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# $NiCl_2{\cdot}6H_2O$ as recyclable heterogeneous catalyst for N-arylation of amines and NH-heterocycles under microwave exposure

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ABSTRACT

$NiCl_2{\cdot}6H_2O$ has been proven to be an effective catalyst for the coupling of amines with aryl iodides without ligand under solvent-free conditions employing microwave irradiation. Reactions cleanly result in coupled products in a short reaction time. The catalyst, being heterogeneous, is recovered by filtration and is recyclable.

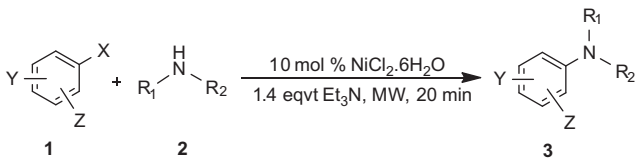


The use of microwave energy to heat chemical reactions has become an increasingly popular technique in the scientific community which is evidenced by a large number of review articles and books published on this subject.[1,2] In many instances, controlled microwave heating under sealed vessel conditions has been shown to dramatically reduce reaction times, increase product yields, and enhance product purities by reducing unwanted side reactions compared to conventional synthetic methods. The advantages of this technology have not only been exploited for organic synthesis and in the context of medicinal chemistry/drug discovery,[3] but have also penetrated the fields such as polymer synthesis,[4] material science,[5] nanotechnology,[6] and biochemical processes.[7]

Transition metal-catalyzed cross-coupling reactions of aryl halides with various nucleophilic compounds are now among the most prominent synthetic methods for the formation of carbon–heteroatom bonds. Among these, the formation of C–N bond has received much attention that finds wide applications in the synthesis of many substances such as drugs, materials, natural products, agrochemicals, and optical devices.[8] Exclusively, these reactions are performed under copper catalysis (Ullmann type reactions)[9] or palladium catalysis (Buchwald–Hartwig reactions).[10] Although significant progress has been made with regard to these reactions, there continues to be an increasing demand for low-cost and environment-friendly catalysts which have attracted other transition metals like iron and nickel in the field.

The first report regarding nickel catalyzed C–N coupling was produced by Buchwald in the form of cyclooctadiene complex of Ni(0) associated with 1,1′-bis(diphenylphosphino)ferrocene or 1,10-phenanthroline for the synthesis of aryl amines.[11] Till then a number of articles regarding nickel-catalysis for C–N bond formation have been published.[12] But nickel chemistry does not enjoy the fame as of palladium and copper and thus demands more studies to be made in the field. In view of the above and as a part of our ongoing research on the development of efficient protocols in organic synthesis,[13] we report herein a ligand and solvent-free Ni(II) catalyzed coupling of aryl halides with different aromatic, aliphatic and heterocyclic amines under controlled microwave protocol (Scheme 1).

As shown in Table 1, our experiments for the optimal conditions began with the coupling of iodobenzene with aniline taking various nickel salts as catalyst. The preliminary findings proved $NiCl_2{\cdot}6H_2O$ to be the most effective for the reaction undertaken (Table 1, entries 1–4). Then, we probed the solvent effect on the reaction and to our delight we hit upon a solvent-free reaction which is far superior to any of the solvents used in the reaction (Table 1, entries 4–13). Some ligands were also incorporated in the reaction but surprisingly none of them could match the yield under




**Scheme 1.** Coupling of aryl halides with amines and NH-heterocycles.

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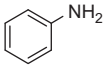
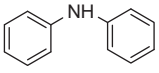
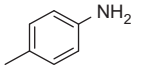
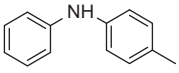
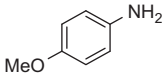
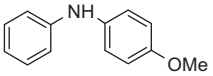
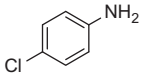
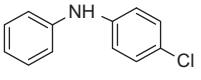
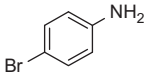
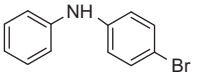
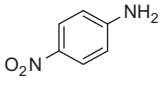
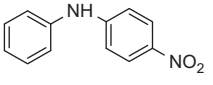
**Table 1**
Optimization of reaction conditions[a]

