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Pd/NHC catalyzed reduction and coupling of nitroaromatics for the synthesis of diarylamines†

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Herein, we report a one-pot approach to diarylamines through the reductive homocoupling of nitroaromatics, employing triethylsilane as the reducing agent and Pd/NHC as the catalyst. This method enables nitroaromatics to serve both as electrophilic reagents and as precursors of nucleophilic reagents, allowing for the direct preparation of diarylamines without the need to isolate aromatic primary amines.

Introduction

Diarylamines and their derivatives are important structural constituents of many pharmaceuticals, pesticides, dyes and pigments. Numerous synthetic methodologies have been developed by using readily available starting materials. Amongst the plethora of methodologies for the synthesis of diarylamines, Buchwald–Hartwig coupling[1] and Ullmann coupling[2] of haloarenes and aromatic amines have proved to be the most valuable synthetic approaches. The success of these C–N approaches pivots on the choice of metal catalysts and appropriate ligands. Various phosphines,[3] amides,[2] and NHC[4,5] ligands were employed in the C–N coupling reactions showing satisfactory efficiency.

Pertinent statistics elucidate that aromatic amines are predominantly derived from the reduction of nitroaromatic hydrocarbons.[6] Transition metal catalyzed direct reductive C–N coupling of nitroarenes with an electrophilic partner would be an ideal approach for diarylamines, which diminishes the necessity for an aromatic amine separation step.

Recently, Xue and coworkers described the C–N coupling of aryl halides with nitroarenes by nickel-bipyridine catalysis under light irradiation and mild basic conditions.[7] Some readily available nitroarenes undergo coupling with a variety of aryl halides and proceed *via* the addition of an aryl radical, generated from a Ni^{I}/Ni^{III} cycle, to a nitrosoarene intermediate (Fig. 1a). Weix and coworkers reported the reductive arylation of nitroarenes with chloroarene to form diarylamines using manganese as the reducing agent (Fig. 1b).[8] Under reducing conditions, palladium–phosphine complexes catalyze the dual *N*-arylation of typically inert azoarenes generated *via* the *in situ* reduction of nitroarenes. Kazemnejadi and coworkers described a one-pot synthetic approach to diarylamines through bimetallic nickel–palladium catalyzed sequential reduction of nitroarenes to aromatic amines and further C–N coupling with haloarenes (Fig. 1c).[9] The reductive coupling reaction is well performed by the bimetallic catalyst in the presence of 2.0 equiv. of $NaBH_4$.

In addition to serving as precursors for nucleophilic reagents, nitroaromatics also possess unique advantages as electrophilic reagents, drawing attention.[10–17] Employing nitroaromatics instead of halogenated aromatic can circumvent halogenated waste contamination and certain halogenated aromatic compounds are synthesized through multistep reactions, using nitroaromatics as starting materials.[18]

In light of the dual roles of nitroaromatics in cross-coupling reactions, we contemplated the introduction of a reducing agent into the Pd/NHC catalytic system previously reported by

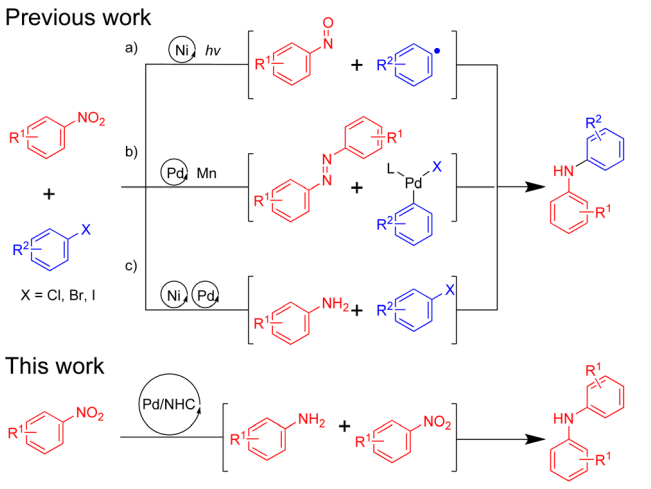

Fig. 1 Transition metal-catalyzed reductive coupling of nitroarenes and haloarenes.

