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Palladium-Catalyzed One-Pot Diarylamine Formation from Nitroarenes and Cyclohexanones

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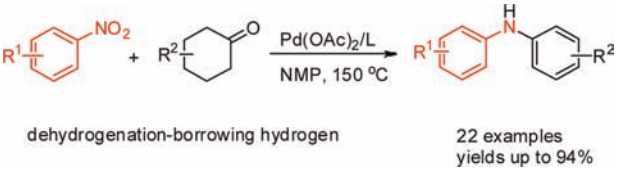
ABSTRACT



The first palladium-catalyzed diarylamine formation from nitroarenes and cyclohexanone derivatives using borrowed hydrogen is described. Various diarylamines were selectively obtained in good to excellent yields. The reaction tolerated a wide range of functionalities. The nitro reduction, cyclohexanone dehydrogenation, and imine formation and reduction were realized in a cascade without an external reducing reagent and oxidant.

The prevalence of diarylamines in pharmaceuticals, agrochemicals, dyes, and electronic industries has prompted the development of novel and efficient methodologies for the construction of aromatic C−N bonds.[1] While many chemical methods exist for the preparation of diarylamines, the search for new strategies that offer concise and regiospecific access remains a topic of considerable interest.[2] Conventional methods toward diarylamine bond construction mainly rely on the Cu-mediated Ullmann coupling between an aryl halide and an aniline under rather high reaction temperatures.[3] These approaches can sometimes be problematic due to harsh conditions, therefore restricting their use in complex molecule synthesis. Since Migita et al. developed a Pd-catalyzed aromatic amination of aryl bromides with *N*, *N*-diethylaminotributyltin,[4] tremendous progress has been made in the field of Pd-catalyzed aromatic C−N bond-forming reactions.[5] In particular, contributions from the research groups of Buchwald and Hartwig have established the powerful nature of this method by reacting aryl halides with anilines in the presence of a suitable ligand and base (the Buchwald−Hartwig coupling).[6] Electrophilic partners other than aryl halides for catalytic aniline arylations have also been exploited.[7] In recent years, the direct amination of C−H bonds presents a powerful alternative synthetic route for arylamines under oxidative conditions and great progress has been made in the intra- and intermolecular amination of C−H bonds (Scheme 1A).[8]

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(3) (a) Ullmann, F. *Ber.* **1903**, *36*, 2382. For reviews, see: (b) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, *15*, 2428. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 1043.

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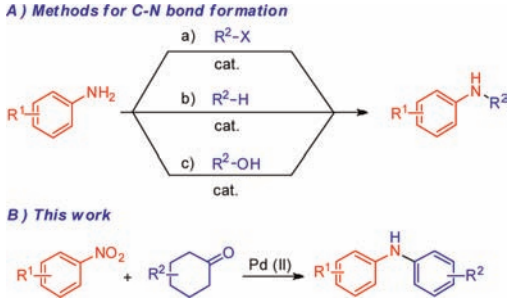
Scheme 1. Different Pathways for the Arylamine Formation



The catalytic oxidative dehydrogenation reactions are very useful tools for the construction of C=C, C=O, and C—N bonds.[9] Very recently, the research groups of Stahl and Huang developed various Pd-catalyzed mild aerobic dehydrogenation reactions of cyclohexanones and ketones/aldehydes using oxygen as the sole oxidant, and various phenols and α,β-unsaturated ketones/aldehydes were synthesized selectively.[10] Milstein et al. successfully developed a Ru-catalyzed amide synthesis from alcohols and amines with the liberation of H_2 without any oxidant.[11]

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(8) For reviews: (a) Collet, F.; Dodd, R.; Dauban, P. *Chem. Commun.* **2009**, 5061. (b) Armstrong, A.; Collins, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282. (c) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068.

(9) For reviews on dehydrogenations: (a) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681. (b) Muzart, J. *Eur. J. Org. Chem.* **2010**, 3779. (c) Scheuermann, C. J. *Chem.—Asian J.* **2010**, *5*, 436. (d) Gunanathan, C.; Milstein, D. *Acc. Chem. Res.* **2011**, *44*, 588. (e) Choi, J.; MacArthur, A.; Brookhart, M.; Goldman, A. S. *Chem. Rev.* **2011**, *111*, 1761.

(10) (a) Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209. (b) Diao, T.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 14566. (c) Gao, W. M.; He, Z.; Qian, Y.; Zhao, J.; Huang, Y. *Chem. Sci.* **2012**, *3*, 883. (d) Diao, T.; Wadzinski, T. T.; Stahl, S. S. *Chem. Sci.* **2012**, *3*, 887.