| Entry | Catalyst (mol %) | Solvent | Ligand | Base | Temp (°C) | Time (min) | Yield [b] (%) |
|---|---|---|---|---|---|---|---|
| 1 | $Ni(OAc)_2.4H_2O$ (20) | DMSO | — | $Et_3N$ | 120 | 20 | 38 |
| 2 | $NiSO_4$ (20) | DMSO | — | $Et_3N$ | 120 | 20 | 44 |
| 3 | $Ni(NO_3)_2$ (20) | DMSO | — | $Et_3N$ | 120 | 20 | 35 |
| 4 | $NiCl_2{\cdot}6H_2O$ (20) | DMSO | — | $Et_3N$ | 120 | 20 | 62 |
| 5 | $NiCl_2{\cdot}6H_2O$ (20) | Toluene | — | $Et_3N$ | 120 | 20 | 16 |
| 6 | $NiCl_2{\cdot}6H_2O$ (20) | Acetonitrile | — | $Et_3N$ | 120 | 20 | 23 |
| 7 | $NiCl_2{\cdot}6H_2O$ (20) | Ethanol | — | $Et_3N$ | 120 | 20 | nr |
| 8 | $NiCl_2{\cdot}6H_2O$ (20) | DMF | — | $Et_3N$ | 120 | 20 | Trace |
| 9 | $NiCl_2{\cdot}6H_2O$ (20) | Water | — | $Et_3N$ | 120 | 20 | nr |
| 10 | $NiCl_2{\cdot}6H_2O$ (20) | Dioxane | — | $Et_3N$ | 120 | 20 | Trace |
| 11 | $NiCl_2{\cdot}6H_2O$ (20) | Ethylene glycol | — | $Et_3N$ | 120 | 20 | 38 |
| 12 | $NiCl_2{\cdot}6H_2O$ (20) | NMP | — | $Et_3N$ | 120 | 20 | 32 |
| 13 | $NiCl_2{\cdot}6H_2O$ (20) | — | — | $Et_3N$ | 120 | 20 | 78 |
| 14 | $NiCl_2{\cdot}6H_2O$ (20) | — | L-Proline | $Et_3N$ | 120 | 20 | 45 |
| 15 | $NiCl_2{\cdot}6H_2O$ (20) | — | Ethylenediamine | $Et_3N$ | 120 | 20 | 54 |
| 16 | $NiCl_2{\cdot}6H_2O$ (20) | — | 1,10-Phenenthroline | $Et_3N$ | 120 | 20 | 32 |
| 17 | $NiCl_2{\cdot}6H_2O$ (20) | — | Ethylacetoacetate | $Et_3N$ | 120 | 20 | 43 |
| 18 | $NiCl_2{\cdot}6H_2O$ (20) | — | — | $Na_2CO_3$ | 120 | 20 | nr |
| 19 | $NiCl_2{\cdot}6H_2O$ (20) | — | — | KOH | 120 | 20 | nr |
| 20 | $NiCl_2{\cdot}6H_2O$ (20) | — | — | NaOH | 120 | 20 | nr |
| 21 | $NiCl_2{\cdot}6H_2O$ (20) | — | — | Pyridine | 120 | 20 | 24 |
| 22 | $NiCl_2{\cdot}6H_2O$ (20) | — | — | — | 120 | 20 | nr |
| 23 | $NiCl_2{\cdot}6H_2O$ (20) | — | — | $Et_3N$ | 120 | 20 | 77[c] |
| 24 | $NiCl_2{\cdot}6H_2O$ (20) | — | — | $Et_3N$ | 120 | 20 | 68[d] |
| 25 | $NiCl_2{\cdot}6H_2O$ (20) | — | — | $Et_3N$ | 120 | 20 | 78[e] |
| 26 | $NiCl_2{\cdot}6H_2O$ (20) | — | — | $Et_3N$ | 110 | 20 | 57 |
| 27 | $NiCl_2{\cdot}6H_2O$ (20) | — | — | $Et_3N$ | 130 | 20 | 85 |
| 28 | $NiCl_2{\cdot}6H_2O$ (20) | — | — | $Et_3N$ | 140 | 20 | 83 |
| 29 | $NiCl_2{\cdot}6H_2O$ (20) | — | — | $Et_3N$ | 130 | 10 | 52 |
| 30 | $NiCl_2{\cdot}6H_2O$ (20) | — | — | $Et_3N$ | 130 | 30 | 82 |
| 31 | $NiCl_2{\cdot}6H_2O$ (20) | — | — | $Et_3N$ | 130 | 40 | 76 |
| 32 | $NiCl_2{\cdot}6H_2O$ (30) | — | — | $Et_3N$ | 130 | 20 | 85 |
| **33** | **$NiCl_2{\cdot}6H_2O$ (10)** | — | — | **$Et_3N$** | **130** | **20** | **85** |
| 34 | $NiCl_2{\cdot}6H_2O$ (5) | — | — | $Et_3N$ | 130 | 20 | 81 |
| 35 | — | — | — | $Et_3N$ | 130 | 20 | nr |
| 36 | $NiCl_2{\cdot}6H_2O$ (10) | — | — | $Et_3N$ | 130 | 60 | 17[f] |

