer efficient and novel approaches to access these important compounds.



After conducting several tests, it was discovered, adding CsF as an additive for boronic acid was suitable for the Heck/Suzuki-Miyaura cascade coupling reaction. Interestingly, it is also observed that using K_2CO_3 as a base led to the creation of a different product. We are currently exploring these types of reactions further.



After all this, when we combine study of all the reaction to determine and find an efficient way for the desired product. Finally, we got this type of reaction mechanism as given.



CONCLUSIONS

In this work, we have pondered and examined the advantages of Pd-catalyzed cascade reaction. We accumulated 100 research papers on Pd-catalyzed cascade reaction and then selected and studied the 30 most relevant of them. Among the many reported methodologies, the palladium-catalyzed synthesis stands out as the most efficient and straight-forward method for preparing heterocyclic compounds likes iso quinolinones. Conducting multiple reactions in a single vessel allows us to create complex molecules from readily available substrates with exceptional efficiency. This approach also reduces the need for additional reagents, separation processes, chemical waste, and overall cost. The products obtained from such cascade reactions hold various functional groups which can further be modified, providing flexibility for additional molecular manipulations.

In recent years palladium-Catalyzed cascade has caught the attention of many organic chemists because of the versatile nature of Pd-catalyst and the high efficacy rate of cascade reaction is because of their atom economic nature. Here Pd-Catalyzed reaction is used for synthesizing various biologically active compounds like quinoline, isoquinoline, indole, bicyclic dihydrofuran, ethers, fused heterocycles, and many more pharmaceutical agents via tandem allylic substitution, heck coupling, Suzuki coupling, C-H bond, activation, carbonylation, aldol condensation, and multistep annulation.

FUTURE SCOPE

The future scope of this study includes.

(i) Catalyst enhancement for better performance.

(ii) Mechanistic understanding through advanced techniques.

(iii) Emphasis on sustainable practices.

(iv) Integration with other catalysts for complex transformations.

(v) Application in drug synthesis and bioactive compound production.

Acknowledgement. We would like to express our sincere gratitude to all the researchers, scholars, and institutions whose contribution in the field of Palladium catalyzed cascade reactions have significantly enriched this review. Their pioneering work serves as the foundation for advancements outlined in this study.

Conflict of Interest. None.

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