A cross-coupling synthesis of functionalised biaryls using Knochel-type organozinc reagents and a pyridine enhanced palladium catalyst

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A variety of functionalised biaryls were synthesised on the 20–30 mmol scale by using Knochel type organozinc reagents (organozinc reagents prepared from aryl halides, Zn powder and LiCl) catalysed by PEPPSI (a pyridine enhanced palladium catalyst). The protocol enabled the Negishi reactions to proceed in a smooth, rapid and mild way to give the corresponding products in excellent yields (80 ~ 96%). Sensitive functional groups, such as CN and COOEt groups, were tolerated in the coupling reaction.

Keywords: preparation, biaryls, PEPPSI, Negishi reaction, organozinc reagents

Biaryls have a wide application as key building blocks in the synthesis of pharmaceutically active molecules, herbicides, liquid crystals, organic semiconductors or metal ligands for catalysis. Consequently, many synthetic methods have been developed, and among these methods, the Pd-catalysed cross-coupling reaction of organometallic reagent with an unsaturated halide is one of the most powerful methods for the formation of aryl–aryl units. The general catalytic cycle, which consists of oxidative addition, transmetalation, and reductive elimination steps, gives the cross-coupling product.

Recently, the discovery of pyridine-enhanced precatalyst preparation stabilisation and initiation (PEPPSI)[1–4] to promote C–C bond formation is very important in modern cross-coupling catalytic chemistry (Fig. 1). The application of the easily-synthesised, air-stable, highly-active, well-defined precatalyst substantially increases the scope, reliability and ease-of-use of the Negishi cross-coupling reaction.

Among many organometallics used in the Negishi cross-coupling, organozinc reagents have proven to be particularly useful.[5–10] These environmentally-friendly organometallics have, however, the drawback of being air and moisture sensitive. Recently, the Knochel group developed a very efficient LiCl-mediated direct insertion of zinc into unsaturated halides.[11] The nature of the activation of the zinc dust with LiCl is, that it removes the organozinc reagent as it is formed rapidly from the metal surface by generating the highly soluble RZnX·LiCl complexes, thus allowing a rapid reaction of a further molecule of R–X and thereby avoiding the competitive deactivation of the active metal sites (Fig. 2).

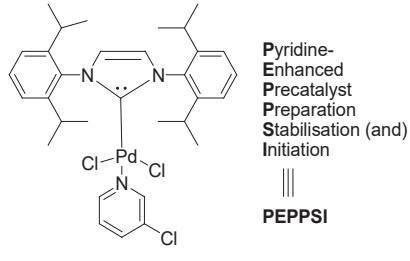

Fig. 1 PEPPSI catalyst.

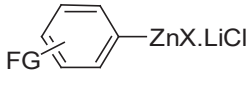

Fig. 2 Knochel type organozinc reagent.

Based on the features mentioned above, we wish to report a scaled-up PEPPSI-catalysed synthesis of functionalised biaryls by using Knochel type zinc reagents. By using this protocol, the cross-coupling reactions proceed smoothly and rapidly giving the desired biaryls on the 20–30 mmol scale in excellent yields. All the reactions were performed using general laboratory techniques and standard laboratory glassware.

