DOI: 10.1002/adsc.200700289

Microwave-Assisted Simple and Efficient Ligand Free Copper Nanoparticle Catalyzed Aryl-Sulfur Bond Formation

Brindaban C. Ranu,[a,]* Amit Saha,[a] and Ranjan Jana[a]

[a] Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata – 700032, India
Fax: (+91)-33-2473-2805; e-mail: ocbcr@iacs.res.in

Received: June 13, 2007; Revised: August 31, 2007; Published online: November 21, 2007

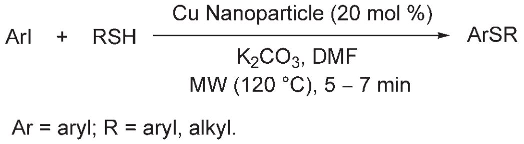
Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A new protocol for the coupling of aryl iodides with thiophenols and alkanethiols catalyzed by copper nanoparticles under ligand-free condition has been developed. A variety of functionalized aryl sulfides are prepared in excellent yields under microwave irradiation for 5–7 min. A plausible radical mechanism has been suggested.

Keywords: aryl-sulfur bond; catalysis; copper nanoparticles; microwave heating; thioethers; thiols

Introduction

The formation of the aryl-sulfur bond is of much importance because of the prevalence of this bond in many molecules of pharmaceutical and material interest[1] and the utility of aryl sulfides as intermediates in organic synthesis.[2] The classical method for the synthesis of aryl sulfides involved condensation of aryl halides with thiols requiring strongly basic and harsh reaction conditions.[3] However, such methods are not desirable for molecules containing sensitive functional groups. The development of transition metal-catalyzed coupling has overcome these difficulties to a great extent.[4] A number of methods have been reported for the synthesis of aryl aryl and aryl alkyl sulfides using palladium,[5] copper,[6] cobalt[7] and other metal catalysts. The various palladium compounds used are $Pd(OAc)_2$/CyPF-*t*-Bu (Josiphos ligand),[5a] $Pd_2(dba)_3$/xantphos,[5b] $[Pd(cod)]Cl_2$/phosphine oxide ligand,[5c] $Pd_2(dba)_3$/DPE-phos[5d] among others. The prominent copper catalysts include CuI/1,1,1-tris(hydroxymethyl)ethane,[6a] CuI/amino acid,[6b] CuI/neocuproine,[6c] $CuI/HOCH_2CH_2OH$,[6d] metallic Cu,[6e,f] and $CuBr/P_2$-Et.[6g] A cobalt-catalyzed reaction in the presence of a ligand, CoI_2(dppe) and Zn have also been reported recently.[7] In general, all these methods involved a metal salt and a ligand other than a base and solvent. Moverover, the high cost and air sensitivity of Pd catalyst systems and often tedious procedures for the preparation of ligands restrict their applications in large-scale processes. On the other hand, Cu-mediated reactions sometimes require the use of copper salts in a more than stoichiometric amount, high temperature (>200 °C) and long reaction time.[6e] Hence, there is a need for improved procedures for this important reaction. We report here a novel ligand-free protocol for the condensation of aryl iodides with thiols using nano copper (20 mol%) under microwave irradiation in the presence of a base (Scheme 1).



$$\text{ArI} + \text{RSH} \xrightarrow[\text{MW (120 °C), 5 – 7 min}]{\text{Cu Nanoparticle (20 mol %)}}_{\;K_2CO_3,\ \text{DMF}} \text{ArSR}$$

Ar = aryl; R = aryl, alkyl.

Scheme 1.

A few ligand-free processes were also reported, such as coupling of arylboronic acid with thiophenol[8a] and *N*-thioimides,[8b] catalyzed by $Cu(OAc)_2$, and CuI-catalyzed coupling of aryl halides and thiols by microwave heating (2–6 h).[8c]

Results and Discussion

The experimental procedure is very simple and convenient. A mixture of an aryl iodide and thiophenol/alkanethiol in DMF was treated under microwave irradiation with K_2CO_3 and Cu nanoparticles (4–6 nm, Figure 1 and Figure 2).[9] Usual work-up provided the product. In absence of a base, the progress of the reaction was only marginal. Although any conventional base such as Na_2CO_3, K_2CO_3, K_3PO_4, NaOH may be used, K_2CO_3 was chosen giving better results in terms of yields.

