

# Use of functionalized aromatic organozinc reagents in the three-component Mannich-type synthesis of diarylmethylamines

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**Abstract**—Efficient syntheses of functionalized diarylmethylamines have been realized according to a one-step three-component coupling between an aromatic aldehyde, a secondary amine and an aromatic organozinc reagent. Phenyl rings can be substituted by functional groups and either aromatic or non-aromatic amines can be used in this process.

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Diarylmethylamines constitute an important class of amines, which are present in many structures showing pharmacological activities<sup>1</sup> and during the last years, there was a growing interest in their enantioselective syntheses. Although chiral reductions of benzophenone chromium tricarbonyl complexes followed by amination have been used,<sup>2</sup> most works in this field deal with stereoselective additions of nucleophiles to imines.<sup>3</sup> It was previously shown that organometallic reagents react with chiral imines to furnish diarylmethylamines in good enantiomeric excess.<sup>4</sup> Stereoselectivity can also be provided through the use of chiral mediators.<sup>5</sup> Thus, it was demonstrated that in the presence of chiral catalysts, strong nucleophiles like organolithium compounds add stereoselectively to aromatic imines.<sup>5a,b</sup> When milder nucleophiles are used, an activation of the C=N bond can be realized using sulfinyl, sulfonyl, formyl, or phosphonyl groups. Thus it was shown that organoboron<sup>4c</sup> or organostannane<sup>5d</sup> compounds associated with a rhodium catalyst react efficiently with activated imines to furnish coupling products in high yield and enantiomeric excess. Organozinc reagents react in a similar manner with activated imines in the presence of a chiral catalyst to provide diarylmethylamines<sup>5c</sup> or alkylarylmethylamines<sup>5f</sup> in excellent yields without requiring the use of an additional transition metal like rhodium. A resolution technique involving tartaric acid

was also successfully employed in the synthesis of the enantiomerically pure antihistamine agent cetirizine.<sup>6</sup>

In the field of racemate synthesis, numerous diarylmethylamines and especially diarylmethylpiperazines with potent biological activity were recently synthesized using a three-step procedure involving the formation of diarylmethanol in an intermediate step.<sup>7</sup> Reductive amination of carbonyl compounds using polymethylhydrosiloxane was successfully employed for the synthesis of racemic alkylarylmethylamines or diarylmethylamines in very good yield.<sup>8</sup> Several reactions involving Grignard reagents as the nucleophile have also been reported. For instance the arylation of iminium salts led to the corresponding coupling product in low to moderate yields.<sup>9</sup> It was also shown that the displacement of polymer-supported benzotriazole using aromatic Grignard reagents allows the formation of diarylmethylamines in moderate to good yield.<sup>10</sup> Several years ago, Petasis et al. described a one-step three-component reaction among organoboronic acids, amines, and aldehydes.<sup>11</sup> This method was successfully applied to the synthesis of some diarylmethylamines bearing a phenol moiety in good yield. However, it was mentioned that only *ortho*-hydroxylated benzaldehydes are efficient in this process. Recently, organotrifluoroborates were used instead of arylboronic acids in a Petasis-related reaction to provide some diarylmethylamines in good yield.<sup>12</sup>

To our knowledge, the use of readily available functionalized aromatic organozinc reagents in three-component Mannich-type reactions has not been described to date.

**Keywords:** Diarylmethylamines; Three-component reaction; Aromatic organozinc reagents; Aromatic aldehydes; Secondary amines.

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However, these compounds are very mild nucleophiles<sup>13</sup> and thus, starting materials can bear various functionalities. This feature could potentially allow access to highly functionalized diarylmethylamines through the one-step coupling of these reagents with aromatic aldehydes and secondary amines. Then, as a part of our

work devoted to the study of organozinc reagents reactivity, we investigated their possible use in Mannich-type reactions and we report herein our preliminary results.

