http://dx.doi.org/10.5012/bkcs.2011.32.12.4167

Articles

Microwave Assisted, Solvent- and Ligand-Free Copper Catalyzed *N*-Arylation of Phenylurea with Aryl Halides

Sandip Gavade, Murlidhar Shingare,† and Dhananjay Mane*

*Organic Research Laboratory, S.C.S. College, Omerga-413 606, (MS), India. *E-mail: dr_dvmane@rediffmail.com*
†Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431 004 (MS), India
Received August 20, 2011, Accepted October 3, 2011

An inexpensive and efficient catalyst system has been developed for the *N*-arylation of phenylurea including a variety of aryl halides. This simple protocol uses Cu_2O as the catalyst, microwave assisted, solvent- and ligand-free, $K_3PO_4 \cdot H_2O$ as the base.

Key Words : Microwave assisted, Ligand free, Solvent free, Phenylurea

Introduction

N-Aryl- and *N*-heteroaryl-substituted ureas, common pharmacophores in biologically active targets,[1,2] are typically prepared by the coupling of amines with isocyanates, active esters or activated carbamates. Traditional methods for the synthesis of diarylureas include the reaction of aromatic amines with isocyanates, phosgene or carbon monoxide, which are highly toxic reagents.[3,4] Recently, the palladium-catalyzed arylation of amines (Buchwald-Hartwig reaction)[5] became a convenient and efficient method for C-N bond formation. Even more recent expansions in the scope of this method allowed one to perform arylation of amides,[6-9] sulfonamides[7,8] and ureas[10] under rather mild conditions tolerating various functional groups. One of the most powerful ligands used in such palladium-catalyzed reactions is Xantphos.[7–10] However, the utility of this ligand is mainly limited to the amidation of electrondeficient aryl halides. Reactions with unactivated aryl halides usually require higher catalyst loadings and give much lower product yields.[7-10] In many cases, especially when an electron donating group like methoxy is present in the aryl halide, the reaction fails.[7,9] Recently, Nandakumar reported a copper catalyst system for the amidation of aryl halides with urea.[11] This method requires a diamine ligand and K_3PO_4 as a base to afford symmetrical *N,N'*-diarylureas in moderate yields.

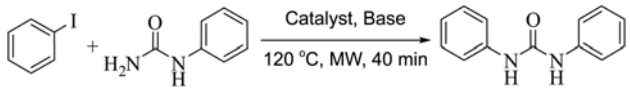
Although a significant number of cross-coupling methodologies have been developed for *N*-arylation,[12] few have been applied to the *N*-arylation of ureas.[13-17]

It has been reported that electron poor aryl bromides are suitable coupling partners for *N*-arylation of ureas.[13] However, unactivated aryl bromides are less reactive.[14] Aryl and heteroaryl chlorides are generally more attractive from a cost and availability perspective compared to their iodo or bromo analogues. However, we have only found literature precedent for urea coupling to 2-chloropyridine[15] and intramolecular coupling with arylchlorides.[16,17] In organic synthesis, increasing attention is being focused on green chemistry[18] using environmentally benign reagents and conditions; specially solvent-free procedures[19] which often lead to clean, ecofriendly, and highly efficient protocols through the simplified workups. The absence of solvent reduces the risk of hazardous explosion when the reaction takes place in a closed vessel. Moreover, aprotic dipolar solvents with high boiling points are expensive and are difficult to remove from the reaction mixtures. Thus, the development and introduction of convenient methods which use green and non hazardous reaction conditions are practically concerned and is still demanded. Herein, we wish to report a microwave assisted, solvent- and ligand-free Cu_2O catalyzed *N*-arylation of phenylurea with aryl halides.

Results and Discussion

Optimization the reaction conditions have in common the use of organic solvents such as DMF, DMSO, nitrobenzene, N-methylpyrrolidone (NMP), dioxane or toluene. These solvents are all volatile and contribute to environmental pollution as volatile organic contaminants (VOCs). Some of the solvents are toxic. It is therefore desirable to see if these reactions can be carried out under solvent-free conditions. Microwave-assisted organic reactions have been applied to a wide range of reaction types, including aromatic nucleophilic substitution, cycloaddition, and organometallic reactions.[20] It accelerates a variety of synthetic transformations *via* time- and energy-saving protocols. We began the preliminary investigation by examining microwave- assisted ligand-free conditions for *N*-arylation of phenylurea with aryl halides.[21] In which we report Cu_2O as a catalyst, *t*-BuOK as a base and NMP as a solvent, but which was applicable for aryl iodide only, Herein we report *N*-arylation of phenylurea with aryl chloride, aryl bromide and aryl