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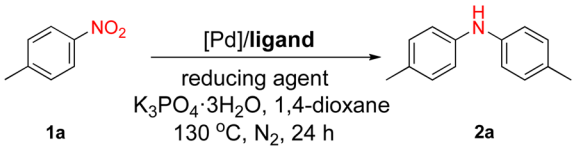
our group.[11,19,20] This would allow nitroaromatics to act both as an electrophilic reagent and as a nitrogen source for the synthesis of diarylamines, thereby broadening the application scope of nitroaromatics and facilitating a novel mode of nitroarene reductive cross-coupling. Although this strategy appears promising, there remain a few challenges to address: (1) achieving the complete reduction of nitroaromatic hydrocarbons; (2) ensuring compatibility between the reduction and the palladium catalytic processes.

Result and discussion

We herein delineate a streamlined synthetic methodology for the construction of diarylamines in a singular step, utilizing nitroaro-matic compounds as the sole aromatic source. This one-step pro-tocol for the synthesis of diarylamines from nitroaromatics cir-cumvents the necessity for amine separation, thereby reducing the overall complexity and number of synthetic steps. To optimize this reaction system, we employed Pd/NHC catalyzed reduction and coupling of 4-nitrotoluene as a model reaction for our inves-tigation.

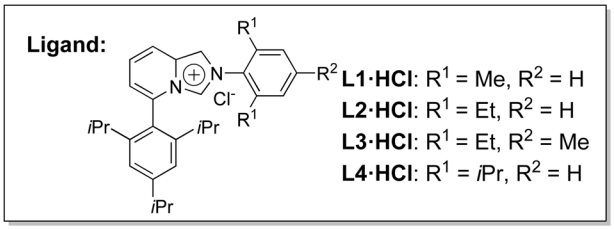
Initially, we employed 4-nitrotoluene as the archetype substrate. A range of reducing agents such as B_2Pin_2, KBH_4, Et_3SiH, and Ph_2SiH_2 were subjected to a rigorous screening process, with the resulting reactions documented in Fig. 2. B_2Pin_2, $B_2(OH)_2$, and KBH_4 are frequently observed in the study of nitroaromatic compound reduction for the synthesis of aromatic amines.[9,21] However, these reagents have proven to be less than ideal within this catalytic system (Fig. 2, entries 1–3), possibly due to their predilection for exhibiting optimal performance in polar solvents, making them unsuitable for deployment in weakly polar environments.[22] Methanol can serve as a hydrogen source, effectuating the reduction of nitroaromatic compounds through hydrogen transfer.[23] It was unfortunately incompatible with this specific reaction environment (Fig. 2, entries 4 and 5). Silanes demonstrate an advantageous ability for the reduction of nitroaromatic compounds invarious polar or weakly polar solvents.[24,25] The amount of triethylsilane has a great influence on the reaction. Utilizing 2.0 equivalents of triethylsilane as the reducing agent results in a yield of 55% for the subsequent product. Alterations in the quantity of the reducing agent, whether an increase or decrease, result in corresponding decreased yields (Fig. 2, entries 7–9).

Among the bases scrutinized, $K_3PO_4\cdot 3H_2O$ emerged as the most efficacious for this reaction. Transitioning from $K_3PO_4\cdot 3H_2O$ to anhydrous K_3PO_4 resulted in diminished product formation (Table S1,† entries 1 and 2). The employment of organic bases fails to yield the desired product (Table S1,† entry 6). Following a solvent screening, we found that the reaction struggles to proceed in highly polar solvents (Table S1,† entry 8), whereas it exhibits modest efficiency in less polar and nonpolar solvents. Amongst these, the nonpolar solvent *n*-octane emerged as the most optimal reaction medium (Table S1,† entry 12). Ultimately, we selected *n*-octane as the reaction solvent. An appraisal of palladium sources revealed $Pd(acac)_2$ as the superior catalyst (Fig. 2, entry 11). $Pd_2(dba)_3$, also exhibited



