Notes

Nitrile Reduction in the Presence of **Boc-Protected Amino Groups by Catalytic Hydrogenation over Palladium-Activated Raney-Nickel**

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Introduction

Polyamines have attracted considerable interest, especially after the discovery of their ubiquitous presence in living cells and their involvement in many metabolic processes.¹ As part of a program to synthesize homologues and derivatives of naturally occurring polyamines, we utilized the reduction of nitriles in the presence of Boc-protected amino groups. Nitriles are a versatile synthon for amines in organic chemistry and can be prepared by a variety of methods.² Furthermore, there are a number of methods available for the subsequent reduction to amines.² Catalytic hydrogenation³ has been carried out using Raney-nickel,^{4,5} Pd(OH)₂/C,⁶ Pd/C,⁷ or PtO₂⁸ as catalyst. Alternatively, complex metal

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(1) For the most recent reviews, see: (a) Kuksa, V.; Buchan, R.; Lin, P. K. T. Synthesis 2000, 1189-1207. (b) Karigiannis, G.; Papaioannou, D. Eur. J. Org. Chem. 2000, 1841-1863.

(2) Excellent reviews are available: (a) The chemistry of the cyano group; Rappoport, Z., Ed.; Interscience: London, 1970. (b) Houben-Weyl, 4th ed.; Grundmann, C., Ed.; Thieme: Stuttgart, 1985; Vol. E5, p 1313-1441

(3) (a) Augustine, R. L. Catalytic Hydrogenation, Techniques and Applications in Organic Synthesis; Marcel Denker, Inc.: New York, 1965. (b) Rylander, P. N. In Hydrogenation Methods, Best Synthetic Methods; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: London, 1985.

(4) For the preparation of Raney-nickel of different activity see: (a) Mozingo, R. Org. Synth. 1941, 21, 15-17. (b) Billica, H. R.; Adkins, H. Org. Synth. 1949, 29, 24-29.

(5) For some recent examples in the presence of Boc-groups, see: (a) Geneste, H.; Hesse, M. *Tetrahedron* 1998, 54, 15199-15214. (b) Kruijtzer, J. A. W.; Lefeber, D. J.; Liskamp, R. M. J. Tetrahedron Lett. **1997**, *38*, 5335–5338. (c) Lim, D.; Burgess, K. J. Org. Chem. **1997**, *62*, 9382–9384. (d) Eisenbrand, G.; Lauck-Birkel, S.; Tang, W. C. Synthesis **1996**, *10*, 1246–1258. (e) Blessing, T.; Remy, J.-S.; Behr, J.-P. J. Am. Chem. Soc. 1998, 120, 8519-8520. (f) Bergeron, R. J.; McMannis, J. S. J. Org. Chem. 1988, 53, 3108-3111. (g) Ravikumar, V. T. Synth. Commun. 1994, 24, 1767-1772.

(6) For some recent examples, see: (a) Huang, D.; Matile, S.; Berova, N.; Nakanishi, K. *Heterocycles* **1996**, *42*, 723–736. (b) Jasys, V. J.; Kelbaugh, P. R.; Nason, D. M.; Phillips, D.; Rosnack, K. J. J. Am. Chem. Soc. 1990, 112, 6696-6704.

hydrides,⁹ especially NaBH₄ + CoCl₂·6H₂O,¹⁰ NaBH₄ + NiCl₂·6H₂O,¹¹ and LiAlH₄ variations,¹² have been used successfully to achieve the nitrile-amine transformation. Here we report the use of palladium activated Raneynickel for the reduction of nitriles to primary amines for cases in which other methods were unsuccessful.