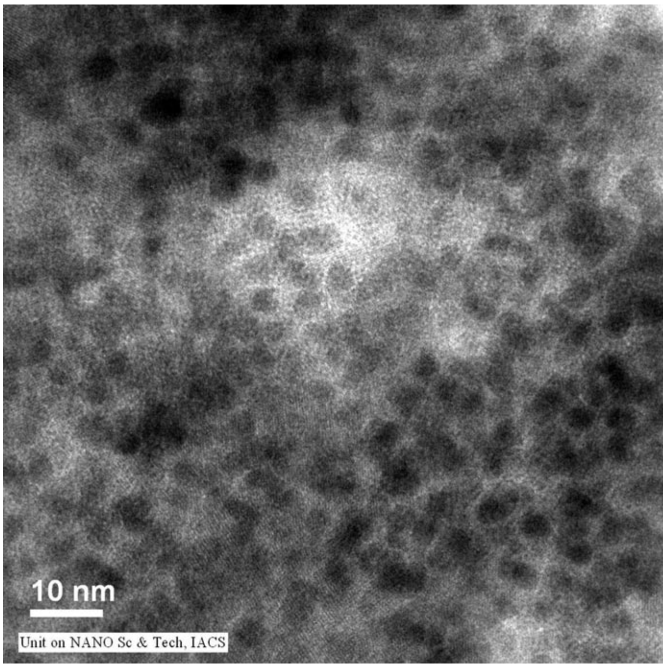


Figure 1. TEM image of Cu nanoparticles.

