Cobalt(II) Chloride−Catalyzed Chemoselective Sodium Borohydride Reduction of Azides in Water

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Abstract: Reduction of azides to amines and amides was carried out with $NaBH_4/CoCl_2•6H_2O$ in sole water at 25 °C under catalytic heterogeneous conditions. A broad spectrum of azides was reduced in a short time, chemoselectively in high yield and purity.

Key words: azide, reduction, cobalt (II) chloride, sodium borohydride

The reduction of the azido group to an amino group has been extensively investigated because of a wide range of applications in organic synthesis, especially in nitrogen-containing heterocycles[1] and carbohydrate chemistry.[2]

Most of the reducing agents that have been used are of a non-hydride type. Some have been known for a long time[3] and others have been discovered in the last decade; the best known are: SmI_2,[4] Sm/I_2,[5] Me_3SiI,[6] $Fe/NiCl_2·6H_2O$,[7] AlI_3,[8] $(PhCH_2NEt_2)_2MoS_4$,[9] $Zn/NiCl_2$,[10] In/NH_4Cl,[11] $H_2N-NMe_2/FeCl_3·6H_2O$,[12] and $S(SiMe_3)_2$.[13]

Hydride-reducing agents are widely employed, but some of them have limitations. Diborane is not applicable to compounds having double or triple bonds.[3] $LiAlH_4$ has to be used in a large excess, requires a long reaction time and is not tolerable to some functionalities (CO_2R, NO_2, CHO, COR, epoxide).[3,14,15] $NaBH_4$ is a mild reducing agent and except for arylsulphonyl azides does not usually reduce azides to amines.[3,14] Improvements have been obtained by using $NaBH_4$ under phase-transfer-catalysis conditions[14] or in THF with stoichiometric amounts of methanol[16] or by using complex reducing agents such as $NaBH_4/NiCl_2$,[17] $NaBH_4/CuSO_4$,[18] however, a complete chemoselectivity is not always achieved. Modified sodium borohydride reducing agents such as borohydride exchange resin-$Ni(OAc)_2$,[19] $Zn(BH_4)_2$,[15] and $LiMe_2NBH_3$[20] have also been used. Bu_3SnH with a catalytic amount of azobis(isobutyronitrile) has been employed to reduce azidonucleosides and azidodeoxysugars.[21]

In all cases, the organic solvent is the preferred reaction medium and to our knowledge, sole water has never been used.[22]

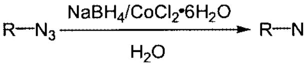
This is quite surprising especially with reference to $NaBH_4$/metal salts as reducing systems. They are usually used in methanol, although $NaBH_4$ in this medium is considerably less stable than in water at pH >7.[25−27] In order to perform the reduction in methanol[26] a large excess (5−10 equivalents) of hydride is required. The use of sole water as a reaction medium should allow us to minimize the excess of $NaBH_4$, and to reuse the catalyst in further runs.

