

N-arylation of imides with arylboronic acids using Cu-Al hydrotalcite

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Abstract

The coupling of imides with various arylboronic acids was performed using Cu-Al hydrotalcite in refluxing methanol with continuous bubbling of air through the mixture without employing base or ligand to afford *N*-arylated products in very good yields. Cu-Al hydrotalcite is used for four cycles successfully with minimal loss of activity.

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Keywords: Arylation; Imides; Arylboronic acids; Copper; Hydrotalcites; Cross-coupling reaction

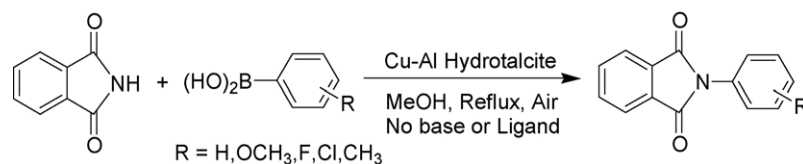
1. Introduction

The *N*-arylation of NH-containing substrates is important in organic synthesis since the resultant products, arylamines and *N*-arylheterocycles are ubiquitous compounds in pharmaceuticals, crop protection chemicals and material sciences [1–5]. Hartwig [6], Buchwald and co-workers [7] and Shakespeare [8] reported the arylation of amines, amides and anilines with aryl halides using Pd/Ni catalysts. The arylation of amides and especially imides is less developed. Copper-mediated carbon–nitrogen (C–N) bond forming cross-coupling reactions of NH-containing substrates has emerged as a powerful methodology. Chan et al. [9], Evans et al. [10], Lam et al. [11] and others [12] reported that arylamines and *N*-arylheterocycles can be prepared using boronic acids and cupric acetate [Cu(OAc)₂] under mild conditions compared to that of conventional Ullmann and Goldberg arylation protocols [13]. There are reports using arylsilanes [14], arylstannanes [11b], arylbismuth [15] and aryllead triacetates reagents [3] as aryl donors using cupric acetate in the presence of base. All these methods require stoichiometric amounts of Cu(OAc)₂. Collman reported the first catalytic version of this reaction using [Cu(OH)·TMEDA]₂Cl₂ as the

catalyst [16]. Other catalytic systems have been reported by Antilla and Buchwald [17], Lam et al. [2] and Xie and co-workers [18] using cupric acetate as the catalyst. Some of the disadvantages of the above methods with respect to arylation of imides are the use of excess of arylboronic acid and/or equimolar ratio of base and longer reaction times [2,7,10,13]. Heterogeneous catalysis has significantly contributed to the development of new methodologies in organic synthesis targeted to dispense the use of conventional and waste generating reagents. Very recently, Chiang and Olsson [19] developed a polymer-supported heterogeneous copper catalyst for the cross-coupling reaction between arylboronic acids and *N*-containing substrates in the presence of triethyl amine.

Layered double hydroxides (LDHs) or hydrotalcite-like compounds (HTLCs) are of current interest and have several applications in organic chemistry. They can be used as supports for reagents/catalysts in organic synthesis [20]. These LDHs consist of alternating cationic M(II)_(1-x)·M(III)_x(OH)₂^{x+} and anionic Aⁿ⁻·zH₂O layers, where M(II) is a divalent cation such as Mg, Cu, Ni, Co, Mn, Zn; M(III) is a trivalent cation such as Al, Fe, Cr, Ru, V, In, Ga; A denotes exchangeable anions [21] such as Cl⁻, CO₃²⁻, NO₃⁻; and the value of *x* is in the range 0.1–0.33. Our recent interest has been in the development of new synthetic methods using HTs as novel environmentally

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Scheme 1.

benign recyclable basic catalysts in various organic transformations [22]. To our knowledge, there is no report on C–N bond forming cross-coupling reaction between imides and arylboronic acids using hydrotalcite catalysts in the literature. We disclose here *N*-arylation of imides with arylboronic acids (Scheme 1) using Cu-Al hydrotalcite.