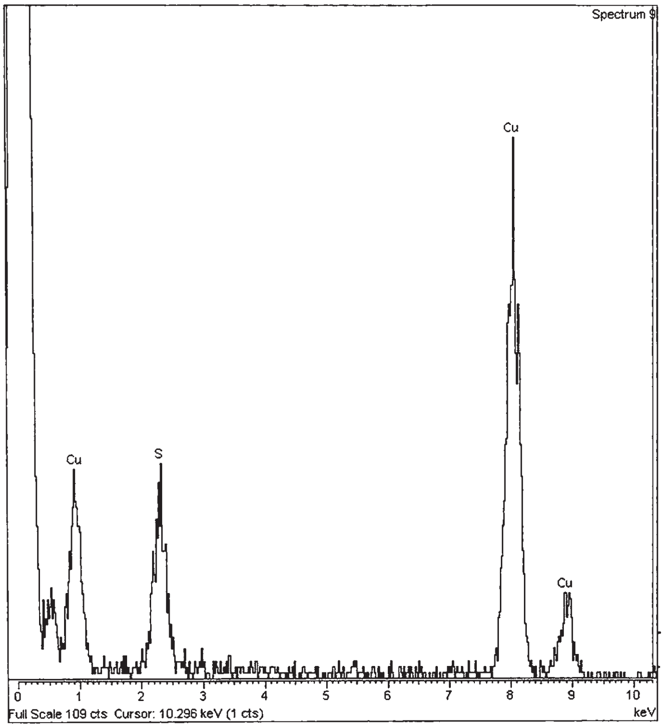


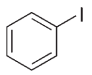
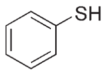
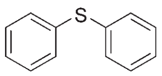
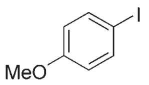
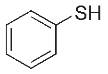
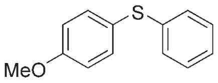
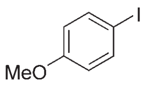
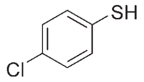
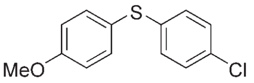
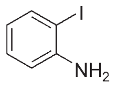
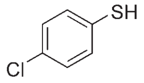
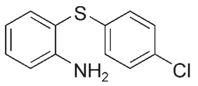
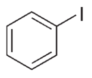
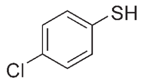
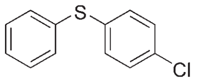
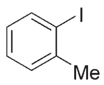
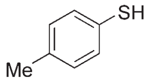
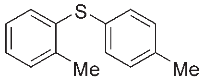
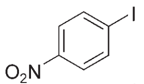
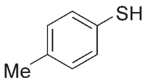
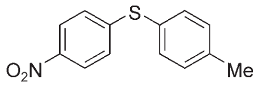
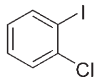
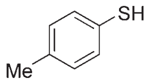
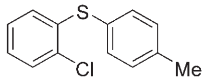
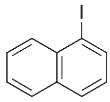
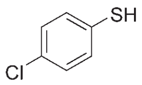
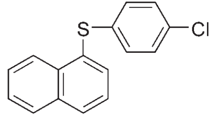
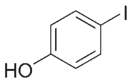
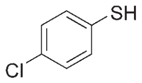
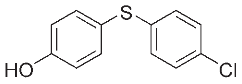
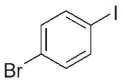
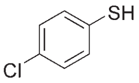
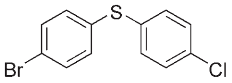
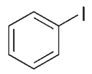
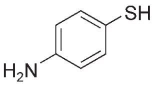
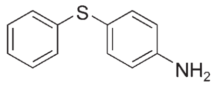
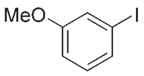
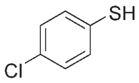
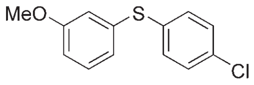
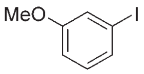
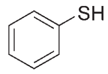
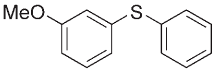
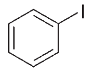
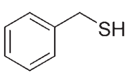
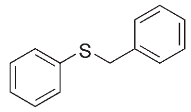
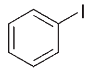
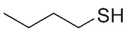
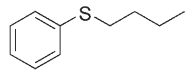
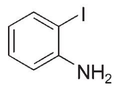
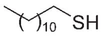
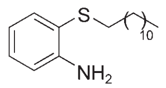
Figure 2. Energy dispersive X-ray spectra of Cu nanoparticles.

Several diversely substituted aryl iodides underwent reactions with a variety of substituted thiophenols, benzyl mercaptan, butane- and dodecanethiols by this procedure to produce the corresponding diaryl/aryl alkyl sulfides. The results are summarized in Table 1. Both electron-donating and electron-withdrawing group-substituted aryl iodides participated in this reaction with similar efficiency. The substitution at the *ortho* position (entries 4, 6, 8, 17, Table 1) did not affect the reaction. The coupling also proceeded well with substituted thiophenols and alkanethiols. This reaction is also very chemoselective. Aryl iodides coupled with thiols without affecting bromo and chloro groups present in the aryl ring (entries 8, 11, Table 1). However, in coupling of *p*-nitroiodobenzene (entry 7, Table 1) a small amount (5%) of product with the nitro group reduced to amino was obtained.

In general, the reactions were very clean and high yielding. However, in several reactions (entries 6, 8, 13–16) small amounts (2–5%) of diaryl/dialkyl disulfides were isolated, which were easily separated during purification by column chromatography. In the absence of Cu nanoparticles the coupling reaction was not initiated at all. It was found that 20 mol% of Cu nanopaticles provided the best results in terms of reaction time and yield. When the reaction was carried out at 120 °C by conventional heating, it required 12–15 h to be completed, whereas under microwave irradiation the reactions were complete within 5–7 min. DMF was found to be the solvent of choice furnishing best results among other solvents such as toluene and THF. The reaction medium is mild enough to tolerate a variety of functional groups such as OMe, OH, Cl, Br, NH_2 etc.

