An Overview of Palladium-Catalyzed *N*-alkylation Reactions

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N-Alkylation of amines is a vital reaction in the synthesis of numerous bioactive compounds and materials. Among transition metals, palladium has emerged as a particularly effective catalyst for these transformations. The unique advantages of palladium arise from its superior catalytic efficiency, ability to operate under mild conditions, high selectivity and recyclability. Additionally, palladium facilitates the borrowing hydrogen methodology, offering sustainable and environmentally friendly alternatives. This review covers advancements in palladium-catalyzed *N*-alkylation reactions. The mechanistic insights and practical applications are discussed, providing a comprehensive overview of the current state of research and future directions in this field, covering literature up to 2024.

1. Introduction

N-Alkylation is an important reaction in organic chemistry, where an alkyl group is introduced into a nitrogen-containing organic compound, resulting in a more substituted product. This reaction typically involves alkylating agents, and the alkyl group can be transferred in the form of an alkyl carbocation, a free radical, a carbanion, or a carbene.

The field of metal-catalyzed *N*-alkylation has gathered significant attention due to its potential for developing more efficient, sustainable, and environmentally friendly synthetic methodologies.[1] *N*-alkylated amines are essential intermediates in the synthesis of pharmaceuticals,[2] agrochemicals,[3] dyes,[4] herbicides,[5] industrial chemicals,[6] insecticides,[7] and functional materials,[8] making the advancement of their synthesis highly desirable. Traditional methods for *N*-alkylation often involve the use of alkyl halides or carbonyl compounds along with reducing agents.[9,10,11,12,13] These processes can generate substantial waste products and require harsh reaction conditions and there exists potential chances of over-alkylation.

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In recent years, palladium catalysts have emerged as a versatile and effective tool for *N*-alkylation reactions, especially under mild conditions that align with the principles of green chemistry. In comparison to other transition metal-based *N*-alkylations such as ruthenium,[14] iridium,[15] silver,[16] cobalt,[17] nickel,[18] iron,[19] etc., palladium offers distinct advantages such as gentler reaction conditions, high selectivity and efficiency, versatility, and compatibility with eco-friendly practices. This review aims to provide a comprehensive overview of the recent advancements in this field, focusing on the mechanistic insights, catalyst design, and practical applications of palladium-catalyzed *N*-alkylation reactions.

The development of borrowing hydrogen technology has shown promising results in achieving efficiency and reliability for *N*-alkylation at ambient conditions, due to its minimal waste generation and non-requirement of an external hydrogen source. The technique generates water as the only by-product, and alcohols are used as alkylating agents (**Figure 1**). The borrowing hydrogen technology works by dehydrogenation of alcohol and its activation by palladium catalyst, which leads to the *in-situ* generation of hydrogen and aldehyde. The aldehyde then condenses with the primary amine, generating the corresponding imine. If secondary amines are the reactants, then an enamine or iminium ion will be formed. In the final step, imines are activated by the catalyst and then reduced with the hydrogen generated earlier, to produce the desired product which is secondary or tertiary amine.

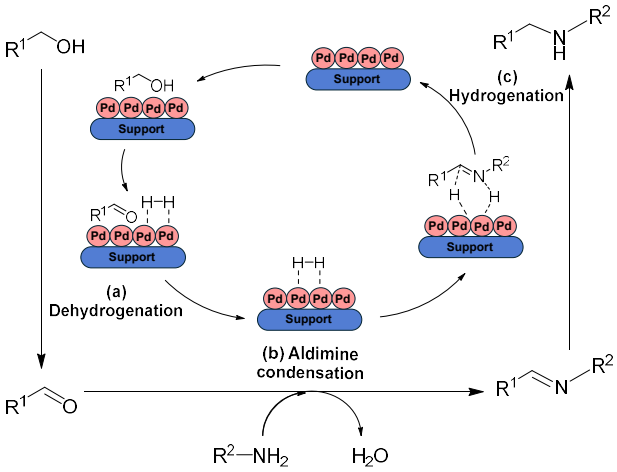


Figure 1: Borrowing hydrogen technology and its sequential steps a) Dehydrogenation, b) Aldimine condensation, c) Hydrogenation.

Despite these advancements, challenges remain in optimizing the efficiency and selectivity of palladium-catalyzed *N*-alkylation reactions. Factors such as the size and dispersion of Pd nanoparticles, the nature of the support material, and the reaction conditions play crucial roles in the overall catalytic performance. Recent studies have highlighted the importance

of controlling these parameters to enhance the activity, scalability, and stability of palladium catalysts.

A review dealing with iron-catalyzed *N*-alkylation reactions was recently published by our group.[20] In the present review, we have summarized palladium-catalyzed *N*-alkylation reactions, and the topic is categorized based on the palladium catalyst employed.

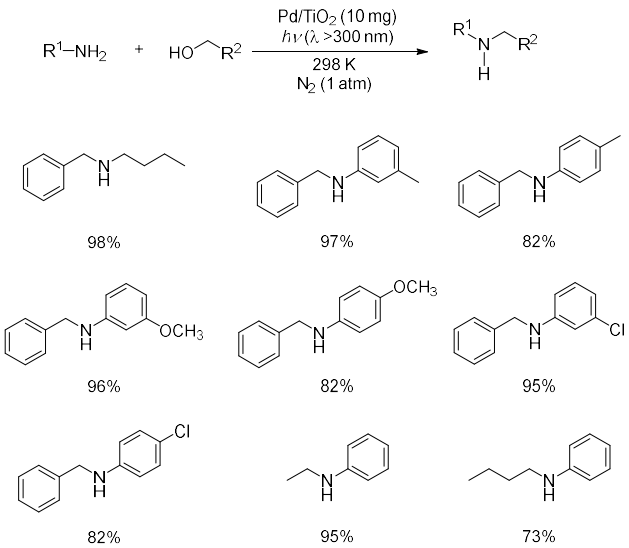
2. Classification

For ease of understanding, the reactions are categorized based on the palladium catalysts as follows: 1) Heterogeneous palladium catalysis, 2) Homogeneous palladium catalysis, and 3) Miscellaneous Reactions. Heterogeneous palladium catalysis is further divided into three subclasses: i) palladium dispersed as nanoparticles, ii) palladium supported on metal/metalloid oxides, and iii) palladium supported on carbon. Homogeneous palladium catalysis includes subcategories such as i) pincer-type ligands, ii) phosphorus-based ligands, and iii) ligand-free reactions.

2.1 Heterogeneous Palladium Catalysis

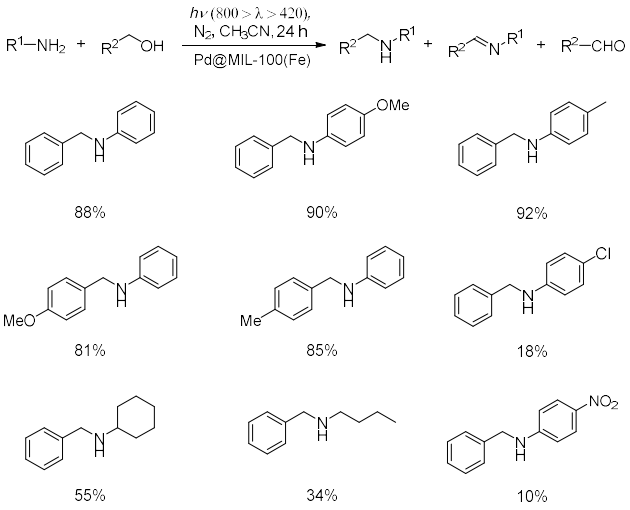
2.1.1 Palladium Dispersed as Nanoparticles

In 2013, Shiraishi and co-workers developed a tandem photocatalytic system for *N*-monoalkylation of amines with alcohols using TiO_2 loaded with Pd nanoparticles, where photocatalysis occurs through the generation of electron-hole pairs in TiO_2 under light irradiation.[21] The catalyst was highly efficient for a range of benzyl- and alkyl alcohols with various primary amines, yielding secondary amines in good to very high yields (**Scheme 1**). Notably, Pd nanoparticles of 2-2.5 nm size were found to be most active, leveraging a tandem mechanism of photocatalytic alcohol oxidation, imine formation, and hydrogenation. This system offered several advantages, including room temperature reactions, the absence of harmful side products, and excellent catalyst reusability.



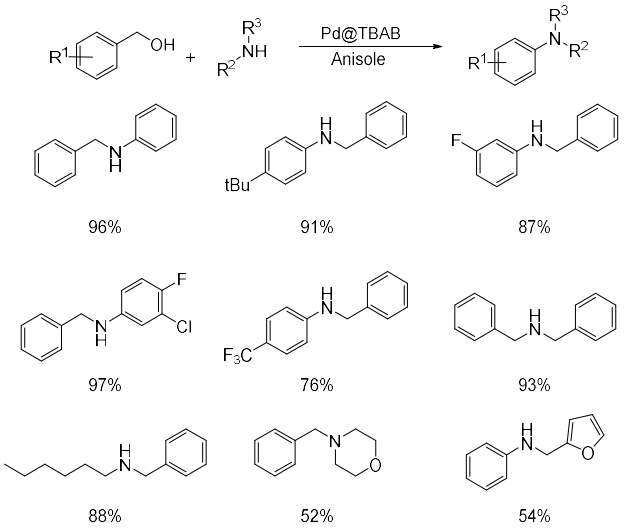
Scheme 1. *N*-Alkylation of various amines with alcohols under photoirradiation with Pd/TiO_2 catalyst.

Li and Wang discovered a novel approach for the *N*-alkylation of amines with alcohols by employing palladium nanoparticles encapsulated in a metal-organic framework [Pd@MIL-100(Fe)] under visible light irradiation.[22] The method demonstrated greener synthetic potential for nanocomposites, as the reaction was devoid of harsh environments and toxic by-products. It was found that this palladium catalyst showed superior activity as compared to Pd/Fe_2O_3, Pd/TiO_2, and conventionally prepared Pd nanoparticles were deposited on the surface. A detailed study of the mechanism showed that dehydrogenation of alcohol was the rate-limiting step, and palladium and metal-organic framework showed a mutualistic relation in activating the alcohol, like a semiconductor photocatalyst under irradiation. Several substituted alcohols and amines were tested, and it was found that the yields were significantly affected by the electronic nature of the substituents (**Scheme 2**). The catalyst could be reused even after five cycles with no significant loss in activity.



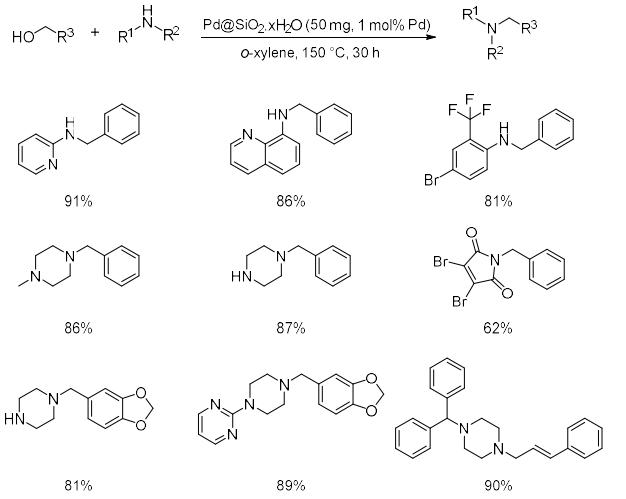
Scheme 2. Substrate scope for the *N*-alkylation of amines with alcohols using Pd@MIL-100(Fe) under visible light irradiation.

A new method that uses hybrid palladium nanocatalysts for the *N*-alkylation reaction was illustrated by Pucheault and co-workers.[23] Palladium nanoparticles were produced in onium salts using ionic liquids along with supercritical carbon dioxide. *N*-Alkylation of amines with different alcohols exhibited remarkable results (**Scheme 3**). Substituted amines showed excellent yields with electron-donating groups, whereas a slight decrease in yield was observed for electron-withdrawing groups and a lack of conversion for *ortho*-substituted ones. Different alcohols were also tested, and good yields were observed for electron-donating and electron-withdrawing groups. Furthermore, the catalyst was made heterogeneous by coating it onto silicon carbide and carbon supports, which allowed for easy separation and reuse, especially with silicon carbide, which maintained high efficiency and recyclability, achieving nearly quantitative yields over several cycles.



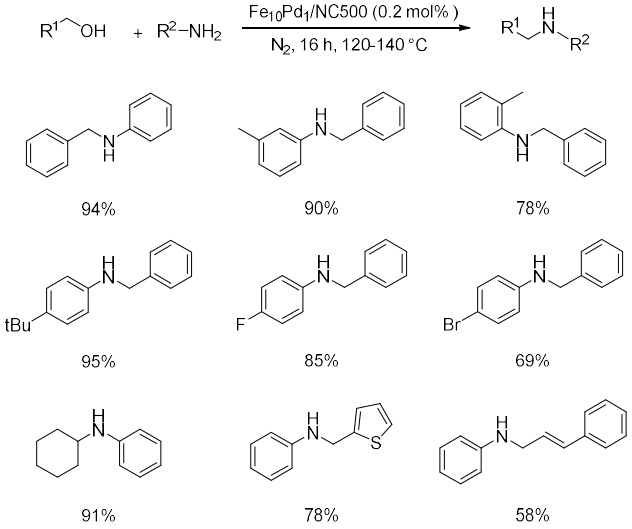
Scheme 3 Substrate scope for the *N*-alkylation of amines with alcohols using Pd@[nBu$_4$][Br] as the catalyst.

