Hydrogen-Transfer Reductive Amination of Aldehydes Catalysed by Nickel Nanoparticles

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Dedicated to Professor Dieter Seebach on the occasion of his 70th birthday

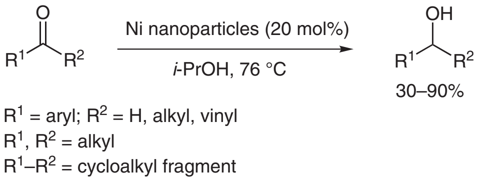
Abstract: Nickel nanoparticles have been found to catalyse the reductive amination of aldehydes by transfer hydrogenation with isopropanol at 76 °C.

Key words: reductive amination, aldehydes, imines, nickel nanoparticles, hydrogen transfer, amines

The reduction of imines is a very useful transformation in organic synthesis since the resulting amines have widespread applications in industry and in synthetic organic chemistry. Three general methods for this reaction can be highlighted involving the use of (a) metal hydrides, (b) dissolving metals, and (c) catalytic hydrogenation.[1] The reductive amination of aldehydes and ketones, an important transformation in biological systems, is, however, a more direct and convenient route to amines.[2] The reductive amination with metal hydrides[3] or by catalytic hydrogenation[4] are the most practiced methods, whereas transfer hydrogenation is more restricted to the reduction of preformed imines.[5]

Hydrogen-transfer reactions[6] are advantageous with respect to other reduction methods for 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 minimized, (c) the mild reaction conditions applied can afford enhanced selectivity, and (d) catalytic asymmetric transfer hydrogenation can be applied in the presence of chiral ligands.[7] These reactions are mostly performed under homogeneous conditions in the presence of noble-metal complexes, whereas less attention has been paid to processes under heterogeneous conditions or involving non-noble metals.

In this sense, and due to our ongoing interest on the reactivity of active metals,[8] we have recently reported the first application of well-defined nickel(0) nanoparticles[9] to the transfer hydrogenation with isopropanol of a variety of carbonyl compounds in the absence of any added base at 76 °C (Scheme 1).[10] It is noteworthy that, in contrast with other transition metals, nickel has been scarcely used in reductive aminations or in the transfer hydrogenation of imines. Reductive aminations involving nickel were performed with hydrazine using borohydride exchange resin–nickel acetate[11] (for primary amines) or with stoichiometric nickel boride in methanol.[12] On the other hand, the transfer hydrogenation of preformed imines was carried out with isopropanol and excess aluminum isopropoxide in the presence of Raney nickel (the reaction failed in the absence of aluminum isopropoxide),[13] or with sodium isopropoxide catalysed by a nickel(0)–N-heterocyclic carbene complex.[14] However, to the best of our knowledge, nickel-mediated reductive amination reactions by transfer hydrogenation have never been reported.



Scheme 1 Hydrogen-transfer reduction of carbonyl compounds catalysed by nickel nanoparticles

We want to report herein the first application of nickel, in the form of nanoparticles, to the hydrogen-transfer reductive amination of aldehydes, using isopropanol as the hydrogen source in the absence of any added base.

The nickel nanoparticles (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. A preliminary study was carried out using benzaldehyde and aniline as model substrates in order to optimise the amount of catalyst and compare with other nickel catalysts (Table 1). A 1:1 NiNPs/substrate molar ratio showed to be very effective with a fast and high conversion into the product *N*-benzylaniline (entry 1). A 1:5 NiNPs/substrate molar ratio (20 mol% Ni) showed a similar conversion to that in the stoichiometric reaction though longer time was needed (entry 2), whereas the yield dropped drastically by using a 1:10 NiNPs/substrate molar ratio (10 mol% Ni). It is noteworthy that under the same conditions as in entry 2, the commercially available Raney nickel (entry 4) and Ni/Al_2O_3 (entry 5) led to the formation of the corresponding imine, which did not undergo reduction at all. The imine was also the only reaction product when the reaction was carried out in the absence of any catalyst (entry 6). In view of the above results, we decided that the reaction conditions involving 20 mol% NiNPs were the most convenient

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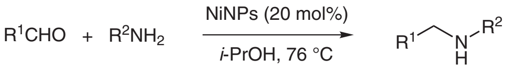
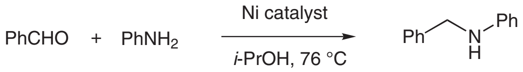


Scheme 2 *Reagents and conditions*: aldehyde (5 mmol), amine (5 mmol), NiNPs (1 mmol), *i*-PrOH (10 mL), 76 °C.

to study the scope of this reductive amination (Scheme 2 and Table 2).

