Mini-Reviews in Organic Chemistry, 2009, *6*, 367-377

Advances on *N*-Arylation of Indoles by Cross-Coupling Reactions

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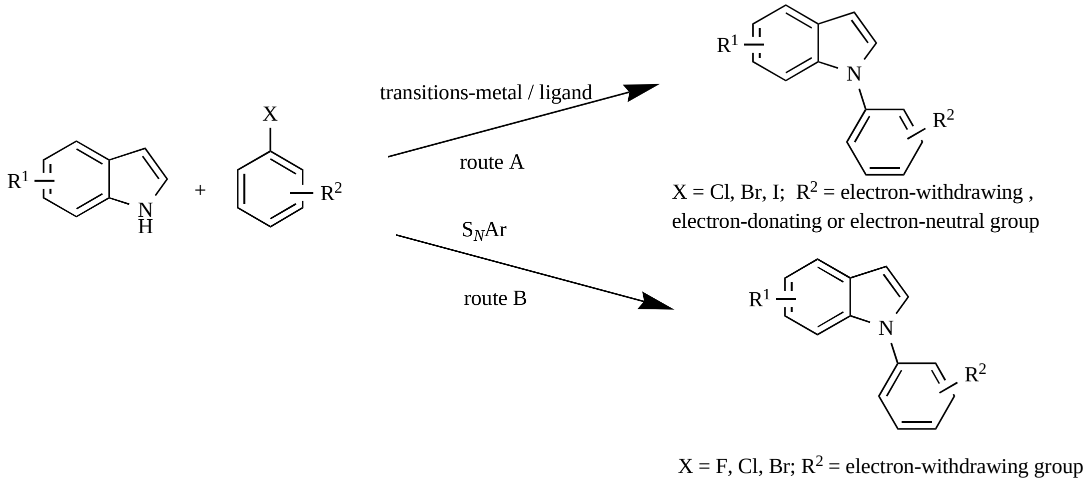
Abstract: *N*-Arylindoles are known to be important subunits due to their key role in medically biological activities. This mini-review initially covers the important advances on the *N*-arylation of indoles with aryl halides by palladium, copper or other transition metals-catalyzed cross-coupling reactions in recent ten years. Subsequently, the synthesis of *N*-arylindoles from indoles with aryl halides, activated by electron-withdrawing substituents, by aromatic nucleophilic substitution reactions (S_NAr) is also surveyed.

Keywords: *N*-Arylindole, indole, cross-coupling, transition metal-catalyst, aromatic nucleophilic substitution reaction.

1. INTRODUCTION

N-Arylindoles are known to be important subunits in a multitude of synthetically and medicinally relevant compounds due to their key role in interestingly biological activities, such as anti-estrogen [1], analgesic [2], antiallergy [3], cyclooxygenase (COX)-1 inhibitors [4], neuroleptic [5], 5-HT_6 receptor antagonists [6], FTase inhibitors (FTIs) [7], and anti HIV-1 activities [8]. Usually the Ullmann-type coupling of indoles with aryl halides represents a straightforward and inexpensive approach to *N*-arylindoles. However, this classical copper-catalyzed Ullmann-type coupling reaction traditionally has some drawbacks, *i.e.*, high reaction temperatures (generally 140 ^{o}C or more), highly polar aprotic solvents, strong bases, requirement of large amounts of aryl halides and stoichiometric amounts of copper reagents, and low yields [9]. Therefore, the development of a mild and efficient method for constructing *N*-arylindole motifs from indoles is highly desirable.

As depicted in Scheme **1**, the transition metals-catalyzed C-N bond formation *via* cross-coupling reactions of indoles with aryl halides has played an important role and has been widely recognized as a useful method in the preparation of *N*-arylindoles (route A) [10]. An excellent mini-review on palladium-catalyzed cross-coupling reactions was reported in 2002 [11].



Scheme 1.

Additionally, in some instances, an alternative approach for the formation of C-N bond is the aromatic nucleophilic substitution reactions (S_NAr) of indoles with aryl halides, activated by electron-withdrawing substituents (route B) [12].

As a consequence, this mini-review will initially focus on the important advances on the *N*-arylation of indoles with aryl halides by palladium, copper or other transition metals-catalyzed cross-coupling reactions in recent ten years (route A). Subsequently, the synthesis of *N*-arylindoles from indoles with aryl halides, activated by electron-withdrawing substituents, by aromatic nucleophilic substitution reactions (S_NAr) is also investigated (route B). In each subsection, the advances are presented in chronological order to demonstrate sequential progress in this area.

2. *N*-ARYLATION OF INDOLES WITH ARYL HALIDES BY TRANSITION METALS-CATALYZED CROSS-COUPLING REACTIONS

2.1. *N*-Arylation of Indoles with Aryl Halides by Palladium-Catalyzed Cross-Coupling Reactions

An efficient *N*-arylation of indole with aryl halides in the presence of Cs_2CO_3 or NaO-*t*-Bu using DPPF (diphenylphosphinoferrocene)-ligated palladium was reported. *N*-Arylindoles were obtained in 72-98% yields (Scheme **2**). But complete reaction of indole with electron-rich or electron-neutral aryl halides was required the higher temperatures and longer reaction time [13].

By choosing an appropriate ligand in combination with $Pd_2(dba)_3$, a wide range of indoles were effectively coupled with a variety of aryl chlorides, bromides, iodides, and triflates to afford the desired coupling products in good yields (Scheme **3**) [14].

As shown in Scheme **4**, by using $Pd(OAc)_2$ with supporting ligand 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene (SIPr)·HCl system, less reactive indoles were efficiently coupled with aryl bromides to produce *N*-arylindoles. The more donating saturated carbene SIPr in combination with an inexpensive

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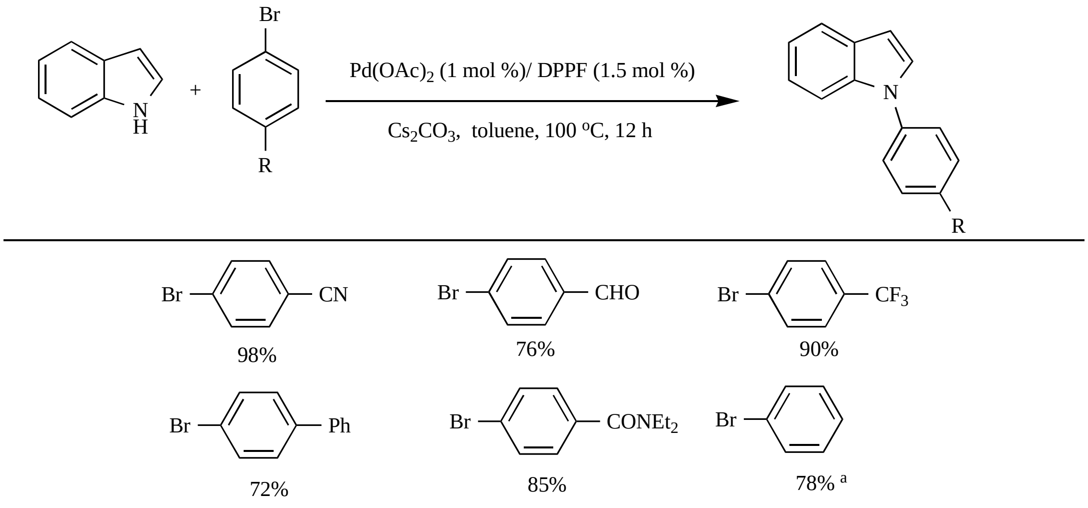
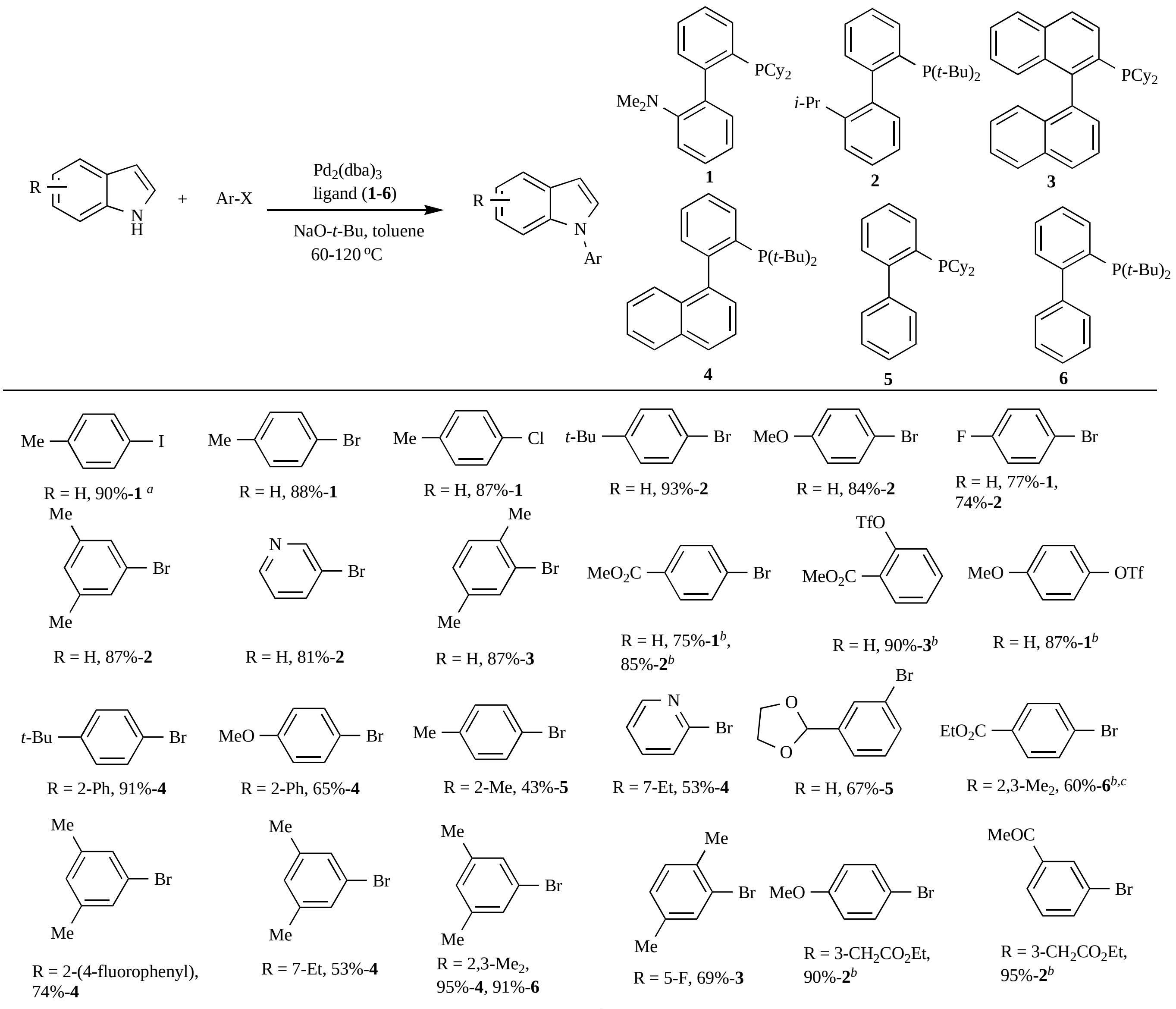


