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Design and Evolution of Copper Apatite Catalysts for N-Arylation of Heterocycles with Chloro- and Fluoroarenes

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N-Arylheterocycles are common motifs in pharmaceutical research.[1] Arylation of heterocyclic nitrogen is a long-standing problem, which is far from being satisfactorily solved. The discovery and development of the catalytic path for N-arylation of heterocycles by Buchwald[2] and Taillefer[3] with bromo- and iodoarenes using copper in the presence of basic ligands generated greater interest in industry. The N-arylation of heterocycles using chloro- and fluoroarenes is of importance, since this reaction involving C−Cl and C−F activation contributes to the fundamental understanding of the reactivity of such very stable bonds. In this direction, N-arylation of heterocycles with chloroarenes containing electron-withdrawing groups (EW) by using copper oxide coated copper nanoparticles and electron-donating groups (ED) by Pd catalysts in the presence of strong bases are performed.[4] Although C−N and C−C coupling reactions with fluoroarenes (EW) are realized using Pd(0) catalysts, the scope is severely restricted to fluoroarenetricarbonylchromium(0) or 2-nitrofluoroarene only.[5]

We conceived the use of strong basic support to make electron-rich copper catalyst that activates C−Cl and C−F bonds in haloarenes for N-arylation of heterocycles.[6] We chose weakly amphoteric apatites as supports, since various kinds of cations and anions can be readily introduced into their framework due to their large ion exchange ability, and such exchanged apatites are already in use in several organic transformations.[7]

In this communication, we report the preparation of recyclable heterogeneous catalysts, copper-exchanged fluorapatite (**1**), and copper-exchanged *tert*-butoxyapatite (**2**) by incorporating basic species F^-/^{t}BuO$^-$ in apatite in situ by coprecipitation and subsequent exchange with Cu(II) (Scheme 1) for N-arylation of imidazoles and other heterocycles with chloroarenes and fluoroarenes (EW), which gave good to excellent yields for the first time. We also present the synthesis and characterization of some of the intermediates of the catalytic cycle[8] to understand the mechanistic aspects of the very important organic transformation, hitherto confined to speculations only. These catalysts were well-characterized by XRD, TPD, XPS, IR, ICP-MS, and DTA-MS (see the Supporting Information, SI).

To identify the best system for N-arylation of imidazole with chlorobenzene, a variety of copper catalysts in conjunction with different bases were screened, and we found that **1**, **2** with K_2CO_3 (2 equiv) and KO^{t}Bu (10 mol %) as additive in DMF at 120 °C afforded the optimum yield (85%). The decreased order of activity **1** + KO^{t}Bu (10 mol %) > **2** + KO^{t}Bu (10 mol %) > **1** > **2** is in accordance to their decreased basicity, while a simple weakly basic copper hydroxyapatite (CuHAP), $Cu(OAc)_2$, CuI, and Cu powder are essentially inactive (see SI).

Scheme 1. Preparation of Catalysts **1** and **2**

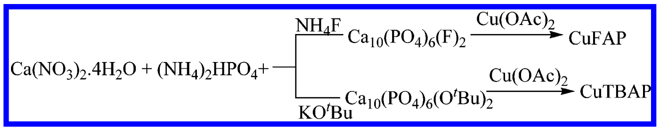
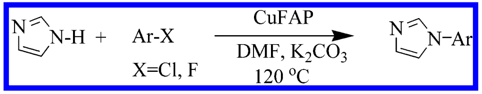


Table 1. N-Arylation of Imidazole with Chloro- and Fluoroarenes[a]



entry	Ar-X	time (h)	yield (%)[b]
1	1-chloro-4-nitrobenzene	1	100 (90) 90[c] 0[d]
2	1-chloro-2-nitrobenzene	3	100 (88)
3	4-chlorobenzonitrile	6	98 (95)
4	2-chloro-5-(trifluoromethyl) benzonitrile	3	100 (92)
5	4-chlorobenzaldehyde	10	88 (82)
6	2-chloropyridine	7	96 (92)
7	2-chloropyrimidine	1	100 (90)
8	4-chlorobenzophenone	6	96 (88)
9	chlorobenzene	36	72 (60) 85[e]
10	4-chlorotoluene	36	65 (55)
11	4-chloroanisole	36	62 (52)
12	2-fluorobenzonitrile	1	95 (82)
13	4-fluorobenzaldehyde	1	92 (80)
14	1-fluoro-4-nitrobenzene	0.5	100 (85)[f]
15	3-chloro-4-fluoronitrobenzene	1	95 (85)[g]

[a] ArX (1 mmol), imidazole (1.2 mmol), catalyst (100 mg), K_2CO_3 (2 mmol), DMF (4 mL), 120 °C. [b] Yields refer to GC yields, and yields in parentheses refer to isolated yields. [c] GC yield after fourth recycle. [d] Yield without copper. [e] GC yield obtained by using 10 mol % of KO^{t}Bu. [f] Yield with CuHAP and CuFAP. [g] Selective C−F coupling product.