Jagadeesh *et al*. demonstrated an efficient way of conducting *N*-alkylation using silica-based palladium catalysts.[24] For this, palladium-based nanoparticles were prepared by reducing the salt of palladium on commercial silica. Similarly, Pd-NPs supported on lab-prepared meso-SiO_2 and commercial SiO_2 were also synthesized. This catalyst was used to conduct an *N*-alkylation reaction between different amines and alcohols (**Scheme 4).** The catalyst was found to have no leaching of Pd upon recycling and was reused without loss of significant activity up to six times.



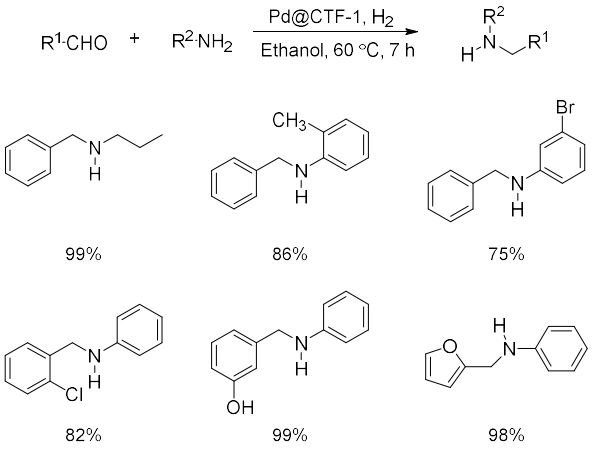
Scheme 4. *N*-Alkylation of different amines with alcohols, catalyzed by Pd@SiO_2.

Cai and co-workers synthesized a bimetallic catalyst (Fe-Pd) and reported its excellent performance in the *N*-alkylation of alcohols with amines.[25] A novel bimetallic catalyst $Fe_{10}Pd_1$/NC500 was synthesized from MOF (metal-organic framework) NH2-MIL-101(Fe10Pd1) using a hydrothermal route and later by pyrolysis. The products were obtained with very good yields when alcohol was reacted with amine at 120 °C under a nitrogen atmosphere (**Scheme 5)**. The *para*- and *meta*-derivatives of toluidine were obtained in excellent yields, whereas steric hindrance caused lower yields for *ortho*-toluidine. Anilines that bear electron-donating groups gave more promising yields than those with electron-withdrawing groups. Efficient conversion for polycyclic aromatic and heterocyclic reactants were also observed. The bimetallic catalyst was found to show advantages over monometallic catalyst due to synergic effects thereby requiring no external base and hydrogen source. The recycled catalyst was found to be stable for up to eight runs.

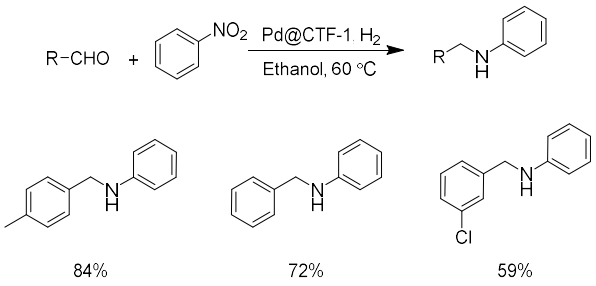


Scheme 5. *N*-Alkylation of alcohols with amines using $Fe_{10}Pd_1$/NC500 catalyst.

Dong and the group reported an easy preparation of palladium nanoparticles (Pd-NPs), which were anchored on CTFs (covalent triazine frameworks) and observed high catalytic activity for *N*-alkylation reactions.[26] The catalyst was utilized in the reaction between amine and benzaldehyde derivatives in the presence of hydrogen gas (1 atm) in ethanol solvent at 60° C for 7 h (**Scheme 6**). The alkylation was proposed to occur in two steps, the first being the condensation reaction to form imine and the second, the hydrogenation reaction to form the final C-N bond. Substrates that are electron-rich and less sterically hindered showed better conversion and selectivity rates. The reaction was also performed with nitrobenzene instead of aniline, which also offered the product (**Scheme 7**). The catalyst was recovered and washed with ethanol and ultrapure water alternatively and thoroughly, for testing its recyclability. The catalyst exhibited excellent selectivity and conversion even after seven cycles of reaction.

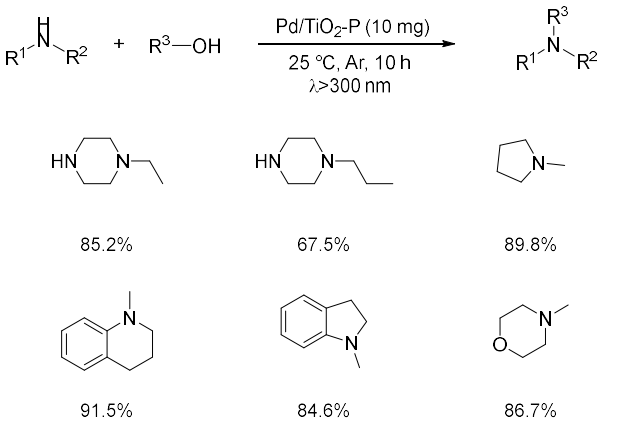


Scheme 6. Substrate scope of amines and benzaldehydes in the *N*-alkylation reaction catalyzed by Pd@CTF.

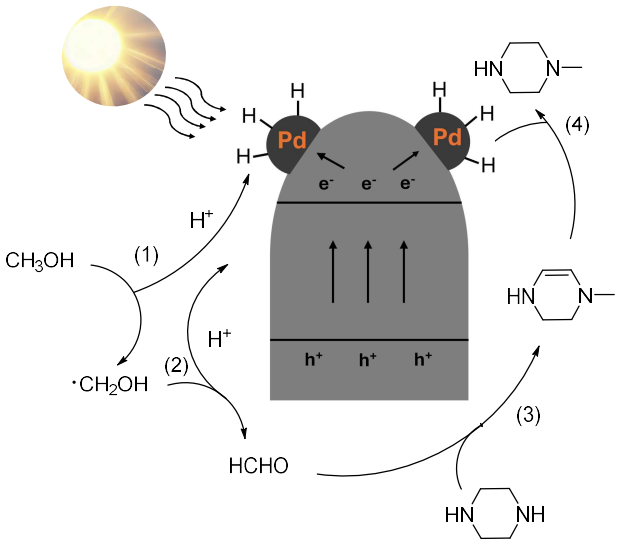


Scheme 7. Substrate scope of benzaldehydes in the *N*-alkylation of nitroarene catalyzed by Pd@CTF.

Yuan *et al.* performed the mechanistic investigation of light-induced *N*-alkylation of piperazine with simple alcohols using palladium nanoparticles supported on TiO_2 *via* borrowing hydrogen methodology.[27] Among all the catalysts and supports evaluated, Pd/TiO_2-P, prepared *via* the photodeposition method, demonstrated the best catalytic performance with an optimal palladium loading of 1.0 wt% for the best conversion and selectivity. Kinetic studies revealed that cleavage of the α-C–H bond of methanol was the rate-determining step in the *N*-methylation reaction. Various *N*-heterocyclic compounds were efficiently *N*-alkylated with different alcohols (**Scheme 8**). Additionally, a light-driven mechanism for the N-methylation of piperazine was proposed (**Scheme 9**). The process starts with methanol being oxidized by photogenerated holes, forming hydroxymethyl radicals (·CH_2OH) and protons (H^+), which are further dehydrogenated to formaldehyde. The protons bind with Pd nanoparticles and combine with photogenerated electrons to create Pd-H species. Piperazine then condenses with formaldehyde to form an enamine, which Pd-H subsequently hydrogenates to produce *N*-alkylated piperazine. The catalyst also showed good stability and reusability, with a slight decrease in conversion rates after four cycles, and no change in selectivity.



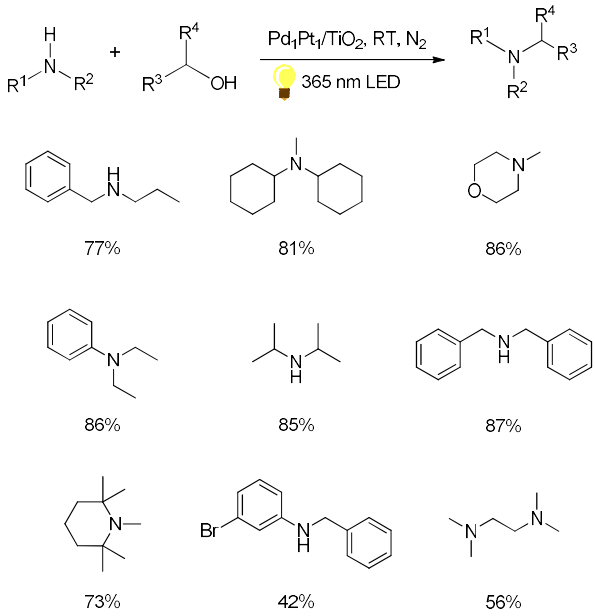
Scheme 8. Substrate scope for photocatalytic *N*-alkylation of *N*-heterocyclic amines with alcohols



Scheme 9. Proposed light-driven mechanism for the *N*-alkylation of piperazine with methanol using Pd/TiO_2.

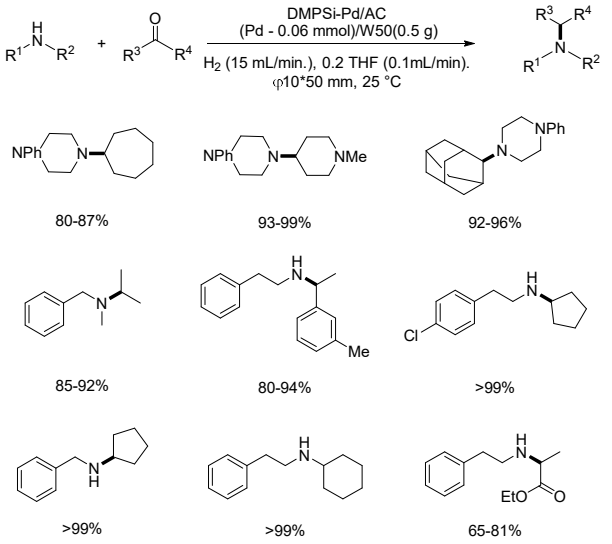
A protocol for the photocatalytic *N*-alkylation of amines with alcohols by employing a novel bimetallic Pt-Pd supported on TiO_2 was put forth by Zhou *et al.*[28] The bimetallic Pd–Pt nanoparticles exhibit a synergistic effect that significantly enhances the photocatalytic activity due to the combined properties of Pd and Pt. Among the different compositions tested, the Pd_1Pt_1/TiO_2 catalyst demonstrated the highest catalytic activity. The photocatalytic system, tested with a range of aromatic and aliphatic amines and alcohols, achieved moderate to excellent yields of the corresponding products (**Scheme 10**). Here, Pd serves as the primary site for hydrogenation, reducing imines to amines. The roles of Pt and Pd were such that Pt promotes the initial photoactivation of alcohols while Pd drives the hydrogenation process and enhances the overall efficiency of the catalytic process. Compared to the previously reported catalysts, Pd_1Pt_1/TiO_2

showed superior catalytic efficiency for the condensation of alcohols and amines.



Scheme 10. Substrate scope for the photocatalytic *N*-alkylation of amines with alcohols over Pd_1Pt_1/TiO_2.

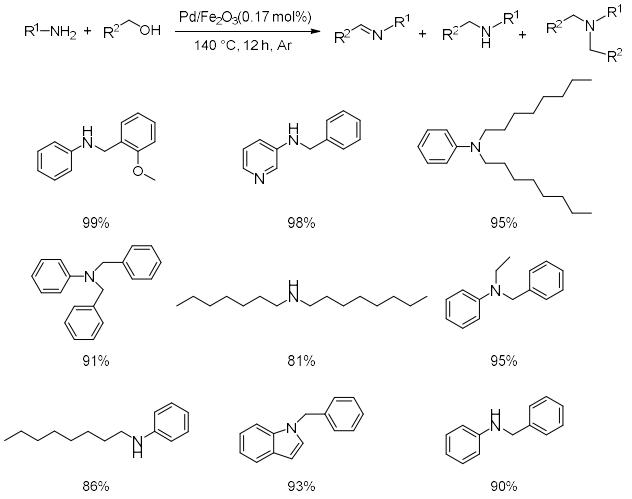
A methodology for the reductive *N*-alkylation of ketones, which are generally less reactive and relatively unexplored as compared to aldehydes, was recently developed by Kobayashi *et al*.[29] They used a continuous flow system with a novel palladium-polysilane catalyst under mild conditions of room temperature and hydrogen at atmospheric pressure. The reaction was optimized with palladium nanoparticles with a loading of 0.05 mmol/g, dispersed on activated carbon, and modified with dimethylpolysilane (DMPSi) under continuous-flow conditions at a flow rate of 0.1 mL/min. using a 0.1 M substrate solution in THF **(Scheme 11)**. The method was applicable to a wide range of secondary amines and ketones, including both cyclic and acyclic variants to produce desired products in excellent yields. The practical utility of this method was demonstrated through the synthesis of an intermediate for teneligliptin, a diabetes drug.



