# Cu–Al Hydrotalcite: An Efficient and Reusable Ligand-Free Catalyst for the Coupling of Aryl Chlorides with Aliphatic, Aromatic, and N(H)-Heterocyclic Amines

B. Sreedhar,* R. Arundhathi, P. Linga Reddy, M. Amarnath Reddy, M. Lakshmi Kantam

Indian Institute of Chemical Technology, Inorganic & Physical Chemistry Division, Hyderabad 500007, India
Fax +91(40)27160921; E-mail: sreedharb@iict.res.in

*Received 11 March 2009; revised 27 April 2009*

**Abstract:** Copper–aluminum hydrotalcite catalysts were effectively used in the coupling of aryl chlorides with aliphatic, aromatic, and N(H)-heterocyclic amines to afford the corresponding N-alkylated/arylated amines in excellent yields. The catalyst was quantitatively recovered from the reaction by simple filtration and reused for a number of cycles with almost consistent activity.

**Key words:** hydrotalcite, copper, aryl chloride, coupling, N-alkylated/arylated amines, reusable catalyst

Aliphatic and N-arylheterocycles are common motifs in pharmaceutical research.[1] Usually these compounds are synthesized by $S_NAr$ substitution with aryl halides bearing electron-withdrawing substituents or by Ullmann-type coupling at high temperatures.[2] After the initial reports of Chan and Lam, the copper-catalyzed cross coupling between N-heterocycles and arylboronic acids has become an important synthetic methodology in modern organic synthesis.[3] However the high cost and poor availability of functionalized boronic acids precludes its wide application. The discovery and development of the catalytic path for the N-arylation of heterocycles by Buchwald with bromo- and iodoarenes using copper in the presence of basic ligands generated greater interest in industry. Initially Buchwald used 1,10-phenanthroline as a ligand and subsequently show that 1,2-diamines were better ligands to promote this N-arylation.[4] Afterwards Cristau et al. reported oxime-type and Schiff base ligands[5] and Ma et al. reported α- and β-amino acids as ligands for effective N-arylation of N-heterocyclic amines with aryl halides.[6] Several ligands[7–9] have also been introduced for the N-arylation of aliphatic amines. However, all of these synthetic protocols suffer from one or more demerits such as high cost of the ligand, N-arylation of the ligand itself, and long duration. So there is still scope for further development of common catalysts for the N-arylation of aliphatic, aromatic, and N-heterocyclic amines.

The development of heterogeneous catalysts for fine chemicals synthesis has become a major area of research recently, as the potential advantages of these materials (simplified recovery and reusability and the potential for incorporation in continuous reactors and microreactors) over homogeneous systems can make a major impact on the environmental performance of a synthesis.[10] Our group reported hydroxyapatite-supported copper (Cu-HAP)[11] and Cu(II)-NaY[12] catalyzed coupling of aryl halides with heterocyclic amines without the use of additives. Although these results are encouraging, there is considerable room for improvement. For example, the above-mentioned are limited in terms of the substrates for which they can be used; in particular, they are ineffective for alkylamine derivatives and electron-donating aryl halides. Therefore, copper-catalyzed C–N cross-coupling reactions need to be modified to expand the scope of these methods and to employ more substrates.

In recent years, *l*ayered *d*ouble *h*ydroxides (LDHs) of magnesium and aluminum have received considerable attention due to their cation exchange capacity of the brucite layer, anion exchange by inter layer, and also as good support in heterogeneous catalysis. By exploiting these properties of LDHs, we reported N-arylation with chloroarenes using layered double hydroxides supported copper catalyst.[13] In continuation of our studies on the catalyst activity in organic transformations, we wish to report efficient Cu/Al-HTB catalyzed N-arylation of aryl halides with various amines under ligand-free conditions. In comparison to currently existing methods of C–N bond formation, our proposed approach has several distinguishing features that are worth mentioning:

(i) it employs an environmentally friendly and economically competitive catalytic system;

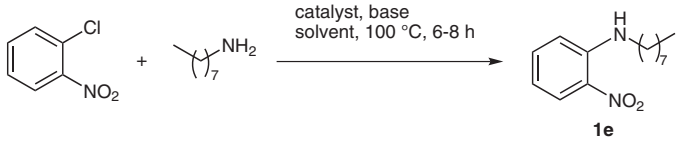
(ii) it offers experimental simplicity and can be performed without protection from air or moisture;

(iii) both aliphatic/aromatic and N(H)-heterocyclic amines and various substituted aryl halides, can be used.

