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Palladium-Catalyzed Aerobic Dehydrogenative Aromatization of Cyclohexanone Imines to Arylamines

Alakananda Hajra, Ye Wei, and Naohiko Yoshikai*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

nyoshikai@ntu.edu.sg

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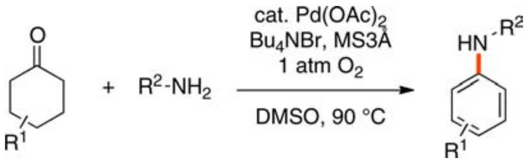
ABSTRACT



Dehydrogenative aromatization of cyclohexanone imines to arylamines has been achieved using a palladium catalyst under aerobic conditions. The reaction is applicable to a variety of imines that are either preformed or generated in situ from cyclohexanone derivatives and aryl or alkylamines.

Arylamines are common core structures of a wide variety of functional molecules with biological activities and optoelectronic properties relevant to pharmaceuticals and materials science, respectively. Consequently, efficient and selective preparation of arylamines has received considerable attention. The most powerful and versatile contemporary synthetic method for arylamines is undoubtedly the transition-metal-catalyzed C–N cross-coupling between aryl halides and amines, as represented by the palladium-catalyzed Buchwald–Hartwig coupling and the copper-catalyzed Ullmann-type coupling reactions.[1–3] Nevertheless, the development of conceptually different and complementary synthetic methods, those not employing halogenated starting materials and basic reaction conditions in particular, remains an important subject.[4]

Recently, we developed a palladium-catalyzed aerobic oxidative cyclization reaction of *N*-aryl imines to indoles.[5] During this study, we noted that an imine derived from α-tetralone and *p*-anisidine underwent dehydrogenation rather than oxidative cyclization to afford an aminonaphthalene derivative (Scheme 1a). This finding, together with the recent development of aerobic palladium catalysis[6] for dehydrogenation of cyclohexanones to phenols[7] and α,*β*-dehydrogenation of alkyl ketones and aldehydes,[8–10] prompted us to explore the feasibility of the aerobic dehydrogenative approach for the synthesis of arylamines. Here, we report that a variety of cyclohexanone imines, either

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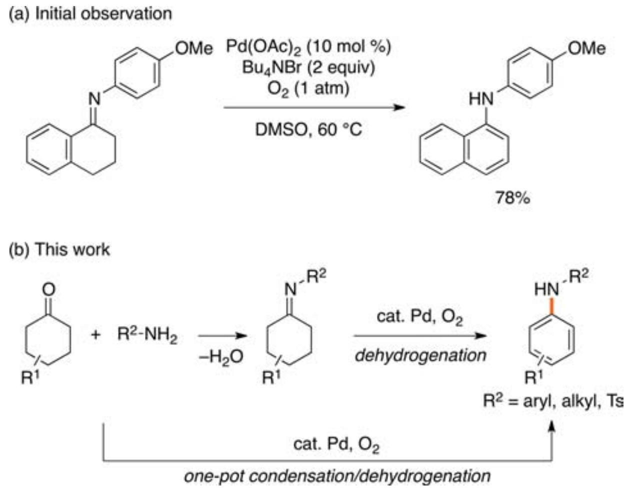
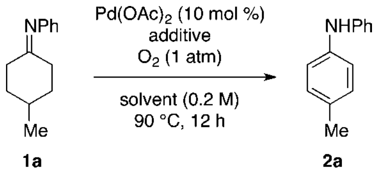
preformed or formed in situ from the corresponding ketones and amines, undergo dehydrogenative aromatization to afford arylamines in moderate to good yields under aerobic palladium catalysis (Scheme 1b).[11,12]

Scheme 1



We commenced our study with a brief optimization of the dehydrogenation reaction of imine **1a** prepared from 4-methylcyclohexanone and aniline (Table 1). The catalytic system consisting of Pd(OAc)$_2$ (10 mol %), Bu$_4$NBr (2 equiv), O$_2$ (1 atm), and DMSO, which we employed previously,[5] promoted the reaction at 90 °C to afford the diarylamine **2a** in 23% yield (entry 1). The addition of Bu$_4$NBr was critical as the reaction became very sluggish in its absence (entry 2). The yield of **2a** was improved slightly by the addition of 3 Å molecular sieves (MS3 Å) (entry 3) and significantly by the change of the solvent from DMSO to toluene (entry 4). An additional improvement was achieved by the use of a toluene/DMSO (9:1) mixed solvent, resulting in the formation of **2a** in 79% isolated yield (entry 5).