1a 2a

Entry	Reducing agent	Pd source	Ligand	yield[b]/%
1	B_2Pin_2 (0.5 eq.)	$Pd(acac)_2$	**L3**·HCl	8
2	KBH_4 (0.5 eq.)	$Pd(acac)_2$	**L3**·HCl	33
3	$B_2(OH)_2$ (1.0 eq.)	$Pd(acac)_2$	**L3**·HCl	Trace
4	MeOH (1.0 eq.)	$Pd(acac)_2$	**L3**·HCl	<5
5	EtOH (1.0 eq.)	$Pd(acac)_2$	**L3**·HCl	<5
6	Zn powder (1.0 eq.)	$Pd(acac)_2$	**L3**·HCl	<5
7	Et_3SiH (1.0 eq.)	$Pd(acac)_2$	**L3**·HCl	38
8	Et_3SiH (2.0 eq.)	$Pd(acac)_2$	**L3**·HCl	55
9	Et_3SiH (3.0 eq.)	$Pd(acac)_2$	**L3**·HCl	13
10	Ph_2SiH_2 (1.0 eq.)	$Pd(acac)_2$	**L3**·HCl	Trace
11	Et_3SiH (2.0 eq.)	$Pd(acac)_2$	**L3**·HCl	78[c]
12	Et_3SiH (2.0 eq.)	$Pd_2(dba)_3$	**L3**·HCl	68[c]
13	Et_3SiH (2.0 eq.)	$[Pd(allyl)Cl]_2$	**L3**·HCl	<5[c]
14	Et_3SiH (2.0 eq.)	$Pd(OAc)_2$	**L3**·HCl	<5[c]
15	Et_3SiH (2.0 eq.)	$Pd(acac)_2$	**L1**·HCl	54[c]
16	Et_3SiH (2.0 eq.)	$Pd(acac)_2$	**L2**·HCl	56[c]
17	Et_3SiH (2.0 eq.)	$Pd(acac)_2$	**L4**·HCl	71[c]



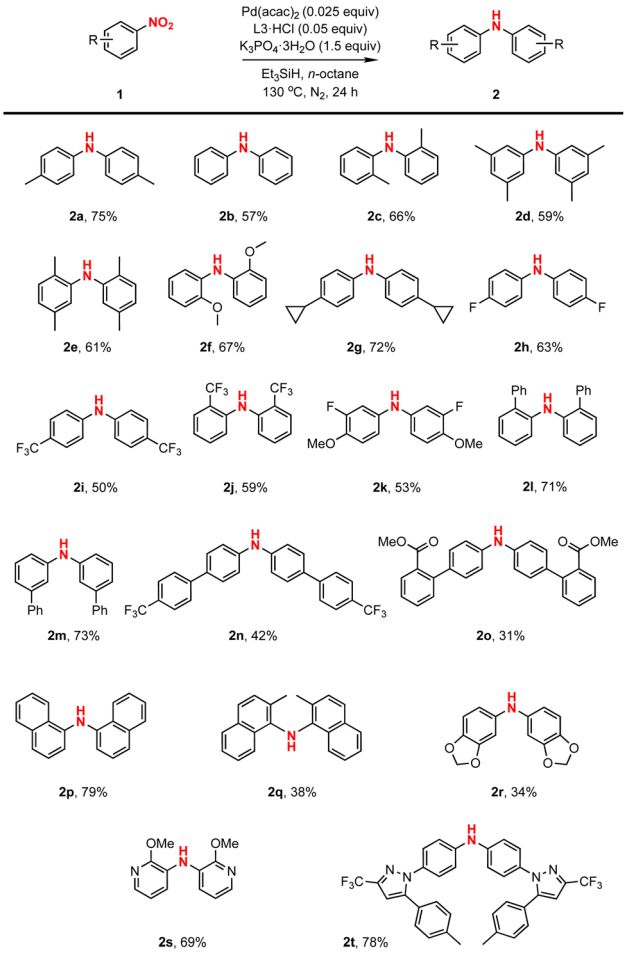
[a] Standard conditions: the reactions were run on a 0.2 mmol scale with 1a (0.2mmol, 1.0 equiv.), $Pd(acac)_2$ (1.5 mg, 0.025 equiv.), L·HCl (5.0 mg, 0.05 equiv.), reducing agent, base (1.5 equiv.), solvent (1.5 mL); [b] The yield is determined by ^{1}H-NMR spectroscopy using CH_2Br_2 as an internal standard; [c] *n*-octane as solvent.