The optimised reaction conditions were first applied to the reductive amination of benzaldehyde with different kinds of primary amines (Table 2).[15] Moderate-to-excellent yields of the corresponding *N*-benzylanilines were obtained for aniline as well as for *para*-, *ortho*- or *meta*-substituted anilines (entries 1–4). The primary alkyl amine octan-1-amine led to *N*-benzyloctan-1-amine in high yield (entry 5), whereas phenethylamine reacted in a modest yield (entry 6). Two benzylic amines were also studied, the more hindered α-methylbenzylamine (entry 8) showing a better performance than benzylamine (entry 7).

Table 1 Hydrogen-Transfer Reductive Amination of Benzaldehyde with Aniline in the Presence of Different Nickel Catalysts



Entry	Ni catalyst/substrate (mmol)	Time (h)	Yield (%)[a]
1	NiNPs 1:1	1	96
2	NiNPs 1:5	9	91
3	NiNPs 1:10	24	8
4	Raney Ni 1:5	24	0[b]
5	Ni/Al$_2$O$_3$ 1:5	24	0[b]
6	none	24	0[b]

[a] GLC yield.

[b] The corresponding imine was obtained.

Table 2 Reductive Amination of Aldehydes by Hydrogen Transfer with Isopropanol Catalysed by Nickel Nanoparticles

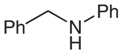
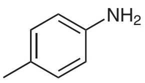
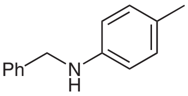
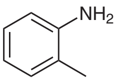
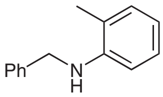
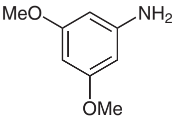
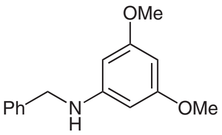
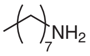
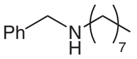
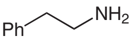
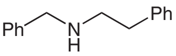
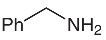
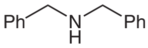
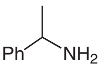
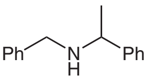
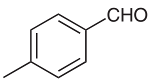
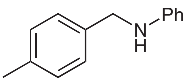
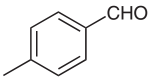
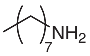
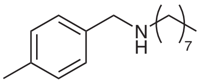
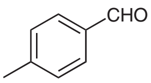
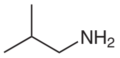
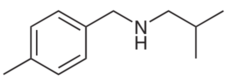
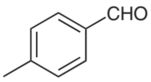
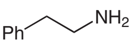
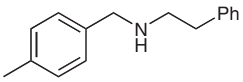
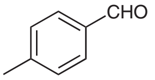
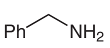
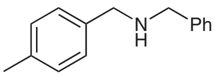
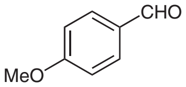
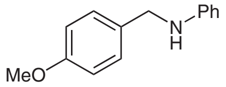
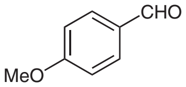
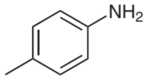
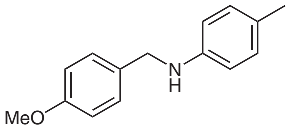
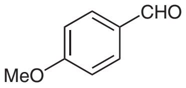
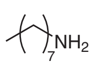
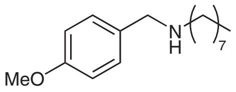
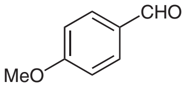
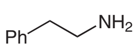
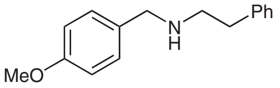
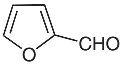
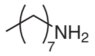
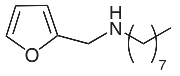
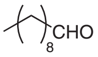
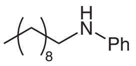
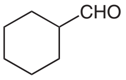
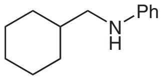
Entry	Aldehyde	Amine	Time (h)	Product[a]	Yield (%)[b]
1	PhCHO	PhNH$_2$	9		73
2	PhCHO		10		65
3	PhCHO		12		99[c]
4	PhCHO		8		80
5	PhCHO		10		90[c]
6	PhCHO		24		43
7	PhCHO		8		77
8	PhCHO		12		92[c]
9		PhNH$_2$	4		97[c]
10			6		85[c]
11			10		87
12			24		80

