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O-Arylation with Nitroarenes: Metal-Catalyzed and Metal-Free Methodologies

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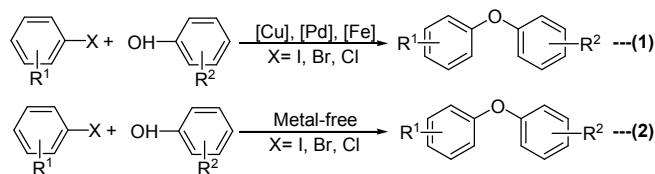
In this article, we focus the introduction of nitroarene as alternative electrophile for C_{aryl}-O cross-coupling chemistry. In polar aprotic solvent and in the presence of base at elevated temperature nitroarene undergoes cross-coupling with arylboronic acids or phenols under metal or metal-free reaction conditions. Compared to the conventional aryl halides, nitroarene provides highly attractive and environment friendly options for the synthesis of diaryl ether derivatives.

1. Introduction

Transition metal-catalyzed cross-coupling reaction has become a significant methodology for the formation of carbon-heteroatom and carbon-carbon bonds *via* the connection of electrophilic and nucleophilic fragments.¹ In this domain, the development of Ullmann chemistry for the synthesis of diaryl ether has received extensive attention. Conventionally, when the term “*O*-arylation chemistry” is mentioned, the prime consideration is the use of aryl halides as electrophile in presence of stoichiometric or catalytic amount of either copper², palladium³ or iron⁴ based catalyst (Scheme 1, eq 1). However, aryl halides are generally environment pollutants, and the byproduct generated from their coupling often hampers the isolation and purification process of the desired products. Additionally, irrespective of their reactivity (Cl << Br < I), their

availability (I << Br < Cl) and cost limits widespread applications. Consequently, numerous novel electron-rich ligands and related metal complexes were developed as catalyst which have brought the successful coupling of even less reactive though abundant and inexpensive aryl chlorides under mild condition.⁵ Although, a plethora of electronically and structurally diverse aryl halides are available these days, some of the structurally targeted substrates required for multistep synthesis may not be easily accessible. However, very few methods for *O*-arylation with activated aryl halides in absence of metal are available in literature⁶ (Scheme 1, eq 2). Thus, the exploration of efficient alternative electrophile is getting considerable attention not only due to academic interest but to provide additional options when a particular application is under consideration.

In addition to the use of aryl halides, nitroarenes are another attractive alternative for C_{aryl}-O bond formation reaction. Activated nitroarenes contain *ortho*- or *para*-substituted electron withdrawing group which facilitates the nucleophilic aromatic substitution (S_NAr) to produce diaryl or aryl-alkyl ether in presence of strong nucleophiles. Although, it was a significant method developed for the synthesis of ethers, the use of highly reactive nucleophiles competes with many functional groups resulting in limited application. Recent developments in this area have stimulated a number of researchers to study the controlled substitution pattern of activated nitroarenes under metal catalyzed



Scheme 1. Conventional metal catalyzed and metal free O-Arylation.



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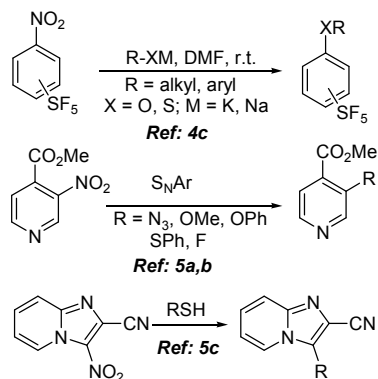
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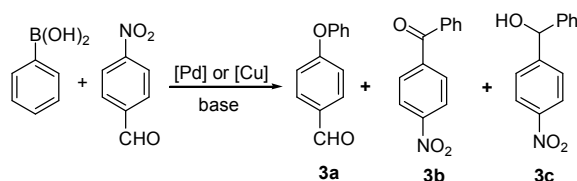
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mild reaction condition.



Scheme 2. S_NAr Reactions of some activated nitroarenes.



