Amidation of Aryl Halides Catalyzed by the Efficient and Recyclable Cu_2O Nanoparticles

Yao, Zijian(姚子健) Wei, Xianwen*(魏先文)

College of Chemistry and Materials Science, Key Laboratory of Functional Molecular Solids, the Ministry of Education, Anhui Laboratory of Molecule-based Materials, Anhui Normal University, Wuhu, Anhui 241000, China

Cu_2O nanoparticles/DMEDA (*N*,*N*'-dimethylethylenediamine) was proved to be an efficient catalyst system for amidation of aryl halides under mild condition. This method displayed excellent selectivity and the catalyst was recyclable without loss of activity. The low cost, simple operation and excellent yields make this approach attractive for industrial applications.

Keywords nanoparticles, aryl halide, cuprous oxide, cross-coupling, catalyst recycling

Introduction

N-Aryl structures are important subunits found in numerous natural products which had great influences on the fields of biological, pharmaceutical, and material sciences.[1] Despite many significant Pd-catalyzed C—N cross coupling reactions have been developed in recent years,[2] the use of expensive palladium and elaborate phosphorated ligands would limit its applications to large-scale production. The classical copper-catalyzed Ullmann and Goldberg reactions represent straightforward and inexpensive method to *N*-arylation compounds.[3,4] In the past decades, researchers have employed several organic ligands to facilitate the reaction greatly, and Cu-catalyzed *N*-arylation of amines,[5] amides,[6] imidazoles,[7] and indoles[8] were all accomplished conveniently under mild conditions. Since the first cuprous iodide catalyzed *N*-arylation of amides was reported,[6e] several CuX/L systems (L＝phenanthroline,[6c] 1,2-diamine,[6e,6f,6i] amino acids,[6j-6l,6n] *etc*.) have been developed for amidation of aryl halides. However, most of the systems involve a homogeneous process, so the use of highly efficient and reusable heterogeneous catalyst is still a challenge.[9] Although CuO nanoparticles[10] and Cu_2O[6q,6r] were used for the amidation, the substrates were limited to aryl iodides. We want to give a more systematic picture including the influences of different ligands and bases, effects of substituted groups of aromatic ring and Cu_2O morphology on the reaction, and to use aryl bromides and aryl chlorides as substrates.

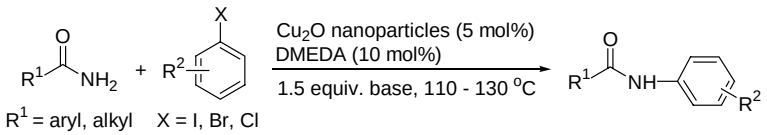
Generally, nanoparticles (NPs) have been studied as effective catalysts[11] in organic synthesis for their large surface area and excellent dispersion activity in the solvent compared with ordinary powder materials,[12] simplified isolation of products and easy recovery of the catalysts is also an advantage.[10] The investigation of NPs as catalysts is booming now, which inspired us to focus on cuprous oxide nanoparticle catalysis for the C—N coupling reaction of amides. Herein a highly efficient method to form a C—N bond was reported, and *N*-arylation of amides catalyzed by recyclable, low cost and environmentally benign Cu_2O NPs were accomplished conveniently (Scheme 1). In particular, acceptable to good yields were obtained for aryl chlorides, which is still a challenge in this field.[9]

Experimental

Preparation of Cu_2O nanoparticles

Cu_2O nanocube[13] First, 0.25 mL of 0.01 mol•L^{-1} $CuSO_4$ was added to 9.0 mL of 0.02 mol•L^{-1} aqueous cetyltrimethylammonium (CTAB) solution, then 0.50 mL of 0.10 mol•L^{-1} sodium ascorbate solution was

Scheme 1 Cross-coupling of aryl halides and amides



* E-mail: xwwei@mail.ahnu.edu.cn; Tel.: 0086-553-3937137; Fax: 0086-553-3869303
Received April 6, 2010; revised June 8, 2010; accepted June 14, 2010.
Project supported by the National Natural Science Foundation of China (Nos. 20671002, 20490217), Science and Technological Fund of Anhui Province for Outstanding Youth (No. 08040106906), the State Education Ministry (EYTP, SRF for ROCS, SRFDP20070370001), and the Education Department of Anhui Province (Nos. 2006KJ006TD, 2008Z028).

CHINESE JOURNAL OF CHEMISTRY

added to the above solution. The mixture was heated to 55 ℃ for 5 min. Then 0.20 mL of 0.50 mol•L^{-1} NaOH solution was added to the mixture, and it was kept at 55 ℃ for another 10 min. Finally, the mixture was cooled to room temperature, the precipitate was washed and dried. Cu_2O nanocubes with size of 200—300 nm were obtained.

Cu_2O nanospheres[14] 2 mmol $Cu(OAc)_2$•H_2O was dissolved in 25 mL of DMF, followed by the addition of 2 mmol poly(vinyl pyrrolidone) and 0.03 g $NaBH_4$. After stirring for 10 min, the mixture was heated to and maintained at 85—95 ℃ in 0.5 min, then cooled to room temperature at once and washed by alcohol several times and dried. Cu_2O nanospheres with diameters of 100—200 nm were obtained.

General procedure for the coupling reaction

A mixture of Cu_2O nanoparticles (3.6 mg, 0.025 mmol), benzamide (0.6 mmol, 72 mg), and K_3PO_4•$3H_2O$ (200 mg, 0.75 mmol) was dispersed in toluene. Then, *N*,*N'*-dimethylethylenediamine (6 μL, 0.05 mmol), iodobenzene (56 μL, 0.5 mmol) were added to the mixture by syringe under Ar atomsphere. After the reaction being kept at 110 ℃ for 10 h, the mixture was cooled to room temperature and diluted with dichloromethane and filtered. The filtrate was washed with brine (5 mL × 1) and distilled water (5 mL × 2), and the aqueous phases were extracted twice with dichloromethane. The organic layers were dried by anhydrous Na_2SO_4, concentrated and purified by silica gel column chromatography (petroleum ether/ethyl acetate, V∶V=5∶1) to yield product *N*-phenylbenzamide (94 mg, 95% yield). The identity and purity of the product was confirmed by ^{1}H, ^{13}C NMR, IR and HRMS.

