

New synthetic methodologies based on active transition metals*

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Abstract: Active transition metals, namely, nickel, copper and iron, have been prepared by the reduction of the corresponding chlorides with lithium and a catalytic amount of an arene. These metals, in the form of nanoparticles, have found application in the reduction of a wide variety of functional groups as well as in the alkylation of methyl ketones with primary alcohols.

Keywords: active metals; nickel; copper; iron; nanoparticles; reduction; alkylation of ketones with alcohols.

INTRODUCTION

In recent years, considerable attention has been devoted to the development of uniform nanometer-sized metal particles because of their unique properties and potential applications in a variety of fields, including electronics, optics, magnetism, energy technology, or chemistry, among others [1]. In particular, transition-metal nanoparticles, in different forms, have emerged as a novel family of catalysts able to promote more efficiently a variety of organic transformations because of their small size and extremely large surface-to-volume ratio [2]. Despite the diverse methodologies available for the synthesis of metal nanoparticles [3], the less noble metal Fe, Co, and Ni nanoparticles are more difficult to generate but of special interest due to their ferromagnetic and catalytic properties [4].

On the other hand, due to our ongoing interest in the discovery of new reducing systems for organic compounds based on transition metals, we have studied a methodology that allows the preparation of active transition metals (e.g., nickel, copper, and iron) [5], which in the form of metal nanoparticles, have found application in the reduction of organic compounds, in many cases with high selectivity. This methodology involves a metal chloride, lithium as reducing agent, and an arene as an electron carrier.

NICKEL

We describe herein a mild methodology for the fast preparation of nickel(0) nanoparticles from different reaction systems and their application in several organic transformations. These reaction systems have in common a NiCl₂ salt, metal lithium, an arene, and THF as solvent. The arene utilized was naphthalene, 4,4'-di-*tert*-butylbiphenyl (DTBB), or it was in a polymer-supported form. The use of the lat-

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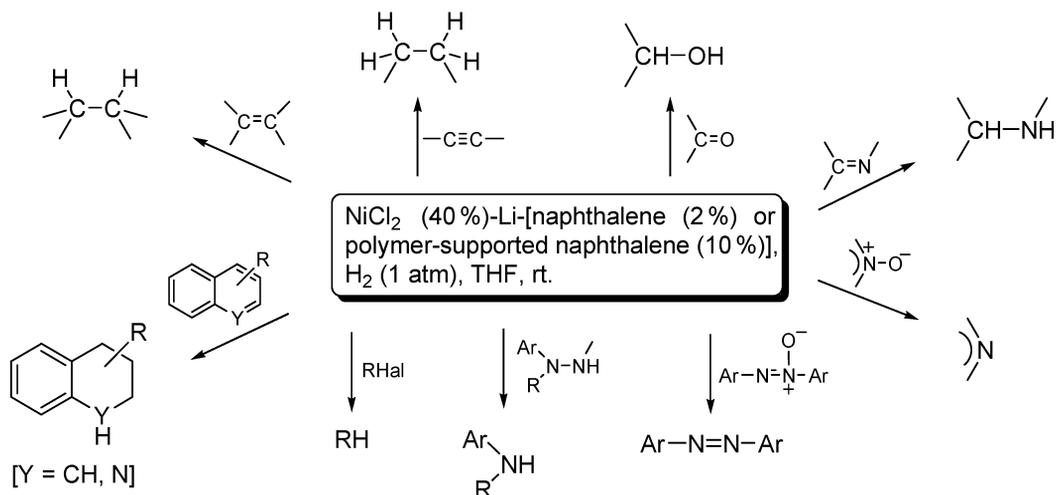
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ter was advantageous since it led to cleaner reaction crudes and could be easily removed from the reaction medium by simple filtration.

Reduction reactions

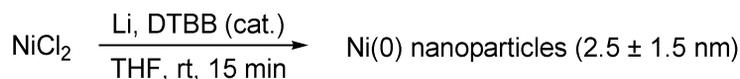
NiCl₂-Li-arene(cat.)

Several years ago, we applied the $NiCl_2$ -Li-arene(cat.) system to the catalytic hydrogenation of a variety of organic compounds, using external molecular hydrogen at room temperature [6]. Alkenes and alkynes were reduced to alkanes; carbonyl compounds to alcohols, imines to amines, halogenated compounds to hydrocarbons; aryl hydrazines to anilines; the partial reduction of aromatic compounds as well as the deoxygenation of azoxy compounds and *N*-oxides was also achieved (Scheme 1). In general, its reactivity resembled somewhat that of Raney nickel.