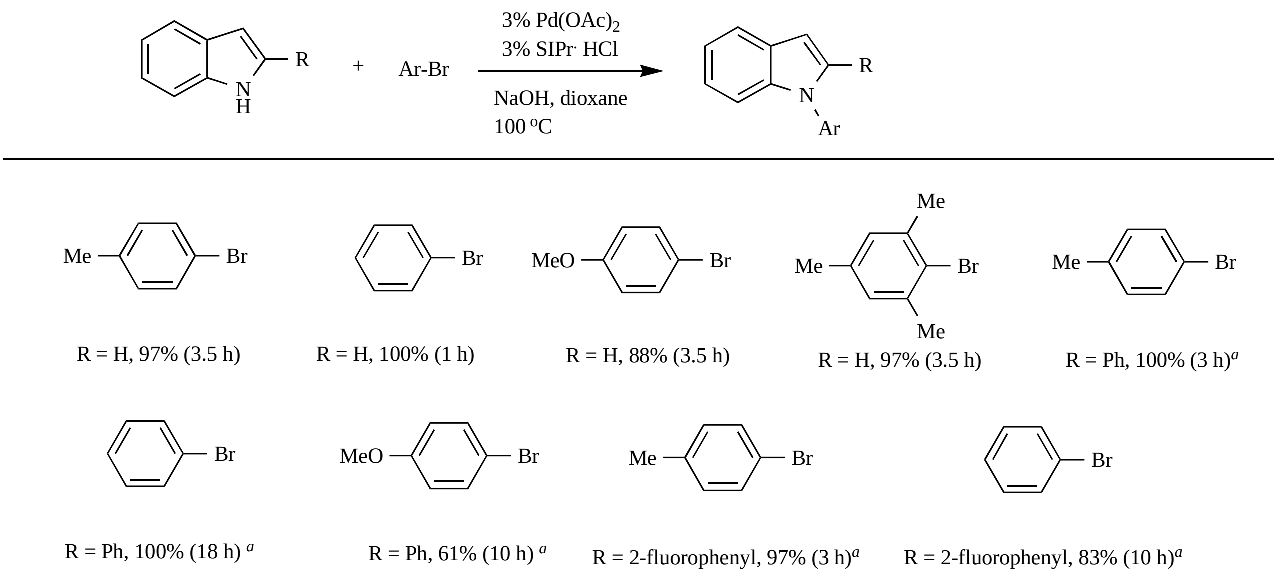
[a]NaO-*t*-Bu as the base, $Pd(OAc)_2$ (5 mol %) / DPPF (6 mol %), 120 ºC, 48 h

Scheme 2.



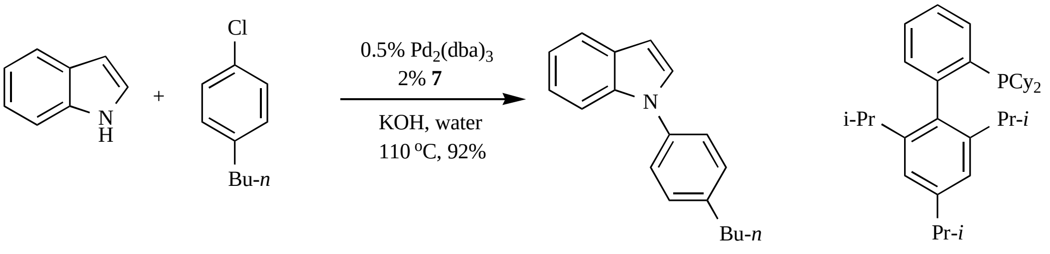
[a] Ligand used as indicated by bold number; [b] K_3PO_4 used as the base, [c] Dioxane used as the solvent.

Scheme 3.



[a] Toluene used as a solvent

Scheme 4.



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Scheme 5.

strong base (NaOH) mediated this process. This catalytic system was found to be effective for a variety of aryl bromides and indole derivatives [15].

Interestingly, *N*-(4-*n*-butylphenyl)indole could be obtained in a 92% yield by the use of $Pd_2(dba)_3$/**7**/KOH/water system (Scheme **5**) [16].

2.2. *N*-Arylation of Indoles with Aryl Halides by Copper-Catalyzed Cross-Coupling Reactions

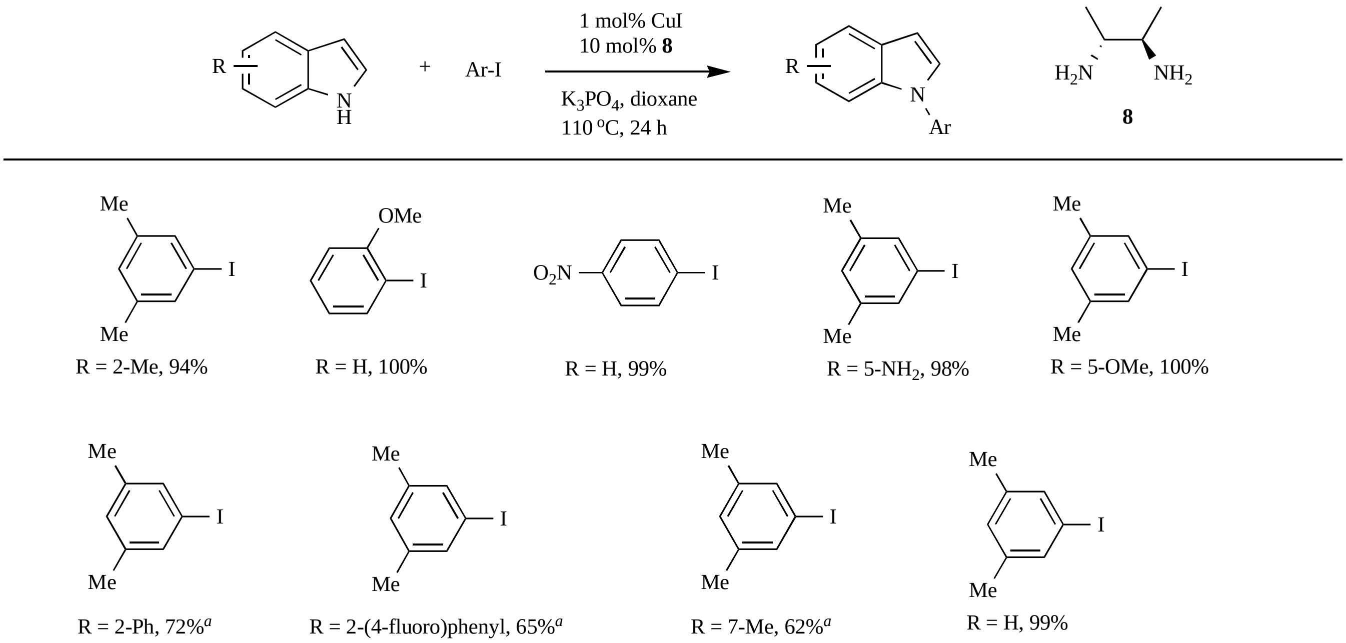
Despite the significant improvements in palladium-catalyzed processes for the formation of C-N bonds of *N*-arylindoles, several important functional groups were incompatible with the above reaction protocols. Furthermore, because of the relatively high cost of palladium, the development of efficient, mild and inexpensive catalysts for the synthesis of *N*-arylindoles is very necessary. Generally, the use of copper-mediated cross-coupling reactions is beneficial for the construction of *N*-arylindoles.