Typical procedure for recovering Cu_2O NPs catalyst

When the coupling reaction of benzamide with 4-iodoanisole in a scale of 0.6 mmol was complete, the reaction mixture was cooled to room temperature. Then the mixture was centrifugated and the residue was washed with deionized water (5 mL), and dried in air at room temperature to recover the Cu_2O NPs catalyst in quantitative yield. The dried Cu_2O NPs catalyst was then reused directly in the next reaction.

Characterization

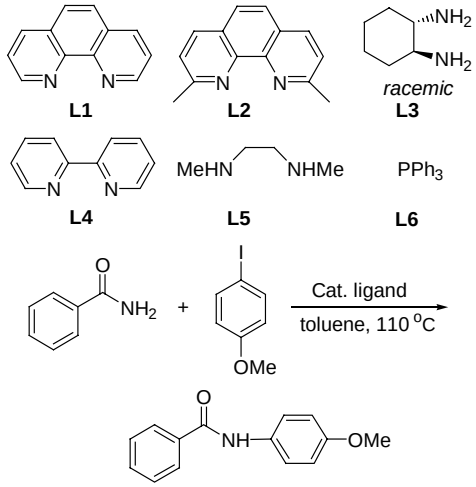
X-ray powder diffraction (XRD) measurements were carried out on a Shimadzu XRD-6000 X-ray diffractometer (Cu Kα radiation, λ=1.5406 Å). Single crystal diffraction data were collected on a Bruker Smart APEX II CCD diffractometer. Scanning electron microscopy (SEM) images were obtained by using a Hitachi S-4800 microscope. Infrared (IR) spectra were obtained with a FTIR Prestige-21 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance NMR spectrometer (300 or 75 MHz, respectively) with $CDCl_3$ as solvent. Chemical shifts are relative to tetramethylsilane as the internal standard. High-resolution mass (HRMS) spectrometry data were collected with an Aligent 6200 LC/MS TOF spectrometer.

Results and discussion

The coupling of benzamide and 4-iodoanisole was first studied as a model reaction with Cu_2O NPs as catalyst. After examining a series of copper sources, ligands, bases, and solvents, the most efficient protocol was exploited. The coupling reaction proceeds smoothly in the presence of 5 mol% Cu_2O NPs and *N*,*N'*-dimethylethylenediamine (DMEDA, **L5**) as ligand, using K_3PO_4•$3H_2O$ as base in toluene at 110 ℃, which afforded *N*-(4-methoxyphenyl)-benzamide (**3b**) in 95% yield. Copper(II) salts such as $CuSO_4$•$5H_2O$, $Cu(OAc)_2$•H_2O and CuO were inferior to Cu_2O NPs (Table 1, Entries 1—3), and the reaction scarcely occurred in the absence of catalyst or ligand (Table 1, Entries 4 and 5). Several chelating ligands such as 1,10-phenanthroline (**L1**), 2,9-dimethyl-1,10-phenanthroline (**L2**), 1,2-diaminocyclohexane (**L3**), 2,2'-bipyridine (**L4**), and PPh_3 (**L6**) were found to be inferior to DMEDA (**L5**), affording **3b** in low yields (Table 1, Entries 8—13). After screening a variety of bases, we found that K_3PO_4•$3H_2O$ was the best choice (Table 1, Entries 12, 14 and 15), and among the solvents studied, toluene gave the best result (Table 1, Entries 6, 7 and 12). In an effort to obtain an optimum Cu_2O/ligand ratio, we found that a 1∶2 Cu_2O/**L5** ratio is the best choice (Table 1, Entries 17—19). It should be noted that no significant effect on reactivity was observed when raising the ratio of Cu_2O/**L5** to 1∶4 (Table 1, Entry 20). When the catalyst amount was reduced to 2 mol%, a decrease of yield was observed (Table 1, Entry 16). Similar yields were obtained when spherical and cubic Cu_2O nanostructures were used as catalyst, but bulk Cu_2O showed a lower activity (Table 2). Although the catalysis effects of Cu_2O morphology on Sonogashira reaction is obvious,[15] we do not find the morphology influence in this work.

To study the scope of the procedure, the reaction of substituted aryl halides with benzamide was examined at the optimal condition. Aryl iodide was found more reactive than corresponding bromides (Table 3, Entries 1—3). No spectacular electronic effects were observed when benzamide was submitted to coupling with electron-rich and electron-poor substituted aryl halides (Table 3, Entries 2, 3 and 6—9), however, steric effects were more significant, *para*-substituted aryl halides gave higher yields obviously than *ortho*-substituted ones did (Table 3, Entries 4, 5). For example, 2-iodotoluene, as a typical hindered substituent, gave relatively low yield (Table 3, Entry 4). But 2-iodoaniline was an exception, it also gave an excellent yield, and this example suggested that benzamide can be selectively arylated in the presence of a free amine NH_2 group (Table 3, Entry 9). This selectivity is interesting, since copper-**L1** derivatives complexes have been reported to catalyze the reaction of aryl amines with aryl halides,[5a,7f] and this

Table 1 Screening for the reaction conditions



Entry	Catalyst	Ligand	Base	Yield[a]/%
1	$CuSO_4$•$5H_2O$	**L5**	K_3PO_4•$3H_2O$	0
2	$Cu(OAc)_2$•H_2O	**L5**	K_3PO_4•$3H_2O$	0
3	CuO	**L5**	K_3PO_4•$3H_2O$	trace
4	Cu_2O NPs	—	K_3PO_4•$3H_2O$	trace
5	—	**L5**	K_3PO_4•$3H_2O$	0
6	Cu_2O NPs	**L5**	K_3PO_4•$3H_2O$	trace[b]
7	Cu_2O NPs	**L5**	K_3PO_4•$3H_2O$	trace[c]
8	Cu_2O NPs	**L1**	K_3PO_4•$3H_2O$	trace
9	Cu_2O NPs	**L2**	K_3PO_4•$3H_2O$	12
10	Cu_2O NPs	**L3**	K_3PO_4•$3H_2O$	21
11	Cu_2O NPs	**L4**	K_3PO_4•$3H_2O$	18
12	Cu_2O NPs	**L5**	K_3PO_4•$3H_2O$	95
13	Cu_2O NPs	**L6**	K_3PO_4•$3H_2O$	8
14	Cu_2O NPs	**L5**	K_2CO_3	41
15	Cu_2O NPs	**L5**	KOH	trace
16	Cu_2O NPs	**L5**	K_3PO_4•$3H_2O$	78[d]
17	Cu_2O NPs	**L5**	K_3PO_4•$3H_2O$	94[e]
18	Cu_2O NPs	**L5**	K_3PO_4•$3H_2O$	94[f]
19	Cu_2O NPs	**L5**	K_3PO_4•$3H_2O$	83[g]
20	Cu_2O NPs	**L5**	K_3PO_4•$3H_2O$	95[h]

