

Active-Metal Based Reduction of Organic Compounds

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Abstract: The reducing system $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$ -Li-arene(cat.) has been applied to the reduction of a wide range of different functionalities including alkenes, alkynes, carbonyl compounds, imines, halogenated compounds, sulfonates, aromatic compounds, hydrazines, azo compounds, azoxy compounds, *N*-oxides, and nitrones. The degree of the reduction can be controlled for some substrates, with easy incorporation of deuterium into the products when used the corresponding deuterated nickel salt. With the Li-arene(cat.) system (in the absence of the nickel salt) nitrones, *N*-alkoxyamides, and acyl azides were also reduced.

Key words: organic compounds, reduction, active metals, arene catalysis

1. Introduction

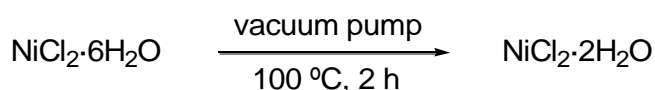
During the last decade, new lithiation methodologies have been developed in our department for the preparation of highly reactive organolithium intermediates based on the use of active metal lithium. By using arenes as electron carriers, we observed that catalytic amounts of an arene, namely naphthalene, biphenyl, or 4,4'-di-*tert*-butylbiphenyl (DTBB), can activate lithium by formation of the corresponding radical anion or dianion species, which in addition can transfer electrons to an appropriate substrate to obtain the corresponding organolithium compound.¹

This arene-catalyzed lithiation has been applied to the preparation of organolithium compounds from non-halogenated precursors,² generation of polyolithium intermediates,³ and preparation of functionalized organolithium intermediates.⁴ Alternatively, these reactions can be performed with polymer-supported arenes as electron carriers,⁵ and the Li-arene system has also found application in the activation of other metals used in reduction processes, which is the subject of this account.

A continuous interest has been shown toward the reduction of organic compounds as a fundamental and common group transformation in synthetic organic chemistry. Among the different methodologies to perform these reductions, three important general procedures can be highlighted involving the use of (a) metal hydrides, (b) dissolving metals, and (c) catalytic hydrogenation.⁶

Although catalytic hydrogenation is a reaction of proven efficiency,⁷ 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 needed 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.

About 7 years ago, we discovered a new reducing system, based on the activation of a transition metal by the Li-Arene pair and using as a source of hydrogen, probably the simplest one, that is to say, water. This system is composed of nickel dichloride dihydrate, obtained by partial dehydration of the corresponding hexahydrate (Scheme 1), an excess of lithium powder, and a catalytic amount of an arene (5-17 mol%), normally naphthalene or 4,4'-di-*tert*-butylbiphenyl (DTBB). The general reaction conditions used are THF as solvent and rt. For any of the functional groups studied, we performed four experiments, one with the above mentioned system, and three blank experiments: (a) with NiCl₂·2H₂O-Li (in the absence of the arene), (b) with NiCl₂-Li-arene(cat.), and (c) with Li-arene(cat.) (without the nickel salt), just to assure the necessity of all the components for the reaction to take place.



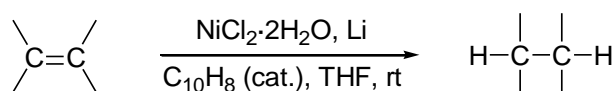
Scheme 1

2. Results and Discussion

2.1. Reduction of Alkenes

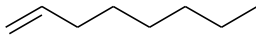
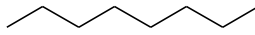
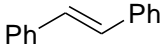
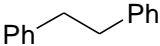
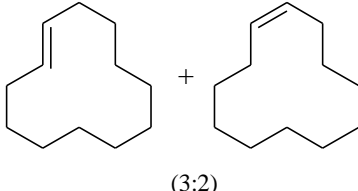
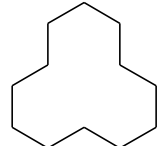
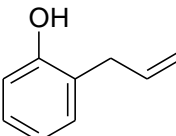
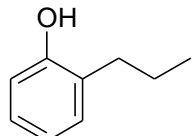
Catalytic hydrogenation, either under heterogeneous or homogeneous conditions, is the most common method utilized for the reduction of alkenes.⁸ Other methodologies, involving diimide, dissolving metals, low-valent species, or metal hydride-transition metal combinations, are of more limited application.⁹

We observed that the reaction of NiCl₂·2H₂O (1.5 mmol), an excess of lithium powder (1:12 molar ratio, referred to the olefin), and a catalytic amount of naphthalene (0.25 mmol, 17 mol%) with monoolefins such as 1-octene, *trans*-stilbene, cyclododecene, or the functionalized *ortho*-allylphenol, furnished the corresponding alkanes in excellent yields (Scheme 2 and Table 1).¹⁰



Scheme 2

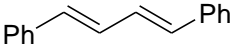
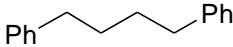
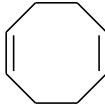
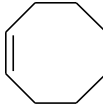
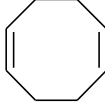
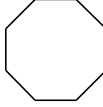
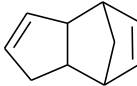
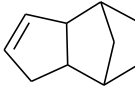
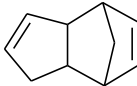
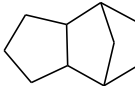
Table 1. Reduction of alkenes

Entry	Substrate	NiCl ₂ ·2H ₂ O equiv	Product	Yield (%) ^a
1		1.5		99 ^b
2		1.5		94
3		1.5		93
4		1.5		97

^a Isolated yield after column chromatography unless otherwise stated. ^b GLC yield.

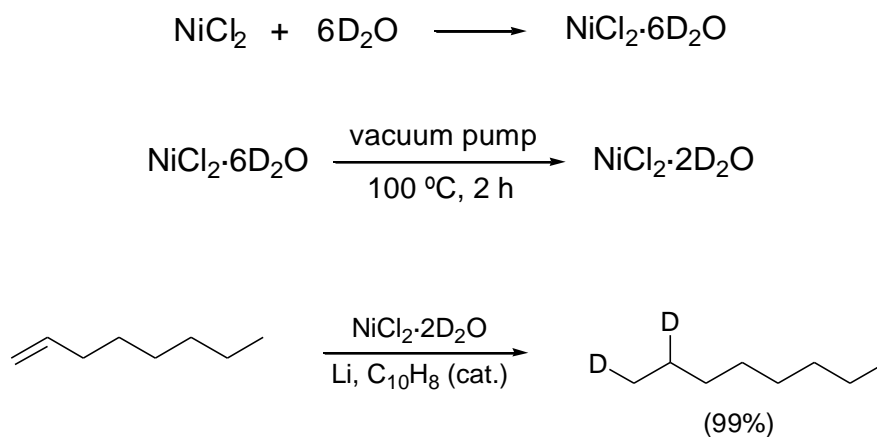
For dienes it was possible to control the degree of reduction by adjusting the stoichiometry of the nickel salt. Thus, 1,5-cyclooctadiene was transformed into cyclooctene with 1.5 equiv. of the nickel hydrated salt (Entry 2, Table 2), whereas dicyclopentadiene underwent regioselective reduction of the six-membered ring carbon–carbon double bond with 1.0 equiv. of the reducing agent (Entry 4, Table 2). In all cases, an excess of NiCl₂·2H₂O allowed the complete reduction of dienes to the corresponding alkanes (Entries 1, 3, and 5, Table 2).