Results and discussion

A variety of functionalised zinc reagents were coupled with unsaturated functionalised aryl halides under mild conditions (1–3 h, 25 °C). Thus the reaction of 3-(methoxy)phenylzinc bromide **1a** (1.2 equiv.), prepared by direct zinc insertion into the corresponding aryl bromide, with 4-(methoxy) bromobenzene **2a** in the presence of PEPPSI (1 mol%) led to the 3,4'-(dimethoxy)-biphenyl **3a** with 95% isolation yield within 1 h at 25 °C (Table 1, entry 1). The 3,4'-(dimethoxy)-biphenyl **3a** was also synthesised in 96% yield using an identical method with a different reagent 4-methoxyarylzinc bromide **1b** to give a further illustration as shown in Table 1, entry 2. Similarly, the reaction of 2-methoxyphenylzinc bromide **1c** with 4-methoxylbromobenzene **2a** in the presence of PEPPSI (1 mol%) led to the 2,4'-(dimethoxy)-biphenyl **3b** in 82% isolated yield within 1 h at 25 °C (entry 3), furthermore, **3b** could be synthesised in the identical method from diverse reagent **1b** with 84% isolation yield (entry 4). 3-(Ethoxycarbonyl) phenylzinc iodide **1d** was also suitable for the cross-coupling procedure and the 3,4'-di(ethoxycarbonyl)biphenyl **3c** was obtained in 89% yield (entry 5) after the reaction with ethyl 4-iodobenzoate **2d**. 4-(Ethoxycarbonyl)phenylzinc iodide **1e** also reacted smoothly with ethyl 3-iodobenzoate **2e** within 1 h at 25 °C, leading to the 3,4'-di(ethoxycarbonyl)biphenyl **3c** in 80% yield (entry 6). Similarly, the reaction of 4-tolylzinc bromide **1f** with ethyl *p*-bromophenyl benzoate **2f** furnished the desired coupling product **3d** in 90% yield (entry 7). Adding the reagent **1f** (1.2 equiv.) to a solution of 4-(methoxy) bromobenzene **2a** and PEPPSI (1 mol%) provided the biphenyl **3e** in 80% yield (entry 8). The reagent **1f** (1.2 equiv.) reacted with 4-(trifluoromethyl) bromobenzene **2g**, leading to the 4-methyl-4'-(trifluoromethyl)-biphenyl **3f** in 86% yield. Finally, 4-tolylzinc bromide **1f** was coupled with 4-(cyano) bromobenzene **2h** to yield 4-methyl-4'-(cyano)biphenyl **3g** in 94% yield (entry 10). The same method was used to synthesise the biaryls **3h** and **3i** in excellent yields respectively (entry 11 and 12). All the reactions were performed on a 20–30 mmol scale, and with a low PEPPSI loading (1 mol%). All the reactions were clean and the desired products were isolated

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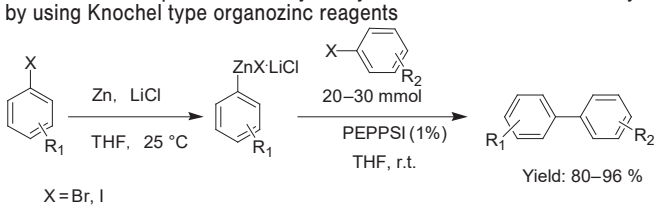
Table 1 Scaled-up PEPPSI-catalysed synthesis of functionalised biaryls by using Knochel type organozinc reagents



Entry	R_1	R_2	Products	Yield/%[a]
1	**1a** 3-OMe	**2a** 4-OMe	**3a**	95
2	**1b** 4-OMe	**2b** 3-OMe	**3a**	96
3	**1c** 2-OMe	**2a**	**3b**	82
4	**1b**	**2c** 2-OMe	**3b**	84
5	**1d** 3-CO_2Et	**2d** 4-CO_2Et	**3c**	89
6	**1e** 4-CO_2Et	**2e** 3-CO_2Et	**3c**	80
7	**1f** 4-Me	**2f** 4-CO_2Et	**3d**	90
8	**1f**	**2a**	**3e**	80
9	**1f**	**2g** 4-CF_3	**3f**	86
10	**1f**	**2h** 4-CN	**3g**	94
11	**1f**	**2i** 3-CN	**3h**	90
12	**1f**	**2j** 2-CN	**3i**	88

[a]Isolated yield of analytically pure product.

with excellent yields. Sensitive functional groups, such as CN and COOEt groups, were tolerated in the coupling reaction.

Conclusions

A practical scaled up synthetic procedure for the preparation of functionalised biaryls by using Knochel type organozinc reagents in the presence of PEPPSI is reported. All the reactions were performed on the 20–30 mmol scale, and with low PEPPSI loading (1 mol%). The reactions were clean and the desired products were isolated in excellent yields. Sensitive functional groups, such as CN and COOEt groups, were tolerated in the coupling reaction. The protocol, which enabled the Negishi reaction to proceed smoothly and rapidly, may be a practical and interesting synthetic procedure to prepare important organic intermediates or precursors.

