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Copper-Catalyzed Direct Amination of Electron-Deficient Arenes with Hydroxylamines

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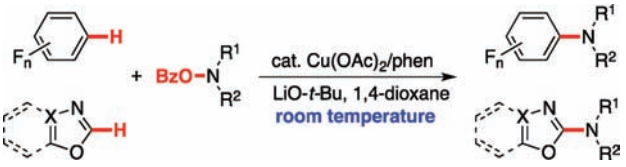
ABSTRACT



The C−H amination of electron-deficient arenes such as polyfluoroarenes and azole compounds with *O*-acylated hydroxylamines effectively proceeds in the presence of a copper catalyst even at room temperature to provide the corresponding anilines and aminoazoles in good yields.

Aryl- and heteroarylamines have received much attention from synthetic chemists because of their ubiquity in pharmaceuticals and functional materials.[1] Among efficient and convergent routes to the target structure is the metal-mediated aromatic sp^2C-N bond forming reaction (Figure 1). Since the pioneering work by Migita and Kosugi,[2] the palladium-catalyzed cross-coupling reaction of aryl halides with amines, so-called the Buchwald–Hartwig amination,[3] has been widely studied and now provides a powerful synthetic tool for C−N bond formation (route a). This has largely widened the applicable substrates compared with the conventional Ullmann coupling. On the other hand, recent advances in the metal-mediated C−H functionalization chemistry[4] have enabled the direct oxidative C−H/N−H coupling as a complementary and potentially more effective process for the synthesis of these amines (route b).[5] However, most precedents are still restricted in generality and selectivity: relatively high temperature is required; the use of a stoichiometric amount of metal oxidant such as copper or silver species is inevitable; the reaction is often limited to an intramolecular

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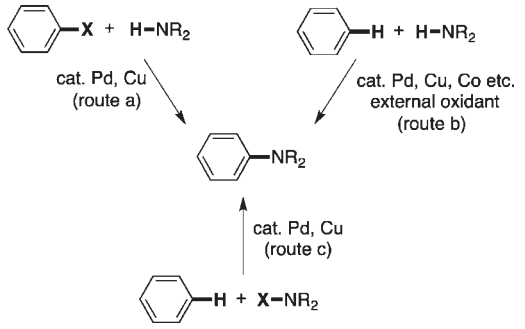
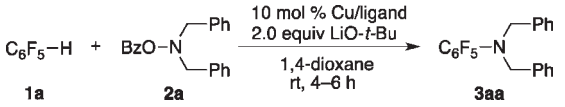


Figure 1. Convergent approaches to aryl- and heteroarylamines.

fashion. In this context, some attention is focused on the direct amination with an electrophilic amination reagent as the third approach (route c). Hartwig and co-workers reported the palladium-catalyzed intramolecular direct amination using oxime esters leading to indole derivatives.[6] Our group also introduced chloroamines for the intermolecular direct amination of heteroaromatic compounds and succeeded in the concise synthesis of 2-aminoazoles even at room temperature.[7] While valuable, the catalysis still suffered from the relatively narrow substrate scope of the starting aromatics. For example, the application to polyfluoroarenes[8] remains unsuccessful. Therefore, further developments of the reaction system are quite appealing. Herein, we report the second-generation copper-based catalysis for the direct amination of electron-deficient arenes involving fluoroarenes as well as azoles. The key to our success is the use of *O*-acylated hydroxylamines as a modified electrophilic nitrogen source.

We began our optimization studies with pentafluorobenzene (**1a**, 0.25 mmol) and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**2a**, 0.30 mmol) as model substrates (Table 1). On the basis of our previous work,[7a] treatment of **1a** with **2a** in the presence of a $Cu(acac)_2$/phen catalyst and LiO-*t*-Bu in 1,4-dioxane afforded the corresponding directly aminated product **3aa** in 22% GC yield (entry 1). Notably, the reaction proceeded even at room temperature albeit with low yield. With the preliminary intriguing result in hand, we extensively screened various combinations of copper salts and ligands. While other nitrogen-based ligands such as dtbpy and[9] TMEDA dropped the yield (entries 2 and 3), some monodentate phosphines improved the reaction efficiency (entries 4–8), with PPh_3 proving to be optimal (entry 4). On the other hand, bidentate phosphines were detrimental (entries 9–11). Next, a variety of copper precursors were tested using PPh_3 as the ligand (entries 12–15). Among them, CuCN and $Cu(OAc)_2$