Fig. 2 Optimization of reaction conditions.

catalytic capability, while some palladium(II) catalysts scarcely produced the desired product (Fig. 2, entries 13 and 14). The experiments showed that upon employing $[Pd(allyl)Cl]_2$ or $Pd(OAc)_2$ as a catalyst, bubbles appeared immediately after the reducing agent's introduction, and the solution exhibited a black and turbid appearance. This observation suggested that $[Pd(allyl)Cl]_2$ and $Pd(OAc)_2$ underwent rapid reduction and inactivation. Upon examining the steric hindrance of ligands, we found that both smaller and larger steric hindrances negatively impact the reaction. Among the ligands investigated, **L3**·HCl was identified as the superior choice. After we determined the optimal reaction conditions, we explored the substrate scope for this catalytic system. Upon screening various substrates, we discovered that nitroarenes featuring various alkyl groups could give the coupling products with satisfactory yields (**2a–2e**). The reductive coupling nitrobenzene bearing an *ortho*-methoxy afforded the corresponding product in 67% yield (**2f**). However, the same reaction of nitrobenzene

having a *para*-methoxy exhibited a reduced yield, with the primary side reaction involving the reduction of *para*-methoxy nitrobenzene to 4-methoxyaniline in 81% yield. Generally, nitroarenes bearing electron-donating groups at *para*-positions often presented an abundance of reduction products with minimal coupling products (Fig. 3).

Fluorine and trifluoromethyl-containing nitrobenzenes could react smoothly giving the target products in satisfactory yields (**2h–2k**). Nitrobenzenes with *ortho* or *meta* phenyl substituents gave their corresponding products in 71% and 73% yields, respectively (**2l** and **2m**). Nitrobiphenyls bearing electron-withdrawing groups were moderately efficient coupling partners, and the corresponding di(biphenyl)amines were attained in lower yields (**2n** and **2o**). Naphthalene derivatives were also suitable for the reductive coupling reaction, and di(naphthalen-1-yl)amine was obtained in 79% yield (**2p**). More steric 2-methyl nitronaphthalene demonstrated a diminished reaction yield, probably due to steric hindrance effects (**2q**). The homocoupling reaction of 2-methoxy-3-nitropyridine yielded product 2 s in a 69% yield. Moreover, using an analog of the drug molecule Celecoxib[26] as the starting material, the reductive coupling product **2t** could be obtained in a yield of 78%.



[a] The reactions were run on a 1.0 mmol scale with **1** (1 mmol, 1.0 equiv.), Et_3SiH (2.0 equiv.), *n*-octane (3.0 mL).

Fig. 3 Substrate scope for the palladium-catalyzed reductive arylation of nitroarenes.

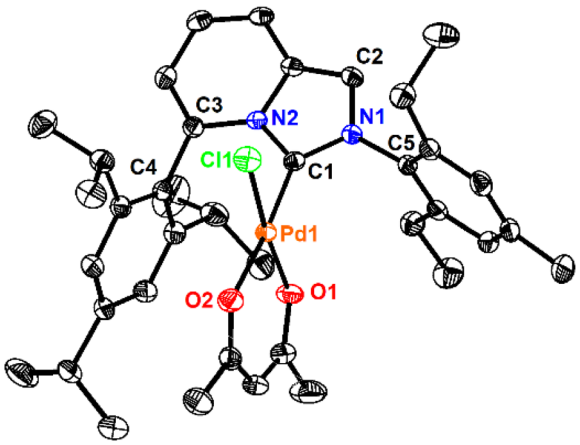


Fig. 4 X-ray crystal structure of [Pd(**L3**)(acac)Cl]. Thermal ellipsoids are given at 50% probability, H atoms are omitted. Selected bond lengths (Å): Pd1–C1 = 1.962(2), Pd1–O1 = 2.012(1), Pd1–O2 = 2.031(1), Pd1–Cl1 = 2.300(1).