In our preliminary studies to find the best catalyst for the coupling reaction under ligand-free conditions, we chose the coupling reaction of octylamine with 1-chloro-2-nitrobenzene to give 2-nitro-*N*-octylaniline (**1e**) with a catalytic amount of copper catalyst as a model reaction (Scheme 1, Table 1). From Table 1, it can be seen that Cu/Al-HTB is the best catalyst amongst the catalysts screened (Table 1, entry 6).

Next we screened different solvent systems and bases (Scheme 1, Table 2) and it was observed that *N*,*N*-dimethylformamide and potassium carbonate provided the best yield of the product (Table 2, entry 6) dimethyl sulfoxide,

**SYNTHESIS** 2009, No. 15, pp 2517–2522
Advanced online publication: 10.07.2009
DOI: 10.1055/s-0029-1216890; Art ID: P03909SS




**Scheme 1** C–N Bond formation between aryl chlorides and aliphatic amines

**Table 1** Catalyst Screening for the Coupling of 1-Chloro-2-nitrobenzene and Octylamine[a]

| Entry | Catalyst[b] | Isolated yield (%) |
|---|---|---|
| 1 | Cu(HAP) | n.r.[c] |
| 2 | Cu(FAP) | n.r.[c] |
| 3 | Cu(II)-NaY | 32 |
| 4 | $SiO_2$-Cu(OAc)$_2$ | 36 |
| 5 | Cu/Al-HTA | 65 |
| 6 | Cu/Al-HTB | 99, 97[d] |
| 7 | Cu/Al-HTC | 90 |

[a] 1-Chloro-2-nitrobenzene (1.0 mmol), octylamine (1.2 mmol), catalyst (2.5 mol%), $K_2CO_3$ (1.2 mmol), DMF (2.0 mL), stirred, 100 °C.
[b] Cu-(HAP) = copper hydroxyapatite; Cu-(FAP) = copper fluoroapatite; Cu/Al-HT's (HT, hydrotalcite of Cu/Al in different ratios) Cu/Al-HTA, 3:1, Cu/Al-HTB, 2.5:1, Cu/Al-HTC, 2:1.
[c] n.r. = no reaction.
[d] Isolated yield after five cycles.

**Table 2** Effect of the Solvent and Base on the Coupling of 1-Chloro-2-nitrobenzene and Octylamine Using Cu/Al-HTB Catalyst[a]

| Entry | Solvent | Base | Time(h) | Isolated yield (%) |
|---|---|---|---|---|
| 1 | DMF | $Cs_2CO_3$ | 17 | 42 |
| 2 | DMSO | $Cs_2CO_3$ | 19 | 37 |
| 3 | NMP | $Cs_2CO_3$ | 21 | 55 |
| 4 | 1,4-dioxane | $Cs_2CO_3$ | 24 | 20 |
| 5 | DMF | $K_3PO_4$ | 15 | 65 |
| 6 | DMF | $K_2CO_3$ | 8 | 99, 97[b] |
| 7 | DMSO | $K_2CO_3$ | 10 | 85 |
| 8 | NMP | $K_3PO_4$ | 10 | 60 |
| 9 | NMP | $K_2CO_3$ | 9 | 73 |
| 10 | DMF | $Na_2CO_3$ | 12 | 79 |
| 11 | DMF | $K_2CO_3$ | 48 | 45[c] |

[a] 1-Chloro-2-nitrobenzene (1.0 mmol), octylamine (1.2 mmol), Cu/Al-HTB (2.5 mol%), base (1.2 mmol), solvent (2.0 mL), 100 °C.
[b] Isolated yield after five cycles.
[c] Isolated yield at r.t.

and *N*-methylpyrrolidin-2-one were also found to be effective. It is also noteworthy, even at room temperature Cu/Al-HTB afforded 45% product in 48 hours with *N*,*N*-dimethylformamide as the solvent albeit in moderate yield (Table 2, entry 11).

