Synthesis of Nitro-Substituted Polyfunctional Biphenyls by Negishi Cross-Coupling of *o*-Nitroarylzinc Reagents

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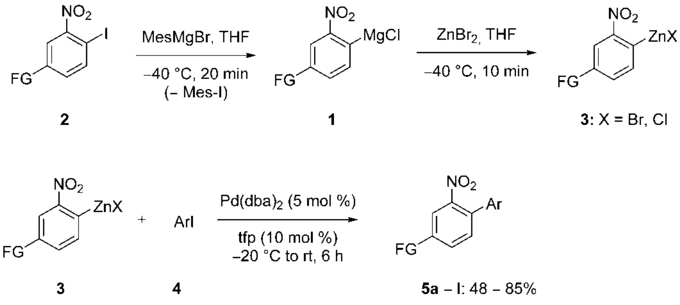
Dedicated with friendship to Joe Richmond on the occasion of his 60th birthday.

The iodine-magnesium exchange reaction allows the preparation of polyfunctional arylmagnesium species bearing a nitro group in the *ortho*-position. After transmetalation to the corresponding arylzinc compound, these organometallics undergo a palladium-catalyzed Negishi cross-coupling with various aryl iodides to provide polyfunctional biphenyls bearing nitro groups in moderate to good yields.

Keywords: biphenyls; functionalized organomagnesium compounds; Negishi cross-coupling; nitroarenes; palladium catalysis

Transition-metal catalyzed cross-coupling reactions between Csp^2-centers have been extensively used for preparing pharmaceuticals and agrochemical intermediates.[1] Whereas Suzuki cross-coupling reactions have found many applications due to the high functional group compatibility of boronic acids and esters,[2] the Negishi cross-coupling reaction[3] involving the reaction of organozinc reagents with organic halides in the presence of a palladium catalyst has found decidedly less applications due to the water- and air-instability of most organozinc species.[4] However, the excellent ability of organozinc species for undergoing transmetalation reactions allows one often to perform Negishi cross-coupling reactions under exceedingly mild reaction conditions.[5] Since polyfunctional organozinc reagents can be readily prepared by direct insertion of zinc[6] or by transmetalation reactions,[7] a number of polyfunctionalized organozinc reagents[4a] are readily available for cross-coupling reactions. This remarkable functional group tolerance allows the synthesis of highly functionalized cross-coupling products without the need of protecting groups. Especially sensitive are functional groups in high oxidation states like a nitro or an azido group.[7] Recently, we have reported that arylmagnesium compounds bearing a nitro group[8] can be readily prepared using an iodine/magnesium exchange[9] reaction at low temperature. This may be surprising since nitro groups were notoriously known to disturb organometallic reactions involving especially polar organometallics like organolithiums. While alkyl- and alkenylmagnesium reagents are known to add to the nitro group or the aromatic ring,[10] arylmagnesium halides enable a clean iodine/magnesium exchange reaction at *o*-iodonitrobenzenes.[8,11] Herein, we report that various *ortho*-nitro-substituted arylmagnesium reagents of type **1** prepared by an iodine-magnesium exchange reaction starting from the corresponding aryl iodides **2** and mesitylmagnesium bromide are readily transmetalated to the corresponding organozinc compounds **3**. These nitro-containing organometallics undergo a smooth cross-coupling reaction[12] with various aryl iodides (**4**) in the presence of bis(dibenzylideneacetone)palladium(0) [Pd(dba)$_2$ 5 mol %][13] and tris(*o*-furyl)phosphine (tfp; 10 mol %)[14] leading to highly functionalized nitro-substituted biphenyls of type **5** (Scheme 1 and Table 1).

Thus, the reaction of ethyl 4-iodo-3-nitrobenzoate (**2a**) with mesitylmagnesium bromide[15] (1.05 equivs.) in THF at –40 °C furnishes within 15 min the desired arylmagnesium species **1a**, which was immediately transmetalated to the corresponding zinc derivative **3a** by the reaction with zinc bromide at –40 °C (10 min). This resulting organozinc (**3a**) is perfectly stable at 20 °C and reacts in the presence of Pd(dba)$_2$ (5 mol %) and tfp (10 mol %) within 6 h at 20 °C with a broad range of aryl iodides. Aromatic halides like 4-nitro-1-iodobenzene (**4a**) react especially well furnishing the desired biphenyl **5a** in 85% yield (entry 1 of Table 1). An aryl iodide



Scheme 1. Negishi cross-coupling of *o*-nitroarylzinc halides with aryl iodides.

