Preparation of Polyfunctional Tertiary Amines via the Electrophilic Amination of Arylmagnesium Compounds Using *N*-Chloroamines

Pradipta Sinha, Paul Knochel*

Department Chemie und Biochemie, Ludwig-Maximilians-Universität München, Butenandtstraße 5–13, 81377 München, Germany
Fax +49(89)218077680; E-mail: Paul.Knochel@cup.uni-muenchen.de

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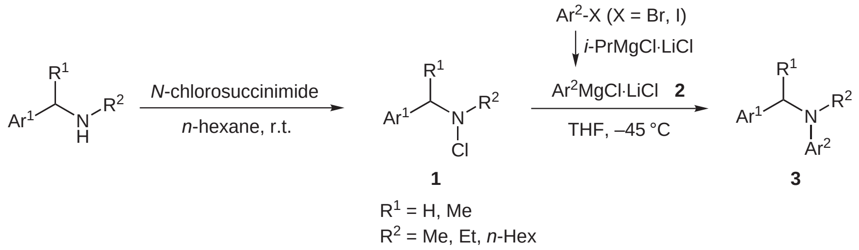
Abstract: Functionalized arylmagnesium compounds prepared via a halogen–magnesium exchange reaction using aryl iodides or bromides and *i*-PrMgCl·LiCl, react rapidly with benzyl-*N*-chloroamines at –45 °C providing polyfunctional tertiary amines in good yields. The methodology is also successfully applied to the preparation of chiral *N*-chloroamines with retention of chirality.

Key words: electrophilic amination, polyfunctional tertiary amines, arylmagnesium compounds, halogen–magnesium exchange, *N*-chloroamines

The electrophilic amination reaction[1] of organometallic species using mono-, di- and trihaloamines has attracted a lot of attention for the synthesis of amines.[2] Only a few cases have been reported using alkylchloroamines as precursor for the synthesis of tertiary amines.[3] Our interest toward the synthesis of polyfunctionalized diarylamines utilizing an electrophilic amination of functionalized organomagnesium reagents with functionalized nitroarenes and arylaza tosylate[4] led us to re-examine this reaction. Herein, we wish to report an improved method for the preparation of polyfunctional tertiary amines of type **3** starting from benzyl-*N*-chloroamines of type **1** and LiCl-complexed functional arylmagnesium reagents of type **2** (Scheme 1, Table 1). The required *N*-benzyl-*N*-chloroamines **1a**–**f** were prepared from the corresponding *N*-benzylamines using the reaction of *N*-chlorosuccinimide in hexane.[5] The arylmagnesium reagents **2a**–**h** were prepared by a bromine–magnesium or iodine–magnesium exchange[6] by the reaction of aryl bromides or iodides with *i*-PrMgCl·LiCl (Scheme 1). The amination reaction occurred very rapidly within 15 minutes in tetrahydrofuran at –45 °C producing tertiary amines **3a**–**l** in moderate to good yields with the formation of biphenyl as byproduct (Table 1). We initiated our study by the reaction of *N*-benzyl-*N*-chloromethylamine (**1a**) with phenylmagnesium chloride lithium chloride (**2a**) at –45 °C, which produced *N*-benzyl-*N*-methylaniline (**3a**) within 15 minutes in 57% of isolated yield (Table 1, entry 1). Under similar reaction conditions, the chloroamine **1a** reacted with 1-naphthylmagnesium chloride lithium chloride complex (**2b**) to produce *N*-benzyl-*N*-methylnaphthalen-1-amine (**3b**) in 56% yield (entry 2). Remarkably, electron-deficient arylmagnesium reagents containing an ester or a cyano functionality react more efficiently with *N*-chloroamines providing tertiary amines in good yields. Thus, 4-carbomethoxyphenylmagnesium chloride lithium chloride complex (**2c**) reacted smoothly with **1a** leading to 4-[*N*-benzyl-*N*-methylamino]benzoic acid methyl ester (**3c**) in 64% yield (entry 3). This methodology has been applied successfully to prepare enantiomerically pure tertiary amines having a chiral center alpha to nitrogen starting from chiral *N*-chloroamines. Therefore, the reaction of *N*-chloro-*N*-[(1*R*)-1-phenylethyl]methylamine (**1b**) with 4-cyanophenylmagnesium chloride lithium chloride complex (**2d**) led to 4-{*N*-methyl-*N*-[(1*R*)-1-phenylethyl]amino}benzonitrile (**3d**) in 70% yield and 99% ee (entry 4). Similarly, **1b** reacted with 2-carbethoxyphenylmagnesium chloride lithium chloride complex (**2e**) producing the tertiary amine **3e** in 67% yield and 99% ee (entry 5). It is interesting to note that the presence of an electron-withdrawing group attached to the phenyl ring of the *N*-chloroamine also exhibits a good reactivity in the amination reaction. Thus, *N*-(4-bromobenzyl)-*N*-chloromethylamine (**1c**) reacted rapidly with 3-cyanophenylmagnesium chloride lithium chloride complex (**2f**) giving rise to