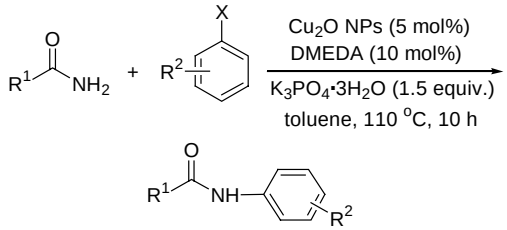
Reaction conditions: benzamide (0.6 mmol), 4-iodoanisole (0.5 mmol), catalyst (10 mol%), ligand (20 mol%), base (0.75 mmol), toluene (3 mL), 10 h, Ar. [a] Isolated yields. [b,c] DMF and dioxane as solvent, respectively. [d] 2 mol% Cat., 5 mol% **L5**. [e] 5 mol% Cat., 10 mol% **L5**. [f] 10 mol% Cat., 10 mol% **L5**. [g] 5 mol% Cat., 5 mol% **L5**. [h] 5 mol% Cat., 20 mol% **L5**.

Table 2 Effects of Cu_2O morphology on the reaction of benzamide with 4-iodoanisole

Entry	Morphology of Cu_2O	Yield[a]/%
1	Cube	95
2	Sphere	94
3	Bulk	79

Reaction Conditions: benzamide (0.6 mmol), 4-iodoanisole (0.5 mmol), Cat. (5 mol%), **L5** (10 mol%), K_3PO_4•$3H_2O$ (0.75 mmol), toluene (3 mL), 10 h, 110 ℃, Ar. [a] Isolated yields.

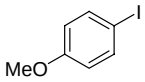
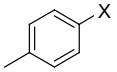
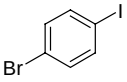
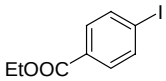
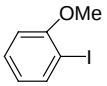
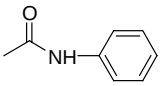
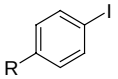
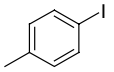
Table 3 Cu_2O-catalyzed coupling reaction of aryl iodides or aryl bromides with amides



Entry	Amide	Aryl halide	Yield[a]/%
1	**1a**		95 (X=I) **3a** 81 (X=Br)
2	**1a**		94 (X=I) **3b** 76 (X=Br)
3	**1a**		92 (X=I) **3c** 75 (X=Br)
4	**1a**		80 **3d**
5	**1a**		86 **3e**
6	**1a**		94 **3f**
7	**1a**		96 **3g**
8	**1a**		82 **3h**
9	**1a**		95 **3i**
10	**1a**		94 **3j**
11	**1a**		90 **3k**
12	**1b**		98 **3l**
13	**1b**		96 **3m**
14	**1c**		81 (X=I) **3n** 52[b] (X=Br)

CHINESE JOURNAL OF CHEMISTRY

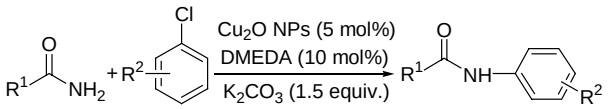
Continued

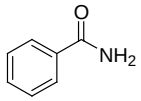
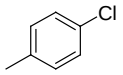
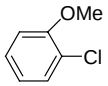
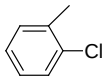
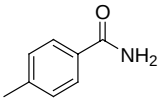
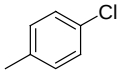
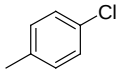
Entry	Amide	Aryl halide	Yield[a]/%
15	**1c**		86 **3o**
16	**1c**		94 (X=I) **3p** 54[b] (X=Br)
17	**1c**		80 **3q**
18	**1c**		96 **3r**
19	**1c**		91[b] **3s**
20	**1c**		82[b] **3t**
21	 **1e**	 R=Me **3v** OMe **3w**	88[b] **3v** 83[b] **3w**
22			trace[c]

Reaction conditions: amide (0.6 mmol), aryl halides (0.5 mmol), Cu_2O NPs (5 mol%), **L5** (10 mol%), K_3PO_4•$3H_2O$ (0.75 mmol), toluene (3 mL), 110 ℃, Ar. [a] Isolated yields. [b] 18 h. [c] In toluene and dioxane, respectively.

method circumvented limitations of the Pd-catalyzed *N*-arylation.[6o] The selectivity was also embodied in the reaction of 4-aminobenzamide, in which only the coupling of amide NH_2 was observed (Scheme 2). Furthermore, heterocyclic halides such as pyridyl and thienyl halides both worked well for this coupling reaction (Table 3, Entries 10, 11). Likewise, 4-toluamide (**1b**) was suitable for the reaction (Table 3, Entries 12, 13). The structure of **3c** (Table 3, Entry 3) was unambiguously showed by single crystal X-ray diffraction (Figure 1).[16] In addition, aliphatic amide such as acetamide was also adapted to the reaction in moderate to excellent yields (Table 3, Entries 14—20). Beside primary amides, secondary amide such as acetanilide also gave good yield (Table 3, Entry 21). Unfortunately, carprolactam has less reactivity (Table 3, Entry 22). Aryl chlorides are much more attractive substrates for industrial production because of their low cost and ready availability, but examples for coupling of aryl chlorides with amides are rare so far, only Buchwald[6i] has reported that the reaction of aryl chlorides can be accomplished under solvent free condition using the CuI/diamine catalytic system. So we decided to study amidation of aryl chlorides using 5 mol% Cu_2O NPs, 10 mol% DMEDA in neat aryl chloride, and the reaction occurred smoothly and gave good yields (Table 4).