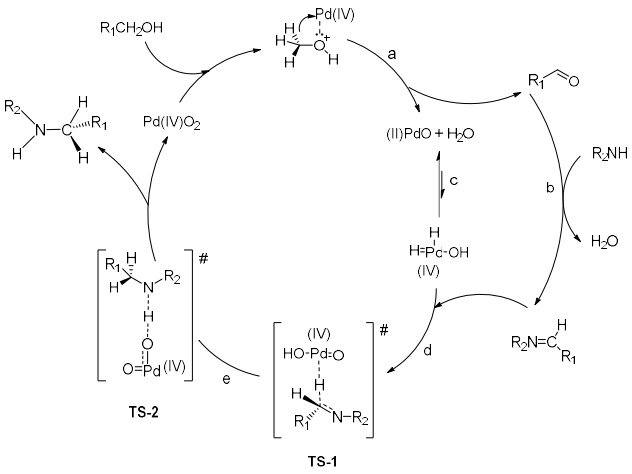
Scheme 11. Substrate scope for the *N*-alkylation of secondary amines with ketones using DMPSi-Pd/AC using a continuous flow system

2.1.2 Palladium supported on metal and metalloid oxides

Shi and co-workers put forward a new method for the *N*-alkylation of amines using alcohols by employing palladium supported on immobilized iron oxide in the absence of organic ligands and bases.[30] Good to excellent yields were obtained, and the selectivity and conversion could be tuned by adjusting the ratio of reactants (**Scheme 12**). They have proposed a mechanism for the *N*-alkylation reaction, which is shown in **Scheme 13**. The proposed mechanism involves a borrowing hydrogen process and begins with alcohol oxidation to a carbonyl compound, forming 'PdO'. The carbonyl then reacts with the amine to form an imine, while a reversible cycle occurs between 'PdO' and the Pd(O)(H)(OH) species. Hydride palladium adds to the imine, leading to product release and regeneration of 'PdO_2'. The catalyst was recovered and reused for the second time, and it showed a remarkable rate of conversion and selectivity.

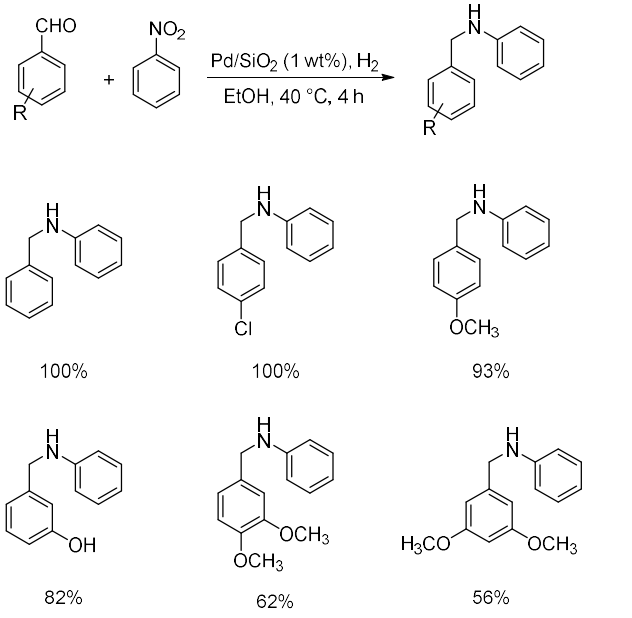


Scheme 12. Substrate scope for the *N*-alkylation of amines using Pd/Fe_2O_3 catalyst.



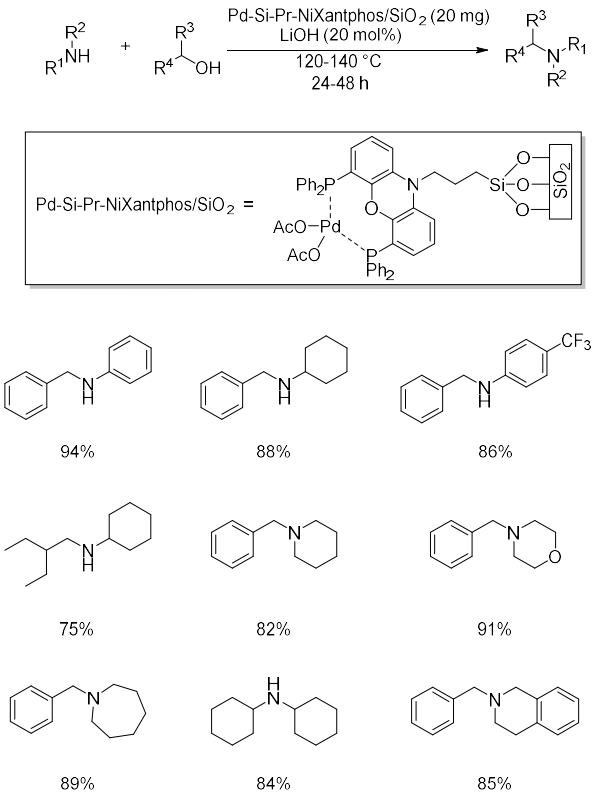
Scheme 13. Proposed mechanism for the palladium-catalyzed *N*-alkylation of amines using Pd/Fe_2O_3 catalyst.

Ma and co-workers disclosed a novel strategy for the one-pot synthesis of secondary amines by using a palladium-based catalyst (Pd/SiO_2).[31] The reductive *N*-monoalkylation of nitro aryls with aromatic aldehydes resulted in the formation of *N*-benzylanilines (**Scheme 14**). The source of H_2 was the atmosphere. The reaction was affected by the structural and electronic properties of substituents present in the aldehyde. Aldehydes with single substituent gave almost quantitative yield. An excellent conversion rate was obtained during the reaction with aliphatic and nitro compounds. Imines formed from nitronaphthalene and aromatic aldehydes were more stable as compared to others. The catalyst was easy to separate by filtration and was reused without much loss in its activity.



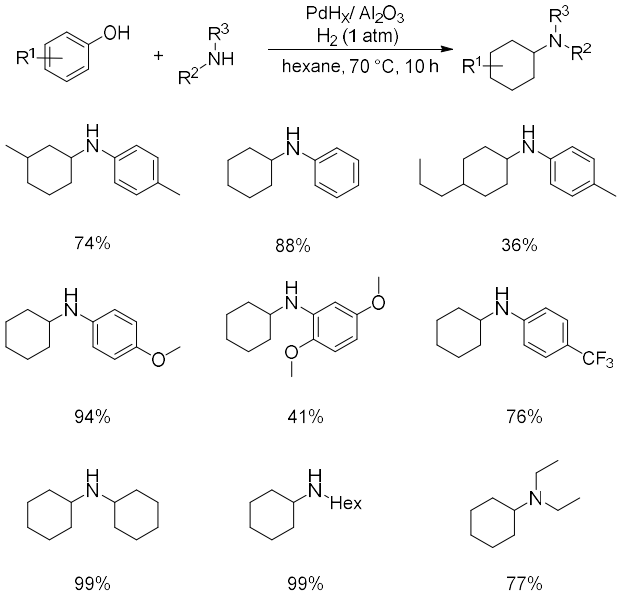
Scheme 14. Pd/SiO_2-catalyzed *N*-alkylation of nitroarenes with different aldehydes.

Seayad and co-workers developed an efficient catalyst, palladium-NiXantphos complex supported on silica, and observed promising turnover numbers for the *N*-alkylation of amines and α-alkylation of ketones.[32] The catalyst was prepared by immobilizing NiXantphos on solid silica support and by adding a palladium precursor ($PdCl_2$ or $Pd(OAc)_2$). The optimum yield was achieved by utilizing 0.0105 mol% of the catalyst along with 20 mol% of LiOH at a temperature of 120 °C (**Scheme 15**). Here, turnover numbers even reached 46000 for the *N*-alkylation of aniline with benzyl alcohol.



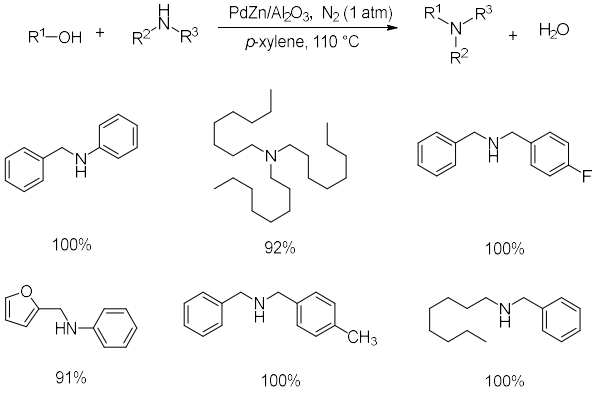
Scheme 15. Substrate scope for the *N*-alkylation of amines employing heterogeneous palladium catalyst supported on SiO_2.

Fu and co-workers prepared a bi-functional palladium hydride (PdH_x) catalyst supported over Al_2O_3 and observed its efficiency in the *N*-alkylation of lignin-derived phenols under mild reaction conditions.[33] The catalyst was found to be stable even after 5 cycles of reaction. It was found that nonpolar solvents showed a better conversion rate for the reaction. Phenol was absorbed and converted to cyclohexanone intermediate before undergoing reductive amination. The *N*-alkylation of different amines and phenols was carried out under the optimized reaction condition (**Scheme 16**). The yield of the desired products was diminished by the steric effects of substituents. Anilines containing either electron-withdrawing or electron-donating groups were suitable for the reaction.



Scheme 16. Substrate scope for the reductive amination of phenols.

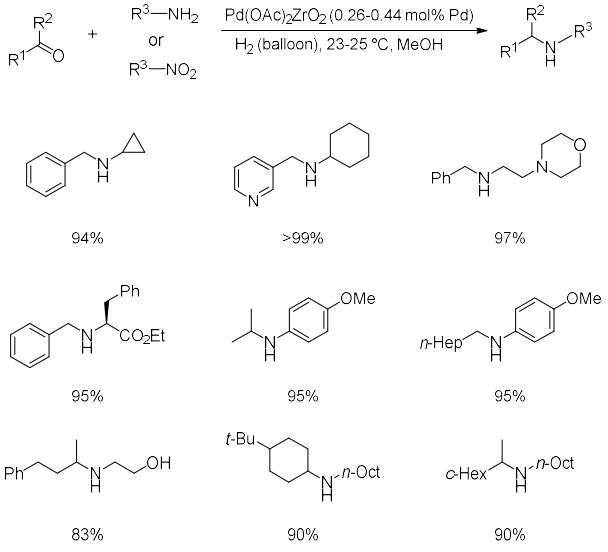
In 2016, Furukawa *et al.* reported the utilization of a palladium-based intermetallic catalyst supported by Al_2O_3 (Pd_xM_y/Al_2O_3) for the *N*-alkylation of amines.[34] The scope of the catalyst was investigated with different metals, where M = Fe, Bi, Ga, Cu, In, Zn, Pb, and Sn. The model substrates used were benzyl alcohol and aniline. Higher yields were obtained with PdCu and Pd_2Ga. A much lower yield was obtained with other Pd-based intermetallic catalysts of Sn, In, Fe, and Bi. PdZn exhibited a good conversion as well as very high selectivity (**Scheme 17**).



Scheme 17. $PdZn/Al_2O_3$ catalyst for the *N*-alkylation of different amines.

Motoyama *et al*. reported palladium complexes dispersed on zirconia (ZrO_2) as an efficient catalyst for the *N*-alkylation of amines and carbonyl compounds.[35] The *N*-alkylation proceeded under mild conditions and tolerated a wide range of substrates which were efficiently converted to the corresponding products (**Scheme 18**). Even though sterically hindered amines required longer reaction time for good yields, the catalyst demonstrated versatility, exhibiting broad functional group tolerance. Detailed insights into the structure of Pd species on ZrO_2 using

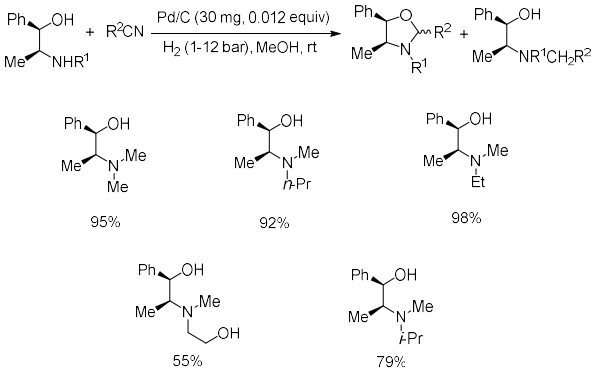
X-ray absorption fine structure (XAFS) revealed that the support donates electrons to Pd atoms, and the Pd species on ZrO_2 includes aggregated hydroxide complexes with electron-rich Pd centers. Pd-O coordination influences the electron density and enhances the catalytic properties. The catalyst can be recycled multiple times, although, over time, the size of Pd clusters increases, leading to a gradual decrease in catalytic activity.



