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Pd/C-Catalyzed Coupling of Nitroarene with Phenol: Biaryl Ether Synthesis and Evidence of an Oxidative-Addition-Promoted Mechanism

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Abstract: Nucleophilic substitution in nitroarenes to form biaryl ethers is of fundamental importance in organic synthesis. Under non-catalytic conditions, this can occur when a highly activated nitroarenes are used, or the nucleophile is activated by strong stoichiometric base. We have established a new method, using ligand-free palladium on carbon (Pd/C) catalyst, for the cross-coupling of activated nitroarenes with relatively non-nucleophilic phenol derivatives, including naphthol, in the absence of harsh bases. Control experiments, hot-filtration, three-phase test and ICP-AES analysis reveals that the catalysis proceeds via a usual oxidative addition step of nitroarene to Pd/C and releases active palladium particles having an extremely high catalytic activity. DFT calculations were made to realize the origin of selectivity of activated nitroarenes.

Palladium-catalyzed cross-coupling reactions has proven to be an excellent method for the selective activation of unreactive bonds such as C-C,^[1] C-N,^[2] C-O^[3] and C-H^[4] to provide unique organic transformations. In contrast, strategy involving the activation of C_{aryl}-N bond of nitroarenes to utilize as arylintermediate has not been widely adopted. Activated nitroarenes typically undergoes S_NAr with alkoxides or aryloxides to give ether (**Scheme 1a**).^[5] However, existing S_NAr methods suffers many drawbacks, such as limited substrate scope, harsh reaction conditions, and the need to use strong nucleophiles.

Given the ubiquitous nature of ethers in bioactive molecules and the drawbacks associated with their conventional synthetic methods, the exploration of alternative synthetic routes is highly desirable. Chen and coworkers have recently reported the first mild cross-coupling approach using a Rh(I)-phosphine catalyst system with arylboronic acid substrates activated by DMF-Cs₂CO₃ (**Scheme 1b**).⁽⁶⁾ Latterly, some Pd and Cu catalyst were also found to activate C_{aryl}-N bond of nitroarenes towards crosscoupling with arylboronic acids^[7] and phenols.^[8] These strategies provide promising scope to study the controlled substitution pattern of nitroarenes and to develop alternatives to eliminate the conventional toxic and expensive aryl halides

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(Scheme 1c).^[9] However, for a method to be ideal for industrial application, efficient separation and reduction of residual metals and ligands during products isolation is a topic of serious concern.^[10] These additional processing steps could be avoided by combining the advantage of molecular catalyst and heterogeneous processes, ideally maintaining or even improving high efficiency and easy recovery.



Scheme 1. Synthesis of ether derivatives using nitroarenes

Recently, we have observed that the Pd/C-catalyzed carbonylative coupling of arylboronic acid with acid chloride gave residual Pd levels lower than 0.030 ppm in the reaction mixture.^[11] With this motivation, we sought to determine if a similar catalytic system could be utilized in cross-coupling of nitroarenes with phenols with residual Pd within acceptable levels. Herein, we investigate the prowess of ligandless Pd/C in the activation of the C_{aryl}-N bond by the oxidative addition, which enables the use of relatively non-nucleophilic phenols that otherwise require stoichiometric activation with strong bases (**Scheme 1d**). We have also investigated whether the catalysis is occurring at the surface of the catalyst or in the solution, which indeed a characteristic of various immobilized catalyst.^[12] Control experiments and ICP-AES study during the reaction provide insight into the behaviour of the Pd/C catalyst, which

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undergoes a reversible dissolution-precipitation of active palladium particles.