Table 2. Reduction of dienes

Entry	Substrate	NiCl ₂ ·2H ₂ O equiv	Product	Yield (%) ^a
1		2.5		72
2		1.5		90 ^b
3		2.5		96 ^b
4		1.0		87
5		2.5		90

^a Isolated yield after column chromatography unless otherwise stated. ^b GLC yield.

A very interesting extension of this methodology is the use of a nickel(II) chloride containing two molecules of deuterium oxide, prepared from anhydrous nickel chloride and excess of deuterium oxide, and followed by the same thermal treatment applied to prepare the analogous hydrated nickel salt. Thus, alkenes could be transformed into dideuterioalkanes, avoiding the use of molecular deuterium (Scheme 3).

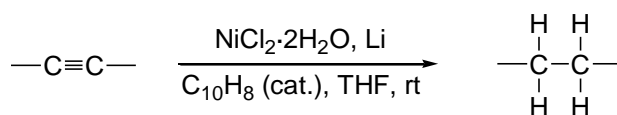
**Scheme 3**

2.2. Reduction of Alkynes

The same general reduction methods used for alkenes are applicable to the reduction of alkynes.^{8,9}

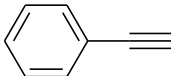
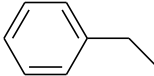
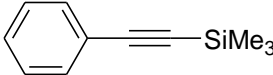
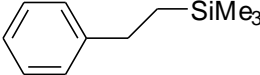
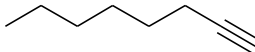
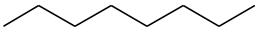

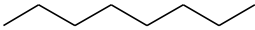
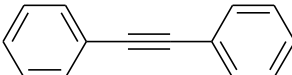
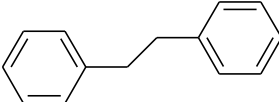
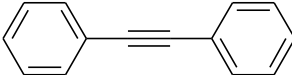
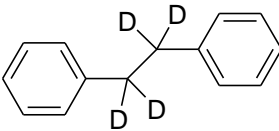
In general, partial reduction of alkynes is more desirable, which depending on the methodology can be converted to *cis*- or *trans*-alkenes. Catalytic hydrogenation gives predominantly *cis*-alkenes, whereas metals and metal salts give mainly *trans*-alkenes.¹¹

When a series of terminal and internal alkynes were reacted with nickel(II) chloride dihydrate (2.0-2.5 mmol), an excess of lithium powder (1:8 molar ratio, referred to the nickel salt), and a catalytic amount of naphthalene (8 mol%), the corresponding alkanes were obtained in good to excellent yields (Scheme 4, Table 3).¹² By using the deuterated nickel salt, diphenylacetylene was transformed into 1,1,2,2-tetradeuterio-1,2-diphenylethane (Entry 6, Table 3).



Scheme 4

Table 3. Reduction of Alkynes

Entry	Substrate	NiCl ₂ ·2H ₂ O equiv.	Product	Yield (%) ^a
1		2.0		70 ^b
2		2.0		77
3		1.0		66 ^b
4		2.5		91 ^b
5		2.0		85
6		2.5 ^c		74

^a Isolated yield after column chromatography unless otherwise stated. ^b GLC yield. ^c NiCl₂·2D₂O was used.

The reaction was also applied to some functionalized alkynes (Entries 1 and 2, Table 4) and in some cases the reduction could be controlled to give the corresponding *trans*-alkene (Entries 4 and 5, Table 4). However, when 4-octyne was subjected to the above mentioned system with 1.0 equiv. of the nickel salt, the corresponding *cis*-4-octene was obtained after 1 h, though isomerization to the *trans*-product was observed for longer reaction times (Entry 3, Table 4).

Table 4. Reduction of Functionalized Alkynes and Semireduction

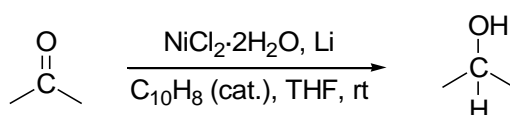
Entry	Substrate	NiCl ₂ ·2H ₂ O equiv.	Product	Yield (%) ^a
1		2.5		90 ^b
2		2.5		70
3		1.0		75 ^b
4		0.5		50
5		1.0		72

^a Isolated yield after column chromatography unless otherwise stated. ^b GLC yield.

2.3. Reduction of Carbonyl Compounds and Imines

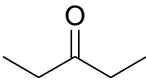
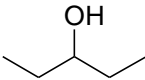
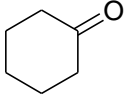
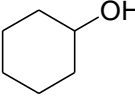
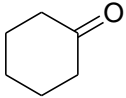
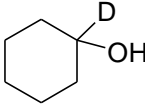
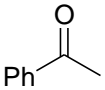
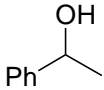
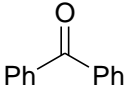
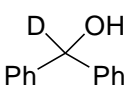
Metal hydrides, dissolving metals, and catalytic hydrogenation are primarily used for the reduction of carbonyl compounds and imines, other methods such as electrochemical or enzymatic methods being of less general application.¹³

By using our reducing system, different ketones such as 3-pentanone, cyclohexanone, and acetophenone, were easily reduced to the corresponding secondary alcohols (Scheme 5, Table 5).¹⁴ In the presence of the deuterated nickel salt, incorporation of deuterium at the 1-position of the alcohol was observed, thus avoiding the use of the expensive metal deuterides (Entries 3 and 5, Table 5).



Scheme 5

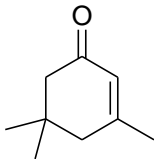
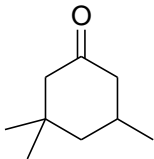
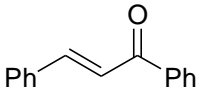
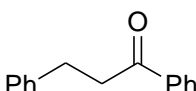
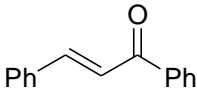
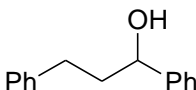
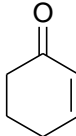
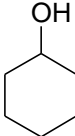
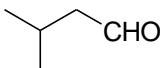
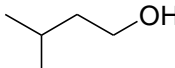
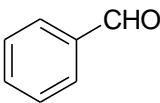
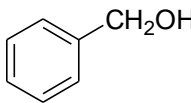
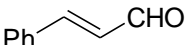
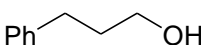
Table 5. Reduction of Ketones

Entry	Substrate	NiCl ₂ ·2H ₂ O equiv/t(h)	Product	Yield (%) ^a
1		1.0 ^b /12		85 ^c
2		1.0 ^b /12		87 ^c
3		1.0 ^d /1.5		>95 ^c
4		1.0/1		75 ^c
5		1.0 ^d /3		88

^a Isolated yield after column chromatography unless otherwise stated. ^b -78 °C. ^c GLC yield. ^d NiCl₂·2D₂O was used.

