Synthesis of polyfunctional secondary amines by the addition of functionalized zinc reagents to nitrosoarenes†

Vasudevan Dhayalan, Christoph Sämann and Paul Knochel*

Addition of functionalized aryl, heteroaryl or adamantyl zinc reagents to various nitroso-arenes in the presence of magnesium salts and LiCl in THF produces after a reductive work-up with FeCl2 and NaBH4 in ethanol the corresponding polyfunctional secondary amines in high yields.

The preparation of arylamines is an important synthetic goal since these compounds often have useful properties for pharmaceuticals or material science applications.1 Transition metal catalyzed aminations have been well studied,2 but the use of expensive and toxic metallic catalysts reduces somewhat the utility of such synthetic methods. Another approach has been the use of electrophilic nitrogen reagents and their reactions with non-expensive and low toxic main-group organometallics.3 A few years ago, we have reported that functionalized arylmagnesium reagents add to nitroso-arenes4 and nitro-arenes.5 Although satisfactory yields were obtained, the high reactivity of the carbon–magnesium bond reduces the functional group tolerance. Furthermore, nitroso-arenes have proven to be versatile reagents for performing nitroso aldol and related reactions.6

Herein, we wish to report a mild synthesis of diaryl or heteroaryl-(aryl)amines as well as functionalized highly sterically hindered adamantyl(aryl)amines. Thus, the treatment of an arylzinc derivative 2, prepared either by the direct insertion of Mg in the presence of LiCl and ZnCl2 (ref. 7) or by an I/Mg-exchange with iPrMgCl-LiCl8 followed by transmetalation with ZnCl2, with various nitroso-arenes of type 3affords an intermediate zinccated hydroxylamine derivative 4 which after reductive work-up with FeCl2 and NaBH4 in ethanol (25 °C, 15 h) produce the corresponding secondary amines of type 5 in excellent yields (Scheme 1). A range of functional groups have been tolerated in the starting arylzinc reagent as shown in Table 1.

Thus, PhZnCl (1.1 equiv.) prepared by the direct insertion of Mg in the presence of LiCl and ZnCl2 reacts with nitrosobenzene 3a (1.0 equiv.) at 25 °C within 2–3 h and produces after reductive work-up with FeCl2 (2.0 equiv.) and NaBH4 (1.0 equiv.) in ethanol (25 °C, 15 h) the corresponding diphenylamine 5a in 85% yield (Table 1, entry 1).10a The presence of both Mg salts and LiCl were found to be essential for achieving a high yield. A variety of arylzinc reagents prepared similarly were used in the addition to 3a. Both electron withdrawing and donating groups can be attached at the aryl ring (Table 1, entries 2–8).10b–g Arylzinc reagent 2c has been prepared via an I/Mg-exchange,8 its reaction with nitrosobenzene (3a) furnishes the corresponding secondary amine 5c in 76% yield (Table 1, entry 3). Although sensitive functional groups like a formyl or an acetyl group are not tolerated, the corresponding bromoacetal (1i) or bromoketal (1j) are readily converted to the zinc reagents (2i and 2j) by the insertion of Mg in the presence of LiCl and ZnCl2.7 The addition of nitrosobenzene (3a) provides after removal of the ethylene glycol protecting group (CF3CO2H in CH2Cl2 at 25 °C for 5–8 h) the secondary amines (5i and 5j) in 64–75% yield (Table 1, entries 9 and 10).

This addition reaction can be extended to various nitroso-arenes (commercially available) or prepared according to the method of Bäckvall.11 Again, electron-donating or accepting substituents are tolerated in the arylnitroso reagents of type 3 furnishing the...
corresponding diarylamines 5k–r in 77–97% yield (Table 2, entries 1–8). Noteworthy, a heterocyclic zinc reagent (2m) has also been used as well as a nitrosopyridine (3g) leading to heteroaryl(aryl)-amines 5s–y in 55–96% yield (Table 2, entries 9–15).

Moreover, tertiary alkylzinc reagents such as t-BuZnCl (6a) and adamantylzinc chloride (6b) add to various nitroso-arenes under similar reaction conditions producing otherwise difficult to prepare tertiaryalkyl(aryl)amines 7a–d in 50–89% yield (Table 3, entries 1–4).