Results and Discussion

Starting materials (Scheme 1) were prepared by adopting literature-reported Michael-addition procedures of the corresponding diamines and acrylonitrile. For the aliphatic nitriles **1a**-g, reactions were carried out in EtOH at room temperature¹³ followed by Boc-protection using Boc-anhydride/Et₃N in MeOH at room temperature.¹⁴ For the aromatic nitriles 1h-j, double-Michael-addition reactions were performed in refluxing 1,4-dioxane with copper(II) acetate as Lewis acid catalyst.¹⁵

Under standard hydrogenation conditions over Raney-Nickel (EtOH/water, NaOH, rt, 45 psi, 8-15 h), nitriles 1a-c were smoothly converted into the amines 2a-c in 80–90% yield, although for R = n-nonyl ($1c \rightarrow 2c$) a prolonged reaction time was necessary. Under the same conditions, the conversion of 1d (R = *n*-dodecyl) was impractically slow. Furthermore, mono- and bisethylated byproducts were detected by electrospray-MS. Presumably, these byproducts were formed via reductive ethylation of an imine intermediate. In all other cases (1e-j), hydrogenation over Raney-nickel did not effect any reaction or led to mixtures containing starting material and ethylated amines.

To find suitable reduction conditions the nitrile 1f was chosen as a model case. Reaction with different complex metal hydrides (NaBH₄ + CoCl₂· $6H_2O$, LiAlH₄ + AlCl₃, BH₃·THF) consumed the starting material within hours. However, no pure product could be isolated, probably due to formation of metal chelates and decomposition of the products under rigorous workup conditions. To avoid problems arising from the chelation of reduction intermediates and products further investigation focused on catalytic hydrogenation.

⁽⁷⁾ For some recent examples, see: (a) Suárez-Gea, M. L.; García-López, M. T.; González-Muñiz, R.; Herrero, S.; Herranz, R. *Tetrahedron Lett.* **1996**, *37*, 2083–2084. (b) Bergeron, R. J.; Ludin, C.; Mueller, R.; Smith, R. E.; Phanstiel, O. J. Org. Chem. 1997, 62, 3285–3290.
(8) For two recent examples, see: (a) Sakai, N.; Matile, S. Tetrahe-

dron Lett. 1997, 38, 2613–2616. (b) Xue, C.-B.; DeGrado W. F. Tetrahedron Lett. 1995, 36, 55–58.

⁽⁹⁾ Hajos, A. Complex Hydrides and related reducing agents in organic synthesis; Elsevier: Amsterdam, 1979.

⁽¹⁰⁾ For some recent examples, see: (a) Ushio-Sata, N.; Matsunaga, (10) For some recent examples, see. (a) Osmo-Sata, N., Matsunaga, S.; Fusetani, N.; Honda, K.; Yasumuro, K. Tetrahedron Lett. 1996, 37, 225–228. (b) Osby, J. O.; Heinzman, S. W.; Ganem, B. J. Am. Chem. Soc. 1986, 108, 67–72. (c) Dallaire, C.; Arya, P. Tetrahedron Lett. 1998, 39, 5129–5132. (d) Ushio-Sata, N.; Sugano, M.; Matsunaga, S.; Fusetani, N. Tetrahedron Lett. 1999, 40, 719–722.
(11) For succent examples, control (c) Kalata, C.; Theodemy, V.;

⁽¹¹⁾ For recent examples, see: (a) Kokotos, G.; Theodorou, V.; Constantinou-Kokotou, V.; Gibbons, W. A.; Roussakis, C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1525–1530. (b) Constantinou-Kokotou, V.; Koko-tos, G. Org. Prep. Proc. Int. **1994**, *26*, 599–602.

⁽¹²⁾ For some recent examples, see: (a) Bergeron, R. J.; Burton, P. S.; McGovern, K. A.; Kline, S. J. Synthesis **1981**, 732–733. (b) Kalivretenos, A. G.; Nakanishi, K. J. Org. Chem. **1993**, *58*, 6596–6608. (13) Edwards, M. L.; Stemerick, D. M.; Bitonti, A. J.; Dumont, J. A.; McCann, P. P.; Bey, P.; Sjoerdsma, A. J. Med. Chem. **1991**, *34*, 100 Content of the second se

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⁽¹⁴⁾ Krakowiak, K. E.; Bradshaw, J. S. J. Heterocycl. Chem. 1995, 32, 1639-1640.

⁽¹⁵⁾ Heininger, S. A. J. Org. Chem. 1957, 22, 1213-1216.