Scheme 18. Substrate scope for the *N*-alkylation of amines and nitroarenes with aldehydes and ketones under $Pd(OAc)_2ZrO_2$ catalysis.

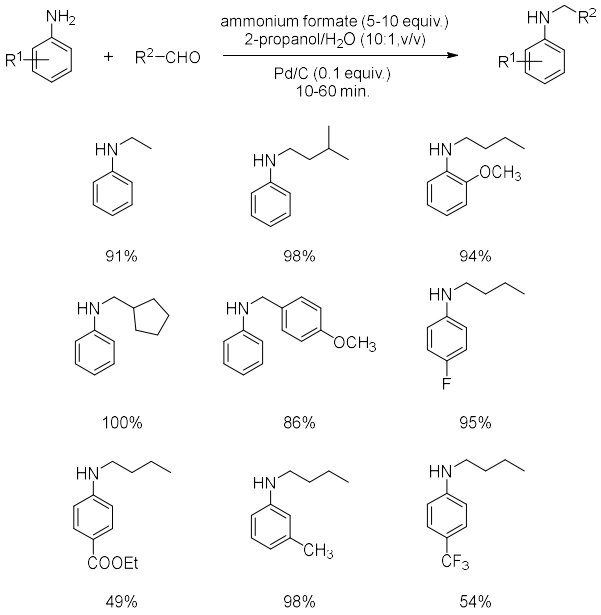
2.1.3 Palladium supported on Carbon

Pd/C, being ubiquitous, easily recyclable, having low chances of contamination, and not requiring any additional ligands, is an excellent choice as a catalyst. A novel method for the *N*-alkylation of 1,2-amino alcohols to form 1,3-oxazolidines and tertiary amino alcohols was reported by Muzart *et al.*[36] Here, *N*-alkylation was achieved by using nitriles for condensation instead of conventional aldehydes or acetals with palladium on charcoal under hydrogen atmosphere **(Scheme 19)**. It was observed that the tertiary amino alcohol was produced by the cleavage of the NC-O bond. The nature of the solvent influenced the efficiency of the *N*-alkylation process. After optimizing the reaction in methanol, different nitriles were reacted with 1,2-diamino alcohols to give excellent yields of the corresponding *N*-alkylated products. Nonetheless, both benzyl-cyanide and isopropyl-cyanide were hesitant to react under simple hydrogen atmosphere conditions and required the use of high-pressure hydrogen in a stainless steel bomb.

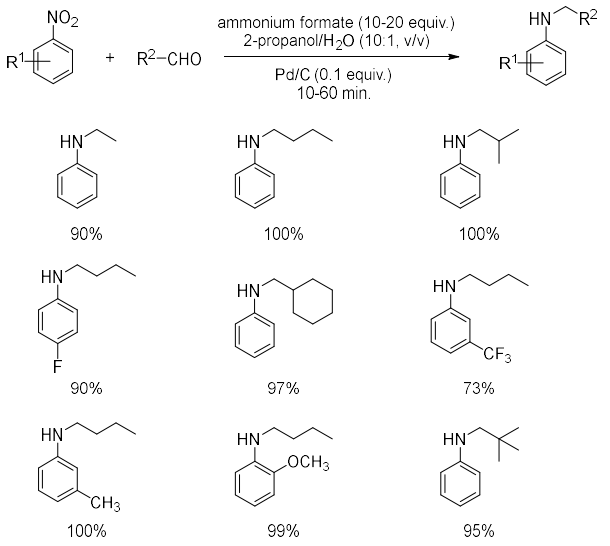


Scheme 19. Substrate scope of different nitriles in the *N*-alkylation of 1,2-amino alcohols

Rhee and co-workers demonstrated an efficient protocol for the mono *N*-alkylation of aniline and nitriles with aldehydes using Pd/C in a one-pot reductive manner, aided by the *in-situ* donation of hydrogen from ammonium formate.[37] The reaction yield was optimized by using 2-propanol/water as the solvent and could obtain excellent yields (**Scheme 20**). In the case of nitriles, the starting material was first reduced to the corresponding aniline (**Scheme 21**). While the *N*-alkylation of substrates containing electron-donating groups proceeded very smoothly, some electron-withdrawing groups showed unsatisfactory yields. This might be due to the stable imine formed in the case of electron-withdrawing groups, hence causing backward reaction which competes with hydrogenation and decreasing the yield. Nevertheless, this protocol showcased an innovative and eco-friendly approach involving cost-effective, convenient, and safe reaction conditions.

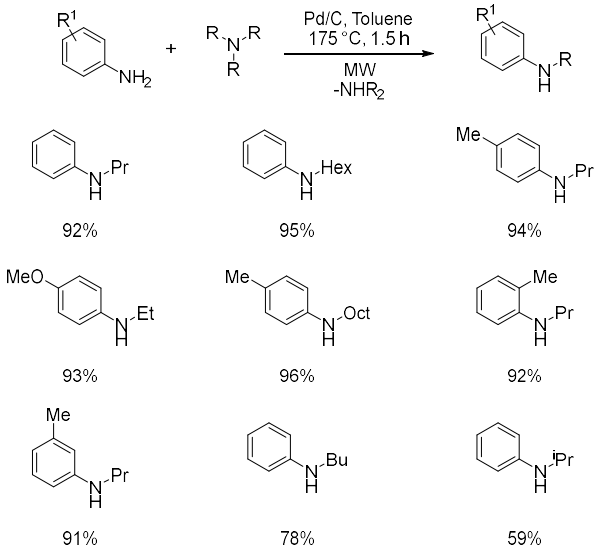


Scheme 20. One-pot mono *N*-alkylation of amines with aldehydes.



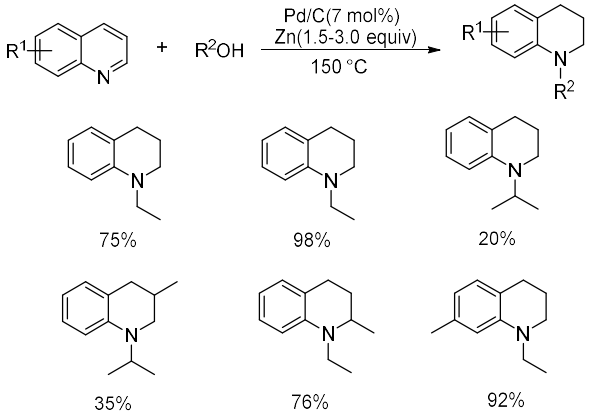
Scheme 21. Substrate scope for the one-pot mono *N*-alkylation of nitroarenes with aldehydes.

Porcheddu *et al.* demonstrated the selective *N*-alkylation of aromatic amines using Pd/C as a catalyst under microwave irradiation.[38] The catalyst provided excellent yields of *N*-alkylated products with tertiary amines and substituted anilines (**Scheme 22**). The substitution in the aromatic ring influenced the yields of products, with activated aniline derivatives showing good to excellent yields and deactivated groups bringing down the yield or resulting in no reaction at all. The catalyst was easily recovered and did not lose efficiency even after five reaction cycles.



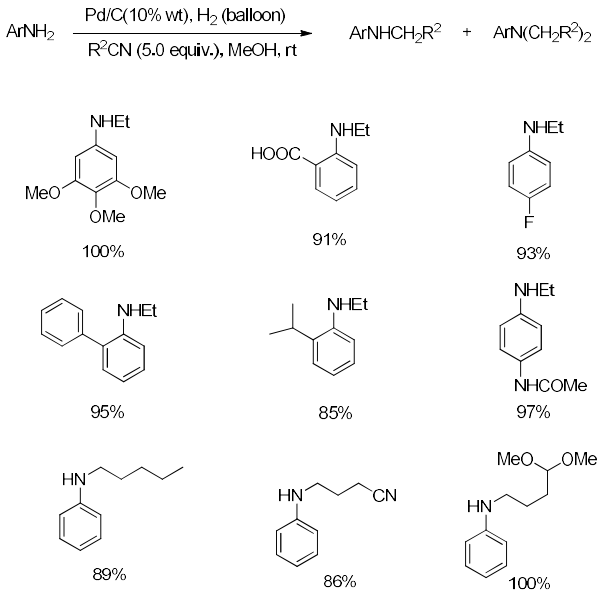
Scheme 22. Selective *N*-monoalkylation of aromatic amines catalyzed by Pd/C.

A new method for the *N*-alkylation of quinolines was proposed by Ballesteros *et al.*[39] A combination of palladium, carbon, and zinc (Pd/C/Zn) was found to show good yields in the N-alkylation reaction using alcohols *via* hydrogen auto transfer in a one-pot manner. Depending on the type of solvent used and the steric effects of the substrates, the catalyst showed selectivity in forming the *N*-alkylated or the hydrogenated product, in which the *N*-alkylation was favoured by the presence of substituents with less steric effects (**Scheme 23**). It was found that zinc makes the borrowing hydrogen process very efficient and leads to the formation of palladium monohydride, the major route for hydrogen transfer and hence responsible for the enhanced activity of the catalyst.

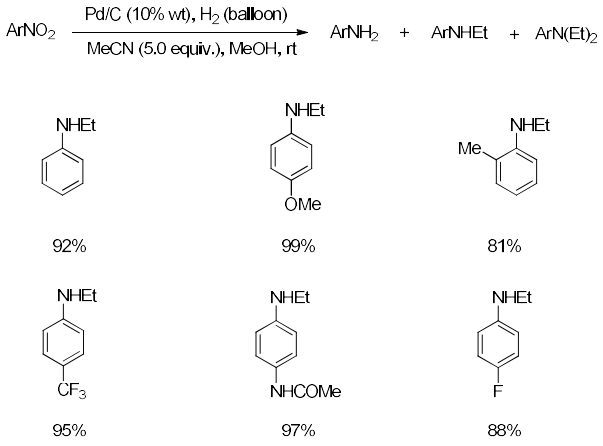


Scheme 23. Substrate scope for *N*-alkylation of quinolines using Pd/C/Zn catalytic system.

Sajiki *et al*. discovered an approach for the selective *N*-monoalkylation of amines from nitriles and nitro compounds by using Pd/C and Rh/C under mild hydrogenation conditions[40]. A wide range of primary-, aliphatic-, aromatic- and secondary nitriles were efficiently converted to the corresponding *N*-alkylated products (**Scheme 24**). Moreover, aromatic nitro compounds were also converted to the corresponding secondary amines in very good yields (**Scheme 25**). The utilization of additives such as NH_4OAc enhanced the reactivity and yield in the case of substrates carrying electron-deficient substituents, while AcOEt prevented over-alkyaltion. Even though only mild temperature condition (60 °C as the optimum temperature) was required, the reaction was heavily affected by catalyst poisoning, and hence distilled substrates were required for maximum yield. Finally, an asymmetric version of the reaction was also developed using a combination of Pd/C and Rh/C.

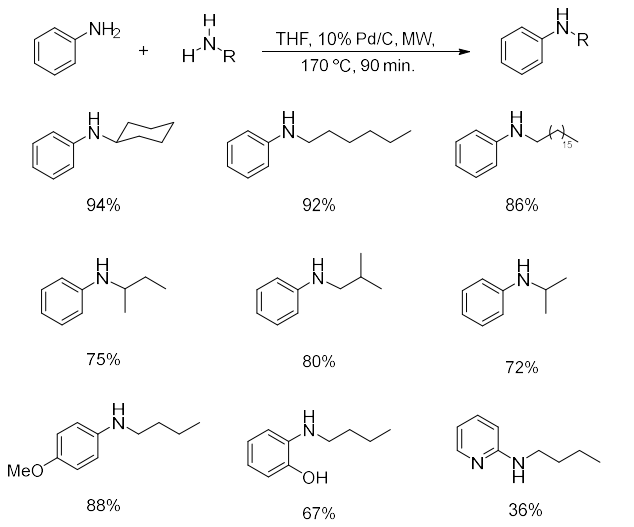


Scheme 24. Substrate scope of aromatic amines and nitriles in the *N*-alkylation reaction under Pd/C catalysis.



Scheme 25. Scope of nitroarenes in the *N*-alkylation reaction under Pd/C catalysis.