Table 1. Dehydrogenative Aromatization of Cyclohexanone Imine **1a**[a]

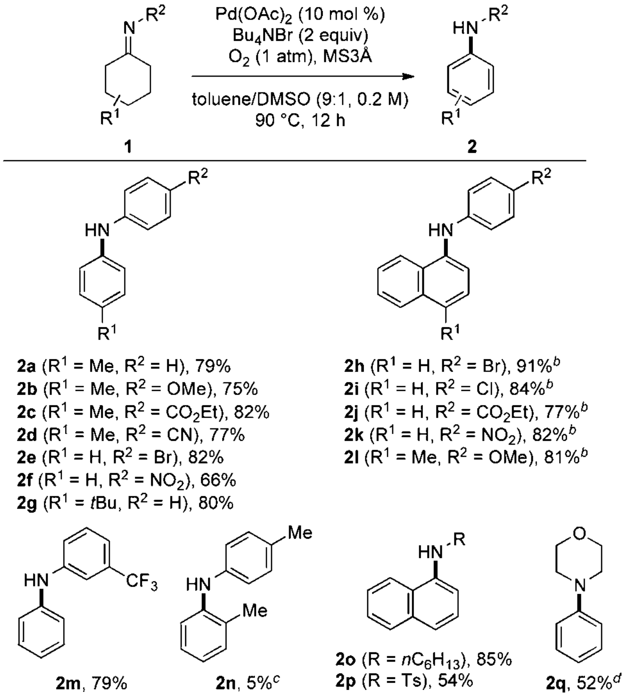


entry	additive (equiv)	solvent	yield (%)[b]
1	Bu$_4$NBr (2)	DMSO	23
2	None	DMSO	<3
3	Bu$_4$NBr (2), MS3 Å	DMSO	30
4	Bu$_4$NBr (2), MS3 Å	toluene	73
5	Bu$_4$NBr (2), MS3 Å	toluene/DMSO (9:1)	79[c]

[a] Reaction was performed on a 0.2 mmol scale. The amount of MS3 Å was 100 mg. [b] Determined by GC using *n*-tridecane as an internal standard. [c] Isolated yield.

With the above catalytic system, we explored the dehydrogenative aromatization reaction of a series of six-membered cyclic imines (Scheme 2). A variety of imines derived from cyclohexanone or α-tetralone derivatives and aniline derivatives participated in the reaction to afford the corresponding diarylamines **2a**–**2m** in good yields, with a tolerance to functional groups such as ester, cyano, bromo, and nitro groups. Unfortunately, the reaction of the imine derived from 2-methylcyclohexanone was rather sluggish, presumably because of steric reasons (see **2n**). An imine derived from *n*-hexylamine and an enamine derived from morpholine were also amenable to the dehydrogenation reaction, affording the products **2o** and **2q** in 85% and 52% yields, respectively.[13] Furthermore, an electron-poor imine bearing the *N*-tosyl group also participated in the reaction to give the product **2p** in 54% yield.

Scheme 2. Dehydrogenative Aromatization of Six-Membered Cyclic Imines[a]



[a] Reaction was performed on a 0.2 mmol scale. Isolated yields are shown. [b] The reaction was performed in DMSO at 60 °C. [c] Yield estimated by GC. [d] The starting material was an enamine derived from cyclohexanone and morpholine.

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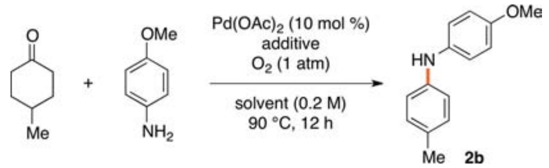
[11] Dehydrogenative aromatization of imines derived from cyclohexanone and aniline derivatives was previously achieved using a Pd/C catalyst and a nitroarene bearing the same aryl group as the aniline as a stoichiometric oxidant, typically at 140–160 °C: (a) Nagata, T.; Kusuda, C.; Wada, M.; Uchida, M. U.S. Patent 5,536,878, 1996. (b) Uchida, M.; Wada, M.; Nagata, T. Jpn. Kokai Tokkyo Koho 07,215,920, 1995.

[12] Deng et al. recently reported diarylamine synthesis via Pd-catalyzed redox-neutral coupling of cyclohexanones and nitroarenes: Xie, Y.; Liu, S.; Liu, Y.; Wen, Y.; Deng, G.-J. *Org. Lett.* **2012**, *14*, 1692.

