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Iron Oxide Supported Palladium Nano-Catalyst: Magnetically Recyclable & Retrievable Heterogeneous Catalyst for C-N Coupling Reactions

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ABSTRACT

Natural product synthesis, medicinal chemistry, and organic materials all depend on nitrogen-based heterocycles as essential building blocks. Methods for their preparation that utilize Pd-catalysed C–N coupling chemistry typically provide significant advantages over traditional ones. Pd-catalysed N-arylation reactions have seen rapid expansion in recent years in the field of process chemistry. In many instances, the desired cross-coupling reaction can be optimized to proceed effectively on a large scale with low catalyst loading, making the procedure potentially cost-effective. Additionally, Pd-catalysed strategies are regarded as a viable alternative to the utilization of potentially hazardous processes or toxic reagents. Occasionally, identical N-arylation reactions are employed in both the discovery and process routes after optimization of the coupling reaction for manufacturing settings. For the Buchwald–Hartwig C–N cross-coupling reaction, various heterogeneous Pd catalyst systems have been developed in this circumstance. Some of the reported palladium–catalyst systems for N-arylation reaction suffer from main drawbacks such as tedious and time-consuming work-up process, high cost, and difficulty in synthesis of these catalyst systems. Other significant concerns include the catalyst's reusability and, more importantly, the leaching of Pd, an expensive metal. From the perspective of both academic and industrial research, the creation of high-performance palladium-catalysed systems and the use of sustainable and environmentally friendly reaction conditions for the Buchwald–Hartwig C–N cross-coupling reaction are highly regarded. The newly designed, simple, efficient method of heterogeneous catalyst has several advantages for Buchwald C-N cross-coupling reactions, including using safe silica on iron oxide-supported nanoparticles for support, the absence of Phosphine ligands, and the absence of solvent and bases for completion of the reaction.

***Keywords**: Pd-catalysed N-arylation, Buchwald-Hartwig C-N Cross Coupling, Phosphine Ligands, Heterogeneous Catalyst.*

Introduction

Since amines are among the most significant functional groups in medicines and natural materials, C–N bond formation processes have garnered a lot of interest. Due to significant drawbacks, including a limited substrate scope, Ullmann and Goldberg's introduction of the C–N bond formation by the SNAr reaction in the presence of copper salts limited its usefulness in the production of complex medications. Polar aprotic solvents, an activated functional group in the reactant, and a lengthy reaction time are required for these reactions. Then, using Pd-catalysts, Buchwald and Hartwig created a C–N cross-coupling reaction. With further advancements, the amination reaction of aryl, vinyl, and heteroaryl halides transformed this reaction into a respectable synthetic chemistry technique [1,2] In many fields of

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fundamental and applied study, the Pd-catalysed cross-coupling of amines with aryl halides and pseudohalides to produce C–N bonds has become a very versatile technique for the synthesis of aromatic amines. [3] .The use of this technique has been remarkably extensive due to the pervasiveness of arylated amines in natural goods, medicines, organic materials, and catalysts. Protocols have become more dependable and general as a result of the ongoing discovery of better ligands and pre-catalysts. The usefulness and adaptability of this transformation have been clearly illustrated in the literature over the last 20 years in a variety of chemical research domains.[4] **.**Extensive mechanistic studies, ligand/precatalyst design, and optimisation studies have led to the discovery of reaction conditions of significant generality since the initial reports of Pd-catalyzed N-arylation processes. This generality, along with the readily available amine nucleophiles, (hetero)aryl halides, and sulfonates (made from the corresponding phenols), makes Pd-catalyzed methods an attractive substitute for more conventional arylamine synthesis techniques, such as Cu-catalyzed Ullmann and Golberg couplings and nucleophilic aromatic substitution (SNAr), both of which have a more constrained substrate scope.[5,6]

Diverse novel catalytic systems with magnificent effectiveness on hindered amines and low-activity compounds were accomplished by developing structurally diverse ligands. For example, phosphine ligands with well-defined structural properties, such as large, bulky, and sterically hindered groups, can perform the coupling of massive kinds of amines, such as heterocyclic, primary, secondary, and electron-deficient, with aryl halides or heteroaryl halides. But even with improvements, phosphine ligand synthesis can still be difficult, especially for complex or chiral compounds.[7] Low yields, challenging purification procedures, and the requirement for specialised tools or reagents are typical problems. Research on using other ligands like NHCs that are more effective and scalable is still ongoing, which can replace the use of bulky phosphine ligands.