Scheme 1 Catalytic hydrogenation of organic compounds with active Ni and external hydrogen.

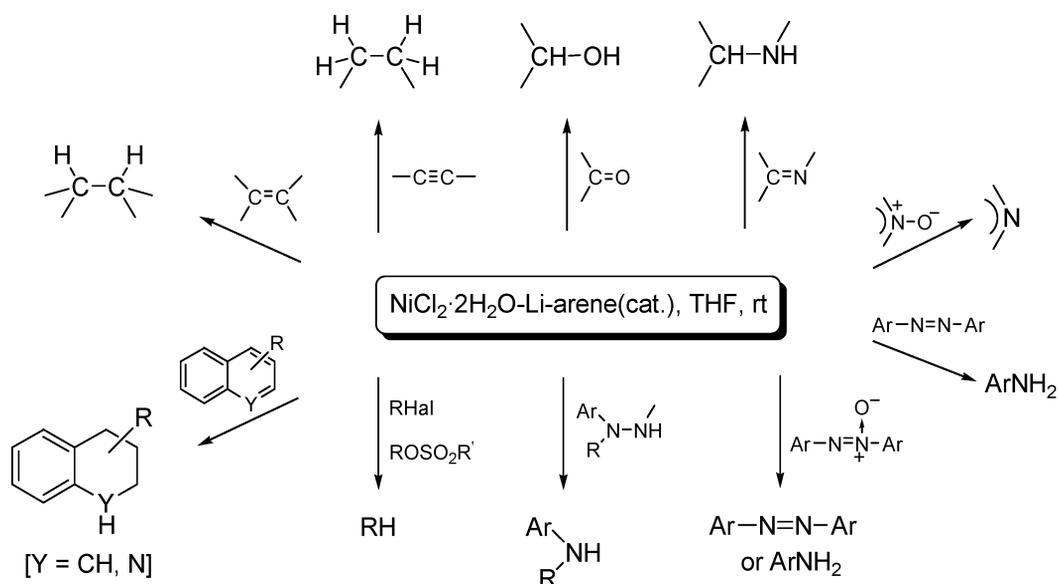
More recently, we have discovered that under these conditions, and in the particular case of using DTBB as the arene, spherical and monodispersed nickel nanoparticles were generated in the absence of any anti-agglomeration additive or nucleation catalyst (Scheme 2) [7]. It is worth noting that the generation of nickel nanoparticles failed in the absence of the electron carrier. This method, which is mild and fast, led to a narrow distribution range of Ni nanoparticles.



Scheme 2

NiCl₂·2H₂O-Li-arene(cat.)

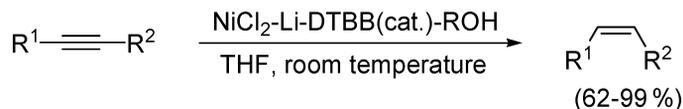
The main feature of this system is that molecular hydrogen is generated in situ by the reaction of the excess of lithium powder with the hydration water of the nickel salt, thus avoiding the handling of molecular hydrogen [8]. It found application in the reduction of a large variety of functional groups with the advantage that in some cases it was possible to control the degree of reduction by adjusting the stoichiometry of the nickel salt (Scheme 3). Interestingly, easy incorporation of deuterium into the products was accomplished by using the corresponding deuterated nickel salt.



Scheme 3 Reduction of organic compounds with active Ni and an internal source of hydrogen.

$\text{NiCl}_2\text{-Li-arene}(\text{cat.})\text{-EtOH}$

More recently, we discovered that the introduction of an alcohol (ethanol or propan-2-ol) as a source of hydrogen in the reducing system was a very convenient method for the highly stereoselective *cis* semihydrogenation of internal alkynes and the semihydrogenation of terminal alkynes (Scheme 4) [9]. Furthermore, this reducing system also found application in the complete reduction of alkenes and alkynes, and in the semi-reduction of dienes [10]. As an example, 1,5-cyclooctadiene was selectively reduced to cyclooctene in high isolated yield (Scheme 5).