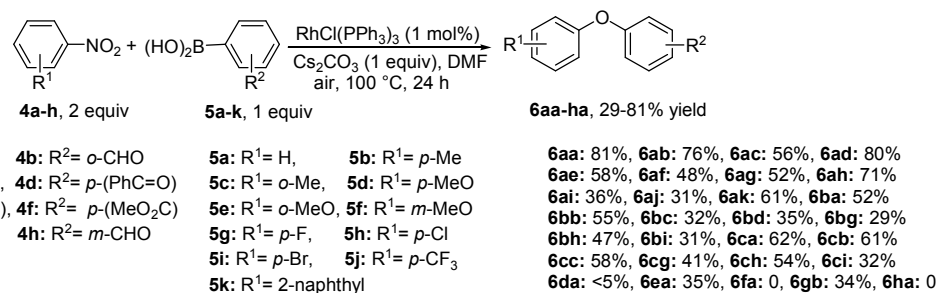
Scheme 3. Pd or Cu catalyzed C-O cross-coupling of nitroarenes.

Apart from being a significant precursor of a variety of substituents in organic system, the nitro group, which is not usually lost in aliphatic systems, is a particularly good leaving group in S_NAr reactions when activated by an *ortho*- or *para*-substituted electron-withdrawing group. The extent of activation is so high, as examined in many studies that the rate of displacement of an activated nitro group increases relatively higher than that of the chlorine or bromine group.^{7a} The presence of *ortho*- or *para*-substituted electron-withdrawing group increases the polarity of carbon-nitrogen bond,

and acts as highly activating group in S_NAr reactions by stabilizing the reaction intermediates through resonance. This disparity facilitates the nucleophilic *ipso*-substitution yielding synthetically important structural motifs *e.g.*, diaryl or aryl-alkyl ethers (and thioethers).⁷ Thus, activated nitroarenes like nitro-(pentafluorosulfonyl)benzenes,^{7c} nitro-pyridine-4-carboxylate^{8a,b} and nitroimidazo[1,2-*a*]pyridine^{8c} have been used in various S_NAr reactions (Scheme 2). Despite the usefulness of these methodologies,⁹ the harsh reaction condition and high sensitivity of the nucleophile towards adjacent functional group generates unwanted side products thereby limiting extensive applications. This drawback has made nitroarene less familiar in the cross-coupling domain until the development of transition metal based catalytic systems.

Wu and co-workers serendipitously discovered that 4-phenoxybenzaldehyde **3a** formed as a secondary product during the palladium- or copper-catalyzed synthesis of (4-nitrophenyl)(phenyl)methanone **3b** and (4-nitrophenyl)(phenyl)methanol **3c** from the coupling of phenylboronic acid **1** with 4-nitrobenzaldehyde **2** (Scheme 3).^{10a}

This finding has opened the door for the introduction of nitroarene reagents as alternative electrophile for C_{aryl} -O cross-coupling chemistry. Encouraged by this observation, Wu and co-workers have developed a rhodium(I)-based catalytic protocol for the synthesis of diaryl ethers using activated nitroarenes and arylboronic acid.^{10a} Thereafter, Wu,^{10b,c} Chang¹¹ and Phan¹² have developed various copper- and palladium-based catalytic protocol for the synthesis of diaryl ethers using activated nitroarene and arylboronic acid or phenol. These novel approaches, reported recently have gained significant popularity, as they proceeds in excellent yields and utilizes easily available substrates. In addition, the reaction condition tolerates all fluoro, chloro and bromo moieties in arylboronic acids (and in nitroarene¹³), which are commonly used in various cross-coupling reactions, and thus has many further synthetic utility. Herein, we focus on the recent developments made



Scheme 4. Rhodium-catalyzed cross-coupling of arylboronic acids with nitroarenes.



Dr Utpal Bora received his PhD degree in 2005 under the guidance of Dr R. C. Boruah at CSIR-NEIST-Jorhat. He was awarded JSPS postdoctoral fellowship in 2005 to work under the supervision of Professor Hironao Sajiki at Gifu Pharmaceutical University, Gifu, Japan. After completion of JSPS postdoctoral tenure, he joined at Syngene International Limited, Bangalore and then moved to the

Department of Chemistry, Dibrugarh University, Dibrugarh as Assistant Professor in 2008. Recently he has joined at the Department of Chemical Sciences, Tezpur University, Tezpur as Assistant Professor. His research interests include catalysis, new synthetic strategies, and green chemistry.