[13] Dehydrogenation of enamines derived from cyclohexanone was previously achieved using a stoichiometric amount of the Pd complex or a combination of the Pd/C catalyst and nitrobenzene oxidant: (a) Ishikawa, T.; Uedo, E.; Tani, R.; Saito, S. *J. Org. Chem.* **2001**, *66*, 186. (b) Cossy, J.; Belotti, D. *Org. Lett.* **2002**, *4*, 2557.

Having achieved dehydrogenative aromatization of various preformed imines, it was natural for us to attempt direct synthesis of arylamines from cyclohexanones and amines via condensation/dehydrogenative aromatization in one pot. Thus, we again performed a screening of reaction conditions using 4-methylcyclohexanone and *p*-anisidine as starting materials (Table 2). Using the combination of $Pd(OAc)_2$, Bu_4NBr, and MS3 Å in DMSO (0.2 M), an equimolar mixture of the ketone and the amine afforded the diarylamine **2b** in 76% yield (entry 1), which was comparable to the yield obtained from the preformed imine (see Scheme 2). For the one-pot reaction, DMSO was clearly superior to toluene as well as to other polar solvents such as DMF and acetonitrile (entries 2–5). While Oct_4NBr and Et_4NBr had similar effects to Bu_4NBr (entries 6 and 7), the use of Bu_4NI or Bu_4NCl led to lower yields (entries 8 and 9). An elevated reaction temperature (110 °C) or a higher concentration (0.5 M) had only negative effects (entries 10 and 11). Attempts to reduce the catalyst loading have not been successful.

Table 2. One-Pot Synthesis of Arylamine **2b**[a]



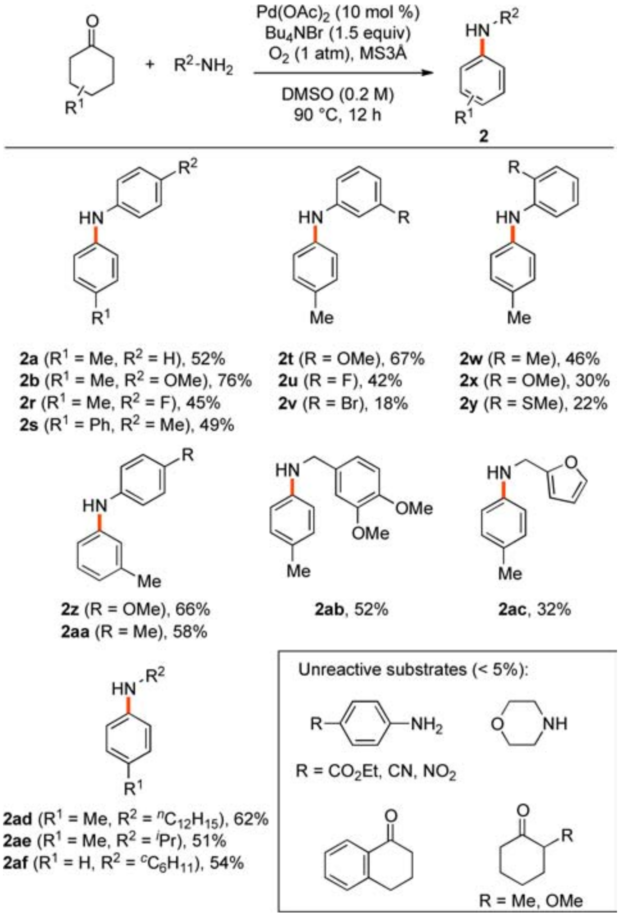
entry	additive (equiv)	solvent	yield (%)[b]
1	Bu_4NBr (1.5), MS3 Å	DMSO	76[c]
2	Bu_4NBr (2)	DMSO	64[c]
3	Bu_4NBr (2)	toluene	8
4	Bu_4NBr (2)	DMF	34
5	Bu_4NBr (2)	MeCN	30
6	Oct_4NBr (1.5), MS3 Å	DMSO	74
7	Et_4NBr (1.5), MS3 Å	DMSO	68
8	Bu_4NI (1.5), MS3 Å	DMSO	46
9	Bu_4NCl (1.5), MS3 Å	DMSO	56
10[d]	Bu_4NBr (1.5), MS3 Å	DMSO	16
11[e]	Bu_4NBr (1.5), MS3 Å	DMSO	24

[a] Reaction was performed on a 0.2 mmol scale using a 1:1 mixture of 4-methylcyclohexanone and *p*-anisidine. The amount of MS3 Å was 100 mg. [b] Determined by GC using *n*-tridecane as an internal standard. [c] Isolated yield. [d] The reaction temperature was 110 °C. [e] The concentration was 0.5 M.

