Scope and Utility of $CsOH·H_2O$ in Amination Reactions via Direct Coupling of Aryl Halides and *sec*-Alicyclic Amines[1]

Ravi Varala, E. Ramu, M. Mujahid Alam, Srinivas R. Adapa*

Inorganic Division, Indian Institute of Chemical Technology, Hyderabad-500 007, India
Fax +91(40)7160921; E-mail: asrinivas_rao@iict.ap.nic.in

Received 1 December 2003

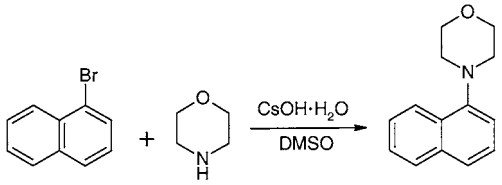
Abstract: Direct coupling of aryl halides with *sec*-alicyclic amines promoted by $CsOH·H_2O$ in DMSO to the corresponding aryl substituted amines, with good to excellent yields, is reported herein. A variety of aryl halides and *sec*-alicyclic amines with a broad range of electronic diversity and functional groups was studied in this transformation, thus offering general applicability in organic synthesis.

Key words: $CsOH·H_2O$, base, aryl halides, *sec*-alicyclic amines, cross coupling

Amination of aryl halides has been an important and frequently required reaction for the synthesis of the interesting compounds containing N-aryl moiety, which have wide occurrence in pharmaceuticals,[2a] agrochemicals,[2b] photography,[2c] xeroxography,[2d] pigments,[2e], and natural products.[2f] Elegant work by Hartwig,[3] Buchwald[4] and others[5] has led to significant improvements in synthetic amination methodology since its original discovery by Migita and co-workers in 1983.[6] A wide range of transition metal complexes has been used as catalysts for these coupling reactions, with attention particularly focused on palladium and copper based complexes. Although these methods are quite reliable, practical success has been relatively limited because they usually require long reaction times or have a relatively narrow substrate application range.[7] Furthermore, use of transition metal complexes leads to the generation of hazardous waste, which has a number of environmental health problems associated with it.[8] Lately, Tu and coworkers[9] have reported transition metal-free cross-coupling reactions between primary and secondary amines and aryl halides using microwave irradiation conditions with potassium *tert*-butoxide as base and DMSO as a solvent. Thus, development of more improved synthetic methods involving transition-metal free synthesis of aryl substituted amines still remain an active research area.

In the last few years, $CsOH·H_2O$-promoted synthetic protocols have been widely applied to the formation of a variety of carbon-hetero atom and carbon-carbon bond forming reactions.[10] Recently, Jung and co-workers reported an elegant synthetic methodology for direct amination reactions promoted by $CsOH·H_2O$.[10j] However, this report is limited to alkylation of primary alkyl halides and primary alkyl amines to form corresponding *sec*-amines in moderate to good yields. Herein, we report our study on $CsOH·H_2O$-promoted direct cross-coupling reactions of aryl halides and *sec*-alicyclic amines to form corresponding *tert*-aryl amines. We have chosen a variety of structurally divergent aryl halides and *sec*-alicyclic amines having a wide range of functional groups in order to better understand both the scope and the general applicability of the $CsOH·H_2O$-promoted reaction.

First, we evaluated the feasibility of direct cross-coupling of 1-bromonaphthalene (1.0 mmol) and morpholine (1.2 mmol) in DMSO using 2 mmol of $CsOH·H_2O$ in a sealed tube (Scheme 1).[11] At ambient temperatures, no reaction between the coupling partners was observed, but heating the reaction mixture to 120 °C for 5 minutes afforded *N*-naphthyl morpholine in 90% yield (entry 1, Table 1).



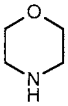
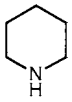
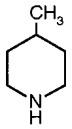
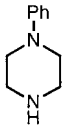
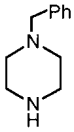
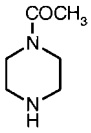
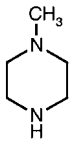
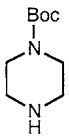
Scheme 1

As a control experiment, the same reaction was carried out in the absence of $CsOH·H_2O$ at 120 °C, when no cross-coupled product was observed even after heating for a longer period of time. The optimum yield of the product is obtained when a ratio of aryl halide to amine of 1:1.2 is used. Of the solvents tested for this reaction (DMSO–THF, H_2O–TBAB, NMP, and DMSO), DMSO was found to be the most efficient. In the absence of DMSO, no product could be isolated from the crude reaction mixture; thus solvent plays a vital role in this reaction.