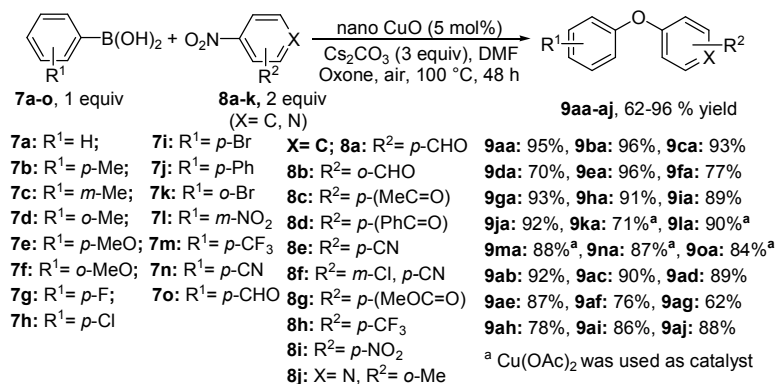
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in the Ullmann cross-coupling of activated nitroarenes with *O*-nucleophiles, such as arylboronic acid and phenol. These reactions are preferentially metal catalyzed; however, under microwave condition at high temperature it precedes without metal.¹³

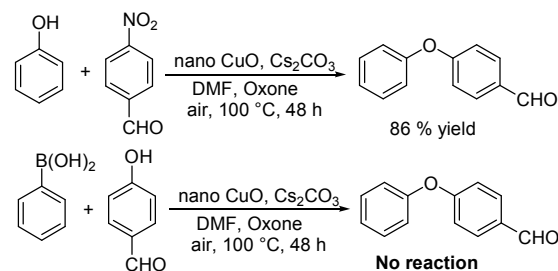
2. *O*-Arylation of arylboronic acids with nitroarenes

2.1 By using a rhodium(I) catalyst

In 2011, Wu and co-workers have reported for the first time that the cross-coupling of activated nitroarenes **4a-h** and arylboronic acids **5a-k** in presence of rhodium(I) complex produces unsymmetrical diaryl ethers **6aa-6ha** in excellent yield (Scheme 4).^{10a} The reaction is compatible with dipolar aprotic solvents such as DMF, DMSO and NMP, delivering best results in presence of Cs₂CO₃. Initial



Scheme 5. Copper-catalyzed O-arylation of arylboronic acids with nitroarenes.



investigation of the model reaction in presence of catalytic amount of Pd(OAc)₂ and PdCl₂ under various reaction conditions provides only trace amount of the desired product. The choice of ligands and metal complexes also plays significant role, as phosphine ligated complex like RhCl(PPh₃)₃ exhibits excellent catalytic activity (upto 81%) compared to complexes having higher or neutral oxidation state. Although, nitroarene bearing *o*- or *p*-formyl, acetyl, sulpho and cyano functional group are well tolerated under this reaction condition, trace or no product was observed with substrates like (4-nitrophenyl)(phenyl)-methanone **4d**, methyl 4-nitrobenzoate **4f** and *m*-formyl nitrobenzene **4h**. Coupling of nitro-pyridine, which is also activating in nature, was not described.

The chemistry behind this reaction, as it includes an organic electrophile, organometallic nucleophile and a base seems mechanistically identical to the general transition metal catalyzed cross-coupling reactions. The observations like: (i) no reaction under metal-free condition, and (ii) formation of aryloxy anion intermediate (by isotope labeling experiment),^{10a,b} suggest that the reaction proceeds *via* oxidative addition of nitroarene with metal followed by the transmetalation of the organometallic intermediate. Moreover, the advantage of using cesium over other alkali-metal bases had been previously revealed in the contexts of Williamson- and Buchwald-ether synthesis.¹⁴ Cesium ion, possessing large cationic charge, low charge density and high electronic polarizability,¹⁵ exhibits lowest degree of solvation compared to analogous alkali metal ions. Hence, in polar aprotic solvents, having high dielectric constant better performance is endorsed to the higher solubility and stability of *in situ* formed cesium aryloxides, which delivers superior nucleophilic reactivity.¹⁶ Nevertheless, in contrast to Cs₂CO₃, K₂CO₃ displays almost identical basicity although less solubility¹⁶ and could be a preferred base when the choice of solvent is DMF or DMSO. However, the use of other strong nucleophilic bases, such as ^tBuOK, LiF, CsF, in the above reaction replaces the