Table 1. Cu/solvent-ligand-free catalyzed *N*-arylation of phenylurea and iodobenzene



Entry	Cu-salt (20 mol %)	Base	Yield (%)[a]
1	CuI	$K_3PO_4·H_2O$	65
2	$CuSO_4$	$K_3PO_4·H_2O$	40
3	CuO	$K_3PO_4·H_2O$	35
4	Cu_2O	$K_3PO_4·H_2O$	90
5	$CuBr_2$	$K_3PO_4·H_2O$	50
6	CuBr	$K_3PO_4·H_2O$	70
7	CuCl	$K_3PO_4·H_2O$	75
8	$Cu(OAc)_2$	$K_3PO_4·H_2O$	45
9	-	$K_3PO_4·H_2O$	0
10	Cu_2O	-	0
11	Cu_2O	$K_3PO_4·H_2O$	70[b]
12	Cu_2O	$K_3PO_4·H_2O$	82[c]
13	Cu_2O	$K_3PO_4·H_2O$	70[d]
14	Cu_2O	$K_3PO_4·H_2O$	55[e]
15	Cu_2O	K_2CO_3	60
16	Cu_2O	*t*-BuOK	40
17	Cu_2O	Cs_2CO_3	70
18	Cu_2O	DBU	30
19	Cu_2O	TEA	25

[a]Isolated yields. [b]temperature was 140 °C. [c]Cu_2O was 10 mol %. [d]$K_3PO_4.H_2O$ was 1.0 mmol. [e]conventional heating at 120 °C.

iodide. When the same reactions were conducted without the solvent NMP, the reactions gave low yields and a very exothermic (Table 1, entry 15). We then used potassium phosphate tribase ($K_3PO_4·H_2O$) instead of potassium tertiary butoxide for the reaction as several reports described the use of K_3PO_4 in C–N coupling reactions.[7] The yields were decreased when 1 equiv of K_3PO_4 was used (Table 1, entries 4 and 13). The reactions were quite convenient as only 20 min of microwave irradiation was required for 1 mmol scale reaction. We report a solvent- and ligand-free copper catalyzed *N*-arylation of phenylurea with aryl halides.

To establish the most efficient solvent- and ligand-free catalyst system under microwave irradiation conditions, various bases and copper sources were screened using the coupling of iodobenzene (**1a**) with phenylurea (**2a**) as a model reaction. The results are summarised in Table 1. All experiments were initially performed with the *N*-arylation of phenylurea (1 mmol) with iodobenzene (1.5 mmol) was investigated with different bases and various Cu salts (20 mol %) at various temperatures for 40 minutes. Other copper sources such as . CuI, $CuSO_4$, CuO, $CuBr_2$, CuBr, CuCl, $Cu(OAc)_2$ catalyzed the coupling reaction, but the yields of product were lower than with Cu_2O (Table 1, entries 1-8). Control experiments confirmed that neither with the base alone (Table 1, entry 9) nor in the presence of copper only (Table 1, entry 10) was the *N*-arylated phenylurea product formed. The yields of product decreased when reducing or elevating reaction temperatures and amount of catalyst Cu_2O

Table 2. The copper-catalyzed *N*-arylation of phenylurea with aryl halide in the presence of $K_3PO_4.H_2O$ for 40 min in MW[a]