Organozinc reagents were synthesized efficiently in acetonitrile from the corresponding aryl bromides accord-

**Table 1.** Three-component coupling between organozinc reagents, secondary amines, and aldehydes

Entry	Organozinc reagent	Amine	Aldehyde	Coupling method <sup>a</sup>	Reaction time (h)	Product	Isolated yield (%)
1				A	3		1 88
2				A	3		2 96
3				A	3		3 83
4				A	3		4 80
5				A	3		5 96
6				B	4		6 83
7				B	4		7 70
8				B	4		8 77

<sup>a</sup> In coupling method A, CuI (ca. 0.3 equiv vs ArZnX) was added into the organozinc solution before addition of the amine and the aldehyde. In coupling method B, the organozinc was added dropwise into the pre-heated mixture of the amine and the aldehyde in acetonitrile. See note 15 for experimental details.

ing to a method previously developed in the laboratory,<sup>14</sup> which was used after some improvements.<sup>15</sup> In order to achieve the three-component coupling reaction, two methods were used.<sup>16</sup> The most simple procedure (coupling method A) consisted in the introduction of a catalytic amount of cuprous iodide<sup>17</sup> in the organozinc-containing acetonitrile solution followed by the addition of the aromatic aldehyde and the secondary amine. The mixture was then allowed to react for a few hours at room temperature. As shown in Table 1 (entries 1–5), this method is very efficient when the phenyl moiety of the organozinc compound is substituted by electron donating groups. However, with an electron withdrawing substituent on the organozinc reagent, the dimeric by-product Ar–Ar arising from the starting ArZnBr is also obtained. In order to avoid this side reaction, the coupling procedure was modified according to coupling method B in which the organozinc-containing acetonitrile solution was added dropwise to a pre-heated mixture of the aromatic aldehyde and the secondary amine in acetonitrile. The corresponding results are reported in entries 6 and 7 of Table 1. It should be noted that coupling method B is more versatile since it can be also applied to compounds bearing electron donating groups as asserted by entry 8 of Table 1.

In each case, the addition of at least 2 equiv of the organozinc species is required to observe efficient couplings. The need for such quantities of arylzinc reagent is likely correlated to a base-assisted hydroxide elimination on the intermediate hemiaminal leading to a formal iminium ion, which is further attacked by the remaining organozinc compound. At this stage, the precise role of each constituent of the reaction medium remains unclear and efforts are in progress to understand precisely the mechanism of the reaction.

This three-component coupling reaction allows the formation of diarylmethylamines<sup>18</sup> in very high yields (70–96%) starting from readily available materials. Experimental conditions are mild and reactions proceed rather quickly (3–4 h). Electron withdrawing or donating groups are compatible with this process and it is worth noting that either a non-aromatic amine (entries 1–3 and 5–8) or an aromatic amine (entry 4) reacts in the same manner, furnishing the coupling product in high yield. Entries 2 and 3 of Table 1 show that functionalized benzaldehydes also react very efficiently. Highly substituted diarylmethylamines might therefore be affordable using both substituted organozinc and aldehyde. It is worth to note that, to our knowledge, all compounds synthesized using this procedure, except compound **8**, are new products.

In conclusion, preliminary results reported in this letter demonstrate that organozinc aromatic reagents are suitable nucleophiles in Mannich-type reactions involving secondary amines and benzaldehyde derivatives. This three-component coupling seems sufficiently versatile to allow numerous combinations between secondary amines, aromatic aldehydes, and starting aromatic bromides thus providing a potential access to highly substituted diarylmethylamines. Preliminary results presented

herein prompt us to examine the scope of the reaction and to investigate the mechanism of this coupling. Furthermore, in the field of asymmetric synthesis, additional experiments might be realized in the presence of chiral ligands in order to test the feasibility and enantioselectivity of the reaction.

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- Owing to the fact that in the original work, organozinc reagents were prepared on a 15 mmol scale and that in this work 30 mmol of the aryl bromide were used, optimization of the original procedure was done: trifluoromethanesulfonic acid was used instead of trifluoroacetic acid

and the mixture was kept at room temperature using a water bath after addition of the aryl bromide. These modifications of experimental conditions resulted in the formation of organozinc species in better yields (typically ranging from 80% to 95%) than using the original procedure (+5–10%).

