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A recyclable Cu/Al-HT catalyst for amination of aryl chlorides

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Abstract—A simple Cu/Al-HT catalyzed amination of aryl chlorides with primary and secondary aromatic amines has been developed. This ligand-free heterogeneous Cu/Al-HT catalyst, in conjunction with base, also efficiently works for the amination of aryl chlorides with cycloalkylamines. This method tolerates a variety of functional groups and does not require an expensive additive.
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N-Arylation of amines is an important reaction in chemical synthesis because N-arylated compounds have wide utility in pharmaceuticals and agrochemicals.[1] Their widespread importance has led to the development of many synthetic methods for the formation of aryl-nitrogen bonds. Amongst them, the classical copper-mediated Ullmann and recently developed palladium(0)-catalyzed aryl coupling are commonly used methods.[2] It has been recognized that development of a clean N-arylation method is an important challenge in green chemistry. The most frequently used method for coupling reactions is still the classical copper-mediated Ullmann type reaction. The contributions of Buchwald and co-workers[3] and Taillefer and co-workers[4] in the development of catalytic N-arylations with bromo- and iodo-arenes using copper in the presence of ligands such as amino acids,[5] diamines,[6] diimines,[7] diols[8] and thiolate[9] has generated significant interest in industry. N-Arylation of heterocycles with chloroarenes using copper oxide coated copper nanoparticles and by palladium catalysis in the presence of strong bases have also been reported.[10] Solid supports such as KF/Al_2O_3[11] and Cu–Fe-hydrotalcite have been used for N-arylation in recent years.[12]

Heterogeneous catalysis is particularly attractive as it allows the production and ready separation of large quantities of products with the use of a small amount of catalyst.

Hydrotalcites (HTs) are a class of layered materials of current interest. They are represented by the general formula, $[M(II)_{1-x}M(III)_x(OH)_2]\ A^{n-}_{x/n}\cdot yH_2O$, where M(II) and M(III) are divalent and trivalent cations such as Cu^{2+}, Mg^{2+} and Al^{3+}, respectively. The counteranions may be OH^-, Cl^-, $NO_3{}^-$, $CO_3{}^{2-}$, etc.[13–15]

Recently, we reported the preparation of recyclable heterogeneous Cu-exchanged fluoroapatite and copper exchanged *tert*-butoxyapatite catalysts, by incorporating the basic species $F^-/t\text{-}BuO^-$ in apatite in situ by co-precipitation and subsequent exchange with Cu(II) for the N-arylation of imidazoles and other heterocycles with chloroarenes and fluoroarenes, with good to excellent yields.[16] In continuation of our work on N-arylation reactions, we herein report Cu/Al-HT catalyzed amination of aryl chlorides with benzylamine, dibenzylamine and cycloalkylamines at 100–160 °C in the presence of base.

To identify the best system for the amination of *para*-nitrochlorobenzene, **1a**, with benzylamine, we employed Cu/Al-HTA (Cu:Al, 3:1), Cu/Al-HTB (Cu:Al, 2.5:1), Cu-HAP, and Cu-FAP as catalysts and it was found that Cu/Al-HTB with K_2CO_3 (1.2 equiv) afforded a good yield of N-arylated product (77%) at 160 °C. The only by-product observed in this reaction was nitrobenzene (5%). Several solvents were screened for the amination of **1a** with benzylamine, and it was observed that high boiling polar solvents such as DMSO and DMF were found to be less effective. Although *N*-methylpyrrolidine (NMP) was found to be effective (60%), benzylamine (benzylamine used as the reagent as well as the solvent) was found to be more effective (77%) with negligible amount of Cu leaching. A control reaction conducted under identical conditions devoid of Cu/Al-HTB gave no coupled product. Cu/Al-HTB

Keywords: N-Arylation; Amination; Cu/Al-HT; Aryl chlorides.