For the homogeneous catalysts to become active, ligands (such as phosphine or N-heterocyclic) must be used. Therefore, the biggest issue in this research has been separating these catalysts (the complex, the ligand, or the Pd metal) from the reaction medium. Since these reactions are at the forefront of the pharmaceutical industry's manufacturing, the catalyst is subsequently absorbed into the finished product, leading to catalyst loss and a devalued product. It takes costly nanofiltration membranes or a lengthy (and typically destructive) column chromatography separation to successfully separate these homogenous catalysts from the product solution.[8]

Determining the characteristics of the active catalyst species has proven to be the primary obstacle in the creation of heterogeneous catalytic systems for C–C cross-coupling processes. The opposite is true for heterogeneous catalysts, whereas the literature on homogeneous systems is well-developed, and the mechanism is well understood. In the subject of cross-coupling reactions, there is still much disagreement over the actual nature of the active catalyst when a solid substance containing palladium is used as a catalyst.

Although palladium catalysts are effective, their immobilisation onto solid supports resolves catalyst recovery and recyclability concerns, improving cost-effectiveness and environmental sustainability in large-scale applications.

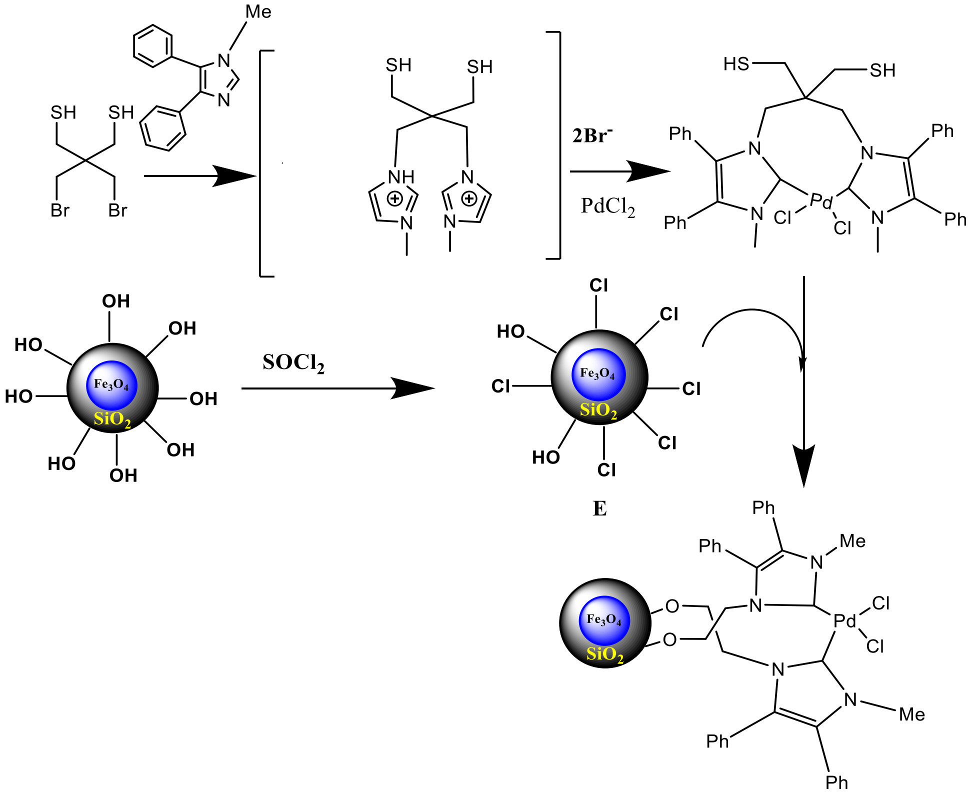
The creation of a hydroxyl-functionalized bis-ionic liquid for use as a bidentate bis (NHC)'s ligand in transition metal catalysis was documented in this work. A significant class of NHCs, bidentate bis-NHCs, is frequently employed as ligands in the synthesis of metallacycle complexes in a variety of applications, particularly catalysis. This type of NHCis not only reactive but also capable of forming extremely stable metal complexes that can be employed in challenging reaction scenarios. This ionic liquid can be directly connected to solid surfaces like MNPs, thanks to its hydroxyl functional groups.[9-14]

