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The $NiCl_2 \cdot 2H_2O$-Li-Arene Combination as Reducing System. Part 3.[1] Reduction of Carbonyl Compounds and Imines

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Abstract: The reaction of different carbonyl compounds or their imines with a mixture of nickel(II) chloride dihydrate, an excess of lithium powder and a catalytic amount of naphthalene (16 mol %) or DTBB (8 mol %) in THF at room temperature, leads to the formation of the corresponding alcohols or amines, respectively. The incorporation of deuterium oxide into the nickel salt complex yields the corresponding deuterated products. The process can also be applied to α,β-unsaturated carbonyl compounds leading either to the hydrogenation of only the carbon-carbon double bond or the full hydrogenation, depending on the amount of the nickel salt and/or reaction times.

INTRODUCTION

The reduction of carbonyl compounds or imines to the corresponding alcohols or amines, respectively, is a common functional group transformation in synthetic organic chemistry. Among the methodologies to perform this reaction three important procedures can be found: (a) metal hydrides, (b) dissolving metals and (c) catalytic hydrogenation under heterogeneous or homogeneous reaction conditions;[2] other methods such as electrochemical or enzimatic reductions are of less general application. Very recently, we have discovered that the system composed of dihydrated nickel(II) chloride and an excess of lithium powder in the presence of a catalytic amount of naphthalene[3-5] is very effective for the hydrogenation of alkenes[1a] and alkynes.[1b] This methodology can be considered as a combination of the general methods (b) and (c) above mentioned; it is supposed that two processes take place in a parallel manner: by means of the activated lithium a reduction of the nickel(II) salt to nickel(0) occurs (a black precipitate appears in every reaction) together with molecular hydrogen generation from the reaction of the two molecules of water contained in the metal salt with the excess of lithium. This last fact is one of the main advantages of this simple methodology, that is to say, the use of water as the hydrogen source. In this paper we report on the use of the mentioned combination for the reduction of carbonyl compounds and imines to alcohols and amines, respectively.

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RESULTS AND DISCUSSION

The reaction of different carbonyl compounds with a mixture of nickel chloride dihydrate (1-2 mmol), an excess of lithium powder (1/8 molar ratio, referred to the nickel salt) and a catalytic amount of naphthalene (0.32 mmol/mmol of nickel salt, 16 mol %) in tetrahydrofuran at room temperature led to the corresponding alcohols (Table 1, entries 4, 10 and 11). When deuterium oxide was used as the ligand in the nickel salt ($NiCl_2{\cdot}2D_2O$) instead of water, the corresponding deuterated alcohols were isolated (Table 1, entry 3 and 5). Whilst in the case of 3-pentanone (Table 1, entry 1) the best results were obtained at low temperature (-78°C) in order to avoid side reactions (mainly the corresponding pinacol coupling), similar results were observed either at low or at room temperature for cyclohexanone (Table 1, compare entries 2 and 3).

Two blank experiments with cyclohexanone demonstrated the necessity of using the hydrated nickel salt: either without the mentioned salt or using the corresponding anhydrous one only the starting material was recovered after stirring overnight at room temperature.

When the above mentioned methodology was applied to α,β-unsaturated carbonyl compounds, the final result depended on the amount of the metal salt employed. For instance, 3,5,5-trimethylcyclohex-2-en-1-one or chalcone (Table 1, entries 7 and 8, respectively) were converted into the corresponding saturated ketones using a 1/1 ketone/nickel salt molar ratio, being so a clear proof that the hydrogenation of the carbon-carbon double bond is easier than the corresponding reduction of the carbon-oxygen double bond.[6] The use of a double amount of the nickel salt with α,β-unsaturated carbonyl compounds (Table 1, entries 6, 9 and 12) afforded the expected corresponding saturated alcohols.