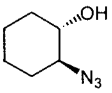
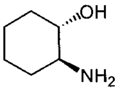
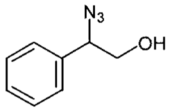
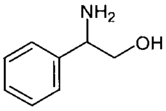
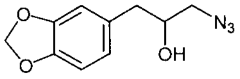
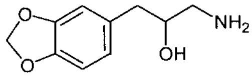
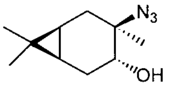
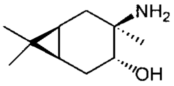
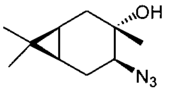
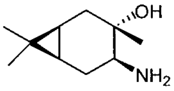
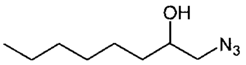
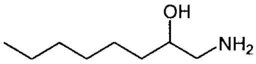
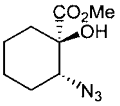
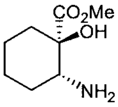
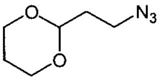
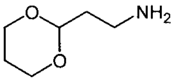
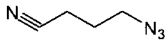
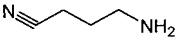
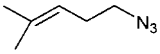
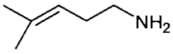
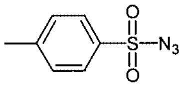
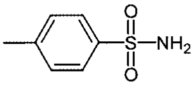
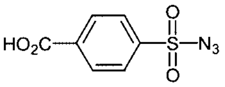
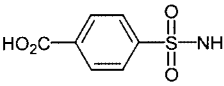
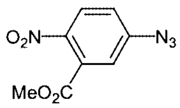
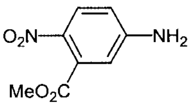
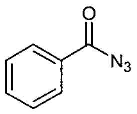
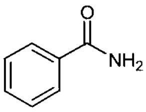
We have been studying organic reactions in water and have shown that an aqueous medium can be conveniently used in aldol-like condensations,[28a] epoxidations,[28b-c] and Diels−Alder cycloadditions.[28d] Recently, we prepared β-azidoalcohols and α-hydroxy-β-azidocarboxylic acids by a pH-controlled and metal-catalyzed azidolysis of alkyl- and aryl-1,2-epoxides[29a] and 2,3-epoxycarboxylic acids respectively.[29b] Our project concerns the synthesis of β-amino alcohols and β-hydroxy-α-amino acids in a one-pot procedure starting from the corresponding epoxides by azidolysis and subsequent reduction of the azido group. Here, we report a mild and efficient $NaBH_4/CoCl_2$-catalyzed reduction, in sole water, of azides to amines and amides. The $NaBH_4/CoCl_2$ system has been used to reduce several functional groups except azido, and has never been used in water only.[27]

A variety of azides were reduced quickly at 25 °C and in excellent yields with a catalytic amount of $CoCl_2•6H_2O$ (0.1 equivalents) in water, in the presence of $NaBH_4$ (2.0 equivalents).[30] The reaction was carried out in heterogeneous phase by simply adding a water solution of $NaBH_4$ to a stirred mixture of azide and $CoCl_2•6H_2O$; this addition was strongly exothermic. When the azide is highly hydrophobic, the best results, in terms of yield and time, are achieved by carrying out the reaction in the presence of 10% equivalents of cetyltrimethylammonium bromide (CTABr). $NaBH_4$ is unreactive towards the azido group in both heterogeneous and homogeneous aqueous medium in the presence of CTABr. The reduction is quantitative and the results are summarized in Table 1. The azides **3a** and **7a**−**10a** and the products **3b**−**10b** are new compounds. Aliphatic, cycloaliphatic, aryl, aroyl, and arysulphonyl azides are efficiently and quickly reduced and the reducing agent tolerates functionalities such as CO_2H, CO_2Me, OH, and OCH_2O. Moreover, the reaction is so fast that NO_2, CMe_2=CRH and CN functionalities are not reduced.[31]

After removing the reaction product by ethyl ether extraction of the aqueous reaction mixture, the mother liquor could be reused but its pH value is of crucial importance. At the end of the reduction process, the aqueous medium is strongly basic (pH>11) and if used as is, the reaction proceeds with low yield. The best efficiency was obtained by lowering the pH of the aqueous mixture to 8.0 by adding some drops of concentrated HCl before adding the

Table 1 Reduction of Azides with $NaBH_4/CoCl_2 \cdot 6H_2O$ in H_2O at 25 °C



	Substrate		Product	Time (min)	Yield[a] (%)
1a		**1b**		10	95
2a		**2b**		10	97
3a		**3b**		30	93[b]
4a		**4b**		15	94
5a		**5b**		10	96
6a		**6b**		20	92[b]
7a		**7b**		10	95
8a		**8b**		60	92
9a		**9b**		10	98
10a		**10b**		20	91
11a		**11b**		10	97
12a		**12b**		10	97
13a		**13b**		20	92
14a		**14b**		10	96

[a] Yield of isolated product; [b] 10% mol equiv of CTABr.

azide and $NaBH_4$. The yields of the 2nd, 3rd, 4th, and 5th runs for azides **1a** and **11a**, chosen as representative examples, were excellent (Table 2).

