# One-pot, nickel triflate-catalysed homocoupling of aryl chlorides in the presence of metallic magnesium

**Dan Lv, Yan-Yan Zhang and Jing-Hua Li***

*College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, 310032, P. R. China*

The homocoupling reaction of aryl chlorides was successfully performed in one-pot without preparation of a Grignard reagent in advance. Various aryl chlorides underwent homocoupling reactions affording the corresponding symmetrical biaryls in moderate to good yields. The nickel triflate catalyst was recovered easily and reused smoothly with only a little loss of its activity.

**Keywords:** homocoupling, aromatic chlorides, nickel triflate

Carbon–carbon coupling reactions using transition metal complexes as catalysts are one of the most important and basic reactions in organic synthesis and are widely used in pharmaceutical chemistry. In 1972, Kumada[1] and Corriu[2] first discovered the aryl-aryl coupling reaction using palladium and nickel complexes as catalysts. This was further developed mainly because its wide scope and excellent compatibility with many functional groups.[3,4] Since then there have been a large number of publications concerning nickel-catalysed coupling reactions.[5-10] However, many catalysts generally involve toxic and ecologically unsatisfactory ligands such as phosphines[11,12] in order to catalyse the coupling reaction effectively. Therefore, a more efficient synthetic methodology for carbon–carbon bond formation is still required. Metal triflates are excellent catalysts with ecological advantages. They are soluble in water and can be recovered and reused with only a little loss of activity after several cycles.[13-17] Aryl chlorides are cheaper than aryl bromides, and are better suited for large-scale application. We report here a convenient one-pot method for the homocoupling of aryl chlorides catalysed by nickel salts in the presence of metallic lithium and magnesium.

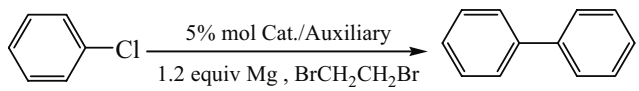
The coupling reaction of chlorobenzene, catalysed by 5% mol $NiCl_2$, when performed in refluxing THF, gave the corresponding coupled product in moderate yield (69%, Scheme 1). The catalytic effect of Ni, Yb, Fe *etc*. on the homocoupling reaction of chlorobenzene was investigated in the presence of 1.2 equiv. magnesium strips and 2% mol $BrCH_2CH_2Br$ (Table 1).

It was found that better yields were obtained with the addition of $PPh_3$, dppe or Li in the presence of the catalyst $NiCl_2$. Lithium gave the most satisfactory result with an 80% isolated yield (entries 2, 3 and 4 in Table 1). When a catalytic amount of $Ni(acac)_2$ or $PhNiCl(PPh_3)_2$ was added with 5% mol Li, the desired biaryl was obtained in moderate yield (entries 5 and 6 in Table 1). A better result was obtained with metal triflates as the catalysts (entry 7 in Table 1).

Compared with $Yb(OTf)_3$ and $Fe(OTf)_3$, $Ni(OTf)_2$ gave the best yield (entries 7–16 in Table 1). Meanwhile, several solvents such as ether, benzene and toluene were examined for the $Ni(OTf)_2$-catalysed coupling reaction, but no improvement was observed (entries 17, 18 and 19 in Table 1).

To explore the scope of this catalytic coupling system, other chloro compounds were used as substrates (Scheme 2 and Table 2). A variety of aryl chlorides underwent homocoupling reactions with the catalytic $Ni(OTf)_2$/Li/Mg system in refluxing THF to give the corresponding symmetrical hydrocarbons in moderate to good yields (Table 2).

Aromatic chlorides substituted with electron-donating groups (methyl, methoxy *etc*.) at the *m*- or *p*- position can be efficiently converted into the corresponding biaryls