Table 1. Optimization Studies for Copper-Catalyzed Direct Amination of Pentafluorobenzene (**1a**) with *O*-Benzoyl-*N*,*N*-dibenzylhydroxylamine (**2a**)[a]



entry	Cu	ligand	**3aa**, yield (%)[b]
1	$Cu(acac)_2$	phen	22
2	$Cu(acac)_2$	dtbpy	14
3	$Cu(acac)_2$	TMEDA	6
4	$Cu(acac)_2$	PPh_3	46
5	$Cu(acac)_2$	PCy_3	trace
6	$Cu(acac)_2$	$P(p\text{-Tol})_3$	46
7	$Cu(acac)_2$	$P(p\text{-MeOC}_6H_4)_3$	32
8	$Cu(acac)_2$	$P(OPh)_3$	5
9	$Cu(acac)_2$	dppbz	9
10	$Cu(acac)_2$	dppp	4
11	$Cu(acac)_2$	binap	18
12	CuI	PPh_3	11
13	$Cu(OTf)_2$	PPh_3	48
14	$Cu(OAc)_2$	PPh_3	61
15	CuCN	PPh_3	69
16[c]	$Cu(OAc)_2$	phen	65 (65)

[a] Reaction conditions: Cu (0.025 mmol), ligand (0.025 or 0.050 mmol for bidentate or monodentate ligands, respectively), LiO-*t*-Bu (0.50 mmol), **1a** (0.25 mmol), **2a** (0.30 mmol), 1,4-dioxane (1.5 mL), rt, 4–6 h, N_2. [b] The yields are determined by GC method. Yield of isolated product is in parentheses. [c] With **1a** (0.30 mmol), **2a** (0.25 mmol), and LiO-*t*-Bu (0.60 mmol).

(6) (a) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. Also see:(b) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (c) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688. (d) Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862.

(7) (a) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. For C–N bond formation with chloroamines or -amides and organometallic reagents; see:(b) He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6414. (c) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598. (d) Hatakeyama, T.; Yoshimoto, Y.; Ghorai, S. K.; Nakamura, M. *Org. Lett.* **2010**, *12*, 1516.

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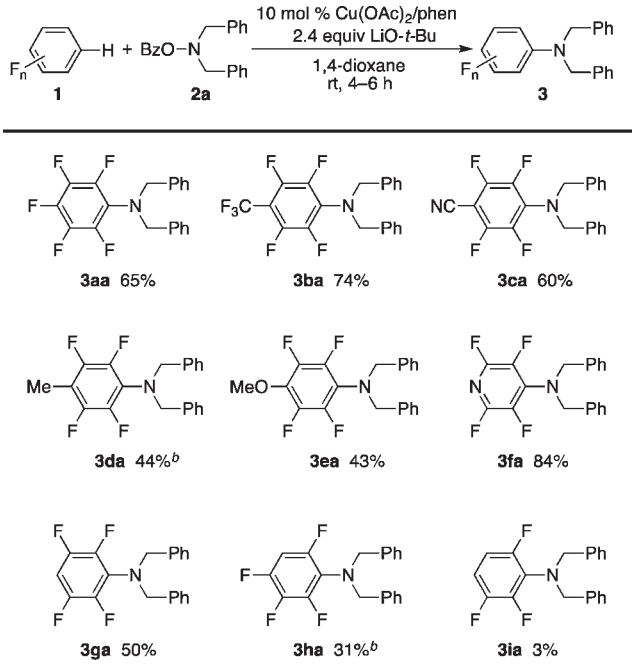
(9) The N–O bond as a useful handle for C–N bond formation; see: (a) Erdick, E.; Ay, M. *Synth. React. Inorg. Met.-Org. Chem.* **1989**, *19*, 663. (b) Tsutsui, H.; Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1997**, *26*, 317. (c) Noack, M.; Göttlich, R. *Chem. Commun.* **2002**, 536. (d) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680. (e) Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799. (f) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219. (g) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521. (h) Zhang, Z.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 3005. (i) Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* ASAP, 10.1021/ol100651r. Alkali-metal-mediated amination of thiadiazoles with NH_2–OH: (j) Rao, V. R.; Srinivasan, V. R. *Indian J. Chem.* **1965**, *3*, 417.