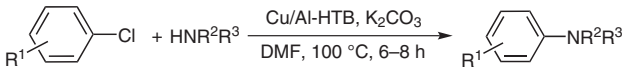
In an effort to extend the scope of this current protocol, we have investigated the N-arylation of aliphatic, aromatic, and N(H)-heterocyclic amines with a variety of chloro-, iodo-, and bromoarenes and the results are summarized in Tables 3 and 4.

Under these optimized conditions, several other aryl chlorides and a wide variety of aliphatic (linear, alicyclic) amines were subjected to this coupling reaction and the results are summarized in Table 3.

Aryl chlorides with electron-withdrawing and electron-donating functionalities afforded excellent to good yields of the corresponding N-alkylated amines **1** (Table 3). The position of the substituents on the aryl halide play a major role in the level of reactivity. Electron-withdrawing groups, such as nitro, cyano, or formyl, in the *ortho*-position of the aryl chlorides gave excellent yields with decreased reaction times compared to the corresponding *meta*- and *para*-substituted aryl chlorides, this can be explained due to the potential of these chelating groups for the copper provide an activating effect (Table 3, entries 4–10). It was noticed that the simple formyl substituent was not inert during the coupling reaction and ultimately was oxidized to a carboxylic group (Table 3, entries 8 and 9), but when 2,4-dichlorobenzaldehyde was used for the coupling reaction the formyl group did not undergo oxidation to the acid (Table 3, entry 11); the chloro group at the *ortho*-position was N-arylated to give **1j**. The *ortho* effect of the chloro group can be visualized when compared with 4-chlorobenzaldehyde (Table 3, entries 8 and 11). Both primary and secondary cyclic amines reacted with equal ease to give products **1m–y** in excellent yields (Table 3, entries 16–26). The increased reaction time in the case of secondary amines may be attributed to steric hindrance caused by the aliphatic groups at the reacting center.

A variety of other nitrogen containing heterocycles such as imidazole, benzimidazole, pyrazole, and morpholine were successfully coupled with chloro-, iodo-, and bromoarenes to give the corresponding N-arylated products **2** in good to excellent yields (Table 4). Chloroarenes containing electron-donating groups afforded the corresponding N-arylated products in diminished yields with longer reaction times (Table 4, entries 2, 3, 6, and 7). N-Arylation of imidazole with chloroarenes containing electron-withdrawing groups, such as nitro, cyano, and trifluoromethyl, gave products **2d**,**e**,**h–j** in high yields (90–99%, Table 4, entries 4, 5, and 8–10) in short reaction times. Treatment of 1-chloro-4-bromobenzene and 1-chloro-4-iodobenzene with imidazole gave selectively 1-(4-chloro-