As shown in Scheme **6**, the indoles, including 2-aryl (72% and 65%) and 7-alkyl (62%), could be efficiently coupled with a variety of aryl iodides in the presence of 1 mol % of CuI and 10 mol % of inexpensive racemic *trans*-1,2-cyclohexanediamine (**8**). Noteworthy was that competitive *C*-arylation of indoles was not observed [17].

With the CuI and *trans-N,N'*-dimethyl-1,2-cyclohexanediamine (**9**) or *N,N'*-dimethyl-ethylenediamine (**10**) catalytic system, *N*-arylindoles were obtained in good to excellent yields by coupling a variety of indoles with aryl iodides or aryl bromides (Scheme **7**). The reaction of hindered 2-*i*-Pr-indole with iodobenzene effectively proceeded and *N*-phenyl-2-*i*-Pr-indole was obtained in a 70% yield. The mild and remarkably chemoselective nature was highlighted in this method. For example, when the iodobenzene was coupled with tryptamine, melatonin, tryptophol, or 5-methoxytryptamine under the above conditions, excellent selectivity was given on the arylation of the indole's nitrogen. The *N*-arylation of methyl indole-3-carboxylate or 2,3-dimethylindole with iodobenzene proceeded smoothly, and the corresponding yields were 96 and 98%, respectively. Moreover, the *N*-arylation of 5-cyanoindole could be realized using commercially available **10** as an alternative ligand to **9** [18].

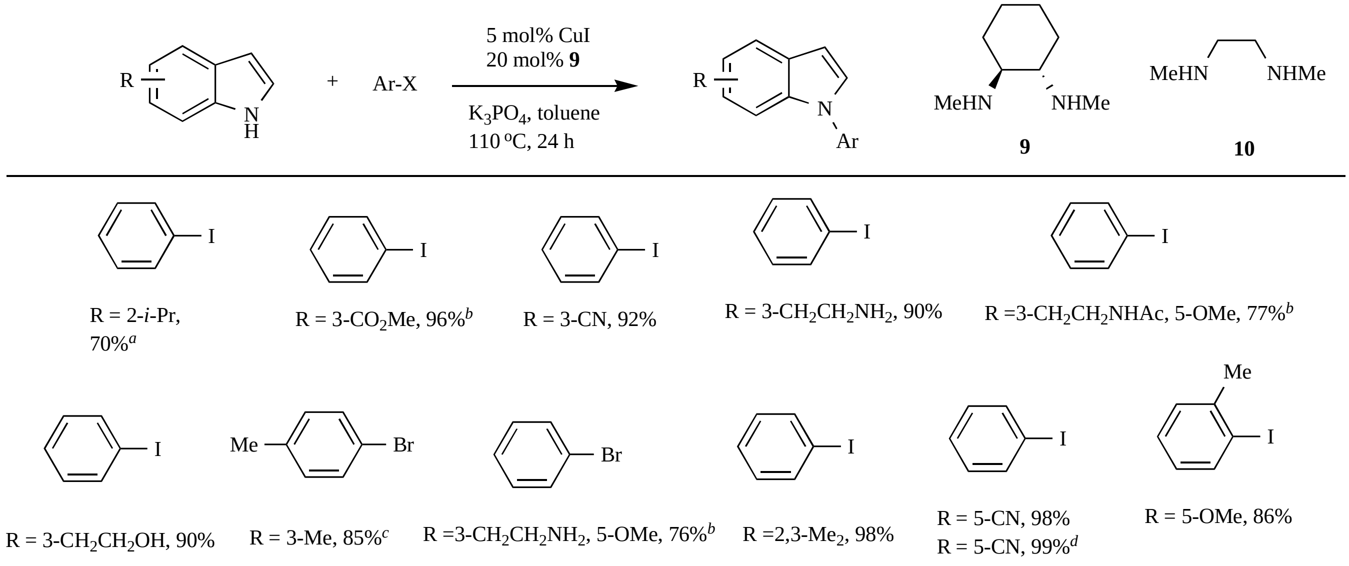
By using the CuI/L-proline catalytic system, the coupling reaction of aryl iodides or aryl bromides with indoles could be carried out at 75-90 °C (Scheme **8**). For example, the coupling reaction of indole with iodobenzene proceeded at 90 °C for 40 h to give *N*-phenylindole in a 85% yield. For electron-deficient aryl iodides, reaction temperature could be lowered to 75-80 °C. Sterically hindered aryl iodides were compatible with these conditions, for example, *N*-(2-methoxyphenyl)indole was obtained in a 79% yield by coupling 2-methoxyphenyl iodide with indole. However, when bromobenzene was coupled with indole, low conversion was observed (33%) [19].

As shown in Scheme **9**, the 5-bromo-*m*-xylene could be coupled with a variety of indoles using the new $(Cu(I)OTf)_2 \cdot PhH$/1,10-phenanthroline (**11**) or 4,7-dichloro-1,10-phenanthroline (**12**) catalytic system. Obviously, the $(Cu(I)OTf)_2 \cdot PhH$/**12** system gave superior conversions compared to the $(Cu(I)OTf)_2 \cdot PhH$/**11** system. The heteroaryl bromides like pyridines and pyrimidines were also con-



[a] Reaction time of 48 h and 2 M in dioxane

Scheme 6.



[a] With 10 mol% CuI and 20 mol% **9**; [b] With 10 mol% **9**; [c] With 1 mol% CuI and 5 mol% **9**; [d] With 20 mol% **10**

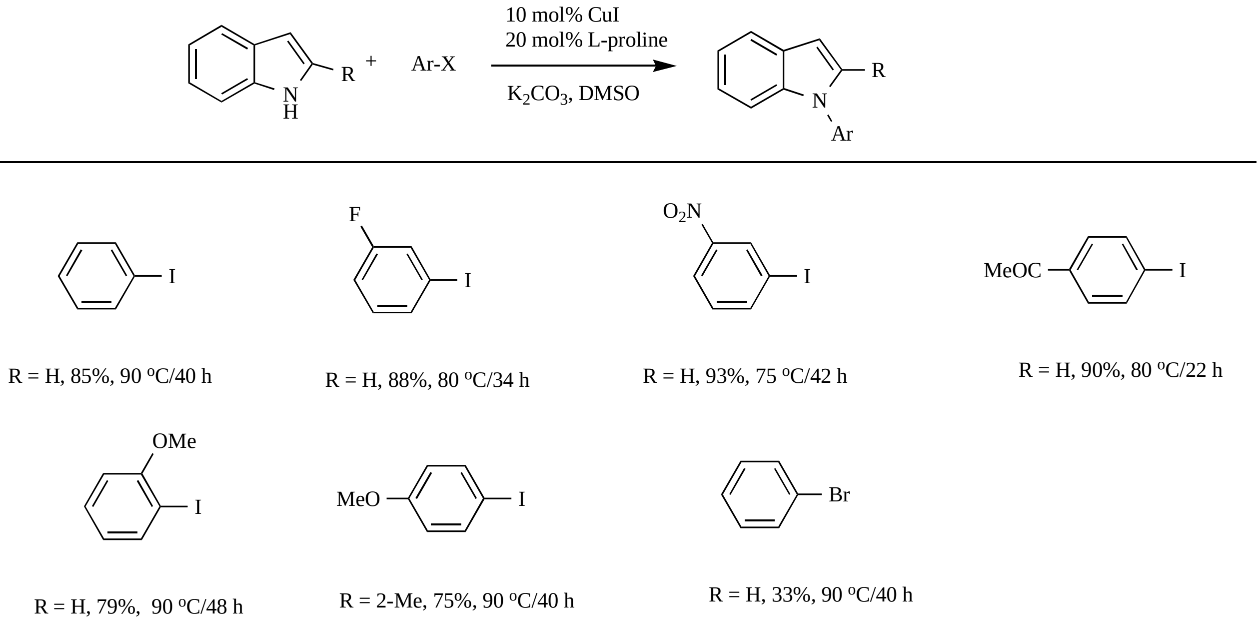
Scheme 7.

verted quantitatively into C–N coupled products. Moreover, the reaction proceeded without the formation of side-products [20].