showed good performances (entries 14 and 15). Some additional investigations into the reaction stoichiometry revealed that the use of **2a** as the limiting reagent under a $Cu(OAc)_2$/phen system gave better generality and reproducibility, and the desired **3aa** was isolated in 65% yield (entry 16). Any changes of reaction solvent and base into toluene, DMSO, K_3PO_4, and NaO-*t*-Bu diminished the yield of **3aa** (not shown).[10]

By using the $Cu(OAc)_2$/phen catalyst, the direct amination of an array of fluoroarenes **1** with **2a** was carried out (Scheme 1). In addition to **1a**, 3-substituted 1,2,4,5-tetrafluorobenzene derivatives bearing not only electron-withdrawing but also electron-donating groups underwent C−H amination, although the latter showed somewhat lower reactivity (**3ba**−**ea**). The pyridine skeleton was also available for use (**3fa**). On the other hand, 1,2,4,5-tetrafluorobenzene and 1,2,3,5-tetrafluorobenzene that contain two possible reactive C−H bonds provided the monoaminated products exclusively albeit with moderate efficiency (**3ga** and **3ha**). However, the reaction of 1,3,5-trifluorobenzene was sluggish (**3ia**), indicating that the step of C−H bond cleavage highly depends on its acidity.[11]

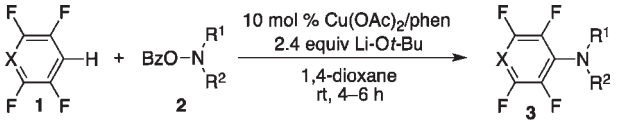
Scheme 1. Copper-Catalyzed Direct Amination of Various Fluoroarenes **1** with *O*-Benzoyl-*N*,*N*-dibenzylhydroxylamine (**2a**)[a]

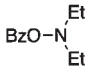
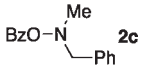
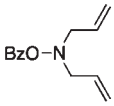
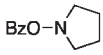
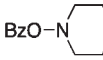
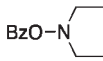
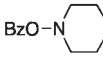
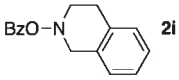
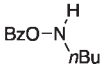


[a] Reaction conditions: see Table 1, entry 16. [b] At 80 °C.

We subsequently investigated the scope of amines **2** (Table 2). Several acyclic substrates containing *N*,*N*-diethyl, *N*-benzyl-*N*-methyl, and *N*,*N*-diallyl substituent patterns were tolerated toward the reaction (entries 1−6). In particular, the resultant benzyl[12] and allyl[13] moieties could be readily deprotected into the free N−H bond, which are versatile handles for further transformations. Cyclic systems such as pyrrolidine, piperidine, and morpholine also participated in the coupling without any difficulties (entries 7−9). Moreover, the Boc-protected piperazine and bicyclic framework, tetrahydroisoquinoline, could be introduced to the polyfluorinated arene directly (entries 10 and 11). It is noteworthy that the secondary amino group was compatible under the reaction conditions (entry 12).

Table 2. Copper-Catalyzed Direct Amination of Fluoroarenes **1** with Various *O*-Benzoylhydroxylamines (**2**)[a]



entry	1	2	3, yield [%][b]
1	**1b**, X = CCF_3	 **2b**	**3bb**, 66
2	**1c**, X = CCN	**2b**	**3cb**, 84
3	**1e**, X = COMe	**2b**	**3eb**, 65
4	**1f**, X = N	**2b**	**3fb**, 83
5	**1f**	 **2c**	**3fc**, 79
6	**1f**	 **2d**	**3fd**, 67
7	**1f**	 **2e**	**3fe**, 66
8	**1f**	 **2f**	**3ff**, 57
9	**1f**	 **2g**	**3fg**, 71
10	**1f**	 **2h**	**3fh**, 52
11	**1f**	 **2i**	**3fi**, 37
12	**1f**	 **2j**	**3fj**, 46

[a] Reaction conditions: see Table 1, entry 16. [b] Yield of isolated product.

A plausible mechanism for the copper-catalyzed direct amination of pentafluorobenzene (**1a**) with *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**2a**) is illustrated in Scheme 2.