Taddei *et al*. proposed an efficient protocol for the *N*-alkylation of anilines with primary amines by employing palladium on charcoal (Pd/C) assisted by microwave heating.[41] The optimized reaction condition found was THF as the solvent, Pd/C loading of 10 mol%, aniline/substrate ratio of 2:1 under microwave heating at about 170 °C for 90 minutes. High yields of products were obtained for the *N*-alkylation of linear and branched amines (**Scheme 26**). Electron-donating groups gave better yields compared to electron-withdrawing ones due to increased nucleophilicity on the nitrogen atom. The catalyst's exceptional recyclability was demonstrated by recovering and reusing it for several times.

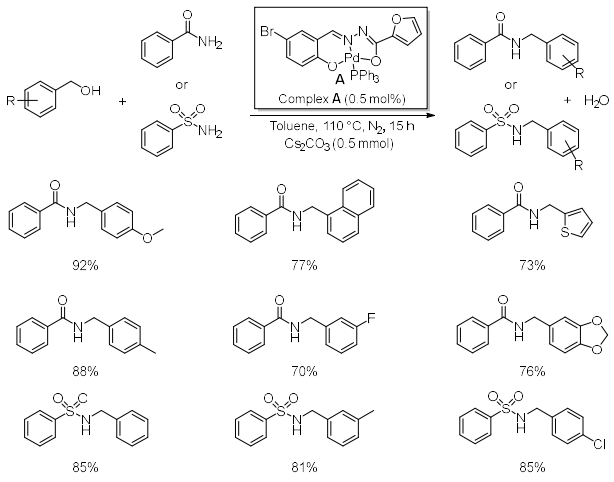


Scheme 26. Substrate scope for *N*-alkylation of different anilines with amines using Pd/C under microwave heating.

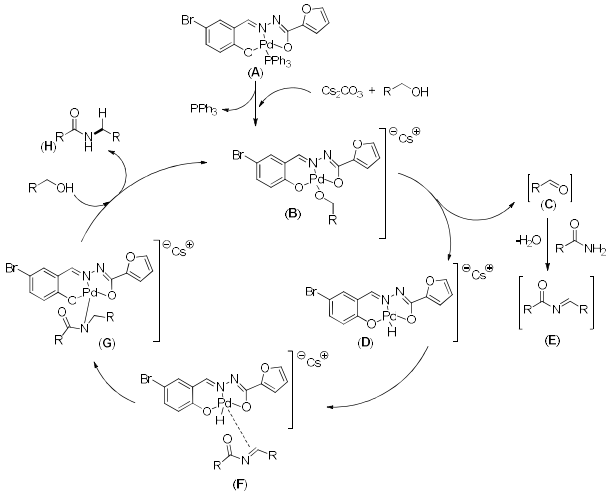
2.2 Homogeneous Palladium Catalysis

2.2.1 Pincer-Type Ligands

Ramesh and Anandaraj explored palladium(II) pincer complexes as catalysts for the *N*-alkylation of benzamides and sulfonamides with alcohols.[42] The optimal condition for the reaction was found to be the use of 0.5 mol% of the catalyst along with Cs_2CO_3 as the base and toluene as the solvent at 110 °C (**Scheme 27**). The catalyst demonstrated high efficiency, providing good to excellent yields for the *N*-alkylation of various benzamides and sulfonamides. However, electron-rich substituents showed better yields and a higher rate of reaction compared to electron-deficient ones. The proposed mechanism involves a borrowing hydrogen pathway where palladium abstracts hydrogen from alcohols through β-hydride elimination, followed by condensation with the amide to form an imine, which was then reduced by the metal hydride (**Scheme 28**).

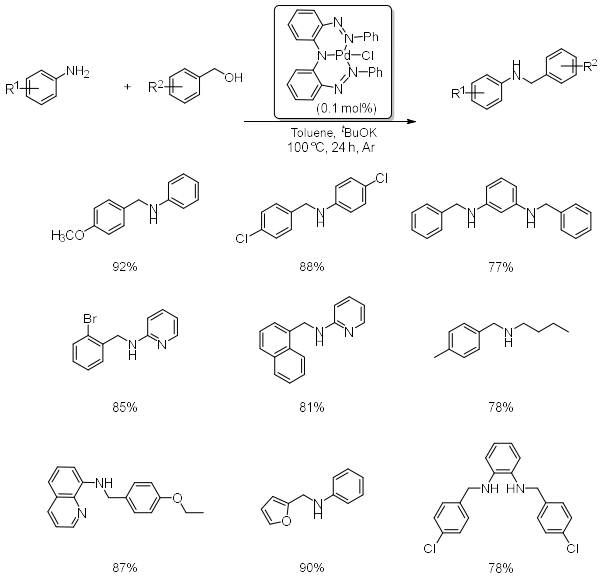


Scheme 27. Substrate scope for the *N*-alkylation of benzamides and sulfonamides with alcohols catalysed by palladium O^N^O pincer type complex.



Scheme 28. Plausible mechanism for *N*-alkylation with palladium OˆNˆO pincer complex.

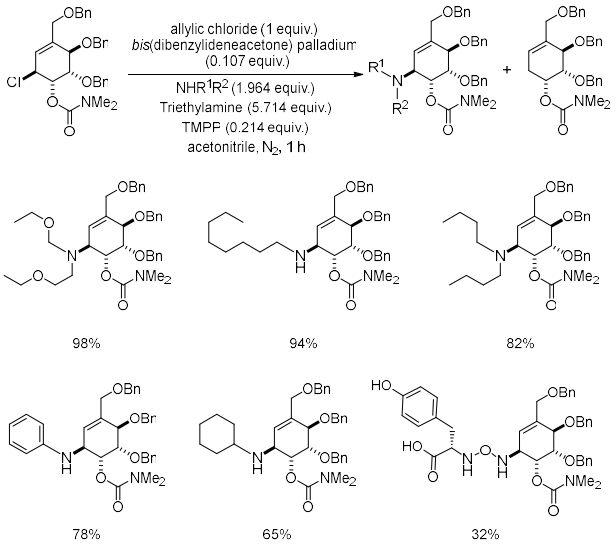
Ghosh *et al*. developed a novel palladium(II) complex, [Pd(L1)Cl] which is air-stable and does not require phosphine ligands, for the *N*-alkylation of amines with alcohols *via* a borrowing hydrogen methodology.[43] The newly developed palladium(II) complex comprises a tridentate bis-azo pincer ligand and demonstrated high catalytic efficiency with a very low catalyst loading of 0.1 mol% under milder conditions with toluene as the solvent and *t*-BuOK as the base. A broad range of primary alcohols, including aromatic, aliphatic, and heteroaromatic alcohols, were efficiently reacted with excellent yields **(Scheme 29)**. Moreover, gram-scale synthesis of the structural motif of the antihistamine tripelennamine and intramolecular cyclization to produce indole derivatives have also been demonstrated. Control experiments suggested that the azo-chromophore in the ligand acted as a hydrogen reservoir during the catalytic cycle, indicating metal-ligand cooperativity where both the Pd centre and the ligand play crucial roles.



Scheme 29. Substrate scope for *N*-alkylation of aniline derivatives with aromatic alcohols using tridentate palladium (II) bis-azo pincer complex.

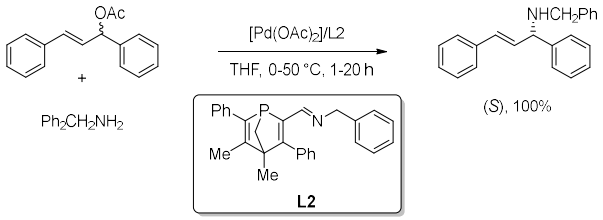
2.2.2 Phosphorus-Based Ligands

Shing and co-workers designed an approach for the synthesis of 2-*epi*-valienamines from allylic chlorides by palladium-catalyzed *N*-alkylative coupling using trimethylolpropane phosphite (TMPP).[44] Both primary and secondary amines were efficiently alkylated in good yields, with a significant fall in yields for bulkier amines (**Scheme 30**). TMPP was found to significantly increase the yields of the products as compared to triphenylphosphine. The retention of configuration in these palladium-catalyzed reactions was demonstrated by comparing the coupling constants between H1 and H2 in diacetate and chlorocarbamate with that observed in the newly synthesized amines. As compared to the earlier classical methods which had problems of poor yields and regioselectivity, this approach was found to be effortless and both regio- and stereospecific.



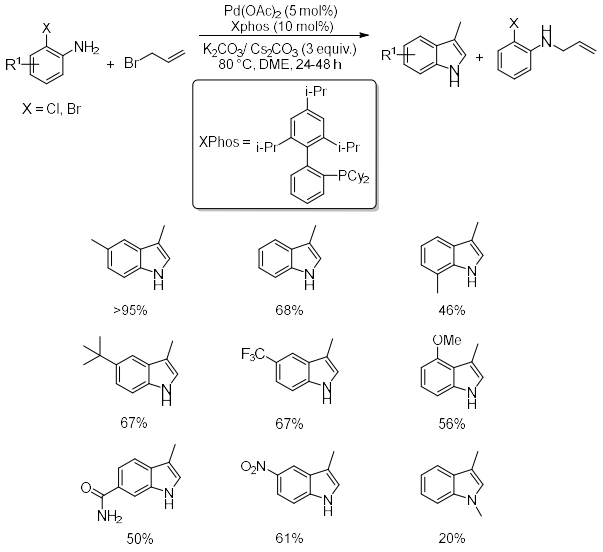
Scheme 30. Substrate scope for the *N*-alkylated coupling of allylic chloride analogues of 2-*epi*-valienamines using $Pd(dba)_2$/TMPP.

Mathey *et al.* reported an easy method for the preparation of enantiopure phosphanorbornadiene-imines and employed it as an excellent ligand for the *N*-alkylation of 1,3-diphenyl-prop-2-enyl acetate with benzyl amine using palladium.[45] Phosphorus atom located at the bridgehead in bicyclic structure can provide enantioselectivity and hence has potential in asymmetric catalysis. The catalysis was optimized with the palladium-to-ligand ratio of 1:3 at lower temperatures. The yields obtained with various ligands were evaluated. The imine derivative containing the benzyl group exhibited the highest efficiency in this reaction (**Scheme 31).**



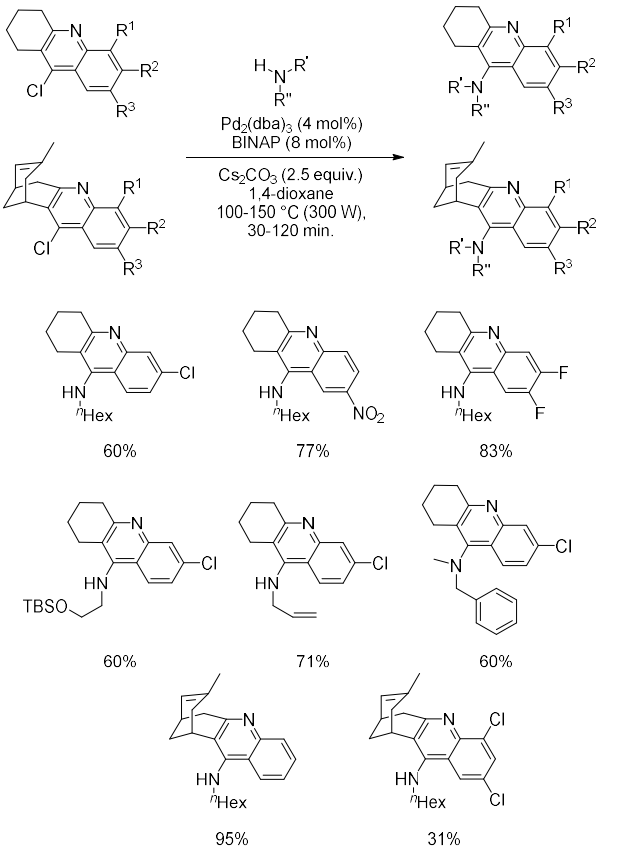
Scheme 31. Enantioselective *N*-alkylation of 1,3-diphenyl-prop-2-enyl acetate with benzyl amine.

Beck and Weinrich achieved the synthesis of substituted indoles using a combination of $Pd(OAc)_2$ and XPhos *via* one-pot cascade *N*-alkylation of amines.[46] It was observed that the combination of catalysts was necessary for higher yields than employing them individually. Probing microwave radiation did not assist indole formation even at higher temperatures. Even though the catalyst proved to be ineffective in providing indoles from 2-fluoroanilines and 2-iodoanilines, it provided good yields for 2-bromoanilines and 2-chloroanilines with a good range of substitution tolerance for 2-chloroanilines (**Scheme 32**). This method was proved to be an efficient way to synthesize indoles, as the catalyst was easily affordable, and the reaction condition was mild.



