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Manganese-Catalyzed Aerobic Heterocoupling of Aryl Grignard Reagents

Hajar Golshahi Ghaleshahi,[a] Giuseppe Antonacci,[a] and Robert Madsen*[a]

Abstract: An improved protocol has been developed for the MnCl2-catalyzed cross coupling of two arylmagnesium bromides under an atmosphere of dioxygen. The reaction is achieved with a 2:1 ratio between the Grignard reagents and 20% of MnCl2. Very good yields of the heterocoupling product can be obtained when the limiting Grignard regent undergoes very little homocoupling under the reaction conditions. Arylmagnesium bromides with p-methoxy, p-dimethylamino, p-fluoro and p-chloro substitutents were shown to give high yields in the cross coupling with a variety of substituted aryl Grignard reagents. Heterocyclic Grignard reagents, on the other hand, were less effective substrates for the transformation due to a rapid homocoupling with these reagents.

Introduction

The biaryl structural motif is an important subunit in many pharmaceuticals, agrochemicals, conducting materials and natural products.[1] The synthesis of biaryl compounds can be performed by a metal-catalyzed cross coupling reaction between aryl halides and various arylmetal (or –boron) species.[2,3,4,5,6,7,8,9] An important alternative is the oxidative coupling of two arylmetal compounds[2] where the reaction with Grignard reagents is particularly attractive due to the ease of their formation. The oxidative homocoupling of organomagnesium halides has been described with a range of different catalysts and stoichiometric oxidants. This includes iron, copper, cobalt, manganese, nickel and ruthenium catalysts with dioxygen, a diaziridinone and a boron species.[10] We have previously studied the reactivity of Grignard reagents[11] and used MnCl2 as a catalyst for a radical-mediated C-C coupling reaction.[12] We speculated that the manganese-catalyzed aerobic coupling of Grignard reagents could be improved and applied to a wider variety of substrates. It should be possible to use a lower amount of the manganese catalyst and to obtain a higher yield of the heterocoupling product. Herein, we describe our optimized procedure for the MnCl2-catalyzed aerobic cross coupling of aryl Grignard reagents.

Results and Discussion

Phenyl- and p-methoxyphenylmagnesium bromide were selected as the two Grignard reagents for the initial experiments. THF was employed as the solvent since MnCl2 is soluble in this solution in the presence of LiCl. On the contrary, MnCl2 is not soluble in Et2O resulting in a very slow transmetalation with organomagnesium halides in Et2O.[10] The conditions for the heterocoupling involve mixing of the components at -5 °C, stirring for 5 min and then allowing a flow of dioxygen to pass through the solution.[12] Under these conditions we obtained a 67% GC yield of 4-methoxybiphenyl (Table 1, Entry 1) while 80% was reported in the earlier study.[7] The yield did not change by using the corresponding chlorides of the Grignard reagents while a slightly lower yield was obtained with dry air instead of dioxygen. With 20% of the manganese catalyst the yield of 4-methoxybiphenyl dropped to a mere 40% (Entry 2). However, stirring the mixture for more than 5 min and at a lower temperature before the addition of dioxygen turned out to have a significant impact on the outcome (Entries 3–5). No reaction occurred before the addition of dioxygen, but the color of the mixture changed from yellow to green by stirring for 10 – 20 min after mixing the reactants. With the longer mixing time and a lower temperature the heterocoupling yield could now be

[a] Department of Chemistry, Technical University of Denmark, 2800 Kgs. Lyngby, Denmark
E-mail: rm@kemi.dtu.dk
http://www.kemi.dtu.dk

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This also made it possible to use a lower amount of the catalyst where essentially the same results were obtained with 50%, 30% and 20% of MnCl₂ while 10% of MnCl₂ gave a moderate yield due to incomplete conversion of the starting materials (Entries 6–10). In addition, the ratio between the two Grignard reagents could be lowered to 2:1 which gave the same result as with the 2.5:1 ratio. The reaction mixture turned black during the addition of dioxygen and a side reaction presumably involves oxidation of manganese(II) to higher valent and inactive species which would explain the need for 20% of MnCl₂. A control experiment revealed that no reaction occurred when MnCl₂ was replaced with MnO₂. As a result, our modified procedure for the heterocoupling employs 20% of MnCl₂ and stirring the reactants at -10 °C for at least 20 min before the addition of dioxygen.