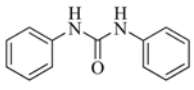
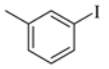
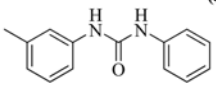
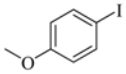
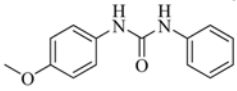
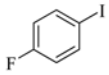
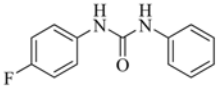
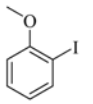
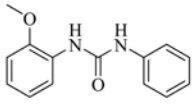
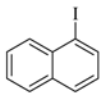
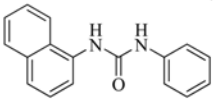
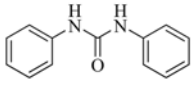
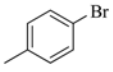
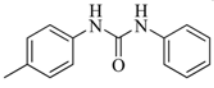
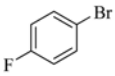
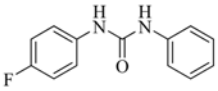
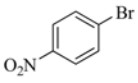
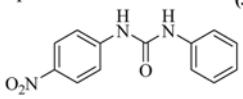
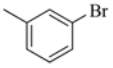
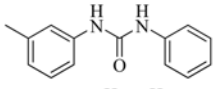
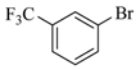
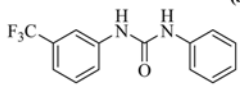
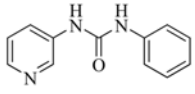
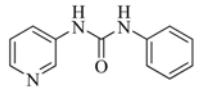
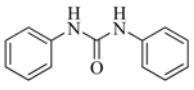
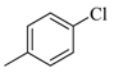
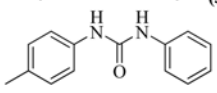
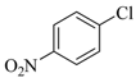
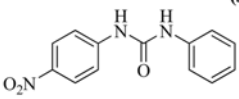
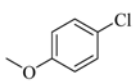
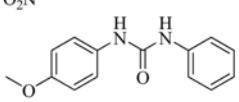
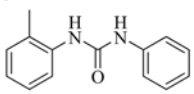
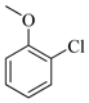
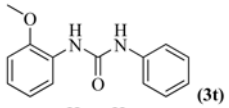
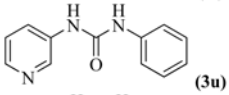
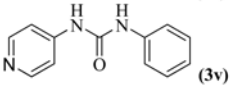
Sr.No.	Aryl halide	Product[a]	Yield (%)[b]
1		 (3a)	90
2		 (3b)	88
3		 (3c)	85
4		 (3d)	93
5		 (3e)	80
6		 (3f)	80
7		 (3g)	68
8		 (3h)	65
9		 (3i)	75
10		 (3j)	80
11		 (3k)	63
12		 (3l)	73
13		 (3m)	70
14		 (3n)	55
15		 (3o)	50
16		 (3p)	55
17		 (3q)	65
18		 (3r)	45
19		 (3s)	40

Table 2. Continued

Sr.No.	Aryl halide	Product[a]	Yield (%)[b]
20		 (3t)	40
21		 (3u)	35
22		 (3v)	56

[a]Reaction condition: phenylurea (1.0 mmol), aryl halide (1.5 mmol), Cu_2O (20 mol %) and base $K_3PO_4{\cdot}H_2O$ (2.0 mmol), 120 °C, MW, x = I. Time 20 min and x = Cl, Br. Time 40 min. [b]Yield of isolated product after flash chromatography

(Table 1, entries 4, 11 and 12). The reaction was carried out by conventional heating but yield was very low as compared to microwave heating (Table 1, entry 14). The reactions using $K_3PO_4.H_2O$ as the base gave the desired product in good yields (compare Table 1, entries 4 and 15-19).

The optimal results were obtained when phenylurea (1.0 mmol), aryl halide (1.5 mmol) and $K_3PO_4{\cdot}H_2O$ (2.0 mmol) as a base were allowed to react with 20 mol % of Cu_2O stirred at 120 °C for 40 min in a microwave. The product was characterized on the basis of its spectral data and by comparison of its melting point with the literature.[21-27]

To probe the effectiveness of this Cu-catalyzed protocol, a variety of ortho, meta, and para-substituted aryl halides were coupled with phenylurea under the optimized conditions. As shown in Table 2, the desired amination products of aryl bromides and iodides were obtained in good to excellent yields (Table 2, entries 1-6 and 7-14), while the coupling reactions for aryl chlorides provided low yields (Table 2, entries 15-22). Aryl iodides showed a higher reactivity than aryl bromides and aryl chlorides in the coupling reactions. Reaction of the bulky aryl halides 1-iodonaphthalene with phenylurea gave *N*-(1-naphthyl)-*N'*-phenylurea in a good yield (Table 1, entry 6). In addition, The substrate possessing electron withdrawing substituent such as CF_3, in the meta position (Table 2, entry 12), fluorine, nitro in the para position (Table 2, entries 9 and 10) were obtained in excellent yields. Aryl halides containing electron-donating groups provided slightly low yields (compare Table 2, entries 1 and 5, 15 and 20). Reaction of heteroaryl halides gave good yield (Table 2, entries 13, 14 and 22).