Experimental

Melting points were determined on the Kofler micro melting point apparatus and were not corrected. ^{1}H NMR (in $CDCl_3$) and ^{13}C NMR (in $CDCl_3$) spectra were measured using TMS as internal standard on a Bruker 600 AC NMR or Bruker 400 AC NMR spectrometer. A high-resolution mass spectra (ESI–HRMS) were determined on an Ion Spec (7.0 T) spectrometer.

All reactions were carried out under an argon atmosphere in dried glassware. All starting materials were purchased from commercial suppliers and used without further purification unless otherwise stated. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated compounds estimated to be > 95% pure as determined by ^{1}H NMR and capillary GC analysis.

Synthesis of Knochel type organozinc reagents; general procedure

Synthesis of organozinc reagent **1a**: Anhydrous LiCl (33 mmol, 1.40 g) was placed in an Ar-flushed flask and dried for 30 min at 250 °C under high vacuum (1 mbar). Zinc powder (90 mmol, 5.88 g) was added under Ar and the heterogenous mixture was dried again for 30 min at 250 °C under high vacuum (1 mbar). After cooling to 25 °C, the flask was evacuated and refilled with Ar three times. THF (30 mL) was added and the zinc was activated with 1,2-dibromoethane (5% mmol) and TMSCl (1–2% mmol). 3-Methoxylbromobenzene (30 mmol, 5.61 g) was added carefully and the reaction mixture was stirred at 25 °C for 24 h. The solution of **1a** was carefully separated from remaining zinc powder by using a syringe and transferred to another dry and Ar-flushed flask. Titration of the zinc reagent (typically 1 mL) with iodine, indicated a concentration of 0.80 M.

Synthesis of substituted biaryls; general procedure

Synthesis of 3,4'-(dimethoxy)biphenyl (Table 1, entry 1, **3a**): 4-(Methoxy)bromobenzene (**2a**, 3.74 g, 20 mmol), PEPPSI (0.136 g, 0.2 mmol) and THF (20 mL) were placed in a dry and argon flushed 250 mL Schlenk-flask. The reaction mixture was stirred for 5 min, and then 3-(methoxy)phenylzinc bromide (**1a**, 30 mL, 0.80 M in THF, 24 mmol) was added. The reaction mixture was stirred for 1 h at 25 °C and then quenched with aqueous saturated NH_4Cl solution, and extracted with ether. The combined organic phases were washed with an aqueous thiourea solution and dried with Na_2SO_4. The crude residue obtained after evaporation of the solvent was purified by flash chromatography (pentane/ether = 10:1) to yield 3,4'-(dimethoxy) biphenyl (**3a**) as a white solid (4.07 g, 95%).

3,4'-(Dimethoxy)biphenyl (Table 1, entry 1, **3a**): White solid; m.p.: 60–61 °C (lit.[12] 58–59 °C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47–7.42 (m, 2H), 7.27–7.22 (m, 1H), 7.08–7.04 (m, 1H), 7.02–7.00 (m, 1H), 6.91–6.86 (m, 2H), 6.80–6.75 (m, 1H), 3.78 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.90, 159.21, 142.33, 133.58, 129.67, 128.16, 119.25, 114.13, 112.49, 111.99, 55.34, 55.28; HRMS *m/z* for $C_{14}H_{14}O_2$ calcd 214.0994; found: 214.0990.

2,4'-(Dimethoxy)biphenyl (Table 1, entry 3, **3b**): White solid; m.p.: 70 °C (lit.[13] 68–70 °C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42–7.35 (m, 2H), 7.24–7.18 (m, 2H), 6.96–6.84 (m, 4H), 3.72 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 158.60, 156.40, 130.85, 130.59, 130.54, 130.28, 128.12, 120.77, 113.44, 111.14, 55.49, 55.22; HRMS *m/z* for $C_{14}H_{14}O_2$ calcd 214.0994; found: 214.0999.

3,4'-Di(ethoxycarbonyl)biphenyl (Table 1, entry 5, **3c**): Pale yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.30 (t, *J* = 1.8 Hz, 1H), 8.14–8.12 (m, 2H), 8.07–8.06 (m, 1H), 7.81–7.79 (m, 1H), 7.70–7.67 (m, 2H), 7.53 (t, *J* = 7.8 Hz, 1 H), 4.43–4.38 (m, 4H), 1.42 (td, *J* = 7.2, 0.6 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.33, 144.39, 140.25, 131.47, 131.19, 130.11, 129.66, 129.00, 128.29, 127.08, 61.16, 61.01, 14.32; HRMS *m/z* for $C_{18}H_{18}O_4$ calcd 298.1205; found: 298.1208.

