Copper Oxide Nanoparticles as a Mild and Efficient Catalyst for N-Arylation of Imidazole and Aniline with Boronic Acids at Room Temperature

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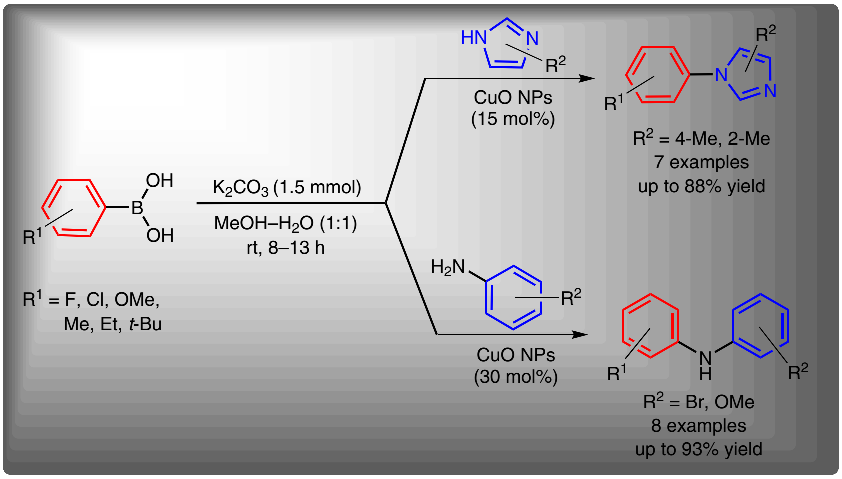

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Abstract The present work describes the excellent catalytic activity of copper(II) oxide nanoparticles (NPs) towards N-arylation of aniline and imidazole at room temperature. The copper(II)oxide NPs were synthesized by a thermal refluxing technique and characterized by FT-IR spectroscopy; powder XRD, SEM, EDX, TEM, TGA, XPS, BET surface area analysis, and particle size analysis. The size of the NPs was found to be around 12 nm having a surface area of 164.180 $m^2\ g^{-1}$.The catalytic system was also found to be recyclable and could be reused in subsequent catalytic runs without a significant loss of activity.

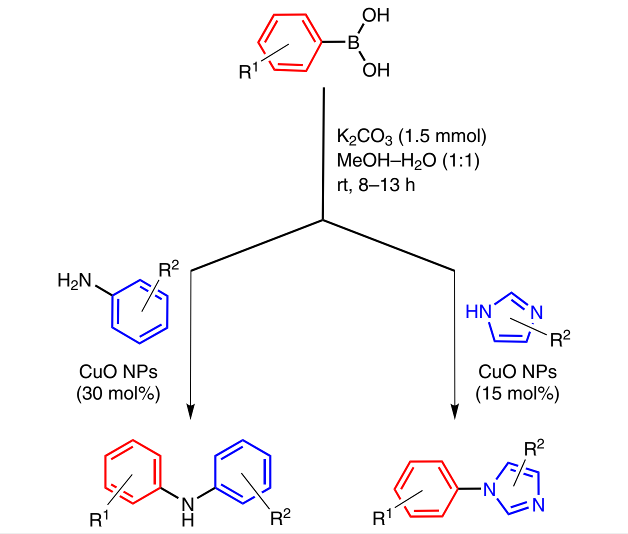
Key words nanoparticles, base, N-arylation, aniline, imidazole, reusability

In the domain of organic synthesis, transition-metal-mediated carbon–heteroatom bond-forming reactions have made a significant contribution to the recent growth. Nitrogen-containing compounds can now be easily generated by transition-metal-catalyzed protocols that find diverse applications in the field of advanced organic synthesis. Among them diarylamines and *N*-arylimidazoles attract particular interest due to their widespread presence in natural products, agrochemicals, materials, dyes, pharmaceuticals,[1] and biologically active inhibitors.[2]

Buchwald and Hartwig developed a method for palladium-catalyzed cross-coupling of aryl halides and triflates with amines.[3] Though the process is credited with milder reaction conditions than Ullmann reaction,[4] there are some limitations, such as difficulties associated with aryl halides having free N–H groups[5] and the use of expensive palladium sources and ligands.

