ORGANIC LETTERS

2012
Vol. 14, No. 21
5606–5609

Pd-Catalyzed Synthesis of Aryl Amines via Oxidative Aromatization of Cyclic Ketones and Amines with Molecular Oxygen

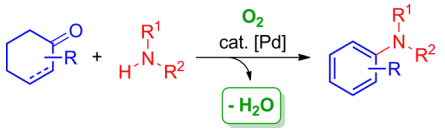
Simon A. Girard,[†,‡] Xiong Hu,[‡,§] Thomas Knauber,[†,∥] Feng Zhou,[†,∥] Marc-Olivier Simon,[†] Guo-Jun Deng,[*,§] and Chao-Jun Li[*,†]

Department of Chemistry and FQRNT Center for Green Chemistry and Catalysis, McGill University, Montreal, QC, H3A 2K6, Canada and Key Laboratory of Environmentally Friendly Chemistry and Application of Ministry of Education, College of Chemistry, Xiangtan University, Xiangtan 411105, China

cj.li@mcgill.ca; gjdeng@xtu.edu.cn

Received October 2, 2012

ABSTRACT



Pd-catalyzed intermolecular aerobic dehydrogenative aromatizations have been developed for the arylation of amines with nonaromatic ketones. Under optimized reaction conditions, primary and secondary amines are selectively arylated in good yields with cyclohexanones and 2-cyclohexen-1-ones in the presence of a Pd-catalyst under an atmosphere of molecular oxygen.

Over the last few decades, an impressive number of transition metal catalyzed tools for the selective synthesis of aryl amines has been developed and found many applications for the synthesis of pharmaceuticals, agrochemicals and functional materials.[1] Arguably, the most prominent reactions include Buchwald-Hartwig-couplings,[2] Ullmann-type reactions[3] and Chan-Lam-type aminations (Scheme 1).[4] In addition to the cross-coupling methodologies, several seminal dehydrogenative aromatization[5] procedures have been developed for the syntheses of aryl amines from nonaromatic enamines and imines (Scheme 1). The group of Semikolenov developed a gas-phase procedure for the synthesis of 2,6-dimethylaniline that involves a Pd-catalyzed cross-dehydrogenative aromatization step.[6] In 2001, the group of Ishikawa and Saito demonstrated that preformed enamines can be smoothly transferred into the corresponding aryl amines in the presence of stoichiometric quantities of a Pd(II) complex.[7] The first Pd-catalyzed protocols have been developed independently by Cossy[8] and Beller[9] using nitro benzene and benzyloxy carbonyl protective groups (Cbz) as hydrogen acceptors, respectively. Recently, the group of Yoshikai encountered an oxidative

[†] McGill University.
[‡] S.A.G. and X.H. contributed equally.
[§] Xiangtan University.
[∥] T.K. and F.Z. contributed equally.

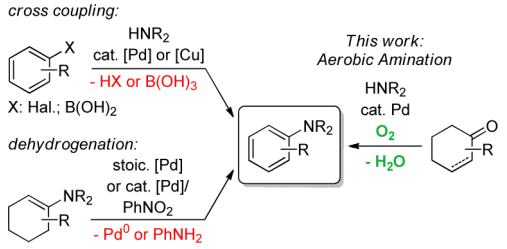
(1) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177–2250.
(2) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852–860. (c) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534–1544. (d) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361.
(3) (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364. (b) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054–3131. (c) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954–6971.
(4) (a) Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941–2944. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449.
(5) (a) Antos, G. J.; Aitani, A. M. *Catalytic Naphtha Reforming*, 2nd ed.; CRC Press: Boca Raton, FL, 2004. (b) Choi, J.; MacArthur, A. H. R.; Brookhart, M.; Goldman, A. S. *Chem. Rev.* **2011**, *111*, 1761–1779. (c) Bamfield, P.; Gordon, P. F. *Chem. Soc. Rev.* **1984**, *13*, 441.
(6) Semikolenov, V. A.; Boldyreva, M. E.; Shmidt, Yu. V.; Stepanov, A. G. *J. Mol. Catal.* **1989**, *55*, 415–428.
(7) Ishikawa, T.; Uedo, E.; Tani, R.; Saito, S. *J. Org. Chem.* **2001**, *66*, 186–191.
(8) Cossy, J.; Belotti, D. *Org. Lett.* **2002**, *4*, 2557–2559.
(9) Neumann, H.; Jacobi von Wangelin, A.; Klaus, S.; Strübing, D.; Gördes, D.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4503–4507.
(10) Wei, Y.; Deb, I.; Yoshikai, N. *J. Am. Chem. Soc.* **2012**, *134*, 9098–9101.