The cross-coupling of 4-nitrobenzaldehyde 1a and phenol 2a using 10% Pd/C was chosen as model reaction, and the optimization is outlined in Table S1 (see: ESI†). Reaction using Pd/C (0.5 mol%) and 1 equiv. K₂CO₃ in DMSO (4 mL) at 100 °C for 6 h provides desired product in 70% yield. Further improvement was observed when water (4 equiv.) was added, which gave a significant increase to 97% yield (Table S1, entry 2). The use of polar aprotic/protic combination of DMSO and water at high temperature was critical to enhance the reaction yield. High yield in polar aprotic solvents are also attributed to the high solubility and stability of in situ formed aryloxides for superior nucleophilic substitution.^[13] These results are highly significant, as most conventional ether synthesis requires high catalyst loading, and strong base.^[14] Use of other commonly employed solvents like THF and toluene (see Table S1, entries 3 and 4) offered no appreciable outcomes in terms of reaction time and yield. Optimization using common bases, such as Na₂CO₃, Na₃PO₄, KOH and *t*-BuONa, provided lower coupling yield (Table S1, entries 6-9). On performing the reaction without any catalyst or base or with charcoal without palladium (Table S1, entries 10-12) no significant conversion occurred; this result confirmed that the catalysis take place in the presence of the palladium and added base.

With optimized conditions, we next examined variations in both coupling partners (**Table 1**). Using 4-nitrobenzaldehyde **3a**, a variety of phenols were analyzed. Phenols bearing 3- and 4-

formyl, bromide, methyl and *t*-butyl substituents were well tolerated, as shown by the formation of ethers **3aa-3af**, respectively. Products derived from electron-deficient phenols provided slightly lower yield, though still > 80%. Fused ring, 2-hydroxynaphthalene, could also be used, as demonstrated by the formation of **3ag**. Substitution on the nitroarene coupling partner was also well tolerated. For example, acetyl- and chloride-containing substrates underwent effective coupling to give ethers **3ba-3ce**.

In cross-coupling reactions involving immobilized palladium catalyst, it is widely reported that the catalyst act as a reservoir for Pd species operates by a release and capture mechanism (a quasi-homogeneous pathway).^[12,15] Consequently, to provide insight into the behaviour of Pd/C catalyst in present reaction, we have conducted a series of established studies^[16] which suggest the homogeneous nature of the active catalyst species and the involve mechanism (see the **ESI**†).

- Hot-Filtration test: The hot reaction mixture was filtered to remove the solid catalyst, and the filtrate was allowed to react and subsequently monitored (see: Figure S1, ESI†). Substrate conversion was observed in the filtrate, suggesting that the leaching of active catalytic species occurs.^[12] ICP-AES analysis of the liquid phase reveals residual Pd level ≈11 ppm. The catalytic activity of this released Pd species should be very high, as the reaction proceeds under a trace amount of Pd species.^[17]
- 2) Three-phase tests[18]: Substrate 1b was replaced by silica bound nitroarene (PNA@silane).^[19] PNA@silane can react with only the leached Pd species (provided no significant metal-free background reaction) from the Pd/C catalyst.^[18] Cross-coupling was performed by adding 1a and PNA@silane, and conversion of both soluble and supported substrate was estimated. The majority of 1a consumed, along with 19% (3ba) product from the coupling of PNA@silane. This result indicates that a small amount of the active Pd species was released from Pd/C into the solution to catalyze the solid substrates. However, negligible amount of surface bound PNA@silane were converted in the absence of 1a. This suggests that the leaching of active palladium particles from Pd/C surface occurs only in the presence of a soluble nitroarene.
- **3) Hg-poisoning test**: It is also supported by a negative Hgpoisoning test, suggesting a homogeneous catalytic species.^[20] Therefore, we can assume that the oxidative addition of **1a** to the Pd/C promotes the release of active Pd(II) species from solid into the solution. These results are in agreement with the mechanisms proposed by Jutand and Amatore,^[21] de Vries,^[22] Reetz,^[23] Beletskaya,^[24] and others.^[25]
- 4) Reusability test: The recycled reaction rates for runs 1 to 5 were excellent to quantitative in all cases (See: Figure S3, ESI†). ICP-AES analysis of the isolated coupling products reveals residual Pd levels ≤1.2 ppm. Slight loss in reactivity during repeated reusability is probably due to physical loss of catalyst^[26] and suggests that the leached Pd get precipitated back into the carbon surface after completion of the catalytic cycle.^[12d, 27]