Considering the above facts, in 1998 Chan, Evan, and Lam[6] developed a mild and efficient protocol for copper-mediated oxidative amination, where arylboronic acids were used as arylating agents instead of aryl halides. Arylboronic acids are organometallic moieties possessing wide applicability in contemporary organic synthesis owing to their stability, structural diversity, and low toxicity.[7] However, the requirement of 1–2 equivalents of $Cu(OAc)_2$ and large excess of arylboronic acid[8] are drawbacks associated with this cross-coupling methodology. Further work on the Chan–Lam coupling reaction resulted in its catalytic version[9] along with its application to other nucleophiles for cross-coupling reactions such as amides,[10] oximes,[11] and sulfoximines.[12] Subsequently, a large number of modifications has been made using different copper salts in the presence of various ligands to improve the efficiency of the reaction.[10–12] However, the long reaction times and high reaction temperatures are disadvantages associated with these protocols and thus, a further optimization is desirable in the case of this reaction.

Additionally, in line with recent trends, nanoparticles (NPs) are considered as very efficient and attractive catalysts compared to their macroscopic counterparts due to their high surface-to-volume ratio as well as very active surface atoms. Although many methods are available for the synthesis of NPs, routes that are based on solution-based processes are more effective leading to well-controlled shapes, sizes, and structures. Amongst the metal NPs, copper-based NPs hold a superior position due to their versatility in various organic conversions such as C–N bond-formation reactions and C–H activation reactions[13] and find wide range of applications due to their stability and easy synthesis.[14] The literature reveals various techniques relating to the synthesis of CuO NPs but these are generally costly, time-consuming, and require large volumes of reagents.[13b,15] Consequently, there is a need for a simple and mild technique to synthesize CuO NPs. Focusing on the above facts, in this article, we report an efficient technique for the preparation CuO NPs, and the resulting catalysts were utilized in a mild protocol for N-arylation of imidazoles and anilines with arylboronic acids at room temperature (Scheme 1).



Scheme 1 N-Arylation of imidazoles and anilines with arylboronic acid

We synthesized the CuO NPs following a simple and cost-effective procedure presented by Goswami et al.[16] with some modifications using $CuCl_2$ as the starting precursor in order to obtain uniform smaller particles. The NPs were characterized using FT-IR spectroscopy, powder XRD, SEM, EDX, TEM, TGA, XPS, BET surface area analysis, and particle-size analysis.

The CuO NPs were first characterized by FT-IR spectroscopy (Figure 1, a). The bands at 2913 and 3440 cm^{-1} are due to symmetric and asymmetric stretching of O–H bond, respectively. The presence of bands at 509 and 598 cm^{-1} correspond to different modes of bending vibration of the Cu–O bond;[16,17] whereas, the band at 1632 cm^{-1} can be assigned to C–C and C–O from residual carbonates and polymer. Powder XRD was used to determine the crystal domain size and the structure of the NPs formed. Figure 1 (b) shows the typical XRD pattern in the 2θ range of 20° to 70°, showing the presence of peaks that can be indexed on the basis of monoclinic CuO (JCPDS card no. 89-5895). The broadening of the XRD peak indicates that the synthesized particles are in the nano range. From the SEM images [Figure 1 (c and d)] the particles possess a needle-like morphology. However, most of the NPs have irregular shapes and sizes, which might be due to agglomeration. The TGA analysis is shown in Figure 2 (a). The initial weight loss up to 100 °C is due to elimination of moisture, and further weight loss up to 300 °C is due to decomposition of organic materials. In order to examine the porous behavior and estimate the surface area, N_2adsorption/desorption experiments were performed at liquid N_2 temperature and are shown in Figure 2 (b).