In conclusion, catalytic amount of the reducing system $NaBH_4/CoCl_2 \cdot 6H_2O$ (catalyst), not previously employed for the reduction of azides, in sole water and under mild conditions, reduces chemoselectively a broad spectrum of azides to amines and amides with high yields. The easy availability of the reducing system, the nature of the reaction medium and the possibility to recycle the catalyst make this procedure attractive and advantageous.

Table 2 Efficiency of the Reused Aqueous Mixture of Reducing System at 25 °C[a]

Run	**1a** → **1b** Yield (%)	**11a** → **11b** Yield (%)
1	95	97
2	97	96
3	98	95
4	96	95
5	96	97

[a] After 10 min of reaction time.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX - ADVANCE 400 MHz spectrometer; chemical shifts are reported in ppm and coupling constants are reported in Hz, using $CDCl_3$ or CD_3OD as solvents with TMS as internal standard. IR spectra were obtained on a FT-IR Bruker IFS 113v spectrophotometer. Microanalyses were performed on *Carlo Erba* Elemental Analyzer mod. 1106. Mps were taken on a Büchi 510 melting point apparatus and are uncorrected. Reaction progress was monitored by GC analysis, performed on a Hewlett Packard 5890 Series II equipped with an SPB-5 fused silica capillary column (30 m, 0.25 mm diameter), an “on column” injector system, a FID detector and H_2 as carrier gas.

Compounds **1a**−**11a**, and **14a** were prepared by following known procedures.[29, 32] Compounds **12a**, **13a**, **1b**, **2b**, and **11b**−**14b** are commercial. Compounds **3a**, **7a**−**10a**, and **3b**−**10b** are new compounds. The azides **3a** and **7a** were prepared by azidolysis of the corresponding epoxides under basic conditions[29a] and Cu(II) catalyzed,[29b] respectively. The azides **8a**, **9a**, and **10a** were prepared by following the described procedure starting from the respective bromide.[32]

1-Azido-3-(1′,3′-benzodioxol-5′-yl)propan-2-ol (3a)

Oil.

IR (CCl_4): ν = 3421, 2916, 2901, 2106, 1503, 1489, 1443, 1249, 928, 810 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.99 (br s, 1H, OH), 2.64−2.67 (m, 2H, H-3), 3.20 (dd, *J* = 6.6, 12.5 Hz, 1H, H-1a), 3.31 (dd, *J* = 3.9, 12.5 Hz, 1H, H-1b), 3.81−3.94 (m, 1H, H-2), 5.87 (s, 2H, $-OCH_2O-$), 6.55−6.74 (m, 3H, H-Ar).

^{13}C NMR ($CDCl_3$): δ = 40.2, 55.6, 71.5, 100.7, 108.1, 109.4, 122.0, 130.7, 146.1, 147.6.

Anal. Calcd for $C_{10}H_{11}N_3O_3$: C, 54.29, H, 5.01, N, 19.00. Found: C, 54.65, H, 4.98, N, 18.79.

Methyl *trans*-2-Azido-1-hydroxycyclohexanecarboxylate (7a)

Oil.

IR (CCl_4): ν = 3521, 2944, 2865, 2102, 1729, 1449, 1436, 1356, 1260, 869 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.20−2.05 (m, 8H), 3.52 (dd, *J* = 4.9, 9.4 Hz, 1H, H-1), 3.61 (br s, 1H, OH), 3.82 (s, 3H, Me).

^{13}C NMR ($CDCl_3$): δ = 21.4, 22.4, 27.3, 33.8, 52.8, 66.2, 76.3, 174.3.