One of the recommended materials to modify MIONPs is SiO_2, an acidic oxide with stable chemical characteristics, biocompatibility, low toxicity, acid resistance, and high temperature resistance; MIONPs coated with SiO_2 have a core–shell structure and are also known as MIONPs@SiO_2 nanoparticles. SiO_2 is rich in hydroxyl groups and can protect MIONPs from electrostatic repulsion. Better adsorption, elution, and purity for DNA extraction may be possible with MIONPs@SiO2's special properties, such as well-dispersion, high saturation magnetisation, good surface topography, and exceptional acid resistance. MIONPs@SiO2 nanoparticles have been synthesised in recent years using better techniques, such as the sol–gel and Stöber processes.[15,16]

Result and Discussion

Preparation of Catalyst

The synthetic route for the synthesis of the Pd-NHC-MNP complex is shown in Scheme 1. As described in Scheme 1, the Pd-NHC-MNP catalyst has been synthesised in a four-step process. First, 2, 2-bis (bromomethyl) propane-1,3-dithiol (A) was reacted with 1-methyl-4,5-diphenyl-1H-imidazole in order to synthesize ionic liquid 1-(3-mercapto-2-(mercaptomethyl)-2-((3-methyl-1-H-imidazol-3-ium-1-yl)methyl)propyl)-3-methyl-1H-3λ^4-imidazol-1-ium(B). The ionic liquid B, in the presence of PdCl2, forms a novel Pd-NHC complex(C). The reaction between chlorinated magnetic nanoparticles E and Pd-NHC catalyst (F; Pd-NHC-MNP). For the synthesis of E, the synthesised magnetic nanoparticles (D) were treated with thionyl chloride to convert them into hydroxyl functional groups on the surface of magnetic nanoparticles to chlorine.



Pd-NHC-MNP

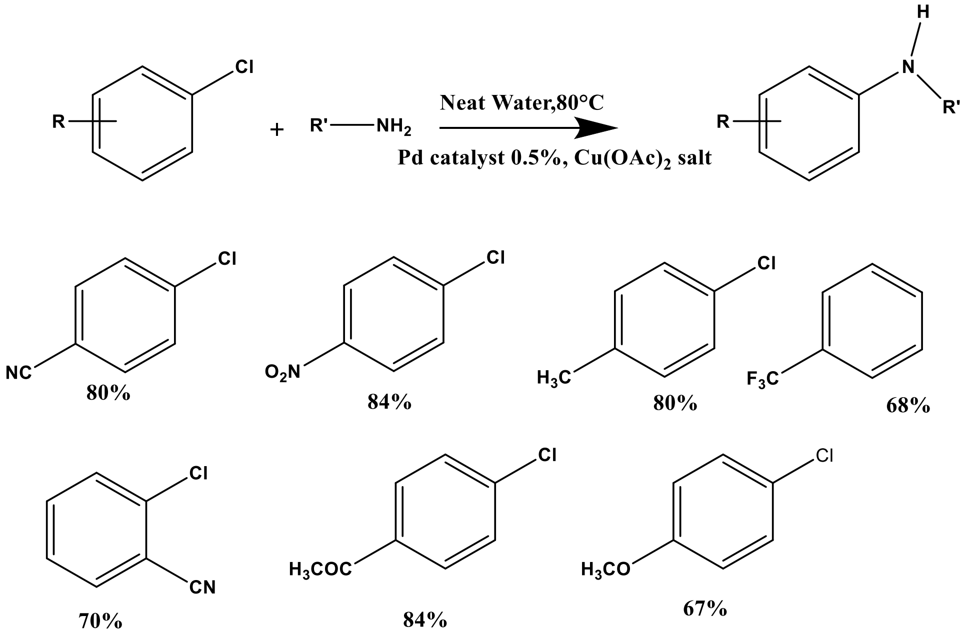
Scheme 1 Synthetic route towards synthesis of Pd-NHC-MNP

Pd-NHC-MNP Catalyst for C-N Coupling Reactions

The catalytic activity of the heterogeneous catalyst was investigated in C-N coupling reactions of aryl halides with methyl amine. In this manner, the reaction parameters such as temperature, catalyst amount, kind of base, and solvent were optimized in the reactions of 4-chlorobenzene with methyl amine in the presence of Pd-NHC. The result was summarized in Table 1. The progression of the reaction was examined by gas chromatography using the MNP catalyst. (GC). Different amounts of catalyst were used, and the best result was obtained by 0.25 mol% of the catalyst (Table 1, entries 1-3). It was also observed that in the absence of a catalyst, no product was detected. This coupling reaction was found to be highly sensitive to reaction temperature. The highest yield was obtained at 90^{o}C (Table 1, entries 5-7).