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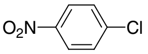
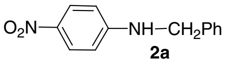
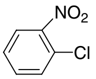
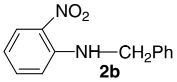
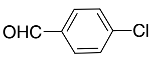
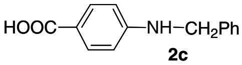
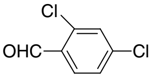
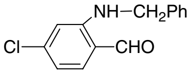
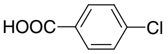
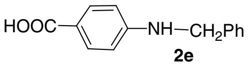
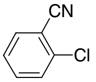
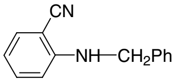
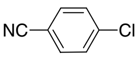
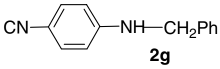
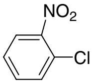
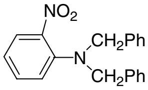
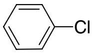
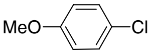
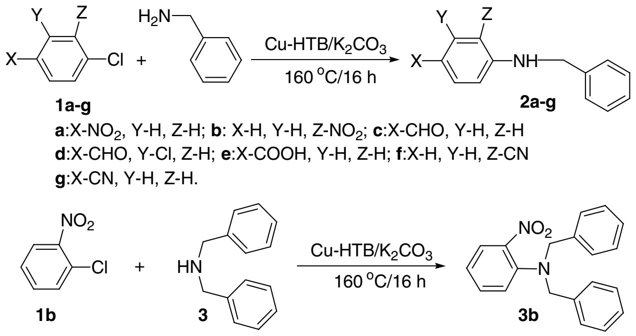
Table 1. Cu/Al-HTB catalyzed amination of aryl chlorides with benzylamines[a]

Entry	Aryl chloride	Production	Time (h)	Yield[b] (%)
1		 **2a**	16	77, 77[c]
2		 **2b**	8	80, 60[d]
3		 **2c**	16	68
4		 **2d**	12	69
5		 **2e**	16	46
6		 **2f**	8	52
7		 **2g**	16	45
8[e]		 **3b**	14	76
9		—	16	—
10		—	16	—

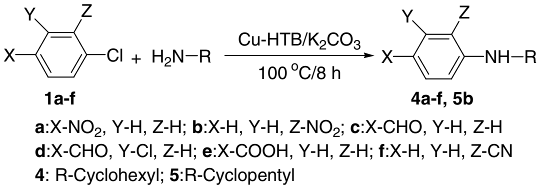
[a] Reaction conditions: 20 wt % catalyst, 3.60 mmol (~1.1 equiv) K_2CO_3, 3.17 mmol aryl chloride, 1.5 ml amine, temperature 160 °C.
[b] Isolated yield. All the products were characterized by ^{1}H NMR and mass spectroscopy and compared with the literature data (Ref. 19).
[c] Recycled catalyst used (isolated yields %: 77, 77, 76, 76).
[d] Using NMP as solvent.
[e] Using dibenzylamine.

was recovered quantitatively by simple filtration and reused, and gave consistent activity even after the fourth cycle (Table 1, entry 1). Moreover, the absence of copper in the filtrate was confirmed by ICP-MS, which reiterated that no leaching of copper had occurred during the reaction and provided evidence for heterogeneity throughout the reaction.

We chose a variety of substituted chloroarenes possessing a wide range of functional groups for our study (Scheme 1) to demonstrate the scope and the generality of the Cu/Al-HTB catalyzed amination of chloroarenes with K_2CO_3 as base, and the results are summarized in Table 1. Chlorobenzenes with electron-withdrawing groups, such as 4-nitro-chlorobenzene, 4-chlorobenzaldehyde and 4-cyano-chlorobenzene provided moderate to good yields (Table 1, entries 1, 3 and 7). Interestingly, *ortho*-substituted electron-withdrawing groups on the aryl chloride provided good yields in shorter times (Table 1, entries 2, 4, 6 and 8) compared with 4-substituted chlorobenzenes. When chlorobenzene and 4-chloroanisole were employed in the reaction, no product formation was observed (Table 1, entries 9 and 10). In the case of 2,4-dichlorobenzaldehyde, the chloro group at the *ortho* position was N-arylated (entry 4). The *ortho*