To check the efficiency of this reaction catalyzed by copper nanoparticles, a comparison of results of a few representative reactions by other similar Cu-mediated procedures is presented in Table 2. It was found that the reactions which were carried out by using 300 mol% of metallic copper in an autoclave at 240 °C for 6 h[6e] were accomplished by the present procedure using 20 mol% of Cu nanoparticles at 120 °C under microwave heating for 5 min in better yields (entries 1–3, Table 2). Another reaction (entry 4, Table 2) took 2 h under microwave heating at 195 °C using 10 mol% of CuI,[8c] whereas nano Cu (20 mol%) accomplished it in 5 min under microwave heating at 120 °C in improved yield. The coupling of *m*-methoxyiodobenzene with *p*-chlorothiophenol was achieved at 80 °C in the presence of 5 mol% CuI and 2 equivalents of ethylene glycol for 18 h;[6d] however the same reaction was carried out at 120 °C under microwave heating in 5 min by 20 mol% of Cu nanoparticles without the requirement of any ligand or additive. A comparison of results of a few representative reactions using Cu powder with those using nano Cu under microwave irradiation, as presented in Table 3, showed significant increases in yields of products in nano Cu-catalyzed reactions compared to those catalyzed by Cu powder, indicating a key role of Cu at the nano stage.

Table 1. Cross-coupling reaction of aryl iodides with thiols catalyzed by Cu nanoparticles.[a]

Entry	Aryl iodide	Thiol	Time [min]	Aryl sulfide	Yield [%][b]	Ref.
1			5		98	7
2			5		94	7
3			5		93	6e
4			6		97	13
5			5		95	6a
6			6		92[c]	14
7			5		87[d]	15
8			6		91[c]	16
9			5		95	17
10			7		72	18
11			6		81	6b
12			7		88	19
13			5		86[c]	6d
14			5		93[c]	8c
15			6		82[c]	20
16			10[e]		63[c]	6c
17			6		61	

---

[a] *General reaction conditions:* aryl iodide (1 mmol) and thiophenol (1.1 mmol) in DMF (0.8 mL) were subjected to microwave irradiation at 120 °C in presence of K_2CO_3 (2 mmol) and nano Cu (20 mol%, optimized to give best yields).

[b] Yields refer to those of purified products characterized by IR, ^1H, and ^{13}C NMR spectroscopic data.

[c] Diaryl/dialkyl disulfides (2–5%) were isolated together with the desired product, the aryl sulfide.

[d] The amino derivative (5%) was produced from reduction of the nitro group.

[e] The reaction was carried out at 90 °C under microwave irradiation.

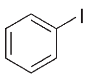
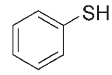
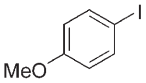
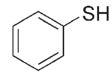
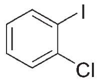
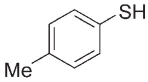
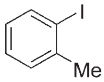
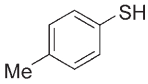
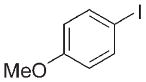
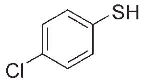
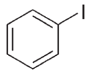
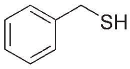
Table 2. Comparison of results of reactions using metallic Cu, CuI, CuI/$(CH_2OH)_2$ with Cu nanoparticles.

Entry	Reaction	Metallic Cu[6e]	CuI[8c]	CuI $(CH_2OH)_2$[6d]	Cu nanoparticles
1	PhI + PhSh	Cu (300 mol %), Autoclave, 240 °C, 6 h, 87%.			Cu (20 mol %), MW, 120 °C, 5 min, 98%.
2	PhI + *p*-ClC_6H_4SH	Cu (300 mol %), Autoclave, 240 °C, 6 h, 86%.			Cu (20 mol %), MW, 120 °C, 5 min, 95%.
3	*p*-$NO_2C_6H_4I$ + PhSH	Cu (300 mol %), Autoclave, 240 °C, 6 h, 43%.			Cu (20 mol %), MW, 120 °C, 5 min, 97%.
4	*m*-$MeOC_6H_4I$ + PhSH		CuI (10 mol %), MW, 195 °C, 2 h, 77%.		Cu (20 mol %), MW, 120 °C, 5 min, 93%.
5	*m*-$MeOC_6H_4I$ + *p*-ClC_6H_4SH			CuI (5 mol %), $(CH_2OH)_2$ (2 equivs.), 80 °C, 18 h, 85%.	Cu (20 mol %), MW, 120 °C, 5 min, 86%.