Anal. Cald for $C_8H_{13}N_3O_3$: C, 48.23, H, 6.58, N, 21.09. Found: C, 48.25, H, 6.61, N, 21.08.

2-(1′, 3′-Dioxan-2′-yl)ethyl Azide (8a)

Oil.

IR (CCl_4): 3674, 3504, 3005, 2961, 2859, 2508, 2114, 1705, 1470 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.20−1.42 (s, 1H, H-5′a), 1.86 (dt, *J* = 5.1, 6.8 Hz, 2H, H-2), 2.03−2.15 (m, 1H, H-5′b), 3.39 (t, *J* = 6.8 Hz, 2H, H-1), 3.81 (m, 2H, H-4′a, H-6′a), 4.10 (m, 2H, H-4′b, H-6′b), 4.65 (t, *J* = 5.0 Hz, 1H, H-2′).

^{13}C NMR ($CDCl_3$): δ = 25.6, 34.4, 46.5, 66.8, 99.4.

Anal. Cald for $C_6H_{11}N_3O_2$: C, 45.85, H, 7.05, N, 26.74. Found: C, 45.91, H, 7.01, N, 26.78.

4-Azidobutanenitrile (9a)

Oil.

IR (CCl_4): 3254, 3014, 3941, 2872, 2504, 2254, 2105, 1731, 1705, 1290, 1258 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.90 (q, *J* = 6.7 Hz, 2H, H-3), 2.40 (t, *J* = 6.7 Hz, 2H, H-2), 3.42 (t, *J* = 6.7, 2H, H-4).

^{13}C NMR ($CDCl_3$): δ = 14.3, 24.7, 49.3, 118.5.

Anal. Cald for $C_4H_6N_4$: C, 43.63, H, 5.49, N, 50.88. Found: C, 43.60, H, 5.51, N, 50.87.

5-Azido-2-methyl-2-pentene (10a)

Oil.

IR (CCl_4): ν = 2972, 2930, 2917, 2876, 2088, 1718, 1675, 1451, 1295, 1265, 828 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.63−1.65 (m, 3H, Me), 1.71−1.73 (m, 3H, Me), 2.30 (br q, *J* = 7.1 Hz, 2H, H-4), 3.24 (t, *J* = 7.1 Hz, 2H, H-5), 5.11 (br t, *J* = 7.1 Hz, 1H, H-3).

^{13}C NMR ($CDCl_3$): δ = 17.6, 25.6, 27.8, 51.0, 119.8, 134.8.

Anal. Calcd for $C_6H_{11}N_3$: C, 57.57, H, 8.86, N, 33.57. Found: C, 57.63, H, 8.83, N, 33.62.

Reduction of Azides with $NaBH_4/CoCl_2·6H_2O$ in H_2O; General Procedure

To a mixture of azide (2.0 mmol) and $CoCl_2•6H_2O$ (0.048 g, 0.2 mmol), and when necessary (Table 1) CTABr (0.07 g, 0.2 mmol), at 25 °C was added dropwise under stirring a solution of $NaBH_4$ (0.0152 g, 4.0 mmol) in H_2O (4 mL). The formation of a black precipitate indicated the formation of a cobalt boride species. The mixture was stirred at 25 °C for more than 10 min when necessary (Table 1). At the end of the reaction the mixture was extracted with Et_2O (5 × 10 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give the pure amine or amide, The yields are reported in Table 1.

Re-use of Reducing Agent

The pH of remaining mother liquor (approx. 4 mL) after extraction with Et_2O of amine or amide was adjusted to 8.0 by adding a few drops of concd HCl. Azide (2.0 mmol) was then added, followed by $NaBH_4$ (0.0152 g, 4.0 mmol) in small doses. The mixture was stirred at 25 °C for more than 10 min. when necessary (Table 1) and then extracted with Et_2O. The mother liquor can continue to be re-used. Two examples are illustrated in Table 2.

