

The NiCl₂–Li–arene(cat.) combination: A versatile reducing mixture

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The NiCl₂·2H₂O–Li–arene(cat.) combination described in this *tutorial review* has shown to be a useful and versatile mixture able to reduce a broad range of functionalities bearing carbon–carbon multiple bonds, as well as carbon–heteroatom and heteroatom–heteroatom single and multiple bonds. The analogous deuterated combination, NiCl₂·2D₂O–Li–arene(cat.), allows the easy incorporation of deuterium in the reaction products. Alternatively, the anhydrous NiCl₂–Li–arene (or polymer-supported arene)(cat.) system generates a highly reactive metallic nickel, which in the presence of molecular hydrogen at atmospheric pressure is able to catalyze the hydrogenation of almost the same type of functionalities mentioned above.

1 Introduction

The reduction of organic molecules is one of the fundamental processes in synthetic organic chemistry, especially useful in methodologies involving functional group transformations. Among the different procedures to carry out reduction reactions, there are three general methods that can be highlighted: (a) catalytic hydrogenation, (b) dissolving metals, and (c) metal hydrides.^{1,2} But probably catalytic hydrogenation is the most commonly used method, allowing the reduction of many functional groups, often with high control of the chemo-, regio-, and stereoselectivity.^{3,4} It involves molecular hydrogen and either a transition metal (heterogeneous conditions) or a transition-metal-derived complex (homogeneous conditions). Heterogeneous catalysts are solids that form a distinct phase in the gas or liquid environment, which at the conclusion of the reduction are filtered from the mixture to leave a solution free of contaminating reagents. Homogeneous catalysts

dissolve in the liquid environment forming a single phase, and therefore their separation is a major disadvantage. The former and the latter are very well represented by palladium supported on carbon, and Wilkinson's catalyst [chlorotris(triphenylphosphine)rhodium(I)], respectively. In general, heterogeneous catalytic hydrogenation⁴ is preferred due to the mild reaction conditions mostly required and to the easy separation of the catalyst. Although catalytic hydrogenation is a reaction of proven efficiency, the experimental requires special care in the handling of hydrogen (a highly flammable and explosive gas), and in some cases quite expensive catalysts and/or high pressures are required for the reaction to take place. An additional inconvenience of catalytic hydrogenation is the low control of the degree of hydrogenation in substrates containing more than one reducible functionality.

Among the many catalysts available, nickel catalysts² are universal and widely used both in the laboratory and in industry. They can be found in a supported form (nickel on kieselguhr,²

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Miguel Yus was born in Zaragoza in 1947. He received the BSc (1969), MSc (1971), and PhD (1973) degrees from the University of Zaragoza. After spending two years as a postdoc at the Max Planck Institut für Kohlenforschung in Mülheim a.d. Ruhr, he returned to the University of Oviedo where he became Associate Professor in 1977, being promoted to full Professor in 1987 at the same university. In 1988 he moved to a chair in organic chemistry at the University of Alicante. Professor Yus has been visiting professor at different institutions such as ETH-Zürich and the universities of Oxford, Harvard, Uppsala, Marseille, Tucson, Okayama, Paris VI and Strasbourg. He is member or fellow of the chemical societies of Argentina, England, Germany, Japan, Spain, Switzerland, and United States. He is co-author of more than 300 papers mainly in the field of the development of new methodologies involving organometallic intermediates in synthetic organic chemistry. Among others, he has recently received the Spanish-French Prize (1999), the Japan Society for the Promotion of Science Prize (2000) and the Stiefvater Memorial Lectureship Award (2001). Professor Yus belongs to the advisory board of the journals *Tetrahedron*, *Tetrahedron Letters* and the *European Journal of Organic Chemistry*. Last year Professor Yus, with other members of the Department of Organic Chemistry including Dr Alonso, founded the new chemical company MEDALCHEMY, S.L. to commercialise fine chemicals.

Francisco Alonso (left) Miguel Yus (right)

alumina,⁵ or carbon⁶), as a nickel–aluminium alloy powder,⁷ or obtained by reduction of nickel salts such as nickel aluminides and nickel borides,⁸ nickel precipitated from a nickel halide and zinc,⁹ or the Nic catalysts [NaH–NaOR–Ni(II) salts],¹⁰ which generate nickel hydride species. Especially reactive are those nickel catalysts in the form of colloids¹¹ or as solvated metal atom dispersed powders.¹² However, Raney nickel is probably by far the most used nickel catalyst because of its high activity, being able to reduce practically any function.^{2,13} Its main disadvantages are: (a) the difficulty in calculating the dosage (it is usually measured as a suspension rather than weighed); (b) ferromagnetic properties that preclude the use of magnetic stirring; (c) it is potentially hazardous (pyrophoric); and (d) it becomes inactive after prolonged storage, presumably because it loses hydrogen slowly.

On the other hand, in recent years we have developed a new reducing agent composed of nickel(II) chloride dihydrate, an excess of lithium powder, and a catalytic amount of an arene, NiCl₂·2H₂O–Li–arene(cat.). The role of the aromatic hydrocarbon catalyst is to act as an electron carrier.¹⁴ The solubility of lithium in THF is very low, and therefore the interaction with the nickel salt is also low. Naphthalene and 4,4'-di-*tert*-butylbiphenyl are aromatic hydrocarbons which undergo reduction by lithium to give the corresponding monoanion radical or dianion. These species, which are soluble in THF, then transfer electrons to substrates prone to reduction, allowing, for instance, the reduction of Ni(II) to Ni(0).

The above described reducing system has been successfully applied to the reduction of a wide variety of functional groups and can be considered as a way of 'hydrogenation without using molecular hydrogen'. The following advantages can be mentioned of this methodology when compared with catalytic hydrogenation: (a) only commercially available or easily prepared reagents are used; (b) simplicity of the procedure since all reagents are solid and the reactions are carried out at room temperature; (c) the degree of hydrogenation can be easily controlled by adjusting the stoichiometry of the nickel salt; (d) when nickel(II) chloride containing two molecules of deuterium oxide is used, the incorporation of deuterium in the products is accomplished, thus avoiding the handling of expensive molecular deuterium; (e) the source of hydrogen is simply water.

As an alternative methodology, a nickel-catalyzed hydrogenation reaction has been developed involving external molecular hydrogen and highly reactive catalytic nickel(0), which has been prepared from anhydrous nickel(II) chloride, lithium, and a catalytic amount of naphthalene (or polymer-supported naphthalene). This catalytic combination has been used as a catalyst for the hydrogenation of different functional groups in the presence of molecular hydrogen at normal pressure and room temperature.

The reducing ability of both systems, NiCl₂·2H₂O–Li–arene and NiCl₂–Li–arene/H₂, resides on the high reactivity of the finely divided nickel(0) generated in such a way.

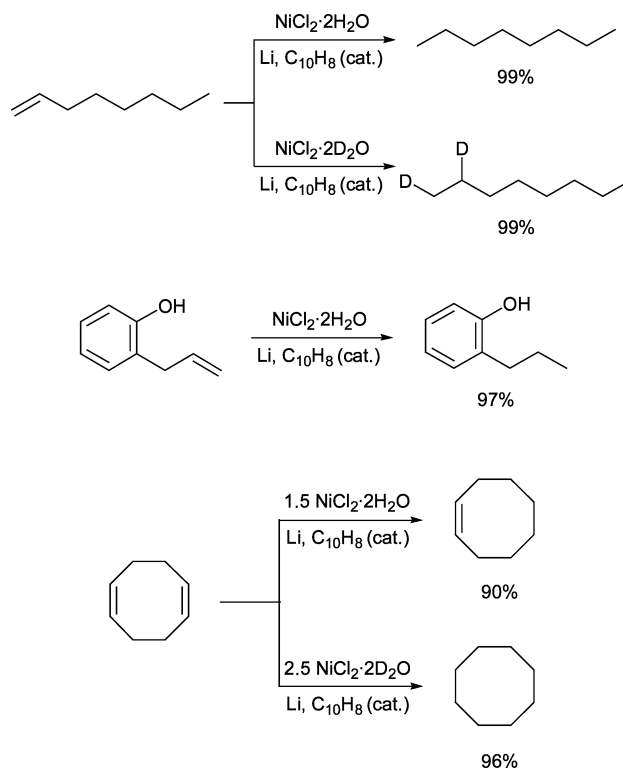
In this account we will show the versatility and usefulness of the above mentioned nickel-based combinations as new methodologies for the reduction of different functional groups. In addition, both methodologies will be compared with each other, taking also other main nickel reducing systems as a reference.