**Table 3** Coupling of Aryl Chlorides with Amines Catalyzed by Cu/Al-HTB[a]



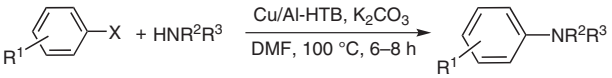

1

| Entry | $R^1$ | $R^2$ | $R^3$ | Product | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | H | H | *n*-$C_8H_{17}$ | **1a** | 24 | n.r.[b] |
| 2 | 4-Me | H | *n*-$C_8H_{17}$ | **1b** | 28 | 52 |
| 3 | 2-Me | H | *n*-$C_8H_{17}$ | **1c** | 32 | 42 |
| 4 | 4-$NO_2$ | H | *n*-$C_8H_{17}$ | **1d** | 8 | 89 |
| 5 | 2-$NO_2$ | H | *n*-$C_8H_{17}$ | **1e** | 6 | 99, 97[c] |
| 6 | 4-CN | H | *n*-$C_8H_{17}$ | **1f** | 12 | 78 |
| 7 | 2-CN | H | *n*-$C_8H_{17}$ | **1g** | 10 | 75 |
| 8 | 4-$CO_2H$[d] | H | *n*-$C_8H_{17}$ | **1h** | 10 | 90 |
| 9 | 2-$CO_2H$[e] | H | *n*-$C_8H_{17}$ | **1i** | 8 | 95 |
| 10 | 4-$CO_2H$ | H | *n*-$C_8H_{17}$ | **1h** | 8 | 97 |
| 11 | 4-Cl-2-CHO | H | *n*-$C_8H_{17}$ | **1j** | 8 | 95 |
| 12 | 4-$NO_2$ | H | *n*-$C_{12}H_{25}$ | **1k** | 6 | 95 |
| 13 | 2-$NO_2$ | H | *n*-$C_{12}H_{25}$ | **1l** | 6 | 99 |
| 14 | H | H | cyclopentyl | **1m** | 16 | n.r.[b] |
| 15 | 2-Me | H | cyclopentyl | **1n** | 20 | n.r.[b] |
| 16 | 4-$NO_2$ | H | cyclopentyl | **1o** | 8 | 90 |
| 17 | 2-$NO_2$ | H | cyclopentyl | **1p** | 8 | 94 |
| 18 | 4-$NO_2$ | H | cyclohexyl | **1q** | 8 | 92 |
| 19 | 2-$NO_2$ | H | cyclohexyl | **1r** | 6 | 99 |
| 20 | 3-CN | H | cyclohexyl | **1s** | 14 | 72 |
| 21 | 4-$CO_2H$ | H | cyclohexyl | **1t** | 14 | 73 |
| 22 | 4-Me | –$(CH_2)_5$– | | **1u** | 28 | 52 |
| 23 | 2-OMe | –$(CH_2)_5$– | | **1v** | 24 | 48 |
| 24 | 4-I | –$(CH_2)_5$– | | **1w** | 9 | 81 |
| 25 | 4-Br | –$(CH_2)_5$– | | **1x** | 10 | 88 |
| 26 | 4-$NO_2$ | –$(CH_2)_5$– | | **1y** | 8 | 94 |

[a] ArCl (1 mmol), $R^2R^3NH$ (1.2 mmol), Cu/Al-HTB (2.5 mol%), $K_2CO_3$ (1.2 mmol), DMF (2.0 mL), 100 °C, stirred.
[b] No reaction.
[c] Isolated yields after five cycles.
[d] Substrate had $R^1$ = 4-CHO.
[e] Substrate had $R^1$ = 2-CHO.

phenyl)-1*H*-imidazole (**2m**) (Table 4, entries 13 and 14). The reaction with iodoarenes resulted in complete conversion in short reaction times in accordance with the literature.[11] When 1-bromo-4-chlorobenzene is used for the coupling reaction with morpholine it resulted in 4-(4-chlorophenyl)morpholine (**2u**) (Table 4, entry 23). Overall it was noticed that iodoarenes were more reactive than chloro- and bromoarenes and this is in line with earlier reports.[5b] Furthermore, aryl halides bearing electron-withdrawing functional groups reacted at a faster rate than the ones containing electron-donating groups.

**Table 4** Coupling of Aryl Chlorides with N(H)-Heterocyclic Amines Catalyzed by Cu/Al-HTB[a]




2

| Entry | X | $R^1$ | $-NR^2R^3$ | Prod. | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|---|
| 1 | Cl | H | imidazol-1-yl | **2a** | 18 | n.r.[b] (92, 80) |
| 2 | Cl | 4-Me | imidazol-1-yl | **2b** | 12 | 27 (89) |
| 3 | Cl | 2-Me | imidazol-1-yl | **2c** | 19 | 18 (65) |
| 4 | Cl | 4-$NO_2$ | imidazol-1-yl | **2d** | 8 | 90 (95) |
| 5 | Cl | 2-$NO_2$ | imidazol-1-yl | **2e** | 6 | 92, 90[c] (99) |
| 6 | Cl | 4-COMe | imidazol-1-yl | **2f** | 18 (5) | 75 (95) |
| 7 | Cl | 4-OMe | imidazol-1-yl | **2g** | 18 | 59 (90) |
| 8 | Cl | 4-CN | imidazol-1-yl | **2h** | 16 | 95 |
| 9 | Cl | 2-CN | imidazol-1-yl | **2i** | 12 | 99 |
| 10 | Cl | 2-$CF_3$ | imidazol-1-yl | **2j** | 7 | 97 |
| 11 | Cl | 4-$CO_2H$[d] | imidazol-1-yl | **2k** | 10 | 73 |
| 12 | Cl | 2-$CO_2H$[e] | imidazo-l-yl | **2l** | 8 | 90 |
| 13 | Br | 4-Cl | imidazo-l-yl | **2m** | 8 | 98 |
| 14 | I | 4-Cl | imidazo-l-yl | **2m** | 6 | 99 |
| 15 | I | 4-COMe | benzimidazol-1-yl | **2n** | 15 | 88 |
| 16 | I | 4-COMe | pyrazol-1-yl | **2o** | 18 | 80 |
| 17 | I | 4-OMe | benzimidazol-1-yl | **2p** | 18 | 85 |
| 18 | I | 4-OMe | pyrazol-1-yl | **2q** | 20 | 80 |
| 19 | I | H | morpholino | **2r** | 8 | 90 |
| 20 | Cl | H | morpholino | **2r** | 26 | n.r.[b] |
| 21 | Cl | 4-$NO_2$ | morpholino | **2s** | 8 | 92 |
| 22 | Cl | 2-$NO_2$ | morpholino | **2t** | 6 | 99 |
| 23 | Br | 4-Cl | morpholino | **2u** | 8 | 90 |
| 24 | I | 4-Br | morpholino | **2v** | 7 | 99 |