10.1021/ol3027279 © 2012 American Chemical Society
Published on Web 10/15/2012

aromatization in the development of a Pd-catalyzed aerobic indole synthesis.[10]

In addition to the Pd-catalyzed procedures, a few aromatizations with stoichiometric quantities of $SnCl_4$, $Hg(OAc)_2$, and $TiCl_4$ have been reported.[11]

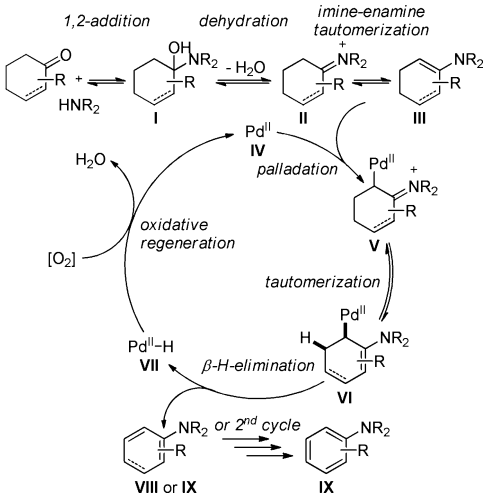
Scheme 1. Strategies for the Synthesis of Aryl Amines



Inspired by pioneering work,[12] the group of Stahl succeeded in the utilization of molecular oxygen in catalytic oxidative aromatization reactions. Cyclohexanone derivatives have been transferred into the corresponding phenols[13] and cyclic enones[14] in the presence of a Pd-catalyst under O_2 atmosphere.[15] In regard of availability and atom efficiency, molecular oxygen is the most attractive oxidant for Pd-catalyzed coupling reactions.[16] This year, our groups have independently developed the first intermolecular arylation reactions of heteroatom nucleophiles with cyclic ketones. Aliphatic alcohols have been arylated with 2-cyclohexen-1-ones in a Cu-catalyzed aerobic ether synthesis,[17] and aryl amines have been accessed from nitro arenes and cyclohexanones in a Pd-catalyzed cross-dehydrogenative arylation.[18]

We envisaged that an aerobic aromatization of various cyclohexanone derivatives with both primary and secondary amines would introduce a direct and atom-economic access to various aryl amines. We reasoned that the transformation might be possible by following the mechanistic

Scheme 2. Postulated Oxidative Arylamine Formation from 2-Cylohexenones and Cyclohexanones



concept outlined in Scheme 2. The prospected reaction starts with an enamine condensation[19] followed by palladation of the enamine species **III**.[20,7] Subsequent tautomerization and β-hydride-elimination will liberate the aryl amine **IX** or a cyclic diene intermediate **VIII** and a metal-hydride species **VII**. The latter could be regenerated into the initial catalyst **IV** in the presence of oxygen.[21] The product **IX** will be formed from the diene species **VIII** in a second catalytic cycle.

To validate this hypothesis, we started with the simpler arylation of amines with 2-cyclohexen-1-one, as only one equivalent of molecular hydrogen and one molecule of water have to be removed. Piperidine was chosen as test substrate, and the results are outlined in Table 1.

The desired *N*-phenyl piperidine **3aa** was detected in 8% yield in the presence of the Cu-catalyst (Table 1, entry 1), which mediates the aerobic synthesis of aryl ethers.[17] Among the tested precatalysts,[22] good yields of 61 and 66% had been obtained with $Pd(OAc)_2$ and $[(PMePh_2)_2PdCl_2]$, respectively (Table 1, entries 2 and 3). However, the reaction was accompanied by the formation of undefined polymeric decomposition products.[23] The addition of P-, N- and O-ligands did not improve the reaction outcome.[22] The reaction progress and the formation of intermediates were thus monitored by ^1H NMR experiments.[22] The hemiaminal **I** was readily formed and accumulated in the reaction mixture. The maximum concentration is reached after full consumption of the piperidine (approximately 2−3 h).[22]

(11) (a) Bigdeli, M. A.; Rahmati, A.; Abbasi-Ghadim, H.; Mahdavinia, G. H. *Tetrahedron Lett.* **2007**, *48*, 4575–4578. (b) Iida, H.; Yuasa, Y.; Kibayashi, C. *Synthesis* **1982**, 471–472. (c) Srinivas, G.; Periasamy, M. *Tetrahedron Lett.* **2002**, *43*, 2785–2788.