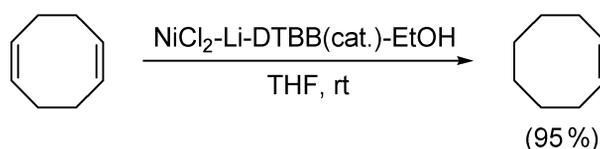
$\text{R}^1 = \text{Me, Et, } n\text{-Pr, } n\text{-Bu, } n\text{-C}_5\text{H}_{11}, n\text{-C}_6\text{H}_{13}, n\text{-C}_8\text{H}_{17}, \text{OMe, PhCH}_2\text{CH}_2, \text{PhNHCH}_2, \text{BnOCHEt}$

$\text{R}^2 = \text{H, } n\text{-Pr, } n\text{-Bu, OMe, CH}_2\text{OH, CH}_2\text{CH}_2\text{OR}^3 \text{ (R}^3 = \text{H, Me, Bn), CH}_2\text{NEt}_2$

$\text{R}^1\text{-R}^2 = (\text{CH}_2)_6$

$\text{R} = \text{Et, } i\text{-Pr}$

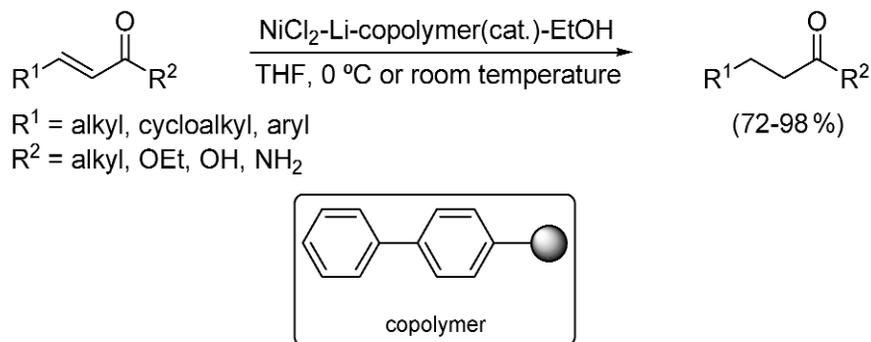
Scheme 4



Scheme 5

NiCl₂-Li-copolymer(cat.)-EtOH

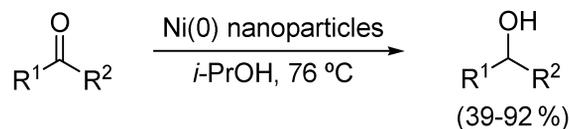
Alternatively to the previously described nickel(II) chloride-containing reducing system, a divinylbenzene-(4-vinylbiphenyl) copolymer was introduced as an electron carrier, making the process more efficient, with easier work-up and no need of product purification. Under these conditions, the selective conjugate reduction of a variety of α,β -unsaturated ketones and carboxylic acid derivatives was successfully accomplished (Scheme 6) [11].



Scheme 6

NiCl₂-Li-arene(cat.)-i-PrOH

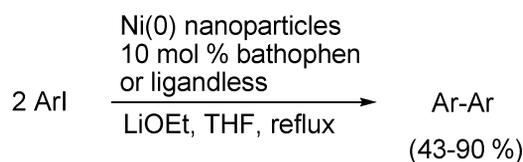
The Ni(0) nanoparticles were also found to promote the reduction of a variety of ketones and aldehydes by hydrogen transfer using propan-2-ol as the hydrogen donor (Scheme 7) [12].



Scheme 7

Carbon–carbon forming reactions*Homocoupling of aryl iodides*

Nickel(0) nanoparticles, in situ generated from nickel(II) chloride, lithium powder, and a catalytic amount of a polymer-supported arene, promoted the homocoupling of various aryl iodides under relatively mild reaction conditions (THF reflux) [13]. The presence of an organic base was fundamental for the reaction to occur, lithium ethoxide, generated in situ, giving the best results. Bathophenanthroline was shown to be the best ligand, albeit the homocoupling also took place in its absence for some substrates with even better yields and shorter reaction times (Scheme 8).