Table 4 Cu_2O-catalyzed amidation of aryl chlorides with amides



Entry	Amide	Aryl chloride	Yield[a]/%
1			86
2	**1a**		82
3	**1a**		82
4	**1a**		78
5			81
6			67

Reaction conditions: 0.5 mmol amides, Cu_2O NPs (5 mol%), **L5** (10 mol%), K_2CO_3 (0.75 mmol), 23 h, 130 ℃, in neat aryl chlorides, Ar. [a] Isolated yields.

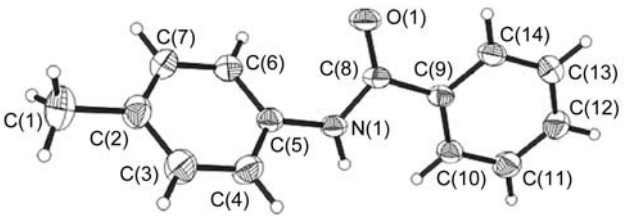
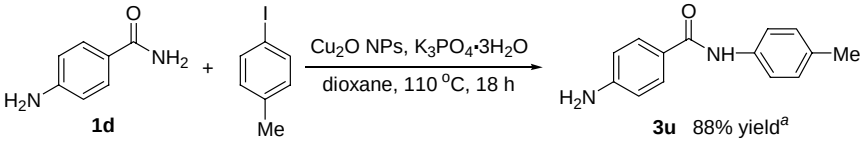


Figure 1 X-ray crystal structure of product **3c**.

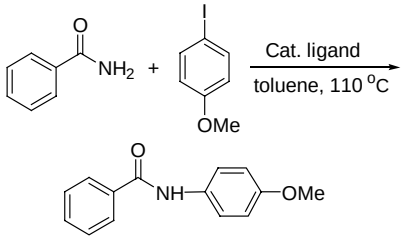
Scheme 2 Cu_2O-catalyzed coupling reaction of 4-aminobenzamide with 4-iodotoluene



Reaction condition: 0.6 mmol **1d**, 0.5 mmol 4-iodotoluene, 5 mol% Cu_2O NPs, 10 mol% DMEDA, 0.75 mmol K_3PO_4•$3H_2O$, dioxane (3 mL), 110 ℃, 18 h. [a] Isolated yield.

To reveal that the reaction are heterogeneous, the Cu_2O NPs were stirred at 110 ℃ for 10 h in toluene in the presence of DMEDA and K_3PO_4•$3H_2O$, the catalyst was then separated by centrifugation, and the solution was independently used for coupling of benzamide and 4-iodoanisole at 110 ℃, 11 % yield was obtained after 16 h, which may be caused by trace copper leaching. The low rate leaching inspired us to check the recyclability of the catalyst, Cu_2O NPs were recovered by centrifugation and reused for the fresh reaction of 4-iodoanisole with benzamide. No loss of the activity was observed even after 5 runs (Table 5). In addition, the scanning electron microscopy and powder X-ray diffraction analyses of Cu_2O NPs, showed identical particle shape, size, and diffraction pattern (Figures 2—7). These experimental results clearly suggest that the reaction involves a heterogeneous process and the catalysis may occur on the surface of Cu_2O NPs. The proposed mechanism for the coupling reaction catalyzed by Cu_2O NPs may be through a coordination-recyclable process via oxidative addition followed by reductive elimination (Scheme 3). In the first step, the oxidative addition of amide to catalyst may occurr and give a copper complex **L2**Cu-Nu, which is thought to be a copper(I) intermediate involving ligands, and ligand is important in the process because it can stabilize the Cu(I) intermediate and enhance the solubility. Then the next step

Table 5 Recyclability of Cu_2O NPs



Run	Recoverability/%	Yield[a]/%
1	98	95
2	97	92
3	95	94
4	92	93
5	92	90

Reaction conditions: 0.6 mmol benzamide, 0.5 mmol 4-iodoanisole, **L5** (10 mol%), K_3PO_4•$3H_2O$ (0.75 mmol), toluene (3 mL), 10 h, 110 ℃, Ar, Cu_2O NPs (5 mol%) was used in the first run, then the recovered catalyst was used directly in the next runs. [a] Isolated yields.

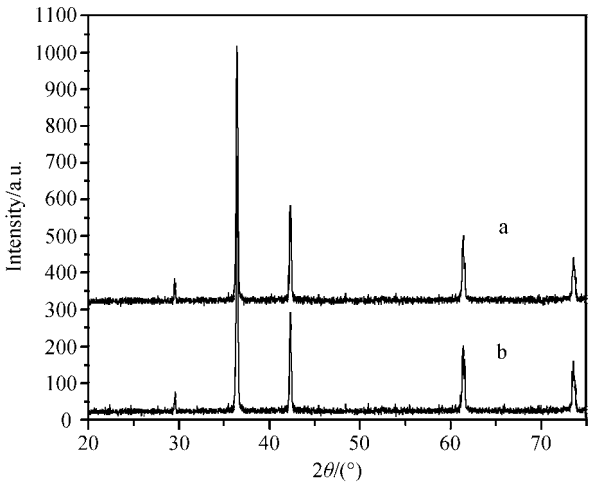


Figure 2 XRD patterns of cubic Cu_2O: (a) fresh and (b) after fifth catalytic cycles.