[a] Isolated yields, yields in parentheses are of iodo and bromoarenes respectively.
[b] n.r. = no reaction.
[c] Isolated yield after five cycles.
[d] In substrate $R^1$ = 4-CHO.
[e] In substrate $R^1$ = 2-CHO.

The Cu/Al-HTB catalyst was separated from the reaction mixture by centrifugation, washed with *N*,*N*-dimethylformamide to make the catalyst free from organic matter, then with water, and finally with acetone, dried, and used in the next cycle. Almost consistent activity was noticed even after the fifth cycle (Table 1, entry 6). Copper content (2.5 mol%) of the fresh and used (after 5th cycle) catalyst was found to be almost the same (by ICP-AES). To check the heterogeneity of the catalyst, a reaction between 1-chloro-2-nitrobenzene and octylamine was terminated at 16% conversion (after 30 min) and the catalyst was separated by simple filtration. The reaction was continued for an additional 12 hours and the conversion remained almost unchanged. Moreover, the filtrate was tested for copper by ICP-AES after the 6th cycle and it was almost the same (only 2% difference) and no copper was found for the five consecutive cycles. These studies clearly demonstrate that no leaching of copper has taken place from the catalyst.

In summary, we have developed a practical and promising protocol for the N-alkylation/arylation of various amines with differently substituted aryl halides using Cu/Al-HTB. The versatility, convenient operation, low cost, ligand-free, and environmental friendliness of this method, in addition to the high yields, make it viable for use both in laboratory research and on a larger industrial scale. Currently, we are exploring the scope and application of the proposed Cu/Al-HTB-catalyzed N-alkylation/arylation with regard to the synthesis of pharmaceutical molecules.

The $^1$H NMR (300 MHz, Bruker Avance or 400 MHz, Varian Inova) chemical shifts were measured relative to tetramethylsilane (TMS). The $^{13}$C NMR (75 MHz, Bruker Avance or 100 MHz, Varian Inova) chemical shifts are given using $CDCl_3$ as the internal standard. Mass spectra (MS) were obtained by EI [VG-7070H Micromass (3 KeV, xenon)] or GC-MS [Thermo Finnigan TRACE DSQ MS spectrophotometer, using a BP-1 (30 × 0.25 × 1.0) capillary column]. Solvents were dried by refluxing for at least 24 h over $CaH_2$ (DMF or DMSO), and freshly distilled prior to use. Unless otherwise indicated, all syntheses and manipulations were carried out under atmospheric conditions. All the reactants were commercially available and used without purification. The spectroscopic data for all known products compared well with reported data.[5,11,14,15]

**1-(2-Nitrophenyl)-1*H*-imidazole (2e); Typical Procedure**

A mixture of 1-chloro-2-nitrobenzene (1 mmol), 1*H*-imidazole (1.2 mmol), $K_2CO_3$ (1.2 mmol), and Cu/Al-HTB (100 mg, 2.5 mol%) in DMF (2 mL) was stirred in a round-bottomed flask at 100 °C. When the reaction was complete (TLC), the catalyst was filtered washed several times with DMF, $H_2O$ and acetone and reused for the next reaction. DMF was removed from the reaction filtrate under reduced pressure and crude material was purified by chromatography (silica gel, 60–120 mesh, hexane–EtOAc) to afford **2e**.[11]

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.56 (m, 6 H), 7.85 (d, *J* = 7.93 Hz, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 122.0, 124.1, 124.6, 125.5, 129.9, 132.0, 135.5, 137.4, 139.9.