In order to gain deeper knowledge on the N-heterocyclic carbene ligands with an imidazo[1,5-*a*]pyridine core in palladium-catalyzed C–N coupling of nitroarenes, we prepared [Pd(**L3**)(acac)Cl] metal complexes through reaction of **L3**·HCl and $Pd(acac)_2$ at 80 °C in 1,4-dioxane (Scheme S1†). The structure of [Pd(**L3**)(acac)Cl] was undoubtedly established using spectroscopic and analytical methods, and [Pd(**L3**)(acac)Cl] was crystallographically characterized (Fig. 4). It can be seen from the single crystal structure that the interaction between the triisopropylphenyl group and the palladium center causes a slight distortion of the structure. X-ray crystallography indicates that the Pd–C bond length in the complex falls within the typical range for Pd/NHC complexes.[27–29] The distance between the Pd1 and C4 measures 3.135(2) Å. The dihedral angle of Pd1–

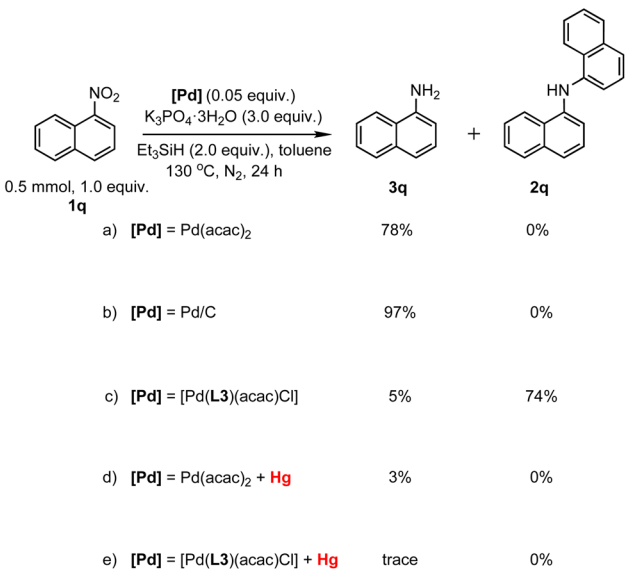


Fig. 5 Mechanism studies.

C1–C3–C4 is 26.073°, suggesting a noticeable offset between the palladium atom and the triisopropylphenyl group, possibly due to weak interactions between them.

To gain an understanding of the reaction mechanism, a series of controlled experiments were carried out. We found that in the absence of NHC ligands $Pd(acac)_2$ itself was not efficient, in such case only naphthalen-1-amine was formed, which suggests that the NHC ligand plays an important role in the denitrative homocoupling (Fig. 5a). The same reduction reaction could be achieved using the classical Pd/C catalyst (Fig. 5b). When [Pd(**L3**)(acac)Cl] was used as catalysts, the reaction could proceed effectively (Fig. 5c). However, mercury test has shown that when $Pd(acac)_2$ or Pd/NHC complexes were used as the catalysts, the reduction of nitroarenes could not be carried out (Fig. 5d and e). The reduction of nitroarenes may be partially catalyzed by acetylacetone palladium *via* the generation of palladium black. Nevertheless, the role of NHC–Pd in cataly tic reduction remains ambiguous.[30,31]

Conclusions

In summary, we have developed a one-pot synthetic approach for the preparation of diarylamine compounds, utilizing nitroaromatics as both the electrophilic reagent and nitrogen source and triethylsilane as a reducing agent. This method streamlines the reaction steps and enhances overall efficiency. We successfully isolated an Pd/NHC precatalyst and conducted preliminary investigations into the reaction mechanism. Further research in this area is currently underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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