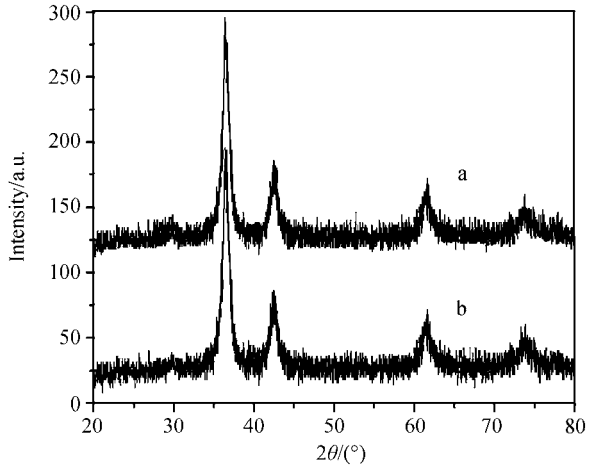
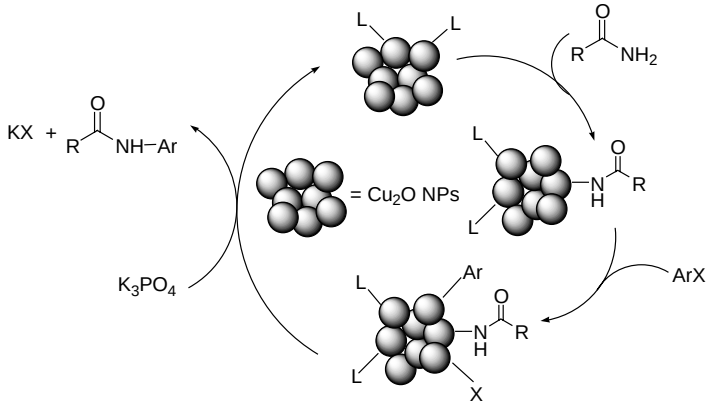


Figure 3 XRD patterns of spherical Cu_2O: (a) fresh and (b) after fifth catalytic cycles.

Scheme 3 Possible mechanism for the coupling reaction



CHINESE JOURNAL OF CHEMISTRY

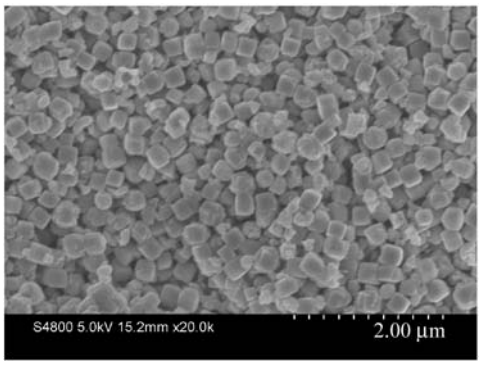


Figure 4 SEM image of fresh cubic Cu_2O.

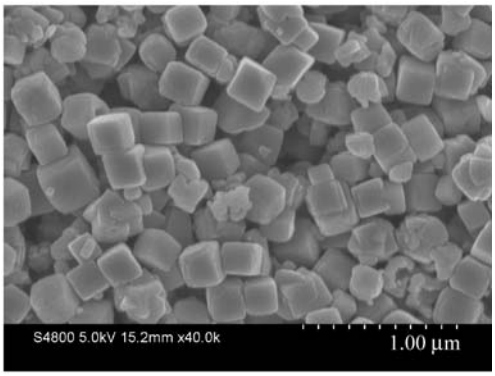


Figure 5 SEM image of cubic Cu_2O after fifth catalytic cycles.

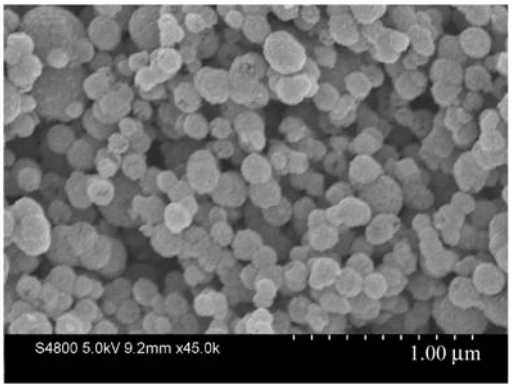


Figure 6 SEM image of fresh spherical Cu_2O.

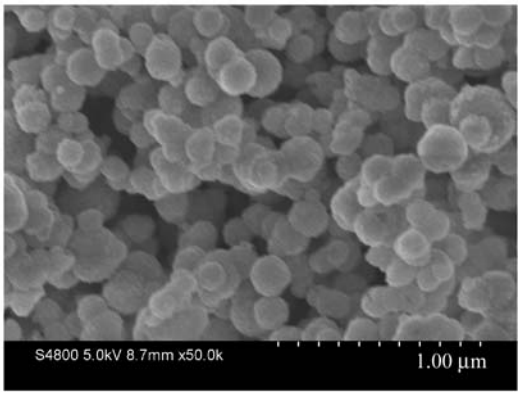


Figure 7 SEM image of spherical Cu_2O after fifth catalytic cycles.

is the addition of aryl halide. Finally, the product is obtained through reductive elimination.

Conclusions

In summary, a novel and efficient method for C—N cross coupling reactions of substituted aryl halides with aromatic/alphatic amides have been successfully accomplished by using inexpensive and recyclable Cu_2O NPs as the catalyst under mild conditions. The low cost, simple operation and environmental benignity, in combination with excellent yields, make this method especially attractive for industrial applications.

Characterization data for the products

***N*-Phenylbenzamide (3a)** White solid (94 mg, 95%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.85 (d, J=7.0 Hz, 4H), 7.62 (d, J=7.7 Hz, 2H), 7.57—7.46 (m, 2H), 7.37 (t, J=7.6 Hz, 2H), 7.15 (t, J=7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.8, 137.9, 134.9, 131.8, 129.1, 128.8, 127.0, 124.6, 120.2; IR (KBr) v: 3344, 1648, 1596, 1531, 1440, 1324, 1253, 749, 677, 645 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{12}NO$ $[M+H]^+$ 198.0920, found 198.0922.

***N*-(4-Methoxyphenyl)-benzamide (3b)** White solid (107 mg, 94%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.84 (d, J=7.2 Hz, 2H), 7.77 (s, 1H), 7.55—7.44 (m, 5H), 6.88 (d, J=8.8 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.6, 156.6, 135.0, 131.7, 130.9, 128.7, 127.0, 122.1, 114.2, 55.5; IR (KBr) v: 3341, 1663, 1513, 1403, 1253, 1034, 814, 704, 644, 554 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$ 228.1026, found 228.1051.

***N*-(4-Methylphenyl)-benzamide (3c)** White solid (97 mg, 92%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.84 (d, J=7.6 Hz, 2H), 7.78 (s, 1H), 7.56—7.45 (m, 5H), 7.16 (d, J=8.0 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.8, 135.4, 135.0, 134.2, 131.7, 129.6, 128.7, 127.1, 120.4, 20.9; IR (KBr) v: 3312, 1648, 1609, 1519, 1409, 1312, 1260, 1033, 910, 812, 696, 509 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{13}NO$ $[M+H]^+$ 212.1110, found 212.1129.