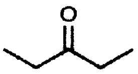
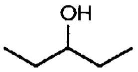
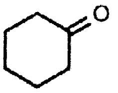
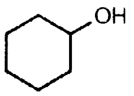
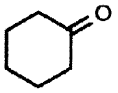
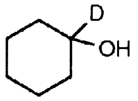
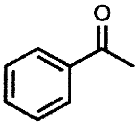
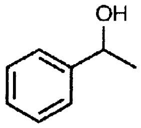
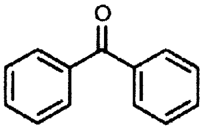
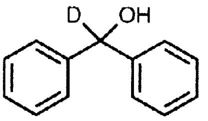
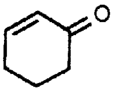
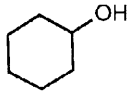
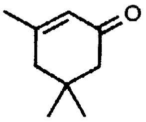
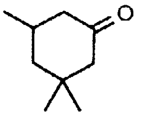
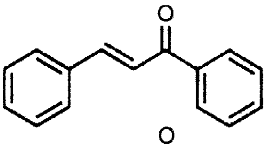
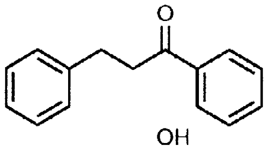
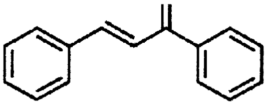
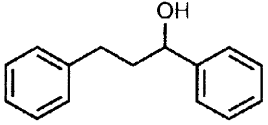
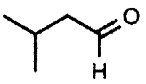
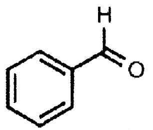
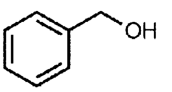
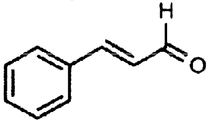
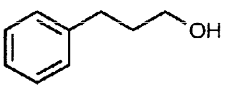
Finally, as a general remark, ketones gave better yields and cleaner reactions than aldehydes (compare entries 1-9 for ketones to 10-12 for aldehydes), even when in both cases the conversion is total. For aldehydes, important amounts (<30%) of the corresponding pinacols were obtained, which were easily separated by column chromatography.

The same protocol applied to the reduction of aldimines and ketimines yielded the corresponding secondary amines (Table 2). For these transformations 4,4'-di-*tert*-butylbiphenyl (DTBB; 8 mol %) showed to be superior in general to naphthalene as electron carrier, minimising the formation of byproducts and making easier the purification step.

Aldimines derived from aniline, such as isobutylideneaniline and benzylideneaniline were reduced to *N*-isobutylaniline and *N*-benzylaniline, respectively, under naphthalene-catalysed reduction conditions (Table 2, entries 1 and 2). On the other hand, the preparation of secondary dialkylamines such as *N*-*tert*-butylhexan-1-amine or dibutylamine was better accomplished by using DTBB as electron carrier (Table 2, entries 4 and 5).

This methodology was also applied to the reduction of ketimines such as those derived from cyclohexanone and cyclohexylamine or acetophenone and benzylamine (Table 2, entries 6 and 7, respectively). In the last case lower yield was observed in comparison to the above reported results because the reduction took also place in some extension at the benzylic position.

Table 1. Reduction of Carbonyl Compounds

Entry	Carbonyl compound	Reaction conditions		Product[a]	
		$NiCl_2.2H_2O$ (eq)	Time (h)	Structure	Yield (%)
1[b]		1.0	12		85[c]
2[b]		1.0	12		87[c]
3		1.0[d]	1.5		>95[c,e]
4		1.0	1		75[c]
5		1.0[d]	3		88[e,f]
6		2.0	0.3		>95[c]
7		1.0	4		70[c]
8		1.0	0.2		60[f]
9		2.0	3		73[f]
10		1.0	12		58[c]
11		1.0	12		64[f]
12		2.0	1		54[f]

