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Hydrogen-transfer reduction of carbonyl compounds catalysed by nickel nanoparticles

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Abstract

We report for the first time the hydrogen-transfer reduction of carbonyl compounds catalysed by well-defined nickel(0) nanoparticles. The nickel nanoparticles could be reutilised several times in a very simple reaction medium composed of the nickel nanoparticles, isopropanol and the substrate, without any added base.

Hydrogen-transfer reactions[1] are advantageous with respect to other reduction methods because of several reasons: (a) the hydrogen donor is easy to handle (no gas containment or pressure vessels are necessary), cheap and environmentally friendly (e.g., isopropanol), (b) possible hazards are minimised, (c) the mild reaction conditions applied can afford enhanced selectivity, (d) catalytic asymmetric transfer hydrogenation can be applied in the presence of chiral ligands.[2] The transfer hydrogenation of ketones has been mostly accomplished using isopropanol as hydrogen donor under homogeneous conditions in the presence of noble metal complexes (such as those of Ru, Rh and Ir).[3] In this field, ruthenium complexes have been by far the most studied catalysts, especially for the asymmetric transfer hydrogenation of aromatic ketones[4] and from the mechanistic point of view.[5] It is worthwhile, however, developing new heterogeneous catalysts[6] that, generally, can (a) simplify the catalytic system, (b) use cheaper transition metals, (c) simplify the purification step and (d) be recycled and reused without significant loss of activity.

In this sense, nickel appears as a potential alternative to the above expensive transition metal complexes but very less studied in hydrogen transfer reactions with isopropanol. It has been used either under homogeneous ($NiBr_2$–NaOH[7] and a macrocyclic nickel complex–NaOH[8]) or heterogeneous conditions ($NiCl_2$-*i*-PrOLi,[9] Ni-stabilized zirconia–KOH[10] and mesoporous NiMCM–KOH[11]) mainly for aromatic substrates. In all these cases, the addition of an external base was mandatory for the reaction to take place. More recently, an excess of Raney nickel in refluxing isopropanol containing a trace of HCl reduced a series of aliphatic aldehydes and ketones to the corresponding primary and secondary alcohols, respectively.[12]

We discovered recently that nickel(0) nanoparticles (NiNPs), prepared from nickel(II) chloride, lithium powder and a catalytic amount of DTBB,[13] can promote readily the transfer hydrogenation with isopropanol of a variety of aromatic and aliphatic ketones and aldehydes in the absence of any added base at 76 °C.[14] Modest to high yield of the corresponding alcohols was obtained, depending on the functional groups and/or the structure of the substrate. The reducing system showed to be diastereoselective for most of the cyclic ketones studied and superior to other forms of nickel under the same reaction conditions. Moreover, the nickel nanoparticles could be reutilised several times maintaining a high activity in a very simple reaction medium composed of the nickel nanoparticles, isopropanol and the substrate, without any added base. The reaction

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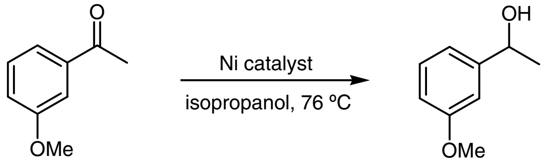
was demonstrated to proceed through a dihydride-type mechanism.

The main drawback of this methodology was that it involved stoichiometric amounts of nickel. In fact, very low yield of the expected product was obtained in the reduction of acetophenone at room temperature by using 10 or 20 mol % NiNPs. In these cases, 10 and 20 mol % NiNPs aliquots were taken from a pre-formed 20 mL suspension of NiNPs and reacted with 1 mmol of acetophenone. In principle, this result practically ruled out the possibility of using the NiNPs in catalytic amounts for the title reaction. However, more recently we have observed that the reaction seems to be sensitive to the concentration and that it is possible to use catalytic NiNPs for a substrate scale larger than 1 mmol. To the best of our knowledge, this is the first time that well-defined and characterised nickel nanoparticles have been applied to the catalytic transfer hydrogenation of carbonyl compounds.