2 The NiCl₂·2H₂O–Li–arene(cat.) combination: A versatile reducing mixture

2.1 Reduction of carbon–carbon multiple bonds: alkenes, alkynes and aromatic compounds

Alkenes. The most common methodology to reduce alkenes to the corresponding alkanes is catalytic hydrogenation, either under homogeneous or heterogeneous conditions; other procedures involving diimine, dissolving metals, low-valent species or metal hydride-transition metal combinations are of more limited application.¹

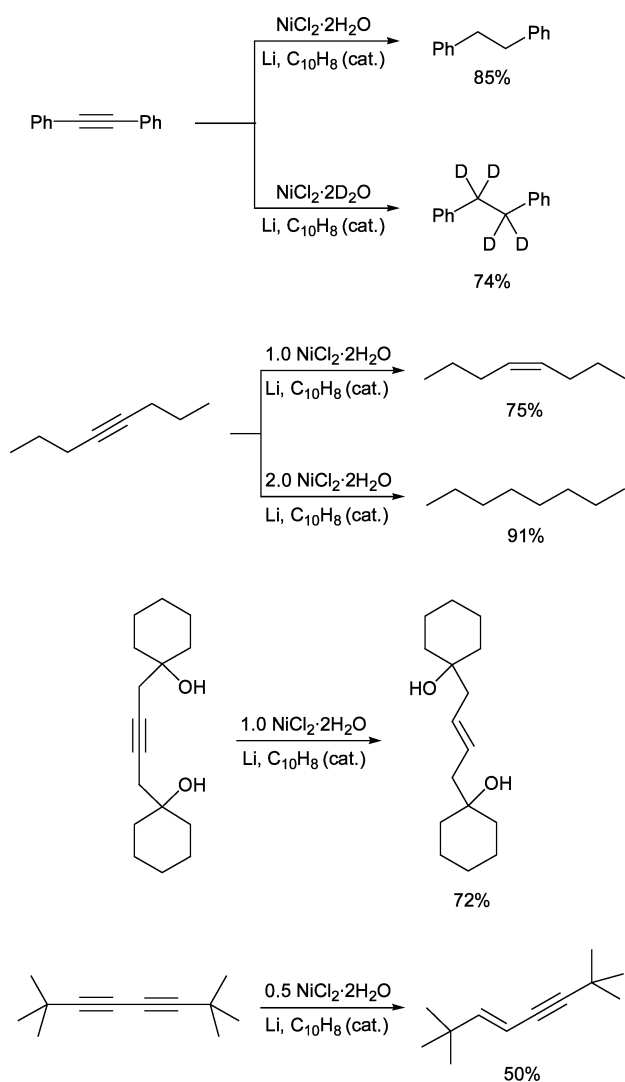
When differently substituted acyclic or cyclic alkenes react with NiCl₂·2H₂O, an excess of lithium, and a catalytic amount of naphthalene (17 mol%), the corresponding alkanes are obtained.^{15,16} The application of this methodology to dienes gives different results depending on the stoichiometry used: for instance, 1,5-cyclooctadiene is transformed exclusively into cyclooctane using 1.5 equiv. of the nickel salt, whereas complete reduction takes place with 2.5 equiv., giving cyclooctane as the only reaction product. In addition, the treatment of an alkene with NiCl₂·2D₂O under similar conditions yields 1,2-dideuterated alkanes, this labelling procedure using the cheapest source of deuterium and therefore avoiding the use of molecular deuterium. Scheme 1 exemplifies the commented processes for 1-octene, *o*-allylphenol, and 1,5-cyclooctadiene as starting materials.



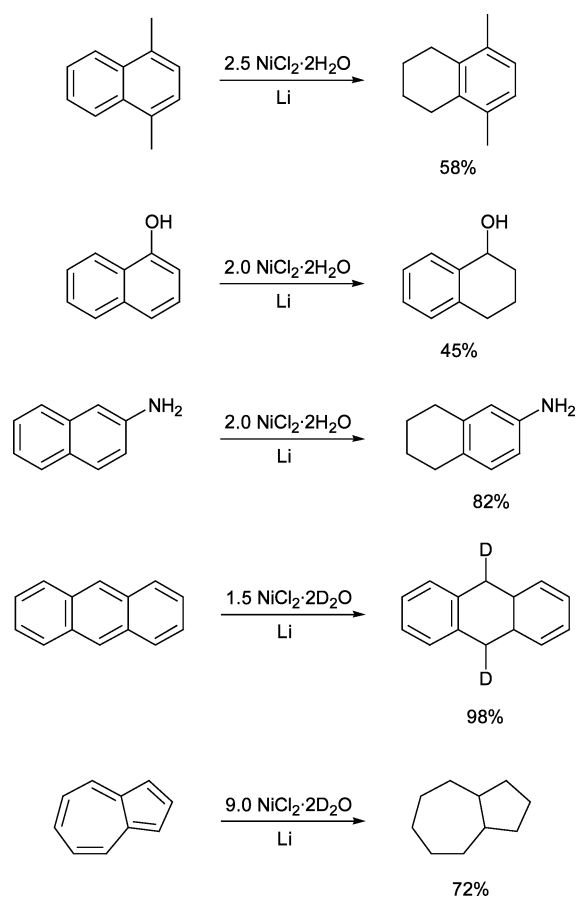
Scheme 1

Alkynes. In the case of alkynes, their reduction is generally accomplished following the same methodologies as for alkenes, the partial selective reduction to the corresponding alkenes being of a great interest. Catalytic hydrogenation gives predominantly *cis*-alkenes, whereas metals and metal salts give mainly *trans*-alkenes.¹ When mono- or disubstituted alkynes are submitted to the reaction with NiCl₂·2H₂O (2 equiv.) and an excess of lithium powder in the presence of a catalytic amount of naphthalene (17 mol%), the corresponding alkanes are obtained (see Scheme 2). The use of the deuterated nickel salt (see above) allows the perdeuteration of the starting material giving tetra-deuterated alkanes. Concerning the monoreduction reaction, the stereochemistry of the obtained alkenes depends on the structure of the starting acetylene: thus, 4-octyne gives *cis*-4-octene, whereas in the case of a substituted alkynediol only the corresponding *trans*-olefin was isolated. In addition, the semireduction of a conjugated diyne can be achieved using a substoichiometric amount of the reducing mixture (0.5 equiv.), to give the corresponding enyne with *trans*-geometry. Examples of the reduction of some alkynes are depicted in Scheme 2.¹⁷

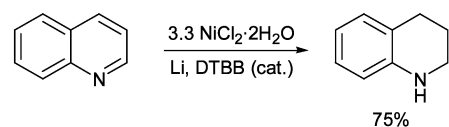
Aromatic compounds. Aromatic compounds are more difficult to reduce compared to alkenes or alkynes, because it is necessary to destroy the resonance stabilisation. However, the well-