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(13) For reaction mechanism study: Hamide, M.; Liana Allen, C.; Lamb, G.; Maxwell, A.; Maytum, H.; Watson, A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766.

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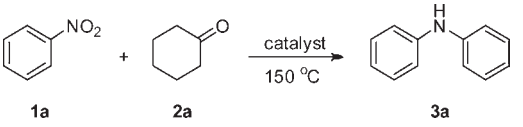
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

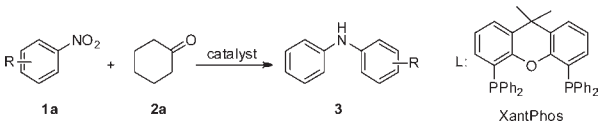
entry	catalyst	ligand	solvent	yield (%)[b]
1	$Pd(OAc)_2$		NMP	trace
2	$Pd(OAc)_2$	DPEPhos	NMP	trace
3	$Pd(OAc)_2$	PPh_3	NMP	29
4	$Pd(OAc)_2$	dppe	NMP	33
5	$Pd(OAc)_2$	dppp	NMP	40
6	$Pd(OAc)_2$	dppm	NMP	72
7	$Pd(OAc)_2$	dppb	NMP	60
8	$Pd(OAc)_2$	Xantphos	NMP	93
9	$Pd(OAc)_2$	bipyridine	NMP	14
10	$Pd(OAc)_2$	2,2′-biquinoline	NMP	74
11	PdO	Xantphos	NMP	trace
12	$PdCl_2$	Xantphos	NMP	trace
13	$Pd(OH)_2$	Xantphos	NMP	62
14	$Pd(acac)_2$	Xantphos	NMP	84
15	$Pd(CF_3CO_2)_2$	Xantphos	NMP	61
16	$Pd(OAc)_2$	Xantphos	DMF	30
17	$Pd(OAc)_2$	Xantphos	DMSO	trace
18	$Pd(OAc)_2$	Xantphos	DMA	75
19	$Pd(OAc)_2$	Xantphos	1,4-dioxane	24
20	$Pd(OAc)_2$	Xantphos	xylene	43
21[c]	$Pd(OAc)_2$	Xantphos	NMP	84

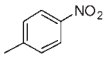
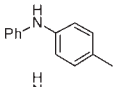
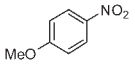
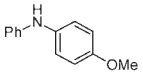
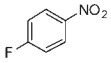
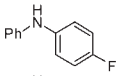
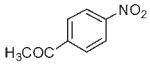
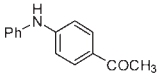
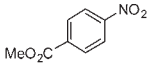
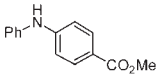
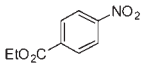
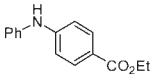
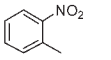
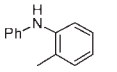
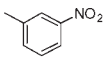
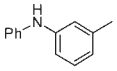
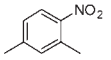
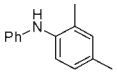
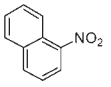
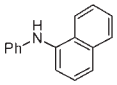
[a] Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (5 mol %), ligand (10 mol %), solvent (0.3 mL), 24 h under argon unless otherwise noted. [b] GC yield based on **1a**. [c] 0.3 mmol of **2a** was used.

Furthermore, Williams et al. developed various catalytic systems for direct amine formation from alcohols and amines using a borrowing hydrogen strategy (or hydrogen transfer).[12,13] We and others further extended this strategy for aromatic C−N bond formation from alcohols and nitroarenes.[14] This method affords a short synthetic route for C−N bond formation. However, the borrowing hydrogen methodology is limited for the alkylation of amines and not suitable for diarylamine preparation. We envisioned that it might be possible using nitroarenes and cyclohexanones instead of alcohols as starting materials for diarylamine formation using a sequent dehydrogenation and borrowing hydrogen strategy. First, nitroarene could be reduced to amine using hydrogen generated from a cyclohexanone oxidation step. The condensation of cyclohexanone (or cyclic enone) with amine will generate an imine intermediate. Second, the imine intermediate could be reduced to diarylamine using the borrowing hydrogen methodology. This method can afford a shortcut for diarylamine synthesis using cheap and stable starting materials without any external reducing reagent and oxidant. *Herein, we report a Pd-catalyzed one-pot diarylamine formation from nitroarenes and cyclohexanones using the dehydrogenation and borrowing hydrogen strategy* (Scheme 1B).