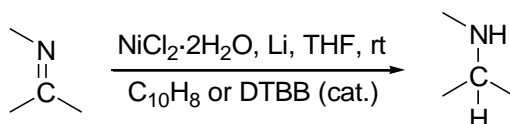
For α,β -unsaturated ketones (Entries 1 and 2, Table 6) the reduction could be controlled selectively at the carbon–carbon double bond giving the corresponding ketone with 1.0 equiv. of NiCl₂·2H₂O, whereas with 2.0 equiv. complete reduction to the saturated alcohol was observed (Entries 3 and 4, Table 6). The reduction of aldehydes did not show to be so effective as for ketones, due in part to the competitive formation of the corresponding pinacol products under the reaction conditions employed (Entries 5-7, Table 6).

Table 6. Reduction of Carbonyl Compounds

Entry	Substrate	NiCl ₂ ·2H ₂ O equiv/t(h)	Product	Yield (%) ^a
1		1.0/4		70 ^b
2		1.0/0.17		60
3		2.0/3		73
4		2.0/0.33		>95 ^b
5		1.0/12		58 ^b
6		1.0/12		64
7		2.0/1		54

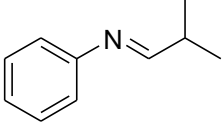
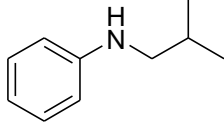
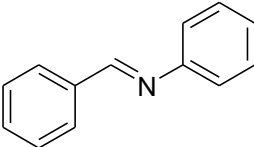
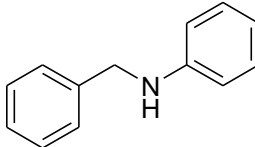
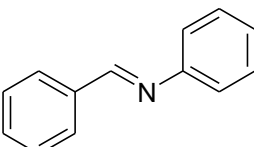
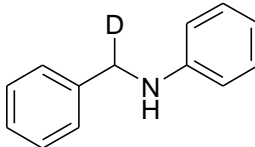
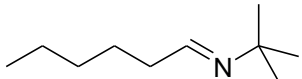
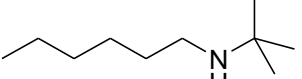
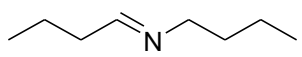
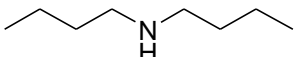
^a Isolated yield after column chromatography unless otherwise stated. ^b GLC yield.

As regards the reduction of imines (Scheme 6), aldimines derived from aniline, such as isobutylideneaniline and benzylideneaniline were reduced to *N*-isobutylaniline and *N*-benzyaniline, respectively, under naphthalene catalysis (Entries 1 and 2, Table 7).¹⁴ However, the preparation of secondary dialkylamines such as *N*-*tert*-butylhexan-1-amine or dibutylamine was better accomplished with DTBB as electron carrier (Entries 4 and 5, Table 7). The same protocol was applied to ketimines (Table 8), lower yield being obtained of the benzyl amines due probably to partial debenzylation under the reaction conditions. 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 (Entry 3 in Tables 7 and 8).



Scheme 6

Table 7. Reduction of Aldimines

Entry	Substrate	NiCl ₂ ·2H ₂ O equiv/t(h)	Product	Yield (%) ^a
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

^a Isolated yield after column chromatography unless otherwise stated. ^b Naphthalene as electron carrier. ^c DTBB as electron carrier ^d NiCl₂·2D₂O was used. ^e GLC yield.

Table 8. Reduction of Ketimines

Entry	Substrate	NiCl ₂ ·2H ₂ O equiv/t(h)	Product	Yield (%) ^a
1		1.5 ^b /6		78
2		1.5 ^b /3		62
3		1.5 ^{b,c} /6		57

^a Isolated yield after column chromatography unless otherwise stated. ^b DTBB as electron carrier. ^d NiCl₂·2D₂O was used.

2.4. Hydrodehalogenation of Organic Halides

Chlorinated organic compounds and especially polychlorinated aromatic compounds, represent a major environmental concern because they are extremely persistent, due to their slow degradation by reductive or oxidative enzymatic pathways, so efficient ways to dehalogenate these recalcitrant compounds are welcome. Numerous reagents and methods based on the use of metals, have been developed for their chemical transformation in less noxious compounds.¹⁵

By applying our methodology (Scheme 7) [nickel(II) chloride dihydrate (1:1 molar ratio), an excess of lithium powder (1:8 molar ratio, referred to the nickel salt) and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (0.1 mol/mol of nickel salt, 10 mol%) in tetrahydrofuran at room temperature], different alkyl chlorides, bromides, and even an alkyl iodide were reduced to the corresponding alkanes (Table 9).¹⁶ When NiCl₂·2D₂O was used instead of the corresponding dihydrate salt, the expected deuterium-labeled compounds were obtained (Entries 2, 5, and 7, Table 9). It is worthy to note that fluorinated materials (for instance 1-fluorononane) are inert to this procedure.

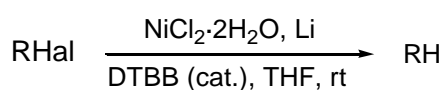
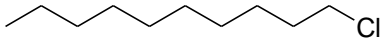
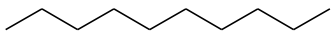
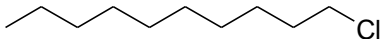
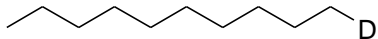
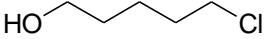
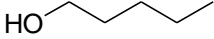
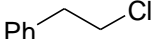
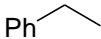
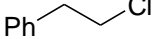
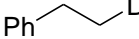
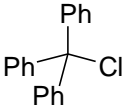
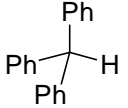
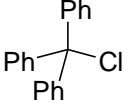
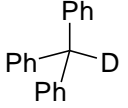
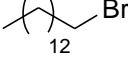
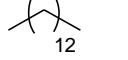
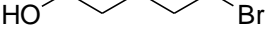
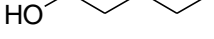
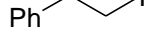
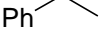
**Scheme 7**

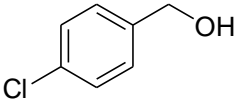
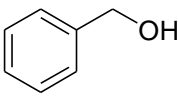
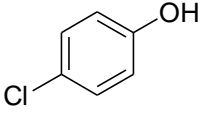
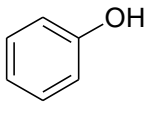
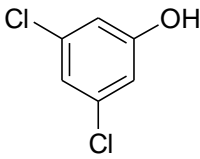
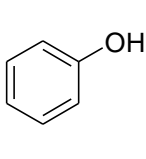
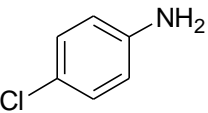
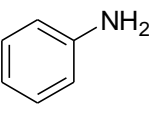
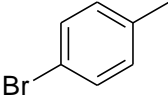
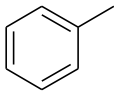
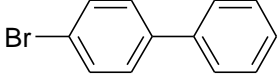
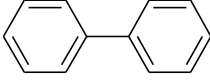
Table 9. Reduction of Halogenated Aliphatic Compounds

Entry	Substrate	Product	Yield (%) ^a
1			80 (55)
2			98 (53) ^b
3			98 (51)
4			99 (50)
5			99 (56) ^b
6			94 (66)
7			93 (60) ^b
8			99 (75)
9			98 (57)
10			89 (54)

^a GLC yield, isolated yield in parenthesis. ^b NiCl₂·2D₂O was used.