16. In a typical procedure, a dried 100 mL tricol was flushed with argon and charged with acetonitrile (40 mL). Dodecane (0.20 mL, used as internal standard), cobalt bromide (0.66 g, 3 mmol), zinc bromide (0.68 g, 3 mmol), phenyl bromide (0.32 mL, 3 mmol), and zinc dust (6 g, 92 mmol) were added to the solution. Trifluoromethanesulfonic acid (0.20 mL) was added to the mixture under vigorous stirring. After ca. 15 min, the aryl bromide (30 mmol) was added to the solution and as soon as the exothermic reaction had began (ca. 5 min), a water bath at room temperature was used to moderate the temperature of the medium. The reaction time, which was monitored using gas chromatography, did not exceed 30 min in most cases. Coupling method A: The organozinc-containing solution was transferred via a syringe into a flask flushed with argon. Cuprous iodide (6 mmol) was first added under stirring into the solution followed by the addition of the aldehyde (10 mmol) and the amine (10 mmol). The stirring was continued for additional 3 h at room temperature. Coupling method B: A three-necked flask was equipped with a vertical water-cooled condenser and charged with acetonitrile (15 mL). The secondary amine (10 mmol) and the aldehyde (10 mmol) were added into the solvent and the mixture was heated at 70 °C. An addition funnel, connected above the condenser, was charged with the organozinc-containing solution. This solution was added dropwise (ca. 2 h) to the pre-heated mixture and stirred for additional 2 h at 70 °C. A typical acid-base workup was then applied to crude light brown oils, which were dissolved in diethyl ether. In each case, the diarylmethylamine was separated from by-products as its ammonium sulfate form by adding sulfuric acid then taken-up in dichloromethane in alkaline conditions. After drying over sodium sulfate and evaporation, analytically pure diarylmethylamines (>97% GC) were obtained as pale yellow liquids, which generally soon crystallized.
17. The nucleophilicity of organozinc reagents can be enhanced by copper I, see: Knochel, P.; Jones, P. In *Organozinc Reagents, A Practical Approach*; Harwood, L. M., Moody, C. J., Eds.; Oxford University Press: Oxford, 1999; pp 179–212.
18. Coupling products were characterized using <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>), <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>), HRMS and when useful FT IR or <sup>19</sup>F NMR (188 MHz, CDCl<sub>3</sub>). All products gave satisfactory spectroscopic data. Data for selected compounds: 4-(4-Methoxyphenyl(piperidin-1-yl)methyl)benzotrile (3): IR,  $\nu$  (cm<sup>-1</sup>): 2230; <sup>1</sup>H NMR,  $\delta$  (ppm): 1.30–1.60 (m, 6H), 2.20–2.40 (m, 4H), 3.74 (s, 3H), 4.23 (s, 1H), 6.81 (AB,  $J$  = 8.7 Hz, 2H), 7.22 (AB,  $J$  = 8.7 Hz, 2H), 7.52 (s, 4H); <sup>13</sup>C NMR,  $\delta$  (ppm): 24.64, 26.24, 53.04, 55.23, 75.60, 110.34, 114.05, 119.07, 128.49, 129.19, 132.28, 133.60, 149.63, 158.86; MS,  $m/z$  (relative intensity): 306 (9), 222 (100), 204 (20), 190 (9), 178 (7); HRMS calcd for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 307.1810, found: 307.1816.  
1-(Phenyl(3-(trifluoromethyl)phenyl)methyl)piperidine (6): <sup>1</sup>H NMR,  $\delta$  (ppm): 1.30–1.60 (m, 6H), 2.20–2.40 (m, 4H), 4.28 (s, 1H), 7.10–7.71 (m, 9H); <sup>13</sup>C NMR,  $\delta$  (ppm): 24.59, 26.17, 53.03, 76.15, 123.60, 124.70, 127.01, 128.04, 128.54, 130.31, 130.95, 142.14, 144.54; <sup>19</sup>F NMR,  $\delta$  (ppm): –62.18; MS,  $m/z$  (relative intensity): 319 (40), 242 (85), 235 (45), 215 (49), 195 (13), 174 (100), 165 (61), 84 (45); HRMS calcd for C<sub>19</sub>H<sub>21</sub>F<sub>3</sub>N [M+H]<sup>+</sup>: 320.1626, found: 320.1634.