Scheme 1

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3-[*N*-(4-bromobenzyl)-*N*-methylamino]benzonitrile (**3f**) in 70% yield (entry 6). The presence of an ester functionality in the organomagnesium reagent **2c** provided the corresponding tertiary amine **3g** in 73% yield by reacting with the chloroamine **1c** (entry 7). Interestingly, 4-iodophenylmagnesium chloride lithium chloride (**2g**) reacted with *N*-chloroamine **1d** producing *N*-benzyl-*N*-ethyl-4-iodoaniline (**3h**) in 33% yield (entry 8). Furthermore, the chloroamine **1d** reacted with electron-deficient arylmagnesium reagent **2e** to give the tertiary amine **3i** in 67% yield (entry 9). The amination reaction takes place even in presence of the less reactive heteroarylmagnesium reagent **2h** yielding *N*-benzyl-*N*-ethylpyridin-3-amine (**3j**) in 27% yield (entry 10). We also examined the reactivity of *N*-chloro-*N*-(1-napthalen-2-ylethyl)methylamine (**1e**) which reacted with **2f** to produce tertiary amine **3k** in 65% yield (entry 11). The chiral *N*-chloroamine **1f** reacted with the Grignard reagent **2c** leading to the chiral tertiary amine **3l** in 34% yield and 98% ee (entry 12).

Table 1 Preparation of Tertiary Amines of Type **3** from Benzyl-*N*-chloroamines of Type **1** and Arylmagnesium Reagents of Type **2**[a]

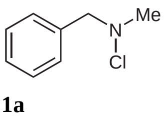
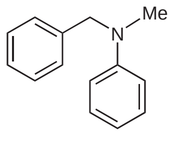
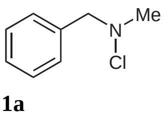
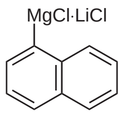
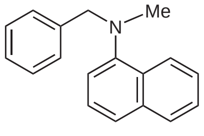
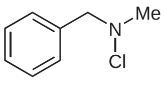
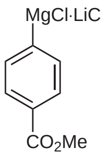
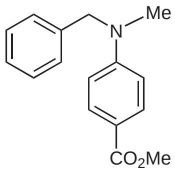
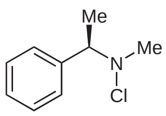
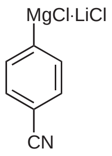
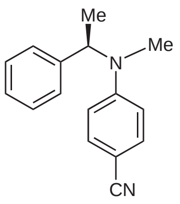
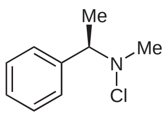
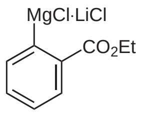
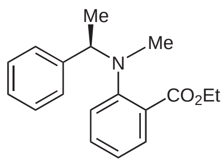
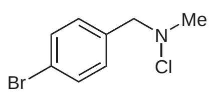
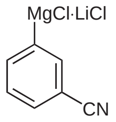
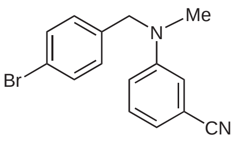
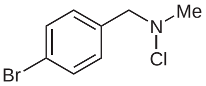
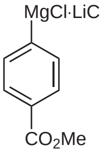
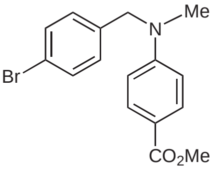
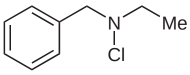
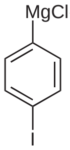
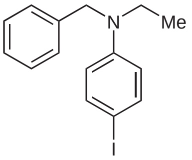
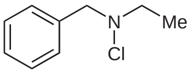
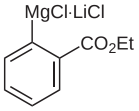
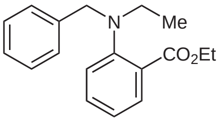
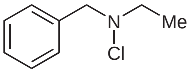
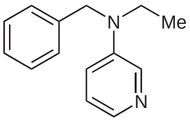
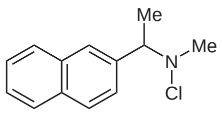
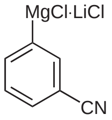
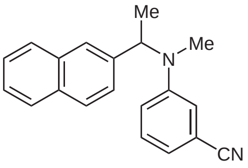
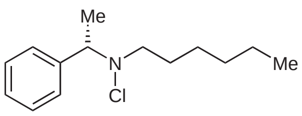
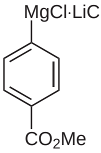
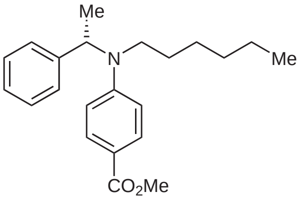
Entry	*N*-Chloroamine of type **1**	Arylmagnesium reagent of type **2**	Product of type **3**	Yield (%)[b,c]
1	 **1a**	 **2a**	 **3a**	57
2	 **1a**	 **2b**	 **3b**	56
3	 **1a**	 **2c**	 **3c**	64
4	 **1b**	 **2d**	 **3d**	70[d]
5	 **1b**	 **2e**	 **3e**	67[e]
6	 **1c**	 **2f**	 **3f**	70