MS (EI): *m*/*z* = 43, 57, 83, 85, 109, 115, 128, 149, 164, 171, 189 ($M^+$).

Anal. Calcd for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.15; H, 3.69; N, 22.30.

**4-Nitro-*N*-octylaniline (1d)**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.79 Hz, 3 H), 1.20–1.43 (m, 10 H), 1.59–1.71 (m, 2 H), 3.12–3.26 (m, 2 H), 6.48 (d, *J* = 9.06 Hz, 2 H), 8.06 (d, *J* = 9.06 Hz, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.8, 27.3, 29.5, 30.2, 32.0, 45.1, 114.1, 121.9, 137.3, 153.9.

MS (EI): *m*/*z* = 43, 57, 83, 105, 119, 138, 151, 250 ($M^+$).

Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.09; H, 8.90; N, 11.18.

**2-Nitro-*N*-octylaniline (1e)**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 6.6 Hz, 3 H), 1.31–1.54 (m, 10 H), 1.68–1.83 (m, 2 H), 3.24–3.33 (m, 2 H), 6.60 (t, *J* = 8.2 Hz, 1 H), 6.80 (d, *J* = 8.2 Hz, 1 H), 7.38 (t, *J* = 8.82 Hz, 1 H), 7.96–8.10 (br s, 1 H), 8.15 (dd, *J* = 8.82, 10.2 Hz, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.9, 26.8, 30.2, 31.6, 44.2, 114.6, 118.2, 121.9, 132.2, 135.5, 138.6.

MS (EI): *m*/*z* = 40, 41, 43, 78, 93, 104, 119, 135, 151, 161, 175, 189, 204, 215, 250 ($M^+$), 252 (M + 2 H).

Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.15; H, 8.85; N, 11.62.

***N*-Dodecyl-4-nitroaniline (1k)**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.59 Hz, 3 H), 1.20–1.50 (m, 20 H), 3.20–3.35 (m, 2 H), 6.80 (d, *J* = 8.03 Hz, 2 H), 8.09 (br s, 1 H), 8.15 (d, *J* = 8.03 Hz, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.9, 27.2, 29.4, 30.1, 30.4, 31.8, 44.9, 114.5, 122.6, 137.8, 153.8.

GC-MS: *m*/*z* = 307 (M + H).

Anal. Calcd for $C_{18}H_{30}N_2O_2$: C, 70.55; H, 9.87; N, 9.14. Found: C, 71.09; H, 9.90; N, 9.38.

***N*-Cyclopentyl-2-nitroaniline (1p)[13]**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.62–1.81 (m, 6 H), 2.00–2.20 (m, 2 H), 3.90–4.01 (m, 1 H), 6.61 (t, *J* = 8.31 Hz, 1 H), 6.85 (d, *J* = 9.82 Hz, 1 H), 7.40 (t, *J* = 8.31 Hz, 1 H), 8.10–8.40 (d, *J* = 9.82 Hz, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 20.7, 31.6, 56.0, 113.3, 117.6, 124.6, 131.9, 136.0, 140.8.

MS (EI): *m*/*z* = 43, 69, 83, 85, 105, 121, 149, 164, 177, 191, 206 ($M^+$).

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.00; H, 6.85; N, 13.60.

***N*-Cyclohexyl-4-nitroaniline (1q)**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.01–1.99 (m, 10 H), 3.01–3.21 (m, 1 H), 6.85 (d, *J* = 8.31 Hz, 2 H), 7.99 (d, *J* = 8.31 Hz, 2 H), 8.05 (br s, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 22.9, 28.2, 34.1, 51.2, 114.6, 121.9, 136.9, 154.1.

GC-MS: *m*/*z* = 220 ($M^+$).

Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 64.92; H, 7.25; N, 13.10.