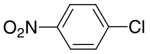
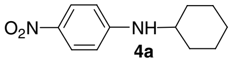
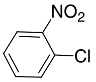
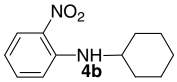
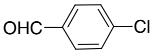
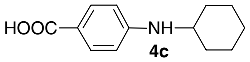
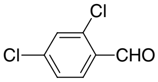
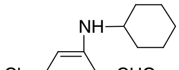
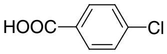
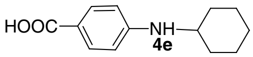
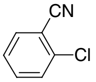
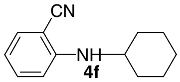
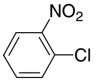
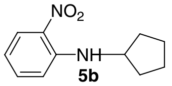


Scheme 1.



Scheme 2.

Table 2. Cu/Al-HTB catalyzed amination of aryl chlorides with cycloalkylamines[a]

Entry	Aryl chloride	Production	Time (h)	Yield[b] (%)
1		 4a	9	71
2		 4b	8	91, 91[c]
3		 4c	8	89
4		 4d	8	56
5		 4e	8	88
6		 4f	9	59
7		 5b	6	93

[a] Reaction conditions: 20 wt % catalyst, 3.6 mmol (~1.1 equiv), K_2CO_3, 3.17 mmol aryl chloride, 2 ml amine, temperature 100 °C.

[b] Isolated yield. All the products were characterized by ^{1}H NMR and mass spectroscopy and compared with the literature data (Ref. 18).

[c] Recycled catalyst used (isolated yields %: 91, 91, 90, 90).

effect of the chloro group can be visualized when compared with *para*-chlorobenzaldehyde. The C–N coupling product bearing an aldehyde group is oxidized to an acid while in the case of 2,4-dichlorobenzaldehyde, no oxidation of the aldehyde group occurred (Table 1, entry 3 vs 4). In the case of the secondary amine, dibenzylamine, the reaction proceeded in a similar manner without the formation of nitrobenzene (entry 8). Benzylamines with electron-donating and electron-withdrawing moieties were found to be inactive in this reaction.

In order to expand the scope of this methodology, the Cu/Al-HTB catalyzed amination protocol was extended to aliphatic amines and cycloalkylamines[17] (Scheme 2). Cycloalkylamines were found to react at relatively low temperature and in short periods of time. A variety of substituted chloroarenes possessing a wide range of functional groups were successfully coupled with cycloalkylamines (cyclohexylamine and cylopentylamine) to give the corresponding N-arylated products in excellent yields and the results are summarized in Table 2. The results on the amination of various aryl chlorides with cycloalkylamines are impressive and reported for the first time.[18]

In conclusion, we have developed a simple and efficient method for the amination of aryl chlorides using Cu/Al-HTB as a heterogeneous catalyst. Various aryl chlorides were coupled with benzylamine, dibenzylamine and cycloalkylamines to yield the corresponding N-arylated products in good to excellent yields (45–93%). The catalyst can be readily recovered and reused.

Acknowledgement

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References and notes

1. (a) Negwer, M. In *Organic-Chemical Drugs and their Synonyms: (An International Survey)*, 7th ed.; Akademie: Berlin, 1994; (b) Southon, I. W.; Buckingham, J. In *Dictionary of Alkaloids*; Saxton, J. E., Ed.; Chapman and Hall: London, 1989.
2. (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433; (b) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *71*, 1417; (c) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232; (d) Hartwig, J. F. *Synlett* **1996**, 329; (e) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J. J.; Buchwald, S. L. *J. Org. Chem* **2000**, *65*, 1158; (f) Djakovitch, L.; Wagner, M.; Kohler, K. *J. Organomet. Chem.* **1999**, *592*, 225.
3. (a) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578; (b) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am.Chem. Soc.* **2002**, *124*, 11684; (c) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727; (d) Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657.
4. (a) Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Eur. J. Org. Chem.* **2004**, 695; (b) Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Tailefer, M. *Chem. Eur. J.* **2004**, *10*, 5607.
5. (a) Ma, D.; Xia, C.; Jiang, J.; Zhang, J.; Tang, W. *J. Org. Chem.* **2003**, *68*, 442; (b) Clement, J.-B.; Hayes, J. F.; Sheldrake, H. M.; Sheldrake, P. W.; Wells, A. S. *Synlett* **2001**, 1423.