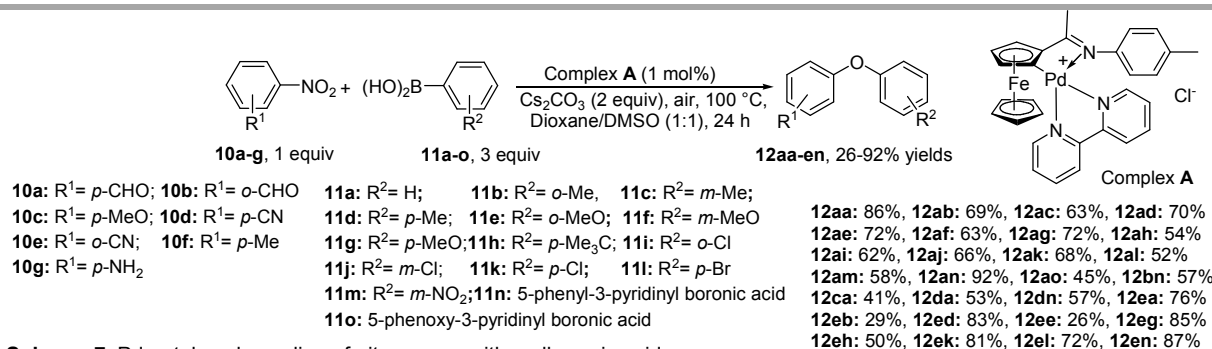
nitro group *in lieu* of aryloxy anion intermediate and lowers the yield of diaryl ether.

2.2 By using a nano CuO catalyst

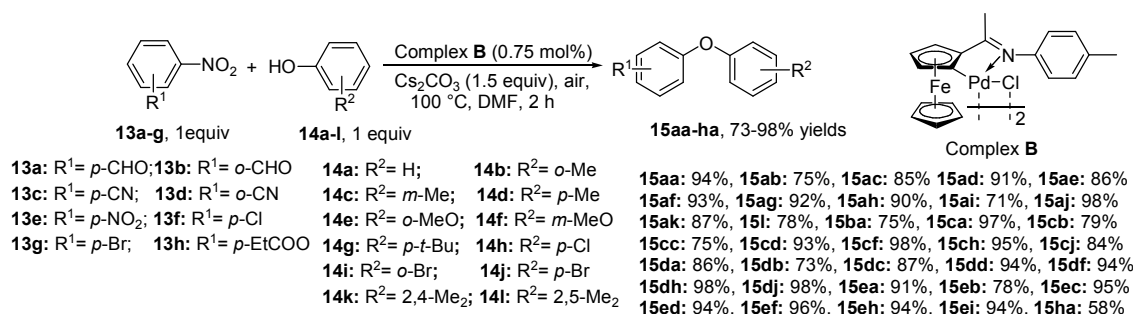
Wu *et al.* reported a great acceleration of C-O cross-coupling catalyzed by copper-oxide nanoparticles and the addition of one equivalent of oxone (potassium peroxymonosulfate, 2KHSO₅·KHSO₄·K₂SO₄), an efficient oxidant in DMF (Scheme 5).^{10b} The electronic property of the substituents on the phenyl ring of arylboronic acids showed negligible effect on the reaction and no side reactions like homo-coupling and protodeboronation were observed. Moreover, heterocyclic nitroarenes and organoborons, such as 2,4,6-triphenylboroxin and 2-phenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, delivers excellent yield. When controlled experiment were performed under standard condition (Scheme 6), the reaction between 4-nitrobenzaldehyde and phenol gave isolated yield of diaryl ether (86%), whereas no product was noticed when phenyl boronic acid and 4-hydroxy-benzaldehyde were treated. These provide conclusive evidence that the reaction proceeds *via* oxidative addition and transmetalation of aryloxy anion intermediate.