Table 2 Reductive Amination of Aldehydes by Hydrogen Transfer with Isopropanol Catalysed by Nickel Nanoparticles (continued)

Entry	Aldehyde	Amine	Time (h)	Product[a]	Yield (%)[b]
13			24		40
14		$PhNH_2$	6		44
15			8		98[c]
16			6		36[d]
17			12		99[c]
18			48		30
19		$PhNH_2$	48		30[d]
20		$PhNH_2$	12		70

[a] All isolated products were ≥95% pure (GLC and/or ^1H NMR).

[b] Isolated yield after column chromatography unless otherwise stated.

[c] Crude yield.

[d] GLC yield.

We next studied the reactivity of substituted benzaldehydes with different amines under the above reaction conditions. 4-Methylbenzaldehyde reacted nicely with aniline (entry 9) or with the alkanamines octan-1-amine (entry 10), 2-methylpropan-1-amine (entry 11), and phenethylamine (entry 12). The reaction of this substrate with benzylamine was, however, rather limited (entry 13). It is noteworthy that aniline and octan-1-amine, which gave good results in the reaction with 4-methylbenzaldehyde, led to much lower yields in the reaction with 4-methoxybenzaldehyde (compare entries 9 and 10 with 14 and 16, respectively). On the other hand, 4-methylaniline and phenethylamine provided the corresponding secondary amines in excellent yields (entries 15 and 17).

Some other aldehydes showed to be more reluctant to undergo the title reaction. For instance, the reductive amination of furfural with octan-1-amine proceeded in rather low yield (entry 18). A similar behaviour was observed for linear alkyl-substituted aldehydes such as decanal (entry 19). In these two examples, as well as in most of the products in which the yields were moderate to low, the secondary amines were accompanied by variable amounts of the corresponding precursor imines. Nonetheless, separation of the desired amine could be easily accomplished by column chromatography. Finally, cyclohexanecarboxaldehyde underwent the nickel-catalysed hydrogen-transfer reductive amination in good isolated yield (entry 20). Unfortunately, any attempt to reuse the nickel nanoparticles failed.[16]

In conclusion, we have demonstrated for the first time that nickel, in the form of nanoparticles, can catalyse the reductive amination of aldehydes by transfer hydrogenation, using isopropanol as the hydrogen source in the absence of any added base. The process is especially effective in the reductive amination of aromatic aldehydes, most of the corresponding secondary amines being obtained in good-to-excellent yields. The application to aliphatic aldehydes is, however, more limited. In general, this methodology is advantageous because (a) the preparation step of the imine is avoided, aldehydes and amines being directly used as starting materials, (b) the source of hydrogen is isopropanol, a cheap and environmentally friendly solvent, and (c) the nickel nanoparticles have been shown to be superior to other nickel catalysts in this reaction.