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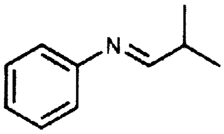
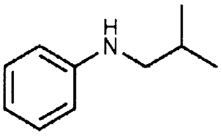
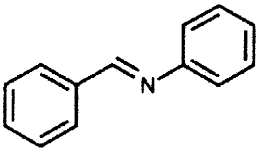
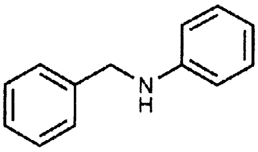
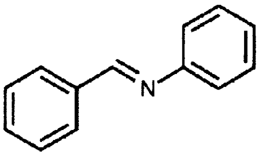
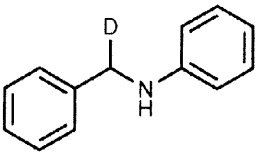
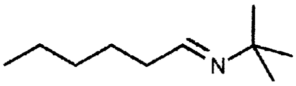
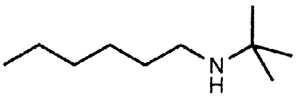
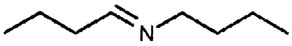
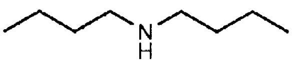
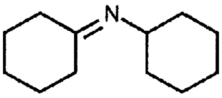
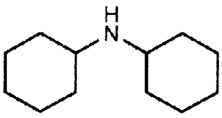
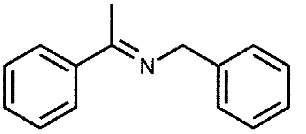
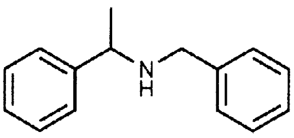
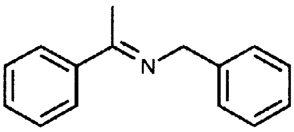
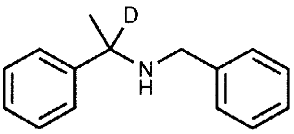
[a] All products were >95% pure (GLC). [b] Reaction performed at -78°C. [c] GLC yield based on the starting carbonyl compound. [d] $NiCl_2.2D_2O$ was used as the salt component. [e] >92 % deuterium incorporation (MS, NMR). [f] Isolated yield after column chromatography (hexane/ether) based on the starting material.

Table 2. Reduction of Imines

Entry	Imine	Reaction conditions		Product[a]	
		$NiCl_2.2H_2O$ (eq)	Time (h)	Structure	Yield (%)
1		1.0[b]	1		77
2		1.5[b]	12		86
3		1.5[c,d]	12		75
4		1.5[c]	3		81
5		1.0[c]	12		78[e]
6		1.5[c]	6		78
7		1.5[c]	3		62
8		1.5[c,d]	6		57

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[a] All products were >95% pure (GLC); isolated yield after column chromatography (hexane/ether) based on the starting material, unless otherwise is stated. [b] Naphthalene was used as electron carrier. [c] DTBB was used as electron carrier. [d] $NiCl_2.2D_2O$ was used as the salt component. [e] GLC yield, based on the precursor carbonyl compound of the *in situ* generated imine.

Finally, when the deuterated nickel salt was used instead of the hydrated one, incorporation of deuterium at the α-position was observed for both aldimines and ketimines (Table 2, entries 3 and 8).

As it was mentioned above and in previous papers in this series,[1] concerning to the possible mechanistic pathway, it is believed that the nickel(0) and molecular hydrogen (adsorbed on the surface of the metal: no gas evolution was observed in all reactions tried), formed under the strongly reductive reaction medium, react with the carbonyl compound or imine giving the corresponding alcohol or amine, respectively.

From the chemistry described in this paper we conclude that the here described methodology results adequate for the reduction of carbonyl compounds and imines under mild reaction conditions. The process is also applicable either to the semireduction of conjugated enones to ketones or their full hydrogenation to saturated alcohols, depending on the amount of salt employed. The use of the deuterium oxide-containing nickel(II) salt allows to label alcohols or amines isotopically at the hydroxy or nitrogen bearing carbon atom in a very simple way. In all cases one important advantage of the method is that the source of hydrogen (or deuterium) is water (deuterium oxide), so avoiding the use of dangerous molecular hydrogen.