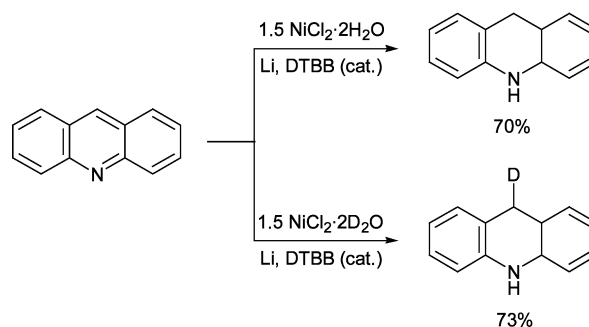
Scheme 2



Scheme 3



Scheme 4



Scheme 4

known Birch methodology, involving dissolving alkali metals in a proton solvent, is still probably the most useful procedure to prepare hydroaromatic compounds.² Scheme 3 includes some examples on the partial or total reduction of aromatic compounds using the $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$ –Li methodology, in these cases without the necessity of using an additional arene as electron carrier. As it is shown, the regiochemistry of the reaction strongly depends on the substitution of the aromatic rings. In addition, the corresponding deuteration can be performed using the deuterium oxide containing nickel salt.¹⁸

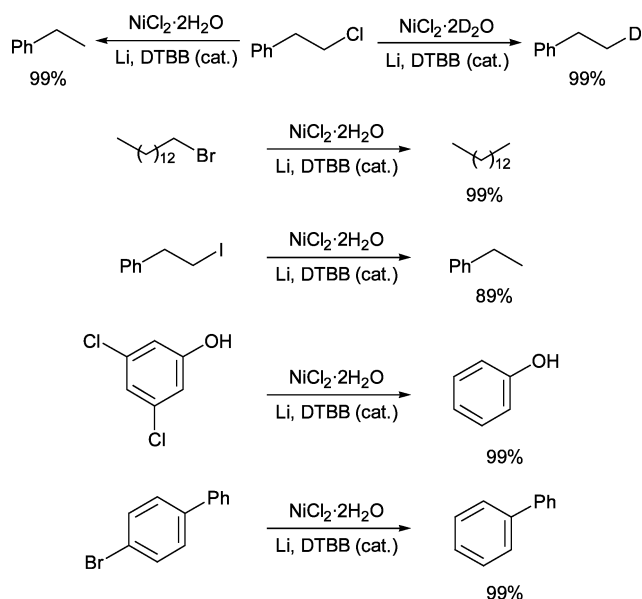
Heteroaromatic compounds. Concerning heterocyclic aromatic compounds, the selective reduction of the heterocyclic ring in benzo-fused systems is an important transformation in the field of alkaloids, which can be carried out using different methodologies including catalytic hydrogenation, dissolving metals or metal hydrides.¹⁹ The application of the $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$ –Li combination (or its deuterated version) requires in this case the use of an arene, 4,4'-di-*tert*-butylbiphenyl (DTBB) being the most efficient one. Under these reaction conditions, the reduction of the heterocyclic ring is easily achieved as show the selected examples included in Scheme 4.¹⁸

2.2 Reduction of carbon–halogen and carbon–oxygen single bonds: organic halides and sulfonates

Organic halides. Halogenated organic compounds, especially polychlorinated materials, represent a major environmental concern because they are extremely persistent due to their difficult

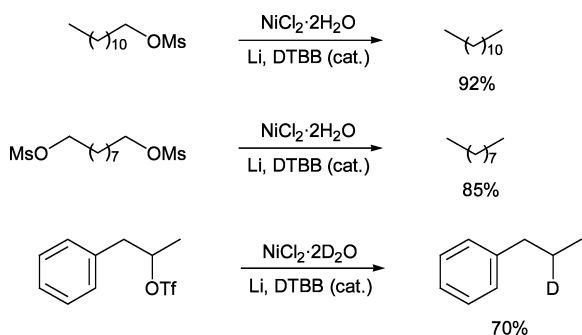
degradation by reductive or oxidative enzymatic reactions. Thus, efficient methods to perform the hydrodehalogenation of these recalcitrant compounds are welcome. Many procedures, based mainly on the use of metals, have been developed in order to transform them into less noxious compounds.²⁰ The treatment of different aliphatic and aromatic chlorides, bromides, or iodides with the $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$ (1 : 1 molar ratio)–Li–DTBB (10 mol%) combination, leads to the corresponding hydrocarbons. However, fluorides (for instance, 1-fluorononane) are inert under the same reaction conditions. The use of the corresponding deuterated nickel salt allows the easy halogen–deuterium exchange. Scheme 5 includes some representative examples of these processes.²¹

Sulfonates. In general, a method to deoxygenate alcohols implies their transformation into sulfonates, followed by reaction



Scheme 5

with sodium iodide and final catalytic hydrogenation or other methodologies.² On the other hand, different mesylates or triflates can be transformed into the corresponding alkanes (or deuterioalkanes) by treatment with the $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$ -Li-DTBB (10 mol%) combination (or with the corresponding deuterated nickel salt). Some representative examples are summarised in the Scheme 6.¹⁸



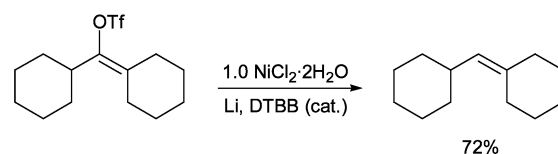
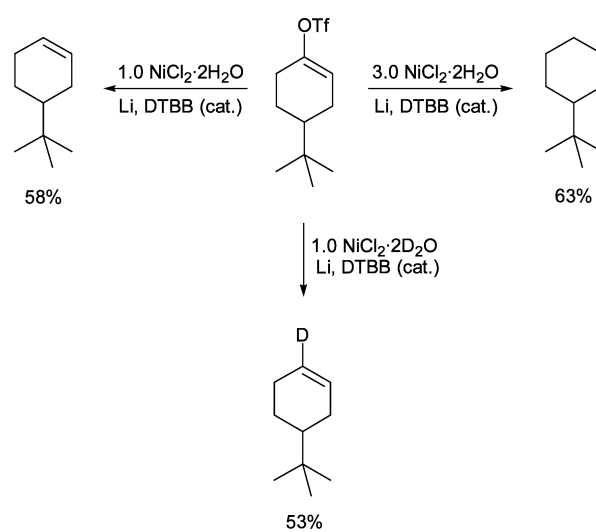
Scheme 6

For enol triflates, the degree of reduction can be easily controlled to yield either the corresponding alkene (with 1.0 equiv. of the nickel salt) or the alkane, using in this case an excess (3.0 equiv.) of the nickel salt. In addition, the incorporation of deuterium is readily achieved using the deuterated version of the reaction, giving rise to vinylic deuterated products. Scheme 7 illustrates some selected cases of carbon-oxygen bond cleavage in enol triflates.¹⁸

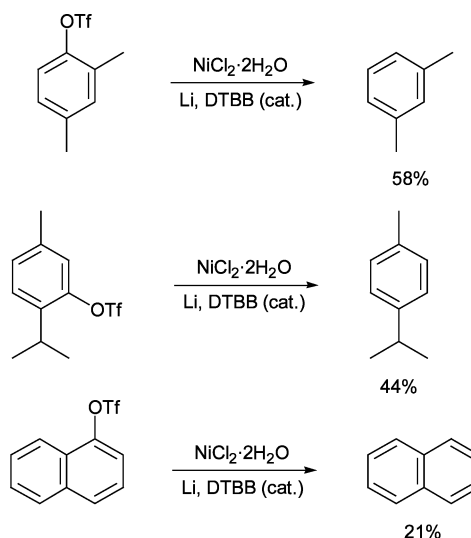
The application of the same methodology to aryl triflates gives the expected arenes but with lower yields than in the case of alkyl or alkenyl triflates (see above), as shown in Scheme 8 for some examples. The corresponding phenols resulting from a competitive oxygen-sulfur bond cleavage are isolated as by-products.¹⁸