In summary, copper-catalyzed *N*-arylation of phenylurea with various aryl halides can be performed under microwave-assisted solvent- and ligand-free conditions providing the corresponding coupling products in moderate to high yields. Therefore, high yields, quick reaction times, simple reaction procedure and workup as well as the benefits of solvent-free reaction conditions are the advantages which make this protocol a useful addition to the present methodologies.

Experimental

All reagents and solvents were purchased and used without further purification. ^{1}H ad ^{13}C NMR spectra were recorded in DMSO solution on either 101 MHz or 400 MHz spectrometer. NMR chemical shifts were reported in δ (ppm) using the δ 2.54 signal of DMSO (^{1}H NMR) and the δ 39.94 signal of DMSO (^{13}C NMR) as internal standards. Microwave reactions were performed on a Biotage microwave reactor. Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO_2 (silica gel 60 F254, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, Merck, 100-200 mesh ASTM). Drying of organic extracts after work-up of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a Büchi rotatory evaporator.

General Procedure for *N*-arylation of Aryl Ureas. A Biotage vial of 0.5-2.0 mL was filled with the substituted phenylurea (1.0 mmol), Phenyl Iodide (1.5 mmol), $K_3PO_4{\cdot}H_2O$ (2.0 mmol), Cu_2O (20 mol %). The vial was degassed with N_2, sealed, and irradiated at 120 °C for 40 min. Once cooled, the reaction mixture was quenched with water, extracted with ethyl acetate and dried over anhydrous $MgSO_4$. The solvents were removed under vacuum and the residue was purified by silica gel chromatography. The identity and purity of the known products was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis, and the new products were fully characterized.

Spectral Analysis.

1, 3-Diphenylurea (Carbanilide) (3a): White solid in 90% isolated yield; mp 237.5 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.63 (s, 2H), 7.45 (d, *J* = 8.6, Hz, 4H), 7.27 (t, *J* = 7.9 Hz, 4H), 6.96 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 151.9, 139.1, 128.2, 121.3, 117.7. HRMS (EI, *m/z*) calcd. for $C_{13}H_{12}N_2O$ (M^+) 212.25, found 212.21.

***N*-(4-Fluorophenyl)-*N'*-phenyl-urea (3d):** White solid in 93 % isolated yield; mp 240-242 °C.

^{1}H NMR (300 MHz, DMSO) δ 8.68 (s, 1H), 8.64 (s, 1H), 7.41-7.52 (m, 4H), 7.27 (t, *J* = 7.9 Hz, 2H), 7.06-7.17 (m, 2H), 6.92-7.01 (m, 1H). ^{13}C NMR (300 MHz, DMSO) δ 159.35, 156.2, 153.07, 140.07, 136.45, 136.42, 129.2, 122.28, 120.46, 120.36, 118.69, 115.83, 115.54. HRMS (EI, *m/z*) calcd. for $C_{13}H_{11}FN_2O$ (M^+) 230.24, found 230.22.

***N*-(4-Methylphenyl)-*N'*-phenyl-urea (3h):** White solid in 65% isolated yield; mp 219-220 °C (lit. 222-223 °C); ^{1}H NMR (400 MHz, DMSO) δ 8.58 (s, 1H), 8.52(s, 1H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.25 (t, *J* = 7.9 Hz, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.94 (t, *J* = 7.3 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 151.9, 139.2, 136.5, 130.1, 128.6, 128.2, 121.2, 117.8, 117.6, 20.4. HRMS (EI, *m/z*) calcd. for $C_{14}H_{14}N_2O$ (M^+) 226.28, found 226.30.

***N*-(3-Trifluoromethylphenyl)-*N'*-phenyl-urea (3l):** White solid in 73% isolated yield; mp 203-205 °C; ^{1}H NMR (300 MHz, DMSO): δ 9.02 (s, 1H), 8.77 (s, 1H), 8.00 (s, 1H), 7.40-7.61 (m, 4H), 7.23-7.37 (m, 3H), 6.92-7.07 (m, 1H).

^{13}C NMR (300 MHz, DMSO): δ 152.9, 141.0, 139.7, 130.4, 130.1, 129.2, 122.6, 122.2, 118.9, 118.6, 118.5, 114.5. HRMS (EI, *m/z*) calcd. for $C_{14}H_{11}F_3N_2O$ (M^+) 280.25, found 280.27.