1-Amino-3-(1′, 3′-benzodioxol-5′-yl)propan-2-ol (3b)

Oil.

^{1}H NMR (CD_3OD): δ = 2.63−2.85 (m, 3H, H-1, H-3), 2.95 (m, 1H. H-1), 3.85−4.00 (m, 1H, H-2), 5.88 (s, 2H, $-OCH_2O-$), 6.63-6.78 (m, 3H, H-Ar).

^{13}C NMR (CD_3OD): δ = 42.1, 45.3, 70.0, 102.1, 107.5, 110.5, 123.4, 132.0, 147.7, 149.0.

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53, H, 6.71, N, 7.17. Found: C, 61.60, H, 6.68, N, 7.21.

(−)-3β-Amino-4α-hydroxy-*trans*-carane (4b)

Mp 88−89 °C (*n*-hexane/Et_2O); $[\alpha]_D{}^{25}$−8° (*c* 0.98, $CHCl_3$)

^{1}H NMR ($CDCl_3$): δ = 0.59−0.71 (m, 2H, H-1, H-6), 0.90 (s, 3H, H-8), 0.93 (s, 3H, H-9), 1.02 (br s, 3H, H-10), 0.97−1.06 (m, 1H, Hβ-2), 1.59 (ddd, *J* = 7.8, 10.2, 14.4 Hz, 1H, Hβ-5), 1.80 (dd, *J* = 9.4, 14.4 Hz, 1H, Hα-2), 1.98 (dd, *J* = 7.2, 14.4 Hz, 1H, Hα-5), 2.15 (br s, 3H, NH_2, OH), 3.09 (dd, *J* = 7.3, 10.2 Hz, 1H, H-4).

^{13}C NMR ($CDCl_3$): δ = 15.8, 17.5, 19.5, 19.6, 21.4, 27.2, 28.8, 35.7, 52.3, 74.2.

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96, H, 11.31, N, 8.27. Found: C, 70.85, H, 11.45, N, 8.25.

(+)-4β-Amino-3α-hydroxy-*cis*-carane (5b)

Mp 113−114 °C (*n*-hexane/Et_2O); $[\alpha]_D{}^{25}$+35° (*c* 1.80, $CHCl_3$)

^{1}H NMR ($CDCl_3$): δ = 0.56−0.71 (m, 2H, H-1, H-6), 0.77−0.88 (m, 1H, Hβ-5), 0.95 (s, 3H, H-8), 0.97 (s, 3H, H-9), 1.07 (s, 3H, H-10), 1.29 (dd, *J* = 6.1, 15.4 Hz, 1H, Hβ-2), 1.81 (dd, *J* = 8.5, 15.4 Hz, 1H, Hα-2), 1.96−2.06 (m, 1H, Hα-5), 2.30 (br s, 3 H, NH_2, OH), 2.78 (dd, *J* = 5.3, 10.5 Hz, 1H, H-4).

^{13}C NMR ($CDCl_3$): δ = 15.8, 18.3, 20.8,, 24.7, 26.9, 28.6, 31.8, 34.2, 56.6, 72.5.

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96, H, 11.31, N, 8.27. Found: C, 70.80, H, 11.40, N, 8.20.

1-Aminooctan-2-ol (6b)

^{1}H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3H, H-8), 1.55−1.75 (m, 10H), 1.55 (br s, 3H, NH_2, OH), 2.51 (dd, *J* = 8.3, 12.6 Hz, 1H, H-1a), 2.86 (dd, *J* = 3.3, 12.6 Hz, 1H, H-1b), 3.40−3.60 (m, 1H, H-2).

^{13}C NMR ($CDCl_3$): δ = 14.4, 23.7, 26.7, 30.5, 33.0, 36.0, 48.0, 72.7.

Anal. Calcd for $C_8H_{19}NO$: C, 66.16, H, 13.19, N, 9.64. Found: C, 66.23, H, 13.12, N, 9.63.