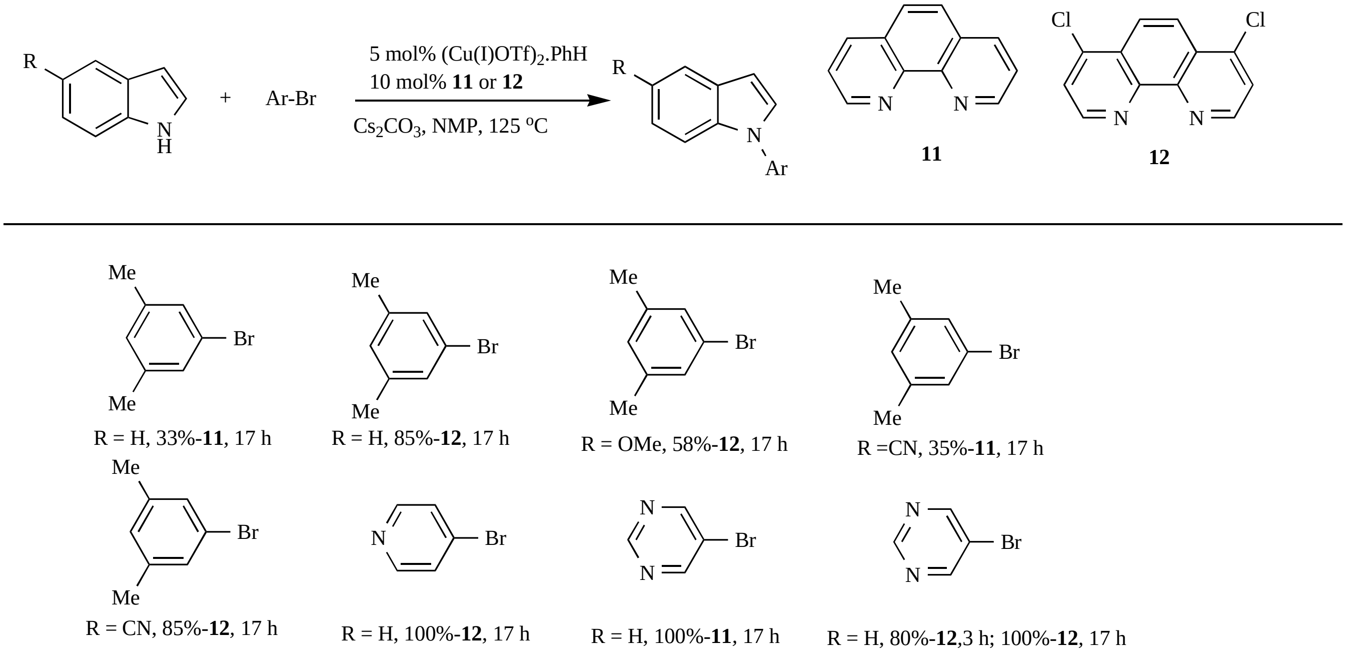
By using K_3PO_4 instead of K_2CO_3 in CuI/L-proline system, the *N*-arylation of indole with aryl iodides or aryl bromides proceeded efficiently in dioxane or DMF (Scheme **10**) [21].

As shown in Scheme **11**, CuOAc-mediated *N*-arylation of indoles with aryl iodides was with excellent *N*-selectivity under base-free and ligandless conditions, and the corresponding *N*-arylindoles were obtained in moderate to good yields. The presence of electron-withdrawing or electron-donating groups at the 4-position of the aryl iodides had no impact on the efficiencies of the *N*-arylation reactions with indoles. Moreover, a phenolic hydroxy group at the 4-position of iodobenzene was well tolerated under the above reaction conditions, and the required *N*-(4-hydroxyphenyl)indole was obtained in a 49% yield [22].

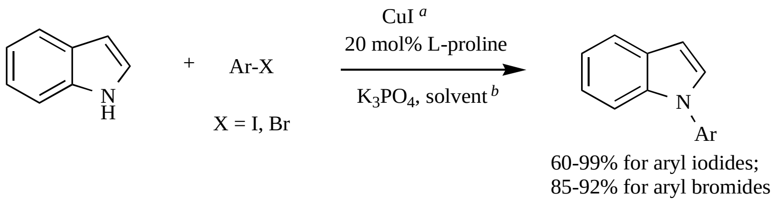
Electron-deficient indoles, having no carbonyl group α to the nitrogen ring, were efficiently *N*-arylated with arylboronic acids in the presence of $Cu(OAc)_2$ (Scheme **12**). The use of DIEA (diisopropylethylamine) as a base for the preparation of *N*-phenyl-3-



Scheme 8.



Scheme 9.



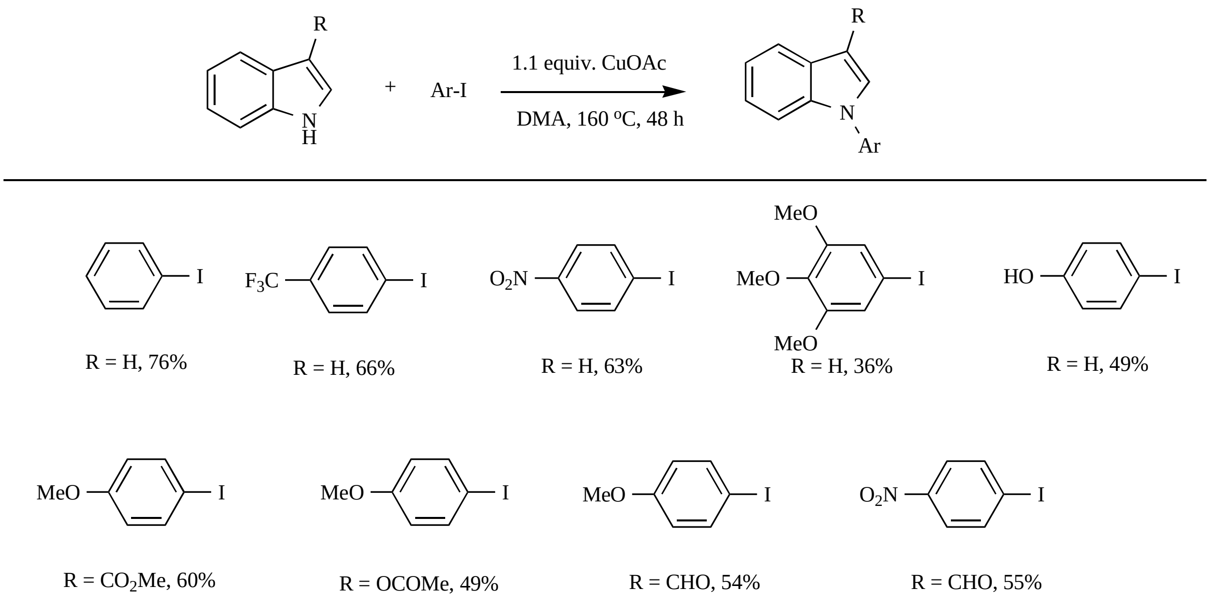
[a] 5 mol% CuI for aryl iodides; 20 mol% CuI for aryl bromides.

[b] Dioxane for aryl iodides; DMF for aryl bromides

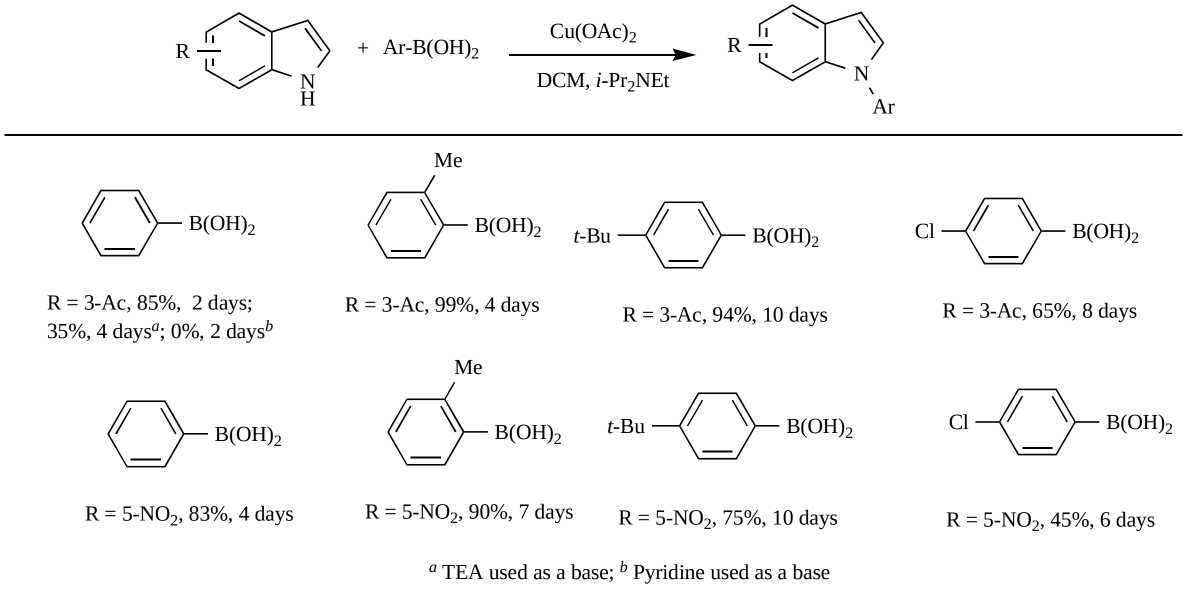
Scheme 10.

acetylindole gave the superior yield (85%) compared to Et_3N (35%) and pyridine (0%). As compared with 5-nitroindole, 3-acetylindole afforded higher product yields when reacted with arylboronic acids [23].