We then explored the scope of the one-pot arylamine synthesis (Scheme 3). The parent aniline and electron-rich anilines such as *p*-anisidine and *p*-toluidine afforded the diarylamine products in reasonable yields (see **2a**, **2b**, **2s**, **2z**, and **2aa**), while the reaction became slower with halogenated anilines (see **2r**, **2u**, and **2v**). The reaction also became slower with *ortho*-substituted anilines (see **2w**–**2y**). Benzylamines such as veratrylamine and furfurylamine participated in the reaction to afford the products **2ab** and **2ac** in moderate yields. Primary alkylamines such as *n*-dodecylamine, isopropylamine, and cyclohexylamine were also amenable to the one-pot reaction, affording the products **2ad**–**2af** in 50–60% yields.

The efficiency of the one-pot reaction appeared to be greatly influenced by the ketone/amine condensation step. Thus, less nucleophilic anilines bearing electron-withdrawing *para*-substituents such as ester, cyano, and nitro groups did not afford the products (Scheme 3 inset), while the imines derived from these anilines were good substrates for the dehydrogenation reaction (Scheme 2). Likewise, morpholine and α-tetralone did not afford the desired products because of the slow condensation of these substrates. These observations suggest that the formation of the imine intermediate is the rate-limiting step of the reaction. In addition, 2-substituted cyclohexanones were unreactive, presumably because both the condensation and dehydrogenation steps were sterically inhibited.

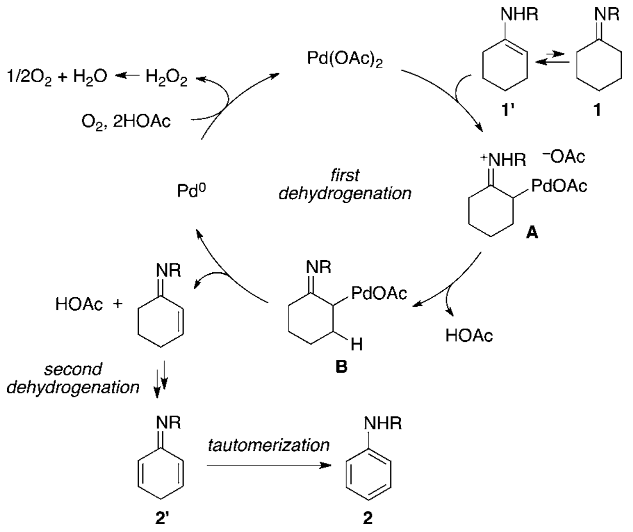
Scheme 3. One-Pot Synthesis of Arylamines[a]



[a] Reaction was performed on a 0.2 mmol scale using a 1:1 mixture of ketone and amine. Isolated yields are shown.

Scheme 4 shows a possible catalytic cycle for the present dehydrogenative aromatization reaction, which is analogous to the mechanism proposed for the dehydrogenation reaction of cyclohexanone to phenol.[7] Enamine **1′** generated through tautomerization of imine **1** would undergo electrophilic palladation (**A**) to afford, through elimination of

Scheme 4. Possible Catalytic Cycle



HOAc, an α-palladated imine **B**.[5,8] The intermediate **B** would then undergo β-hydride elimination to afford cyclohexenone imine and Pd(0). While Pd(0) is reoxidized to Pd(II) with the aid of molecular oxygen and HOAc,[6] the cyclohexenone imine goes through a corresponding dehydrogenation catalytic cycle to afford cyclohexadienone imine **2′**, which should quickly tautomerize to the aniline product **2**. A possible role of the ammonium salt is to stabilize the catalytically active Pd species, which could be in the form of nanoclusters or nanoparticles.[14]

In summary, we have developed a palladium-catalyzed aerobic dehydrogenation reaction for the synthesis of arylamines. A variety of cyclohexanone imines, either preformed or generated in situ, participated in the reaction to afford the corresponding arylamines in moderate to good yields. The tolerance to functional groups such as an aryl—Br bond implies potential applicability of the present reaction as a method orthogonal to the Buchwald—Hartwig and the Ullmann-type coupling reactions. Further studies will be focused on the expansion of the substrate scope and the search for more robust and efficient catalytic systems.

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Supporting Information Available. Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.