More interesting from the environmental point of view was the reduction of polychlorinated aromatics, such as *p*-chlorobenzyl alcohol, *p*-chlorophenol, and *p*-chloroaniline (Entries 1, 2, and 4, Table 10). Even the polychlorinated 3,5-dichlorophenol was completely dechlorinated in excellent both GLC and isolated yields (Entry 3, Table 10). Good results were also obtained for the *p*-brominated toluene and biphenyl (Entries 5 and 6, Table 10), the latter being a close relative of the noxious polybrominated biphenyls (PBBs).

Table 10. Reduction of Halogenated Aromatic Compounds

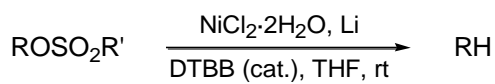
Entry	Substrate	Product	Yield (%) ^a
1			84 (53)
2			98 (73)
3			99 (90)
4			92 (65)
5			99
6			89 (65)

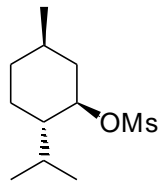
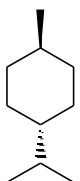
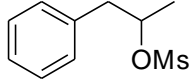
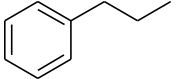
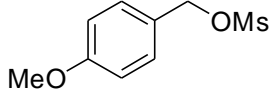
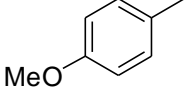
^a GLC yield, isolated yield in parenthesis.

2.5. Reduction of Sulfonates

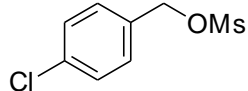
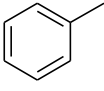
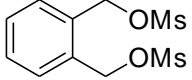
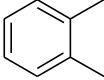
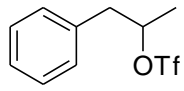
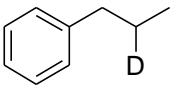
One of the most practical methods to deoxygenate alcohols involves the transformation into their tosylates, followed by reaction with sodium iodide and final palladium-catalysed hydrogenation or other reduction methodologies.¹⁷ On the other hand, vinyl and aryl triflates can be reduced to the corresponding olefins or alkanes, and arenes, respectively,¹⁸ using catalytic hydrogenation,¹⁹ catalytic reaction with silanes²⁰ or stannanes,²¹ with formic acid under palladium-catalysed conditions,²² or zinc and methanol in the presence of a Ni(0) catalyst.²³

Our reduction system showed to be very effective and versatile in the reduction of sulfonates under mild reaction conditions (Scheme 8).²⁴ Thus, primary alkyl, secondary, and benzylic mesylates were reduced to the corresponding alkanes in good yields (Table 11). For alkyl and aryl chlorinated mesylates both functionalities were completely reduced (Entries 1 and 2, Table 12), the same behaviour being observed for dimesylates (Entries 3 and 4, Table 12). Alternatively, an alkyl triflate could be used as starting material, which in the presence of the deuterated nickel salt gave the expected deuterium-labeled product (Entry 5, Table 12).

**Scheme 8****Table 11.** Reduction of Sulfonates

Entry	Starting material	Product	Yield (%) ^a
1	<chem>CH3(CH2)10CH2OMs</chem>	<chem>CH3(CH2)10CH3</chem>	85 (92)
2			72 (92)
3			72 (98)
4			73 (95)

^a Isolated yield, GLC yield in parenthesis**Table 12.** Reduction of Functionalized Sulfonates and Triflates

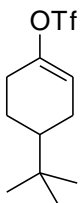
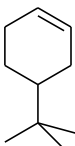
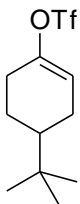
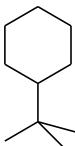
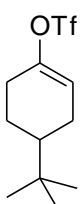
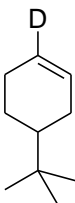
Entry	Starting material	Product	Yield (%) ^a
1	<chem>ClCH2(CH2)4CH2OMs</chem>	<chem>CH3(CH2)4CH3</chem>	(100)
2			43
3	<chem>MsOCH2(CH2)7CH2OMs</chem>	<chem>CH3(CH2)7CH3</chem>	70 (85)
4			57 (66)
5 ^b			70

^a Isolated yield, GLC yield in parenthesis. ^b $\text{NiCl}_2 \cdot 2\text{D}_2\text{O}$ was used.

The versatility of our methodology was clearly demonstrated in the reduction of enol triflates. Thus, the same starting enol triflate could be transformed into the corresponding alkene with

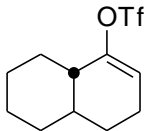
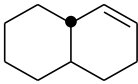
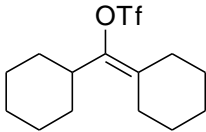
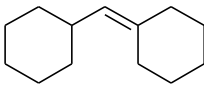
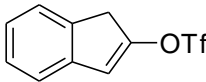
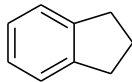
equimolecular amounts of the triflate and the nickel salt, alkane, with an excess of the nickel salt (3 equivalents), and deuterated vinylic compound with the deuterated nickel salt (Table 13). Some more examples in which the reaction could be stopped at the olefin or alkane stage are shown in Table 14.

Table 13. Reduction of 4-*tert*-Butylcyclohexanone Enol Triflate

Entry	Starting material	Product	Yield (%) ^a
1			58
2 ^b			63
3 ^c			53

^a Isolated yield after distillation. ^b 3 equiv. of $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$ were used. ^c $\text{NiCl}_2 \cdot 2\text{D}_2\text{O}$ was used.

Table 14. Reduction of Other Enol Triflates

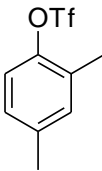
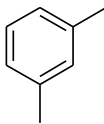
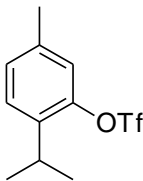
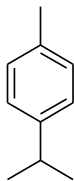
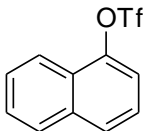
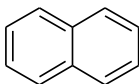
Entry	Starting material	Product	Yield (%) ^a
1	$\text{CH}_3(\text{CH}_2)_4\text{C}(\text{OTf})=\text{CH}(\text{CH}_2)_3\text{CH}_3^b$	$\text{CH}_3(\text{CH}_2)_4\text{CH}=\text{CH}(\text{CH}_2)_3\text{CH}_3^b$	68 ^b
2 ^c			45 ^d
3			72
4			47

^a Isolated yield, GLC yield in parenthesis. ^b As a *ca.* 1:1 *cis-trans* mixture. ^c 0.85 equiv. of $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$ were used.