To provide a mechanistic rationale of this nano Cu-catalyzed coupling of aryl iodides and thiols, a tentative pathway was proposed based on some experimental findings. In a metallic copper-catalyzed coupling reaction of thiophenols with aryl halides Yamamoto[6e] postulated an intermediate of diaryl disulfide which then led to the diaryl sulfide. To check the involvement of this intermediate in our reaction, a coupling reaction of aryl iodide with diphenyl disulfide was carried out under identical reaction conditions. However, no reaction occurred and the starting materials remained unaffected. Thus, the possiblity of this pathway was ruled out. It may be recalled that the progressive decrease in size of metal particles having a diameter in the nano range is accompanied by an increase in Fermi potential. Thus, a stepwise lowering in the radox potential value takes place and this makes it easier for a nano particle to transfer electrons to other species.[10] Hence, the possibility of a single eletron transfer process is considered. It was observed that when the reaction was carried out in the presence of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), a radical quencher, under idential reaction conditions, the reaction was substantially (>60%) arrested. Thus, a radical pathway may be a possibility. Two possible routes were considered (Scheme 2, paths **a** and **b**). In path **a**, Cu initiates the redical chain process by transferring its one electron[11] to ArI to form an Ar radical which then combines with RSH to provide the product ArSR and an H radical which propagates the process (Scheme 2, path **a**). However, we did not isolate any biaryl compound, Ar−Ar or ArH in any amount from this reaction, which is usually expected from this type of free radical reaction. Our attempts to trap this Ar radical by an electron-deficient unit also failed. This led us to explore the possibility of an alternative path **b** where nano Cu transfers its electron to the thiol to produce the RS radical which then, in interaction with ArI, forms the product, ArSR releasing an iodo radical. The iodo radical then

Table 3. Comparison of results of coupling reactions using Cu nanoparticles and metallic Cu powder under microwave irradiation.

$$\mathrm{ArI} + \mathrm{RSH} \xrightarrow[\substack{K_2CO_3\ (2\ \text{equivs.}),\ DMF\\ MW\ (120\ °C)}]{\text{Cu catalyst (20 mol \%)}} \mathrm{ArSR}$$

Entry	Aryl iodide	Thiol	Time [min]	Yield [%] Cu nanoparticles	Yield [%] metallic Cu powder
1			5	98	40
2			5	94	38
3			6	91	35
4			6	92	30
5			5	93	35
6			6	82	25

propagates the process forming a fresh RS radical. If the reaction takes this course CuH should be produced in the intial electron transfer reaction of Cu nanoparticles. The evidence of the formation of CuH is now substantiated by an observation of reduction of the nitro group in the reaction of *p*-nitroiodobenzene with *p*-methylthiophenol (entry 7, Table 1),[12] as mentioned earlier. The formation of CuH in this process is also confirmed by a reaction of thiophenol with *m*-nitrotoluene in place of iodobenzene under identical reaction conditions producing *m*-toluidine and diphenyl disulfide. This route also gains support by isolation of 2–5 % of disulfides, ArS–SAr in several reactions (entries 6, 8, 13–16). The HI produced during the reaction was neutralized by K_2CO_3. The mechanism in path **b** is also supported by the fact that the RS radical is logical to favour the formation of RSAr through S–C bond rather than RSSR by S–S bond formation because of the greater stability of the S–C bond compared to the S–S bond, as indicated by the larger value of relative free energy for S–C bond scission (approx. 108 kcal/mol) in diphenyl sulfide compared to S–S bond scission (47 kcal/mol) in diphenyl disulfide.[21] In view of these findings, path **b** is suggested as the possible pathway.