When the model reaction is carried out in the absence of base, a good yield is obtained. It was also observed that the presence of copper acetate was necessary for the completion of the reaction. Different copper salts were examined as a co-catalyst for C-N coupling reactions, Table 1 (entry 11-12). It was found that 4mol% of $Cu(OAc)_2$ is sufficient to produce an optimum yield of C-N coupling reactions. Then we further move to optimise the reaction with the type of solvent. Different aqueous solvents such as DMF, DMSO, EtOH, and toluene were used as reaction media, and the best result was obtained in water (Table 1, entries 13-16).

Entry	Solvent	$Cu(OAc)_2$ mol%	Cu-salt	Pd(%)	T°C	Yield(%)
1	Water	4	$Cu(OAc)_2$	0	90	0
2	Water	4	$Cu(OAc)_2$	0.12	90	78
3	Water	4	$Cu(OAc)_2$	0.20	90	86
4	Water	4	$Cu(OAc)_2$	0.25	90	97
5	Water	4	$Cu(OAc)_2$	0.25	r.t	Nd
6	Water	4	$Cu(OAc)_2$	0.25	50	58
7	Water	4	$Cu(OAc)_2$	0.25	120	97
8	Water	1	$Cu(OAc)_2$	0.25	90	50
9	Water	2	$Cu(OAc)_2$	0.25	90	68
10	Water	3	$Cu(OAc)_2$	0.25	90	80
11	Water	4	$CuCl_2$	0.25	90	45
12	Water	4	Cu-salt	0.25	90	48
13	DMF	4	$Cu(OAc)_2$	0.25	90	38
14	Toluene	4	$Cu(OAc)_2$	0.25	90	45
15	EtOH	4	$Cu(OAc)_2$	0.25	90	40
16	DMSO	4	$Cu(OAc)_2$	0.25	90	34



Scheme 2 Substrate scope of aryl chloride with primary amines

Conclusion

For the Buchwald C-N coupling reaction of aryl and heteroaryl iodides, we have created an effective, diverse, and reusable catalytic system. The Buchwald C-N coupling reaction of various amines with a range of aryl and heteroaryl halides could be carried out using the reaction, which was optimised with respect to several parameters. This showed the wide range of applications of the methodology by providing good to excellent yields of the desired products. The designed catalyst was shown to be efficiently recyclable for four successive cycles without a discernible reduction in catalytic activity, and catalyst reusability and Pd leaching were also investigated.

Experiment-Sections: Every chemical was purchased from Lancaster (Alfa-Aesar), Sigma Aldrich, and used straight away. For every study, amorphous Pd/C (10 wt.%) was utilised. GC analysis using a Perkin-Elmer chromatograph (30 m * 0.32 mm, 1D-0.25 µm BP-10) was the basis for optimised yields. GC-MS analysis (Shimadzu QP 2010) and 1H and 13C NMR spectroscopy (Varian Mercury 300 NMR Spectrometer) were used to characterise each product.

General experimental protocol for C-N coupling Reactions: An oven-dried resealable tube equipped with a stir bar and Teflon septum was charged with pre-catalyst, aryl halide (1.00 mmol), and amine (1.20 mmol) if they are solids. Then the aryl halide and amine are added if they are liquid, followed by 1 mL of distilled water. The reaction was heated at 80° C and monitored by thin-layer chromatography or gas chromatography, observing the disappearance of the aryl halide. After completion, the reaction was cooled to room temperature, diluted with ethyl acetate, and filtered through Silica gel. The crude product was then purified by flash chromatography.

These pre-catalysts are expected to significantly expand the range of cross-coupling reactions that are catalysed by palladium.

Recycling of the Catalyst

The process for recycling a catalyst involved first washing it with 10 mL of distilled water and then with 5 mL of methanol to get rid of any organic material that might have been present. After 12 hours of drying at 200 °C in an oven, the catalyst was utilised for the following cycle.

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