Table 1. Optimization of the MnCl₂-catalyzed aerobic cross coupling.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mixing time of 1 and 2 [min]</th>
<th>%a</th>
<th>T [°C]</th>
<th>Yield [%]¹⁺²</th>
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<tr>
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<td>5</td>
<td>70</td>
<td>67[H]</td>
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<tr>
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<td>5</td>
<td>20</td>
<td>40</td>
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<td>96</td>
</tr>
<tr>
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<td>2:1</td>
<td>20</td>
<td>70</td>
<td>96</td>
</tr>
<tr>
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<td>2:1</td>
<td>20</td>
<td>50</td>
<td>96</td>
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<td>95</td>
</tr>
<tr>
<td>10</td>
<td>2:1</td>
<td>20</td>
<td>10</td>
<td>57</td>
</tr>
</tbody>
</table>

[¹] GC yield. [²] 8% of 4,4'-dimethoxybiphenyl was also obtained.

Under these conditions a 95% yield of 4-methoxybiphenyl was obtained with a 2:1 ratio of the two Grignard reagents (Table 1, Entry 9). Clearly, the two starting materials do not react to give a pure statistical mixture of the homo- and heterocoupling products which would only result in 67% of 4-methoxybiphenyl. The explanation came by monitoring the coupling during the first 6 min by withdrawing samples and quenching with iodine. This showed that p-methoxyphenylmagnesium bromide undergoes very little homocoupling while the homocoupling of phenylmagnesium bromide and the desired heterocoupling occur to approximately the same degree (Figure 1). Consequently, the heterocoupling may afford a very high yield when the limiting Grignard reagent, on which the yield is based,
$p$-Dimethylaminophenylmagnesium bromide is also a Grignard reagent that undergoes very little homocoupling under the reaction conditions. As a result, very high yields could be obtained in the heterocoupling with phenyl- and $p$-fluorophenylmagnesium bromide (Entries 6 and 7). During the latter experiment it was discovered that the para-fluoro reagent reacted faster in the heterocoupling than in the homocoupling. Consequently, it should be possible to use Grignard reagents
with electron-withdrawing groups as the limiting agent and still obtain a good yield in the cross coupling. Reversing the two coupling partners in Entry 7 gave only a slightly lower yield (Entry 8). Coupling of 3-fluorophenylnitromethane bromide with phenyl-, 3-toly-, 3-cyanophenyl- and 3-chlorophenylnitromethane bromide gave the corresponding biphenyl products in similar yields (Entries 9 – 12). Reversing the Grignard reagents in the last experiment led to only a small decrease in the yield (Entry 13) showing that p-chlorophenylnitromethane bromide also reacts slower in the homocoupling than in the heterocoupling. This was confirmed by reacting p-chlorophenylnitromethane bromide with phenylmagnesium bromide to give 4-chlorobiphenyl in 81% yield (Entry 14). The same reaction with p-methoxyphenylmagnesium bromide increased the yield to 87% due to the slow homocoupling of the latter (Entry 15). Coupling of p-fluorophenylnitromethane bromide with several heterocyclic Grignard reagents led to moderate yields (Entries 16 – 18), which is presumably caused by the rapid homocoupling of these heterocyclic reagents as noted above.

Grignard reagents with ortho and meta substituents could also be used in the cross coupling. The reaction between o-methoxyphenylmagnesium bromide and phenylmagnesium bromide afforded the product in 70% yield (Entry 19) while the transformation with several meta-substituted reagents gave moderate to good yields (Entries 20 – 22). The lower yield with the ortho-substituted substrate in Entry 19 illustrates the influence of steric effects when compared with the para reagent in Entry 1.