***N*-(2-Methylphenyl)-benzamide (3d)** White solid (85 mg, 80%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.97—7.87 (m, 3H), 7.67 (s, 1H), 7.56—7.50 (m, 3H), 7.22 (d, J=8.4 Hz, 2H), 7.11 (d, J=7.2 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.7, 135.7, 135.0, 131.9, 130.6, 129.2, 128.9, 127.1, 126.9, 125.4, 123.1, 17.9; IR (KBr) v: 3320, 1654, 1525, 1486, 1305, 910, 749, 709, 600 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{13}NO$ $[M+H]^+$ 212.1110, found 212.1102.

***N*-(2-Methoxyphenyl)-benzamide (3e)** White solid (98 mg, 86%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.54—8.52 (m, 2H), 7.89 (t, J=5.4 Hz, 2H), 7.55—7.49 (m, 3H), 7.08—7.01 (m, 2H), 6.92 (t, J=5.4 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.3, 148.1, 135.3, 131.8, 128.8, 127.8, 127.1, 123.9, 121.2, 119.8, 109.9, 55.8; IR (KBr) v: 3240, 1654, 1595, 1526,

1454, 1305, 1253, 1124, 1040, 917, 754, 709, 638, 521 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$ 228.1026, found 228.1062.

***N*-Benzoylbenzocaine (3f)** White solid (126 mg, 94%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.07 (d, J=8.7 Hz, 2H), 7.98 (s, 1H), 7.88 (d, J=7.0 Hz, 2H), 7.74 (d, J=8.7 Hz, 2H), 7.59—7.50 (m, 3H), 4.39 (q, J=7.1 Hz, 2H), 1.41 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.2, 164.9, 141.1, 133.4, 131.0, 129.7, 127.7, 126.0, 125.0, 118.2, 59.8, 13.2; IR (KBr) v: 3344, 1712, 1649, 1603, 1531, 1409, 1272, 1182, 1110, 1033, 852, 768, 690, 651, 502 cm^{-1}.

***N*-(4-Chlorophenyl)-benzamide (3g)** White solid (111 mg, 96%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.88—7.86 (d, J=7.4 Hz, 2H), 7.82 (s, 1H), 7.63—7.48 (m, 5H), 7.36—7.33 (d, J=10.3 Hz, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 165.0, 137.5, 134.1, 131.0, 127.9, 127.7, 127.0, 126.6, 121.2; IR (KBr) v: 3351, 1649, 1603, 1519, 1486, 1396, 1312, 1091, 1007, 819, 722, 638, 509 cm^{-1}.

***N*-(4-Bromophenyl)-benzamide (3h)** White solid (113 mg, 82%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.84 (d, J=7.2 Hz, 2H), 7.79 (s, 1H), 7.56—7.46 (m, 7H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 166.1, 139.0, 135.2, 132.2, 131.9, 128.9, 128.2, 122.6, 115.8; IR (KBr) v: 3388, 1648, 1596, 1525, 1486, 1389, 1312, 1072, 1014, 819, 722, 651, 515 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{11}NOBr$ $[M+H]^+$ 278.0004, found 278.0006.

***N*-(2-Aminophenyl)-benzamide (3i)** White solid (100 mg, 95%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.91 (d, J=6.6 Hz, 2H), 7.86 (s, 1H), 7.58—7.50 (m, 3H), 7.34 (d, J=6.8 Hz, 1H), 7.12 (t, J=7.2 Hz, 1H), 6.88 (m, 2H), 3.89 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 164.8, 139.7, 133.1, 130.8, 127.6, 126.2, 126.1, 124.2, 123.4, 118.6, 117.2; IR (KBr) v: 3273, 1648, 1531, 1505, 1440, 1318, 1163, 910, 761, 703, 605 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{13}N_2O$ $[M+H]^+$ 213.1030, found 213.1034.

N-(2-Pyridinyl)-benzamide (3j) White solid (93 mg, 94%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.94 (s, 1H), 8.38 (d, J=8.3 Hz, 1H), 8.20 (s, 1H), 7.90 (d, J=7.1 Hz, 2H), 7.77—7.72 (m, 1H), 7.58—7.45 (m, 3H), 7.04 (t, J=6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.4, 151.9, 147.7, 138.5, 134.5, 132.1, 128.7, 127.5, 119.8, 114.5; IR (KBr) v: 3189, 1670, 1577, 1525, 1435, 1305, 1156, 903, 787, 717, 684, 612, 502 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{11}N_2O$ $[M+H]^+$ 200.0906, found 200.0908.

***N*-(2-Thienyl)-benzamide (3k)** White solid (91 mg, 90%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.59 (s, 1H), 7.90 (d, J=7.1 Hz, 2H), 7.62—7.49 (m, 3H), 6.98—6.90 (m, 2H), 6.81 (d, J=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 163.9, 139.2, 133.1, 132.1, 128.8, 127.1, 123.9, 118.3, 112.4; IR (KBr) v: 3230, 1644, 1563, 1494, 1364, 1304, 895, 815, 703 cm^{-1}.

***N*-(4-Methoxyphenyl)-toluamide (3l)** White solid (118 mg, 98%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.76 (d, J=7.6 Hz, 2H), 7.73 (s, 1H), 7.54 (d, J=8.3 Hz, 2H), 7.28 (d, J=8.3 Hz, 2H), 6.91 (d, J=8.5 Hz, 2H), 3.83 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 164.5, 155.4, 141.0, 131.0, 130.0, 128.3, 125.9, 121.0, 113.1, 54.4, 20.4; IR (KBr) v: 3338, 1648, 1519, 1415, 1253, 1182, 1035, 826, 749, 670, 554, 521 cm^{-1}.