Conclusions

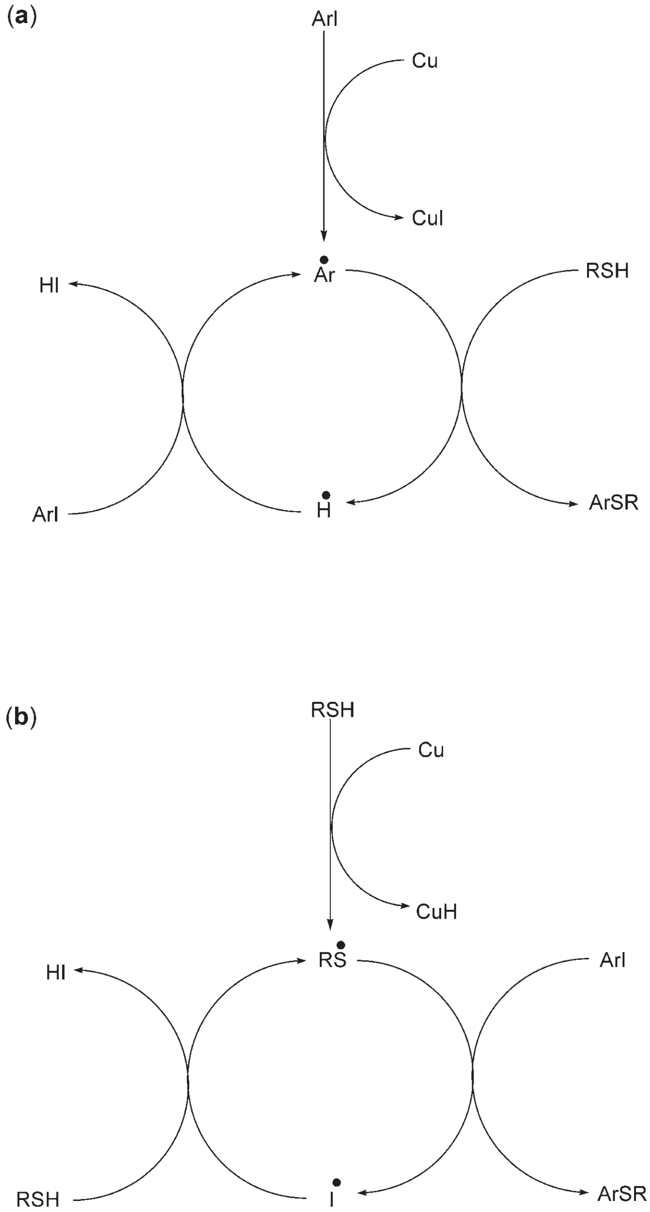
In conclusion, the present procedure using copper nanoparticles provides a very efficient and convenient methodology for the coupling of aryl iodides and thiophenols. To the best of our knowledge this is the first report of aryl-sulfur bond formation using nano Cu. The significant improvements offered by this procedure are operational simplicity, no involvement of ligand, general applicability to both aromatic and aliphatic thiols, fast reaction (5–7 min) and comparatively high isolated yields of products. Moreover, this work demonstrates the potential of Cu nanoparticles in carbon-heteroatom bond formation, which is less explored compared to C–C bond formation involving nano metals.[22]

Experimental Section

IR spectra were taken as thin films for liquid compounds and as KBr pellets for solids on a FT-8300 Shimadzu spectrometer. NMR spectra were recorded on a Bruker DPX 300 instrument at 300 MHz for ^{1}H NMR and at 75 MHz for ^{13}C NMR in $CDCl_3$ solutions. A mono-mode microwave reactor, manufactured by CEM Corporation, USA was used.