EXPERIMENTAL PART

General.- Melting points were obtained with a Reichert Thermovar apparatus. FT-IT spectra were obtained on a Nicolet Impact 400D spectrophotometer. NMR spectra were recorded on a Bruker AC-300 (300MHz for ^{1}H and 75 MHz for ^{13}C) using $CDCl_3$ as solvent and TMS as internal standard; chemical shifts are given in δ (ppm) and coupling constants (*J*) in Hz. Mass spectra (EI) were obtained at 70 eV on a Shimadzu QP-5000 spectrometer, fragment ions in *m/z* with relative intensities (%) in parentheses. The purity of volatile products and the chromatographic analyses (GLC) were determinated with a Hewlet Packard HP-5890 instrument equipped with a flame ionization detector and a 12 m capillary column (0.2 mm diam, 0.33 mm film thickness), using nitrogen (2 ml/min) as carrier gas, $T_{injector}$ = 275°C, T_{column} = 60°C (3 min) and 60-270°C (15°C/min). Thin layer chromatography (TLC) was carried out on Schleicher & Schuell F1500/LS 254 plates coated with 0.2 mm layer of silica gel; R_f values are given under these conditions. Column chromatography was performed using silica gel 60 of 40-60 microns. All starting carbonyl compounds were commercially available (Acros, Aldrich, Fluka) of the best grade and were used without further purification. THF was dried over benzophenone ketyl under an argon atmosphere and destilled before use. Dihydrated nickel (II) chloride or its deuterated derivative were prepared according to the literature procedure.[1a] Imines showed in entries 1,[7] 2,[8] 4,[7] 5,[7] 6,[9] and 7[7] (Table 2) were prepared according to the literature procedures. In all cases, except for benzylidenaniline, the crude imine was used for the reduction step without further purification.

Reduction of Carbonyl Compounds or Imines using the $NiCl_2.2H_2O$-Li-Arene Combination. General Procedure.- To a mixture of nickel(II) chloride dihydrate (166 mg, 1 mmol) or its deuterated salt, lithium powder (56 mg, 8 mmol) and naphthalene (40 mg, 0.32 mmol) or DTBB (43 mg, 0.16 mmol), was added a solution of the corresponding carbonyl derivative (1 mmol) in THF (10 ml) at room temperature under an argon atmosphere. The reaction mixture, which was initially dark green, changed to black indicating that nickel(0) was formed. The reaction time was monitored by GLC. After total conversion of the starting material, the resulting suspension was diluted with ether (10 ml), carefully hydrolysed with water (10 ml) and acidified with 2M hydrochloric acid for carbonyl compounds . The organic layer was dried over anhydrous sodium sulfate and evaporated (15 Torr) to give a residue, which was purified by column chromatography (silica gel, hexane/ether) to give the corresponding pure compound. For volatile products the dried organic layer was analysed by GLC using an internal standard. 3-pentanol, cyclohexanol, *sec*-phenethyl alcohol, 3-methyl-1-butanol, benzyl alcohol, 3-phenyl-1-propanol, as well as *N*-phenylbenzylamine, dibutylamine, and dicyclohexylamine were characterised by comparison of their chromatographic and spectral data with those of the corresponding commercially available pure samples (Aldrich). For the other compounds, yields are included in Tables 1 and 2. Physical and spectroscopic data as well as literature references for known compounds follow.

1-Deuteriocyclohexanol:[10] t_r = 13.15 min; *m/z* 101 (M^+, 3%), 100 (M^+-1, 1%), 84 (39), 83 (80), 82 (21), 73 (21), 72 (33), 71 (14), 69 (19), 68 (53), 67 (31), 59 (39), 58 (100), 57 (77), 56 (31), 55 (24), 54 (20), 46 (13), 45 (43), 44 (27).

1-Deuteriodiphenylmethanol:[11] t_r = 7.50 min; R_f = 0.62 (hexane/ether 1:1); m.p. 65-66°C (hexane); ν (KBr) 3295 (OH), 3083, 3055, 3022, 1598, 1492 (HC=C), 1262, 1089, 1033 cm^{-1} (C-O); δ_H 2.60 (1H, s, OH), 7.19-7.33 (10H, m, ArH); δ_C 75.5 (CD, J_{CD} = 21.4), 126.5, 127.4, 128.4 (ArC), 143.7 (2C, d, J_{CD} = 4.9, ArC); *m/z* 186 (M^++1, 5%), 185 (M^+, 33%), 184 (19), 106 (28), 105 (100).