Scheme 1



When the nitrile 1f was shaken in a hydrogen atmosphere (45 psi) at rt using a mixture of Pd/C and Raneynickel as catalyst in 1,4-dioxane/water (4:1) and LiOH as base, the desired amine (2f) was formed within 20 h in almost quantitative yield. 1,4-Dioxane was chosen as inert solvent to suppress the formation of N-alkylated byproducts, which were found with ethanol as solvent. The presence of water was necessary as in the absence of water virtually no reaction took place. Similarly, neither Raney-nickel nor Pd/C alone affected any reaction under a diversity of conditions. Other catalyst mixtures such as Raney-nickel + PtO_2 or Pd/C + PtO_2 failed to give the desired product. As aging of the catalyst might be a factor in some cases,³ the hydrogenation was performed with freshly purchased catalysts as well as with at least 1-year-old catalysts without any change in results. The choice of base might be less crucial, although the rather weak base LiOH seems to be very well suited. Reactions in acidic media were not investigated as problems with partial deprotection, acylation, and salt formation were expected. Finally, the hydrogenation over palladium activated Raney-nickel was also carried out successfully under atmospheric hydrogen pressure at 50 °C avoiding the use of a Parr hydrogenator. No formation of any byproducts, such as secondary amines, aldehydes, and amino alcohols, was observed under these conditions.

The optimized hydrogenation conditions (Scheme 1) were successfully applied to the other cases. The aliphatic nitriles 1c-g were cleanly reduced to the corresponding amines 2c-g within 15-20 h and isolated in 85-95% yield. While nitrile 1c could be reduced in the presence and absence of additional Pd-catalyst without significant changes in reaction time and yield, hydrogenation of compounds 1d-g was only successful in the presence of Pd.

The aromatic nitriles **1h** and **1i** were cleanly converted into the amines 2h and 2i as indicated by ES-MS. 2h and 2i are highly polar, very sensitive compounds, which are hardly extracted into CH₂Cl₂, EtOAc, or toluene. However, the crude products isolated after filtration and removal of the solvents in vacuo gave satisfactory MS and ¹H and ¹³C NMR analysis, although they contained large amounts of LiOH. All purification attempts by cation-exchange chromatography on Dowex50WX2-200 or column chromatography on SiO₂ and deactivated Al₂O₃ (basic, Brockmann grade V) with different alkaline and neutral solvent mixtures resulted in complete decomposition. In the hydrogenation of nitrile 1j under identical conditions two products were formed. The mixture was identified by MS and ¹H and ¹³C NMR spectroscopy to contain amine 2j and the hydrogenated mono-retroMichael addition product N^1 -(3-aminopropyl)-1,4-benzenediamine in a 60:40 ratio. Attempted separation resulted in decomposition. Replacing LiOH with other bases, such as aqueous NH₃, or omitting the base totally caused formation of several side products.

In conclusion, we reported a highly efficient hydrogenation procedure for the reduction of nitriles to primary amines, which can be carried out under atmospheric hydrogen pressure using commercially available catalysts. Both Boc groups and aromatic moieties present in the starting material are well tolerated under the mild optimized conditions. Therefore, this procedure should complement available hydrogenation methods especially for some more tedious cases.

Experimental Section

Solvents and reagents were used as purchased. All new compounds were characterized by their $^1\text{H},\,^{13}\text{C},$ and MS data. ¹H and ¹³C NMR data were recorded in CDCl₃ (2b-g) or CD₃-OD (2h-i) on a 300 MHz NMR spectrometer using CHCl₃ or CH₃OH as internal standard. Mass spectra were recorded at a Platform II mass spectrometer (Micromass). Ionization was achieved in the positive electrospray mode using a 1:1 solvent mixture of acetonitrile and water or methanol as mobile phase (ES-MS). High-resolution mass spectra were recorded by the National Mass Spectrometry Service Centre in Swansea using the same ionization procedure. Accurate mass measurement was performed by peak matching. Combustion analyses were performed by MEDAC LTD, Surrey, U.K. The synthesis of 2a by hydrogenation over Raney-nickel^{5e} and by hydride reduction using NaBH₄ + CoCl₂·6H₂O^{10d} has been reported previously without analytical data. The synthesis of **2b**¹⁶ and **2j**¹⁷ by hydrogenation over Raney-nickel has been reported previously without experimental details.