Coupling of Iodobenzene with Thiophenol; Typical Procedure (entry 1, Table 1)

To a solution of iodobenzene (204 mg, 1 mmol) and thiophenol (121 mg, 1.1 mmol) in DMF (0.8 mL) was added K_2CO_3 (276 mg, 2 mmol) and copper nanoparticles (13 mg, 20 mol%) and the mixture was subjected to irradiation in a microwave reactor (CEM, Discover, USA) at 120 °C (250 W) for 5 min (as monitored by TLC). The reaction mixture was



Scheme 2.

allowed to cool and diluted with Et_2O (10 mL) and washed with aqueous (10%) NaOH solution (2×2 mL) and brine. The organic phase was dried (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography over silica gel (hexane) to provide pure diphenyl sulfide as a colorless liquid; yield: 182 mg (98%); R_f: 0.85; IR: $\nu = 3059$, 1580, 1475, 1024 cm^{-1}; ^{1}H NMR: $\delta =$ 7.38–7.36 (m, 4H), 7.33–7.21 (m, 6H); ^{13}C NMR: $\delta = 135.88$ (2C), 131.10 (4C), 129.26 (4C), 127.10 (2C). These data are in good agreement with those of an authentic sample.[7]

Most of these products except one (entry 17, Table 1) are known compounds (refs. in Table 1) and were easily characterized by comparison of their spectra with those reported. The unknown compound was also properly characterized by the following data.

2-Dodecylsulfanyl-phenylamine (entry 17, Table 1): Colorless liquid: R_f: 0.65; IR: $\nu = 2926$, 2854, 1606, 1479, 1448 cm^{-1}; ^{1}H NMR: $\delta = 7.39$–7.36 (m, 1H), 7.14–7.09 (m, 1H), 6.80–6.69 (m, 2H), 4.24 (broad, 2H), 2.74 (t, $J =$ 7.32 Hz, 2H), 1.61–1.51 (m, 2H), 1.39–1.25 (m, 18H), 0.88 (t, $J = 6.92$ Hz, 3H); ^{13}C NMR: $\delta = 147.28$, 135.68, 129.49, 119.29, 116.29, 115.54, 35.11, 32.06, 29.85, 29.79, 29.77, 29.73, 29.67, 29.49, 29.33, 28.86, 22.84, 14.27; HR-MS: $m/z =$ 294.2247, calcd. for $C_{18}H_{32}NS$ $(M+1)^+$: 294.2255.

This procedure was followed for all the reactions listed in Table 1. Although the representative procedure is based on mmol scale reactions, it has been scaled up to gram quantities with reproducible results.

Supporting Information

Characterization data including ^{1}H NMR and ^{13}C NMR spectra of all the products listed in Table 1 are available as Supporting Information.

Acknowledgements

We are pleased to acknolwedge the financial support from CSIR, New Delhi [Grant No. 01(1936)/04] for this investigation. A.S. and R.J. are also thankful to CSIR for their fellowships.

References

[1] a) R. K. Dua, E. W. Taylor, R. S. Phillips, *J. Am. Chem. Soc.* **1993**, *115*, 1264–1270; b) D. J. Procter, *J. Chem. Soc., Perkin Trans. 1* **2001**, 335–354; c) D. N. Jones, *Comprehensive Organic Chemistry*, (Eds.: D. H. Barton, D. W. Ollis), Pergamon, New York, **1979**, Vol. 3.

[2] M. Tiecco, *Synthesis* **1988**, 749–759.

[3] N. A. Sasaki, C. Hashimoto, P. Potier, *Tetrahedron Lett.* **1987**, *28*, 6069–6072, and references cited therein.

[4] T. Kondo, T.-Q. Mitsudo, *Chem. Rev.* **2000**, *100*, 3205–3220.

[5] a) M. A. Fernandez-Rodriguez, Q. Shen, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 2180–2181; b) T. Itoh, T. Mase, *Org. Lett.* **2004**, *6*, 4587–4590; c) G. Y. Li, *Angew. Chem. Int. Ed.* **2001**, *40*, 1513–1516; d) U. Schopfer, A. Schlapbach, *Tetrahedron* **2001**, *57*, 3069–3073; e) G. Y. Li, G. Zheng, A. F. Noonan, *J. Org. Chem.* **2001**, *66*, 8677–8681.