^d 35% of unreacted starting material was recovered.

The reduction of aryl sulfonates was not so effective. In fact, aryl mesylates failed to be reduced, whereas aryl triflates led to the expected reduced products in low yields, as a result of competitive oxygen-sulfur bond cleavage leading to the corresponding phenols (Table 15). Even considering this drawback, the method can be useful due to the easy separation of both reaction products.

Table 15. Reduction of Aryl Triflates

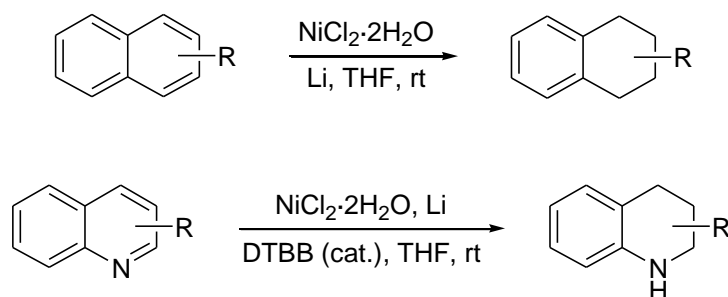
Entry	Starting material	Product	Yield (%) ^a
1			58 ^b (71)
2			44 ^c
3			21 ^d

^a Isolated yield, GLC yield in parenthesis. ^b 15% of 2,4-dimethylphenol was also isolated. ^c 52% of 2-isopropyl-5-methylphenol was also isolated. ^d α -Naphthol was the main product (80%).

2.6. Reduction of Aromatic Compounds

Since any reduction of an aromatic system destroys the resonance stabilisation, and consequently must overcome the resonance energy, the reduction of such compounds is generally more difficult than that of alkenes, dienes or alkynes. For example, catalytic hydrogenation of benzene is more difficult than that of unsaturated aliphatic hydrocarbons, carbonyl compounds, nitriles and halogen or nitro compounds, and therefore it is possible to reduce these functions preferentially.²⁵ Probably, the most convenient method to partially reduce aromatic compounds is the so-called Birch reaction,²⁶ which consists in using dissolving alkali metals in a protic solvent, such as ammonia, primary amines or alcohols.²⁷ Concerning heterocyclic aromatic compounds, the selective reduction of the heterocyclic ring in benzo fused systems, such as quinolines or isoquinolines, is an important transformation since the resulting compounds are useful synthetic intermediates in the field of alkaloids.²⁸ In this case a number of methods have been developed, including catalytic hydrogenation, dissolving metals or the use of boron hydrides.^{28,29}

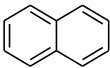
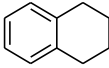
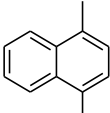
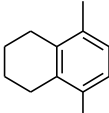
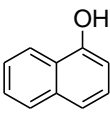
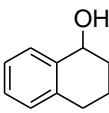
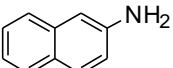
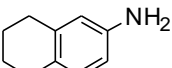
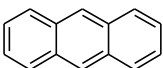
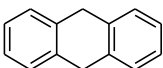
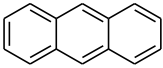
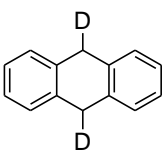
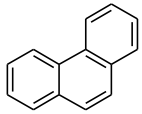
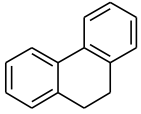
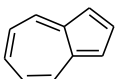
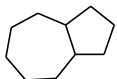
With our reducing system, aromatic compounds could be also reduced, the substrate itself acting as electron carrier, whereas for heteroaromatic compounds the addition of a catalytic amount of DTBB was necessary for the reaction to take place (Scheme 9).



Scheme 9

For instance, the reaction of naphthalene with 3 equivalents of the nickel salt and an excess of lithium powder led to the formation of 1,2,3,4-tetrahydronaphthalene (Entry 1, Table 16).²⁴ The presence of different substituents on the naphthalene ring did not show any reduction pattern, since the hydroxy group (activates the ring) led to the reduction of its own ring, whereas the methyl or amino groups led to the reduction of the other ring (see Entries 2-4, Table 16). In the case of starting from anthracene, the reduction took place at the central ring, the dideuterated compound being obtained when treated with the deuterated nickel salt (Entries 5 and 6, Table 16). However, a large excess of the nickel salt was needed to reduce the central ring of phenanthrene (Entry 7, Table 16), such a large excess allowing the total hydrogenation of azulene (a 3:1 diastereomeric ratio was obtained) (Entry 8, Table 16).

Table 16. Reduction of Aromatic Compounds

Entry	Starting material	NiCl ₂ ·2H ₂ O ^a equiv.	Product	Yield (%) ^b
1		3.0		80
2		2.5		58
3		2.0		45
4		2.0		82
5		1.5		94
6 ^c		1.5		98
7		10.0		45 ^c
8		9.0		72 ^d

^a The substrate itself was used as electron carrier, unless otherwise stated. ^b Isolated yield. ^c NiCl₂·2D₂O was used.

For nitrogen-containing heteroaromatics it was necessary to use a catalytic amount of DTBB as electron carrier for the reaction to occur, in all the cases the reduction taking place on the nitrogenated ring.²⁴ Thus, quinoline, acridine or 1,10-phenanthroline, were transformed into the corresponding dihydro or tetrahydro derivatives. By using the deuterated nickel salt, acridine was deuterated at the 9-position (Table 17).

Table 17. Reduction of Heteroaromatic Compounds

Entry	Starting material	NiCl ₂ ·2H ₂ O ^a equiv.	Product	Yield (%) ^b
1		3.3		75
2		1.5		70
3 ^c		1.5		73
4		1.5		57

^a DTBB was used as electron carrier. ^b Isolated yield. ^c NiCl₂·2D₂O was used.