Table 1 Preparation of Tertiary Amines of Type **3** from Benzyl-*N*-chloroamines of Type **1** and Arylmagnesium Reagents of Type **2**[a] (continued)

Entry	*N*-Chloroamine of type **1**	Arylmagnesium reagent of type **2**	Product of type **3**	Yield (%)[b,c]
7	 **1c**	 **2c**	 **3g**	73
8	 **1d**	 **2g**	 **3h**	33
9	 **1d**	 **2e**	 **3i**	67
10	 **1d**	 **2h**	 **3j**	27
11	 **1e**	 **2f**	 **3k**	65
12	 **1f**	 **2c**	 **3l**	34[f]

[a] All reactions were carried out using the *N*-chloroamines (1 mmol) and the arylmagnesium reagents (1.02 mmol).

[b] Isolated yield of analytically pure product.

[c] To determine the enantiomeric excess of the product, HPLC Chiralcel OD-H (0.46 cm × 25 cm) column was used.

[d] HPLC eluent: heptane–*i*-PrOH = 95:5, 0.4 mL/min, t_R (major) = 41.67 min, t_R (minor) = 38.21 min; ee 99%.

[e] HPLC eluent: heptane–*i*-PrOH = 99:1, 0.4 mL/min, t_R (major) = 34.27 min, t_R (minor) = 20.01 min; ee 99%.

[f] HPLC eluent: heptane–*i*-PrOH = 98:2, 0.5 mL/min, t_R (major) = 26.80 min, t_R (minor) = 22.46 min; ee 98%.

In summary, we have shown that *N*-chloroamines react rapidly with functionalized arylmagnesium reagents complexed with LiCl at low temperature yielding polyfunctional tertiary amines.[7] This electrophilic amination reaction can also be applied to chiral *N*-chloroamines leading to the corresponding chiral tertiary amines. However, the amination process is limited to benzyl-*N*-chloroamines only. This methodology offers a possible alternative strategy to transition-metal-catalyzed amination reactions which usually require a strong base. Extensions of this method are currently underway in our laboratory.

Acknowledgment

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(7) **Preparation of 4-{*N*-Methyl-*N*-[(1*R*)-1-phenylethyl]amino}benzonitrile (3d); Typical Procedure**:
A flame-dried argon-flushed 25-mL two-necked round-bottomed flask equipped with a magnetic stirrer and septum was charged with 4-bromobenzonitrile (186 mg, 1.02 mmol) dissolved in THF (1 mL) and cooled to –20 °C. Isopropylmagnesium chloride lithium chloride (0.71 mL, 1.1 mmol, 1.55 M in THF) was added dropwise to the above solution and I–Mg exchange was monitored by GC analysis until completion. The organomagnesium reagent thus formed was further cooled to –45 °C and a solution of *N*-chloro-*N*-[(1*R*)-1-phenylethyl]methylamine (**1b**; 170 mg, 1.0 mmol) in THF (2 mL) was added to it dropwise. The reaction mixture was stirred at –45 °C for 15 min and was quenched with a sat. solution of NH_4Cl and the residue was extracted with Et_2O (2×10 mL), washed with brine (2×10 mL), and dried over Na_2SO_4. Solvent removal under reduced pressure followed by flash chromatography over silica gel (eluent: pentane–Et_2O, 90:10) afforded **3d** (165 mg, 70%) as a viscous yellow liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 9.1 Hz, 2 H), 7.14–7.29 (m, 5 H), 6.67 (d, *J* = 9.1 Hz, 2 H), 5.09 (q, 1 H), 2.67 (s, 3 H), 1.50 (d, *J* = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 141.2, 133.5, 128.6, 127.3, 126.5, 120.5, 111.8, 97.6, 55.9, 31.9, 16.9. MS (EI, 70 eV): *m*/*z* (%) = 236 (48), 221 (53), 205 (9), 132 (23), 105(100), 103 (7). HRMS: *m*/*z* calcd for $C_{16}H_{16}N_2$: 236.1313; found: 236.1326. IR (film): 3029, 2977, 2213, 1605, 1519, 1449, 1385, 1180, 817, 701 cm^{-1}.