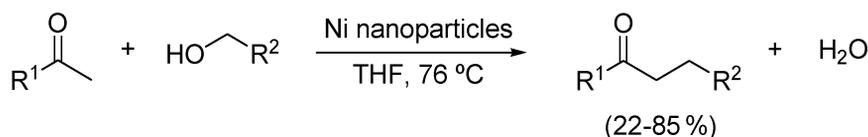


Ar = Ph, 4-YC₆H₄ (Y = Me, OMe, F, CF₃),
3-MeOC₆H₄, 2-thienyl, 3-thienyl,
5-methyl-2-thienyl

Scheme 8

α-Alkylation of ketones with primary alcohols

In the last five years, there has been increasing interest in the transition-metal-catalyzed α -alkylation of ketones with primary alcohols, as an alternative strategy to the standard α -alkylation of ketone enolates with alkyl halides, which can improve the regioselectivity of the process at the time that produces only water as a side product. This field, however, seems to be restricted to catalysts containing some noble metals, such as ruthenium, iridium, and palladium. We have demonstrated for the first time that nickel, in the form of nanoparticles, is a potential alternative to the use of noble-metal-based catalysts for the α -alkylation of ketones with alcohols. The reaction proceeds in short reaction times and in the absence of any added ligand or base, under mild conditions (Scheme 9) [14].

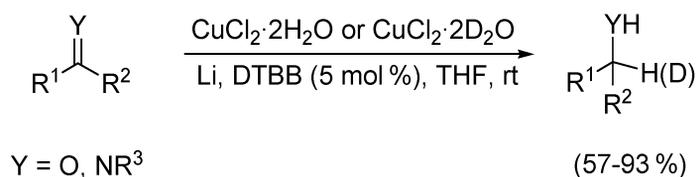


R¹ = Ph, 4-MeOC₆H₄, 4-F₃CC₆H₄, *n*-Bu, *n*-C₅H₁₁, *t*-Bu, Me
R² = Me, Et, 4-MeOC₆H₄, 4-ClC₆H₄, Ph

Scheme 9

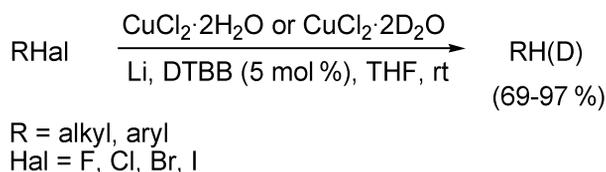
COPPER

Active copper was generated in a similar way as for nickel starting from CuCl₂·2H₂O, with the advantages that the copper salt is commercially available and less toxic than the analogous nickel salt. The copper nanoparticles generated in this way were applied to the reduction of carbonyl compounds and imines with results comparable to those with nickel (Scheme 10) [15].



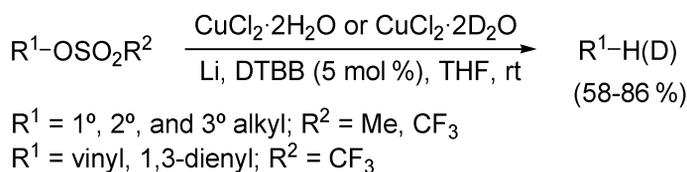
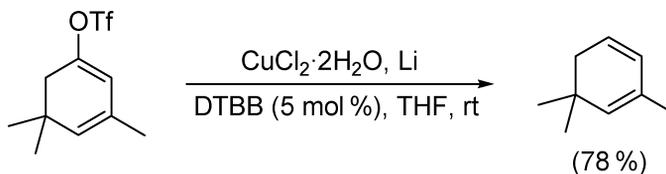
Scheme 10

This copper salt was also efficiently applied to the hydrodehalogenation of alkyl and aryl halides [16] under mild conditions, providing the corresponding alkenes and arenes in high yields (Scheme 11)

**Scheme 11**

[17]. In contrast with active nickel, in this case not only chlorides, bromides, and iodides were reduced, but also fluorides.

This copper system was also applied to the reduction of a series of alkyl and vinyl sulfonates under very mild conditions (Scheme 12). The main feature of this reaction is the selective reduction of enol and dienol triflates to the corresponding alkenes and dienes, respectively (see one example in Scheme 13) [18]. All the above reactions allowed the incorporation of deuterium into the products by using the corresponding deuterated copper salt.

**Scheme 12****Scheme 13****IRON**

More recently, we studied and applied the FeCl₂·4H₂O-Li-DTBB(cat.) system to the reduction of carbonyl compounds and imines (Scheme 14) [19]. The main features of this system are: (a) the iron salt is a commercially available and cheap reagent, (b) it is environmentally friendly, and (c) it shows a remarkable behavior in stereoselective reduction of cyclic ketones.