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It is highly intriguing that these experiments suggest, as shown in **Scheme 2**, that the oxidative addition of nitroarene to the Pd surface atoms favors their extraction, yielding ArPd(II)NO₂ moieties into the solution to ultimately deliver the final product and free Pd(0), which can either further react or redeposit onto Pd/C surfaces. The precipitation of leached Pd into the surface may occurs as the concentration of nitroarene get decreased.^[28] Indeed, it is also in consistent with the reports on reversible dissolution-precipitation of palladium.^[12] Although the chemical basis for the relation between oxidative addition step and dissolution of the palladium particles from Pd/C surface is not clear at this stage, a likely explanation is a net electron flow from the Pd surface to the adsorbed aryl group, implying a decrease in electron density on the palladium and subsequent desorption from Pd/C surface.



Scheme 2. Plausible reaction mechanism and dissolution-precipitation of Pd

In contrast to the conventional halide substrates, an unusual divergence in selectivity is seen in the cross-coupling of nitroarenes. Cross-coupling with nitroarenes are restricted to the use of activated nitroarenes only.^[7c] To understand this, we have calculated LUMO energies of p-nitrotoluene, nitrobenzene and p-nitrobenzaldehyde at LC-BLYP/6-31++G(d,p) level of theory (Table 2). All the calculations were performed using GAUSSIAN09 suite of program.^[29] It is seen that, LUMO of pnitrobenzaldehyde is highly stabilized in comparison to both pnitrotoluene and nitrobenzene. This indicates that the flow of electron from Pd(0) to substrate is more efficient in pnitrobenzaldehyde (lowest in energy) than in p-nitrotoluene or nitrobenzene, which then undergoes oxidative addition to produce intermediate TS1. This enables relatively nonnucleophilic phenol (in presence of weak base) to undergo nucleophilic substitution with TS1 to give coordinated complex TS2. The subsequent reductive elimination will be facile, and the complex TS2 eventually releases the product and regenerates intermediate Pd(0) for the next catalytic cycle. With the optimized reaction conditions, we carried out a large scale diaryl ether synthesis, and the 10 mmol scale reaction preceded smoothly giving 98.1% yield of the desired product. Overall, the

present method is an excellent example of an ideal and real green method. $^{\left[30\right] }$



In conclusion, a simple ligandfree approach for the crosscoupling between nitroarenes and phenols to access diverse diaryl ethers is developed. Various electronically diverse activated nitroarenes were evaluated to expand the scope of non-conventional electrophiles that can be utilized for ether synthesis in the absence of harsh bases. It is also established that the catalysis proceeds via the oxidative addition of C-N bonds, which then releases active Pd(II) species into the solutions. With the merit of commercial catalyst, low loading, rapid and ease of reaction (open air), and a usable^[31] nonflammable solvent, this protocol expands the synthetic portfolio of nitroarenes. The work done are highly significant in investigating the mechanistic insights and improving current methodologies, as well as developing new strategies for distinguishing homogeneous and a true heterogeneous catalyst.

Acknowledgements

T. B. and M.P.B. are thankful to CSIR, New Delhi, for CSIR-Senior Research Fellowship.

Keywords: C-O coupling • palladium • ethers • density functional theory • palladium leaching

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Pd/C activates C-N bond of nitroarene generate aryl-palladiumto intermediate, which undergo coupling non-nucleophilic with relatively phenols in the presence of a weak base (K₂CO₃) under open air. From mechanistic investigations, the reaction undergoes oxidative-additionmechanism. DFT promoted calculations were made to realize the origin of limited selectivity of activated nitroarenes.



C-O Bond Coupling

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