2-{*N*-Methyl-*N*-[(1*R*)-1-phenylethyl]amino}benzoic Acid Ethyl Ester (3e): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49 (m, 1 H), 7.09–7.23 (m, 6 H), 6.81–6.89 (m, 2 H), 4.51 (q, 1 H), 4.16–4.32 (m, 2 H), 2.47 (s, 3 H), 1.36 (d, *J* = 7.1 Hz, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 151.4, 142.2, 131.4, 130.4, 128.1, 127.1, 126.8, 125.3, 120.5, 120.3, 61.8, 60.8, 36.0, 17.7, 14.2. MS (EI, 70 eV): *m*/*z* (%) = 283 (10), 268 (100), 254 (36), 222 (16), 178 (25), 132 (29), 105(87), 77 (21). HRMS: *m*/*z* calcd for $C_{18}H_{21}NO_2$: 283.1572; found: 283.1554. IR (film): 3028, 2979, 1716, 1596, 1448, 1366, 1121, 701 cm^{-1}.

3-[*N*-(4-Bromobenzyl)-*N*-methylamino]benzonitrile (3f): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.8 Hz, 2 H), 7.18 (m, 1 H), 6.97 (d, *J* = 8.8 Hz, 2 H), 6.88 (m, 1 H), 6.82 (m, 2 H), 4.42 (s, 2 H), 2.98 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.3, 136.6, 131.9, 129.9, 128.1, 121.0, 120.0, 119.6, 116.3, 114.8, 113.0, 55.8, 38.7. MS (EI, 70 eV): *m*/*z* (%) = 302 (34), 300(35), 171 (98), 169 (100), 145 (10), 102 (9), 90 (18). HRMS: *m*/*z* calcd for $C_{15}H_{13}BrN_2$: 300.0262; found ($C_{15}H_{13}{}^{79}BrN_2$): 300.0238. HRMS: *m*/*z* calcd for $C_{15}H_{13}BrN_2$: 300.0262; found ($C_{15}H_{13}{}^{81}BrN_2$): 302.0220. IR (film): 3042, 2922, 2225, 1599, 1486, 1382, 1071, 1010, 774 cm^{-1}.

4-[*N*-(4-Bromobenzyl)-*N*-methylamino]benzoic Acid Methyl Ester (3g): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 9.1 Hz, 2 H), 7.40 (d, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 8.4 Hz, 2 H), 6.63 (d, *J* = 9.1 Hz, 2 H), 4.53 (s, 2 H), 3.83 (s, 3 H), 3.07 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 152.5, 136.8, 131.8, 131.4, 128.2, 120.9, 117.8, 110.9, 55.5, 51.5, 38.6. MS (EI, 70 eV): *m*/*z* (%) = 335 (36), 333 (38), 304 (6), 302 (8), 178 (31), 171 (99), 169 (100), 132 (17), 90 (30), 89 (24), 77 (10). HRMS: *m*/*z* calcd for $C_{16}H_{16}BrNO_2$: 333.0364; found ($C_{16}H_{16}{}^{79}BrNO_2$): 333.0353. HRMS: *m*/*z* calcd for $C_{16}H_{16}BrNO_2$: 333.0364; found ($C_{16}H_{16}{}^{81}BrNO_2$): 335.0321. IR (film): 2952, 1698, 1607, 1434, 1386, 1287, 1191, 770 cm^{-1}.