2.3 Reduction of carbon-oxygen and carbon-nitrogen double bonds: carbonyl compounds and imines

Carbonyl compounds. Carbonyl compounds can be reduced to the corresponding alcohols using the three general methodologies mentioned in the introduction section: catalytic hydrogenation, dissolving metals and metal hydrides.¹ The use of the $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$ -Li-C₁₀H₈ (16 mol%) allows the easy reduction of carbonyl compounds to alcohols, the process working better for



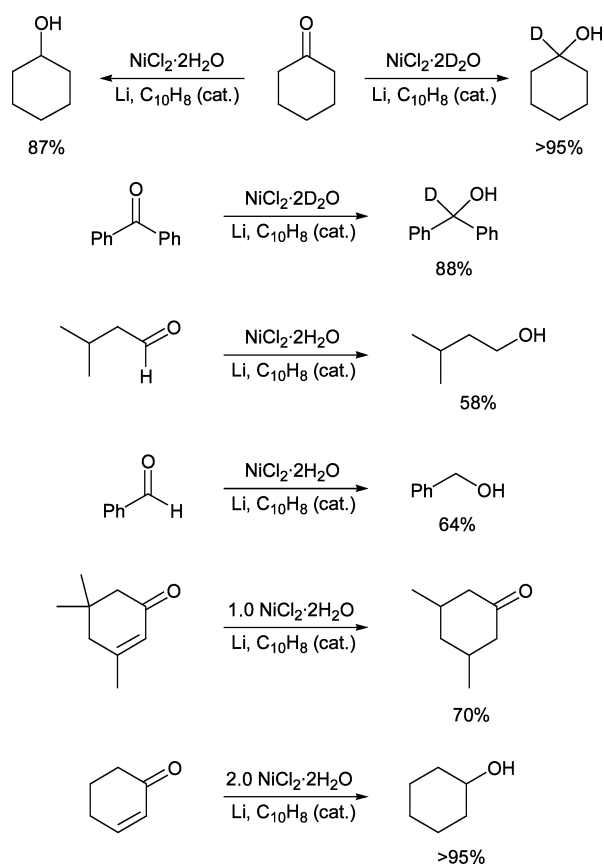
Scheme 7



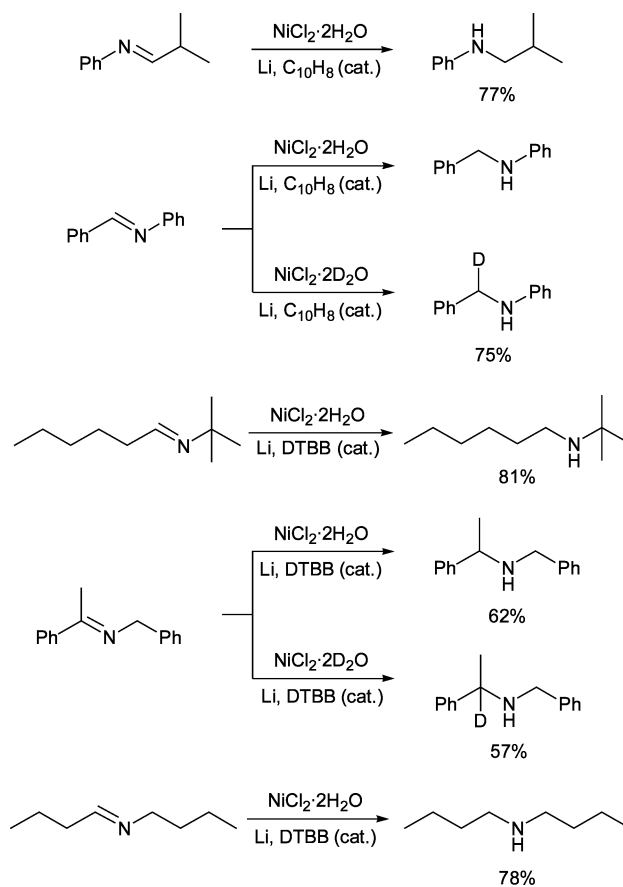
Scheme 8

ketones than for aldehydes. Also here, the deuterated version of the reaction yields the expected isotopically labelled alcohols. This represents a major advantage over the use of the expensive LiAlD_4 . By adjusting the stoichiometry of the reactants, it is possible to drive the reduction of α,β -unsaturated carbonyl compounds toward the formation of saturated ketones (1.0 equiv. of the nickel salt) or the corresponding alcohols (2.0 equiv. of the nickel salt). Some typical examples are collected in Scheme 9.²²

Imines. The three general methods utilized in the reduction of carbonyl compounds can be also applied to the reduction of imines.¹ Aldimines with alkyl-aryl, diaryl, or dialkyl substituents were easily reduced to the corresponding secondary amines with $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$ -Li, in the presence of either naphthalene (16 mol%) or DTBB (8 mol%) as electron carriers. Incorporation of deuterium at the α -position was easily effected by using the deuterated nickel salt. The same protocol was applied to ketimines, deuteration also being easy. The lower yields observed for some benzyl amines could be due to partial debenzylation under the reductive reaction



Scheme 9



Scheme 10

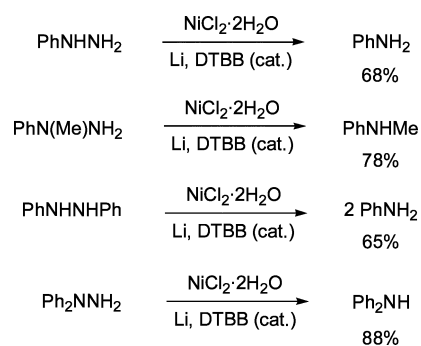
conditions. Significant examples of these processes, including a deuteration reaction, are summarised in Scheme 10.²²

2.4 Reduction of nitrogen–nitrogen single and double bonds: hydrazines, azo compounds and azides

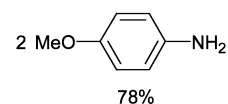
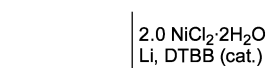
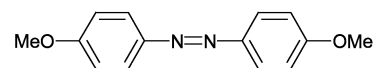
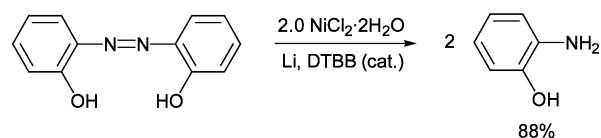
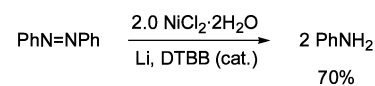
Hydrazines. There are few general methods to reduce the nitrogen–nitrogen bond in hydrazines, catalytic hydrogenation or dissolving metals being the most commonly used.²³ However, differently monosubstituted, *N,N*- or *N,N'*-disubstituted hydrazines are reduced to the corresponding primary or secondary amines by means of the $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$ – Li – DTBB (10 mol%) combination. Alternatively, a polymer-supported biphenyl can be used as the electron carrier catalyst. This is an attractive alternative to DTBB since although the yields are comparable, separation of the arene from the reaction medium is much easier by simple filtration. Some representative examples of this reaction are shown in Scheme 11.²⁴

Azo compounds. The most important methods to reduce azo compounds lead to hydrazo derivatives, including diimine, metal hydrides, and metal-mediated procedures.^{23,25} The reduction of different aromatic azo compounds with the $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$ (2.0 equiv.)– Li – DTBB (10 mol%) combination leads to the formation of the corresponding anilines, some representative examples being included in Scheme 12.²⁴ Also in this case, the use of a polymer-supported biphenyl as electron-carrier catalyst gives similar yields as employing DTBB .