With optimized experimental conditions for morpholine in hand, we then investigated direct cross-coupling reactions using a variety of electronically divergent *sec*-alicyclic amines and 1-bromonaphthalene. The amines used for the study include piperidine, 4-methylpiperidine, pyrrolidine, and N-substituted piperazines. We have deliberately chosen N-substituted piperazines for the study to evaluate both the functional group tolerance and to evaluate general applicability of $CsOH·H_2O$-promoted direct amination reaction. The results from this study are shown in Table 1. All *sec*-alicyclic amine substrates underwent direct cross-coupling reactions to afford the corresponding products in

SYNLETT 2004, No. 10, pp 1747–1750
Advanced online publication: 28.07.2004
DOI: 10.1055/s-2004-830853; Art ID: D30903ST

Table 1 $CsOH·H_2O$-Promoted Cross-Coupling of 1-Bromonaphthalene and Various *sec*-Aliphatic Amines

Entry	Amine	Time (min)	Yield (%)[a]
1		5	90
2		10	85
3		20	58
4		15	66
5		10	75
6		15	62
7		15	69
8[12]		10	78
9		10	74

[a] Isolated yields.

moderate to good yields, and the reaction times are also very short (5–20 min) for all examples. In contrast, reported procedures involving transition-metal complexes require several hours for direct amination reactions.[3–5] Among various amines tested, morpholine (entry 1, Table 1), and piperidine (entry 2, Table 1) gave very good yields but 4-methyl piperidine and pyrrolidine gave the corresponding coupled products in only moderate yields (entry 3 and 4, Table 1). The order of reactivity for these amines in terms of yield and reaction time can be generalized as morpholine>piperidine>pyrrolidine>4-methyl piperidine under our reaction conditions. For N-substituted piperazines, all substrates gave the corresponding adducts in good yields (entries 5–8, Table 1). Interestingly, even under strongly alkaline reaction conditions, piperazines containing functional groups such as *N*-Boc and *N*-acetyl remained inert, as no hydrolysis to corresponding amines (entry 9, Table 1) and no side products were observed (entry 7, Table 1) during the reaction. These results strongly demonstrate good functional group tolerance for $CsOH·H_2O$-promoted direct amination of substituted piperazines.

We have further studied the reaction using a variety of functionalized aryl halides. The results from this study are shown in Table 2. Aryl halides having a variety of functional groups undergo smooth reaction providing moderate to excellent yields of the corresponding adducts (entries 1–18, Table 2). However, aryl halides that contain *p*-hydroxy, *p*-formyl and *p*-methoxy substituents do not undergo adduct formation at all under our experimental conditions (entries 8–10, Table 2). The reaction of 1-bromo-4-nitrobenzene and 1-bromo-4-cyanobenzene with morpholine and piperidine required no heating at all, as the reaction took place at room temperature in excellent yields, respectively (entries 2 and 3, Table 2). Similarly, their corresponding iodo analogues underwent smooth reaction with morpholine and piperidine at room temperature affording excellent yields (entries 12 and 16, Table 2).