Our initial investigations were focused on the arylation of commercially available and inexpensive nitrobenzene

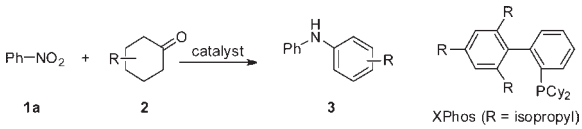
Table 2. Reaction of **2a** with Various Nitroarenes[a]

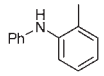
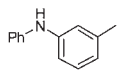
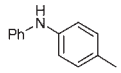
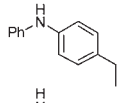
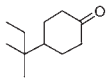
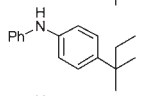
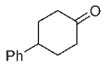
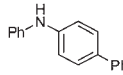
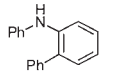
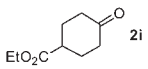
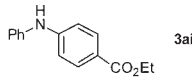
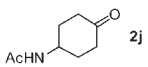


entry	nitroarene		product		yield (%)[b]
1	Ph–NO_2	**1a**		**3aa**	88
2		**1b**		**3ba**	84
3		**1c**		**3ca**	75
4		**1d**		**3da**	82
5		**1e**		**3ea**	70
6		**1f**		**3fa**	83
7		**1g**		**3ga**	81
8		**1h**		**3ha**	84
9		**1i**		**3ia**	92
10		**1j**		**3ja**	71
11		**1k**		**3ka**	92

[a] Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (5 mol %), Xantphos (10 mol %), NMP (0.3 mL), 150 °C, 24 h under argon unless otherwise noted. [b] Isolated yields based on **1**.

Table 3. Reaction of **1a** with Cyclohexanones[a]



entry	cyclohexanone		product		yield (%)[b]
1		**2b**		**3ab**	82
2		**2c**		**3ac**	88
3		**2d**		**3ad**	88
4		**2e**		**3ae**	92
5[c]		**2f**		**3af**	88
6[c]		**2g**		**3ag**	86
7[c]		**2h**		**3ah**	70
8		**2i**		**3ai**	79
9[c]		**2j**		**3aj**	72
10[d]		**2k**		**3ak**	94
11[e]		**2l**		**3al**	88

[a] Conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (5 mol %), Xantphos (10 mol %), NMP (0.3 mL), 150 °C, 24 h under argon unless otherwise noted. [b] Isolated yields based on **1a**. [c] XPhos (10 mol %) was used. [d] 4 equiv of **2k** were used. [e] 3 equiv of **2l** were used.

(**1a**) with cyclohexanone (**2a**), and the results are summarized in Table 1. When $Pd(OAc)_2$ catalyzed the reaction of nitrobenzene with 2 equiv of cyclohexanone in the absence of ligand in NMP at 150 °C, no desired diphenylamine (**3aa**) was formed as determined by GC-MS and ^1H NMR methods (Table 1, entry 1). Subsequently, various ligands were tested for this reaction under an atmosphere of argon using $Pd(OAc)_2$ as the catalyst. No desired product was observed when DPEPhos was used as the ligand (entry 2). The desired product was obtained in 29% yield when 10 mol % of PPh_3 was employed (entry 3). The use of dppe, dppp, dppm, dppb all effectively catalyzed the reactions (entries 4–7). The best yield was obtained when Xantphos was used, and the desired product was obtained in 93% yield (entry 8). Nitrogen-containing ligand bipyridine was not effective for this transformation (entry 9). However, a good yield was achieved when 2,2′-biquinoline was used as the ligand (entry 10). Subsequently, various palladium salts were investigated using Xantphos as the ligand. PdO and $PdCl_2$ were inefficient in this reaction (entries 11 and 12). Other palladium salts such as $Pd(OH)_2$, $Pd(acac)_2$, and $Pd(CF_3CO_2)_2$ were effective and gave the desired product in good yields (entries 13–15). The effect of solvents on this reaction was also investigated (entries 16–20). The reaction was efficient in DMA (entry 18). Other solvents were not proper reaction media for this transformation. Notably, a good yield was obtained when the amount of **2a** was reduced to 1.5 equiv, and the desired product was obtained in 84% yield (entry 21).