N¹,N⁴-Di(tert-butyloxycarbonyl)-N¹,N⁴-di(3-aminopropyl)-1,4-butanediamine (2a). Nitrile 1a (1.70 g, 4.31 mmol) was dissolved in a mixture of absolute ethanol (80 mL) and THF (20 mL). Raney-nickel (2.1 g, 17.8 mmol) as a 50% suspension in water was added together with NaOH (10 mL, 2 N solution in water), and the reaction mixture was shaken under 45 psi hydrogen pressure at room temperature for 8 h. The catalyst was filtered off, the solvents were removed in vacuo, and a mixture of water (100 mL) and CH₂Cl₂ (30 mL) was added. After phase separation, the aqueous phase was extracted three times with CH₂Cl₂ (30 mL), the combined organic layers were dried over sodium sulfate, and the solvent was removed in vacuo. Amine 2a (1.45 g, 84%) was obtained as yellow, highly viscous oil: R_f (SiO₂, 35% aq NH₃/MeOH 1:10) 0.36; ¹H NMR δ 3.21 (m, 4H), 3.14 (m, 4H), 2.66 (t, 4H, ${}^{3}J = 6.68$ Hz), 1.68 (m, 4H, NH₂), 1.61 (t, 4H, ${}^{3}J = 6.86$ Hz), 1.50–1.38 (m, 4H), 1.42 (s, 18H); ${}^{13}C$ NMR δ 155.8 (s), 79.4 (s), 46.6 (t), 44.0 (t), 39.2 (t), 31.8 (t), 25.6 (t), 28.5 (q); MS m/z 403 (M + H⁺, 30), 303 (M + 2H⁺ -- CO₂t-Bu⁺, 12), 202 ((M + 2H⁺)/2, 65); HRMS calcd for $C_{20}H_{43}N_4O_4^+$ 403.3284, found 403.3286. Column chromatography on SiO₂ using Et₃N/MeOH 1:10 as eluent afforded an analytically pure sample. Anal. Calcd for $C_{20}H_{42}N_4O_4$: C, 59.67; H, 10.52; N, 13.92. Found: C, 59.74; H, 10.24; N, 13.90.

 N^4 , N'-Di(*tert*-butyloxycarbonyl)- N^4 , N'-di(3-aminopropyl)-1,7-heptanediamine (2b). Nitrile 1b (1.49 g, 3.41 mmol) was dissolved in a mixture of absolute ethanol (80 mL) and THF (20 mL). Raney-nickel (0.8 g, 6.8 mmol) as a 50% suspension in water was added together with NaOH (10 mL, 2 N solution in water), and the reaction mixture was shaken under 45 psi hydrogen pressure at room temperature for 8 h. The catalyst was filtered off, the solvents were removed in vacuo, and a mixture of water (100 mL) and CH₂Cl₂ (30 mL) was added. After phase separation, the aqueous phase was extracted three times

⁽¹⁶⁾ Tye, C.-K.; Kasinathan, G.; Barrett, M. P.; Brun, R.; Doyle, V. E.; Fairlamb, A. H.; Weaver, R.; Gilbert, I. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 811–816.

⁽¹⁷⁾ Weinstock, L. T.; Rost, W. J.; Cheng, C. C. J. Pharm. Sci. 1981, 70, 956–959.

with CH₂Cl₂ (30 mL), the combined organic layers were dried over sodium sulfate, and the solvent was removed in vacuo. Amine **2b** (1.21 g, 80%) was obtained as yellow, highly viscous oil: R_f (SiO₂, 35% aq NH₃/MeOH 1:10) 0.38; ¹H NMR δ 3.24 (m, 4H), 3.12 (m, 4H), 2.74 (t, 4H, ³J = 6.60 Hz), 1.62 (m, 4H), 1.70–1.57 (m, 4H, NH₂), 1.50–1.42 (m, 22H), 1.35–1.30 (m, 6H); ¹³C NMR δ 156.0 (s), 79.5 (s), 47.1 (t), 44.2 (t), 39.6 (t), 32.8 (t), 32.2 (t), 29.6 (t), 27.3 (t), 28.7 (q); MS *m/z* 467 (M + Na⁺, 23), 445 (M + H⁺, 100), 223 ((M + 2H⁺)/2, 30); HRMS calcd for C₂₃H₄₉N₄O₄+ 445.3754, found 445.3753.