[6] a) Y.-J. Chen, H.-H. Chen, *Org. Lett.* **2006**, *8*, 5609–5612; b) W. Deng, Y. Zou, Y.-F. Wang, L. Liu, Q.-X. Guo, *Synlett* **2004**, 1254–1258; c) C. G. Bates, R. K. Gujadhur, D. Venkataramana, *Org. Lett.* **2002**, *4*, 2803–2806; d) F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 3517–3520; e) T. Yamamoto, Y. Sekine, *Can. J. Chem.* **1984**, *62*, 1544–1547; f) G. Braunerova, V. Buchta, L. Silva, J. Kunes, K. Palat, *Farmaco* **2004**, *59*, 443–450; g) C. Palomo, M. Oiarbide, R. Lopez, ; E. Gomez-Bengoa, *Tetrahedron Lett.* **2000**, *41*, 1283–1286.

[7] Y.-C. Wong, T. T. Jayanth, C.-H. Cheng, *Org. Lett.* **2006**, *8*, 5613–5616.

[8] a) P. S. Herradura, K. A. Pendola, R. K. Guy, *Org. Lett.* **2000**, *2*, 2019–2022; b) C. Savartin, J. Srogl, L. S. Liebeskind, *Org. Lett.* **2002**, *4*, 4309–4312; c) Y.-J. Wu, H. He, *Synlett* **2003**, 1789–1790.

[9] The Cu nanoparticles were prepared following a reported procedure: H. Zhu, C. Zhang, Y. Yin, *Nanotechnology* **2005**, *16*, 3079–3083.

[10] N. Pradhan, A. Pal, T. Pal, *Langmuir* **2001**, *17*, 1800–1802.

[11] J. O. Metzger, R. Mahler, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 902–904.

[12] a) W. S. Mahoney, D. M. Brestensky, J. M. Stryker, *J. Am. Chem. Soc.* **1988**, *110*, 291–293; b) J.-X. Chen, J. F. Daeuble, D. M. Brestensky, J. M. Stryker, *Tetrahedron* **2000**, *56*, 2153–2166; c) B. H. Lipshutz, C. C. Caires, P. Kuipers, W. Chrisman, *Org. Lett.* **2003**, *5*, 3085–3088; d) B. H. Lipshutz, K. Noson, W. Chrisman, A. Lower, *J. Am. Chem. Soc.* **2003**, *125*, 8779–8789; e) P. Chiu, S. K. Leung, *Chem. Commun.* **2004**, 2308–2309.

[13] S. Oae, I. Kazuyuki, K. Shinhama, T. Takata, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2374–2378.

[14] N. Taniguchi, T. Onami, *J. Org. Chem.* **2004**, *69*, 915–920.

[15] D. J. Harrison, N. C. Tam, C. M. Vogels, R. F. Langler, R. T. Baker, A. Decken, S. A. Westcott, *Tetrahedron Lett.* **2004**, *45*, 8493–8496.

[16] C. Imboden, P. Renaud, *Tetrahedron: Asymmetry* **1999**, *10*, 1051–1060.

[17] T. Nakazawa, N. Horose, K. Itabashi, *Synthesis* **1989**, 955–957.

[18] G. W. Ivie, D. L. Bull, R. L. Ridlen, *J. Agric. Food Chem.* **1981**, *29*, 1146–1149.

[19] N. Taniguchi, *Synlett* **2006**, 1351–1354.

[20] E. S. Park, S. H. Lee, J. H. Lee, J. Hak, C. M. Yoon, *Synthesis* **2005**, 3499–3501.

[21] M. Nuzzi, S. S. Combust, S. D. Milanese, *Rivista dei Combustibili* **1992**, *46*, 3–10.

[22] a) M. Moreno-Manas, R. Pleixats, *Acc. Chem. Res.* **2003**, *36*, 638–643; b) M. T. Reetz, J. G. de Vries, *Chem. Commun.* **2004**, 1559–1563; c) D. Astruc, F. Lu, J. R. Aranzaes, *Angew. Chem. Int. Ed.* **2005**, *44*, 7852–7872.