Conclusions

In summary, we have developed an improved protocol for the MnCl₂-catalyzed aerobic cross coupling of arylmagnesium halides. It is important to allow the two Grignard reagents to react with MnCl₂ before the addition of dioxygen since the subsequent oxidative coupling is a very fast reaction. Under these conditions high yields could be obtained in a number of cases with a 2:1 ratio between the Grignard reagents and 20% of MnCl₂. The successful cross-coupling reactions were achieved when the limiting arylmagnesium halide show only little inclination to undergo a competing self-coupling. Very little homocoupling was observed with p-methoxy- and p-dimethylaminophenylnitromethane bromide while relatively little homocoupling occurred with p-fluoro- and p-chlorophenylnitromethane bromide. The successful coupling of Grignard reagents with electron-withdrawing substituents constitutes a new development for this transformation. Heterocyclic Grignard reagents, on the other hand, were not good coupling partners since the self-coupling with these reagents is a fast reaction.

Experimental Section

General: Gas chromatography was performed on a Shimadzu GCMS-QP2010S instrument fitted with an Equity 5, 30 m × 0.25 mm × 0.25 μm column. Flash column chromatography separations were performed on silica gel 60 (40 – 63 μm). NMR spectra were recorded on a Bruker Ascend 400 spectrometer. Chemical shifts were measured relative to the signals of residual CHCl₃ (δ = 7.26 ppm) and CDCl₃ (δ = 77.16 ppm). HRMS measurements were made using ESI with TOF detection.

Grignard reagents: The heterocyclic Grignard reagents and p-cyanophenylnitromethane bromide were prepared from the corresponding bromides and magnesium in THF while the remaining reagents were purchased from commercial suppliers. All Grignard reagents were titrated with a 0.06 M solution of Li in Et₂O to determine the concentration: phenylmagnesium bromide (1.5 M in 2-methyltetrahydrofuran), p-methoxyphenylmagnesium bromide (0.6 M in THF), p-fluorophenylnitromethane bromide (0.3 M in THF), 2-thiophenylnitromethane bromide (1.2 M in THF), 3-pyridylmagnesium bromide (0.5 M in THF), p-fluorophenylnitromethane bromide (0.5 M in THF), p-tolylmagnesium bromide (0.3 M in Et₂O), p-chlorophenylnitromethane bromide (0.5 M in Et₂O), 2-furymagnesium bromide (0.2 M in THF), o-methoxyphenylmagnesium bromide (0.6 M in THF), m-fluorophenylnitromethane bromide (0.6 M in THF), m-chlorophenylnitromethane bromide (0.6 M in THF), and m-methoxyphenylmagnesium bromide (0.6 M in THF).

General Procedure for Aerobic Heterocoupling of Two Grignard Reagents: A dry three-neck round-bottom flask was equipped with a stir bar, a thermometer and a nitrogen inlet. The flask was flushed with nitrogen and charged with MnCl₂ (51 mg, 0.403 mmol), LiCl (37 mg, 0.873 mmol) and dry THF (3 mL). The mixture was stirred for about 10 min to completely dissolve MnCl₂ and LiCl followed by cooling to -10 °C. A solution of the Grignard reagent in excess (4 mmol) was added dropwise over 4 min and the mixture was then stirred for an additional 2 min before dropwise addition of the limiting Grignard reagent (2 mmol) over 4 min. The mixture was stirred for 20 – 30 min after which time the nitrogen flow was stopped and a balloon of dioxygen was connected through a septum with a needle. A continuous flow of dioxygen was allowed into the reaction flask for 10 min which caused the temperature to rise to +10 – +20 °C and the color to change to black. Decane (0.4 mL, 2 mmol) was then injected as an internal standard for determining the yield by GC and the reaction was quenched with saturated ammonium chloride solution (10 mL). The mixture was extracted with EtOAc (2 × 10 mL) and the combined organic layers were concentrated and the residue purified by flash column chromatography.

1-Methoxy-1,1-biphenyl[57] Table 1 and Table 2, Entry 1. Purified by flash chromatography (heptane/EtOAc, 99:1) to afford a white solid. ¹H NMR (400 MHz, CDCl₃): δ = 3.86 (s, 3H), 6.99 (d, J = 8.8 Hz, 2H), 7.31 (t, J = 7.8 Hz, 1H), 7.42 (dd, J = 8.5, 6.9 Hz, 2H), 7.55 (t, J = 8.2 Hz, 2H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 140.1, 128.5, 128.5, 128.5, 128.5, 130.6, 130.6, 130.6, 130.6 ppm. MS: m/z = 184.10 [M⁻].