N¹, N⁹-Di(*tert*-butyloxycarbonyl)-N¹, N⁹-di(3-aminopropyl)-1,9-nonanediamine (2c). Nitrile 1c (1.15 g, 2.48 mmol) was dissolved in a mixture of dioxane (80 mL) and water (20 mL). Raney-nickel (550 mg, 4.69 mmol) as a 50% suspension in water and 10% palladium on charcoal (165 mg, 0.155 mmol) were added together with lithium hydroxide monohydrate (225 mg, 5.36 mmol), and the reaction mixture was stirred under hydrogen atmosphere at 50 °C for 18 h. The catalyst was filtered off, the solvents were removed in vacuo, and a mixture of water (100 mL) and CH₂Cl₂ (30 mL) was added. After phase separation, the aqueous phase was extracted three times with CH_2Cl_2 (30 mL), the combined organic layers were dried over sodium sulfate, and the solvent was removed in vacuo. Amine 2c (1.01 g, 86%) was obtained as a yellow, highly viscous oil: R_f (SiO₂, 35% aq NH₃/MeOH 1:10) 0.38; ¹H NMR δ 3.22 (m, 4H), 3.10 (m, 4H), 2.64 (t, 4H, ${}^{3}J$ = 6.59 Hz), 1.61 (m, 4H), 1.68–1.55 (m, 4H, NH₂), 1.42 (m, 22H), 1.24 (m, 10H); $^{13}\mathrm{C}$ NMR δ 155.9 (s), 79.3 (s), 47.0 (t), 44.5 (t), 43.9 (t), 39.5 (t), 39.3 (t), 32.7 (t), 31.9 (t), 29.7 (t), 29.4 (t), 28.6 (q), 27.0 (t); MS m/z 473 (M + H⁺, 20), 237 ((M + $2H^+)/2$, 30), 181 ((M + 3Na⁺)/3, 30), 159 ((M + 3H⁺)/3, 30), 137 (100); HRMS calcd for $C_{25}H_{53}N_4O_4^+$ 473.4067, found 473.4063.

N¹,N¹²-Di(*tert*-butyloxycarbonyl)-N¹,N¹²-di(3-aminopropyl)-1,12-dodecanediamine (2d). Nitrile 1d (800 mg, 1.58 mmol) was dissolved in a mixture of dioxane (20 mL) and water (5 mL). Raney-nickel (200 mg, 1.70 mmol) as a 50% suspension in water and 10% palladium on charcoal (165 mg, 0.155 mmol) were added together with lithium hydroxide monohydrate (135 mg, 3.22 mmol), and the reaction mixture was stirred under hydrogen atmosphere at 50 °C for 20 h. The catalysts were filtered off, the solvents were removed in vacuo, and a mixture of water (50 mL) and CH₂Cl₂ (25 mL) was added. After phase separation, which was accelerated by addition of sodium chloride, the aqueous phase was extracted three times with CH₂Cl₂ (15 mL), the combined organic layers were dried over sodium sulfate, and the solvent was removed in vacuo. Amine 2d (750 mg, 92%) was obtained as light yellow oil: R_f (SiO₂, 35% aq NH₃/ MeOH 1:10) 0.40; ¹H NMR & 3.24 (m, 4H), 3.12 (m, 4H), 2.67-2.59 (m, 4H), 1.85 (m, 4H, NH₂), 1.63 (m, 4H), 1.55-1.38 (m, 4H), 1.44 (s, 18H), 1.25 (m, 16H); 13 C NMR δ 156.0 (s) 155.7 (s), 79.2 (s), 47.0 (t), 44.1 (t), 39.2 (t), 32.0 (t), 29.7 (t), 29.6 (t) 29.5 (t), 28.5 (q), 27.0 (t); MS m/z 515 (M + H⁺, 100); HRMS calcd for C₂₈H₅₉N₄O₄⁺ 515.4536, found 515.4540. Column chromatography on SiO₂ using Et₃N/MeOH 1:10 as eluent afforded an analytically pure sample. Anal. Calcd for C₂₈H₅₈N₄O₄: C, 65.33; H, 11.36; N, 10.88. Found: C, 64.98; H, 11.19; N, 10.49.