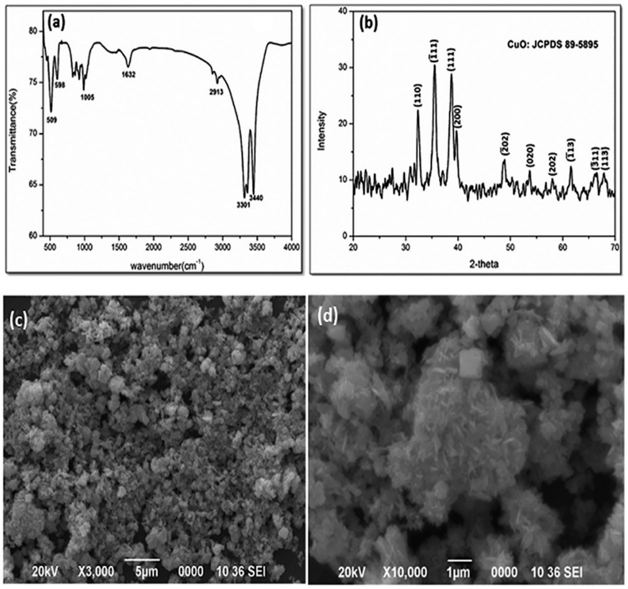


Figure 1 (a) FT-IR spectrum, (b) PXRD pattern, (c) and (d) SEM images of the synthesized CuO NPs.

The N_2 adsorption/desorption isotherm belongs to type IV with a combination of H1 and H3 hysteresis loop, which is a characteristic of mesoporous materials. The N_2 physisorption (BET) investigation of the CuO nanostructure provides a surface area of about 164.180 m^2 g^{-1} which is much larger than that found for commercial CuO. Energy-dispersive X-ray (EDX) analysis of the CuO NPs reveals the presence of Cu and O signals and shows the NPs are devoid of any other metal impurities. The TEM and HRTEM images [Figure 2 (d and e, respectively)] show that the NPs are cylindrical in shape. The interplanar distance of 0.23 nm can be ascribed to the (111) plane of the monoclinic CuO. The corresponding selected area electron-diffraction (SAED) pattern of the CuO nanostructure [inset, Figure 2 (e)] shows that the particles are crystalline in nature and possess three well-resolved rings for (110), (–111), and (111) planes. The two poorly resolved rings are for (200) and (–202) planes. The size distribution of the NPs [Figure 2,(f)] showed that most of the particles fall in the range 7–17 nm, and the mean particle diameter is about 12 ± 0.99 nm. XPS analysis

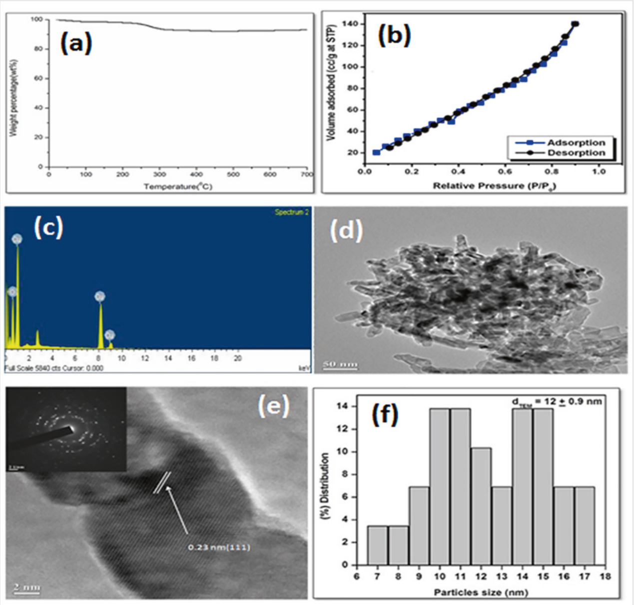
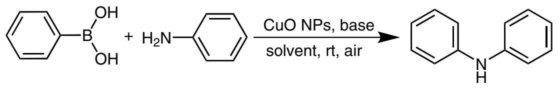


Figure 2 (a) TGA curve, (b) N_2 adsorption/desorption isotherm, (c) EDX pattern, (d) TEM, (e) HRTEM and in inset is the SAED pattern, and (f) particle-size distribution of the CuO NPs.