The NiNPs were generated from anhydrous nickel(II) chloride, lithium powder and a catalytic amount of DTBB (4,4′-di-*tert*-butylbiphenyl, 5 mol %) in THF at room temperature. The presence of isopropanol at 76 °C was shown to have a beneficial effect in the generation of the NiNPs as regards their size and uniformity. Spherical, monodispersed and highly uniform nanoparticles were obtained (0.75–2.88 nm, ca. 1.75 ± 1.00 nm), most of them with diameters <2 nm (ca. 75%).[14]

A preliminary study was carried out using 3-methoxyacetophenone as a model substrate in order to optimise the amount of catalyst (Table 1). A 1:5 NiNPs/substrate molar ratio (20 mol % Ni) showed to be the most effective with complete conversion into the product 1-(3-methoxyphenyl)ethanol (entry 1). Although the reaction with a 1:10 NiNPs/substrate molar ratio (10 mol % Ni) led to the product in a relatively short time and moderate yield, further progress of the reaction from this point was not observed (entry 2). Surprisingly, no product was formed when using a 1:20 NiNPs/substrate molar ratio (5 mol % Ni). It is noteworthy that under the same conditions as in entry 1, Raney nickel led to a mixture of the expected alcohol (41%), 3-ethylanisole (20%) and ethylbenzene (38%), whereas Ni/Al_2O_3 showed no catalytic activity in this reaction.

Table 1
Transfer hydrogenation of 3-methoxyacetophenone catalysed by different nickel catalysts



Entry	Ni catalyst/substrate (mmol)	*t* (h)	Yield[a] (%)
1	NiNPs 1:5	4	100
2	NiNPs 1:10	2[b]	58
3	NiNPs 1:20	24	0
4	Raney Ni 1:5	4[b]	41[c]
5	Ni/Al_2O_3 1:5	4[b]	0

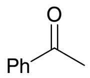
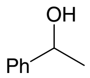
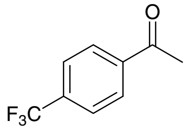
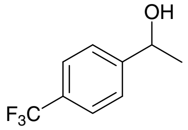
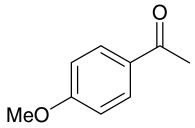
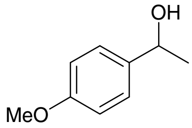
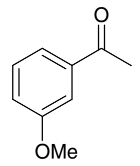
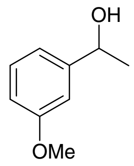
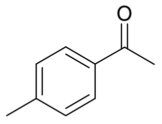
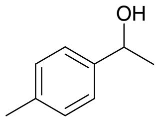
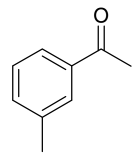
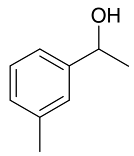
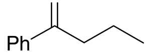
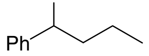
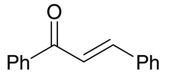
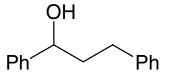
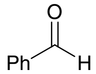
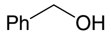
[a] GLC yield.

[b] No change in yield was observed after this time.

[c] 3-Ethylanisole (20%) and ethylbenzene (38%) were also obtained.

Under the optimised reaction conditions, a series of aromatic carbonyl compounds were reduced to the corresponding alcohols in modest to good yields and in relatively short reaction times (Table 2).[15] The reduction of substituted acetophenones was shown to be very dependent on the electronic character and position of the substi-

Table 2
Transfer hydrogenation of aromatic ketones and aldehydes catalysed by NiNPs[a]

Entry	Substrate	*t* (h)	Product	Yield[b] (%)
1		1		80 (87)
2		3		73 (93)
3		3		(33)
4		4		72 (97)
5		3		40 (61)
6		5		52 (81)
7		4		52 (77)
8		3		63 (82)
9		3		(30)

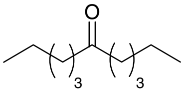
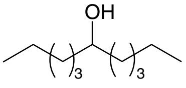
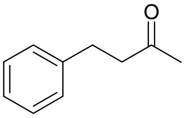
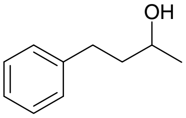
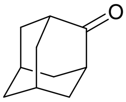
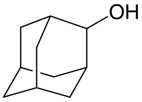
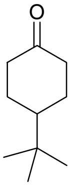
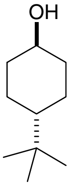
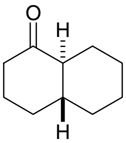
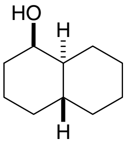
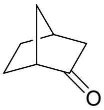
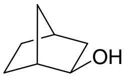
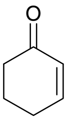
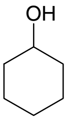
[a] Substrate (5 mmol), NiNPs (1 mmol) in THF (2 mL), isopropanol (4 mL), 76 °C.

[b] Isolated yield after column chromatography (hexane/EtOAc). Conversion is given in parentheses.

tuent. In general, the presence of an electron-withdrawing group at the para position (entry 2) or electron-donating groups at the meta position (entries 4 and 6) facilitated the ketone reduction. On the other hand, acetophenones bearing electron-donating substituents at the para position were more reluctant to react (entries 3 and 5). Butyrophenone was reduced in moderate isolated yield (entry 7) while chalcone led to the corresponding saturated alcohol (entry 8). The conversion of benzaldehyde into benzyl alcohol was rather modest (entry 9).