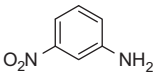
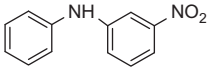
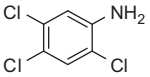
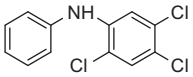
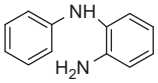
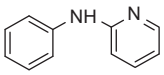
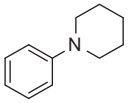
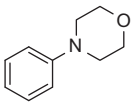
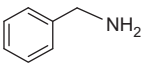
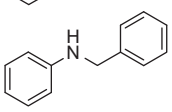
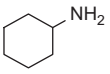
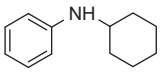
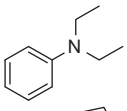
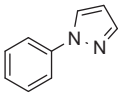
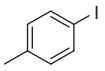
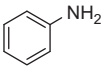
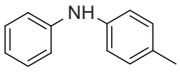
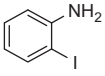
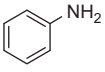
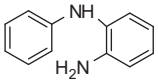
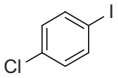
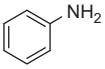
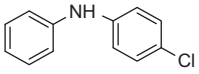
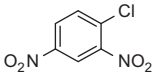
The bold values in Table 1 signify the optimized reaction conditions.
[a] Reaction using 1 mmol iodobenzene, 1.5 mmol aniline and 1.4 equiv base.
[b] Isolated yield.
[c] Reaction performed with 2 equiv of $Et_3N$.
[d] Reaction using 1.2 mmol aniline.
[e] Reaction using 2 mmol aniline.
[f] Reaction by conventional heating.

**Table 2**
Coupling of aryl halides with various amines and NH-heterocycles[14]

| Entry | Aryl halide | Amine | Product | | Temp (°C) | Yield [a] (%) |
|---|---|---|---|---|---|---|
| 1 |  X= I, Br, Cl |  |  | **3a** | 120<br>140<br>140<br>160 | 85 (X = I)<br>62 (X = Br)<br>Trace (X = Cl)<br>34 (X = Cl) |
| 2 |  |  |  | **3b** | 125 | 92[b]<br>89[c]<br>88[d]<br>86[e] |
| 3 |  |  |  | **3c** | 125 | 88 |
| 4 |  |  |  | **3d** | 110 | 72 |
| 5 |  |  |  | **3e** | 120 | 70 |
| 6 |  |  |  | **3f** | 150 | 75 |

(*continued on next page*)

**Table 2** (*continued*)

| Entry | Aryl halide | Amine | Product | | Temp (°C) | Yield [a] (%) |
|---|---|---|---|---|---|---|
| 7 |  |  |  | **3g** | 150 | 78 |
| 8 |  |  |  | **3h** | 150 | 56 |
| 9 |  |  |  | **3i** | 150 | 47 |
| 10 |  |  |  | **3j** | 140 | 52 |
| 11 |  X= I, Br, Cl |  |  | **3k** | 140<br>140<br>140<br>160 | 72 (X = I)<br>57 (X = Br)<br>nr (X = Cl)<br>Trace (X = Cl) |
| 12 |  |  |  | **3l** | 140 | 57 |
| 13 |  |  |  | **3m** | 150 | 62 |
| 14 |  |  |  | **3n** | 160 | 36 |
| 15 |  |  |  | **3o** | 140 | Trace |
| 16 |  |  |  | **3p** | 140 | 54 |
| 17 |  |  |  | **3b** | 130 | 72 |
| 18 |  |  |  | **3i** | 160 | 28 |
| 19 |  |  |  | **3d** | 110 | 76 |
| 20 |  |  |  | **3q** | 140 | 87 |
| 21 |  |  |  | **3r** | 150 | 74 |