2.3 By using a 2,2'-bipyridine-palladacycle catalyst

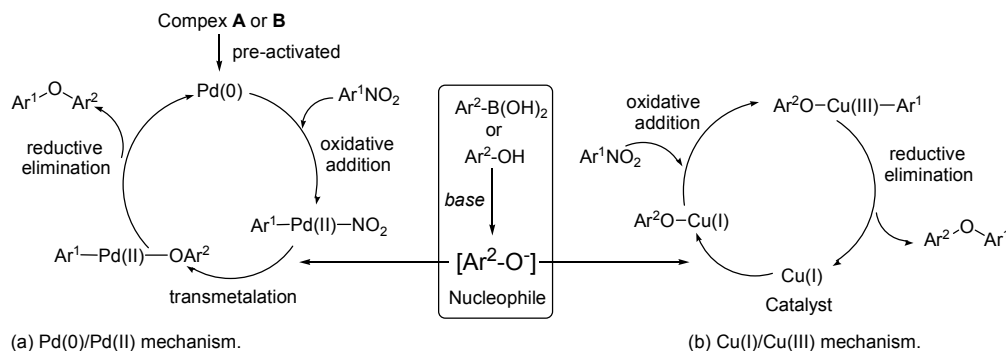
Meanwhile, chemists have started to investigate other possible metal catalyst for attaining this catalytic conversion effectively. The first example on palladium-catalyzed denitrated cross-coupling was achieved in co-solvent dioxane/DMSO systems (Scheme 7).^{11a} Chang *et al.* used this strategy employing a highly electron rich cyclopalladated ferrocenylimine complex **A** (Scheme 7). They used a combination of both Pd and Fe metal as the catalytic species and Cs₂CO₃ as base at 100 °C. Although, the method tolerates many heterocyclic boronic acids, *ortho*-substituted arylboronic acids are



Scheme 7. Pd-catalyzed coupling of nitroarenes with arylboronic acid.



Scheme 8. Palladium-catalyzed O-arylation of nitroarenes with phenols.



Scheme 9. Probable reaction pathways.

sensitive to steric effect and resulted in much lower yields. Moreover, under present reaction condition, palladium promotes homo-coupling and protodeboronation of boronic acid (side reactions) hampering isolation and purification process. Controlled experiment with 4-nitrobenzaldehyde and phenol gave nearly quantitative yield of the desired product.

3. O-Arylation of phenols with nitroarenes

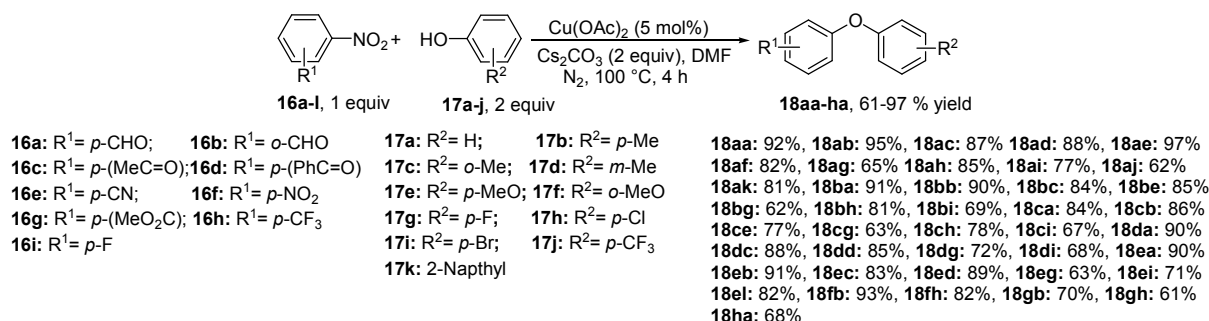
3.1 By using a cyclopalladated ferrocenylimine catalyst