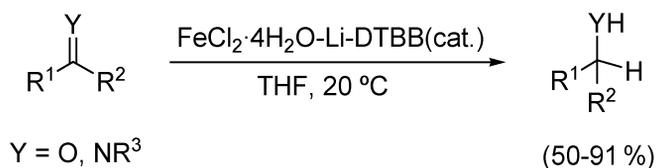
**Scheme 14**

Figure 1 shows the results obtained for the stereoselective reduction of 4-*tert*-butylcyclohexanone, 2-methylcyclohexanone, 2-allylcyclohexanone, *trans*-decalone, (\pm)-camphor, isophorone, and (+)-pulegone. In general, the stereoselectivity achieved with active iron was superior to that achieved with active nickel or copper.

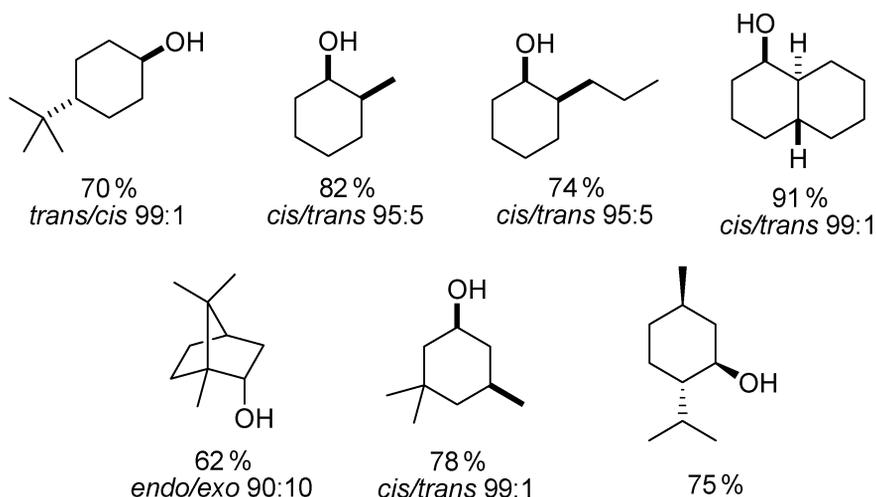
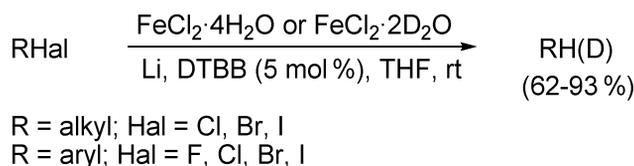


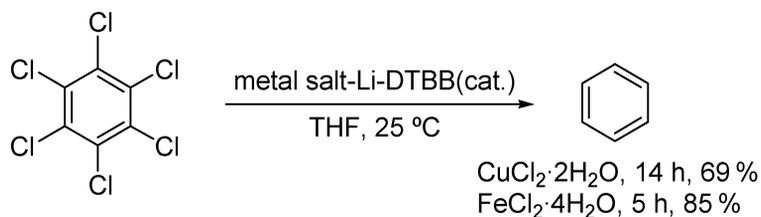
Fig. 1 Stereoselective reduction of cyclic ketones promoted by active iron.

Another recent application of the active iron was the hydrodehalogenation of halogenated organic halides using either the hydrated iron salt or the deuterated one [20]. This reducing system was demonstrated to be very efficient for alkyl and aryl chlorides, bromides and iodides, as well as aryl fluorides in short reaction times (≤ 5 h) (Scheme 15). However, it did not reduce alkyl fluorides.



Scheme 15

Moreover, polychlorinated aromatic compounds, which represent a major environmental concern because they are extremely persistent, were efficiently hydrodehalogenated to the corresponding aromatic compounds with active iron (see one example in Scheme 16). The process was much more efficient with active iron than with active copper.



Scheme 16

CONCLUSION

The reduction of nickel, copper, and iron chlorides with lithium and a catalytic amount of an arene led to the formation of the corresponding active metals in the form of nanoparticles. These metals were mainly applied to the reduction of a variety of functional groups where they exhibited a different behavior. In addition, the nickel nanoparticles were successfully applied to the hydrogen-transfer reduction of carbonyl compounds and to the α -alkylation of methyl ketones with primary alcohols.

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