***N*-(4-Methylphenyl)-toluamide (3m)** White solid (108 mg, 96%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.76 (d, J=7.8 Hz, 3H), 7.52 (d, J=7.8 Hz, 2H), 7.27 (d, J=7.2 Hz, 2H), 7.17 (d, J=7.8 Hz, 2H), 2.43 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 164.8, 140.9, 134.5, 132.9, 131.1, 128.4, 128.2, 126.0, 119.4, 20.4, 19.8; IR (KBr) v: 3351, 1648, 1596, 1519, 1402, 1318, 1247, 1105, 891, 812, 760, 658, 502 cm^{-1}.

***N*-Phenylacetamide (3n)** White solid (55 mg, 81%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.49 (d, J=7.4 Hz, 2H), 7.36—7.27 (m, 3H), 7.12 (t, J=7.4 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 168.7, 137.9, 128.9, 124.3, 120.0, 24.6; IR (KBr) v: 3293, 1663, 1593, 1543, 1434, 1314, 755, 515 cm^{-1}.

***N*-(4-Methoxyphenyl)-acetamide (3o)** White solid (71 mg, 86%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.39 (d, J=7.2 Hz, 2H), 7.11 (s, 1H), 6.86 (d, J=7.1 Hz, 2H), 3.78 (s, 3H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 168.6, 156.3, 131.0, 122.0, 114.0, 55.5, 24.3; IR (KBr) v: 3270, 1653, 1573, 1514, 1314, 1254, 1035, 835, 755, 615, 536 cm^{-1}.

***N*-(4-Methylphenyl)-acetamide (3p)** White solid (70 mg, 94%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.34 (d, J=8.1 Hz, 2H), 7.10 (d, J=7.8 Hz, 3H), 2.30 (s, 3H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 168.6, 135.3, 133.9, 129.5, 24.5, 20.9; IR (KBr) v: 3290, 1650, 1554, 1503, 1401, 1324, 1024, 835, 755, 515 cm^{-1}.

***N*-(4-Bromophenyl)-acetamide (3q)** White solid (85 mg, 80%); ^1H NMR (DMSO-d_6, 300 MHz) δ: 10.0 (s, 1H), 7.54 (d, J=8.4 Hz, 2H), 7.44 (d, J=8.4 Hz, 2H), 2.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.8, 138.0, 130.8, 120.2, 113.8, 23.4; IR (KBr) v: 3300, 1674, 1596, 1533, 1394, 1314, 1241, 994, 825, 725, 496 cm^{-1}.

***N*-Acetylbenzocaine (3r)** White solid (99 mg, 96%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.00 (d, J=8.2 Hz, 2H), 7.58 (d, J=8.2 Hz, 2H), 7.43 (s, 1H), 4.38 (q, J=7.0 Hz, 2H), 2.22 (s, 3H), 1.40 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 168.0, 165.3, 141.2, 129.6, 124.6, 117.9, 59.8, 24.5, 13.2; IR (KBr) v: 3338, 1701, 1677, 1596, 1519, 1370, 1305, 1178, 1124, 1008, 865, 774, 709, 593 cm^{-1}.

***N*-(2-Methoxyphenyl)-acetamide (3s)** White solid (75 mg, 91%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.36 (d, J=7.8 Hz, 1H), 7.77 (s, 1H), 7.08—6.95 (m, 2H), 6.88 (d, J=7.9 Hz, 1H), 3.90 (s, 3H), 2.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 168.2, 147.7, 127.6, 123.6, 120.9, 119.8, 109.9, 55.6, 24.8; IR (KBr) v: 3254, 1654, 1596, 1544, 1486, 1363, 1253, 1177, 1020, 749, 658, 521 cm^{-1}.

***N*-(2-Methylphenyl)-acetamide (3t)** White solid (62 mg, 81%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.73 (d, J=7.7 Hz, 1H), 7.25—7.17 (m, 3H), 7.10—7.01 (m, 2H), 2.25 (s, 3H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.0, 135.6, 130.5, 127.9, 127.0, 126.5, 124.2,

23.9, 17.9; IR (KBr) *v*: 3293, 1648, 1531, 1460, 1363, 1286, 1033, 956, 768, 696, 612, 541 cm^{-1}.

***N*-(4-Methylphenyl)-4-aminobenzamide (3u)** White solid (99 mg, 88%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.70 (d, J=8.0 Hz, 2H), 7.66 (s, 1H), 7.49 (d, J=7.7 Hz, 2H), 7.16 (d, J=7.5 Hz, 2H), 6.70 (d, J=7.7 Hz, 2H), 4.03 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 165.6, 152.5, 137.7, 132.2, 129.7, 129.3, 121.7, 120.6, 113.0, 20.9; IR (KBr) *v*: 3470, 3370, 1614, 1503, 1413, 1314, 1254, 1165, 805, 765, 615, 506 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{15}N_2O$ $[M+H]^+$ 227.1186, found 227.1193.

***N*-Phenyl-*N*-*p*-tolylacetamide (3v)** White solid (99 mg, 88%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.29—7.13 (m, 9H), 2.32 (s, 3H), 2.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.5, 137.8, 136.0, 130.2, 129.6, 128.8, 128.2, 127.7, 126.3, 23.8, 21.0; IR (KBr) *v*: 1663, 1584, 1503, 1374, 1324, 1287, 1024, 815, 745, 686, 575 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{16}NO$ $[M+H]^+$ 226.1187, found 226.1192.

***N*-Phenyl-*N*-(4-methoxyphenyl)-acetamide (3w)** White solid (100 mg, 83%); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.24—6.86 (m, 9H), 3.76 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.7, 136.2, 135.6, 129.5, 128.8, 128.2, 127.8, 126.1, 114.8, 55.4, 22.7; IR (KBr) *v*: 1674, 1593, 1494, 1380, 1234, 1174, 1035, 835, 765, 695, 585 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{16}NO_2$ $[M+H]^+$ 242.1136, found 242.1140.

References

1 Negwar, M. In *Organic-Chemical Drugs and Their Synonyms*: *An International Survey*, 7th ed., Akademie, Berlin, Germany, **1994**.

2 Pd reviews, see: (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.
(b) Jiang, L.; Buchwald, S. L. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Eds.: de Meijere, A.; Diederich, F., Wiley-VCH, Weinheim, Germany, **2004**, pp. 699—760.
(c) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev*. **2007**, *107*, 5318.

