

**Figure 1.** ORTEP drawing<sup>7</sup> of *trans*-FeHCl(dppe)<sub>2</sub> showing the atom-labeling scheme and 50% probability thermal ellipsoids.

tra of this compound exhibit a singlet at  $\delta$  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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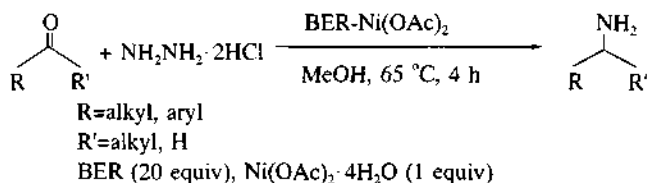
Reductive amination is an important transformation which allows the direct conversion of carbonyl compounds into the corresponding amines in chemical and biological systems.<sup>1</sup> It is commonly carried out using cyanoborohydrides<sup>2-4</sup> since the hydrides are stable under weakly acidic conditions which is essential for the formation of the imine intermediate. However, borane pyridine (BAP),<sup>5</sup> sodium triacetoxyborohydride,<sup>6</sup> and borohydride exchange resin (BER)<sup>7</sup> 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<sup>2b</sup> and BER.<sup>7</sup> 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.<sup>8</sup>

Recently, we have reported that BER-Ni(OAc)<sub>2</sub> in methanol is an excellent reducing system for azides<sup>9</sup> and nitro<sup>10</sup> 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)<sub>2</sub> 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<sub>3</sub>CN<sup>2(a)</sup> (entry 1). 2-Heptylamine was obtained in 87% yield, whereas only 25% yield was obtained using BER<sup>7</sup> in the presence of NH<sub>4</sub>OAc (entry 6). In the case of acetophenone, 1-phenethylamine was obtained in 77% yield, comparable yield with NaBH<sub>3</sub>CN (77%).<sup>2(a)</sup> 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)<sub>2</sub> 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 benzalacetone was simultaneously reduced to give 3-

### Scheme 1.



**Table 1.** Reductive Amination of Ketones and Aldehydes with Hydrazine using Borohydride Exchange Resin (BER)-Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O in Methanol

entry	substrate	product	yield (%) <sup>a</sup>
1	cyclohexanone	cyclohexylamine	88
2	2-methylcyclohexanone	2-methylcyclohexylamine	82 <sup>b</sup>
3	4- <i>tert</i> -butylcyclohexanone	4- <i>tert</i> -butylcyclohexylamine	88 <sup>b</sup>
4	cyclooctanone	cyclooctylamine	73
5	norcamphor	2-aminonorbornane	82 <sup>c</sup>
6	2-heptanone	2-heptylamine	87
7	4-heptanone	4-heptylamine	82
8	acetophenone	1-phenethylamine	77
9	benzalacetone	3-amino-1-phenylbutane	80
10	methyl 6-oxoheptanoate	methyl 6-aminoheptanoate	81
11	hexanal	hexylamine	(26), 58 <sup>d</sup>
12	benzaldehyde	benzylamine	70

<sup>a</sup> Isolated yields. Figures in parenthesis are GC yields. <sup>b</sup> The ratios of *cis/trans* isomers were 62/38 for 2-methylcyclohexylamines,<sup>11</sup> and 58/42 for 4-*tert*-butylcyclohexylamines.<sup>12</sup> <sup>c</sup> The ratio of *endo/exo* isomers was 86/14.<sup>13</sup> <sup>d</sup> The corresponding phenylhydrazone (3 mmol) reacted with BER (30 mmol) and Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O (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)<sub>2</sub> is inert to these functional groups.<sup>10</sup> 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<sub>3</sub>CN gave only *endo* isomer, this *exo* isomer may be formed by the intramolecular reduction of the norcamphor hydrazone borohydride complex.<sup>14</sup>

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<sub>2</sub>-NH<sub>2</sub>·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)<sub>2</sub>·4H<sub>2</sub>O (0.37 g, 1.5 mmol) to the mixture which was then, refluxed for 3 h. Additional BER (10.23 g, 30 mmol) and Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O

(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<sub>2</sub>Cl<sub>2</sub>) 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.<sup>11</sup> 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 hydrazones 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.