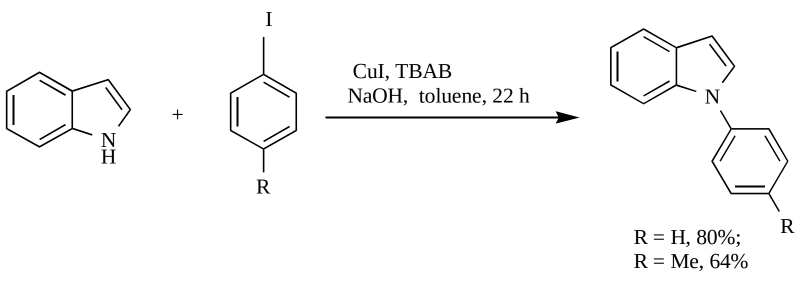
Under ligandless and additive-free conditions, indole was efficiently coupled with iodobenzene or 4-iodotoluene under the 5 mol% CuI/5 mol% *n*-Bu_4NBr (TBAB)/NaOH catalytic system, and



Scheme 11.



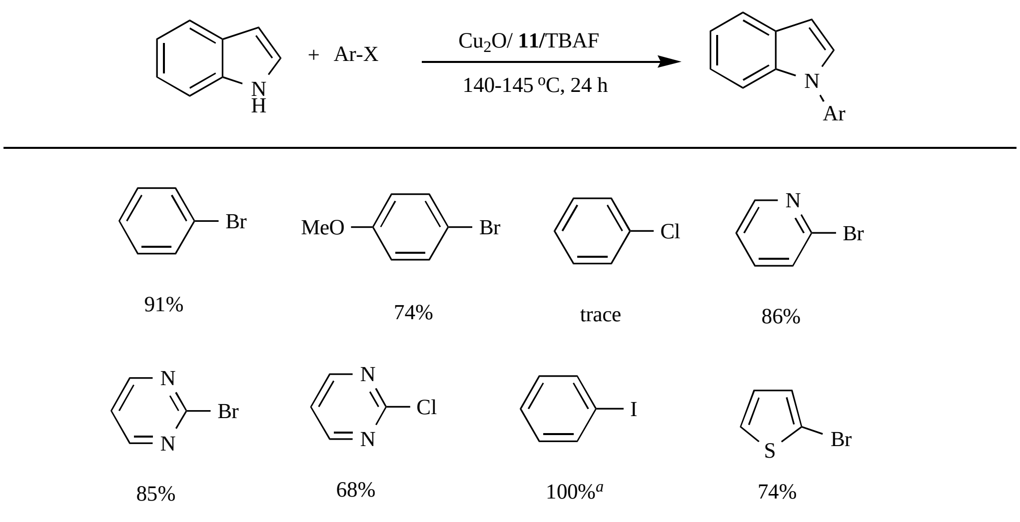
Scheme 12.



Scheme 13.

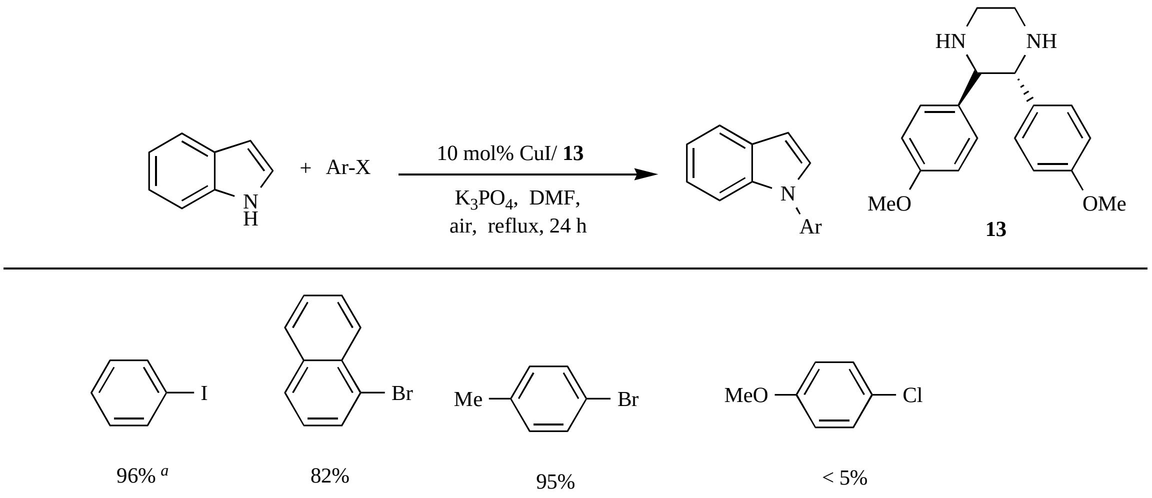
the corresponding products were obtained in 80% and 64% yields, respectively (Scheme **13**) [24].

In the presence of cubic Cu_2O nanoparticles, 1,10-phenanthroline (**11**) and tetra-*n*-butylammonium fluoride (TBAF), indole smoothly underwent *N*-arylation with aryl halides to give the corresponding products in moderate to excellent yields under solvent-free conditions (Scheme **14**). Moreover, satisfactory yields (68-86%) were obtained from the reactions of indole with nitrogen- and



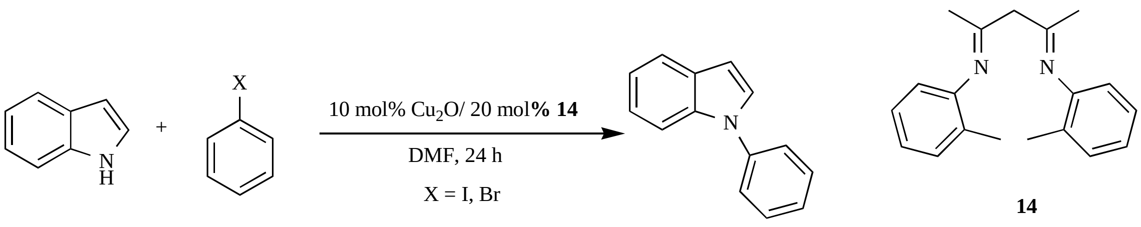
[a] At 110-115 °C for 36 h

Scheme 14.



[a] Toluene used as a solvent

Scheme 15.



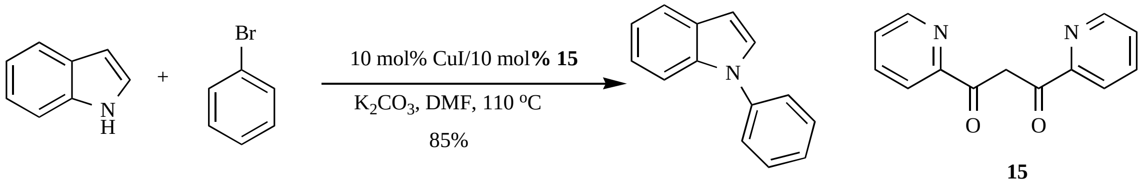
95% for iodobenzene at 110 °C
45% for bromobenzene at 130 °C

Scheme 16.

sulfur-containing heteroaryl halides under the above conditions. However, the chlorobenzene was not a suitable substrate for the reaction with indole under the same conditions [25].

A new method of *N*-arylation of indole with aryl halides was described in the presence of CuI/(±)-*trans*-2,3-bis(4-methoxyphenyl)piperazine (**13**) catalytic system (Scheme **15**). When the indole reacted with the iodophenyl, 1-bromonaphthalene, or 4-bromotoluene, the corresponding yields were 96%, 82% and 95%, respectively. But only a trace amount of product was obtained when 4-chloroanisole reacted with indole [26].

An efficient *N*-arylation of indole with iodobenzene and bromobenzene was developed by using Cu_2O/β-ketoimine (**14**) catalyst system (Scheme **16**). For example, *N*-phenylindole was obtained in a 95% yield in the reaction of indole with iodobenzene. However,



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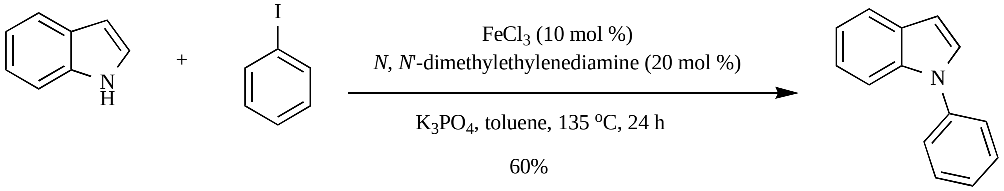
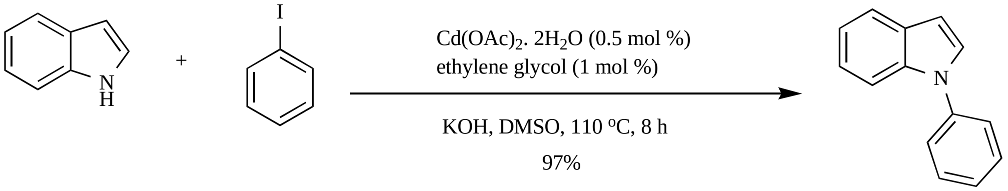
Scheme 17.