Our hypothesis was successfully amenable to the N-arylation of the imidazole with a wide range of chloro- and fluoroarenes using catalyst **1**, and the results are described in Table 1. As illustrated in Table 1, chloroarenes (EW), 2-chloropyridine, and 2-chloropyrimidine provide excellent yields in shorter reaction times than chlorobenzene and chloroarenes (ED) (entries 1−11). Cyano, nitro, and trifluromethyl groups are well-tolerated (entries 1, 3, and 4). These N-arylation results of deactivated chloroarenes using K_2CO_3 as a base are quite impressive over the unreactive system using nanocopper and Cs_2CO_3 base[4a] (see SI). Another significant feature is that, under similar conditions, the N-arylation of imidazole with chlorobenzene affords moderate yields, which could be further improved by the addition of KO^{t}Bu (entry 9 and SI). N-Arylation of heterocycles developed here using the cheaper chloroarenes is more attractive than the one using the expensive bromo- and iodoarenes in terms of economic feasibility. The catalyst is recycled four times with a slight decrease in activity (entry 1). Interestingly, fluoroarenes composed of several *o*- or *p*-EW groups (entries 12−15) are also coupled with imidazole to afford the corresponding N-arylated products in excellent yields. Faster reactivity over the chloroarenes (entries 1, 5, 13, and 14) and selective coupling involving C−F activation only in chlorofluoroarene (entry 15) are

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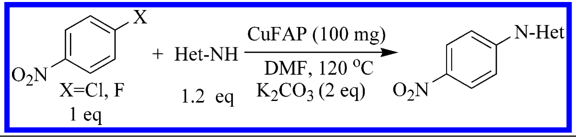
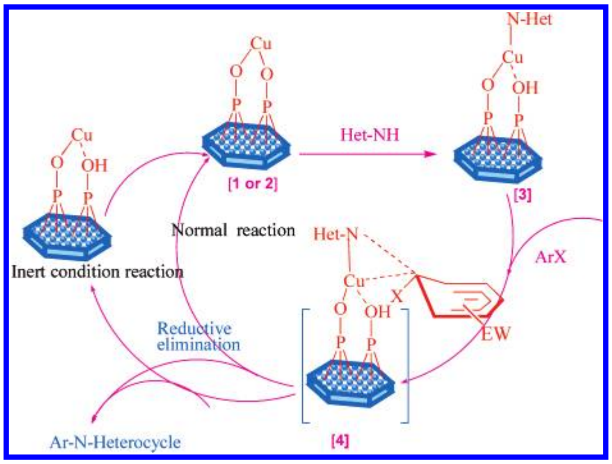
Table 2. N-Arylation of Various Nitrogen Heterocycles



		X = Cl		X = F	
entry	Het-NH	time (h)	yield (%)[a]	time (h)	yield (%)[a]
1	pyrrole	4	90 (80) 0[b]	2	95 (85) 0[b]
2	pyrazole	3	95 (85)	1	90 (80)
3	benzimidazole	12	85 (72)	9	85 (75)
4	piperidine	5	90 (80)	1	95 (85)

[a] Yields refer to GC yields, and yields in parentheses refer to isolated yields. [b] Without Cu, reaction with ArX and ArX(ED).

Scheme 2. Possible Mechanism for the N-Arylation of Heterocycles



other attributes of this innovative coupling. Such precedence of higher reactivity of C−F over C−Cl for fluoroarenes (EW) in Suzuki reaction is recorded.[5b] In N-arylation of heterocycles with fluoroarenes (EW), even CuHAP showed good performance (entry 14). On detailed examination, the in situ formed catalyst **1** as indicated by XPS and FTIR (see SI) is indeed found to be the real catalyst. However, there was no N-arylation reaction with fluorobenzene by catalyst **1**. As shown in Table 2, benzimidazole, pyrrole, pyrazole, and piperidine are also coupled with 1-chloro-4-nitrobenzene and 1-fluoro-4-nitrobenzene to give the corresponding N-arylated products in very excellent yields.

To understand the mechanism of the N-arylation of imidazole, a series of experiments were conducted. The reaction of catalyst **1** with imidazole gives a deep blue Cu−imidazole complex (**3**), which is considered to be the first step of the catalytic cycle as described in Scheme 2, since there was no reaction between catalyst **1** and chloro- or fluorobenzaldehyde. The XPS of N 1s (**3**) lines appears at 401.8 and 399.6 eV (see SI), which are assigned to Cu−N and C=N bonds, respectively.[9] The FTIR of **3** indicates P−OH (see SI), which is in consonance to the identical hydride(enolato)-ruthenium(II)apatite complex reported earlier.[7c] Subsequent reaction of complex **3** with chloro- or fluorobenzaldehyde affords the final product *N*-arylimidazole instantly and leaves the **1** [Cu(II)] catalyst in normal conditions and Cu(I) in nitrogen atmosphere (see SI). The FTIR spectrum of the used catalyst **1** obtained in normal conditions (see SI) shows the disappearance of the P−OH bond, indicating the regeneration of **1** to initiate another cycle. Although we are unable to isolate any intermediate complex, the identification of Cu(I) complex in nitrogen atmosphere presumes copper-assisted nucleophilic displacement of X^- of the arene by N^--Het, providing coupling product via transient **4**. In normal conditions, the formed Cu(I) may be reoxidized to **1**. Similarly, in a reaction with the chloroarene, the deep blue complex **3** obtained from **2** also provides coupling product. The deep blue complex formed on the treatment of a simple copper hydroxyapatite with imidazole is inert in the coupling reaction with the chlorobenzaldehyde. The above results and the identification of intermediates provide better comprehension on the mechanism and the necessity of strong basic sites in the apatite for the transformation of **3** to give the coupling product.

In conclusion, newly designed and developed copper basic apatites are found to be potential candidates for N-arylation of heterocycles of both chloroarenes (EW and ED) and fluoroarenes (EW).

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Supporting Information Available: Full characterization of all catalysts with detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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