**Scheme 1**

**Table 1** Optimisation of the catalytic homocoupling reaction of chlorbenzene[a]

| Entry | Catalyst | Auxiliary | Solvent | Yield/[b]% |
|---|---|---|---|---|
| 1 | $NiCl_2$ | 0 | THF | 69 |
| 2 | $NiCl_2$ | $PPh_3$ | THF | 75 |
| 3 | $NiCl_2$ | dppe | THF | 68 |
| 4 | $NiCl_2$ | Li | THF | 80 |
| 5 | $Ni(acac)_2$ | Li | THF | 81 |
| 6 | $PhNiCl(PPh_3)_2$ | Li | THF | 78 |
| 7 | $Ni(OTf)_2$ | Li | THF | 89 |
| 8 | $Ni(OTf)_2$ | 0 | THF | 77 |
| 9 | $Yb(OTf)_3$ | Li | THF | 68 |
| 10 | $VO(OTf)_2$ | Li | THF | 62 |
| 11 | $Mn(OTf)_2$ | Li | THF | 65 |
| 12 | $Fe(OTf)_3$ | Li | THF | 84 |
| 13 | $Zn(OTf)_2$ | Li | THF | 72 |
| 14 | $Gd(OTf)_3$ | Li | THF | 68 |
| 15 | $Cu(OTf)_2$ | Li | THF | 62 |
| 16 | $Sc(OTf)_3$ | Li | THF | 64 |
| 17 | $Ni(OTf)_2$ | Li | Ether | 80 |
| 18 | $Ni(OTf)_2$ | Li | Benzene | 75 |
| 19 | $Ni(OTf)_2$ | Li | Toluene | 77 |

[a]Reaction condition: 1 mmol PhCl, 1.2 mmol Mg, 0.02 mmol $BrCH_2CH_2Br$, 0.05 mmol Cat., 0.05 mmol auxilary reagents, reflux temperature, time: 6 h, solvent: 5 mL.
[b]Isolated yield.

(entries 2, 3, 5 and 6 in Table 2). Note that the present reaction system is tolerant of strong electron-withdrawing group such as trifluoromethyl and carbonyl, but the desired products were obtained in low yields (entries 7, 8 and 9 in Table 2). Heteroaryl chlorides such as 2-chlorothiophene and α-chloronaphthalene reacted poorly in this system (entries 10 and 11 in Table 2). These require further study in the catalytic homocoupling reaction.

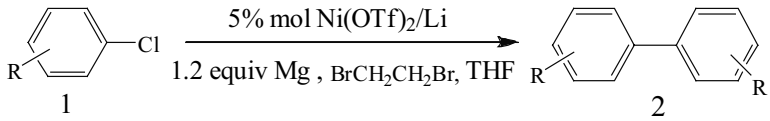
An advantage of the catalyst is that it could be recovered from the aqueous layer during the work-up of the reaction and reused in subsequent reactions (see Table 3). It was found that the activity was maintained at a satisfactory level.

In summary, an efficient homocoupling reaction of chloro compounds is reported employing a combination of the catalytic $Ni(OTf)_2$/Li/Mg system. The reaction can be carried out in one-pot and the catalyst was recovered easily and reused smoothly with only a little loss of its activity.

## Experimental

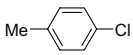
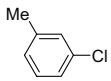
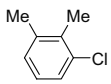
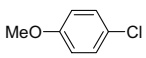
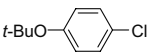
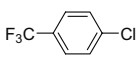
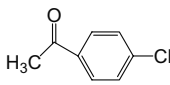
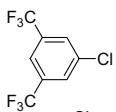
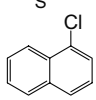
All reactions were carried out under an atmosphere of nitrogen in oven dried glassware with magnetic stirring, THF was distilled from a benzophenone-sodium adduct and stored over sodium wire.

* Correspondent. E-mail: lijh@zjut.edu.cn




**Scheme 2**

**Table 2** $Ni(OTf)_2$ catalysed homocoupling reaction of substituted aryl chlorides[a]

| Entry | Reagent **1** | Product **2** | Yield/[b]% |
|---|---|---|---|
| 1 |  | **2a** | 89 |
| 2 |  | **2b** | 81 |
| 3 |  | **2c** | 79 |
| 4 |  | **2d** | 70 |
| 5 |  | **2e** | 86 |
| 6 |  | **2f** | 88 |
| 7 |  | **2g** | 45 |
| 8 |  | **2h** | 56 |
| 9 |  | **2i** | 40 |
| 10 |  | **2j** | 52 |
| 11 |  | **2k** | 48 |

[a]Reaction condition: 1 mmol ArCl, 1.2 mmol Mg, 0.05 mmol $Ni(OTf)_2$/Li, 0.02 mmol $BrCH_2CH_2Br$, reflux temperature, time: 6 h, solvent: 5 mL THF.
[b]Isolated yield.

**Table 3** Catalyst recycling[a]

| Use | Recovery of catalyst/% | Yield/[b]% |
|---|---|---|
| 1st | 92 | 80 |
| 2nd | 91 | 76 |
| 3rd | 92 | 78 |

[a]Reaction condition: 1 mmol PhCl, 1.2 mmol Mg, 0.05 mmol $Ni(OTf)_2$/Li, 0.02 mmol $BrCH_2CH_2Br$, reflux temperature, time: 6 h, solvent: 5 mL THF.
[b]Isolated yield.