In another case, when an equimolar amount of nitroarene and phenol were treated in presence of complex **B** (Scheme 8), Cs₂CO₃ and DMF, excellent yield of diaryl ether was obtained within 2 h (Scheme 8).^{11b} In these above-mentioned reactions, it is observed that the reactivity of the activated nitroarene for the coupling reaction is opposite to that observed for general aromatic nucleophilic substitution S_NAr, as it relies on the use of metal catalyst. The conclusion is that probably the metal is involved in the activation of the nucleophile and may to a certain extent interact with the nitroarene. Considering the standard Pd-catalyzed cross-coupling reactions, it can be assumed that these reaction also

proceeds with the pre-activation of palladacycle (complex **A** and **B**) forming Pd(0). Moreover, it appears that the oxidative addition of nitroarene forms arylpalladium species and the presence of base transforms boronic acid or phenol into aryloxy anion intermediate. The arylpalladium species provides diaryl ether *via* transmetalation with aryloxy anion intermediate followed by reductive elimination (Scheme 9a). Whereas, in case of the copper,¹⁸ it is believed that the actual catalytic Cu(I) is first activated by the nucleophile (to give CuNu or CuOPh) followed by oxidative addition of ArNO₂ (*via* a Cu(III)), finally the product is obtained by reductive elimination (Scheme 9b). Another probable mechanistic pathway may include the involvement of the single electron transfer (SET), as it is known that the copper compounds are capable of electron transfer¹⁹ and promotes radical nucleophilic substitution reactions in aromatic systems.²⁰

3.2 By using a copper acetate catalyst

In another attempt, Wu *et al.* have used copper catalyst for the C-O denitrated coupling of nitroarene with phenol.^{10c} In presence of copper acetate under N₂ atmosphere the reaction completes within 4 h and tolerates almost every electronically diverse substrate with

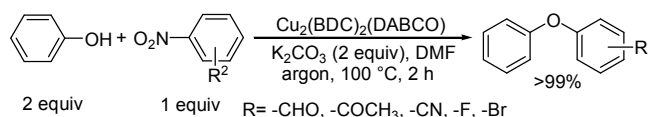


Scheme 10. Synthesis of diaryl ether starting with phenol derivatives.

negligible steric and electronic intervention (Scheme 10).

3.3 By using a recyclable $\text{Cu}_2(\text{BDC})_2(\text{DABCO})$ catalyst

Phan *et al.* have also contributed to the denitrated coupling reaction catalyzed by copper complexes supported on organic framework.¹² They found that a highly crystalline and porous $\text{Cu}_2(\text{BDC})_2(\text{DABCO})$ complex ($H_2\text{BDC}=1,4\text{-benzenedicarboxylic acid}$, $\text{DABCO}=1,4\text{-diazabicyclo}[2.2.2]\text{octane}$) is very active (>99% conversion) for the coupling of nitroarene with phenol at 100 °C. It was evident from the result of optimization that the reaction relies on high temperature and catalyst concentration, and no conversion took place at 30 °C or in the absence of Cu-catalyst after 2 h. The main advantages of this methodology were the use of less expensive K_2CO_3 as base and the catalyst reusability for six consecutive runs without any noticeable decrease in activity. The substrate scope and reactivity are consistent with above-mentioned methods but the role of the bulky Cu-complex in the reaction was not discussed (Scheme 11). Moreover, under both above-stated copper catalyzed conditions 2 equiv. of phenol is necessary to provide optimal yield.



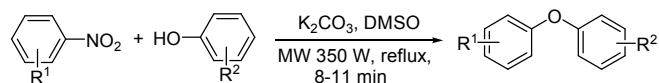
Scheme 11. Recyclable copper based catalyst for coupling of phenol and nitroarene derivatives.

4. Microwave assisted metal-free arylation of phenols with nitroarenes

Until now, it has been considered that the formation of $\text{C}_{\text{aryl}}\text{-O}$ bonds between nitroarenes and O -nucleophile reaction depends on the $\text{S}_{\text{N}}\text{Ar}$ or metal catalyzed conditions. However, the use of a metal catalyst and activated nitroarene is not always necessary, as recently Shinde *et al.* have achieved the denitrated cross-coupling of non-activated nitroarenes with phenols under high temperature microwave-irradiation without a metal catalyst.¹³ Optimum yields of the product were obtained at reflux within 8-11 min (70-92% conversion) in the presence of K_2CO_3 and DMSO (Scheme 12). Similar report on the arylation of O - and N -nucleophiles with activated haloarenes, with or without added metal was recently reported by the Taillefer group.^{6c}

