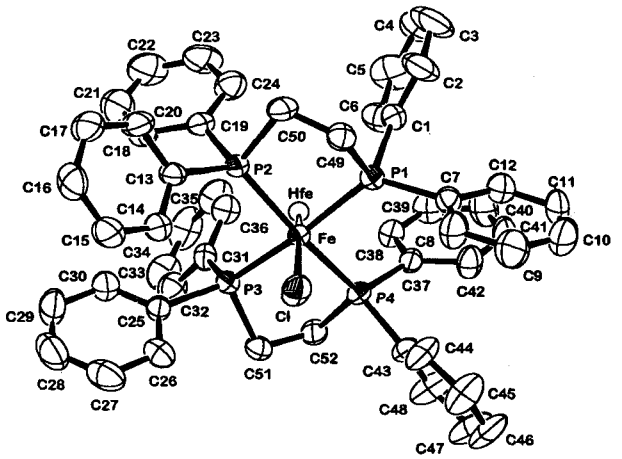

Figure 1. ORTEP drawing[7] of *trans*-FeHCl(dppe)$_2$ showing the atom-labeling scheme and 50% probability thermal ellipsoids.

tra of this compound exhibit a singlet at δ 81.5 ppm. The results of the X-ray crystal structure and NMR spectral data indicate that the molecule has the same structure both in solution and in the solid state.

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Reductive Amination of Ketones and Aldehydes with Hydrazine Using Borohydride Exchange Resin (BER)-Nickel Acetate in Methanol

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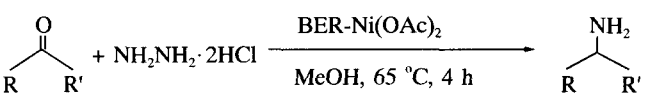
Reductive amination is an important transformation which allows the direct conversion of carbonyl compounds into the corresponding amines in chemical and biological system.[1] It is commonly carried out using cyanoborohydrides[2-4] since the hydrides are stable under weakly acidic conditions which is essential for the formation of the imine intermediate. However, borane pyridine (BAP),[5] sodium triacetoxyborohydride,[6] and borohydride exchange resin (BER)[7] were also reported as alternative, less expensive, and less toxic reagents. Using these methods, secondary and tertiary amines are prepared in very good yields; however, primary amines are obtained in poor to moderate yields using cyanoborohydride[2b] and BER.[7] Alternatively primary amines are prepared by the reduction of hydrazones with catecholborane, followed by catalytic hydrogenation of the resulting hydrazines over Raney Ni at 3.5-3.8 bar.[8]

Recently, we have reported that BER-Ni(OAc)$_2$ in methanol is an excellent reducing system for azides[9] and nitro[10] compounds. In the course of these studies, we found that azobenzene was reduced cleanly to aniline with this reducing system. This suggests that the *N-N* bond could be cleaved readily by this system. Therefore we decided to study the synthesis of primary amines by the reductive amination of aldehydes and ketones via hydrazones using BER-Ni(OAc)$_2$ in methanol.

The results are summarized in Table 1. As shown in Table 1, yields were relatively good compared with other reported reducing agents. For example, cyclohexylamine was obtained in 88% yield; however only 45% yield was obtained using $NaBH_3CN$[2(a)] (entry 1). 2-Heptylamine was obained in 87% yield, wherease only 25% yield was obtained using BER[7] in the presence of NH_4OAc (entry 6). In the case of acetophenone, 1-phenethylamine was obtained in 77% yield, comparable yield with $NaBH_3CN$ (77%).[2(a)] In the reductive amination of aldehydes, benzylamine was obtained in a moderate yield (70%), but hexanal gave only 26% yield. However, 58% yield of hexylamine could be obtained by the reduction of hexanal phenylhydrazone.

The BER-Ni(OAc)$_2$ system tolerates the presence of ester functional group as shown in the synthesis of methyl 6-amino heptanoate (entry 10); however, the conjugated double bond of benzalaceton was simultaneously reduced to give 3-

Scheme 1.