N¹,N²-Di(*tert*-butyloxycarbonyl)-N¹,N²-di(3-aminopropyl)-1,2-propanediamine (2e). Nitrile 1e (500 mg, 1.31 mmol) was dissolved in a mixture of dioxane (20 mL) and water (5 mL). Raney-nickel (200 mg, 1.70 mmol) as a 50% suspension in water and 10% palladium on charcoal (120 mg, 0.113 mmol) were added together with lithium hydroxide monohydrate (170 mg, 4.05 mmol), and the reaction mixture was stirred under hydrogen atmosphere at 50 °C for 20 h. The catalysts were filtered off, the solvents were removed in vacuo, and a mixture of water (50 mL) and CH₂Cl₂ (25 mL) was added. After phase separation, the aqueous phase was extracted twice with CH_2Cl_2 (15 mL), the combined organic layers were dried over sodium sulfate, and the solvent was removed in vacuo. Amine 2e (430 mg, 84%) was obtained as a colorless, highly viscous oil: R_f (SiO₂, 35% ag NH₃/ MeOH 1:10) 0.36; ¹H NMR & 4.18-3.71 (m, 1H), 3.53-2.94 (m, 6H), 2.72-2.56 (m, 4H), 1.60 (m, 4H), 1.42 (s, 18H), 1.33 (s, 4H, NH₂), 1.13 (d, 3H, ${}^{3}J$ = 6.40 Hz); ${}^{13}C$ NMR δ 155.6 (s), 79.7 (s), 52.6 (d), 51.7 (d), 50.8 (d), 49.9 (t), 49.1 (t), 45.5 (t), 44.9 (t), 44.2 (t), 43.8 (t), 43.5 (t), 40.0 (t), 39.7 (t), 39.4 (t), 34.3 (t), 33.5 (t), 32.7 (t), 31.9 (t), 28.6 (q), 17.2 (q), 16.2 (q); MS m/z 411 (M + Na⁺, 36), 389 (M + H⁺, 60), 195 ($(M + 2H^{+})/2$, 12); HRMS calcd for C₁₉H₄₁N₄O₄⁺ 389.3128, found 389.3131.

N¹, N²-Di(*tert*-butyloxycarbonyl)-N¹, N²-di(3-aminopropyl)-1,2-cyclohexanediamine (2f). Nitrile 1f (500 mg, 1.19 mmol) was dissolved in a mixture of dioxane (20 mL) and water (5 mL). Raney-nickel (200 mg, 1.70 mmol) as a 50% suspension in water and 10% palladium on charcoal (120 mg, 0.113 mmol) were added together with lithium hydroxide monohydrate (150 mg, 3.57 mmol), and the reaction mixture was stirred under hydrogen atmosphere at 50 °C for 20 h. The catalysts were filtered off, the solvents were removed in vacuo, and a mixture of water (50 mL) and CH₂Cl₂ (25 mL) was added. After phase separation, the aqueous phase was extracted twice with CH₂Cl₂ (15 mL), the combined organic layers were dried over sodium sulfate, and the solvent was removed in vacuo. Amine 2f (480 mg, 94%) was obtained as colorless, highly viscous oil: R_f (SiO₂, 35% aq NH₃/ MeOH 1:10) 0.47; ¹H NMR & 4.11-3.97/3.85-3.56 (2m, 2H), 3.29-3.01/2.94-2.76 (2m, 4H), 2.61 (t, 4H, ${}^{3}J = 6.86$ Hz), 1.93-1.76 (m, 2H), 1.76-1.59 (m, 4H), 1.50-1.30 (m, 6H, NH among here), 1.42 (s, 18H), 1.30–1.15 (m, 4H); 13 C NMR δ 155.8 (s), 79.3 (s), 55.1 (d), 41.2 (t), 40.3 (t), 34.9 (t), 31.3 (t), 28.6 (q), 25.5 (t); MS *m*/*z* 429 (M + H⁺, 100), 329 (M - Boc + 2H⁺, 10); HRMS calcd for $C_{22}H_{45}N_4O_4^+$ 429.3441, found 429.3435. Column chromatography on SiO₂ using Et₃N/MeOH 1:10 as eluent afforded an analytically pure sample. Anal. Calcd for C₂₂H₄₅N₄O₄: C, 61.65; H, 10.35; N, 13.07. Found: C, 61.27; H, 10.29; N, 12.88.