This finding have opened a new avenue of opportunity in the domain of nitroarene-based $\text{C}_{\text{aryl}}\text{-O}$ bond formation chemistry as, until now, it was believed that a transition metal or a strong nucleophile is essential to break the strong sp^2 aryl C-N bond of nitroarene. This metal-free protocol provides:

(i) efficient denitrated coupling with even non-activated nitrobenzene,



19a-d, 1 equiv **20a-i**, 1-1.2 equiv **21aa-ai**, 70-92%

19a: $\text{R}^1 = \text{H}$ **20a:** $\text{R}^2 = \text{H}$, **20b:** $\text{R}^2 = p\text{-F}$ **21aa:** 92%, **21ba:** 82%, **21ca:** 78%
19b: $\text{R}^1 = \text{Br}$ **20c:** $\text{R}^2 = p\text{-Cl}$, **20d:** $\text{R}^2 = p\text{-I}$ **21da:** 78%, **21ab:** 87%, **21ac:** 80%
19c: $\text{R}^1 = \text{Cl}$ **20e:** $\text{R}^2 = p\text{-MeO}$ **21ad:** 82%, **21ae:** 72%, **21af:** 85%
19d: $\text{R}^1 = \text{F}$ **20f:** $\text{R}^2 = 2\text{-NH}_2$, 4-Br **21ag:** 89%, **21ah:** 75%, **21ai:** 70%
20g: $\text{R}^2 = 2\text{-Br}$, 4- NO_2
20h: $\text{R}^2 = 2,5\text{-Me}_2$, **20i:** $\text{R}^2 = 2\text{-Cl}$, 4-Me

Scheme 12. Microwave-assisted denitrated coupling of nitroarenes.

(ii) selective nitro substitution; C-X (-Br, -Cl, -F) and C-NH₂ bond showed no reactivity, and

(iii) coupling under reduced reaction time.

Although, a microwave provides focused and rapid superheating, it may be too early to consider it as the only driving factor for the reaction and to exclude the previous observations related to metal catalysis. Moreover, one can also speculate the possible generation of aryl or aryloxy radical at high temperature condition. Clearly, further information like frontier orbital theory and electrochemical measurement of the reacting partners are needed to understand the mechanistic basis of the coupling. Determination of trace metal impurities (using ICP-AES analysis) in the reaction system may show the presence of other possible catalytic species.²¹⁻²²

Conclusion and Perspective

Replacement of aryl halides from Ullmann chemistry with nitroarenes will undoubtedly provide a sustainable chemical process for the synthesis of diaryl ethers. Although the catalysis under thermal heating conditions is limited to activated nitroarenes, the microwave assisted method proceeds efficiently with both activated and deactivated substrates. Thus, proper understanding with Density functional theory (DFT) calculations of the active catalytic intermediate along with electronic charge distribution of coupling partners will be a major forwarding step to overcome the substrate limitations.

While significant progress has been attained, a series of control experiments, such as thermal coupling, radical scavenging experiments (with traps like 2,2,6,6-tetramethylpiperidine N-oxide (TEMPO), CBrCl_3 , Bu_3SnH , galvinoxyl, electron-deficient olefins, diaryl diselenide) and kinetic isotope effects on the reaction components are still necessary to model the exact pathway of the reaction. Moreover, exploration of unconventional aqueous system will undoubtedly provide significant outcomes, as the plausible mechanism/isotopic experiments (in case of metal-based studies) confirms the generation of aryloxy anion in presence of ambient water.

Thus, these findings need to be confirmed with further studies performed under different experimental conditions. We expect further progress in this area of research, which will lead to a mild and efficient reaction protocol that will tolerate a wide array of substrates, providing better possibilities for cross-coupling chemistry.

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Notes and references

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Table of Content Entry:**Ullmann Chemistry with Nitroarenes: Metal-Catalyzed and Metal-Free Methodologies****Manoj Mondal, Saitanya K. Bharadwaj and Utpal Bora**

Emergence of nitroarene as an alternative to aryl halides in *O*-arylation of arylboronic acid or phenols has been highlighted.