Table 1 Optimization of Reaction Conditions[a]



Entry	Solvent	Base	Catalyst (mol%)	Time (h)	Yield (%)[b]
1	no solvent	K_2CO_3	15	10	20
2	H_2O	K_2CO_3	15	10	68
3	CH_2Cl_2	K_2CO_3	15	10	54
4	*i*-PrOH–H_2O (1:1)	K_2CO_3	15	10	58
5	MeOH–H_2O (1:1)	K_2CO_3	15	10	74
6	MeOH–H_2O (1:1)	K_2CO_3	21	10	82
7	MeOH–H_2O (1:1)	K_2CO_3	30	8	92
8	MeOH–H_2O (1:1)	K_2CO_3	36	8	93
9	MeOH–H_2O (1:1)	Na_2CO_3	30	8	86
10	MeOH–H_2O (1:1)	Cs_2CO_3	30	8	88
11	MeOH–H_2O (1:1)	KOH	30	8	66
12	MeOH–H_2O (1:1)	K_2CO_3	–	24	0
13[c]	MeOH–H_2O (1:1)	K_2CO_3	30	8	78
14[d]	MeOH–H_2O (1:1)	K_2CO_3	30	8	92
15[e]	MeOH–H_2O (1:1)	K_2CO_3	30	10	90
16[f]	MeOH–H_2O (1:1)	K_2CO_3	30	10	61
17[g]	MeOH–H_2O (1:1)	K_2CO_3	30	10	0

[a] Reaction conditions: phenylboronic acid (1 mmol), aniline (0.5 mmol), K_2CO_3 (1.5 mmol), r.t., stirring.
[b] Isolated yield.
[c] 1 mmol of K_2CO_3.
[d] 2 mmol of K_2CO_3.
[e] 0.75 mmol phenylboronic acid used.
[f] 0.60 mmol phenylboronic acid was used.
[g] Nitrogen atmosphere was used.

confirmed the presence of Cu^{2+} (Figure S1, Supporting Information). Recycled samples contain some hydroxide but, CuO still dominates (Figure S2, Supporting Information).

With the aim to find out the effect of various solvents, bases, and amount of catalyst, we chose phenylboronic acid and aniline as the model substrates, and the results are summarized in Table 1.

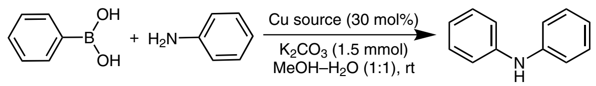
An initial screening of the effect of different solvents using K_2CO_3 as base and 15 mol% of the catalyst showed that MeOH–H_2O (1:1, v/v) was the most efficient solvent system (Table 1, entry 5). After optimizing the solvent system, we studied the effect of the amount of catalyst (Table 1, entries 5–8), and it was found that 30 mol% catalytic amount of the catalyst with respect to aniline was the optimized amount for the coupling reaction (Table 1, entry 7). The reaction also proceeded in the presence of other bases such as Na_2CO_3, Cs_2CO_3, and KOH with comparable yields (Table 1, entries 9–11). The control reaction conducted under identical conditions but devoid of catalyst gave no coupled product even with prolonged reaction time (Table 1, entry 12). We carried out the reaction with 1–2 mmol of K_2CO_3 (Table 1, entries 13 and 14) and found that 1.5 mmol was the optimal amount. Notably, the presence of an oxidant is critical and an important parameter for the copper-promoted N-arylation reaction.[18] The reaction did not proceed under nitrogen atmosphere (Table 1, entry 17), which indicates the requirement of air as oxidant for the reaction. Thus, optimum conditions involved the reaction being carried out under air at room temperature in MeOH–H_2O (1:1) in the presence of 30 mol% of nanocatalyst with respect to aniline and K_2CO_3 (1.5 mmol) as the base (Table 1, entry 7).

We also examined the reaction with copper(II) salts such as $Cu(OAc)_2·H_2O$, $CuSO_4·5H_2O$, $CuCl_2·2H_2O$, and CuI for the N-arylation reaction of aniline under the optimized reaction conditions and found only 15–30% of the product diphenylamine (Table 2, entries 1–3).

After optimizing the conditions for aniline, our next endeavor was to extend the scope of this method for N-arylation of imidazole. For this, we took imidazole (1 mmol) and phenylboronic acid (1.2 mmol) as the model substrates. In this case, the reaction also proceeded smoothly but required a comparatively longer time than in the case of N-arylation of aniline.

To evaluate the scope and limitation of the current procedure, a wide range of electronically diverse anilines and imidazoles with different phenylboronic acid substrates was examined. The results are summarized in Table 3.