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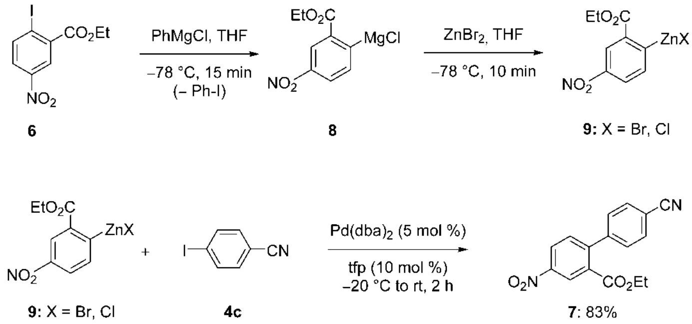
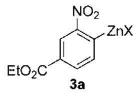
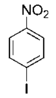
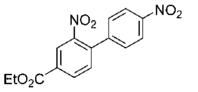
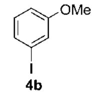
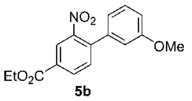
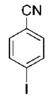
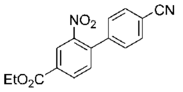
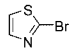
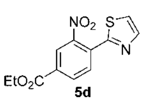
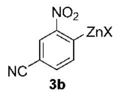
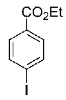
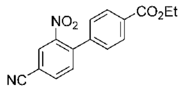
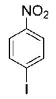
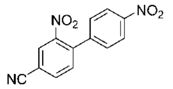
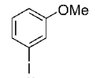
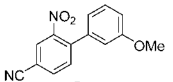
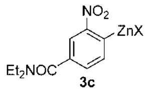
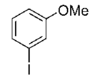
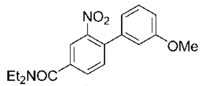
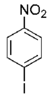
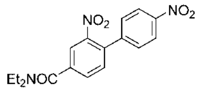
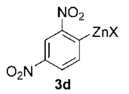
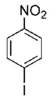
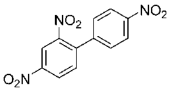
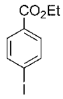
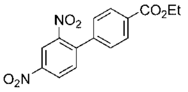
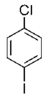
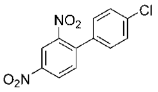


Scheme 2. Negishi cross-coupling using PhMgCl for generating the intermediate arylmagnesium halide.

bearing an electron-withdrawing group like 3-methoxy-1-iodobenzene (**4b**) reacts similarly with **3a** affording the corresponding biphenyl **5b** in 80% yield (entry 2). Interestingly, 4-iodobenzonitrile (**4c**) produces the biphenyl **5c** only in 53% yield (entry 3). A heterocyclic bromide such as 2-bromothiazole (**4d**) provides the desired cross-coupling product **5d** in 48% yield (entry 4). Similarly the cyano-substituted zinc reagent **3b** reacts with aryl iodides (**4a, b, e**) as expected leading to the polyfunctional biphenyls **5e–g** in 68–73% yield (entries 5–7). An amide substituted organozinc compound like **3c** leads to the Negishi cross-coupling products **5h, i** in 67 and 74% (entries 8 and 9). Remarkably, the 2,4-dinitro-substituted arylzinc compound **3d** can also be prepared according to our method and shows as well a good thermal stability under the reaction conditions. Its cross-coupling with the functionalized aryl iodides **4a, e, f** provides the expected biphenyls **5j–l** in 55–68% (entries 10–12). Especially interesting is the synthesis of the biphenyl **5i**, which bears three nitro groups but does not undergo any electron-transfer reaction, showing that Negishi cross-coupling reactions are compatible with the presence of reagents bearing nitro functionalities. In all these cross-coupling reactions, mesitylmagnesium bromide was chosen for performing the preparation of the starting organomagnesium species of type **1** (Scheme 1) instead of phenylmagnesium chloride used in the original report.[8] This was to avoid the production of iodobenzene, which could compete during the cross-coupling reaction with the aryl iodide (**4**) added for performing the cross-coupling. In the case of mesitylmagnesium bromide, the iodine-magnesium exchange reaction produces mesityl iodide, which undergoes only reluctantly an insertion of palladium due to the steric hindrance of the two *ortho*-methyl groups and the electron-donating effects of the methyl substituents. However, by using an excess of the aryl iodide of type **4**, phenylmagnesium chloride can be used as well. Thus, the reaction of ethyl 2-iodo-4-nitrobenzoate **6** with phenylmagnesium chloride at −78 °C for 10 min in THF produces the desired magnesium species which after transmetalation with $ZnBr_2$ (−78 °C, 10 min) undergoes a smooth cross-

Table 1. Polyfunctional biphenyls **5a – l** obtained by Pd-catalyzed cross-couplings of nitro-substituted arylzinc compounds.