2. Experimental

Cu(NO₃)₂·3H₂O, Al(NO₃)₃·9H₂O, NaOH, Na₂CO₃, succinimide, phthalimide, dibenzylamine and boronic acids were purchased from Aldrich or Fluka and used without further purification. ACME silica gel (100–200 mesh) was used for column chromatography and thin-layer chromatography was performed on Merck-precoated silica gel 60-F₂₅₄ plates. All the other solvents and chemicals were obtained from commercial sources and purified using standard methods.

2.1. Preparation of the catalyst

2.1.1. Synthesis of Cu-Al hydrotalcite catalyst

Cu-Al hydrotalcite (Cu/Al, 3:1) was prepared as follows [23]: a mixture of solution of Cu(NO₃)₂·3H₂O (32.92 g, 0.1404 mol) and Al(NO₃)₃·9H₂O (16.88 g, 0.045 mol) in deionised and decarbonated water (140 mL) and the aqueous solutions of sodium hydroxide (13.124 g, 0.328 mol) and sodium carbonate (8.9252 g, 0.0842 mol) in deionised and decarbonated water (140 mL) were added simultaneously drop-wise from the respective burettes into the round bottomed flask. The pH of the reaction mixture was maintained constantly (8–9) by the continuous addition of base solution. The resulting slurry was aged at 65 °C for 30 min. The solid product was isolated by filtration, washed thoroughly with deionised and decarbonated water, and dried under vacuum. The weight of the catalyst obtained was 17.6 g. The catalyst was characterized by XRD and it is similar to that reported earlier [23].

2.1.2. General reaction procedure and reusability protocol for *N*-arylation of imides

In a typical procedure, imide (1.2 mmol) and arylboronic acid (1 mmol) were stirred in methanol (5 mL), then Cu-Al hydrotalcite (0.15 g) was charged and the reaction mixture was stirred with continuous bubbling of air through the mixture at refluxing temperature. After completion of the reaction as monitored by TLC, the reaction mixture was filtered. The solvent was removed under reduced

pressure and the crude product was purified by column chromatography. The reusability of the catalyst was carried out with phthalimide and phenylboronic acid in methanol by adopting the following protocol under similar experimental conditions as described above. After completion of the reaction, the reaction mixture was centrifuged and the supernatant solution was pumped out from the reaction flask. The catalyst was washed with methanol, centrifuged and the supernatant solution was pumped out. Fresh quantities of phthalimide and phenylboronic acid were introduced. The Cu-Al hydrotalcite catalyst was, thus, used for four cycles adopting the identical protocol.

3. Results and discussion

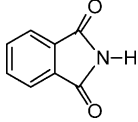
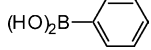
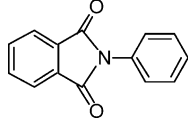
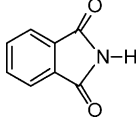
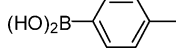
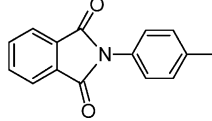
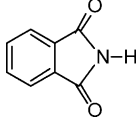
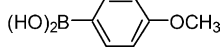
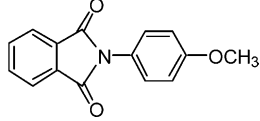
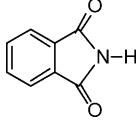
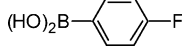
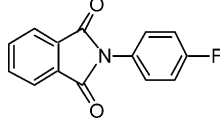
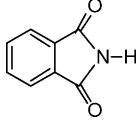
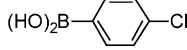
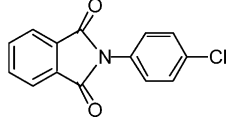
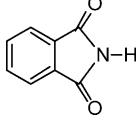
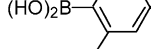
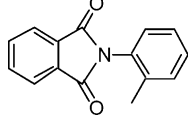
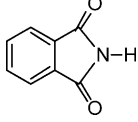
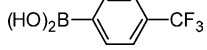
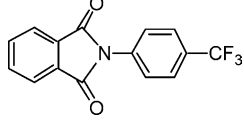
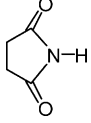
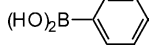
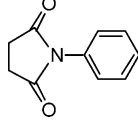
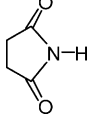
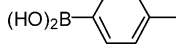
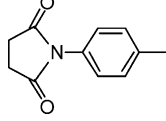
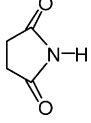
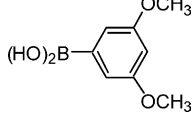
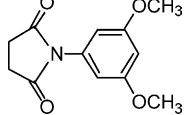
Initial experiment was performed between phthalimide and phenylboronic acid in refluxing methanol using Cu-Al hydrotalcite catalyst with continuous bubbling of air through the mixture, in the absence of a base or ligand, and the *N*-arylated product was obtained in 91% isolated yield. However, the use of calcined Cu-Al hydrotalcite catalyst (450 °C for 6 h in the presence of air) gave low yield of cross-coupled product (ca. 45%) in 5 h under similar reaction conditions. The yield obtained by the reaction of phthalimide and phenylboronic acid was comparable to the literature value using the homogeneous catalyst, copper acetate [18] (Table 1, entry 1).