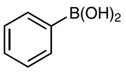
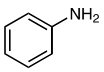
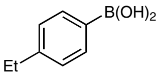
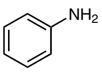
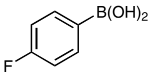
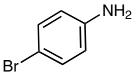
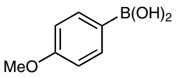
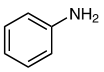
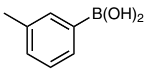
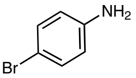
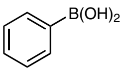
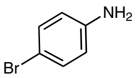
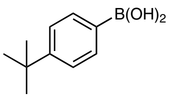
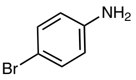
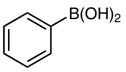
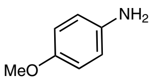
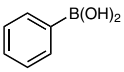
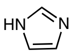
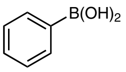
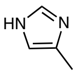
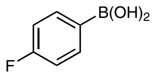
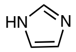
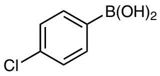
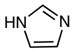
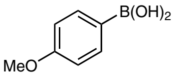
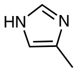
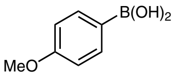
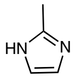
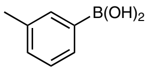
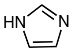
Table 2 N-Arylation of Aniline Using Different Copper(II) Salts[a]



Entry	Copper source (mol%)	Time (h)	Yield (%)[b]
1	$Cu(OAc)_2 \cdot H_2O$ (30)	24	30
2	$CuSO_4 \cdot 5H_2O$ (30)	24	16
3	$CuCl_2 \cdot 2H_2O$ (30)	24	28
4	CuCl (30)	24	15
5	CuI (30)	24	30
6	CuO NPs (30)	8	92

[a] Reaction conditions: phenylboronic acid (1 mmol), aniline (0.5 mmol), K_2CO_3 (1.5 mmol), MeOH–H_2O (1:1), r.t., stirring.
[b] Isolated yield.

Table 3 Reaction of Different Arylboronic Acids with Different Anilines[19] and Imidazoles[20]

Entry	Arylboronic acid	Aniline[a]	Imidazole[b]	Time (h)	Yield (%)[c]
1[21a]			–	8	92
2[21b]			–	8	90
3[22]			–	10	84
4[21c]			–	8	93
5[21d]			–	10	86
6[21e]			–	9	90
7[21f]			–	8	90
8[21c]			–	8	92
9[21g]		–		10	88
10[21h]		–		11	84
11[21i]		–		13	81
12[21j]		–		12	86
13[21k]		–		11	86
14[21l]		–		12	82
15[21g]		–		12	82

[a] Conditions: aniline (0.5 mmol), arylboronic acid (1 mmol), nanocatalyst (30 mol% w.r.t. aniline substrate), MeOH–H_2O (1:1, v/v, 4 mL), K_2CO_3 (1.5 mmol), r.t.
[b] Imidazole (1 mmol), arylboronic acid (1.2 mmol), nanocatalyst (15 mol% w.r.t. imidazole substrate), MeOH–H_2O (1:1, v/v, 4 mL), K_2CO_3 (1.5 mmol), r.t.
[c] Isolated yield.

From the substrate study, it was found that the cross-coupling reaction of arylboronic acids with different anilines gave good to excellent yields of the cross-coupling products. Both electron-deficient and electron-rich anilines coupled efficiently under the optimized reaction conditions resulting in good to excellent yields of the products. However, phenylboronic acids with an electron-donating group react more rapidly, giving higher yields (Table 3, entries 4, 7, 13, and 14) than those with electron-withdrawing groups (Table 3, entries 3, 11, and 12). The compatibility of the reaction with the functional groups (CN, CO_2R, COR, NO_2) on the boronic acids were tested under the same reaction conditions, but the results were not encouraging even after heating and very low yields were observed (less than 25%). The presence of an alkyl substituent on the imidazole ring has a slight effect in terms of the efficiency of the reaction. For example, 4-methylimidazole requires a longer reaction time (Table 3, entry 10) compared to imidazole (Table 3, entry 9).

To assess the reusability of the CuO NPs, a series of six consecutive runs was carried out using aniline and phenylboronic acid under optimized conditions. After the end of each reaction, the reaction mixture was filtered and the catalyst was reused for the next batch. We find that the catalyst was reusable up to a 5th cycle without any significant loss of catalytic activity. After the 5th cycle, a notable loss of catalytic activity was observed (Figure 3).