***N*-(3-Pyridinyl)-*N′*-phenyl-urea (3n):** White solid in 55% isolated yield; mp 164-166 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.83 (s, 1H), 8.79 (s, 1H), 8.18 (d, *J* = 3.5 Hz, 1H), 7.93 (ddd, *J* = 1.5, 2.5, 8.3 Hz, 1H), 7.49-7.41 (m, 2H), 7.34-7.24 (m, 3H), 6.98 (t, *J* = 7.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 151.9, 142.2, 139.5, 138.8, 135.9, 128.3, 124.6, 123.1, 121.6, 117.9. HRMS (EI, *m/z*) calcd. for $C_{12}H_{11}N_3O$ (M^+) 213.24, found 213.26.

***N*-(4-Methoxyphenyl)-*N′*-phenyl-urea (3r):** White solid in 45% isolated yield; mp 195-196 °C (lit. 193-194 °C); ^{1}H NMR (400 MHz, DMSO) δ 8.54 (s, 1H), 8.43 (s, 1H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 9.1 Hz, 2H), 7.25 (t, *J* = 7.9 Hz, 2H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.85 (d, *J* = 9.1 Hz, 2H), 3.71 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 153.8, 152.1, 139.3, 132.2, 128.2, 121.1, 119.5, 117.6, 113.5, 55.0). HRMS (EI, *m/z*) calcd. for $C_{14}H_{14}N_2O_2$ (M^+) 243.28, found 243.31.

N-(2-Methylphenyl)-N'-phenyl-urea (3s): White solid in 40% isolated yield; mp 199-200 °C (lit. 201-203); ^{1}H NMR (400 MHz, DMSO) δ 8.99 (s, 1H), 7.90 (s, 1H), 7.83 (dd, *J* = 1.1, 8.1 Hz, 1H), 7.45 (dt, *J* = 1.6, 8.7 Hz, 3H), 7.30-7.24 (m, 3H), 7.18-7.10 (m, *J* = 7.6, 15.5 Hz, 3H), 6.99-6.90 (m, 2H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 152.0, 139.3, 136.8, 129.6, 128.3, 126.9, 125.6, 122.1, 121.2, 120.5, 117.5, 18.0). HRMS (EI, *m/z*) calcd. for $C_{14}H_{14}N_2O$ (M^+) 226.28, found 226.28.

***N*-(4-Pyridinyl)-*N′*-phenyl-urea (3v):** White solid in 56% isolated yield; mp 181-183 °C (lit. 184 °C); ^{1}H NMR (300 MHz, DMSO): δ 9.15 (s, 1H), 8.89 (s, 1H), 8.36 (d, *J* = 5.5, 2H), 7.39-7.48 (m, 4H), 7.27-7.33 (m, 2H), 6.99-7.05 (m, 1H). ^{13}C NMR (300 MHz, DMSO): δ 151.5, 149.5, 145.9, 138.5, 128.3, 121.9, 118.1, 111.8. HRMS (EI, *m/z*) calcd. for $C_{12}H_{11}N_3O$ (M^+) 213.24, found 213.24.

Acknowledgments. Authors are thankful to Head of Department of Chemistry, S.C.S. College, Omerga for providing the necessary laboratory facilities.