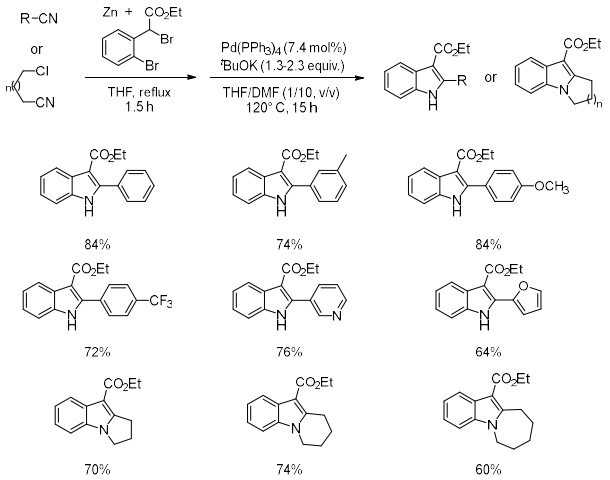
Scheme 32. Substrate scope for one-pot cascade *N*-alkylation of amines using allyl halides.

In 2011, Renard *et al.* put forward a novel approach for the preparation of *N*-alkylated tacrine and huprine compounds using palladium as the catalyst and microwave as the heating source.[47] The optimized condition obtained was the use of 4 mol% of $Pd_2(dba)_3$, 8 mol% of BINAP and 2.5 equiv. of Cs_2CO_3 in 1,4-dioxane at 150 °C (**Scheme 33**). The selectivity was low for coupling reactions of trihalogenated compounds with *n*-hexylamine. Most of the chloroquinolines were effectively coupled with *n*-hexylamine by utilizing the catalyst. Similarly, a wide range of *N*-alkylated tacrines and huprines were obtained with good to excellent yields.



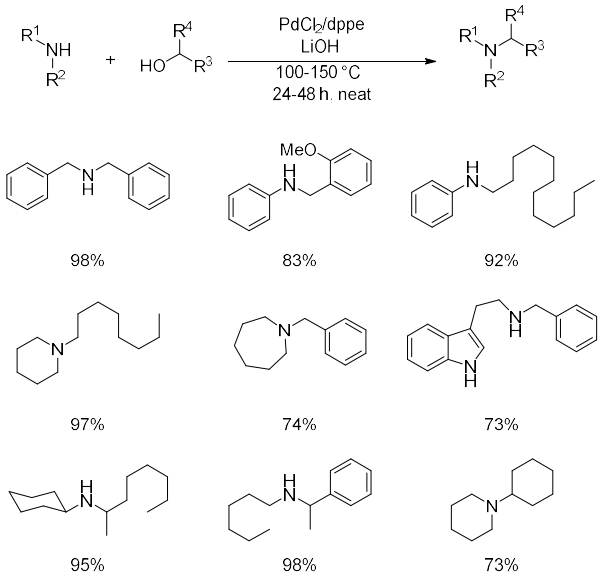
Scheme 33. *N*-Alkylation of tacrine and huprine like aminoquinolines with amines.

A novel strategy for the synthesis of indoles and *N*-fused indole moieties by tandem *N*-alkylation using nitriles *via* palladium-catalyzed intramolecular trapping of Blaise's reaction intermediates was proposed by Lee and co-workers.[48] The reaction was optimized using $Pd(PPh_3)$ (7.4 mol%) and t-BuOK (1.3 equiv.) in THF/DMF as the solvent mixture (**Scheme 34**). The reaction tolerated various nitriles containing electron-donating and electron-withdrawing groups and afforded the corresponding indoles and *N*-fused indoles. It was noteworthy that the reaction was not influenced by the electronic nature of the substituents.



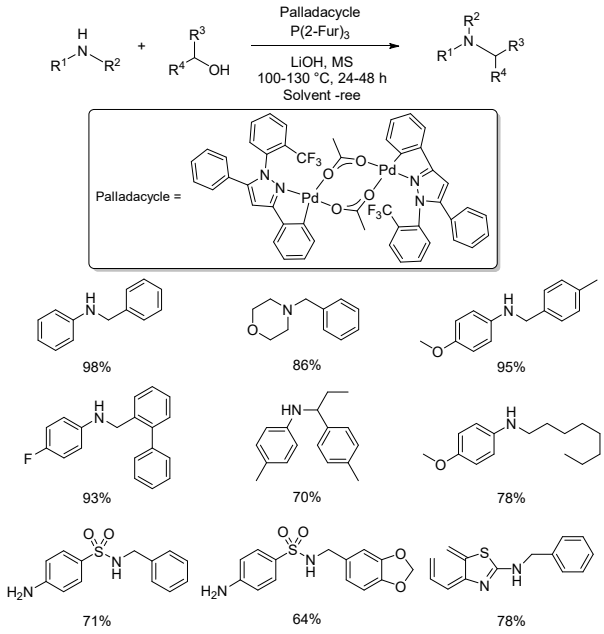
Scheme 34. One-pot synthesis of indole derivatives and *N*-fused indoles via *N*-alkylation.

A novel and efficient strategy for *N*-alkylation was reported by Seayad *et al.*, in 2013.[49] They have reported the use of palladium chloride ($PdCl_2$) in presence of ligands such as dppe (1,2-*bis*(diphenylphosphino)ethane), Xantphos, PPh_3, BINAP, etc. and have obtained excellent yields for *N*-alkylation at moderate temperatures, simultaneously achieving high TON (**Scheme 35**). Dppe was chosen for further studies due to its accessibility and affordability. A wide range of substrates including cyclic secondary amines, heterocyclic amines etc. were efficiently *N*-alkylated to obtain good to excellent yields of the corresponding products.

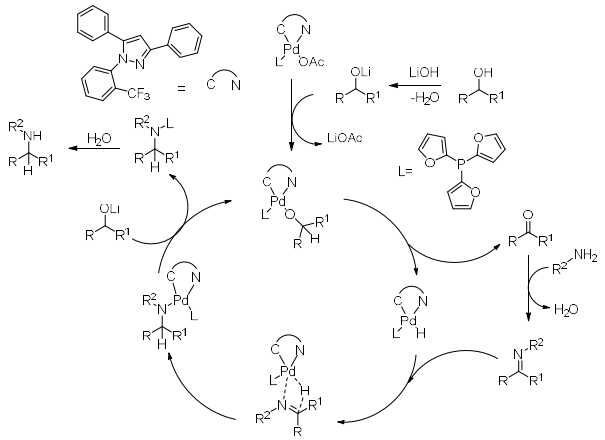


Scheme 35. Substrate scope for the *N*-alkylation of amines with alcohols using $PdCl_2$ in presence of dppe.

Venkatasubbaiah and co-workers generated pyrazole-based palladium homogenous pre-catalysts for efficient *N*-alkylation of amines and could observe very high turnover numbers.[50] The pre-catalyst was prepared by cyclopalladation of 3,5-diphenyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrazole by using palladium acetate. The reaction was optimized under solvent-free conditions using LiOH as base and $P(2\text{-Fur})_3$ as ligand, in the presence of 4 Å molecular sieves (**Scheme 36**). The *N*-alkylation of most of the amines were achieved with excellent yields. Challenging alcohols such as secondary alcohols and sterically hindered alcohols were used effectively and could achieve good yields of the corresponding products. The catalyst was also used for the *N*-alkylation of sulphanilamides and benzothiazoles and could obtain more than 60% yield. The catalytic pathway involving the palladacycle for *N*-alkylation has also been proposed. It follows borrowing hydrogen technology, where the palladacycle catalyst first dehydrogenates the alcohol to form an aldehyde. The aldehyde then condenses with the amine to form an imine, which was subsequently reduced by the hydrogen previously "borrowed" from the alcohol, yielding the *N*-alkylated amine. The catalyst is regenerated to continue the cycle (**Scheme 37**). This process is efficient and environmentally friendly, generating only water as a byproduct.

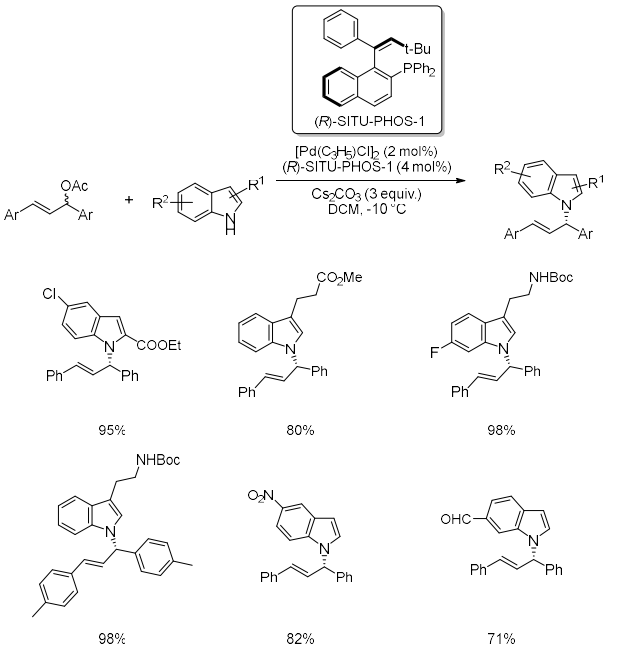


Scheme 36. Substrate scope for *N*-alkylation of different amines and alcohols using palladacycle catalyst.



Scheme 37. Suggested catalytic pathway for *N*-alkylation.

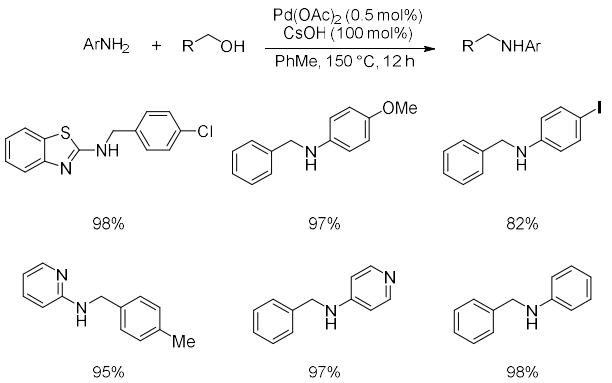
Zhang *et al*. developed a novel axially chiral styrene-phosphine ligand ((*R*)-SJTU-PHOS-1) to enhance the performance of palladium catalysts in the *N*-alkylation of indoles.[51] The reaction was optimized using $[Pd(C_3H_5)Cl]_2$ (2 mol%) as the catalyst and (*R*)-SJTU-PHOS-1 as the ligand (4 mol%) along with cesium carbonate (3 equiv.) as the base in dichloromethane (CH_2Cl_2) solvent at a temperature of -10 ^oC under an argon atmosphere (**Scheme 38**). The catalyst was found to be versatile as the reaction accommodates a wide range of indole substrates, including various electron-donating and electron-withdrawing groups at different positions of the indole ring, with good yields and high enantioselectivity. This performance was also maintained when the reaction was scaled up to gram levels. DFT calculations indicated the formation of two intermediates and nucleation pathways with differing free energies, influenced by steric effects. The lower energy pathway leads to the formation of the (*S*)-product, consistent with X-ray crystallographic analysis.



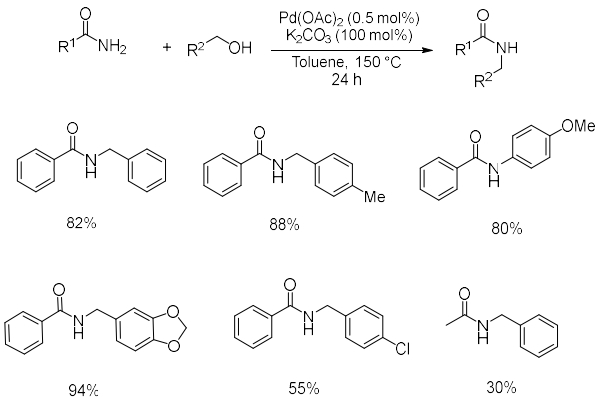
Scheme 38. Asymmetric synthesis of indoles by direct *N*-alkylation catalyzed by $Pd(C_3H_5)Cl_2$ in presence of novel ligand ((R)-SJTU-PHOS-1).

2.2.3 Ligand-Free Reactions

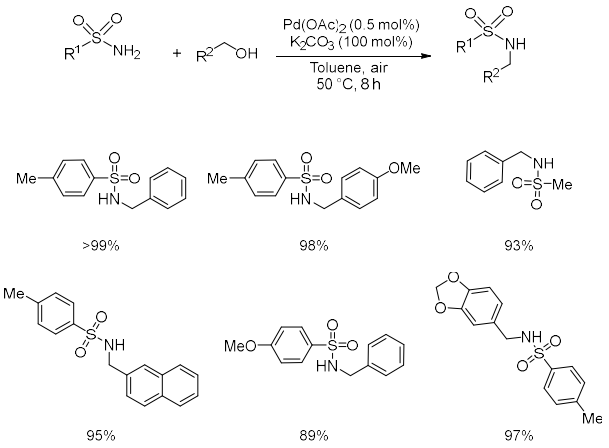
Ramón *et al.* put forward a novel strategy for the *N*-alkylation of aromatic amines, phosphazines, sulfonamides and related nitrogenated compounds by utilizing alcohols.[52] The reaction was investigated with a wide range of substrates (**Scheme 39**). 4-Chlorobenzyl alcohol gave a lower yield because of the dehalogenation side reaction, while only a single isolated product was obtained for 4-iodobenzyl alcohol. Similarly, furan-2-ylmethanol gave a low yield. On reaction with carboxamides, aliphatic alcohols gave a modest yield (**Scheme 40**). Aliphatic sulfonamides with other functional groups gave an excellent yield (**Scheme 41**). Finally, they investigated the indirect aza-Wittig reaction, in which α-branched primary alcohol gave better results compared to normal aliphatic alcohols.