4-Methyl-4'-(ethoxycarbonyl)biphenyl (Table 1, entry 7, **3d**): White solid; m.p.: 75–77 °C (lit.[14] 78–79 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11–8.05 (m, 2H), 7.65–7.60 (m, 2H), 7.54–7.47 (m, 2H), 7.30–7.24 (m, 2H), 4.38 (q, *J* = 6.8 Hz, 2H), 2.39 (s, 3H), 1.39 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz): δ 166.56, 145.45, 138.05, 137.15, 130.02, 129.63, 128.95, 127.09, 126.73, 60.91, 21.14, 14.37; HRMS *m/z* for $C_{16}H_{16}O_2$ calcd 240.1150; found: 240.1152.

4-Methyl-4'-(methoxy)biphenyl (Table 1, entry 8, **3e**): White solid; m.p.: 111–112 °C (lit.[15] 115–118 °C). ^{1}H NMR (400 MHz): δ 7.46–7.41 (m, 2H), 7.40–7.35 (m, 2H), 7.17–7.13 (m, 2H), 6.92–6.87 (m, 2H), 3.77 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz): δ 158.89, 137.93, 136.30, 133.72, 129.38, 127.90, 126.54, 114.12, 55.30, 21.00; HRMS *m/z* for $C_{14}H_{14}O$ calcd 198.1045; found: 198.1050.

4-Methyl-4'-(trifluoromethyl)biphenyl (Table 1, entry 9, **3f**): White solid; m.p.: 121–122 °C (lit.[16] 120 °C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.68–7.67 (m, 4H), 7.53–7.49 (m, 2H), 7.31–7.26 (m, 2H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.62 (q, $^4J_{C-F}$ = 1.5 Hz), 138.13, 136.84, 129.68, 129.01 (q, $^2J_{C-F}$ = 32 Hz), 127.15, 127.08, 125.64 (q, $^3J_{C-F}$ = 3.7 Hz), 124.33 (q, $^1J_{C-F}$ = 270 Hz), 21.13; HRMS *m/z* for $C_{14}H_{11}F_3$ calcd 236.0813; found: 236.0820.

4-Methyl-4'-(cyano)biphenyl (Table 1, entry 10, **3g**): White solid; m.p.: 110–112 °C (lit.[14] 110–111 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66–7.56 (m, 4H), 7.44–7.39 (m, 2H), 7.24–7.19 (m, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.59, 138.73, 136.25, 132.54, 129.81, 127.44, 127.03, 119.00, 110.54, 21.16; HRMS *m/z* for $C_{14}H_{11}N$ calcd 193.0891; found: 193.0899.

4-Methyl-3'-(cyano)biphenyl (Table 1, entry 11, **3h**): White solid; m.p.: 74–75 °C (lit.[17] 66–68 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80–7.70 (m, 2H), 7.58 (td, *J* = 7.6, 1.4 Hz, 1H), 7.52–7.43 (m, 3H), 7.28–7.25 (m, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ

142.36, 138.37, 135.97, 131.24, 130.42, 130.31, 129.82, 129.51, 126.88, 118.91, 112.89, 21.13; HRMS *m/z* for $C_{14}H_{11}N$ calcd 193.0891; found: 193.0898.

4-Methyl-2'-(cyano)biphenyl (Table 1, entry 12, **3i**): White solid; m.p.: 47–48 °C (lit.[18] 48–50 °C). ^{1}H NMR (400 MHz): δ 7.69–7.65 (m, 1H), 7.57–7.51 (m, 1H), 7.45–7.30 (m, 4H), 7.23–7.21 (m, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz): δ 145.52, 138.67, 135.25, 133.68, 132.71, 129.94, 129.41, 128.58, 127.23, 118.83, 111.19, 21.23; HRMS *m/z* for $C_{14}H_{11}N$ calcd 193.0891; found: 193.0897.

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