R=alkyl, aryl
R'=alkyl, H
BER (20 equiv), Ni(OAc)$_2$·4H$_2$O (1 equiv)

Table 1. Reductive Amination of Ketones and Aldehydes with Hydrazine using Borohydride Excnange Resin (BER)-$Ni(OAc)_2 \cdot 4H_2O$ in Methanol

entry	substrate	product	yield (%)[a]
1	cyclohexanone	cyclohexylamine	88
2	2-methylcycol-hexanone	2-methylcyclo-hexylamine	82[b]
3	4-*tert*-butylcyclo-hexanone	4-*tert*-butylcyclo-hexylamine	88[b]
4	cyclooctanone	cyclooctylamine	73
5	norcamphor	2-aminonorbornane	82[c]
6	2-heptanone	2-heptylamine	87
7	4-heptanone	4-heptylamine	82
8	acetophenone	1-phenethylamine	77
9	benzalacetone	3-amino-1-phyenyl-butane	80
10	methyl 6-oxo-heptanoate	methyl 6-amino-heptanoate	81
11	hexanal	hexylamine	(26), 58[d]
12	benzaldehyde	benzylamine	70

[a] Isolated yields. Figures in parenthesis are GC yields. [b] The ratios of *cis/trans* isomers were 62/38 for 2-methylcyclohexylamines,[11] and 58/42 for 4-*tert*-butylcyclohexylamines.[12] [c] The ratio of *ando/exo* isomers was 86/14.[13] [d] The corresponding phenylhydrazone (3 mmol) reacted with BER (30 mmol) and $Ni(OAc)_2 \cdot 4H_2O$ (1.5 mmol) at 65 °C for 3 h.

amino-1-phenylbutane (entry 9). Amides, nitriles, and epoxides are also expected to be tolerated in this reductive amination, since BER-$Ni(OAc)_2$ is inert to these functional groups.[10] The stereochemistry of the reductive amination of cyclic ketones is shown in entries 2, 3, and 5. The predominant formation of the *cis* amines suggested the predominant reduction of hydrazones from the less hindered site. We obtained 2-aminonorbornane with an *endo/exo* ratio of 86/14. Since, $NaBH_3CN$ gave only *endo* isomer, this *exo* isomer may be formed by the intramolecular reduction of the norcamphor hydrazone borohydride complex.[14]

In conclusion, the synthesis of primary amines by the present method is a good alternative to the cyanoborohydride method which is expensive and toxic, and may be much more convenient than catecholborane-Raney Ni reduction.

Experimental

General Procedure. The reaction of 2-methylcyclohexanone is representative. BER (10.23 g, 30 mmol) was placed in 15 mL methanol and a sonicated solution (15 mL) of 2-methylcyclohexanone (0.34 g, 3 mmol) and NH_2-$NH_2 \cdot 2HCl$ (0.31 g, 3 mmol) was added. The mixture was stirred at room temperature for 1 h, followed by addition of a methanol solution (15 ml) of $Ni(OAc)_2 \cdot 4H_2O$ (0.37 g, 1.5 mmol) of to the mixture which was then, refluxed for 3 h. Additional BER (10.23 g, 30 mmol) and $Ni(OAc)_2 \cdot 4H_2O$ (0.37 g, 1.5 mmol) were added and the mixture was refluxed one more hour. After the reaction was completed, the acidic solution was neutralized by the addition of NaOH (0.24 g, 6 mmol). Then the resin was removed by filtration and the methanol was evaporated under reduced pressure. The crude residue was chromatographed on a silicagel (eluent 1% $MeOH/CH_2Cl_2$) to give the pure 2-methylcyclohexylamine (0.27 g, 82%). The ratio of the *cis/trans*-2-methylcyclohexylamines was 62/38 as determined by GC.[11] All the reductive amination products possessed physical characteristics that matched previously reported values.

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13. The ratio of *endo/exo* isomer was determined by GC using *exo*-2-aminonorbornane (Aldrich).
14. Norcamphor hydrazone may be able to form a complex with borohydride by forming a N-B bond through hydrogen evolution between the active hydrogen of hydrzones and borohydride. The reductive amination of *N, N*-dimethylhydrazone of norcamphor, which has no active hydrogen, gave pure *endo*-2-aminonorbornane in a 25% yield.