**4-(Cyclohexylamino)benzoic Acid (1t)**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.01–1.99 (m, 10 H), 3.01–3.21 (m, 1 H), 7.20 (d, *J* = 8.31 Hz, 2 H), 7.61 (d, *J* = 8.31 Hz, 2 H), 8.05 (br s, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 23.2, 28.1, 33.9, 51.0, 113.6, 118.9, 131.0, 153.1, 169.5.

GC-MS: *m*/*z* = 219 ($M^+$).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.25; H, 7.17; N, 6.41.

**1-Phenyl-1*H*-imidazole (2a)[11]**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.21 (br s, 1 H), 7.29 (br s, 1 H), 7.34–7.40 (m, 3 H), 7.46–7.51 (m, 2 H), 7.87 (s, 1 H).

13C NMR (75 MHz, CDCl3): δ = 118.2, 121.3, 127.4, 129.7, 130.1, 135.5, 137.1.

GC-MS: *m*/*z* = 144 ($M^+$).

Anal. Calcd for $C_9H_8N_2$: C, 74.98; H, 5.59; N, 19.43. Found: C, 75.15; H, 5.58; N, 19.41.

**1-(4-Methoxyphenyl)-1*H*-imidazole (2g)[11]**
$^1$H NMR (400 MHz, $CDCl_3$): δ = 3.87 (s, 3 H), 6.99–7.02 (m, 2 H), 7.21 (s, 1 H), 7.23 (s, 1 H), 7.29–7.34 (m, 2 H), 7.80 (s, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 55.6, 114.8, 118.7, 123.1, 130.0, 130.7, 135.8, 158.9.

GC-MS: *m*/*z* = 174 ($M^+$).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.99; H, 5.78; N, 16.41.

**4-Phenylmorpholine (2r)[14c]**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.17 (t, *J* = 4.47 Hz, 4 H), 3.63 (t, *J* = 4.47 Hz, 4 H), 6.57–6.60 (m, 3 H), 6.85 (t, *J* = 7.20 Hz, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 45.8, 99.9, 113.9, 117.0, 126.0, 126.9, 129.0, 133.1, 143.7, 148.2.

GC-MS: *m*/*z* = 164 (M + H).

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58; Found: C, 73.62; H, 8.05; N, 8.61.

**4-(4-Nitrophenyl)morpholine (2s)**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.20 (t, *J* = 4.49 Hz, 4 H), 3.67 (t, *J* = 4.49 Hz, 4 H), 6.89 (d, *J* = 8.39 Hz, 2 H), 8.02 (d, *J* = 8.39 Hz, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 46.4, 66.7, 115.2, 123.2, 138.3, 156.1.

MS (EI): *m*/*z* = 51, 57, 77, 91, 104, 120, 134, 150, 161, 177, 1293, 208 ($M^+$).

Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45; Found: C, 57.66; H, 5.79; N, 13.60.

**4-(2-Nitrophenyl)morpholine (2t)**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.15 (t, *J* = 4.24 Hz, 4 H), 3.85 (t, *J* = 4.24 Hz, 4 H), 7.10 (t, *J* = 7.63 Hz, 1 H), 7.15 (d, *J* = 8.49 Hz, 1 H), 7.51 (t, *J* = 6.78 Hz, 1 H), 7.80 (d, *J* = 8.49 Hz, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 51.9, 66.7, 120.8, 122.1, 125.7, 133.4, 143.5, 145.6.

MS (EI): *m*/*z* = 51, 65, 77, 92, 105, 119, 133, 145, 161, 174, 191, 208 ($M^+$).

Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45; Found: C, 58.01; H, 5.80; N, 13.41.

**4-(4-Chlorophenyl)morpholine (2u)[15c]**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.11 (t, *J* = 4.80 Hz, 4 H), 3.85 (t, *J* = 4.80 Hz, 4 H), 6.80–6.84 (d, *J* = 8.94 Hz, 2 H), 7.21 (d, *J* = 8.94 Hz, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 49.4, 66.9, 117.0, 125.0, 129.1, 150.0.

GC-MS: *m*/*z* = 198 (M + H).

Anal. Calcd for $C_{10}H_{12}ClNO$: C, 60.76; H, 6.12; N, 7.09; Found: C, 60.68; H, 5.99; N, 7.10.