Acknowledgment

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(15) **General Procedure for the Hydrogen-Transfer Reductive Amination of Aldehydes Catalysed by Nickel Nanoparticles**
A solution of the aldehyde (5 mmol) and the amine (5 mmol) was prepared in *i*-PrOH (10 mL) and stirred for about 1 h. Meanwhile, NiCl$_2$ (130 mg, 1 mmol) was added over a suspension of lithium (14 mg, 2 mmol) and DTBB (13 mg, 0.05 mmol) in THF (2 mL) at r.t. under argon. The reaction mixture, which was initially dark blue, changed to black indicating that nickel(0) was formed. After 10 min, the initially prepared solution of the aldehyde and amine was added to the nickel suspension. The reaction mixture was warmed up to 76 °C and monitored by GLC-MS. The resulting suspension was filtered through a pad containing Celite and the filtrate was dried over MgSO$_4$. The residue obtained after removal of the solvent (15 Torr), when necessary, was purified by column chromatography (SiO$_2$, hexane–EtOAc) to give the pure secondary amine. *N*-Benzylaniline, *N*-benzyl-2-phenylethanamine, dibenzylamine, and *N*-benzyl-1-phenylethanamine were characterized by comparison of their physical and spectroscopic analyses with those of commercially available samples (Aldrich). *N*-Benzyl-4-methylaniline,[17] *N*-benzyl-2-methylaniline,[17] *N*-benzyl-3,5-dimethoxyaniline,[18] *N*-benzyloctan-1-amine,[19] *N*-(4-methylbenzyl)aniline,[20] *N*-(4-methylbenzyl)octan-1-amine,[21] *N*-(4-methylbenzyl)-2-phenylethanamine,[22] *N*-benzyl-4-methylbenzylamine,[23] *N*-(4-methoxybenzyl)aniline,[24] *N*-(4-methoxybenzyl)-4-methylaniline,[25] *N*-(4-methoxybenzyl)octan-1-amine,[21] *N*-(4-methoxybenzyl)-2-phenylethanamine,[26] *N*-[(furan-2-yl)methyl]octan-1-amine, *N*-(*n*-decyl)aniline,[27] and *N*-(cyclohexylmethyl)aniline[28] were characterised by comparison of their physical and spectroscopic data with those described in the literature.
Spectroscopic Data of New Compounds
***N*-(4-Methylbenzyl)-2-methylpropan-1-amine**
Yellow oil; R_f = 0.18 (hexane–EtOAc, 1:1). IR (neat): 3345 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.91 (d, J = 6.7, 6 H, 2 × CH_3CH), 1.69 (br s, 1 H, NH), 1.76–1.85 (m, 1 H, CHCH$_3$), 2.34 (s, 3 H, CH$_3$C), 2.42 (d, J = 7.0, 2 H, CH_2CH), 3.71 (s, 2 H, CH$_2$C), 7.15, 7.19 (AB system, J = 8.2, 4 H, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 20.2, 20.8 (3 × CH$_3$), 27.5 (CHCH$_3$), 53.1, 56.6 (2 × CH$_2$), 128.0, 129.0 (4 × ArCH), 136.0, 137.0 (2 × ArC). MS (70 eV): *m/z* = 177 [M$^+$], 134, 106, 105, 77. HRMS: *m/z* [M$^+$] calcd for C$_{12}$H$_{19}$N: 177.1517; found: 177.1516.
***N*-[(Furan-2-yl)methyl]octan-1-amine**
Yellow oil; R_f = 0.24 (hexane–EtOAc, 1:1). IR (neat): 3325 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.86 (t, J = 6.2, 3 H, CH$_3$), 1.26 [br s, 10 H, (CH_2)$_5$CH$_3$], 1.48 (m, 2 H, CH_2CH$_2$N), 1.98 (br s, 1 H, NH), 2.59 (t, J = 6.9, 2 H, CH$_2$CH_2N), 3.77 (s, 2 H, CH$_2$C), 6.16, 6.30, 7.35 (3 s, 3 H, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.0 (CH$_3$), 22.6, 27.3, 29.2, 29.4, 29.9, 31.7, 46.2, 49.1 (8 × CH$_2$), 106.7, 110.0, 142.0 (3 × ArCH), 154.0 (ArC). MS (70 eV): *m/z* = 209 [M$^+$], 110, 81. HRMS: *m/z* [M$^+$] calcd for C$_{13}$H$_{23}$NO: 209.1779; found: 209.1777.

(16) In principle, deactivation of the catalyst cannot be attributed to particle agglomeration as confirmed by transmission electron microscopy (TEM) analysis of a sample of the reused suspension. Further studies to understand the properties, reactivity, and deactivation mechanism of the catalyst are under way.

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