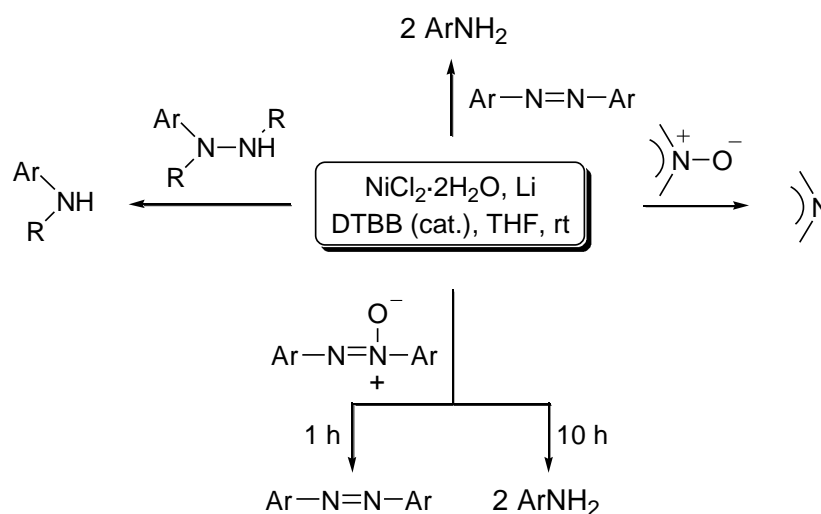
2.7. Reduction of Hydrazines, Azo Compounds, Azoxy Compounds, and *N*-Oxides

Next we studied the reduction of different nitrogenated functionalities, such as hydrazines, azo and azoxy compounds, and amine *N*-oxides. There are few general methods to reduce the nitrogen-nitrogen bond in hydrazines, and the conditions required to cleave this bond depend markedly on the substituents attached to it.³⁰ However, substituted hydrazines can be reduced to the corresponding amines by catalytic hydrogenation³¹ or using metals in a protic solvent.^{32,33} In the first case, usually it is necessary to work under pressure and acidic medium, and in the second case, liquid ammonia is the most common solvent.

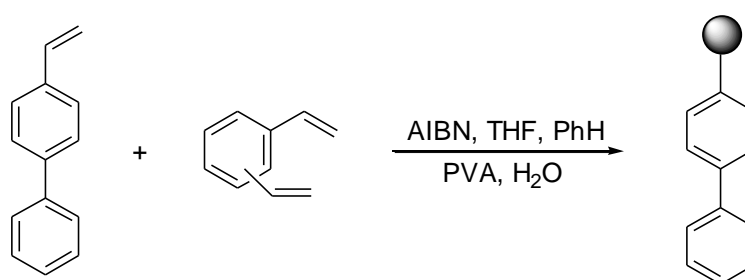
The most important methods to reduce azo compounds lead to the corresponding hydrazo derivatives.³⁴ They include diimide, complex metal hydrides or cobalt boride in the presence of hydrazine,³⁵ as well as metal mediated procedures.^{36,37} Concerning azoxy compounds, the corresponding deoxygenation is the most studied reaction:³⁸ well-established methods include catalytic hydrogenation³⁹ and metal-mediated procedures.⁴⁰ In addition, azoxy compounds are cleaved to amines by potassium borohydride and copper(I) chloride.⁴¹

General methods⁴² for the deoxygenation of *N*-oxides include mainly catalytic hydrogenation⁴³ and metal promoted reductions.⁴⁴ The use of metal hydrides works only with borane⁴⁵ due to overreduction reactions.⁴⁶

Thus, with the NiCl₂·2H₂O-Li-DTBB(cat.) system aryl bearing hydrazines were reduced to anilines, azo compounds also to anilines, azoxy compounds to azo compounds or anilines depending on the reaction conditions, and *N*-oxides to amines (Scheme 10).⁴⁷ Alternatively, some experiments were performed with a polymer-supported biphenyl as electron carrier, prepared by radical copolymerization of 4-vinylbiphenyl and divinylbenzene as crosslinking agent (Scheme 11).^{5,48}



Scheme 10



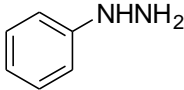
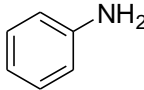
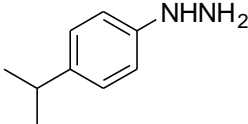
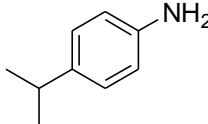
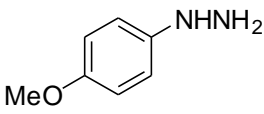
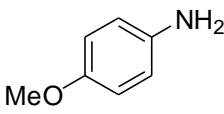
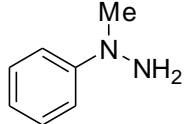
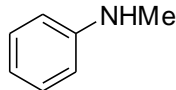
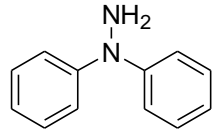
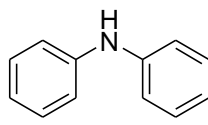
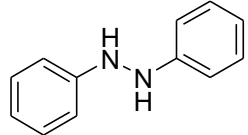
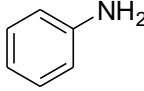
Scheme 11

The reduction of monosubstituted, *N,N*- or *N,N'*-disubstituted hydrazines led to the formation of the corresponding primary or secondary amines (Table 18). In order to get good results, the starting hydrazine has to bear at least one aryl group in one of the nitrogen atoms. Alternatively, the polymer-supported biphenyl was used as catalytic electron transfer improving slightly the yield in the reduction of *N*-methyl-*N*-phenylhydrazine (Entry 4, Table 18).

The application of the same procedure to azo compounds led to the corresponding anilines, the use of a polymer-supported biphenyl showing similar behaviour to DTBB (Table 19). In the case of azoxy compounds, the corresponding azo compounds were isolated for short reactions times (ca. 1 h), whereas either longer reaction time (10 h) or 2.5 equiv. of dihydrated nickel(II) chloride led to full reduction to the corresponding anilines (Table 20). Also here, the use of a polymer-supported arene showed to be as effective as DTBB (Entry 3, Table 20).

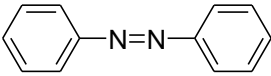
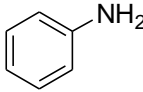
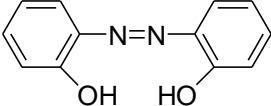
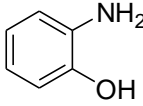
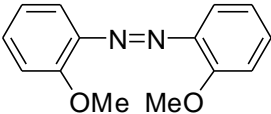
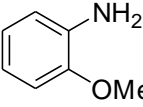
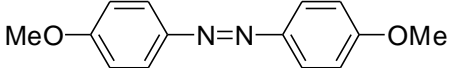
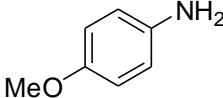
We also managed to deoxygenate a series of aromatic and one aliphatic *N*-oxide in moderate to good yields (Table 21). As in the previous mentioned functional groups, the reduction could be also carried out using the same polymer-supported arene, the process working with similar yield.

Table 18. Reduction of Hydrazines

Entry	Starting material	Product	Yield (%) ^a
1			68
2			72
3			73
4			78 (87) ^b
5			88
6			65

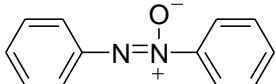
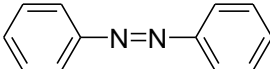
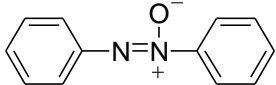
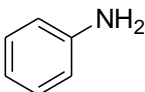
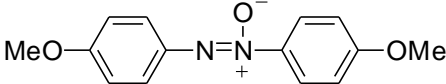
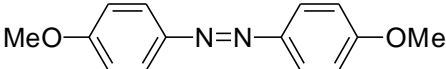
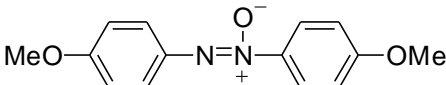
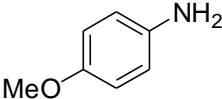
^a Isolated yield after acid-base extraction. ^b A vinylbiphenyl-divinylbenzene copolymer was used as electron carrier.