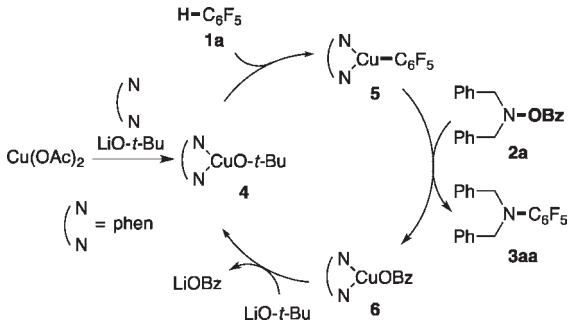
(10) Without any copper catalysts, no formation of **3aa** was detected by gas chromatography analysis.

(11) For pK_a values of representative fluoroarenes; see: Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568.

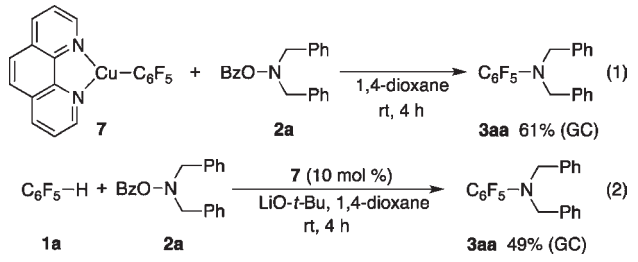
(12) Wang, J.-Y.; Wang, D.-X.; Zheng, Q.-Y.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2007**, *72*, 2040.

(13) (a) Jaime-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett.* **1998**, *39*, 1313. (b) Cadierno, V.; García-Garrido, S. E.; Gimeno, J.; Nebra, N. *Chem. Commun.* **2005**, 4086.

Scheme 2



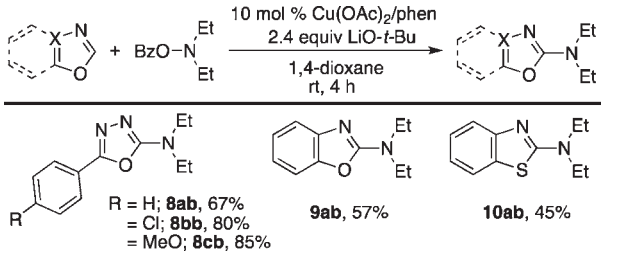
Scheme 3



Initial reduction of Cu(II) into Cu(I)[14] and complexation with phen and LiO-*t*-Bu forms the copper alkoxide **4**. Subsequent direct cupration of **1a** with the aid of an anionic O-*t*-Bu ligand of strongly basic nature[15] generates the arylcopper species **5** as the key intermediate. The C–N bond-forming reaction then occurs to provide the aminated product **3aa** along with the CuOBz complex **6**. Final ligand exchange with LiO-*t*-Bu regenerates the starting active catalyst **4** to complete the catalytic cycle. The results of the reactions with the isolated (phen)CuC_6F_5 (**7**)[16] under both stoichiometric and catalytic conditions are consistent with the proposed pathway (Scheme 3). However, the effect of an OAc ancillary ligand and the detailed mechanism for C–N bond formation still remain obscure, and further efforts are required for uncovering the process.[17]

Finally, we applied the above copper catalysis to relatively acidic azoles (Scheme 4). Pleasingly, the direct amination of 1,3,4-oxadiazoles, benzoxazole, and benzothiazole took place under standard conditions to furnish the corresponding 2-aminoazoles **8ab**–**cb**, **9ab**, and **10ab** in moderate to good yields. The wider substrate scope is suggestive of superiority of the present catalysis based on hydroxylamines as the electrophilic amination reagents, compared to the previous system using chloroamines.[7a]

Scheme 4



In conclusion, we have developed a copper-catalyzed direct amination of electron-deficient arenes involving fluoroarenes and azoles with *O*-acylated hydroxylamines. The catalysis enabled the rapid and concise construction of polyfluoroanilines[18] and aminoazoles,[19] which are of importance in pharmaceutical and medicinal chemistry.

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

(14) The detailed mechanism for the reduction is not clear at this stage.

(15) For O-*t*-Bu ligand-assisted direct cupration, see: (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (b) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2009**, *11*, 1511. (c) Besseliévre, F.; Piguel, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9553. (d) Zhang, L.; Cheng, J.; Ohnishi, T.; Hou, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 8670. (e) Kawano, T.; Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2010**, *75*, 1764 and refs 7a and 8i–8k.

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(17) For mechanistic studies with organozinc reagents, see: ref 9g. At this stage, a radical pathway could not be completely excluded; see: ref 9c.

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