$^1$H NMR spectra were performed on a Varian Plus-400(400 MHZ) apparatus($CDCl_3$ solution), MS spectra were performed on an AEI MS-902 apparatus, melting points were performed on X-4/micro melting point apparatus.

*Homocoupling reaction catalysed by $Ni(OTf)_2$ and the recovery of $Ni(OTf)_2$*

The general synthetic process is as follows: Mg strips (29 mg 1.2 mmol), anhydrous THF 3 mL, $Ni(OTf)_2$ (18 mg 0.05 mmol), were placed in a 50 mL three-necked round-bottom flask equipped with a magnetic stirrer, a septum under nitrogen, a dropping funnel, a reflux condenser, the top of which was connected to a calcium chloride drying tube. The Mg strips were activated with one drop (about 40 mg) of 10% 1,2-dibromoethane/THF. The resulting mixture was stirred at room temperature and a piece of Li (about 4 mg for 10 pieces of Li) was added and ArCl 1 mmol in THF 2 mL was then slowly added. The reaction mixture was stirred under reflux for 6 h, and then quenched with saturated $NH_4Cl$. The solvent was evaporated and the residue treated with $Et_2O$ (10 mL) and water (15 mL). The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (3 × 10 mL). Concentration of the combined organic layer, dried over $MgSO_4$ in advance, afforded the crude product which was further purified by column chromatography on silica gel to give the pure homocoupling product.

The aqueous layer containing $Ni(OTf)_2$ in the above work-up procedure was evaporated under reduced pressure and the residue was extracted with ethyl acetate (3 × 10 mL). The organic phases were combined, evaporated under reduced pressure and dried at 70 °C for 2 h to give pure $Ni(OTf)_2$ in 92% recovery. The recovered catalyst was reused in the same way for the next run.

*Biphenyl* (**2a**): M.p. 68–70 °C (lit.[18] 68–71 °C). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.35–7.47 (m, 6H), 7.58–7.62 (m, 4H). MS (EI): *m/z* (%): 154 (M+, 100), 153 (35), 152(20), 115 (3), 76 (13), 51(4).

*4,4′-Dimethylbiphenyl* (**2b**): M.p. 119–120 °C (lit.[18] 119–120 °C). $^1$H NMR (400 MHz, $CDCl_3$): δ 2.56 (s, 6H), 7.41 (d, 4H, *J* = 7.6 Hz), 7.66 (d, 4H, *J* = 7.6 Hz). MS (EI): *m/z* (%): 182 (M+, 100), 167 (55), 152 (12), 89 (11), 76 (3).

*3,3′-Dimethylbiphenyl* (**2c**): Oil.[18] $^1$H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 6H), 7.16 (d, 2H, *J* = 6.0 Hz), 7.32–7.40 (m, 6H). MS (EI): *m/z* (%): 182 (M+, 100), 167 (33), 152 (12), 89 (8), 76 (4).

*2,3,2′,3′-Tetramethylbiphenyl* (**2d**): M.p. 114–115 °C (lit.[19]114–115 °C). $^1$H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 6H), 2.33 (s, 6H), 6.96 (d, 2H, *J* = 6.8 Hz), 7.16–7.10 (m, 4H). MS (EI): *m/z* (%): 210 (M+, 93), 195 (100), 180 (25), 165 (19), 89 (11), 76 (3).

*4,4′-Dimethoxydiphenyl* (**2e**): M.p. 177–179 °C (lit.[18] 177–179 °C). $^1$H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 6H), 6.95 (d, 4H, *J* = 8.8 Hz), 7.47 (d, 4H, *J* = 8.8 Hz). MS (EI): *m/z* (%): 182 (M+, 100), 167 (55), 152 (12), 89 (11), 76 (3).

*4,4′-Diisobutyloxydiphenyl* (**2f**)[20]: M.p. 149–150 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 18H), 7.05 (d, 4H), 7.48 (d, 4H). MS (EI): *m/z* (%): 298 (2), 186 (100), 157 (9), 57 (31).

*4,4′-Bis(trifluoromethyl)biphenyl* (**2g**): M.p. 89–91 °C (lit.[21]83–84 °C). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, 4H, *J* = 8.0 Hz), 7.48 (d, 4H, *J* = 8.0 Hz). MS (EI): *m/z* (%): 290 (M+, 100), 271 (25), 240 (10), 219 (6), 201 (20), 152 (14), 145 (5).

*4,4′-Diacetylbiphenyl* (**2h**): M.p. 191–192 °C (lit.[22] 190–192 °C). $^1$H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 6H), 7.67 (d, 4H), 8.02 (d, 4H). $^{13}$C NMR (100 HZ, $CDCl_3$): δ 197.5, 144.3, 136.6, 129.0, 127.4, 26.7.