Table 19. Reduction of Azo Compounds

Entry	Starting material	Product ^a	Yield (%) ^b
1			70 (71) ^c
2			88
3			74
4			78

^a Overnight reaction with 2 equiv of $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$. ^b Isolated yield. ^c A vinylbiphenyl-divinylbenzene copolymer was used as electron carrier.

Table 20. Reduction of Azoxy Compounds

Entry	Starting material	Product ^a	Yield (%) ^b
1			83 ^c
2			66 ^d
3			79 ^c (82) ^e
4			57 ^d

^a Overnight reaction with 2 equiv of $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$. ^b Isolated yield. ^c 1 h reaction time. ^d 10 h reaction time. ^e A vinylbiphenyl-divinylbenzene copolymer was used as electron carrier.

Table 21. Reduction of Amine *N*-Oxides

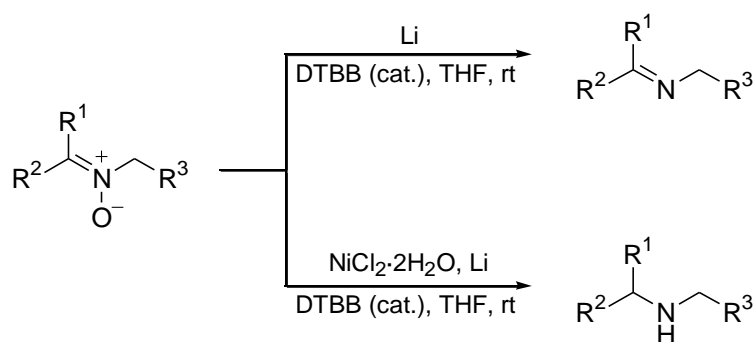
Entry	Starting material	Product	Yield (%) ^a
1			68
2			66
3			55
4			70 (74) ^b
5			75
6			80

^a Isolated yield. ^c A vinylbiphenyl-divinylbenzene copolymer was used as electron carrier.

2.8. Reduction of Nitrones

Other reactions of considerable interest in organic synthesis are the deoxygenation^{42b,49} and reduction⁵⁰ of nitrones. However, most of the deoxygenation methods are of limited applicability due to the harsh reaction conditions required and practically all the literature available on the reduction of nitrones is reported in order to achieve their specific transformation into hydroxylamines, so new and alternative methodologies on these topics are welcome.

We observed that the deoxygenation of nitrones could be achieved with the Li-DTBB(cat.) system in the absence of the hydrated nickel salt, whereas in its presence, further reduction to the corresponding secondary amines was observed (Scheme 12).⁵¹

**Scheme 12**

The methodology showed to be effective in the deoxygenation of α,N -dialkyl nitrones, cyclic nitrones, α -aryl- N -alkyl nitrones, and an α,N -diaryl nitron (Table 22). Using the polymer-supported biphenyl, a slightly better yield was obtained for the deoxygenation of α -propyl- N -butyl nitron (Entry 1, Table 22).

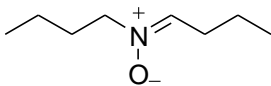
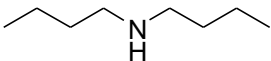
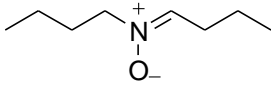
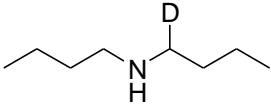
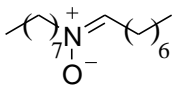
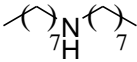
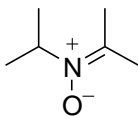
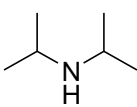
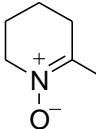
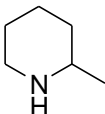
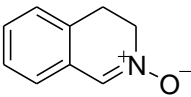
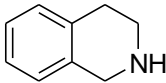
In the presence of the nickel salt, a wide range of structurally different nitrones, such as α,N -dialkyl and cyclic nitrones (Table 23), as well as α -aryl- N -alkyl, α,N -diaryl, and α -aryl- N -benzyl nitrones (Table 24) were directly transformed into the corresponding secondary amines. The use of the deuterated nickel salt allowed the preparation of isotopically labeled secondary amines by incorporation of deuterium at the α -position (Entry 2, Table 23, and Entry 3, Table 24). In the presence of the polymer-supported biphenyl, α -phenyl- N -*tert*-butyl nitron was reduced to the corresponding amine in 89% yield (Entry 2, Table 24).

Table 22. Deoxygenation of nitrones

Entry	Starting material	Product	Yield (%) ^a
1			60 (73) ^b
2			72
3			67
4			79
5			79
6			83
7			65

^a Isolated yield after short column chromatography. ^b A vinylbiphenyl-divinylbenzene copolymer was used as electron carrier.

Table 23. Reduction of Nitrones to Amines

Entry	Starting material	Product	Yield (%) ^a
1			65
2			61 ^b
3			80
4			58
5			71
6			78

^a Isolated yield after acid-base extraction. ^b NiCl₂·2D₂O was used.

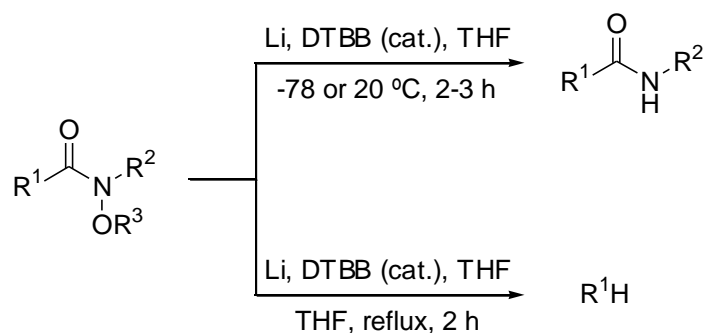
Table 24. Reduction of Aryl Nitrones

Entry	Starting material	Product	Yield (%) ^a
1			67
2			76 (89) ^b
3			80 ^c
4			69
5			41

^a Isolated yield after acid-base extraction. ^b A vinylbiphenyl-divinylbenzene copolymer was used as electron carrier. ^c NiCl₂·2D₂O was used.