Entry	Arylzinc reagent **3**	Aryl Iodide of Type **4**	Biphenyl of Type **5**	Yield [%][a]
1	 **3a**	 **4a**	 **5a**	85
2	**3a**	 **4b**	 **5b**	80
3	**3a**	 **4c**	 **5c**	53
4	**3a**	 **4d**	 **5d**	48
5	 **3b**	 **4e**	 **5e**	73
6	**3b**	 **4a**	 **5f**	68
7	**3b**	 **4b**	 **5g**	75
8	 **3c**	 **4b**	 **5h**	67
9	**3c**	 **4a**	 **5i**	74
10	 **3d**	 **4a**	 **5j**	55
11	**3d**	 **4e**	 **5k**	68
12	**3d**	 **4f**	 **5l**	55

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[a] Isolated yield of analytically pure products

coupling reaction with 4-iodobenzonitrile (**4c**) used in excess (2.2 equivs.) producing the desired biphenyl **7** in 83% yield (Scheme 2).

In summary, we have developed reaction conditions allowing the Negishi cross-coupling of various nitro-substituted arylzinc compounds with various aryl iodides providing nitro-containing biphenyls, which cannot be prepared by electrophilic nitration.

Experimental Section

Materials and Instrumentation

Melting points are uncorrected. Mesitylmagnesium bromide and phenylmagnesium chloride were titrated prior to use according to the method of Paquette.[16] $ZnBr_2$ was used as a 1 M solution prepared by drying $ZnBr_2$ (3.78 g, 15 mmol) under vacuum for 4 h at 140 °C and dissolving the cold salt in 15 mL of dry THF. THF was dried with sodium/benzophenone. Gas chromatographic analysis (GC) was carried out on a Hewlett-Packard 5890 Series II with an HP 5 column and the compounds were detected with a flame ionization detector.

Ethyl 2,4′-Dinitro[1,1′-biphenyl]-4-carboxylate (5a)

A dry and argon flushed 25 mL flask, equipped with a magnetic stirrer and a septum, was charged with ethyl 4-iodo-3-nitrobenzoate (321 mg, 1 mmol). Dry THF (5 mL) was added, the mixture cooled to −40 °C and mesitylmagnesium bromide (1.6 mL, 1.1 mmol, 0.7 M in THF) was added dropwise. The I/Mg exchange was complete after 15 min (checked by GC analysis of reaction aliquots) and zinc bromide (1.1 mL, 1.1 mmol, 1 M in THF) was added to the magnesiated benzoate. Another dry two-necked flask equipped with a magnetic stirrer and a septum was charged with bis(dibenzylideneacetone)palladium(0) [$Pd(dba)_2$; 29 mg, 5 mol %] and tris(*o*-furyl)phosphine (tfp; 25 mg, 10 mol %) followed by THF (2 mL). The initial red color disappeared after 2 min leading to a yellow solution and 4-iodo-1-nitrobenzene (374 mg, 1.5 mmol) was added. This solution was added via cannula after 10 min of stirring to the reaction mixture at −40 °C and the cooling bath was removed. The reaction mixture was stirred for 5 h at room temperature, treated with ethanol (2 mL) and poured into water (25 mL). The aqueous phase was extracted with ethyl acetate (3 × 40 mL), the collected organic phases were washed with brine (30 mL), dried (Na_2SO_4) and concentrated under vacuum. Purification by flash chromatography (pentane/diethyl ether = 3:1) afforded ethyl 2,4′-dinitro[1,1′-biphenyl]-4-carboxylate (**5a**) as a pale yellow solid; yield: 269 mg, (85%); mp 124.5–125 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.61 (s, 1H), 8.34–8.28 (m, 3H), 7.54–7.47 (m, 3H), 4.44 (q, $^3J_{H,H} = 7$ Hz, 2H), 1.43 (t, $^3J_{H,H} = 7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 163.9, 148.6, 147.9, 143.3, 138.1, 133.4, 131.9, 128.9, 125.6, 123.9, 62.1, 14.2. MS (70 eV, EI): *m/z* (%) = 316 (51) [M^+], 299 (50), 271 (88), 255 (9), 242 (53), 225 (46), 214 (72), 195 (36), 179 (72), 168 (26), 150 (100), 139 (67), 125 (13), 115 (21), 99 (9), 75 (24), 63 (10); IR (KBr): ν = 1722 (vs), 1530 (s), 1517 (s), 1353 (vs), 1307 (s), 1286 (s), 1242 (m), 1126 (m), 1110 (m), 857 (m), 850 (m), 749 cm^{-1} (m); anal. calcd. for $C_{15}H_{12}N_2O_6$: C 56.96, H 3.82, N 8.86; found: C 56.69, H 3.74, N 8.78; HRMS calcd. for $C_{15}H_{12}N_2O_6$: 316.0695; found: 316.0686.