Scheme 18.



Scheme 19.

the *N*-arylation of indole with bromobenzene afforded the same product only in a 45% yield, even the reaction temperature was increased to 130 °C [27].

The combination of CuI and 1,3-di(pyridin-2-yl)propane-1,3-dione (**15**) was also very efficient for C-N coupling reactions to afford the *N*-phenylindole in a 85% yield (Scheme **17**) [28].

2.3. *N*-Arylation of Indoles with Aryl Halides by Other Transition Metals-Catalyzed Cross-Coupling Reactions

Although the significant progress was made in the development of palladium- and copper-catalyzed cross-coupling reactions for the preparation of *N*-arylindoles, there is still a need for new methods that involve inexpensive and environmentally friendly catalysts.

Recently, by using the novel and promising ligand-assisted iron-catalyzed system ($FeCl_3$ and *N*, *N*'-dimethylethylenediamine), *N*-phenylindole was obtained in a 60% yield (Scheme **18**) [29].

Punniyamurthy *et al.* discovered that $Cd(OAc)_2 \cdot 2H_2O$ in combination with ethylene glycol could efficiently catalyze the C-N cross-coupling of amines with aryl iodides in excellent yields, for example, *N*-phenylindole was obtained in a 97% yield under the above reaction conditions (Scheme **19**) [30].

3. *N*-ARYLATION OF INDOLES WITH ACTIVATED ARYL HALIDES BY AROMATIC NUCLEOPHILIC SUBSTITUTION REACTIONS (S_NAr)

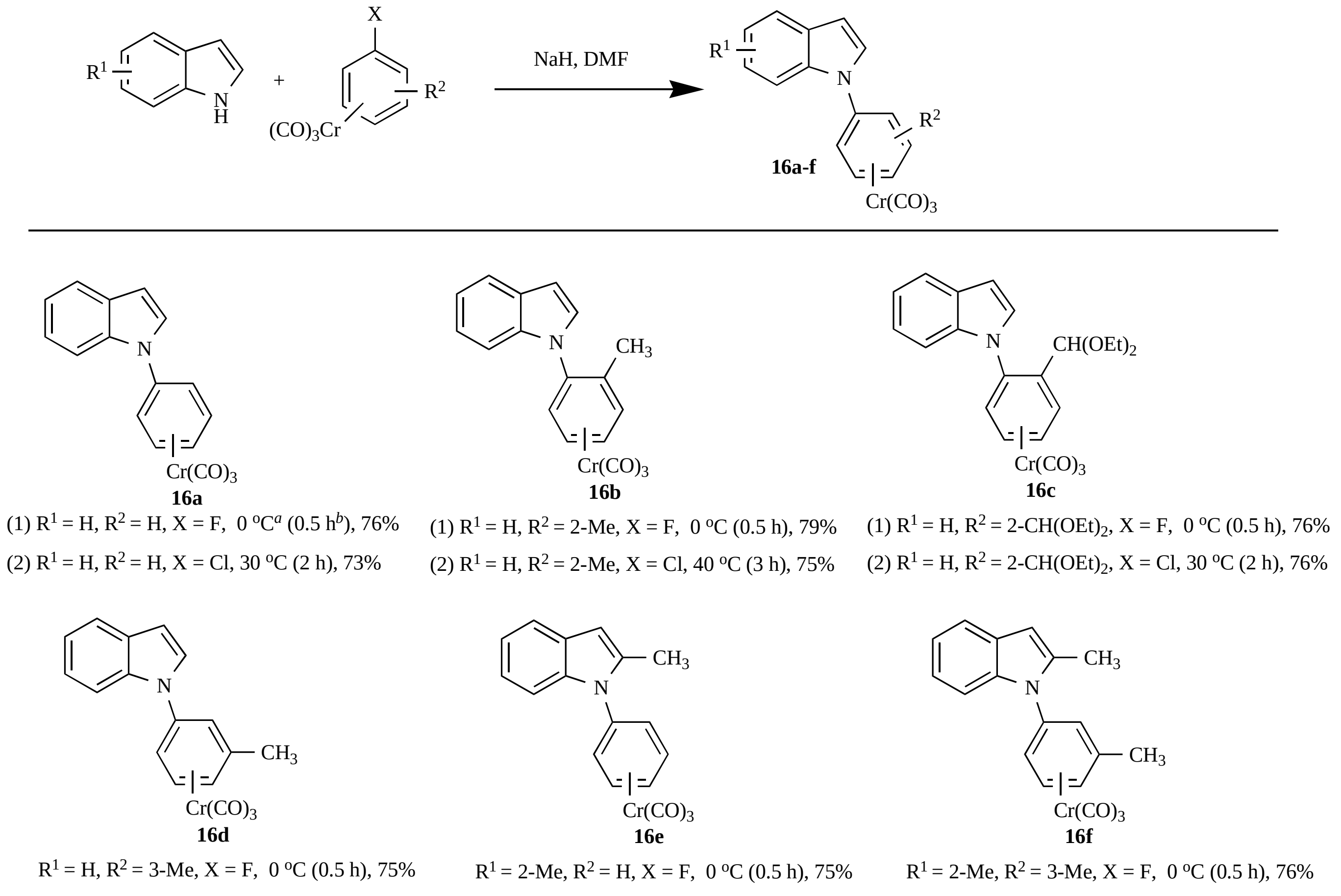
Aromatic nucleophilic substitution reactions (S_NAr) has also been considered as an effective method for the *N*-arylation of indoles with activated aryl halides.

Maiorana *et al*. reported the synthesis of *N*-arylindoles from indoles with various haloarene chromium tricarbonyl complexes by S_NAr reactions (Scheme **20**). The fluoroarenes were more reactive than the chloroarenes. For example, the fluoro complexes reacted rapidly with indoles to give complexes **16a-f** in good yields at 0°C (0.5 h). However, when the chloro derivatives reacted with indoles in order to obtain the same yields as the fluoro ones, the reaction temperature should be at 30-40°C and the reaction time should be prolonged to 2-3 h. Only 2-methylindole could react with (fluorobenzene)$Cr(CO)_3$ or (3-fluorotoluene)$Cr(CO)_3$, and the corresponding yields of the expected *N*-derivatives were 75% and 76%, respectively. Probably due to steric effects, (2-fluorotoluene)$Cr(CO)_3$ did not react with 2-methylindole even when the temperature was increased to 60 °C for a long time. Hence the *ortho* substitution in the complexed aromatic ring seemed to be incompatible with any substitutent at the 2-position of the indole ring [31].

Smith *et al.* reported potassium fluoride/alumina as an effective mediator for the preparation of *N*-(2-, 3-, or 4-pyridyl)indoles *via* S_NAr reactions. As shown in Scheme **21**, the fluoropyridines were more reactive than the chloropyridines. For example, when the 2-fluoropyridine and 2-chloropyridine reacted with indole, the corresponding yields were 90% and 61%, respectively. The same results were also found for 3-fluoropyridine (38%) and 3-chloropyridine (27%). Surprisingly, a 38% yield was obtained when 3-fluoropyridine reacted with indole as compared with 2-fluoropyridine [32].

Once the electron-withdrawing group was introduced on the halopyridines, the S_NAr reaction of which with indole could be more facile. As shown in Scheme **22**, the cross-coupling reaction of indole with 2-chloro-6-cyanopyridine proceeded easily to give the predicted product in a 92% yield [32].

We described an efficient S_NAr reactions to synthesize *N*-arylindoles *via* C(sp^2)–N(sp^2) bond formation in the presence of K_2CO_3 or Cs_2CO_3 under microwave irradiation (Scheme **23**). It was noteworthy that the electron-poor 5-nitroindole could smoothly be coupled with 4-fluoronitrobenzene or 2-fluoronitrobenzene, and the corresponding yields were 94% and 91%, respectively. The steric effect was observed. Although K_2CO_3 was a good base for coupling the activated fluoroarenes with indole, 5-nitroindole or 3-methylindole, it was ineffective in the coupling reaction with 7-methylindole. For example, when 7-methylindole was coupled with



16a

(1) R^1 = H, R^2 = H, X = F, 0 °C^a (0.5 h^b), 76%

(2) R^1 = H, R^2 = H, X = Cl, 30 °C (2 h), 73%

16b

(1) R^1 = H, R^2 = 2-Me, X = F, 0 °C (0.5 h), 79%

(2) R^1 = H, R^2 = 2-Me, X = Cl, 40 °C (3 h), 75%

16c

(1) R^1 = H, R^2 = 2-CH(OEt)$_2$, X = F, 0 °C (0.5 h), 76%

(2) R^1 = H, R^2 = 2-CH(OEt)$_2$, X = Cl, 30 °C (2 h), 76%

16d

R^1 = H, R^2 = 3-Me, X = F, 0 °C (0.5 h), 75%

16e

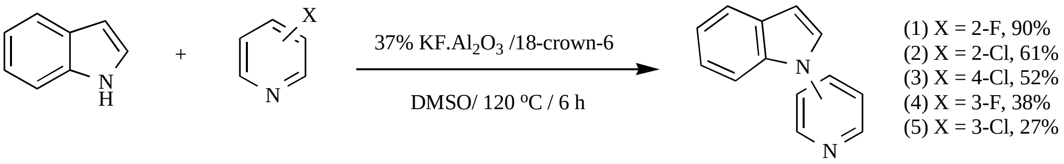
R^1 = 2-Me, R^2 = H, X = F, 0 °C (0.5 h), 75%