2.9. Reduction of *N*-Alkoxyamides

Weinreb amides suffer a formal reduction by demethoxylation upon exposure to LDA or *tert*-butyldimethylsilyl triflate and triethylamine by loss of formaldehyde.⁵² However, Weinreb amides with alpha substituents react very slowly or not at all. Other methodologies for the reduction of the N–O bond have been developed but applied to some particular substrates.⁵³ To the best of our knowledge no work has been published on the N–O bond cleavage in secondary *N*-alkoxy amides. However, we observed that *N*-alkoxyamides could be dealkoxylated with the Li-DTBB(cat.) system under very mild reaction conditions. Very surprisingly, when the reaction was performed at reflux the corresponding alkanes were obtained from a formal dealkoxyaminocarbonylation (Scheme 13).⁵⁴

**Scheme 13**

With an excess of lithium powder and a catalytic amount of DTBB (10 mol%) in THF at -78°C for 3 h, linear and branched *N*-methoxy alkyl-, *N*-methoxy cycloalkyl-, and arenecarboxamides were reduced to the corresponding primary amides (Table 25). The reaction showed to be also effective for different *O*-substituted amides, such as *N*-phenoxy and *N*-benzyloxy amides (Entries 1 and 2, Table 26). On the other hand, Weinreb amides underwent demethoxylation by the Li-DTBB(cat.) system in 2 h at room temperature, furnishing the corresponding secondary amides in good yields (Entries 3-6, Table 26).

Table 25. Dealkoxylation of Secondary *N*-Methoxyamides

Entry	Starting material	Product	Yield (%) ^{a,b}
1			81
2			65
3			64
4			74
5			71

^a Reaction performed at -78°C for 3 h. ^b Isolated yield.

Table 26. Dealkoxylation of Secondary and Weinreb *N*-Alkoxyamides

Entry	Starting material	Product	Yield (%) ^a
1			70 ^b
2			62 ^b
3			82 ^c
4			88 ^c
5			80 ^c
6			68 ^c

^a Isolated yield. ^b Reaction performed at -78 °C, 3 h. ^c Reaction performed at rt, 2 h.

A very interesting and unprecedented result was obtained when secondary *N*-alkoxy amides were subjected to Li-DTBB(cat.) reduction at reflux, yielding the corresponding alkanes (Table 27). Acyclic, cyclic, aromatic *N*-methoxyamides, as well as *N*-phenoxy and *N*-benzyloxy amides led to the corresponding alkanes with moderate to good yields and through a mechanism that remains unclear so far.

Table 27. Reduction of *N*-Alkoxyamides to Alkanes

Entry	Starting material	Product	Yield (%) ^{a,b}
1			87
2			60
3			90
4			53
5			92
6			83

^a Isolated yield. ^b Reaction performed under reflux for 2 h.

2.10. Reduction of Acyl Azides

Some of the published methodologies for the transformation of acyl azides into primary amides involve the use of metal borohydrides,⁵⁵ tetrathiomolybdate,⁵⁶ iodotrimethylsilane,⁵⁷ $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ /transition metal,⁵⁸ or FeCl_3/Zn .⁵⁹ As an alternative to these systems, we report herein a new and simple method, based on the Li-DTBB(cat.) combination, to accomplish the reduction of acyl azides to amides.

Acyl azides gave the corresponding primary amides with an excess of lithium powder (8:1 molar ratio, based on the starting material), and a catalytic amount of DTBB (10 mol%) in THF at room temperature for 2 h (Scheme 14). The transformation was successfully achieved for acyclic alkyl-, cyclic-, and aromatic acyl azides (Table 28).⁵⁴

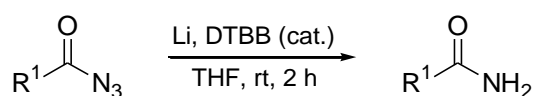
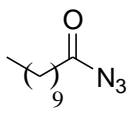
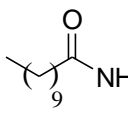
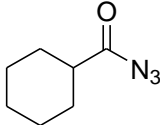
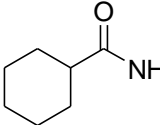
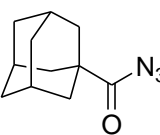
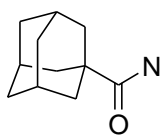
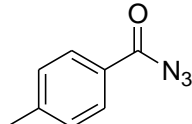
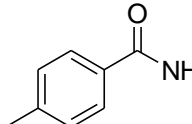
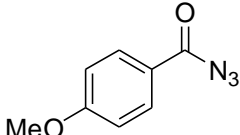
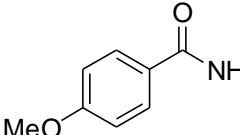
**Scheme 14**

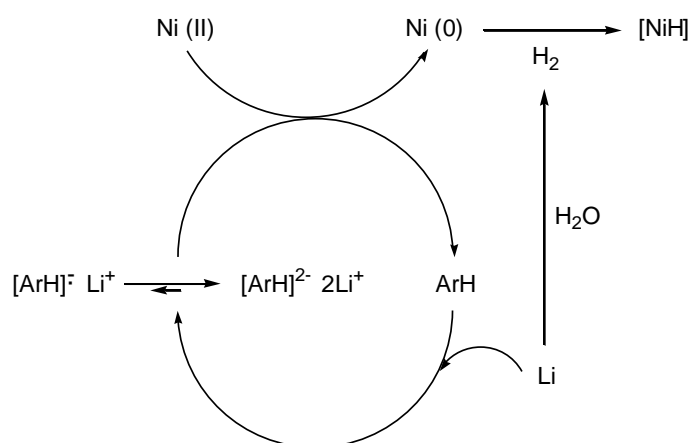
Table 28. Reduction of Acyl Azides

Entry	Starting material	Product	Yield (%) ^{a,b}
1			69
2			77
3			81
4			73
5			43

^a Isolated yield. ^b Reaction performed at rt for 2 h.

3. Mechanistic considerations

Concerning the use of the nickel chloride dihydrate and from a mechanistic point of view, we have got some evidence that the reaction pathway can depend on the type of substrate.⁶⁰ Anyway, we have suggested a general mechanism involving two clearly different processes: (a) the reduction of Ni(II) to Ni(0) by the Li-arene pair, and (b) the generation of molecular hydrogen by reaction of the excess of lithium with the hydration water released from the nickel salt, leading to nickel hydride species (Scheme 15). Nonetheless, a dissolving-metal type mechanism or even a combination of both mechanisms must not be ruled out for certain substrates.



Scheme 15

4. Conclusions

The NiCl₂·2H₂O-Li-arene(cat.) combination can be considered an alternative and useful reducing system to attain the reduction a wide variety of organic compounds including alkenes, alkynes, carbonyl compounds, imines, halogenated compounds, sulfonates, aromatic compounds, hydrazines, azo compounds, azoxy compounds, *N*-oxides, and nitrones. The following advantages can be mentioned about this reducing system: (a) commercially available or easily prepared reagents are used, (b) simplicity of the procedure, since all the reagents are solid and most of the reactions are carried out at room temperature, (c) the degree of reduction can be easily controlled for many substrates, (d) easy incorporation of deuterium into the products is achieved by using the deuterated reducing system, and (e) the source of hydrogen is simply water. In the absence of the nickel salt and with the Li-arene(cat.) system, nitrones, *N*-alkoxyamides, and acyl azides were also reduced.

Acknowledgements

This work was generously supported by the Dirección General de Enseñanza Superior (DGES) of the Spanish Ministerio de Educación, Cultura y Deporte (MECD; grants no. PB97-0133 and BQU2001-0538). G. R. thanks the CONICET (Buenos Aires, Argentina) for a fellowship.

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Graphical Abstract