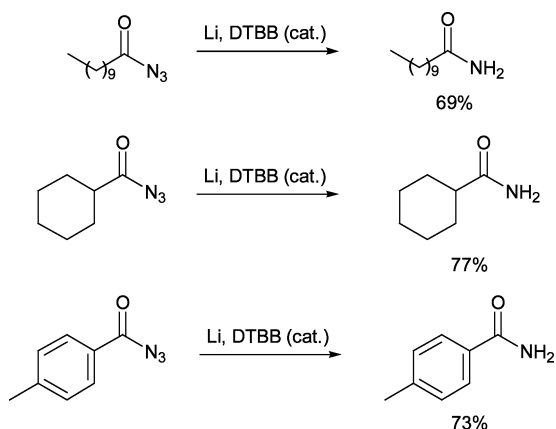
Azides. Acyl azides are interesting compounds as synthetic intermediates, especially involved in the preparation of amides, isocyanates and primary amides.²⁶ In this case, their reduction to the corresponding primary amides is accomplished using lithium and a catalytic amount of DTBB (10 mol%) in the absence of the nickel salt, as it is shown in the examples given in Scheme 13.²⁷



Scheme 11



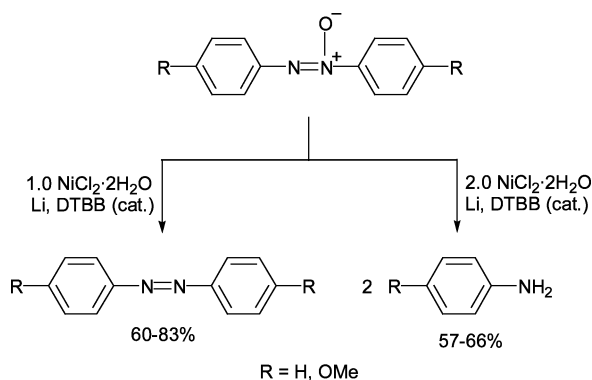
Scheme 12



Scheme 13

2.5 Reduction of nitrogen–oxygen bonds: azoxy compounds, amine *N*-oxides, nitrones and *N*-alkoxy amides

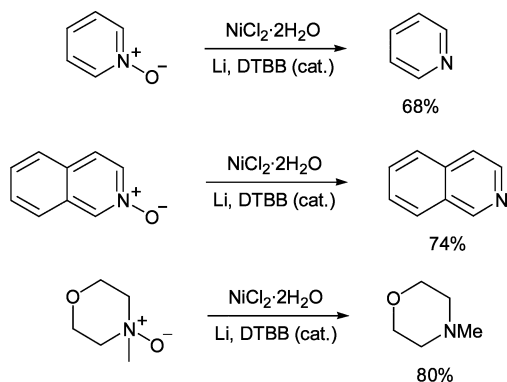
Azoxy compounds. The most studied reduction of azoxy compounds is their deoxygenation, which can be carried out by catalytic hydrogenation and metal-mediated procedures.¹ For this type of compound, the result of the reduction with the $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$ –Li–DTBB (10 mol%) system depends on the reaction conditions used. Thus, a short reaction time (1 h) and a stoichiometric amount of the nickel salt gives the corresponding azo compounds, whereas either longer reaction times (10 h) or using an excess of the nickel salt (2.5 equiv.) favours the formation of the corresponding aniline (see above). Alternatively, a polymer-supported biphenyl is equally efficient as electron carrier in these transformations. See Scheme 14 for some representative examples.²⁴



Scheme 14

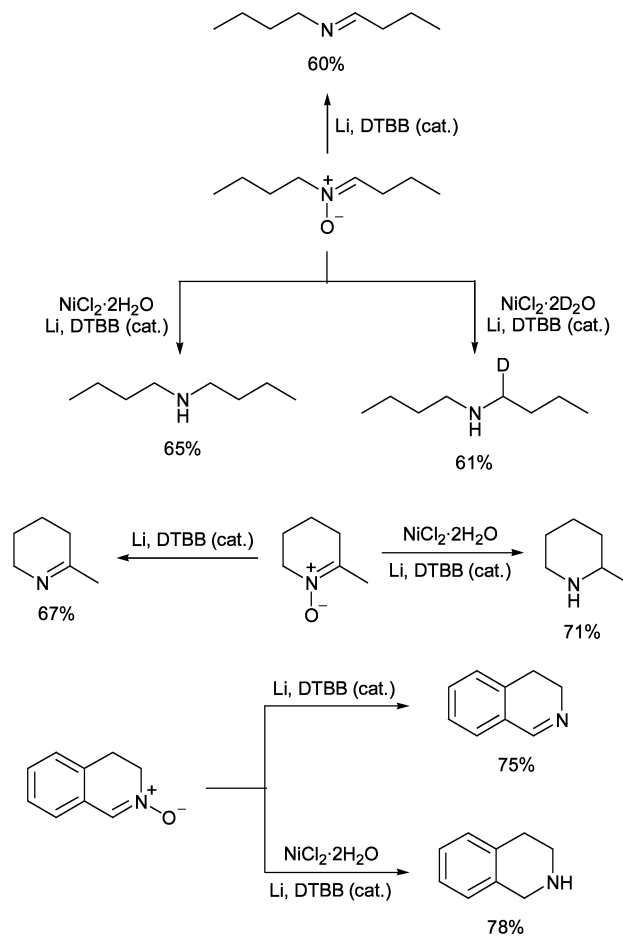
Amine *N*-oxides. The deoxygenation of amine *N*-oxides to the corresponding tertiary amines is an interesting reaction, especially in aromatic nitrogen-containing heterocycles and in relation to the different reactivity of both compounds (the heterocycles and their *N*-oxides) towards electrophilic substitution.²⁸ Methods to perform this deoxygenation include catalytic hydrogenation and metal-promoted reactions, metal hydrides leading, in general, to over-reduced products with the exception of diborane.^{1,2} The reaction of different aromatic and aliphatic amine *N*-oxides with the $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$ –Li–DTBB (10 mol%) system affords the corresponding amines, the polymer-supported biphenyl version showing also the same reactivity. Typical examples are depicted in Scheme 15.²⁴

Nitrones. Nitrones are interesting reagents in synthetic organic chemistry, especially in reactions involving organometallic compounds or 1,3-cycloadditions.²⁹ However, most of the deoxygenation reactions are of limited applicability due to the harsh reaction conditions required.¹ On the other hand, we observed that the



Scheme 15

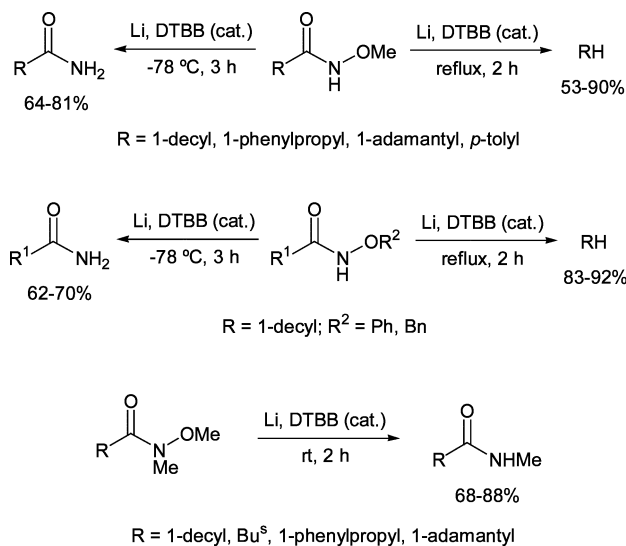
degree of reduction on nitrones can be nicely modulated by the absence or presence of the nickel salt in the reducing system. Thus, with Li–DTBB (10 mol%), the corresponding imines are obtained as a result of a deoxygenation process. Interestingly, full reduction of the starting nitrone is achieved when the reaction is performed with $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$ –Li–DTBB (cat.), furnishing the expected secondary amines (see some examples in Scheme 16).³⁰ Moreover, isotopically labelled secondary amines are obtained with $\text{NiCl}_2 \cdot 2\text{D}_2\text{O}$ –Li–DTBB (cat.).