Methyl *trans*-2-amino-1-hydroxy-cyclohexanecarboxylate (7b)

Oil.

IR (CCl_4): ν = 3526, 2941, 2864, 2362, 1725, 1450, 1436, 1362, 1302, 1231 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.20−2.08 (m, 8H), 2.23 (br s, 1H, OH), 2.73 (dd, *J* = 5.0, 10.2 Hz, 1H, H-2), 3.77 (s, 3H, Me).

^{13}C NMR ($CDCl_3$): δ = 22.4, 23.9, 31.3, 35.0, 52.1, 57.4, 77.8, 174.9.

Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47, H, 8.73, N, 8.09. Found: C, 55.48, H, 8.77, N, 8.10.

2-(1′, 3’-dioxan-2′-yl)ethyl amine (8b)

Oil.

IR (CCl_4): 3379, 2972, 2860, 2338, 1588, 1379, 1143, 1003, 804.3 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.20−1.32 (m, 1H, H-5′a), 1.68 (dt, *J* = 5.1, 6.6 Hz, 2H, H-2), 1.85 (br s, 2H, NH_2), 1.94−2.12 (m, 1H, H-5′b), 2.75 (t, *J* = 6.6 Hz, 2H, H-1), 3.60−3.78 (m, 2H, H.4′a, H-6′a), 3.95−4.10 (m, 2H, H-4′b, H-6′b), 4.58 (t, *J* = 5.1 Hz, 1H, H-2′).

^{13}C NMR ($CDCl_3$): δ = 22.2, 25.6, 37.1, 38.4, 66.7, 101.1.

Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94, H, 9.99, N, 10.68. Found: C, 54.99, H, 9.97, N, 10.71.

4-Aminobutanenitrile (9b)

Oil.

IR (CCl_4): 3383, 3319, 2957, 2872, 2478, 2250, 2104, 1699, 1602, 1426, 1377, 1315, 1090, 885, 859 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.95 (q, *J* = 6.9 Hz, 2H, H-3), 2.41 (t, *J* = 6.9 Hz, 2H, H-2), 2.81 (t, *J* = 6.9 Hz, 2H, H-4).

^{13}C NMR ($CDCl_3$): δ = 14.5, 28.7, 40.4, 120.7.

Anal. Calcd for $C_4H_8N_2$: C, 57.11, H, 9.59, N, 33.30. Found: C, 57.13, H, 9.64, N, 33.31.

4-Methylpent-3-enylamine (10b)

IR (CCl_4): ν = 2970, 2910, 2903, 2856, 1718, 1681, 1429, 1291, 1210, 821 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.60 (s, 3H, Me), 1.68 (s, 3H, Me), 1.78 (br s, 2H, NH_2), 2.10 (dd, *J* = 6.8, 13.7 Hz, 2H, H-2), 2.70 (dd, *J* = 6.6, 6.7, Hz, 2H, H-1), 5.06 (m, 1H, H-3).

^{13}C NMR ($CDCl_3$): δ = 17.7, 25.7, 32.1, 41.9, 121.6, 132.7.

Anal. Calcd for $C_6H_{13}N$: C, 72.66, H, 13.21, N, 14.12. Found: C, 72.58, H, 13.25, N, 14.13.

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(22) The water was used in a phase-transfer procedure[14] as reagent in the reduction that uses PPh_3,[23] and as co-solvent in the reduction with H_2S[24a] and $TiCl_3$.[24b]

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(30) Cobalt (II) chloride with aqueous $NaBH_4$ generates a black precipitate of cobalt boride, which catalyzes the decomposition of borohydride with hydrogen evolution. The reduction is more like catalytic hydrogenation, but a cobalt hydride species as active reducing agent cannot be excluded.[27]

(31) When the reaction time is extended to 4 hours, the double bond of compound **10b** is reduced.

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