(12) (a) Horning, E. C.; Horning, M. G. *J. Am. Chem. Soc.* **1947**, *69*, 1359–1361. (b) Bamfield, P.; Gordon, P. F. *Chem. Soc. Rev.* **1984**, *13*, 441–488. (c) Muzart, J.; Pete, J. P. *J. Mol. Catal.* **1982**, *15*, 373–376. (d) Muzart, J. *Eur. J. Org. Chem.* **2010**, 3779–3790. (e) Wenzel, T. T. *J. Chem. Soc., Chem. Commun.* **1989**, 932–933. (f) Horrillo-Martínez, P.; Virolleaud, M.-A.; Jaekel, C. *ChemCatChem* **2010**, *2*, 175–181.

(13) Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209–213.

(14) Diao, T.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 14566–14569.

(15) For acyclic enones: Gao, W.; He, Z.; Qian, Y.; Zhao, J.; Huang, Y. *Chem. Sci.* **2012**, *3*, 883–886.

(16) (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (b) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420.

(17) Simon, M.-O.; Girard, S. A.; Li, C.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 7537–7540.

(18) Xie, Y.; Liu, S.; Liu, Y.; Wen, Y.; Deng, G.-J. *Org. Lett.* **2012**, *14*, 1692–1695.

(19) Smith, M. B; March, J. *Advanced Organic Chemistry*, 6th ed.; Wiley Interscience: New York, 2007; pp 1281−1284.

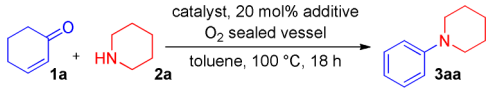
(20) (a) Ge, H.; Niphakis, M. J.; Georg, G. I. *J. Am. Chem. Soc.* **2008**, *130*, 3708–3709. (b) Neumann, J. J.; Rakshit, S.; Dröge, T.; Würtz, S.; Glorius, F. *Chem.—Eur. J.* **2011**, *17*, 7298–7303.

(21) (a) Konnick, M. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 5753–5762. (b) Mueller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9724–9734. (c) Steinhoff, B. A.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 11268–11278. (d) Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188–7189. (e) Konnick, M. M.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 10212–10213. (f) Muzart, J. *Chem. Asian J.* **2006**, *1*, 508–515.

(22) See Supporting Information for experimental details.

(23) Hay, A. S.; Blanchard, H. S.; Endres, G. F.; Eustance, J. W. *J. Am. Chem. Soc.* **1959**, *81*, 6335–6336.

Table 1. Optimization of the Pd-catalyst for the Aerobic Amination of 2-Cyclohexen-1-one with Piperidine



	catalyst (mol %)	additive	**3aa** (%)[a]
1	$Cu(OTf)_2$ (10)	NHPI/H_2O/KI[b]	8
2	$Pd(OAc)_2$ (10)	-	61
3	$[(PPh_2Me)_2PdCl_2]$ (10)	-	66
4	〃	AcOH	74
5	〃	$^tBuCO_2H$	75
6	〃	4-$MeOC_6H_4CO_2H$	78
7	〃	$PhCO_2H$	78
8	〃	TsOH/MS 4 Å	44
9	〃	CF_3CO_2H	61
10	$[(PPh_2Me)_2PdCl_2]$ (2)	$PhCO_2H$	93
11[c]	〃	〃	93(82)

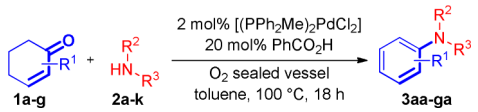
[a] **1a** (0.2 mmol), **2a** (0.1 mmol), Pd-source, additive (20 mol %), O_2 saturated toluene (0.2 mL), 100 °C, 18 h. Yields were determined by ^1H NMR analysis with 1,3,5-trimethoxy benzene as internal standard. Isolated yields in brackets. [b] NHPI (20 mol %), H_2O (1.0 equiv), KI (1.0 equiv). [c] **2a** (1.3 equiv).