Ethyl 4′-Cyano-4-nitro[1,1′-biphenyl]-2-carboxylate (7)

A dry and argon flushed 25 mL flask, equipped with a magnetic stirrer and a septum, was charged with ethyl 2-iodo-5-nitrobenzoate (**6**; 321 mg, 1 mmol). Dry THF (5 mL) was added, the mixture cooled to −78 °C and phenylmagnesium chloride (0.65 mL, 1.05 mmol, 1.6 M in THF) was added dropwise. The I/Mg-exchange was complete after 10 min (checked by GC analysis of reaction aliquots) and zinc bromide (1.1 mL, 1.1 mmol, 1 M in THF) was added to the magnesiated benzoate at −78 °C. Another dry two-necked flask equipped with a magnetic stirrer and a septum was charged with bis(dibenzylideneacetone)palladium(0) [$Pd(dba)_2$; 29 mg, 5 mol %) and tris(*o*-furyl)phosphine (tfp; 25 mg, 10 mol %) followed by THF (2 mL). The initial red color disappeared after 2 min leading to a yellow solution and 4-iodobenzonitrile (458 mg, 2 mmol) was added. This solution was added via cannula after 10 min of stirring to the reaction mixture at −78 °C and the cooling bath was removed. The reaction mixture was stirred for 2 h at room temperature, treated with ethanol (2 mL) and poured into water (25 mL). The aqueous phase was extracted with ethyl acetate (3 × 40 mL), the collected organic phases were washed with brine (30 mL), dried (Na_2SO_4) and concentrated under vacuum. Purification by flash chromatography (pentane/diethyl ether = 2:1) furnished ethyl 4′-cyano-4-nitro[1,1′-biphenyl]-2-carboxylate (**7**) as a pale yellow solid; yield: 245 mg (83%); mp 105–106 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.77 (d, $^4J_{H,H} = 3$ Hz, 1H), 8.40 (dd, $^3J_{H,H} = 8$ Hz and $^4J_{H,H} = 3$ Hz, 1H), 7.72 (d, $^3J_{H,H} = 8$ Hz, 2H), 7.53 (d, $^3J_{H,H} = 8$ Hz, 1H), 7.40 (d, $^3J_{H,H} = 8$ Hz, 2H), 4.20 (q, $^3J_{H,H} = 7$ Hz, 2H), 1.12 (d, $^3J_{H,H} = 7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.7, 147.6, 144.5, 132.4, 132.1, 128.9, 126.9, 124.9, 118.8, 114.0, 112.9, 89.1, 62.5, 14.3; MS (70 eV, EI): *m/z* (%) = 296 (51) [M^+], 268 (53), 251 (100), 205 (32), 177 (28), 150 (12), 140 (8); IR (KBr): ν = 2228 (s), 1710 (vs), 1609 (s), 1525 (vs), 1474 (s), 1419 (m), 1353 (vs), 1304 (s), 1283 (vs), 1262 (m), 1153 (s), 1143 (s), 1006 (s), 837 (m), 733 cm^{-1} (m); anal. calcd. for $C_{16}H_{12}N_2O_4$: C 64.86, H 4.08, N 9.20; found: C 65.14, H 4.09, N 9.20; HRMS: calcd. for $C_{16}H_{12}N_2O_4$: 296.0797; found: 296.0865.

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