Scheme 16

***N*-Alkoxyamides.** *N*-Alkoxyamides are useful intermediates in a variety of synthetic transformations. In particular, *N*-methoxy-*N*-methyl derivatives (Weinreb amides) are of especial interest in the direct acylation of organolithium and Grignard reagents,³¹ as well as in their reduction to aldehydes by the aluminium and boron hydrides.³² In this case, the reduction of different *N*-alkoxyamides with lithium and a catalytic amount (10 mol%) of DTBB, in the absence of nickel chloride dihydrate, gives the expected deal-

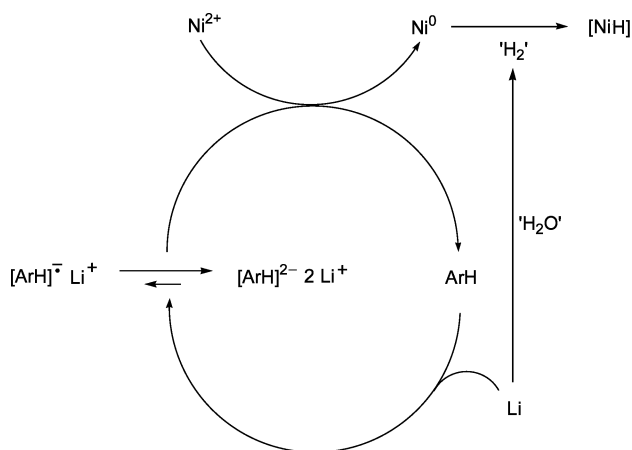
koxyated amides at low ($-78\text{ }^{\circ}\text{C}$) or room temperature. However, under THF reflux, secondary *N*-alkoxyamides give an unprecedented dealkoxy carbamoylation reaction, yielding the corresponding hydrocarbons. Scheme 17 shows some representative examples of these reactions.²⁷



Scheme 17

2.6 Mechanistic considerations

Concerning the use of nickel(II) chloride dihydrate with lithium and a catalytic amount of an arene, two different and independent processes have been postulated to take part in the reduction pathway: (a) the reduction of nickel(II) to nickel(0) by the action of the radical anion and/or the dianion derived from the activation of lithium by the arene, and (b) the generation of molecular hydrogen by reaction of the excess of lithium and the crystallisation water present in the nickel salt. The combination of this molecular hydrogen with the highly reactive nickel(0) would lead to a sort of nickel hydride species, which is the real reducing agent (Scheme 18). Nonetheless, a typical dissolving metal type mechanism can operate for certain substrates, as well as in those reactions carried out with Li-arene(cat.), in the absence of the nickel salt.



Scheme 18

2.7 Comparison with other nickel reductants

As regards alkenes, practically any form of nickel, such as those mentioned in the introduction, is able to cleanly reduce alkenes to alkanes.¹⁻¹³ However, the nickel-aluminium alloy only reduces conjugated carbon-carbon double bonds,⁷ whereas other reducing systems require the use of molecular hydrogen. A very interesting option is the BER (borohydride exchange resin)-Ni₂B-MeOH

system, which in addition allows the selective reduction of dienes to alkenes.³³ Very similar behaviour shows the NiCl₂·2H₂O-Li-arene(cat.) system, since the alkene reduction is performed in the absence of external molecular hydrogen, with easy control of the degree of hydrogenation over dienes. One more advantage of the latter methodology is the easy deuterium labelling of compounds by using the homologous NiCl₂·2D₂O-Li-arene(cat.) system.

The NiCl₂·2H₂O-Li-arene(cat.) combination also works well in the reduction of alkynes to alkanes (deuteration being possible), though apparently the semihydrogenation is limited to a few examples. This attractive transformation is better achieved with the NaH-NaOR-Ni(II)¹⁰ or BER-Ni₂B catalysts,³⁴ albeit molecular hydrogen is necessary.

The nickel-aluminium alloy,⁷ nickel borides,⁸ Raney nickel,^{2,13} and the NiCl₂·2H₂O-Li-arene(cat.) combination, exhibit notable effectiveness in the reduction of aromatic and heteroaromatic compounds. They complement each other, the reagent of choice depending on the degree of hydrogenation and regioselectivity pursued. In general, milder reaction conditions (room temperature) are required with the NiCl₂·2H₂O-Li-arene(cat.) system, with easy incorporation of deuterium into the products.

The hydrodehalogenation of organic halides has been successfully accomplished with homogeneous nickel complexes but mainly with heterogenous catalysts such as Raney nickel, metallic nickel prepared by reduction of a nickel salt with a metal, Ni, BER-Ni(II), and Ni₂B catalysts, or metallic nickel on different supports.²⁰ In general, the NiCl₂·2H₂O-Li-arene(cat.) system shows a comparable behaviour to the above mentioned nickel catalysts, the reduction of organic fluorides being a common limitation. However, the latter transformation can be achieved with powder alkali-metal hydrides of nanometric size in the presence of catalytic amounts of nickel(II) acetate.²⁰

The reduction of sulfonates has been little studied with nickel catalysts and it is practically limited to the catalytic hydrogenation with Raney nickel under heating, leading to the parent alcohols.² However, the reduction of sulfonates with the NiCl₂·2H₂O-Li-arene(cat.) system has shown to be very versatile and effective under mild reaction conditions (room temperature). Thus, not only alkyl sulfonates have been reduced to alkanes and deuterated alkanes, but the reactivity can be controlled to transform enol triflates into the corresponding alkanes, alkenes, or deuterated alkenes.

Concerning the reduction of carbonyl compounds, practically any type of nickel catalyst mentioned in the introduction is able to transform aldehydes and ketones to the corresponding alcohols.² However, in most cases higher temperatures and pressures than normal are required. On the other hand, imines have been reduced to amines by catalytic hydrogenation or transfer hydrogenation over nickel and Raney nickel catalysts.² The main contribution of the NiCl₂·2H₂O-Li-arene(cat.) reducing system to this field is probably the easy and cheap incorporation of deuterium into the products, compared to the use of molecular deuterium or even LiAlD₄. In addition, the reaction conditions are very mild, though the selective reduction of α,β -unsaturated compounds to the corresponding carbonyl compounds does not seem to be very general.

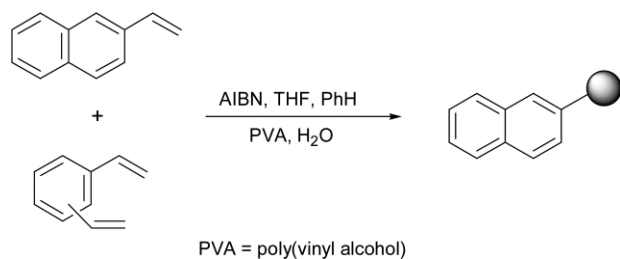
The reduction of nitrogen-nitrogen bonds in hydrazines and azo compounds to amines has been reported to take place by catalytic hydrogenation with Raney nickel and with the Ni-Al alloy, respectively.² The NiCl₂·2H₂O-Li-arene(cat.) combination can be used as an alternative reducing agent of these type of compounds under very mild reaction conditions. On the other hand, acyl azides have been reduced to amides with NaBH₄-NiCl₂·6H₂O, albeit applicable only to aryl azides.³⁴ In this case, we observed that the Li-arene(cat.), in the absence of the nickel salt, can reduce alkanoyl and aryl azides to the corresponding primary amides in a fast and mild fashion.