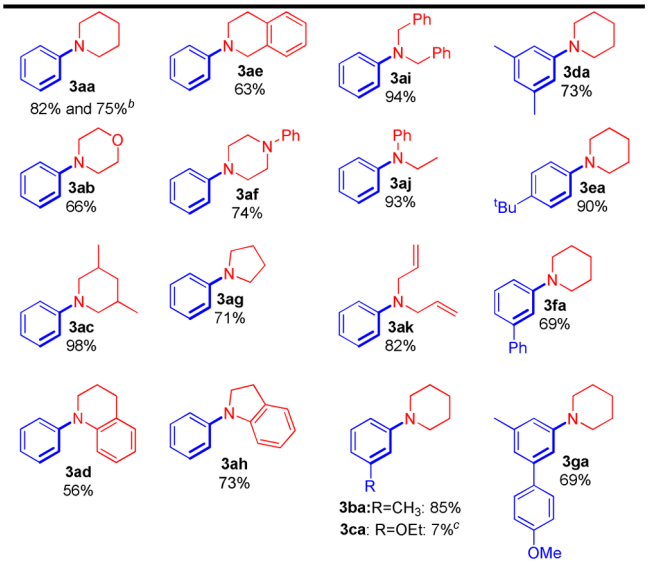
The rate of the dehydration step releasing the enamine **III** from **I** could be controlled by the addition of catalytic quantities of moderately strong Brønsted acids ($pK_a \approx 4$) (Table 1, entries 4–7). The best results were obtained with anisic acid and benzoic acid which gave the desired product in 78% yield (Table 1, entries 6 and 7). In contrast, the addition of strong acids (Table 1, entries 8 and 9) resulted in a too rapid release of the enamine which was decomposed[24] before it could be converted efficiently by the catalyst. The yield was further improved by lowering the catalyst loading (Table 1, entry 10), and under optimized conditions (Table 1, entry 11), **3aa** was detected in 93% yield.

The scope of the procedure is illustrated in Table 2. Under optimized reaction conditions various heterocyclic and aliphatic secondary amines are arylated with 2-cyclohexen-1-one in good yields. Amines containing β-hydrogen atoms such as **2i** or **2j** were arylated in high yields. The reaction conditions are mild enough to be tolerated by delicate amines, and the oxidatively sensitive compounds **2d** or **2h** and sensitive diallylamine **2k** were smoothly converted into the corresponding aryl amines. However, weakly nucleophilic heterocyclic amines such as indole, pyrrole or imidazole could not be arylated, and the substrates were recovered after the reaction time. Various moderately electron rich 2-cyclohexenones are converted into the corresponding aryl amines in good yields. However, particular electron rich and less electrophilic 2-cyclohexen-1-ones such as **1c** resulted in low yields, and 78% of unconverted **1c** was detected even after 36 h reaction time.

(24) (a) Ebitani, K.; Nagashima, K.; Mizugaki, T.; Kaneda, K. *Chem. Commun.* **2000**, 869–870. (b) Blau, K.; Burgemeister, I.; Grasnick, J.; Voerckel, V. *J. Prak. Chem.* **1991**, *333*, 455–466. (c) Blau, K.; Kapst, U.; Voerckel, V. *J. Prak. Chem.* **1989**, *331*, 671–676. (d) Höft, E.; Schultze, H. *Z. Chem.* **1967**, *7*, 137–148.

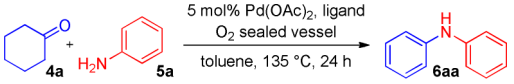
Table 2. Scope of the Aerobic Amination of 2-Cyclohexen-1-ones[a]





[a] **1a–g** (0.39 mmol, 1.3 equiv), **2a–k** (0.3 mmol, 1.0 equiv), $[(PPh_2Me)_2PdCl_2]$ (2 mol %), $PhCO_2H$ (20 mol %), O_2 saturated toluene (0.6 mL), 100 °C, 18 h. Isolated yields are based on **2**. [b] Reaction on 2.00 mmol scale. [c] Yield determined by ^1H NMR.

Table 3. Optimization of the Pd-catalyzed Aerobic Aromatization of Cyclohexanone and Aniline