Scheme 39. Substrate scope for the *N*-alkylation of aromatic amines using $Pd(OAc)_2$.

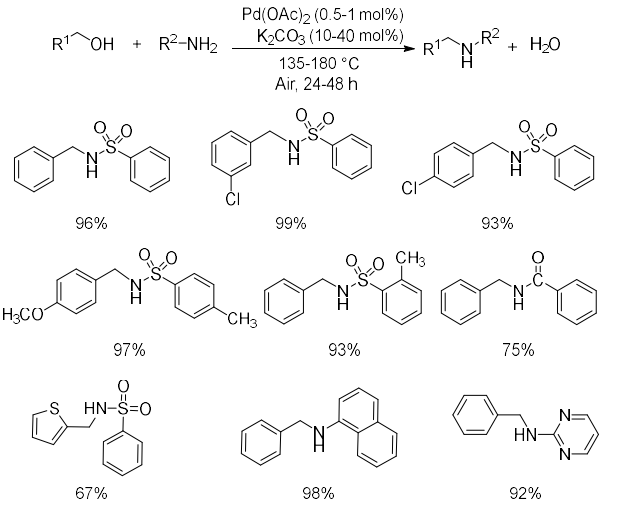


Scheme 40. Substrate scope for the *N*-alkylation of carboxamides using $Pd(OAc)_2$.



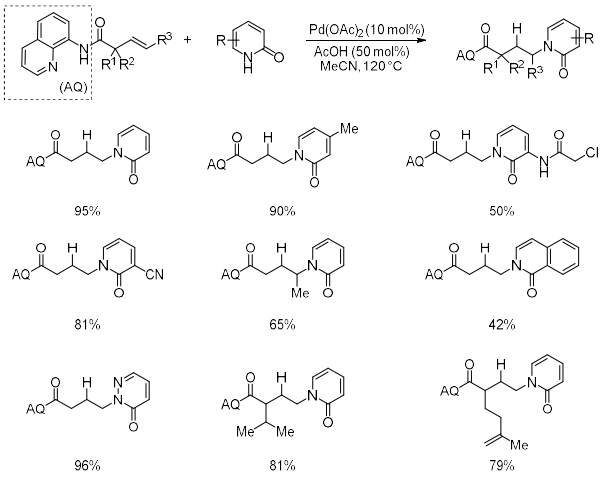
Scheme 41. Substrate scope for the *N*-alkylation of sulphonamides using $Pd(OAc)_2$.

In 2012, the first effective and successful homogenous Pd-catalyzed *N*-alkylation reaction of amines and amides using alcohols was reported by Qing *et al*.[53] Bases of alkali metal hydroxides gave better yields. The reaction could tolerate a wide array of substrates (**Scheme 42**). High selectivity and good yields were obtained for benzyl alcohol with *meta*- and *para*-substituents. However, low yields were obtained for the one with methoxy group at the *ortho*-position. But, in the case of benzenesulfonamides, all the substituents, both electron-withdrawing, and electron-donating, and even the bulky *ortho*-substituents, gave high yields of the corresponding products. Whereas, the yield was moderate for some of the other sulfonamides like alkyl sulfonamide. The major advantage of the reported reaction was that it was carried out under ligand- and solvent-free conditions.

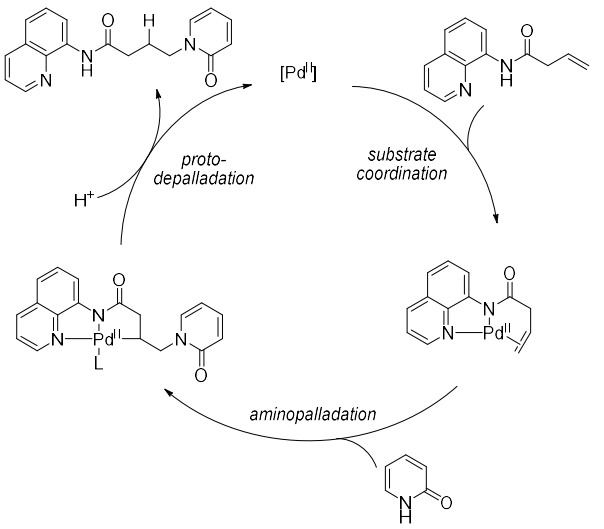


Scheme 42. Aerobic *N*-alkylation of amines and amides with alcohols using palladium.

Engle *et al*. proposed a novel strategy for the palladium-catalyzed *N*-alkylation of 2-pyridones and other related heterocycles with un-activated alkenes *via* intermolecular alkene hydroamination.[54] The reaction used removable 8-aminoquinoline (AQ) as an auxiliary amide to 3-butenoic acid. Selective alkylation of the nucleophile, 2-pyridone, was catalyzed by 10 mol% of $Pd(OAc)_2$ (**Scheme 43)**. Excellent yields of products were obtained and the reaction was found to have high tolerance with an array of electronically diverse pyridones. Substituents present in alkene does not seem to affect the reaction rate. The reaction was found to be chemoselective, as the alkene proximal to the directing group was functionalized in the case of disubstituted alkenes, and a *trans*-relationship was observed with the nucleophile and directing group. In the proposed catalytic cycle, palladium(II) first coordinates with the 2-pyridone substrate *via* the 8-aminoquinoline directing group (substrate coordination). Next, the alkene inserts into the Pd–N bond through aminopalladation, forming the N-alkylated product. Finally, protodemetalation releases the product and regenerates the palladium catalyst for another cycle **(Scheme 44)**.



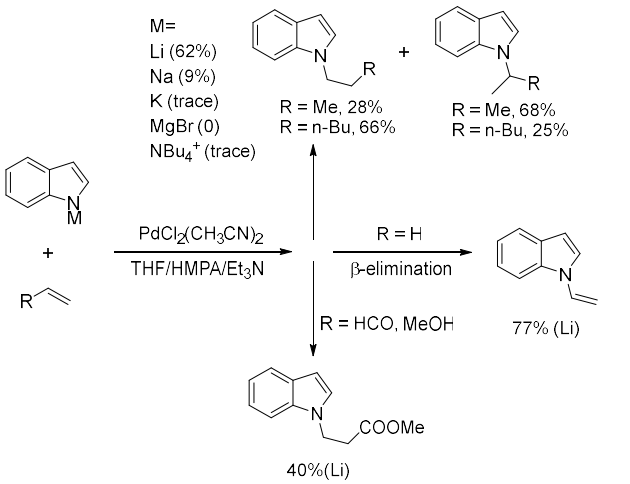
Scheme 43. Substrate scope for the *N*-alkylation of 2-pyridone derivatives with alkenes *via* hydroamination.



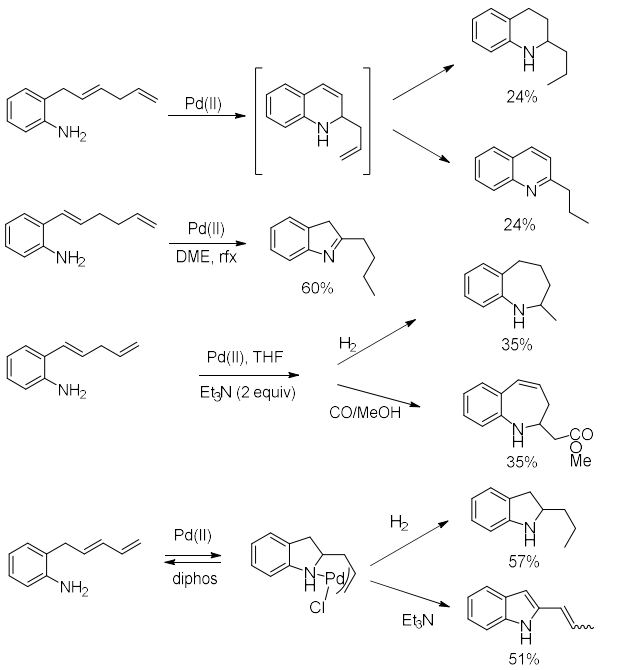
Scheme 44. Proposed mechanism for the hydroamination of 2-pyridones.

2.3 Miscellaneous Reactions

Hegedus *et al.* conducted the intramolecular *N*-alkylation and polycyclization of indole moieties by using palladium complexes of alkenes such as ethene, propene, and hexene.[55] Among the indolyl anions with metals, lithium salts were found to be the most efficient for the *N*-alkylation reaction (**Scheme 45**). Efforts to polycyclize during the *N*-alkylation from 2-allyl-skatole were met with several setbacks, and all methods were ineffective. Ring closure was achieved with several dienyl olefin side chains at the *ortho*-position (**Scheme 46**). For instance, in the case of 2,4-pentadiene, a stable allylpalladium complex was formed. However, the formation of a second ring was unsuccessful. This failure was attributed to the lack of knowledge regarding suitable conditions required for polycyclization.

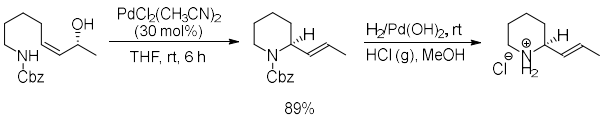


Scheme 45. Palladium-catalyzed *N*-alkylation of indoles using different metal salts under $PdCl_2(CH_3CN)_2$.



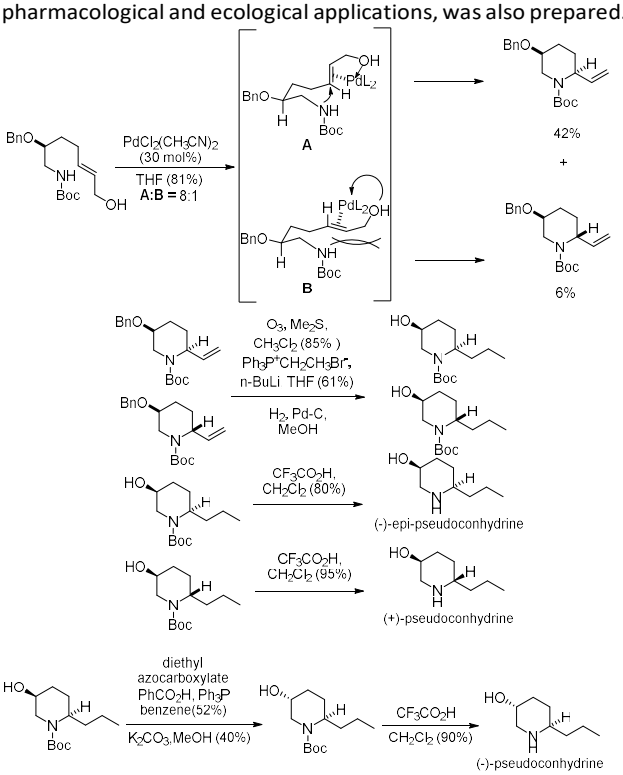
Scheme 46. Attempted polycylization of aniline with dienyl side chains, utilizing palladium.

Hirai and Nagatsu reported a palladium-catalyzed *N*-alkyl cyclization of optically active urethanes into piperidines with high intramolecular chirality.[56] The urethane containing allylic alcohol was prepared from N-Cbz-5-amino-1-pentanol through sequential steps involving Swern oxidation, Wittig reaction and reduction followed by conversion into allylic alcohol with super hydride. The intramolecular cyclization of the urethane was catalyzed by *bis*(acetonitrile)palladium(II) chloride in THF, which yielded chiral 2-functionalized piperidine (which are building blocks of Sedum alkaloids) in 89% yield (**Scheme 47**). The recyclability of the catalyst was the advantage of this approach.



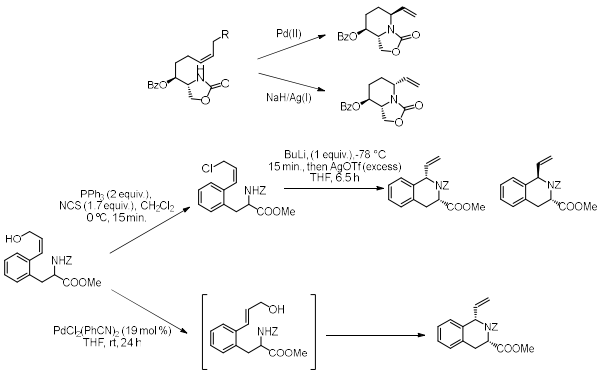
Scheme 47. Palladium-catalyzed intramolecular *N*-alkyl cyclization of optically active urethane and its conversion to coniine hydrochloride.