In general, better yields were obtained when aliphatic ketones were subjected to the NiNPs-catalysed transfer hydrogenation (Table 3). Dialkyl ketones such as 6-undecanone and 4-phenyl-2-butanone were transformed into the corresponding alcohols in good yields (entries 1 and 2). As regards cyclic ketones, 2-adamantanone furnished 2-adamantanol in good isolated yield (entry 3) whereas some other cyclic ketones furnished a mixture of diastereomeric alcohol products. In the case of 4-*tert*-butylcyclohexanone, the thermodynamically more stable equatorial alcohol *trans*-4-*tert*-butylcyclohexanol (70% yield) was the major product (eq/ax 78:22) (entry 4). The reduction of *trans*-decalone provided an ax/eq 66:34 ratio of the corresponding epimeric alcohols (entry 5), while (±)-norcamphor led mainly to the most stable of the two possible norborneol stereoisomers: *exo*/*endo* 80:20 (entry 6). The stereoselectivity achieved with the catalytic NiNPs is somewhat lower than that achieved with stoichiometric NiNPs.[14] The α,β-unsaturated ketone 2-cyclohexenone led to cyclohexanol in a much lower conversion than the other ketones (entry 7).

Table 3
Transfer hydrogenation of aliphatic ketones catalysed by NiNPs[a]

Entry	Substrate	*t* (h)	Product	Yield[b] (%)
1		4		73 (87)
2		3		90 (94)
3		4		76 (99)
4		3		70[c] (100)
5		3		78[d] (100)
6		4		81[e] (100)
7		1		(34)

[a] Substrate (5 mmol), NiNPs (1 mmol) in THF (2 mL), isopropanol (4 mL), 76 °C.

[b] Isolated yield after column chromatography (hexane/EtOAc). Conversion is given in parentheses.

[c] Isolated yield of the *trans* stereoisomer. Diastereomeric ratio: *trans*/*cis* 78:22.

[d] Diastereomeric ratio: *trans*/*cis* 66:34.

[e] Diastereomeric ratio: *exo*/*endo* 80:20.

Table 4
Reutilisation of NiNPs in the hydrogen transfer reduction of acetophenone

Run	1	2	3	4	5
Yield[a] (%)	87	89	87	70	77

[a] GLC yield after 1 h.

We also studied the possibility of reutilisation of the NiNPs using acetophenone as a substrate. For each cycle, the NiNPs were decanted and the supernatant was removed, followed by the addition of more isopropanol and the substrate. The NiNPs could be reused during three consecutive runs (1 h reaction time each) without any apparent loss of activity (Table 4). A decrease in activity was observed for the fourth and fifth runs albeit the yields were still reasonably good.[16] At any rate, no byproducts (such as those formed when using Raney Ni) arose in these experiments. It is worthy to note that this reusable catalytic system is very simple, composed of only the NiNPs and isopropanol, with no base.

In conclusion, we have reported for the first time the application of catalytic nickel(0) nanoparticles to the transfer hydrogenation with isopropanol of a variety of carbonyl compounds in the absence of any added base at 76 °C. The reducing system showed to be superior to other forms of nickel and could be reutilised several times in a very simple reaction medium composed of the nickel nanoparticles, isopropanol and the substrate.

Acknowledgements

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15. *In a typical procedure*: Nickel chloride (130 mg, 1 mmol) was added over a suspension of lithium (14 mg, 2 mmol) and DTBB (13 mg, 0.05 mmol) in dry THF (2 mL) at room temperature under argon. The reaction mixture, which was initially dark blue, changed to black indicating that nickel(0) nanoparticles were formed. After 10 min, *i*-PrOH (4 mL) and the corresponding carbonyl compound (5 mmol) were successively added. The reaction mixture was warmed up to 76 °C and monitored by GLC–MS until total or steady conversion of the starting material. The resulting suspension was diluted with diethyl ether (20 mL), filtered through a pad containing Celite, and the filtrate was dried over $MgSO_4$. The residue obtained after removal of the solvent (15 Torr) was purified by column chromatography (silica gel, hexane/EtOAc) to give the corresponding pure alcohol.
16. The deactivation of some common heterogeneous hydrogenation catalysts (e.g., Pd/C and Raney Ni) after aging them in alcoholic solvents has been recently reported: Singh, U. K.; Krska, S. W.; Sun, Y. *Org. Process Res. Dev.* **2006**, *10*, 1153–1156.