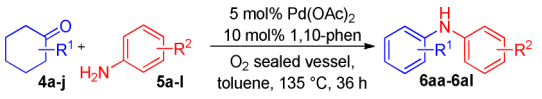


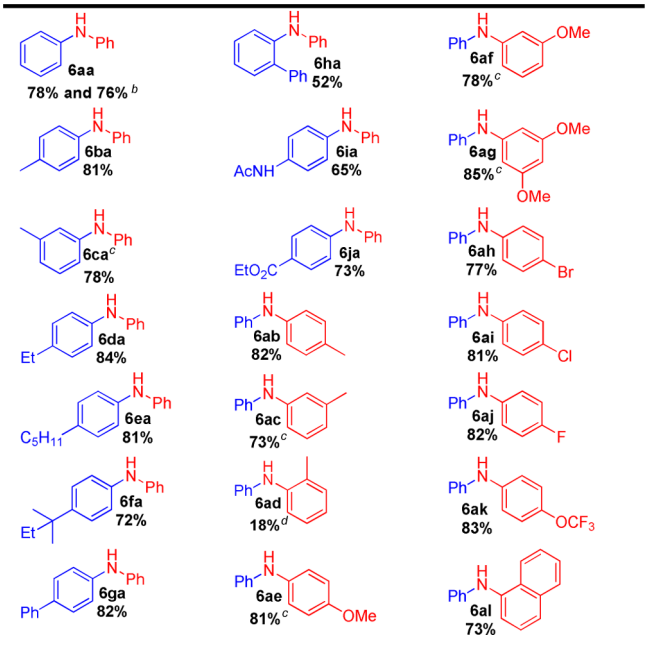
	ligand (mol %)	**6aa** (%)[a]
1	-	67
2	PhCOOH (5)	83
3	4-N,N-dimethylaminopyridine (5)	84
4	1,10-phenanthroline (5)	89
5	1,10-phenanthroline (10)	91

[a] **4a** (0.24 mmol), **5a** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), ligand, O_2 saturated solvent (0.5 mL), 135 °C, 24 h. Yields were determined by GC-analysis using mesitylene as internal standard.

Once the development of the simpler reaction was successful, we decided to tackle the more challenging but also more desirable arylation employing cheaper and more readily available cyclohexanone. Unfortunately, low yields (3%) were detected with piperidine under the optimized conditions along with the decomposition of the substrates.[22] Consequently, aniline (**5a**) was chosen as a robust test

Table 4. Scope of the Aerobic Amination of Cyclohexanones with Anilines[a]





[a] **4a**–**j** (0.24 mmol), **5a**–**l** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), 1,10-phenanthroline (10 mol %), O_2 sat. toluene (0.5 mL), 135 °C, 36 h. Isolated yields are based on **5**. [b] 2.00 mmol scale. [c] 4-*N*,*N*-dimethylaminopyridine (10 mol %) was used as ligand. [d] Yield was determined by GC-analysis.

substrate (Table 3). *N*,*N*-Diphenylamine (**6aa**) was detected in 67% yield in the presence of $Pd(OAc)_2$ at 135 °C in toluene (Table 3, entry 1). Premature catalyst deactivation by precipitation of Pd-black was minimized by the addition of oxidatively stable N- and O-containing ligands (Table 3, entries 2–4). The best results were obtained with 10 mol % of 1,10-phenanthroline (Table 3, entry 5).

Under optimized reaction conditions, **4a** and **5a** were smoothly converted into the product **6aa** in 91% yield.[25] The scope of the new protocol is illustrated in Table 4. Aniline (**5a**) was arylated with functionalized cyclohexanone derivatives in good yields. Aromatic rings, linear or branched alkyl chains, amides and esters were well tolerated on the cyclohexanones. Electron rich (**5g**) and electron deficient anilines (**5j**) were arylated in good yields. Halogen and trifluoromethoxy groups were well tolerated. However, nitro- and cyano-groups underwent undesired hydrogen transfer reduction and only small quantities of the corresponding diaryl amines were obtained. Good results were obtained with 4-*N*,*N*-dimethylpyridine as ligand instead of 1,10-phenanthroline for *meta*-substituted substrates (such as **4c** or **5c**). However, heterocyclic anilines resulted in low yields, for example, 2-amino pyridine was arylated in 15% yield.

In conclusion, two protocols have been developed for the arylation of amines with nonaromatic ketones via a Pd-catalyzed aerobic dehydrogenative aromatization. Secondary amines are arylated with 2-cyclohexen-1-ones in the presence of a $[(PMePh_2)_2PdCl_2]/PhCO_2H$ catalyst system, whereas a $Pd(OAc)_2$/1,10-phenanthroline catalyst mediates the conversion of anilines into the corresponding diaryl amines with cyclohexanones. Current investigations aim at developing more reactive catalyst systems that allow broadening the scope for the amines as well as extending the aerobic dehydrogenative aromatization reaction on the utilization of other heteroatom nucleophiles.

Acknowledgment. We thank the DAAD (postdoctoral fellowship for T.K.), NSERC, FQRNT, the Canada Research Chair (to C.-J.L.), the National Natural Science Foundation of China (20902076, 21172185), and the Hunan Provincial Natural Science Foundation of China (11JJ1003) for financial support.

Supporting Information Available. Full experimental details and spectral data for all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

(25) The reaction conditions do not apply for the arylation with 2-cyclohexen-1-one (16% of **6ab** and 40% of **3aa** have been detected with **5b** and **2a**, respectively).

The authors declare no competing financial interest.