6. Wang, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040; Padwa, A.; Crawford, K. R.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2003**, *68*, 2609.
7. Kuil, M.; Bekedam, E. K.; Visser, G. M.; van den Hoogenband, A.; Terpastra, J. W.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; van Strijdonck, G. P. F. *Tetrahedron Lett.* **2005**, *46*, 2405.
8. (a) Enguehard, C.; Allouchi, H.; Gueiffier, A.; Buchwald, S. L. *J .Org. Chem.* **2003**, *68*, 4367; (b) Buchwald, S. L.; Klapars, A.; Antilla, J. C.; Job, G. E.; Wolter, M.; Kwong, F. Y.; Nordmann, G. Hennessy, E. J. Patent WO 02/085838 A1, 2002, CA2445159 (A1).
9. Jerphagnon, T.; Van Klink, G. P. M.; De Vries, J. G.; Van Koten, G. *Org. Lett.* **2005**, *7*, 5241.
10. (a) Son, S. U.; Park, I. K.; Park, J.; Hyeon, T. *Chem. Commun.* **2004**, *778*; (b) Amrani, R. O.; Schneider, R.; Fort, Y. *Synthesis* **2004**, *15*, 2527.
11. Smith, W. J.; Sawyer, J. S. *Tetrahedron Lett.* **1996**, *37*, 299.
12. Jadhav, V. H.; Dunbre, D. K.; Phapale, V. B.; Borate, H. B.; Wakharkar, R. D. *Catal. Commun.* **2007**, *8*, 65.
13. Velu, S.; Swamy, C. S. *Appl. Catal.* **1994**, *119*, 241.
14. Cavani, F.; Trifiro, F.; Vaccari, A. *Catal. Today* **1991**, *11*, 173.
15. Trifiro, F.; Vaccari, A. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., MacNicol, D. D., Davies, J. E. D., Vogle, F., Eds.; Pergamon Press: Oxford, 1995; Vol. 7, Chapter 10.
16. Choudary, B. M.; Sridhar, C.; Kantam, M. L.; Venkanna, G. T.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 9948.
17. Typical procedure for the amination of aryl chloride with cyclohexylamine (Table 2, entry 2, **4b**): Cu/Al-HTB (100 mg, 20 wt %) and, K_2CO_3 (0.5 g, 3.62 mmol) were added to a mixture of *ortho*-nitrochlorobenzene (0.5 g, 3.17 mmol) in freshly distilled cyclohexylamine (2 ml) and the mixture was stirred in an oil bath (preheated to the given reaction temperature) for the required time. After completion of the reaction as monitored by TLC, the reaction mixture was cooled to room temperature, centrifuged and the solid catalyst was separated. The organic layer was treated with water, washed with brine and dried (Na_2SO_4). The resultant organic layer was concentrated to give crude *N*-(2-nitrophenyl) cyclohexylamine and unreacted *ortho*-nitrochlorobenzene. Column chromatography was performed using silica gel (60–200 mesh, eluent-hexane) to afford the pure product. Yield 91%, Orange solid, mp −108 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (1H, d, $J = 8.3$ Hz), 8.24 (1H, NH), 7.49 (1H, t, $J = 7.4$ Hz), 6.85 (1H, d, $J = 8.3$ Hz), 6.61 (1H, t, $J = 8.3$ Hz), 3.49 (1H, s), 2.21–1.35 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.9, 127.8, 115.5, 114.5, 51.9, 33.0, 26.1, 25.1. MS (ESI): $m/z = 220$. CHN Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.4; H, 7.2; N, 12.7. Found: C, 65.6; H, 6.9; N,12.6.
18. (a) Wolf, C.; Liu, S.; Mei, X.; August, A. T.; Casimir, M. D. *J .Org. Chem.* **2006**, *71*, 3270; (b) Lei, X.; Zhu, Di; Wu, F.; Wang, R.; Wan, B. *Tetrahedron* **2005**, *61*, 6553.
19. Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581.