Good yields of cross-coupled products were obtained with a variety of substrates bearing chloride, fluoride, methoxy, dimethoxy, methyl and trifluoromethyl groups flanked on the phenyl ring of boronic acid using either phthalimide or succinimide under our generalized conditions (Table 1, entries 1–10). The reaction between arylboronic acids and succinimide were slightly rapid compared to the phthalimide, albeit yields were comparable (Table 1, entries 8–10).

The reusability of the Cu-Al hydrotalcite was studied between phthalimide and phenylboronic acid and results are presented in Table 2. These results indicate that the Cu-Al hydrotalcite can be used for four cycles successfully with minimal loss of activity. AAS results indicate leaching of 6.3% of copper in Cu-Al hydrotalcite after the fourth cycle.

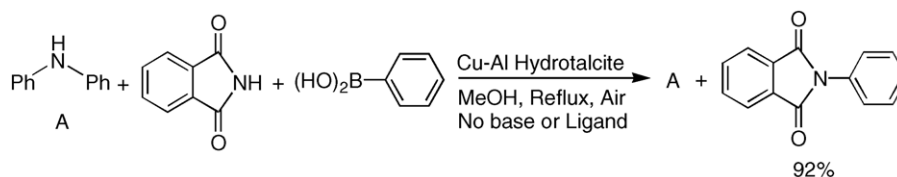
There is no reaction with amines and the inertness of amines is further exemplified by taking an equimolar mixture of diphenylamine and phthalimide with phenylboronic acid under similar reaction conditions. As expected phthalimide afforded the arylated product in 92% yield (Scheme 2). This substrate selectivity could be useful in synthetic organic chemistry.

Table 1
N-arylation of imides with boronic acids by Cu-Al hydrotalcite^a

Entry	Imide	Arylboronic acid	Time (h)	Product	Yield (%) ^b
1			5		91
2			6		90
3			6		90
4			6		87
5			6		91
6			7		87
7			7		88
8			4		91
9			4		90
10			4		89

^a Reaction conditions: phthalimide (1.2 mmol), phenylboronic acid (1 mmol), catalyst (0.15 g), in refluxing methanol.

^b Isolated yields after chromatography.



Scheme 2.

Table 2

Reusability of Cu-Al hydrotalcite in *N*-arylation of phthalimide with phenylboronic acid^a

Cycle	Time (h)	Isolated yield (%) ^b
1	5.0	91
2	5.0	90
3	5.0	90
4	6.0	90

^a Reaction conditions: phthalimide (1.2 mmol), phenylboronic acid (1 mmol), catalyst (0.15 g), in refluxing methanol (5 mL).

^b Yield after silica gel column chromatography.

4. Conclusions

In summary, we have demonstrated that Cu-Al hydrotalcite acts as an efficient, convenient and reusable catalyst for cross-coupling reactions between imides and arylboronic acids.

Acknowledgements

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