1,3-Diphenyl-1-propanone:[12] t_r = 14.97 min; R_f = 0.33 (hexane/ether 9:1); m.p. 70-72°C (ethanol); ν (KBr) 3059, 3024, 1595 (HC=C), 1680 cm^{-1} (C=O); δ_H 3.07 (2H, t, *J* = 7.6, $PhC\mathit{H}_2$), 3.31 (2H, t, *J* = 7.6, CH_2CO), 7.18-7.32 (5H, m, ArH), 7.45 (2H, d, *J* = 7.8, ArH), 7.55 (1H, t, *J* = 7.02, ArH), 7.96 (2H, d, *J* = 7.8, ArH); δ_C 30.1 ($Ar\mathit{C}H_2$), 40.4 ($\mathit{C}H_2CO$), 126.1, 128.0, 128.4, 128.5, 128.6, 128.7, 133.0, 136.8, 141.3 (ArC), 199.2 (CO); *m/z* 211 (M^++1, 27%), 210 (M^+, 69%), 131 (10), 106 (42), 105 (100), 103 (22), 91 (55), 79 (16), 78 (30), 77 (75), 65 (25), 51 (46), 50 (12).

1,3-Diphenyl-1-propanol:[13] t_r = 14.94 min; R_f = 0.43 (hexane/ether 1:1); ν (film) 3393 (OH), 3084, 3060, 3026, 1602, 1495 cm^{-1} (HC=C); δ_H 1.96-2.15 (3H, m, $PhC\mathit{H}_2$, OH), 2.57-2.73 (2H, m, $PhCH_2C\mathit{H}_2$), 4.61 (1H, dd, *J* = 5.5, 7.6, $C\mathit{H}OH$), 7.00-7.31 (10H, m, ArH); δ_C 31.9 ($Ph\mathit{C}H_2$), 40.3 ($PhCH_2\mathit{C}H_2$), 73.7 (*C*HOH), 125.8, 125.9, 127.5, 128.3, 128.4, 141.7, 144.5 (ArC); *m/z* 213 (M^++1, 5%), 212 (M^+, 39%), 195 (39), 194 (63), 193 (50), 179 (41), 178 (26), 165 (14), 134 (14), 133 (21), 121 (29), 120 (10), 117 (19), 116 (39), 115 (42), 108 (38), 107 (100), 105 (52), 104 (35), 103 (51), 92 (53), 91 (61), 89 (16), 80 (20), 79 (60), 78 (47), 77 (70), 65 (48), 63 (20), 53 (12), 52 (17), 51 (49), 50 (16), 43 (13).

3,3,5-Trimethylcyclohexanone:[14] t_r = 6.67 min; R_f = 0.37 (hexane); ν (film) 1709 cm^{-1} (C=O); δ_H 0.88, 1.06 [6H, 2s, $C(CH_3)_2$], 1.02 (3H, d, *J* = 6.1, $CHC\mathit{H}_3$), 1.17-2.35 (7H, m, 3 x CH_2, CH); δ_C 22.5 ($\mathit{C}H_3CH$), 25.8, 29.7 [$(\mathit{C}H_3)_2C$], 32.1 ($CH_3\mathit{C}H$), 35.4 [$(CH_3)_2\mathit{C}$], 47.3 [$(CH_3)_2C\mathit{C}H_2CHCH_3$], 49.2, 54.2 (2 x $\mathit{C}H_2CO$), 210.5 (CO); *m/z* 141 (M^++1, 1%), 140 (M^+, 15%), 83 (100), 69 (64), 57 (14), 56 (52), 44 (51), 43

(21), 42 (26).

N-*Isobutylaniline*:[15] t_r = 10.01 min; R_f = 0.65 (hexane/ether 9:1); ν (film) 3417 (NH), 3052, 3020, 1603, 1507 cm^{-1} (HC=C); δ_H 0.97 (6H, d, *J* = 6.7, 2 x CH_3), 1.87 (1H, septet, *J* = 6.7, $CHCH_2$), 2.91 (2H, d, *J* = 7.0, CH_2), 3.6 (1H, br s, NH), 6.58 (2H, d, *J* = 8.6, ArH), 6.66 (1H, dt, *J* = 7.3, 1.2, ArH), 7.15 (2H, t, *J* = 7.3, ArH); δ_C 20.4 (CH_3), 28.0 (CH), 51.8 (CH_2), 112.6, 116.9, 129.2, 148.5 (ArC); *m/z* 150 (M^++1, 1%), 149 (M^+, 13%), 106 (100), 77 (18), 51 (11).