Table 2 $CsOH·H_2O$-Promoted Cross-Coupling of Aryl Halides and Amines

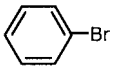
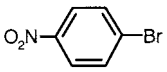
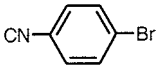
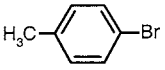
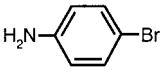
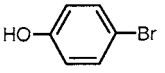
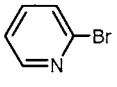
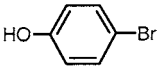
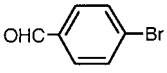
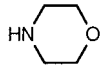
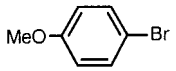
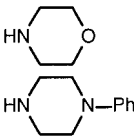
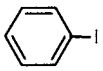
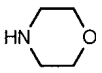
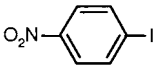
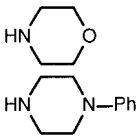
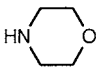
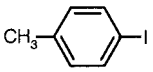
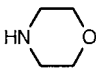
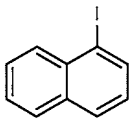
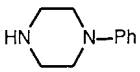
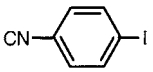
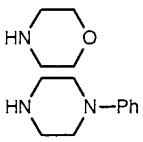
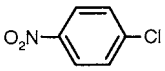
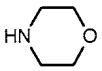
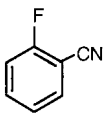
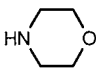
Entry	Ar-X	Amine	Time (min)	Yield (%)
1			10	
2[b]		 	180 210	90 85
3[b]		 	240 270	87 82
4			10	60
5			10	52
6			15	82
7			15	55
8			20	0
9			20	0

Table 2 $CsOH{\cdot}H_2O$-Promoted Cross-Coupling of Aryl Halides and Amines (continued)

Entry	Ar-X	Amine	Time (min)	Yield (%)
10			20	0
11			10	95
12[b]			150 180	94 87
13			15	55
14			10	62
15			5	82
16[b]			180 210	90 85
17			10	72
18			15	75

[a] Isolated yields.
[b] Room temperature.

Reaction times for the iodo analogues are shorter than those required for the corresponding bromo analogues. Chlorobenzene and fluorobenzene did not react at all under our experimental conditions. However, when 4-nitrochlorobenzene and 2-cyanofluorobenzene were subjected to reaction with morpholine (entries 17 and 18, Table 2), we obtained the corresponding adducts in good yields in about 10–15 minutes. These results clearly demonstrate that highly electron-withdrawing substituents on the aryl moiety of the coupling fragment strongly facilitate coupling. Furthermore, it can be generalized that electron rich aryl halides gave poor yields or no product under our experimental conditions with the exception that *p*-aminobromobenzene upon coupling with morpholine gave the corresponding meta-amination product in poor yield (entry 5, Table 2). We have not observed products that are derived from direct coupling between two *p*-aminobromobenzene fragments. Likewise, in case of entry 14, Table 2 the addition product corresponds to a mixture of the *meta*/*para* substitution (1:1). The use of a heterocyclic aryl bromide (2-bromopyridine) also gave the corresponding adduct in moderate yield (entry 7, Table 2). It is worthy of note that our studies also demonstrate good functional group tolerance for $CsOH{\cdot}H_2O$-promoted amination reaction for aryl halides containing sensitive functional groups. For example, even under strong alkaline conditions, aryl halides containing *p*-cyano groups did not undergo hydrolysis. Similarly, aryl halides containing the potentially polymerizable vinyl group (entry 6 and 13, Table 2) also underwent smooth reaction and gave the corresponding amines in good isolated yields, no base induced polymerization being observed.

It has earlier been proposed that direct amination reactions promoted by strong bases such as potassium *tert*-butoxide proceed through a mechanism involving a benzyne intermediate. In fact, direct evidence for a benzyne intermediate in direct amination reactions has been demonstrated by experiments involving successful trapping through [2+4] cycloaddition reactions.[9,12] It is highly likely that a similar benzyne intermediate mediated mechanism is applicable to $CsOH{\cdot}H_2O$-promoted reactions as well.

In conclusion, we have shown a rapid and efficient direct cross coupling of variety of aryl halides and *sec*-alicyclic amines having structurally divergent functional groups and can be carried out using $CsOH{\cdot}H_2O$. Our studies also highlight tolerance for sensitive functional groups present on both the coupling fragments. The wide nature of coupling fragments studied in work offers not only the wide-scope but also general applicability of $CsOH{\cdot}H_2O$ in routine synthetic protocols. Efforts to expand the scope of the method are currently underway in our laboratory.

Acknowledgment

V. R and M. M. Alam are thankful to Dr. B. M. Choudary for constant encouragement and Dr. H. Maheswaran for discussions. V. R. and M. M. Alam also thank Council of Scientific Industrial Research for financial support.