*3,5,3′,5′-Tetrakis(trifluoromethyl)biphenyl* (**2i**): M.p. 68–70 °C (lit.[18] 68–71 °C). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 2H), 8.04 (s, 4H). MS (EI): *m/z* (%): 426 ($M^+$, 100), 407 (42), 357 (15), 337 (15), 287 (10), 213 (8).

*3,3′-Bithienyl* (**2j**): M.p. 130–131 °C (lit.[23] 132–133 °C). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.33–7.35 (m, 4H), 7.37–7.38 (m, 2H). MS (EI): *m/z* (%): 166 (M+, 100), 83 (21).

*1,1′-Binaphthyl* (**2k**): M.p. 154–156 °C (lit.[19] 154–156 °C). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, 2H, *J* = 48.2 Hz), 7.94 (d, 2H, *J* = 8.0 Hz),7.59 (t, 2H, *J* = 8.0 Hz,), 7.50–7.47 (m, 4H), 7.38 (d, 2H, *J* = 8.3 Hz), 7.28 (t, 2H, *J* = 7.8 Hz); $^{13}$C NMR (100 HZ, $CDCl_3$): δ 138.8, 133.5, 132.8, 128.1, 127.9, 127.8, 126.6, 126.0, 125.8, 125.3.

*Received 16 February 2009; accepted 14 April 2009*
*Paper 09/0449 doi: 10.3184/030823409X460759*
*Published online: 2 July 2009*

## References

1 K. Tamao, K. Sumitani and M. Kumada, *J. Am. Chem. Soc.,* 1972, **94**, 4374.
2 K.J.P. Corriu and J.P. Masse, *J. Chem. Soc., Chem. Commun.,* 1972, 144.
3 J. Tsuji, *Palladium reagents and catalysts: innovations in organic synthesis*, Wiley, New York: 1996.
4 E. Negishi, ed. *Handbook of organopalladium chemistry for organic synthesis*, Wiley, New York: 2002.

5 T. Kohei, *J. Organomet. Chem.,* 2002, **653**, 23.
6 P.W. Volker, T.W. Bohm, W.K. Christin, G. Stottmayr and A.H. Wolfgang, *Angew. Chem. Int. Ed.*, 2000, **39**,1602.
7 A. Lutz, B. Robert, H.S. Julia and M. Daniel, *Angew. Chem. Int. Ed.,* 2005, **44**, 7216.
8 Y. Naohiko, M. Hiroko and N. Eiichi, *J. Am. Chem. Soc.*, 2005, **127**, 17978.
9 J.W. Zhao, L.P. Song, Y.K. Wang and S.Z. Zhu. *J. Fluor. Chem.,* 2006, **127**, 405.
10 W. Joffrey, L. Agnes, N. Michael, J.C. Daran and P. Rinaldo, *J. Mol. Catal. A: Chem.,* 2006, **259**, 205.
11 P.W. Volker, A. Wolfgang, W. Thomas, W.K. Christian and P. Herrmann, *Angew. Chem. Int. Ed.,* 2000, **39**, 1602.
12 W. Joffrey, L. Agnes and P. Rinaldo, *J. Organomet. Chem.,* 2006, **691**, 433.
13 S. Kobayashi, M. Sugiura, H. Kitagawa and W.L. William, *Chem. Rev.,* 2002, **102**, 2227.
14 C. Zhang, T. Cheng and R. Li, *Acta Chim. Sinica.,* 2002, **60**, 481.
15 X. Li, X. Du and Z. Xu, *Chin. J. Org. Chem.,* 2006, **26**, 1111.
16 J. Lin, Y. Zheng and J. Li, *J. Zhejiang Univ. Technol.,* 2007, **35**, 190.
17 J.A. Schwindeman, D.E. Sutton, R.C. Morrison and S.S. Stryker, US 5626798, 1997.
18 X.L. Xu, D.P. Cheng and W. Pei, *J. Org. Chem.*, 2006, **71**, 6637.
19 M. Tashro and T. Yamato, *J. Org. Chem.,* 1979, **44**, 3037.
20 M. Watanabe and Y. Koie, JP 11158103, 1999.
21 N. Ma, Z. Zhu and Y. Wu, *Tetrahedron,* 2007, **63**, 4625.
22 C.S. Chao, C.H. Cheng and T.T. Chang, *J. Org. Chem.,* 1983, **48**, 4909.
23 L. Wang, Y. Zhang and L. Liu, *J. Org. Chem.,* 2006, **71**, 1284.