[a] Isolated yield.
[b] Fresh catalyst.
[c] First cycle.
[d] Second cycle.
[e] Third cycle.

ligand-free conditions (Table 1, entries 14–17). Next, the role of the base was examined and out of all the bases tried, triethylamine was found to be the best (Table 1, entries 13, 18–21). A series of experiments were performed at different temperatures and 130 °C was found to be optimum for the reaction. Finally the effect of catalyst loading was examined and 10 mol % of the catalyst was concluded to be the optimum to promote the reaction (Table 1, entries 32–34). The model reaction was also carried out by conventional heating which is not at all comparable to the microwave conditions (Table 1, entry 36).

With the optimum reaction conditions (Table 1, entry 33) in hand, the versatility of the reaction was extended to a number of aryl halides with various arylamines, alkylamines and NH-heterocycles. The outcome of the experiments is shown in Table 2.

A perusal of Table 2 reveals that almost all kinds of amines and NH-heterocycles couple with iodobenzene in good to excellent conversion (Table 2, entries 1–16). The aromatic amines with electron donating groups react more efficiently in comparison to those bearing electron withdrawing groups (Table 2, entries 2–7). Aliphatic amines and NH-heterocycles also exhibit good conversion

in the reaction (Table 2, entries 11–16). The role of various aryl halides was also examined in the reaction using aniline as counter-substrate and it was found that iodobenzene is more reactive than bromobenzene. Chlorobenzene being reluctant, showed some reactivity under harsh reaction conditions (Table 2, entry 1–11); albeit, chloroderivatives with electron withdrawing groups readily couple in the reaction (Table 2, entries 20 and 21).

It is worthwhile to note that the catalyst $NiCl_2{\cdot}6H_2O$ being insoluble in the reaction mixture is easily recovered by simple filtration and is reused three times without any significant diminution in its amount and activity (Table 2, entry 2).

In summary, we have developed a convenient, rapid, economical and environmentally friendly Ni(II) catalyzed protocol for the N-arylation of amines with aryl halides under microwave irradiation. The key features of the reaction are (1) solvent-free conditions (2) no ligand needed (3) recoverable and recyclable catalyst (4) no need of inert atmosphere and (5) very short reaction time and operational simplicity.