1-Methoxy-N,N-dimethyl[1,1'-biphenyl]-4-amine[58] Table 2, Entry 2. Purified by flash chromatography (heptane/EtOAc, 10:1) to afford a white solid. ¹H NMR (400 MHz, CDCl₃): δ = 2.99 (s, 6H), 3.85 (s, 3 H), 6.83 (d, J = 8.3 Hz, 2H), 6.96 (d, J = 8.3 Hz, 2H), 7.48 (t, J = 9.0 Hz, 4H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 50.7, 55.2, 114.0, 126.8, 126.8, 128.5, 130.6, 130.6, 137.3, 149.1, 158.1 ppm. MS: m/z = 227.00 [M⁺].

1-Methoxy-[1,1'-biphenyl]-4-carbonitrile[59] Table 2, Entry 3. Purified by flash chromatography (heptane/EtOAc, 98:2) to yield a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ = 3.86 (s, 3H), 7.00 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.74–7.61 (m, 4H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 55.8, 110.5, 115.0, 119.5, 127.5, 128.8, 131.9, 133.0, 145.6, 160.6 ppm. MS: m/z = 209.00 [M⁺].

2-[4-Methoxyphenyl]thiophene[57] Table 2, Entry 4. Purified by flash chromatography (pentane) to give a white solid. ¹H NMR (400 MHz,
CDCl₃): δ = 3.84, 3 (s, 4 H), 6.92 (d, J = 8.8 Hz, 2 H), 7.06 (dd, J = 5.1, 3.6 Hz, 1 H), 7.17–7.23 (m, 2 H), 7.54 (d, J = 8.8 Hz, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 55.8, 114.7, 122.5, 124.3, 127.7, 128.4, 144.8, 159.6 ppm. MS: m/z = 189.95 [M⁺].

3-[(4-Methoxyphenyl)pyridine][16] Table 2, Entry 5. Purified by flash chromatography (heptane/EtOAc, 3:1) to afford a white solid. ¹H NMR (400 MHz, CDCl₃): δ = 3.86 (s, 3 H), 7.02 (d, J = 8.8 Hz, 2 H), 7.37 (dd, J = 8.0, 4.8 Hz, 1 H), 7.52 (d, J = 8.8 Hz, 2 H), 7.73–7.97 (m, 1 H), 8.54 (dd, J = 5.0, 1.5 Hz, 1 H), 8.82 (d, J = 2.4 Hz, 1 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 55.9, 115.1, 124.2, 128.7, 130.4, 134.8, 137.0, 147.8, 160.3 ppm. MS: m/z = 185.00 [M⁺].

N,N-Dimethyl-1,1'-biphenyl-4-amine[16] Table 2, Entry 6. Purified by flash chromatography (heptane/EtOAc, 10:1) to furnish a white solid. ¹H NMR (400 MHz, CDCl₃): δ = 3.04 (s, 6 H), 6.87 (d, J = 8.3 Hz, 2 H), 7.32 (t, J = 7.4 Hz, 1 H), 7.46 (t, J = 7.6 Hz, 2 H), 7.58 (d, J = 8.4 Hz, 2 H), 7.63 (d, J = 7.6 Hz, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 41.1, 113.3, 126.0, 126.7, 128.2, 129.1, 129.8, 141.6, 160.3 ppm. MS: m/z = 197.15 [M⁺].

4'-Fluoro-N,N-dimethyl-1,1'-Biphenyl-4-amine[16] Table 2, Entries 7 and 8. Purified by flash chromatography (heptane/EtOAc, 3:1) to yield a pink solid. ¹H NMR (400 MHz, CDCl₃): δ = 3.01 (s, 6 H), 6.84 (d, J = 8.4 Hz, 2 H), 7.09 (t, J = 8.7 Hz, 2 H), 7.55–7.42 (m, 4 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 41.2, 113.5, 115.9 (d, J = 21 Hz), 128.2 (d, J = 7 Hz), 128.2, 137.8 (d, J = 3 Hz), 150.2, 160.8, 161.2 (d, J = 244 Hz) ppm. HRMS: calcld. for C₁₄H₁₄NO₂: [M⁺] m/z = 216.1188, found 216.1183.