As regards the reduction of nitrogen-oxygen bonds, aromatic azoxy compounds have been reduced to anilines with NiCl₂-

NaBH₄-MeOH, whereas amine *N*-oxides can be deoxygenated with Raney nickel-EtOH or the Ni-Al alloy.¹ The degree of reduction of azoxy compounds to either azo compounds or anilines has been easily controlled with the NiCl₂·2H₂O-Li-arene(cat.) system, which represents a major advantage over the above mentioned reductants. Comparable results have been observed in the deoxygenation of amine *N*-oxides with NiCl₂·2H₂O-Li-arene(cat.) referred to other nickel-based reagents. On the other hand, the NiCl₂·2H₂O-Li-arene(cat.) system represents one of the very few reducing combinations able to directly reduce nitrones to secondary amines, deuterium-labelled compounds being obtained when the deuterated nickel salt is utilized. Finally, this reducing system, but in the absence of the nickel salt, is also unique in the dealkoxylation of *N*-alkoxyamides (especially secondary amides) under very mild reaction conditions. The reduction of secondary *N*-alkoxyamides to alkanes with Li-arene(cat.) is without any doubt an unprecedented result in this field.

3 The NiCl₂-Li-arene(cat.)/H₂ combination: a reasonable alternative to Raney nickel

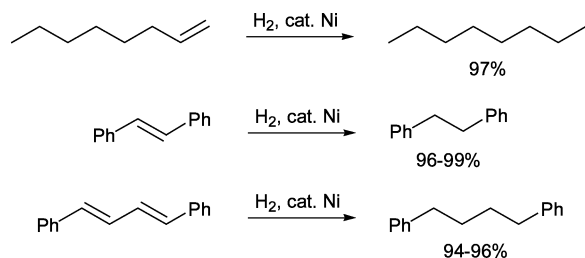
We present in this section an alternative methodology to the above described for the reduction of different functionalities, based on the use of NiCl₂·2H₂O-Li-naphthalene(cat.) (1 : 5 : 0.05 molar ratio) as catalytic system, and an external source of molecular hydrogen. The three solid components of the catalytic system are premixed and utilized in all the reduction reactions in aliquots that represent a 40 mol% Ni. It is worthy of note that a polymer-supported naphthalene, prepared by radical copolymerization of 2-vinylnaphthalene and divinylbenzene, can be alternatively used as electron carrier in this hydrogenation (Scheme 19).³⁵ The easy recovery and recycling of the latter are their major advantages respect to the soluble unsupported naphthalene.



Scheme 19

3.1 Reduction of carbon-carbon multiple bonds: alkenes, alkynes and aromatic compounds

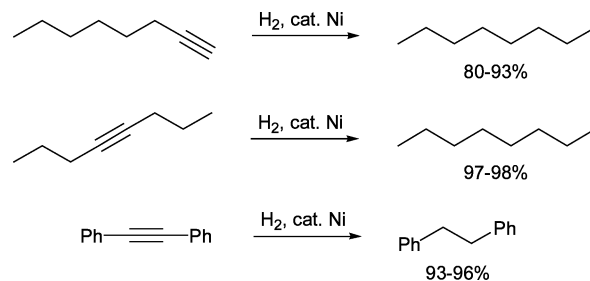
Alkenes. Different alkenes and dienes have been fully hydrogenated with molecular hydrogen at normal pressure and the NiCl₂-Li-C₁₀H₈(2 mol%) combination as the catalyst (40% based on Ni). Alternatively, the polymer-supported naphthalene above described can be used as the electron-carrier catalyst (10 mol%) giving similar results. Scheme 20 shows some selected examples of the mentioned processes.^{36,37}



Scheme 20

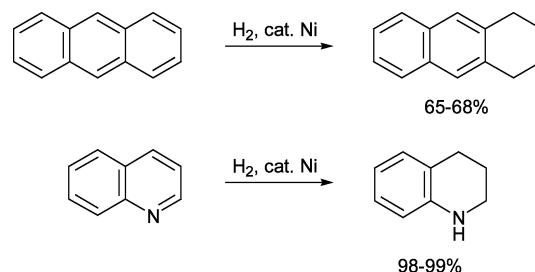
Alkynes. Terminal and internal alkynes are directly converted into the corresponding alkanes by using molecular hydrogen and

NiCl₂-Li-C₁₀H₈(2 mol%) or NiCl₂-Li-[polymer-supported C₁₀H₈ (10 mol%)] as catalysts. Good to excellent yields of the products are obtained almost independently of the catalytic system utilized. Representative examples of terminal, internal and conjugated alkynes are illustrated in Scheme 21.^{36,37}



Scheme 21

Aromatic and heterocyclic compounds. The above mentioned catalytic systems have been successfully applied to the hydrogenation of anthracene and quinoline (Scheme 22).^{36,37} It is



Scheme 22

noteworthy that in the former case 1,2,3,4-tetrahydroanthracene is mainly obtained, in contrast to the result obtained with the NiCl₂·2H₂O version of the reduction (see section 2.1), where 9,10-dihydroanthracene is the only reaction product isolated. Apparently, the reduction of anthracene by the NiCl₂·2H₂O-Li system is dominated by a dissolving-metal type mechanism.

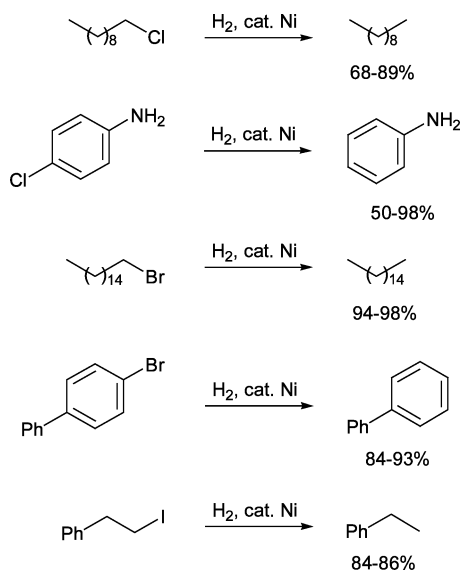
3.2 Reduction of carbon-halogen bonds: organic halides

The hydrodehalogenation of organic halides is easily accomplished with any of the nickel-based catalytic systems and molecular hydrogen under very mild reaction conditions (room temperature and 1 atm H₂). Thus, different aliphatic and aromatic chlorides, bromides and iodides are transformed into the corresponding hydrocarbons as a result of a halogen-hydrogen exchange. See for instance examples in the Scheme 23.^{36,37}

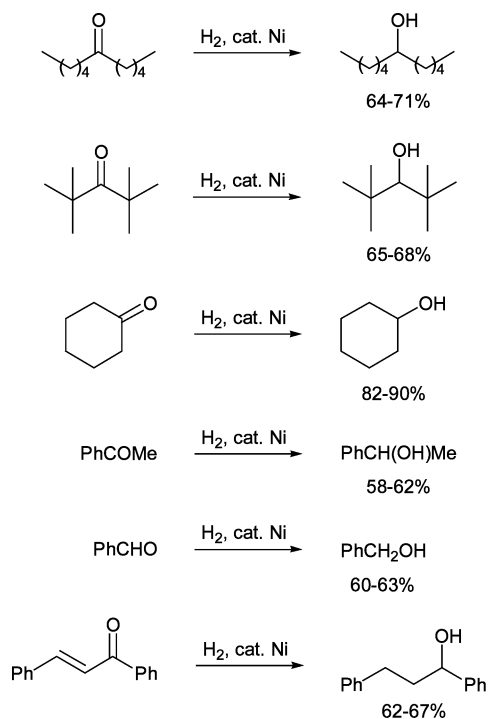
3.3 Reduction of carbon-oxygen and carbon-nitrogen bonds: carbonyl compounds and imines

Carbonyl compounds. A series of differently substituted aldehydes and ketones, as well as α,β-unsaturated ketones are fully reduced to the corresponding alcohols, using normal pressure of molecular hydrogen and the NiCl₂-Li-C₁₀H₈(2 mol%) (40 mol% Ni) (or the polymer version) combination. However, for crowded ketones better yields are obtained heating the reaction mixture at 50 °C. Scheme 24 shows typical examples of these reactions.^{36,37}

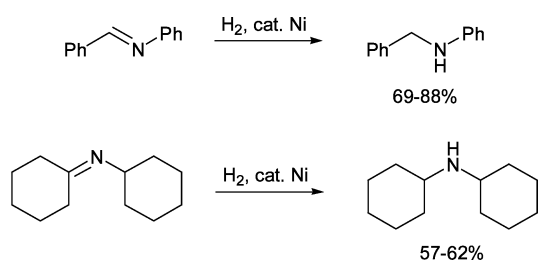
Imines. Scheme 25 includes two examples of an aldimine and a ketimine that are easily reduced to the corresponding secondary amines with molecular hydrogen at normal pressure, catalyzed by NiCl₂-Li-C₁₀H₈(2 mol%) (40 mol% Ni) (or the polymer supported version).^{36,37} In general, better yields are obtained for the reduction of aldimines.