References

1. Gallou, I. *Org. Prep. Proced. Int.* **2007**, *4*, 355.
2. For example: (a) Looker, A. R.; Littler, B. J.; Blythe, T. A.; Snoonian, J. R.; Ansell, G. K.; Jones, A. D.; Nyce, P.; Chen, M.; Neubert, B. J. *Org. Process Res. Dev.* **2008**, *12*(4), 666. (b) Dai, Y.; Hartandi, K.; Ji, Z.; Ahmed, A. A.; Albert, D. H.; Bauch, J. L.; Bouska, J. J.; Bousquet, P. F.; Cunha, G. A.; Glaser, K. B.; Harris, C. M.; Hickman, D.; Guo, J.; Li, J.; Marcotte, P. A.; Marsh, K. C.; Moskey, M. D.; Martin, R. L.; Olson, A. M.; Osterling, D. J.; Pease, L. J.; Soni, N. B.; Stewart, K. D.; Stoll, V. S.; Tapang, P.; Reuter, D. R.; Davidsen, S. K.; Michaelides, M. R. *J. Med. Chem.* **2007**, *50*(7), 1584.
3. Vyshnyakova, T. P.; Golubeva, I. A.; Glebova, E. V. *Russ. Chem. Rev. (Engl. Transl.)* **1985**, *54*, 249.
4. (a) Melnikov, N. N.; Novozhilov, K. V.; Belan, S. P. *Pesticides and Plant Growth Regulators; Khimia: Moscow* **1995** (pp 27-486, in Russian); (b) Movsumzadze, E. M.; Valitov, R. B.; Bazunova, G. G.; Aminova, G. K. *Growth Stimulators and a Harvest; Reactiv: Ufa*, **2000** (pp 52-99, in Russian).
5. (a) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley- Interscience: New York, 2002; Vol. 2, pp 1051-1097. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (d) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (e) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144. (f) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.
6. (a) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525. (b) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417. (c) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35. (d) Shakespeare, W. C. *Tetrahedron Lett.* **1999**, *40*, 2035. (e) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575.
7. Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101.
8. Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043.
9. (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539. (b) Browning, R. G.; Mahmud, H.; Badarinarayana, V.; Lovely, C. J. *Tetrahedron Lett.* **2001**, *42*, 7155.
10. Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Zh. Org. Khim. Russian Journal of Organic Chemistry* **2002**, *38*, 563.
11. Nandakumar, M. V. *Tetrahedron Lett.* **2004**, *45*, 1989
12. (a) Hartwig, J. F.; Shekhar, S.; Shen, Q.; Barrios-Landeros, F. In *Chemistry of Anilines*; Rapporport, Z., Ed.; Wiley-Interscience: New York **2007**, *1*, 455. (b) Jiang, L.; Buchwald, S. L. In *Metal-Catalyzed Cross-Coupling Reactions*; 2nd ed.; De Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004.
13. Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Tetrahedron Lett*. **2001**, *42*, 4381.
14. Sergeev, A. G.; Artamkina, G. A.; Beletskaya, I. P. *Tetrahedron Lett.* **2003**, *44*, 4719.
15. Abad, A.; Agullo, C.; Cunat, A. C.; Vilanova, C. *Synthesis* **2005**, *6*, 915.
16. McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3311.
17. Willis, M. C.; Snell, R. H.; Fletcher, A. J.; Woodward, R. L. *Org. Lett*. **2006**, *8*, 5089.
18. (a) Dunn, P. J.; Wells, A. S.; Williams, M. T. *Green Chemistry in the Pharmaceutical Industry*; Wiley-VCH: Weinheim, 2010. (b) Sheldon, R. A.; Arends, I.; Hanefeld, U. *Green Chemistry and Catalysis*; Wiley-VCH: Weinheim, 2007. (c) Doble, M.; Kumar, A. *Green Chemistry and Engineering*; Elsevier: New York, 2007. (d) Doxsee, K.; Hutchison, *J. Green Organic Chemistry: Strategies, Tools, and Laboratory Experiments*; Brooks/Cole: Belmont, CA, 2004.
19. Tanaka, K. *Solvent-free Organic Synthesis*; 2nd ed., Wiley-VCH: Weinheim, 2009.
20. For recent efforts on microwave-assistted reactions, please see: (a) Sun, L. P.; Dai, W. M. *Angew. Chem., Int. Ed*. **2006**, *45*, 7255. (b) Shore, G.; Morin, S.; Organ, M. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2761. (c) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1589. (d) Kappe, C. O. *Angew. Chem., Int. Ed*. **2004**, *43*, 6250. (e) Huang, H.; Liu, H.; Chen, K. X.; Jiang, H. L. *J. Comb. Chem*. **2007**, *9*, 197.
21. Gavade, S. N.; Balaskar, R. S.; Mane, M. S.; Shingare, M. S.; Mane D. V. *Chinese Chemical Letters* **2011**, *22*, 292.
22. Davis, T. L.; Blanchard, K. C. *J. Am. Chem. Soc*. **1929**, *51*, 1790.
23. Skowronska-Serafin, B. and Urbanski, T. *Tetrahedron* **1960**, *10*, 12.
24. Dondori, A.; Barbaro, G.; Battaglia, A. *J. Org. Chem.* **1977**, *42*, 3372.
25. Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrahimi, M. *et al. J. Am. Chem. Soc.* **1990**, *112*, 8415.
26. Briody, T. A.; Hegarty, A. F.; Scott, F. L. *Tetrahedron* **1977**, *33*, 1469.
27. Minatchy, S.; Mathew, N. *Indian J. Chem.* **1998**, *37B*, 1066.