4-Fluoro-1,1'-biphenyl[16] Table 2, Entry 9. Purified by flash chromatography (pentane) to furnish a white solid which contains small amounts of 1,1'-biphenyl and 4,4'-difluoro-1,1'-biphenyl. ¹H NMR (400 MHz, CDCl₃): δ = 7.19 (t, J = 8.7, 4.1 Hz, 2 H), 7.42 (t, J = 7.1, 1.7 Hz, 1 H), 7.57–7.47 (m, 2 H), 7.61 (t, J = 5.8, 1.8 Hz, 4 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 116.0 (d, J = 21 Hz), 127.7, 128.9 (d, J = 8 Hz), 129.2, 129.3, 136.8 (d, J = 3 Hz), 140.7, 162.6 (d, J = 254 Hz) ppm. MS: m/z = 172.10 [M⁺].

4-Fluoro-4'-methyl-1,1'-biphenyl[16] Table 2, Entry 10. Purified by flash chromatography (pentane) to give a white solid which contains a small amount of 4,4'-dimethyl-1,1'-biphenyl. ¹H NMR (400 MHz, CDCl₃): δ = 2.22 (s, 3 H), 6.94 (d, J = 8.7, 2.9 Hz, 2 H), 7.07 (dd, J = 8.2, 1.9 Hz, 2 H), 7.21–7.43 (m, 4 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 21.5, 116.0 (d, J = 21 Hz), 127.3, 128.9 (d, J = 9.0 Hz), 130.0, 137.5, 137.7 (d, J = 2.0 Hz), 137.8, 162.7 (d, J = 244 Hz) ppm. MS: m/z = 185.95 [M⁺].

4'-Fluoro-[1,1'-biphenyl]-4-carboxonitrile[16] Table 2, Entry 11. Purified by flash chromatography (heptane/EtOAc, 98:2) to give a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ = 3.92 (s, 3 H), 7.06 (d, J = 8.4 Hz, 2 H), 7.72 (d, J = 8.6 Hz, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 111.1, 116.3 (d, J = 21 Hz), 119.0, 127.7, 129.1 (d, J = 8 Hz), 132.8, 135.4, 144.8, 163.4 (d, J = 247 Hz) ppm. MS: m/z = 196.95 [M⁺].

4-Chloro-4'-fluoro-1,1'-biphenyl[16] Table 2, Entries 12 and 13. Purified by flash chromatography (pentane) to afford a white solid which contains a small amount of 4,4'-dichloro-1,1'-biphenyl. ¹H NMR (400 MHz, CDCl₃): δ = 7.13 (t, J = 8.8, 2.7 Hz, 2 H), 7.35–7.53 (m, 6 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 116.2 (d, J = 22 Hz), 128.7, 129.0 (d, J = 8 Hz), 129.4, 133.9, 136.6 (d, J = 4 Hz), 139.1, 163.1 (d, J = 245 Hz) ppm. MS: m/z = 206.10 [M⁺].

4-Chloro-1,1'-biphenyl[16] Table 2, Entry 14. Purified by flash chromatography (pentane) to give a white solid. ¹H NMR (400 MHz, CDCl₃): δ = 7.58–7.48 (m, 4 H), 7.48–7.33 (m, 5 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 127.5, 128.5, 128.9, 129.3, 133.8, 140.1, 140.5 ppm. MS: m/z = 184.05 [M⁺].
We thank the Danish Council for Independent Research – Technology and Production Sciences for financial support.

**Keywords:** Cross-coupling • Grignard reagent • Homogeneous catalysis • Manganese • Oxygen


[8] In reference 7 the amount of MnCl₂-LiCl is reported as 20%, but according to the supporting information the percentage is calculated from the Grignard reagent in excess (2.5 equiv.) and not from the limiting agent (1 equiv.). As a result, it is more appropriate to list the amount as 70% since the yields are also based on the limiting Grignard reagent.


Oxidative cross coupling of Grignard reagents can be achieved in good yield for a number of substituted arylmagnesium bromides where the competing homocoupling is a slow reaction.

*one or two words that highlight the emphasis of the paper or the field of the study