Scheme 23



Scheme 24

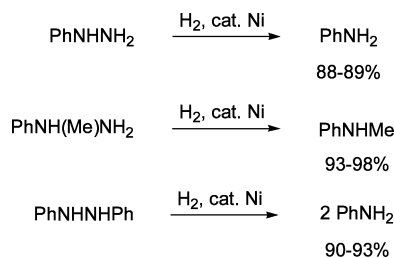


Scheme 25

3.4 Reduction of nitrogen–nitrogen and nitrogen–oxygen single and double bonds: hydrazines, azoxy compounds and amine *N*-oxides

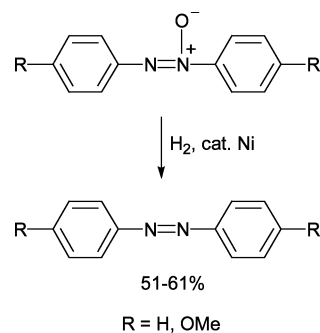
Hydrazines. Differently aryl-substituted hydrazines are transformed into the corresponding anilines by the cleavage of the nitrogen–nitrogen bond using both versions (naphthalene or

polymer-supported naphthalene) of the nickel-based catalytic system at normal pressure of hydrogen and room temperature. Several examples are depicted in Scheme 26.^{36,37}



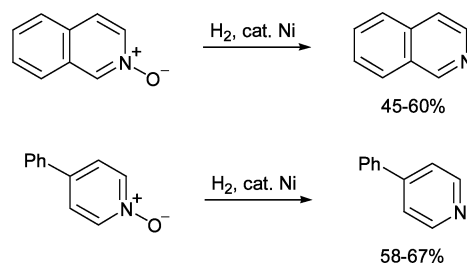
Scheme 26

Azoxy compounds. Scheme 27 includes two examples of the transformation of azoxy compounds into the corresponding azo compounds using molecular hydrogen at atmospheric pressure and the NiCl₂–Li–C₁₀H₈ (2 mol%) combination as the catalyst. The obtained azo compounds do not undergo further hydrogenation to the hydrazo compounds or anilines under the reaction conditions assayed. The use of the polymer-supported naphthalene as electron-transfer reagent does not improve substantially the obtained results.^{36,37}



Scheme 27

Amine *N*-oxides. Any of the two mentioned catalysts, in the presence of molecular hydrogen, are able to deoxygenate aromatic amine *N*-oxides to the expected free aromatic amines. See the examples in Scheme 28.^{36,37}



Scheme 28

3.5 Mechanistic considerations

As has been mentioned before (section 2.6), the activated lithium (either in the form of the corresponding arene radical anion or dianion species) is able to rapidly reduce nickel(II) to nickel(0). This highly reactive nickel(0) adsorbs hydrogen on the very active surface, behaving as a typical transition-metal catalyst for heterogeneous hydrogenation.⁴

The nickel(0) prepared in the mentioned manner is very finely divided, standing as a suspension even after several days, and has shown to be highly reactive as any attempt to support it failed, resulting in deactivation.

3.6 Comparison with other reductants

In general, the reactivity of the $\text{NiCl}_2\text{-Li-C}_{10}\text{H}_8$ or $\text{NiCl}_2\text{-Li-}$ (polymer-supported C_{10}H_8) catalysts is comparable to that of Raney nickel as regards the hydrogenation of alkenes, alkynes, ketones, and hydrazines, which is also accomplished under gentle reaction conditions.² However, the reduction of aromatic compounds, alkyl chlorides, azoxy compounds, and *N*-oxides by Raney nickel either does not take place or harsh reaction conditions are required.² Our catalysts also showed to be superior to the nickel boride obtained with the $\text{NiCl}_2\text{-NaBH}_4\text{-DMF}$ combination in the reduction of alkyl chlorides,⁸ and milder reaction conditions were required in the hydrogenation of ketones and that of aromatic and heteroaromatic compounds in comparison with other nickel catalysts ($\text{H}_2\text{-Ni-EtOH}$, $\text{NiCl}_2\text{-Zn-MeOH}$).² Better behaviour of our catalysts was observed in the reduction of carbon-carbon double and triple bonds in comparison with the nickel-aluminium alloy, the latter being used in large excess in a basic medium and only affecting these functions when they are benzylic or conjugated with a carbonyl group.⁷ Finally, and as an example of the reactivity of our catalyst, the hydrogenation of anthracene to furnish 1,2,3,4-tetrahydroanthracene is carried out in 2 h at room temperature with $\text{NiCl}_2\text{-Li-naphthalene(cat.)}$, whereas hydrogenation over the widely used palladium on charcoal requires the use of tetralin as solvent in a sealed tube at 340 °C.²

On the other hand, it is worth comparing the $\text{NiCl}_2\text{-Li-C}_{10}\text{H}_8$ and $\text{NiCl}_2\text{-Li-}$ (polymer-supported C_{10}H_8) systems used in catalytic hydrogenation with the $\text{NiCl}_2\cdot 2\text{H}_2\text{O-Li-arene(cat.)}$ reducing system. We can state that the latter is more selective in the sense that it makes the control of the degree of reduction easier in many transformations (*e.g.*, dienes to alkenes or alkanes, alkynes to alkenes or alkanes, α,β -unsaturated carbonyl compounds to saturated carbonyl compounds or saturated alcohols, azoxy compounds to azo compounds or amines, *etc.*). The application of the two nickel catalysts require the handling of molecular hydrogen and deuteration is only possible in the presence of the very expensive molecular deuterium. However, all components are solids in $\text{NiCl}_2\cdot 2\text{H}_2\text{O-Li-arene(cat.)}$ and hydrogen is generated *in situ*, thus minimizing the risk of handling a large amount of such a highly flammable and explosive gas as hydrogen. Moreover, deuteration reactions can be easily effected with $\text{NiCl}_2\cdot 2\text{D}_2\text{O-Li-arene(cat.)}$ at a low cost.

4 Concluding remarks

The $\text{NiCl}_2\cdot 2\text{H}_2\text{O-Li-arene(cat.)}$ combination is a useful system to reduce a variety of organic compounds including alkenes, alkynes, aromatic and heteroaromatic compounds, organic halides, sulfonates, carbonyl compounds, imines, hydrazines, azo and azoxy compounds, amine *N*-oxides and nitrones. The use of $\text{NiCl}_2\cdot 2\text{D}_2\text{O}$ as the nickel salt component allows the easy deuteration (addition or substitution) of the different substrates above mentioned. In the absence of the nickel salt, and using the Li-arene(cat.) system, nitrones, *N*-alkoxyamides and acyl azides are also reduced. It is possible to hydrogenate almost all the types of compounds mentioned above using the anhydrous nickel salt under a molecular hydrogen atmosphere at normal pressure, in a process that represents a reasonable alternative to the use of Raney nickel. In addition, a polymer-supported arene can be used as electron-transfer agent, instead of the free arene, this methodology being

interesting due to the ease of recovery and reuse of the arene component.

Acknowledgements

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