*α-Deuterio-*N-*phenylbenzylamine*:[16] t_r = 13.89 min; R_f = 0.53 (hexane/ether 8:2); ν (film) 3418 (NH), 3084, 3053, 3025, 1601, 1504 cm^{-1} (HC=C); δ_H 3.89 (1H, br s, NH), 4.20 (1H, t, J_{HD} = 2.7, CH), 6.52 (2H, d, *J* = 8.6, ArH), 6.61 (1H, t, *J* = 7.3, ArH), 7.18 (2H, t, *J* = 7.3, ArH), 7.20-7.25 (5H, m, Ar'H); δ_C 47.9 (CD, J_{CD} = 21.0), 112.8, 117.5, 127.2, 127.4, 128.5, 129.2, 139.4, 148.1 (ArC); *m/z* 186 (M^++2, 7%), 185 (M^++1, 20%), 184 (M^+, 39%), 183 (27), 182 (11), 107 (14), 93 (27), 92 (100), 91 (53), 78 (12), 77 (24), 66 (13), 65 (15), 51 (16).

N-tert-*Butylhexylamine*:[17] t_r = 7.35 min; R_f = 0.15 (ether); ν (film) 3423 (NH); δ_H 0.88 (3H, t, *J* = 7.9, CH_3CH_2), 1.18-1.35 (8H, m, 4 x CH_2), 1.25 [9H, s, $C(CH_3)_3$], 2.67 (2H, t, *J* = 7.9, CH_2N); δ_C 13.8 (CH_3CH_2), 22.4, 26.9, 28.1, 31.4 ($CH_3CH_2CH_2CH_2CH_2$), 27.03 [$C(CH_3)_3$], 41.8 (CH_2N), 53.1 (CN); *m/z* 157 (M^+, 4%), 142 (82), 86 (29), 58 (77), 57 (36), 56 (17), 55 (13), 44 (100), 43 (46).

N-*Benzyl-1-phenethylamine*:[18] t_r = 13.82 min; R_f = 0.53 (hexane/ether 1:1); ν (film) 3328 (NH), 3085, 3062, 3027, 1602 cm^{-1} (HC=C); δ_H 1.37 (3H, d, *J* = 6.4, CH_3), 1.85 (1H, br s, NH), 3.59, 3.67 (2H, AB system, *J* = 13.1, CH_2), 3.82 (1H, q, *J* = 6.4, $CHCH_3$), 7.23-7.36 (10H, m, ArH); δ_C 24.4 (CH_3), 51.5 (CH_2), 57.4 ($CHCH_3$), 126.6, 126.8, 126.9, 128.1, 128.3, 128.4, 140.5, 145.4 (ArC); *m/z* 211 (M^+, 1%), 210 (M^+-1, 4%), 196 (59), 195 (12), 105 (20), 91 (100), 77 (16), 65 (14), 51 (12).

N-*Benzyl-α-deuterio-1-phenethylamine*: t_r = 13.86 min; R_f = 0.53 (hexane/ether 1:1); ν (film) 3331 (NH), 3083, 3062, 3026, 1602 cm^{-1} (HC=C); δ_H 1.34 (3H, s, CH_3), 1.70 (1H, br s, NH), 3.59, 3.66 (2H, AB system, *J* = 13.3, CH_2), 7.23-7.36 (10H, m, ArH); δ_C 24.4 (CH_3), 51.6 (CH_2), 57.4 (CD, J_{CD} = 4.3), 126.7, 126.8, 126.9, 128.1, 128.3, 128.4, 140.6, 145.5 (ArC); *m/z* 212 (M^+, 2%), 211 (M^+-1, 7%), 210 (14), 197 (27), 196 (63), 195 (37), 92 (14), 91 (100), 65 (12).

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