N¹,N⁴-Di(*tert*-butyloxycarbonyl)-N¹,N⁴-di(3-aminopropyl)-1,4-cyclohexanediamine (2g). Nitrile 1g (1.67 g, 3.97 mmol) was dissolved in a mixture of dioxane (40 mL) and water (10 mL). Raney-nickel (500 mg, 4.26 mmol) as a 50% suspension in water and 10% palladium on charcoal (400 mg, 0.376 mmol) were added together with lithium hydroxide monohydrate (450 mg, 10.7 mmol), and the reaction mixture was stirred under hydrogen atmosphere at 50 °C for 20 h. The catalysts were filtered off, the solvents were removed in vacuo, and a mixture of water (100 mL) and CH₂Cl₂ (30 mL) was added. After phase separation, the aqueous phase was extracted four times with CH_2Cl_2 (30 mL), the combined organic layers were dried over sodium sulfate, and the solvent was removed in vacuo. Amine 2g (1.53 g, 90%) was obtained as yellow, highly viscous oil: R_f (SiO₂, 35% aq NH₃/ MeOH 1:10) 0.29; ¹H NMR δ 3.54–3.24 (m, 2H), 3.20–2.97 (m, 4H). 2.68-2.48 (m, 4H). 1.72 (m, 4H, NH₂). 1.59 (m, 8H). 1.47-1.32 (m, 4H); $^{13}\mathrm{C}$ NMR δ 155.6 (s), 79.5 (s), 56.0 (d), 54.2 (d), 41.5 (t), 39.7 (t), 34.8 (t), 30.1 (t), 28.6 (q); MS m/z 429 (M + H⁺) 100), 329 (M - Boc + 2H⁺, 50); HRMS calcd for $C_{22}H_{45}N_4O_4^+$ 429.3441, found 429.3445.

N¹, N²-Di(3-aminopropyl)-1, 2-benzenediamine (2h). Nitrile 1h (500 mg, 2.33 mmol) was dissolved in a mixture of dioxane (20 mL) and water (5 mL). Raney-nickel (270 mg, 2.30 mmol) as a 50% suspension in water and 10% palladium on charcoal (200 mg, 0.188 mmol) were added together with lithium hydroxide monohydrate (200 mg, 4.77 mmol), and the reaction mixture was stirred under hydrogen atmosphere at 50 °C for 20 h. The catalysts were filtered off and rinsed with a mixture of dioxane (20 mL) and water (10 mL), and the solvents were removed from the filtrate in vacuo. A mixture (530 mg) of LiOH and amine **2h** was obtained as a brownish highly viscous oil: R_f (SiO₂, 35% aq NH₃/MeOH 1:10) baseline; ¹H NMR δ 6.70-6.59 (m, 4H), 3.13 (t, 4H, ${}^{3}J = 6.95$ Hz), 2.76 (t, 4H, ${}^{3}J = 7.04$ Hz), 1.80 (tt, 4H, ${}^{3}J = 6.95$, ${}^{3}J = 7.04$ Hz), NH exchanged; ${}^{13}C$ NMR δ 138.3 (s), 119.7 (d), 112.5 (d), 43.2 (t), 40.7 (t), 33.5 (t); MS m/z 229 (M + Li⁺, 50), 223 (M + H⁺, 100); HRMS calcd for $C_{12}H_{23}N_4^+$ 223.1922, found 223.1926.