References

(1) IICT Communication No. 031213.
(2) (a) Negwer, M. *Organic-Chemical Drugs and their Synonyms (An International Survey)*, 7th ed; Akademie Verlag GmbH: Berlin, **1994**. (b) Montgomery, J. H. *Agrochemicals Desk Reference: Environmental Data*; Lewis Publishers: Chelsea, MI, **1993**. (c) Loutfy R. O., Hsiao C. K., Kazmaier P. M.; *Photogr. Sci. Eng.*; **1983**, *27*: 5. (d) Schein, L. B. *Electrophotography and Development Physics*, 2nd ed.; Springer-Verlag: Berlin, **1992**. (e) *Pigment Handbook*; Lewis, P. A., Ed.; John Wiley & Sons: New York, **1988**, Vol. 1. (f) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1988**, *120*, 6417.
(3) (a) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (c) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423.

(4) (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348. (b) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (c) Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560. (d) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1999**, *38*, 2413. (e) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (f) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054.

(5) (a) Huang, J.; Grasa, G. A.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307. (b) Herrmann, W. A.; Kocher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2163. (c) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729. (d) Bei, X.; Uno, T.; Norris, J.; Turner, H. W.; Weinberg, W. H.; Guram, A. S. *Organometallics* **1999**, *18*, 1840. (e) Artamkina, G. A.; Ivushkin, V. A.; Beletskaya, P. *Russ. J. Org. Chem.* **1970**, *35*, 1797. (f) Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* **2000**, *65*, 169. (g) Li, R.; He, M. Y.; deShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600. (h) Okano, T.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 4987.

(6) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.

(7) For palladium-catalyzed N-arylation of amines, see: (a) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Yang, B. Y.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.

(8) Leadbeater, N. E.; Marco, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 1407.

(9) Shi, L.; Wang, M.; Zhang, F. M.; Tu, Y. Q. *Org. Lett.* **2003**, *19*, 3515.

(10) For $CsOH·H_2O$-catalyzed reactions, see: (a) Salvatore, R. N.; Schmidt, S. E.; Jung, K. W. *Org. Lett.* **1999**, *1*, 1893. (b) Tzalis, D.; Knochel, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 1463. (c) Koradin, C.; Rodriguez, A.; Knochel, P. *Synlett* **2000**, *10*, 1452. (d) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193. (e) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347. (f) Corey, E. J.; Bo, Y.; Petersen, J. B. *J. Am. Chem. Soc.* **1998**, *120*, 13000. (g) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (h) Busch-Peterson, J.; Bo, Y.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 2065. (i) Segura, J. L.; Martin, N. *Angew. Chem.* **2001**, *113*, 1416. (j) Salvatore, R. N.; Nagle, A. S.; Jung, K. W. *J. Org. Chem.* **2002**, *67*, 674.

(11) **General Procedure for the $CsOH·H_2O$-Promoted Amination of Aromatic Halides:**
A mixture of aryl halide (1 mmol), the amine (1.2 mmol) and CsOH·H2O (2 mmol) in DMSO (3 mL) were taken in a sealed tube placed in preheated oil bath at 120 °C and then held at that temperature for 5–20 min. Then the reaction mixture was cooled to r.t., poured into water containing crushed ice, and stirred for 5 min. Sat. aq NH_4Cl solution was added to this mixture, and the organic portion was extracted with Et_2O (3×20 mL). The combined organic extracts were washed with a sat. NH_4Cl solution and brine, and dried over anhyd Na_2SO_4. After removal of the solvent the residue was purified by column chromatography on silica gel to furnish the product. All isolated compounds were fully characterized by comparing their spectroscopic data with authentic compounds.
Spectral data for selected compounds:
1-Methyl-4-(1-naphthyl) Piperazine (entry 8, Table 1): see ref. 13.
***N*-(4-Nitrophenyl) Piperidine** (entry 2, Table 2): Yellow solid; mp 95 °C (lit. mp 104 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, 2 H, J = 9.3 Hz), 6.79 (d, 2 H, J = 9.9 Hz), 3.50 (m, 4 H), 1.75–1.65 (m, 6 H). MS (EI): m/z = 208.
N-(4-Methyl Phenyl) Morpholine (entry 4, Table 2): see ref. 14.

(12) Chapman, O. L.; Mattes, K.; McIntosh, C. L.; Pacansky, J.; Calder, G. V.; Orr, G. *J. Am. Chem. Soc.* **1973**, *95*, 6134.

(13) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829.

(14) Wolf, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.