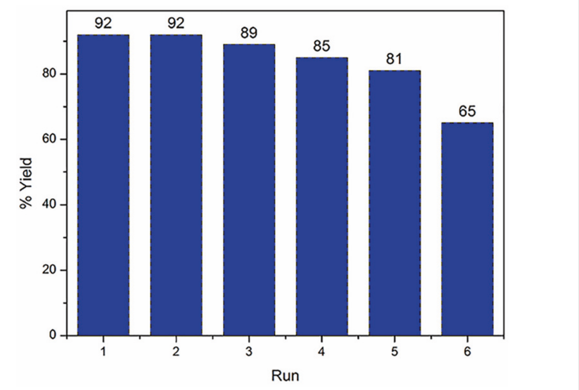


Figure 3 Reusability of CuO NPs

In conclusion, we have developed an efficient process for CuO NPs synthesis and these can effectively catalyze N-arylation of imidazoles and anilines under mild conditions. The reaction is carried out at room temperature and the procedure works well with a variety of imidazole, aniline, and boronic acid substrates having both electron-donating and electron-withdrawing groups, affording good to excellent yields and the catalyst can be recycled.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588741.

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Modified Procedure for Preparing CuO NPs

Copper(II) chloride dihydrate (6.8 g), NaOH (3.2 g), and capping solvent (polyethylene glycol) were mixed in a 2:1:1.5 ratio with EtOH–H_2O (1:1, v/v, 200 mL) in a round-bottom flask fitted with a reflux condenser. The mixture was heated to reflux for 12 h and allowed to cool to r.t. Then the mixture was again heated to reflux for 5 h. The dark brown precipitate was centrifuged and washed with EtOH, acetone, and hot H_2O sequentially. Finally, the product was dried at r.t, heated to 120 °C in a vacuum oven and allowed to cool to r.t..

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(19) **Typical Procedure: N-Arylation of Aniline with Phenylboronic Acid**

In a 50 mL round-bottomed flask, aniline (0.5 mmol), phenylboronic acid (1 mmol), K_2CO_3 (1.5 mmol), nanocatalyst (30 mol% with respect to aniline substrate) were added and stirred in MeOH–H_2O (1:1) under air at r.t. for the required time, monitoring by TLC. After completion, the mixture was diluted with H_2O, and the product was extracted with EtOAc (3×). The combined

extracts were washed with brine (3×) and dried over Na_2SO_4. The product was purified by column chromatography (60–120 mesh silica gel, eluting with EtOAc–hexane solvent). The product was a grey crystalline solid, mp 54 °C; isolated yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.63 (br s, 1 H), 6.90 (t, *J* = 8 Hz, 2 H), 7.04–7.02 (m, 4 H), 7.25–7.21 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2, 129.5, 121.1, 117.9 ppm.

(20) **Typical Procedure: N-Arylation of Imidazole with Phenylboronic Acid**
In a 50 mL round-bottomed flask, imidazole (1 mmol), phenylboronic acid (1.2 mmol), K_2CO_3 (1.5 mmol), nanocatalyst (15 mol% with respect to imidazole substrate) were added and stirred in MeOH–H_2O (1:1) under air at r.t. for the required time, monitoring by TLC. After completion, the mixture was diluted with H_2O and the product was extracted with EtOAc (3×). The combined extracts were washed with brine (3×) and dried over Na_2SO_4. The product was purified using column chromatography (60–120 mesh silica gel, eluting with EtOAc–hexane). The product was isolated as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (s, 1 H), 7.50–7.47 (m, 2 H), 7.40–7.35 (m, 3 H), 2.28 (m, 1 H), 7.21 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.4, 135.6, 130.3, 129.9, 127.6, 121.6, 118.3 ppm.

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(22) **Analytical Data for 4-Bromo-*N*-(4-fluorophenyl)benzenamine (Table 3, Entry 3)**
Colorless crystals; mp 43 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.54 (br s, 1 H), 7.32–7.25 (m, 2 H), 7.02–6.96 (m, 4 H), 6.82 (d, *J* = 8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 132.2, 121.3, 121.2, 118.1, 116.2, 116.0, 112.2 ppm.