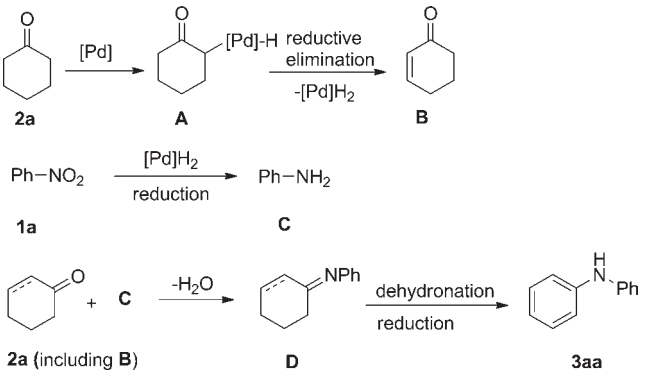
With the optimized reaction conditions established, the scope of the reaction with respect to cyclohexanone and various nitroarenes was investigated (Table 2). The reactions with nitroarenes bearing electron-donating groups (entries 2 and 3) and electron-withdrawing substituents *para* to the nitro group (entry 4) proceeded smoothly to

give the desired products in good yields. A slightly lower yield was obtained when *p*-nitroacetophenone (**1e**) was used (entry 5). Ester functional groups were well tolerated under the optimized conditions, and the reactions of methyl 4-nitrobenzoate (**1f**) and ethyl 4-nitrobenzoate (**1g**) with **2a** resulted in the desired products in 83% and 81% yields, respectively. The position of the substituents on the phenyl ring of nitroarenes did not affect the reaction yield significantly. Good to excellent yields were obtained when 2-nitrotoluene (**1h**), 3-nitrotoluene (**1i**), and 2, 4-dimethylnitrobenzene (**1j**) were used as starting materials (entries 8−10). More steric substrates such as 1-nitronaphthalene (**1k**) also efficiently coupled with **2a** and gave the desired product in 92% yield (entry 11). Unfortunately, aliphatic nitro compounds were not effective substrates for this kind of transformation.

To further explore the scope of the reaction, a number of substituted cyclohexanone derivatives were employed to react with nitrobenzene. In general, good to excellent yields were obtained under the standard optimized or modified reaction conditions (Table 3). Varying the position of the methyl substituent on the cyclohexanone had little effect on the outcome of the reaction; the corresponding **3ab**, **3ac**, and **3ad** were each obtained in good yields (entries 1−3). However, the position of the phenyl group affected the reaction yields significantly (entries 4 and 5). Other functional groups including ethyl, *tert*-pentyl, acetyl-amino, and ester were well tolerated, and all afforded the corresponding products in good yields. Notably, 3,4-dihydro-2-napthol (**2k**) and 3-methyl-2-cyclohexen-1-one (**2l**) both successfully reacted with **1a** and gave the desired products in 94% and 88% yields, respectively (entries 10 and 11). However, 4 and 3 equiv of **2k** and **2l** were required to obtain high yields because less hydrogen was generated for these substrates. In general, the direct arylation of nitroarenes showed very good selectivity and diarylamines were formed as the sole products.

Based on observations by Stahl et al. and ourselves, a tentative mechanism to rationalize this transformation is illustrated in Scheme 2. The reaction of cyclohexanone with a Pd catalyst generates a complex **A**, which subsequently affords cyclohex-2-enone **B** through β-H elimination and transfers dihydrogen to the palladium catalyst. In the meantime, nitrobenzene **1a** can be reduced into aniline **C** by the hydride borrowed from the dehydrogenation reaction of cyclohexanone. The condensation of cyclohexanone (including cyclohex-2-enone) with aniline generates an imine intermediate **D**. Finally, dehydrogenation and reduction of this intermediate afford the final diphenylamine **3aa**.

Scheme 2. Proposed Reaction Mechanism



In summary, we have developed a novel Pd-catalyzed direct arylation of nitroarenes with cyclohexanone derivatives using the dehydrogenation and borrowing hydrogen methodology. Cyclohexanone derivatives acted as both hydrogen donors and aryl sources, and no external reducing reagent was required. Various diarylamines were formed in good to excellent yields. The reaction showed very good selectivity, and secondary arylamines were formed as the sole products in all cases. Functional groups such as methyl, ethyl, methoxy, ester, and acetyl were well tolerated under the optimized conditions. The nitro reduction, cyclohexanone dehydrogenation, and imine formation and reduction were realized in a cascade. Further investigation, including the scope and mechanism of this reaction, is in progress in our laboratory.

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Supporting Information Available. General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.