In summary, we have shown that aryl, heteroaryl or adamantyl zinc reagents add to various nitroso-arenes in the presence of Mg-salts and LiCl. Both Mg and Li salts are necessary to achieve high yields for the synthesis of the corresponding functionalized secondary amines. Further extensions of this work are currently underway in our laboratories.

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Table 1 Synthesis of diarylamines of type 5 via the reaction of functionalized arylzinc reagents 2a–j with nitrosobenzene 3a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zn-reagent</th>
<th>Product, yield&lt;sup&gt;a,b&lt;/sup&gt; (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>2a, PhZnCl</td>
<td>PhNHPh</td>
</tr>
<tr>
<td>2</td>
<td>2b, FG = CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>5b: 69</td>
</tr>
<tr>
<td>3</td>
<td>2c, FG = CO&lt;sub&gt;2&lt;/sub&gt;Et&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5c: 76</td>
</tr>
<tr>
<td>4</td>
<td>2d, FG = tBu</td>
<td>5d: 96</td>
</tr>
<tr>
<td>5</td>
<td>2e, FG = SCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>5e: 70</td>
</tr>
<tr>
<td>6</td>
<td>2f, FG = OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>5f: 78</td>
</tr>
<tr>
<td>7</td>
<td>2g, FG = OTMS</td>
<td>5g: 80&lt;sup&gt;d&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup> General reaction conditions: arylzinc reagent (1.1 equiv.), nitroso electrophile (1.0 equiv.), NaBH<sub>4</sub> (1.0 equiv.), FeCl<sub>2</sub> (2.0 equiv.).
<sup>b</sup> Yield of analytically pure isolated product as determined by ‘H-NMR analysis.
<sup>c</sup> Prepared by I/Mg-exchange with iPrMgCl/LiCl.<sup>8</sup>
<sup>d</sup> The TMS-group was cleaved during workup and column chromatography purification.
<sup>e</sup> The aryldiazomethane reagents (2i and 2j) were prepared from the corresponding bromides (see ESI).
<sup>f</sup> Obtained after removal of the ethylene glycol group with CF<sub>3</sub>CO<sub>2</sub>H in CH<sub>2</sub>Cl<sub>2</sub> (see ESI).

Table 2 Synthesis of polyfunctional secondary amines of type 5 by the addition of aryl and heteroaryl zinc reagents 2a–m to various nitroso compounds 3a–g

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zn-reagent</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield&lt;sup&gt;a,b&lt;/sup&gt; (%)</th>
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<tr>
<td>1</td>
<td>2a</td>
<td>3b</td>
<td>5k</td>
<td>79</td>
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<tr>
<td>2</td>
<td>2a</td>
<td>3c</td>
<td>5k</td>
<td>77</td>
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<tr>
<td>3</td>
<td>2a</td>
<td>3d</td>
<td>5k</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>2a</td>
<td>3e</td>
<td>5k</td>
<td>97</td>
</tr>
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<td>5</td>
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<td>6</td>
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<td>3g</td>
<td>5k</td>
<td>81</td>
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<tr>
<td>7</td>
<td>2a</td>
<td>3h</td>
<td>5k</td>
<td>97&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>2a</td>
<td>3i</td>
<td>5k</td>
<td>75&lt;sup&gt;f&lt;/sup&gt;</td>
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Table 2 (continued)

<table>
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<tr>
<th>Ar-1-ZnX + Ar-2-NO</th>
<th>1. THF, 0 to 25 °C, 2-3 h</th>
<th>FeCl2 (2 equiv)</th>
<th>NaBH4 (1 equiv)</th>
<th>EtOH, 25 °C, 15 h</th>
<th>Ar-1-NHAr-2</th>
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<tr>
<td>Entry</td>
<td>Zn-reagent (Ar1)</td>
<td>Electrophile (Ar2)</td>
<td>Product</td>
<td>Yield (8) (%)</td>
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</tr>
<tr>
<td>14</td>
<td>2c</td>
<td>3g</td>
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<tr>
<td>15</td>
<td>2m</td>
<td>3g</td>
<td></td>
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</tr>
</tbody>
</table>

Notes and references

1 G. Thomas, Medicinal Chemistry, Wiley-VCH, Weinheim, 2000;

For the reaction of nitroarenes with Grignard reagents: (a) I. Saptowidjojo and P. Knochel, J. Am. Chem. Soc., 2002, 124, 9390;

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(e) M. Kim and S. Chang, Org. Lett., 2010, 12, 1640.