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## References and notes

1. Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2005.
2. (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284; (b) Hayes, B. L. *Aldrichim. Acta* **2004**, *37*, 66; (c) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653–661; (d) De La Hoz, A.; Diaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164–178; (e) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223; (f) Kuhnert, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1863–1866; (g) Strauss, C. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3589–3591.
3. (a) Larhed, M.; Hallberg, A. *Drug Discovery Today* **2001**, *6*, 406–416; (b) Wathey, B.; Tierney, J.; Lidström, P.; Westman, J. *Drug Discovery Today* **2002**, *7*, 373–380; (c) Al-Obeidi, F.; Austin, R. E.; Okonya, J. F.; Bond, D. R. S. *Mini-Rev. Med. Chem.* **2003**, *3*, 449–460; (d) Kappe, C. O.; Dallinger, D. *Nat. Rev. Drug Disc.* **2006**, *5*, 51–63.
4. (a) Bogdal, D.; Penczek, P.; Pielichowski, J.; Prociak, A. *Adv. Polym. Sci.* **2003**, *163*, 193–263; (b) Wiesbrock, F.; Hoogenboom, R.; Schubert, U. S. *Macromol. Rapid Commun.* **2004**, *25*, 1739–1764.
5. (a) Barlow, S.; Marder, S. R. *Adv. Funct. Mater.* **2003**, *13*, 517–518; (b) Zhu, Y.-J.; Wang, W. W.; Qi, R.-J.; Hu, X.-L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1410–1414.
6. Tsuji, M.; Hashimoto, M.; Nishizawa, Y.; Kubokawa, M.; Tsuji, T. *Chem. Eur. J.* **2005**, *11*, 440–452.
7. (a) Orrling, K.; Nilsson, P.; Gullberg, M.; Larhed, M. *Chem. Commun.* **2004**, 790–791; (b) Zhong, H.; Zhang, Y.; Wen, Z.; Li, L. *Nat. Biotechnol.* **2004**, *22*, 1291–1296; (c) Zhong, H.; Marcus, S. L.; Li, L. *J. Am. Soc. Mass Spectrom.* **2005**, *16*, 471–481.
8. (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364; (b) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318–5365; (c) Corbert, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710; (d) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449.
9. (a) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164–5173; (b) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450–1460; (c) Xia, N.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 337–339; (d) Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586–5687; (e) Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 78–88.
10. (a) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553–5566; (b) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23–39; (c) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523–6527; (d) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734–7735.
11. Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054–6058.
12. (a) Brenner, E.; Fort, Y. *Tetrahedron Lett.* **1998**, *39*, 5359–5362; (b) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829–12842; (c) Desmarates, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2000**, *41*, 2875–2879; (d) Gradel, B.; Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2001**, *42*, 5689–5692; (e) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **2002**, *58*, 6913–6924; (f) Desmarates, C.; Schneider, R.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 3029–3036; (g) Chen, C.; Yang, L.-M. *Org. Lett.* **2005**, *7*, 2209–2211; (h) Kuhl, S.; Fort, Y.; Schneider, R. *J. Organomet. Chem.* **2005**, *690*, 6169–6177; Gao, C.-Y.; Yang, M.-L. *J. Org. Chem.* **2008**, *73*, 1624–1627; (j) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596–1636.
13. (a) Allam, B. K.; Singh, K. N. *Tetrahedron Lett.* **2011**, *52*, 5851–5854; (b) Raghuvanshi, D. S.; Singh, K. N. *Tetrahedron Lett.* **2011**, *52*, 5702–5705; (c) Singh, N.; Singh, S. K.; Khanna, R. S.; Singh, K. N. *Tetrahedron Lett.* **2011**, *52*, 2419–2422; (d) Raghuvanshi, D. S.; Singh, K. N. *Synlett* **2011**, 373–377; (e) Allam, B. K.; Singh, K. N. *Synthesis* **2011**, 1125–1131.
14. *General procedure for preparation of N-arylated amines* ***3***: Aryl halide (1 mmol), amine (1.5 mmol), $NiCl_2{\cdot}6H_2O$ (10 mol % relative to aryl halide) and triethylamine (1.4 equiv) were taken in a 10 mL pressurized microwave vial with snap on cap. The reaction mixture was subjected to microwave exposure for 20 min at 300 W at appropriate temperature as indicated above. The progress of the reaction was monitored by TLC (Thin Layer Chromatography). After the reaction was completed, the reaction mixture was diluted with DCM and the insoluble catalyst was recovered and recycled without loss of activity. The filtrate was concentrated and subjected to column chromatography with *n*-hexane and ethyl acetate (2–10% depending upon the product) as eluent to afford the pure product.
*N-(p-Tolyl) phenyl amine (**3b**):* colorless solid; mp 88 °C; IR (KBr): $\nu$ 3344 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 2.30 (s, 3H), 5.59 (s, 1H), 6.85 (t, $J$ = 7.2 Hz, 1H), 6.99 (m, 4H), 7.07 (m, 2H), 7.20 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 20.7, 116.8, 118.9, 120.3, 129.3, 129.8, 130.9, 140.3, 143.9.
*N-(4-Methoxyphenyl) aniline (**3c**):* Colorless solid; mp 105 °C; IR (KBr): $\nu$ 3402 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 3.79 (s, 3H), 5.48 (s, 1H) 6.80–6.91 (m, 5H), 7.05–7.08 (m, 2H) 7.18–7.25 (m, 2H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 55.5, 114.6, 115.6, 119.5, 122.2, 129.3, 135.7, 145.1, 155.2.