**4-(4-Bromophenyl)morpholine (2v)**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.12 (t, *J* = 4.47 Hz, 4 H), 3.81 (t, *J* = 4.47 Hz, 4 H), 6.71 (d, *J* = 8.80 Hz, 2 H), 7.35 (d, *J* = 8.80 Hz, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 46.2, 66.9, 112.9, 118.1, 133.8, 148.7.

MS (EI): *m*/*z* = 95, 115, 133, 138, 164, 166, 186, 208, 223, 242 ($M^+$), 244 (M + 2 H).

Anal. Calcd for $C_{10}H_{12}BrNO$: C, 49.61; H, 5.00; N, 5.79; Found: C, 49.62; H, 5.01; N, 5.88.

## Acknowledgment

R.A. wishes to thank DST (GAP-0152) for financial support and Department of Science and Technology for providing research fellowship.

## References and Notes

(1) (a) 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. (b) Combs, A. P.; Saubern, S.; Rafalski, M.; Lam, P. Y. S. *Tetrahedron Lett.* **1999**, *40*, 1623. (c) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415. (d) Collman, J. P.; Zhong, M.; Zhang, C.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 7892.

(2) (a) Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657. (b) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (c) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684. (d) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578.

(3) (a) Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Eur. J. Org. Chem.* **2004**, *69*, 695. (b) Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607.

(4) (a) Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y.; Ma, D. *Synthesis* **2005**, 496. (b) Ma, D.; Cai, Q. *Synlett* **2004**, 128.

(5) (a) Ohmori, J.; Shimizu-Sasamata, M.; Okada, M.; Sakamoto, S. *J. Med. Chem.* **1996**, *39*, 3971. (b) Antonini, I.; Cristalli, G.; Franchetti, P.; Grifantini, M.; Martelli, S. *Synthesis* **1983**, 47.

(6) (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. (b) Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657. (c) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(7) (a) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453. (b) Zang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164.

(8) (a) Lu, Z.; Twieg, R. J.; Huang, S. D. *Tetrahedron Lett.* **2003**, *44*, 6289. (b) Lu, Z.; Twieg, R. J. *Tetrahedron* **2005**, *61*, 903. (c) Zang, Z.; Mao, J.; Zhu, D.; Wu, F.; Chen, H.; Wan, B. *Tetrahedron* **2006**, *62*, 4435.

(9) (a) Xu, L.; Zhu, D.; Wu, F.; Wang, R.; Wan, B. *Tetrahedron* **2005**, *61*, 6553. (b) Zhu, D.; Wang, R.; Xu, J.; Mao, J.; Xu, L.; Wu, F.; Wan, B. *J. Mol. Catal. A: Chem.* **2006**, *256*, 256. (c) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742.

(10) Sels, F.; De Vos, D. E.; Jacobs, P. A. *Catal. Rev.* **2001**, *43*, 443.
(11) Choudary, B. M.; Sridhar, Ch.; Kantam, M. L.; Venkanna, G. T.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 9948.
(12) Kantam, M. L.; Purna Chandar Rao, P.; Choudary, B. M.; Sudarshan Reddy, R. *Synlett* **2006**, 2195.
(13) Likhar, P. R.; Arundhathi, R.; Kantam, M. L. *Tetrahedron Lett.* **2007**, *48*, 3911.
(14) (a) Koelsch, C. F.; Carney, J. J. O. *J. Am. Chem. Soc.* **1950**, *72*, 2285. (b) Randell, K. D.; Johnston, B. D.; Green, D. F.; Pinto, B. M. *J. Org. Chem.* **2000**, *65*, 220. (c) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829. (d) Xie, X.; Zhang, T. Y.; Zhang, Z. *J. Org. Chem.* **2006**, *71*, 6522. (e) Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron* **1995**, *51*, 7959. (f) Heutling, A.; Pohlki, F.; Doye, S. *Chem. Eur. J.* **2004**, *10*, 3059.
(15) (a) Zim, D.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2413. (b) Jiang, D.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2007**, *72*, 672. (c) Pearson, A. J.; Gelormini, A. M. *J. Org. Chem.* **1994**, *59*, 4561.