16f

R^1 = 2-Me, R^2 = 3-Me, X = F, 0 °C (0.5 h), 76%

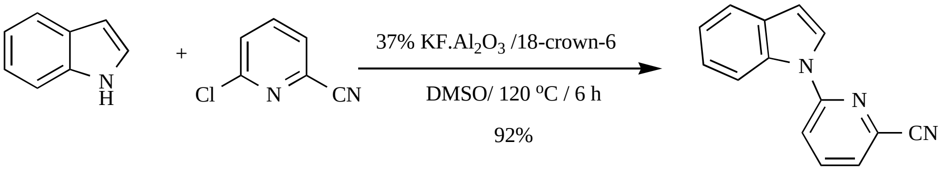
^{a} Reaction temperature; ^{b} Reaction time

Scheme 20.



(1) X = 2-F, 90%
(2) X = 2-Cl, 61%
(3) X = 4-Cl, 52%
(4) X = 3-F, 38%
(5) X = 3-Cl, 27%

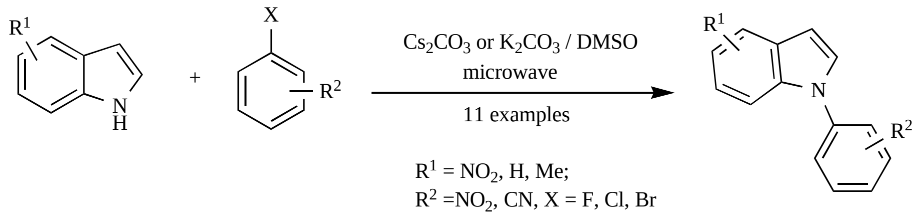
Scheme 21.



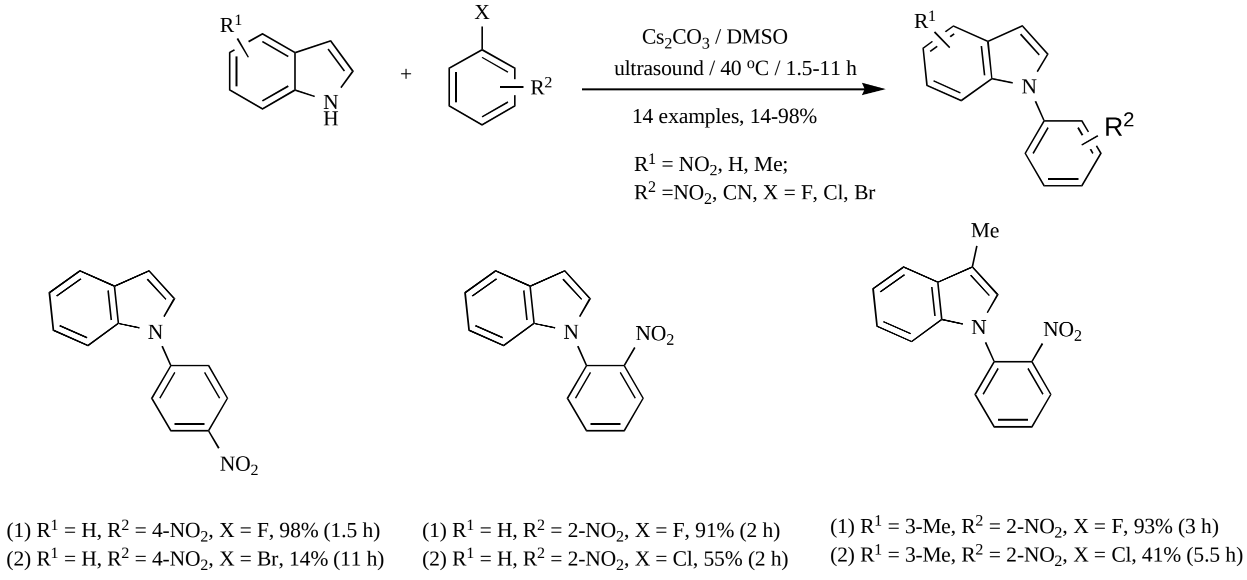
Scheme 22.

4-fluoronitrobenzene in the presence of K_2CO_3 for 6×5 min, no target compound was monitored by thin layer chromatography (TLC) analysis because the nitrogen atom of 7-methylindole was strongly hindered. However, when the *N*-arylation of 7-methylindole with 4-fluoronitrobenzene or 2-fluoronitrobenzene in the presence of Cs_2CO_3, the corresponding yields were 62% and 46 %, respectively. Finally, the reactivity of aryl halides was also investigated and the order was F > Cl > Br [33].

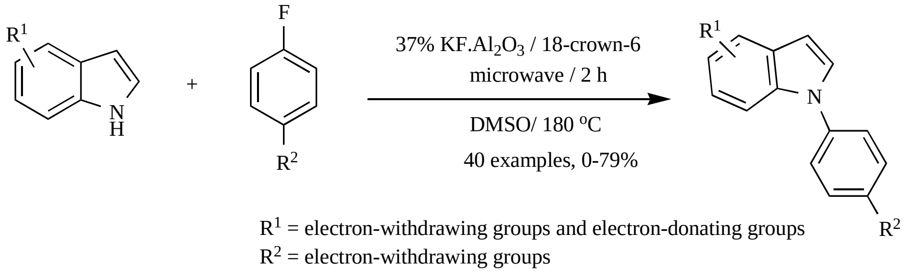
We further studied the coupling reaction of various indoles with activated haloarenes (X = F, Cl and Br) in the presence of Cs_2CO_3 under ultrasonic irradiation (Scheme **24**). When various indoles reacted with activated fluoroarenes using sonication by S_NAr reactions, *N*-arylindoles were achieved in 55-98 % yields. Distinct steric effect was also observed. For example, when 2-fluoronitrobenzene reacted with indole or 7-methylindole, the corresponding yields were 91 % and 55 %, respectively. The fluoroarenes underwent S_NAr reactions with indoles more easily than those chloro and bromo analogues as the same as our previous report [33]. For example, when indole reacted with 2-fluoronitrobenzene or 2-chloronitrobenzene**,** the corresponding yields were 91 % and 55 %, respectively. Especially when indole reacted with 4-bromonitrobenzene, even if the reaction time was prolonged to 11 h, the corresponding yield of *N*-(4-nitrophenyl)indole was only 14 % as compared with 4-fluoronitrobenzene (98% for 1.5 h) [34].



Scheme 23.



Scheme 24.



Scheme 25.

With the assistance of microwave technology, the scope and reactivity of variously substituted indoles with activated aryl fluorides for constructing *N*-arylindoles mediated by potassium fluoride on basic alumina was investigated. The reactivity of the substituted indoles was position 4 ≈ 5 ≈ 6 >> 2 ≈ 7. The yields of *N*-arylindoles were related with the substituents on the indoles, generally, indoles having electron-donating groups reacted with activated aryl fluorides to give higher product yields when compared with those having electron-withdrawing ones (Scheme **25**) [35].

ACKNOWLEDGEMENTS

This work has been supported by the program for New Century Excellent University Talents, State Education Ministry of China (NCET-06-0868), the Key Project of Chinese Ministry of Education (No.107105), and the Research Fund for the Doctoral Program of Higher Education of China, State Education Ministry of China (No.20070712025).

REFERENCES

[1] Von Angerer, E.; Strohmeier, J. 2-Phenylindoles. Effect of N-benzylation on estrogen receptor affinity, estrogenic properties, and mammary tumor inhibiting activity. *J. Med. Chem.*, **1987**, *30*, 131-136.

[2] Glamkowski, E. J.; Fortunato, J. M.; Spaulding, T. C.; Wilker, J. C.; Ellis, D. B. 3-(1-Indolinyl)benzylamines: A new class of analgesic agents. *J. Med. Chem.*, **1985**, *28*, 66-73.

[3] Unangst, P. C.; Carethers, M. E.; Webster, K.; Janik, G. M.; Robichaud, L. J. Acidic furo[3,2-b]indoles. A new series of potent antiallergy agents. *J. Med. Chem.*, **1984**, *27*, 1629-1633.

[4] Sano, H.; Noguchi, T.; Miyajima, A.; Hashimoto, Y.; Miyachi, H. Anti-angiogenic activity of basic-type, selective cyclooxygenase (COX)-1 inhibitors. *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 3068-3072.