3 For a general review, see: (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.
(b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.
(c) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, *15*, 2428.
(d) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337.
(e) Corbet, J. P.; Mignani, G. *Chem. Rev*. **2006**, *106*, 2651.
(f) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev*. **2008**, *108*, 3054.
(g) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954.

4 (a) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691.
(b) Yamamoto, T.; Kurata, Y. *Can. J. Chem.* **1983**, *61*, 86.

5 (a) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315.
(b) Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem*. **2005**, *70*, 8107.
(c) Wolf, C.; Liu, S.; Mei, X.; August, A. T.; Casimir, M. D. *J. Org. Chem*. **2006**, *71*, 3270.
(d) Rout, L.; Jammi, S.; Punniyamurthy, T. *Org. Lett*. **2007**, *9*, 3397.
(e) Nandurkar, N. S.; Bhanushali, M. J.; Bhor, M. D.; Bhanage, B. M. *Tetrahedron Lett.* **2007**, *48*, 6573.
(f) Jones, K. L.; Porzelle, A.; Hall, A.; Woodrow, M. D.; Tomkinson, N. C. O. *Org. Lett*. **2008**, *10*, 797.
(g) Wang, H.; Li, Y.; Sun, F.; Feng, Y.; Jin, K.; Wang, X. *J. Org. Chem.* **2008**, *73*, 8639.
(h) Bolliger, J. L.; Frech, C. M. *Tetrahedron* **2009**, *85*, 1180.
(i) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 973.

6 (a) Yamamoto, T.; Ehara, Y.; Kubota, M.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1299.
(b) Shen, R.; Porco, J. A. Jr. *Org. Lett.* **2000**, *2*, 1333.
(c) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670.
(d) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc*. **2000**, *122*, 5043.
(e) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.
(f) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803.
(g) Crawford, K. R.; Padwa, A. *Tetrahedron Lett.* **2002**, *43*, 7365.
(h) Kang, S. K.; Kim, D. H.; Park, J. N. *Synlett* **2002**, 427.
(i) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.
(j) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667.
(k) Deng, W.; Wang, Y.-F.; Zou, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett*. **2004**, *45*, 2311.
(l) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809.
(m) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120.
(n) Chen, W.; Li, J.; Fang, D.; Feng, C.; Zhang, C. *Org. Lett*. **2008**, *10*, 4565.
(o) Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc*. **2009**, *131*, 78.
(p) Larsson, P. F.; Correa, A.; Carril, M.; Norrby, P. O.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5691.
(q) Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586.
(r) Jammi, S.; Krishnamoorthy, S.; Saha, P.; Kundu, D. S.; Sakthivel, S.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *Synlett* **2009**, 3323.

7 (a) Kiyomori, A.; Marcoux. J. F.; Buchwald, S. L. *Tetrahedron Lett*. **1999**, *40*, 2657.
(b) Liu, L.; Frohn, M.; Xi, N.; Dominguez, C.; Hungate, R.; Reider, P. J. *J. Org. Chem.* **2005**, *70*, 10135.
(c) Jerphagnon, T.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *Org. Lett*. **2005**, *7*, 5241.
(d) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779.
(e) Zhu, L.; Cheng, L.; Zhang, Y.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 2737.
(f) Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org.*

Chem. **2007**, *72*, 6190.
(g) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863.
(h) Zhu, L.; Guo, P.; Li, G.; Lan, J.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 8535.
(i) Ma, H.-C.; Jiang, X.-Z. *J. Org. Chem*. **2007**, *72*, 8943.
(j) Verma, A. K.; Singh, J.; Sankar, V. K.; Chaudhary, R.; Chandra, R. *Tetrahedron Lett.* **2007**, *48*, 4207.
(k) Xue, F.; Cai, C.; Sun, H.; Shen, Q.; Rui, J. *Tetrahedron Lett.* **2008**, *49*, 4386.
(l) Kaddouri, H.; Vicente, V.; Ouali, A.; Ouazzani, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 333.
(m) Son, S. U.; Park, I. K.; Park, J.; Hyeon, T. *Chem. Commun.* **2004**, 778.
(n) Yan, J.-C.; Zhou, L.; Wang, L. *Chin. J. Chem*. **2008**, *26*, 165.

8 (a) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 11684.
(b) Hong, C. S.; Seo, J. Y.; Yum, E. K. *Tetrahedron Lett*. **2007**, *48*, 4831.
(c) Mao, J.; Guo, J.; Song, H.; Ji, S.-J. *Tetrahedron* **2008**, *64*, 1383.

9 Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096.

10 Jammi, S.; Sakthivel, S.; Rout, L.; Mukherjee, T.; Mandal, S.; Mitra, R.; Saha, P.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 1971.

11 (a) White, R. J.; Luque, R.; Budarin, V. L.; Clark, J. H.; Macquarrie, D. J. *Chem. Soc. Rev.* **2009**, *38*, 481.
(b) Campelo, J. M.; Luna, D.; Luque, R.; Marinas, J. M.; Romero, A. A. *ChemSusChem* **2009**, *2*, 18.

12 (a) Choudary, B. M.; Kantam, M. L.; Ranganath, K. V. S.; Mahender, K.; Sreedhar, B. *J. Am. Chem. Soc.* **2004**, *126*, 3396.
(b) Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167.
(c) Rout, L.; Sen, T. K.; Punniyamurthy, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5583.
(d) Reddy, V. P.; Kumar, A. V.; Swapna, K.; Rao, K. R. *Org. Lett.* **2009**, *11*, 1697.
(e) Tang, B.-X.; Wang, F.; Li, J.-H.; Xie, Y.-X.; Zhang, M.-B. *J. Org. Chem.* **2007**, *72*, 6294.

13 Guo, L.; Murphy, C. J. *Nano Lett.* **2003**, *3*, 231.

14 Zhang, J.; Liu, J.; Peng, Q.; Wang, X.; Li, Y. *Chem. Mater*. **2006**, *18*, 867.

15 Tang, B.-X.; Wang, F.; Li, J.-H.; Xie, Y.-X.; Zhang, M.-B. *J. Org. Chem*. **2007**, *72*, 6294.

16 Crystallographic data for compound **3c** reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-748906. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internet.)＋44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

(E1004061 Pan, B.)