***N*-Benzyl-*N*-ethyl-4-iodoaniline (3h)**: ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 9.1 Hz, 2 H), 7.11–7.26 (m, 5 H), 6.37 (d, *J* = 9.1 Hz, 2 H), 4.41 (s, 2 H), 3.36 (q, 2 H), 1.12 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.9, 138.5, 137.7, 128.6, 126.9, 126.4, 114.4, 76.6, 53.8, 45.3, 11.9. MS (EI, 70 eV): *m*/*z* (%) = 337 (100), 322 (42), 260 (9), 230 (5), 195 (7), 91 (56), 77 (2). HRMS: *m*/*z* calcd for $C_{15}H_{16}IN$: 337.0327; found: 337.0308. IR (film): 2966, 2922, 1589, 1454, 1359, 1268, 1076, 733 cm^{-1}.

2-(*N*-Benzyl-*N*-ethylamino)benzoic Acid Ethyl Ester (3i): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.51 (m, 1 H), 7.09–7.27 (m, 6 H), 6.95 (m, 1 H), 6.85 (m, 1 H), 4.25 (q, 2 H), 4.21 (s, 2 H), 3.01 (q, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 0.93 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 150.4, 138.8, 131.4, 130.6, 128.2, 128.1, 126.8, 126.3, 121.3, 120.8, 60.8, 56.6, 47.3, 14.2, 11.8. MS (EI, 70 eV): *m*/*z* = 283 (2), 255 (13), 254 (76), 208 (100), 192 (16), 146 (39), 91 (49), 77 (9). HRMS: *m*/*z* calcd for $C_{18}H_{21}NO_2$: 283.1572; found: 283.1548. IR (film): 3063, 2977, 2931, 2872, 1720, 1597, 1446, 1366, 1249, 761, 732 cm^{-1}.

***N*-Benzyl-*N*-ethylpyridin-3-amine (3j)**: ^1H NMR (300 MHz, $CDCl_3$): δ = 8.06 (m, 1 H), 7.85 (m, 1 H), 7.14–7.27 (m, 5 H), 6.97 (m, 1 H), 6.85 (m, 1 H), 4.45 (s, 2 H), 3.42 (q, 2 H), 1.15 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.2, 138.2, 137.5, 134.9, 128.7, 127.0, 126.4, 123.5, 118.4, 53.7, 45.1, 11.9. MS (EI, 70 eV): *m*/*z* (%) = 212 (21), 197 (20), 135 (6), 91 (100), 65 (8). HRMS: *m*/*z* calcd for $C_{14}H_{16}N_2$: 212.1313; found: 212.1292. IR (film): 2971, 2926, 1730, 1582, 1494, 1432, 791, 731 cm^{-1}.

3-{*N*-Methyl-*N*-[1-(naphthalen-2-yl)ethyl]amino}benzonitrile (3k): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (m, 3 H), 7.71 (m, 1 H), 7.49 (m, 2 H), 7.25–7.38 (m, 2 H), 6.98–7.07 (m, 3 H), 5.23 (q, 1 H), 2.73 (s, 3 H), 1.66 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.0, 139.2, 133.3, 132.6, 129.9, 128.4, 127.9, 127.6, 126.3, 125.9, 125.4, 124.9, 119.8, 119.7, 116.8, 115.4, 113.0, 56.5, 31.9, 16.3. MS (EI, 70 eV): *m*/*z* (%) = 286 (9), 271 (6), 255 (2), 155 (100), 135 (5), 115 (3). HRMS: *m*/*z* calcd for $C_{20}H_{18}N_2$: 286.1470; found: 286.1476. IR (film): 3057, 2973, 2882, 2226, 1593, 1496, 1376, 1112, 821, 761 cm^{-1}.

4-{*N*-Hexyl-*N*-[(1*S*)-1-phenylethyl]amino}benzoic Acid Methyl Ester (3l): ^{1}H NMR (300 MHz, $CDCl_3$): δ =7.91 (d, *J* = 9.1 Hz, 2 H), 7.26–7.38 (m, 5 H), 6.73 (d, *J* = 9.1 Hz, 2 H), 5.21 (q, 1 H), 3.88 (s, 3 H), 3.14–3.26 (m, 2 H), 1.66 (d, *J* = 6.6 Hz, 3 H), 1.53 (m, 2 H), 1.27 (m, 6 H), 0.90 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 151.9, 141.8, 131.3, 128.5, 127.1, 126.9, 116.9, 111.5, 56.2, 51.4, 46.3, 31.3, 28.2, 26.7, 22.5, 17.6, 13.9. MS (EI, 70 eV): *m*/*z* (%) = 339 (14), 324 (17), 268 (13), 164 (41), 105 (100), 77 (5). HRMS: *m*/*z* calcd for $C_{22}H_{29}NO_2$: 339.2198; found: 339.2188. IR (film): 2929, 2855, 1709, 1606, 1519, 1278, 1186, 769 cm^{-1}.