[5] Perregaard, J.; Arnt, J.; Boegesoe, K. P.; Hyttel, J.; Sanchez, C. Noncataleptogenic, centrally acting dopamine D-2 and serotonin 5-HT_2 antagonists within a series of 3-substituted 1-(4-fluorophenyl)-1H-indoles. *J. Med. Chem.*, **1992**, *35*, 1092-1101.

[6] Cole, D. C.; Ellingboe, J. W.; Lennox, W. J.; Mazandarani, H.; Smith, D. L.; Stock, J. R.; Zhang, G. M.; Zhou, P.; Schechter, L. E. N_1-Arylsulfonyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole derivatives are potent and selective 5-HT_6 receptor antagonists. *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 379-383.

[7] Li, Q.; Li, T. M.; Woods, K. W.; Gu, W. Z.; Cohen, J.; Stoll, V. S.; Galicia, T.; Hutchins, C.; Frost, D.; Rosenberg, S. H.; Sham, H. L. Benzimidazolones and indoles as non-thiol farnesyltransferase inhibitors based on tipifarnib scaffold: synthesis and activity. *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 2918-2922.

[8] Xu, H.; Liu, W. Q.; Fan, L. L.; Chen, Y.; Yang, L. M.; Lv, L.; Zheng, Y. T. Synthesis and HIV-1 integrase inhibition activity of some N-arylindoles. *Chem. Pharm. Bull.*, **2008**, *56*, 720-722.

[9] Pozharskii, A. F.; Martsokha, B. K.; Simonov, A. M. Direct N-arylation of five-membered heterocycles. *Zh. Obshch. Khim*., **1963**, *33*, 1005-1007.

[10] (a) Barton, D. H. R.; Blazejewski, J. C.; Charpiot, B.; Finet, J. P.; Motherwell, W. B.; Papoula, M. T. B.; Stanforth, S. P. Phenylation of enols and of enolate and other anions. *J. Chem. Soc., Perkin Trans. I*, **1985**, 2667-2675; (b) Bartona, D. H. R.; Fineta, J. P.; Khamsia, J. Copper catalysed phenylation of indoles by triphenylbismuthBIS-trifluoroacetate. *Tetrahedron Lett.*, **1988**, *29,* 1115-1118; (c) Brown, R. A.; Fernando, S. I. S.; Roberts, R. M. G. Decomplexation of (η-arene)(η-cyciopentadienyl)iron(II) hexafluorophosphates: A convenient one-pot arylation procedure. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 197-201.

[11] Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. Catalytic cross-coupling reactions mediated by palladium/nucleophilic carbene systems. *J. Organomet. Chem*., **2002**, *653*, 69-82.

[12] (a) Stabler, S. R.; Jahangir. Preparation of N-arylated heterocycles by nucleophilic aromatic substitution. *Synth. Commun*., **1994**, *24,* 123-129; (b) Seki, K.; Ohkura, K.; Terashima, M.; Kanaoka, Y. A facile synthesis of N-(2-pyridyl and 4-pyridyl)indoles. *Heterocycles*, **1994**, *37*, 993-996; (c) Smith III, W. J.; Sawyer, J. S. A novel and selective method for the N-arylation of indoles mediated by KF/Al$_2$O$_3$. *Tetrahedron Lett.*, **1996**, *37*, 299-302.

[13] Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernandez-Rivas, C. Palladium-catalyzed C-N (sp^2) bond formation: N-Arylation of aromatic and unsaturated nitrogen and the reductive elimination chemistry of palladium azolyl and methyleneamido complexes. *J. Am. Chem. Soc*., **1998**, *120*, 827-828.

[14] Old, D. W.; Harris, M. C.; Buchwald, S. L. Efficient palladium-catalyzed N-arylation of indoles. *Org. Lett*., **2000**, *2*, 1403-1406.

[15] Grasa, G. A.; Viciu, M. S.; Huang, J. K.; Nolan, S. P. Amination reactions of aryl halides with nitrogen-containing reagents mediated by palladium/imidazolium salt systems. *J. Org. Chem*., **2001**, *66*, 7729-7737.

[16] Huang, X. H.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. Expanding Pd-catalyzed C-N bond-forming processes: The first amidation of aryl sulfonates, aqueous amination, and complementarity with Cu-catalyzed reactions. *J. Am. Chem. Soc*., **2003**, *125*, 6653-6655.

[17] Klapars, A.; Antilla, J. C.; Huang, X. H.; Buchwald, S. L. A general and efficient copper catalyst for the amidation of aryl halides and the N-arylation of nitrogen heterocycles. *J. Am. Chem. Soc*., **2001**, *123*, 7727-7729.

[18] Antilla, J. C.; Klapars, A.; Buchwald, S. L. The copper-catalyzed N-arylation of indoles. *J. Am. Chem. Soc*., **2002**, *124*, 11684-11688.

[19] Zhang, H.; Cai, Q.; Ma, D. W. Amino acid promoted CuI-catalyzed C-N bond formation between aryl halides and amines or N-containing heterocycles. *J. Org. Chem*., **2005**, *70*, 5164-5173.

[20] Kuil, M.; Bekedam, E. K.; Visser, G. M.; van den Hoogenband, A.; Terpstra, J. W.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; van Strijdonck, G. P. F. Mild copper-catalyzed N-arylation of azaheterocycles with aryl halides. *Tetrahedron Lett.*, **2005**, *46*, 2405-2409.

[21] Deng, W.; Wang, Y. F.; Zhang, C.; Liu, L.; Guo, Q. X. CuI/proline-catalyzed N-arylation of nitrogen heterocycles. *Chin. Chem. Lett*., **2006**, *17,* 313-316.

[22] Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. Selective, efficient and functional group-tolerant CuOAc-mediated N-arylation of 1H-indoles and 9H-carbazole with aryl iodides under base-free and ligandless conditions. *Eur. J. Org. Chem*., **2007**, 2147-2151.

[23] Bekolo, H. Copper-mediated N-arylation of electron-deficient pyrroles and indoles. *Can. J. Chem*., **2007**, *85*, 42-46.

[24] Chang, J. W. W.; Xu, X. H.; Chan, P. W. H. Practical copper-catalyzed N-arylartion of nitrogen heterocycles with aryl halides under ligand and additive free conditions. *Tetrahedron Lett.*, **2007**, *48*, 245-248.

[25] Tang, B. X.; Guo, S. M.; Zhang, M. B.; Li, J. H. N-Arylartion of nitrogen-containing heterocycles with aryl and heteroaryl halides using a copper(I) oxide nanoparticle/1,10-phenanthroline catalytic system. *Synthesis*, **2008**, 1707-1716.

[26] Periasamy, M.; Vairaprakash, P.; Dalai, M. New diimine-copper complexes: An efficient and simple catalyst system for Buchwald N-arylation of indole. *Organometallics*, **2008**, *27*, 1963-1966.

[27] Xue, F.; Cai, C. Y.; Sun, H. M.; Shen, Q.; Rui, J. β-Ketoimine as an efficient ligand for copper-catalyzed N-arylation of nitrogen-containing heterocycles with aryl halides. *Tetrahedron Lett.*, **2008**, *49*, 4386-4389.

[28] Xi, Z. X.; Liu, F. H.; Zhou, Y. B.; Chen, W. Z. CuI/L (L=pyridine-functionalized 1,3-diketones) catalyzed C-N coupling reactions of aryl halides with NH-containing heterocycles. *Tetrahedron*, **2008**, *64*, 4254-4259.

[29] Correa, A.; Bolm, C. Iron-catalyzed N-arylation of nitrogen nucleophiles. *Angew. Chem. Int. Ed.*, **2007**, *46,* 8862-8863.

[30] Rout, L.; Saha, P.; Jammi, S.; Punniyamurthy, T. Cadmium(II)-catalyzed C - N cross-coupling of amines with aryl iodides. *Adv. Synth. Catal*., **2008**, *350*, 395-398.

[31] Maiorana, S.; Baldoli, C.; Buttero, P. D.; Ciolo, M. D.; Papagni, A. Aromatic nucleophilic substitution on haloarene chromium tricarbonyl complexes: Mild N-arylation of indoles. *Synthesis*, **1998**, 735-738.

[32] Smith III, W. J.; Sawyer, J. S. An S$_N$Ar-base preparation of 1-(2-,3-,and 4-pyridyl)indoles using KF/Al$_2$O$_3$. *Heterocycles*, **1999**, *51*, 157-160.

[33] Xu, H.; Fan, L. L. Microwave-assisted N-arylation of indoles via C(sp^2)-N(sp^2) bond formation by aromatic nucleophilic substitution reactions. *Z. Naturforsch*., **2008**, *63B*, 298-302.

[34] Xu, H.; Lv, L.; Fan, L. L.; He, X. Q. Ultrasound-assisted N-arylation of indoles without any catalyst. *Heterocycles*, **2008**, *76*, 249-256.

[35] Frayne, G. L.; Green, G. M. Investigation of the N-arylation of various substituted indoles using microwave-assisted technology. *Tetrahedron Lett.*, **2008**, *49*, 7328-7329.

Received: December 08, 2008 Revised: April 15, 2009 Accepted: April 18, 2009