N⁴,**N**³-**Di**(3-aminopropyl)-1,3-benzenediamine (2i). Nitrile **1i** (500 mg, 2.33 mmol) was dissolved in a mixture of dioxane (20 mL) and water (5 mL). Raney-nickel (270 mg, 2.30 mmol) as a 50% suspension in water and 10% palladium on charcoal (270 mg, 0.254 mmol) were added together with lithium hydroxide monohydrate (200 mg, 4.77 mmol), and the reaction mixture was stirred under hydrogen atmosphere at 50 °C for 20 h. The catalysts were filtered off and rinsed with a mixture of dioxane (20 mL) and water (10 mL), and the solvents were removed from the filtrate in vacuo. A mixture (560 mg) of LiOH and amine **2i** was obtained as a brownish solid: R_f (SiO₂, 35% aq NH₃/MeOH 1:10) baseline; ¹H NMR δ 6.88 (m, 1H), 6.14–5.99 (m, 1H), 6.02 (m, 2H), 3.09 (t, 4H, ${}^{3}J$ = 6.95 Hz), 2.72 (t, 4H, ${}^{3}J$ = 7.04 Hz), 1.74 (tt, 4H, ${}^{3}J$ = 6.95 Hz, ${}^{3}J$ = 7.04 Hz), NH exchanged; ¹³C NMR δ 151.2 (s), 130.6 (d), 104.4 (d), 99.3 (d), 42.8 (t), 40.5 (t), 33.5 (t); MS m/z 229 (M + Li⁺, 30), 223 (M + H⁺, 100), 112 ((M + 2H⁺)/2, 15); HRMS calcd for $C_{12}H_{23}N_4^+$ 223.1922, found 223.1924.

 N^{1} , N^{1} -Di(3-aminopropyl)-1,4-benzenediamine (2j) and N^{1} -(3-Aminopropyl)-1,4-benzenediamine (Byproduct). Nitrile 1j (500 mg, 2.33 mmol) was dissolved in a mixture of dioxane (20 mL) and water (5 mL). Raney-nickel (270 mg, 2.30 mmol) as a 50% suspension in water and 10% palladium on charcoal (200 mg, 0.188 mmol) were added together with lithium hydroxide monohydrate (100 mg, 2.38 mmol), and the reaction mixture was stirred under hydrogen atmosphere at 50 °C for 20 h. The catalysts were filtered off and rinsed with a mixture of dioxane (20 mL) and water (10 mL), and the solvents were removed from the filtrate in vacuo. A mixture (560 mg) of LiOH, amine 2j, and a byproduct (N^{1} -(3-aminopropyl)-1,4-benzene-diamine) was obtained as a brownish solid: R_{f} (SiO₂, 35% aq

NH₃/MeOH 1:10); ¹H NMR δ **2j** (60%) 6.63 (m, 4H), 3.06 (t, 4H, ³*J* = 7.01 Hz), 2.71 (t, 4H, ³*J* = 7.04 Hz), 1.73 (tt, 4H, ³*J* = 7.04, 6.95 Hz); **byproduct** (40%) 6.63 (m, 4H), 3.06 (t, 2H, ³*J* = 7.01 Hz), 2.71 (t, 2H, ³*J* = 7.04 Hz), 1.73 (tt, 2H, ³*J* = 7.04, 6.95 Hz), NH exchanged; ¹³C NMR **2j** δ 142.5 (s), 116.8 (d), 44.5 (t), 40.5 (t), 33.5 (t), **byproduct** δ 143.2 (s), 139.5 (s), 118.6 (d), 116.6 (d), 44.9 (t), 40.9 (t), 33.9 (t); MS *m*/*z* 229 (M_{2j} + Li⁺, 25), 223 (M_{2j} + H⁺, 100), 166 (M_{byproduct} + H⁺, 45).

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