Later, they extended this methodology and reported a new work in which the allylic alcohol was prepared from (R)-O-t-butylsilylglycidol in several sequential steps, and the efficient cyclization was achieved by employing bis(acetonitrile)palladium(II) chloride in THF through a 1,4-asymmetric induction.[57] The product was also converted to a hemlock alkaloid, (+)-pseudoconhydrine stereoselectively in subsequent steps involving ozonolysis, Wittig reaction, hydrogenation, and by treatment with trifluoroacetic acid **(Scheme 48)**. Similarly, by providing Mitsunobu conditions to the intermediate, (-)-pseudoconhydrine, which is used in pharmacological and ecological applications, was also prepared.



Scheme 48. Intramolecular *N*-alkyl cyclization of optically active urethane catalyzed by palladium chloride

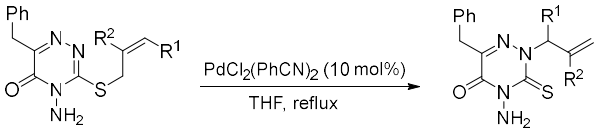
Yamamoto *et al*. studied the intramolecular *N*-alkylation of 1,3-disubstituted tetrahydroisoquinolines and 2,5-disubstituted pyrrolidines, establishing stereoselective control based on palladium and silver catalysts.[58] They noticed that in the case of tetrahydroisoquinolines, silver and palladium catalysts lead to the production of *cis* and *trans* products, respectively, in the absence of additional substituents (**Scheme 49**). While in the presence of substituents and in the case of pyrrolidines, palladium-induced intramolecular N-alkylation leads to cis-isomers, while silver leads to *trans*-isomers. The phenomenon has also been explained using a tentative half-chair cyclic carbamate transition state.



Scheme 49. Stereochemical control of *N*-alkylation by employing palladium and silver catalysts.

In 2015, Liu *et al.* put forward a mechanistic study of the alkylation of amines by alcohols using energy span models and DFT methods.[59] Based on the experimental study reported by Seayed and co-workers,[49] the reaction was catalyzed by $PdCl_2$/1,2-*bis*(diphenylphosphino)ethane (dppe) along with LiOH as the base. The most favorable pathway was identified as an inner-sphere hydrogen transfer involving the three-coordinated alkoxide complex Int4i. The most efficient catalytic cycle (CC1) shows a high turnover frequency, influenced by key off-cycle intermediates like $LiCl_2$-coordinated complexes. The study suggests that adding AgOTf or $AgBF_4$ can significantly enhance the TOF. The stability and reactivity of Pd(II) intermediates are governed by both electronic and steric effects, and DFT methods were used to optimize the reaction conditions and improve catalyst design.

In 2016, Knight *et al.* reported the synthesis of *N*-thioalkyl derivatives by the *N*-alkylation of 3-thioxo-1,2,4-triazin-5-ones.[60] Moderate yields were obtained for the thio-Claisen rearrangement at 120-140 ˚C in xylene (**Scheme 50**). 1,1-Disubstituted alkene was an exception and failed to both thermal activation and palladium-based catalysis.



Scheme 50. Thio-Claisen rearrangements using palladium catalyst..

Finally, we have summarized the findings from each paper and it is presented as a table.

Table 1. Summary of various palladium-catalyzed *N*-alkylation reactions

No.	Substrate	Products	Catalyst	Ligand/ Base	Yield Range (%)	Ref.
1	Primary amines and primary alcohols	*N*-alkylated Secondary amines	Pd/TiO_2	N.A.	82-98	21
2	Primary amines and primary alcohols	*N*-alkylated secondary amines	Pd@MIL-100(Fe)	N.A.	8-77	22
3	Primary amines and primary alcohols	*N*-alkylated secondary amines	$Pd@[nBu_4N][Br]$	N.A.	50-97	23
4	Primary, secondary amines and alcohols	Secondary and tertiary *N*-alkylated amines	$Pd@SiO_2$	N.A.	44-97	24
5	Primary amines, primary alcohols and secondary alcohols	*N*-alkylated secondary amines	$Fe_{10}Pd_1/NC500$	N-doped carbon	58-97	25
6	Primary amines, aldehydes and nitrobenzene	*N*-alkylated amines	Pd@CTF-1	N.A.	50.7-100*	26
7	Piperazine, *N*-heterocyclic amines and alcohols	N-methylpiperazine, *N*-alkylated heterocyclic amines	Pd/TiO_2-P	N.A.	25.9-88.28*	27
8	Primary amines, primary alcohols and secondary amines	*N*-alkylated secondary and tertiary amines	Pd_1Pt_1/TiO_2	N.A.	42-87	28
9	Ketones, primary and secondary amines	Secondary and tertiary *N*-alkylated amines	DMPSi–Pd/AC	N.A.	69-99	29
10	Primary amines, primary alcohols, secondary amines and aliphatic alcohols	Secondary and tertiary *N*-alkylated amines	Pd/Fe_2O_3	N.A.	72-99	30
11	Nitro aryls and aromatic aldehydes	*N*-alkylated secondary amines	Pd/SiO_2	N.A.	23-100	31
12	Primary amines, primary alcohols, secondary alcohols and ketones	Secondary amines and α-alkylated ketones	Pd–Si–Pr–NiXantphos/SiO_2	NiXantphos, LiOH	53-99	32
13	Primary amines and phenols	N-alkylated secondary amines	$PdHx/Al_2O_3$	N.A.	15-99	33
14	Primary amines, primary alcohols, Secondary amines and various alcohols	*N*-alkylated secondary and tertiary amines	$PdZn/Al_2O_3$	N.A.	48-100*	34
15	Primary amines, aldehydes, ketones and nitroarenes	Secondary amines	$Pd(OAc)_2/ZrO_2$	N.A.	53-99	35
16	1,2-amino alcohols and nitriles	N-alkylated amino alcohols	Pd/C	N.A.	34-100	36

17	Primary amines, nitroarene derivatives and aldehydes	Secondary amines	Pd/C	N.A.	45-100	37
18	Primary amines and tertiary amines	*N*-alkylated secondary amines	Pd/C	N.A.	31-96	38
19	Quinolines and primary alcohols	1,2,3,4-tetrahydroquinolines and *N*-alkylated tetrahydroquinolines.	Pd/C	N.A.	6-96	39
20	Primary amines and nitriles	Secondary amines and tertiary amines	Pd/C and Rh/C	NH_4OAc	8-100	40
21	Aniline and primary amines	*N*-alkylated anilines	Pd/C	N.A.	32-99	41
22	Benzamides and sulfonamides with aromatic alcohols	N-alkylated benzamides and N-alkylated sulfonamides.	Pd(II) pincer complexes	tridentate O^N^O ligand, Cs_2CO_3	57- 92	42
23	Primary amines and primary alcohols	*N*-alkylated amines	Pd(II) complex [Pd(L1)Cl]	bis-azo pincer ligand, KOtBu	52-92	43
24	Allylic chlorides, primary and secondary amines	*N*-alkylated 2-epi-valienamines.	$Pd(dba)_2$	trimethylolpropane phosphite (TMMP), triethylamine (Et_3N)	13-90	44
25	Benzylamine, dimethyl malonate, and 1,3-diphenylprop-2-enyl acetate	*N*-alkylated benzylamines and C-alkylated dimethyl malonate derivatives.	$Pd(dba)_2$	1-phosphanorbornadiene-imines	22-87[#]	45
26	2-Bromoaniline and 2-chloroaniline, with allyl bromide and allyl chloride	*N*-allylanilines and substituted indoles	$Pd(OAc)_2$	XPhos, K_2CO_3, Cs_2CO_3	14-99[γ]	46
27	Chloroquinolines and primary amines	*N*-alkylated tacrine and huprine compounds	$Pd_2(dba)_3$	(±)-BINAP, Cs_2CO_3	10-95	47
28	Nitriles and Reformatsky reagents	Indole derivatives and N-fused indoles.	$Pd(dba)_2$, $Pd(PPh_3)_4$	t-BuOK	47-84	48
29	Primary amines, primary alcohols and secondary alcohols	N-alkylated secondary and tertiary amines	$PdCl_2$	dppe or Xantphos(t-Bu), LiOH	59-99	49
30	Primary and secondary amines, primary and secondary alcohols, sulfanilamides	*N*-alkylated amines and *N*-alkylated sulfanilamides.	Cyclometalated palladium pre-catalyst	$P(2\text{-}Fur)_3$, LiOH	64-98	50
31	Indoles and benzyl alcohols or its derivatives.	N-alkylated indoles.	$Pd(C_3H_5)Cl]_2$	(R)-SJTU-PHOS-1, K_2CO_3	60-98	51
32	Aromatic amines sulfonamides, and carboxamides.	*N*-alkylated amines, *N*-alkylated sulfonamides, and N-alkylated carboxamides.	$Pd(OAc)_2$	CsOH, K_2CO_3	5-99	52
33	Amides, amines, sulphonamides and alcohols	*N*-alkylated amides, *N*-alkylated amines and N-alkylated sulphonamides	$Pd(OAc)_2$	K_2CO_3	45-99	53
34	2-pyridones and unactivated alkenes	*N*-alkylated pyridones	$Pd(OAc)_2$	N.A.	7-95	54
35	Indole derivatives	N-alkylated indoles	$PdCl_2(CH_3CN)_2$	Coordinated olefins, triethylamine (Et_3N)	trace-95	55
36	Optically active urethans	2-functionalized piperidines	$PdCl_2$	N.A.	Upto 89	56
37	Optically active urethanes	2-functionalized 5-hydroxypiperidines and their derivatives	$[PdCl_2(CH_3CN)_2]$	N.A.	Upto 81	57
38	1,3-disubstituted tetrahydroisoquinolines and	cis-1,3-disubstituted tetrahydroisoquinolines	$PdCl_2(PhCN)_2$	BuLi	Upto 78	58

	2,5-disubstituted pyrrolidines.	and cis-2,5-disubstituted pyrrolidines.				
39	3-thioxo-1,2,4-triazin-5-ones and allylic halides	*S*-alkylated and *N*-alkylated derivatives of 3-thioxo-1,2,4-triazin-5-ones.	$PdCl_2(PhCN)_2$	K_2CO_3	15-86	60

*- Instead of yield, selectivity is shown
#- Instead of yield, conversion is shown
γ - instead of yield, enantiomeric excess is shown

3. Conclusion

Advancements in palladium-catalyzed *N*-alkylation have significantly expanded the capabilities for efficient and selective synthesis of *N*-alkyl amines, paving new ways in the branch of synthetic organic chemistry. The unique properties of palladium, such as higher reactivity, selectivity, and functional group tolerance, combined with innovative ligand systems, reaction mechanisms and following green chemistry principles, have greatly enhanced the scope and applicability of these reactions. Both homogeneous and heterogeneous Pd-based catalytic systems have demonstrated exceptional efficiency, atom economy and selectivity under mild conditions, often surpassing other transition metals like Ru, Ir, and Ni.

Although the main substrates were amines, a wide range of nitrogen-containing compounds such as amides, sulfonamides, nitriles, indoles, *N*-heterocyclic amines, pyridines, benzothiazoles, phosphazenes, and quinolines have smoothly undergone reactions under appropriate conditions, with various alkylating agents including primary and secondary alcohols, aldehydes, ketones, heteroaromatics, and phenols, leading to their respective products in excellent yields. Most of these reactions were carried out under moderate conditions, and some even utilized visible light, ensuring atom efficiency and reduced energy consumption. These innovations highlight the versatility and broad applicability of palladium-catalyzed *N*-alkylation in synthesizing a wide array of complex nitrogen-containing compounds.

Mechanistic studies have provided valuable insights into the reaction pathways and rate-determining steps, guiding further optimization of these catalytic systems. This review discusses the various strategies employed to address these challenges, including homogeneous and heterogeneous catalysts, the development of novel catalyst supports, such as metal-organic frameworks (MOFs) and nanoparticles, the use of photocatalytic methods, and the exploration of different Pd precursors. Additionally, the review covered the broader implications of these catalytic systems in industrial applications and their alignment with sustainable chemistry practices.

Future research should focus on expanding the substrate scope, improving enantioselectivity, and developing more sustainable catalytic systems. Additionally, efforts should be made to explore target products to new *N*-heterocyclic compounds, enhance the stability and recyclability of Pd catalysts, and scale up reactions for industrial applications. Integrating palladium-catalyzed *N*-alkylation into industrial processes holds great promise for the large-scale production of valuable amine derivatives, contributing to the advancement of green chemistry. By continuing to refine these catalytic systems, the broader application of palladium-catalyzed *N*-alkylation in sustainable chemical synthesis can be fully realized.

Conflicts of interest

There are no conflicts to declare.

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