

# Transfer Hydrogenation of Imines Catalyzed by a Nickel(0)/NHC Complex

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**Summary:** Transfer hydrogenation of imines to the corresponding amines by  $Et_2CHONa$  catalyzed by the mono-coordinate Ni(0)/N-heterocyclic carbene species Ni(0)/IMes has been studied. Using this catalyst, a variety of aldimines and ketimines were reduced in good to excellent yields under mild conditions.

Catalytic reduction of polar functional groups such as ketones and imines mediated by transition-metal complexes has emerged as a complement to stoichiometric reduction by metal hydrides. Among the catalytic methods available for reduction, transfer hydrogenation has advantages over other processes in operational simplicity that avoids some of the technical and safety concerns associated with using hydrogen gas.<sup>1</sup>

The use of N-heterocyclic carbene (NHC) transition-metal complexes in catalysis is an area of intense current research activity.<sup>2</sup> On the basis of the accepted analogy between NHCs and trialkylphosphines (strong  $\sigma$ -donors and negligible  $\pi$ -accepting ability), many of these complexes have been targeted as catalysts in a variety of reactions, including the Suzuki–Miyaura reaction,<sup>3</sup> the Sonogashira reaction,<sup>4</sup> aryl amination,<sup>5</sup> and alkene metathesis.<sup>6</sup> The use of NHCs in transfer hydrogenation reactions has so far been limited. Only four examples of transfer hydrogenation reactions mediated by organometallic complexes containing NHCs have been reported. The use of transition-metal/NHC complexes in catalytic transfer hydrogenation was pioneered by Nolan.<sup>7</sup> The cationic iridium complex

[Ir(cod)(py)(ICy)]PF<sub>6</sub> (ICy = 1,3-bis(cyclohexyl)imidazol-2-ylidene) was found to be highly active for the reduction of ketones. Faller and Crabtree also developed new and air-stable iridium(III) bis(carbene) complexes, which were found to be active in the transfer hydrogenation of ketones.<sup>8</sup> C=N bonds are, however, more difficult to reduce than C=C and C=O bonds, and relatively few examples are known for their transfer hydrogenation. Perin and Danopoulos reported respectively the use of bis(carbene)rhodium(III) and tridentate pyridinobis(carbene)ruthenium(II) complexes for the transfer hydrogenation of ketones and imines.<sup>9,10</sup> Several organometallic complexes of ruthenium<sup>11</sup> and rhodium<sup>12</sup> bound with other ligands have been more commonly used for the transfer hydrogenation of these substrates. Finally, to the best of our knowledge, association of aluminum isopropoxide with W-2 Raney nickel is the only report of imine reduction by transfer hydrogenation under Ni catalysis.<sup>13</sup>

We have recently shown that Ni–carbene species can be formed in situ by reduction of a nickel(II) precursor with alkoxide-activated sodium hydride in the presence of imidazolium salts and demonstrated that the Ni(0)/NHC complexes obtained are efficient catalysts in various C–N coupling<sup>14</sup> and dehalogenation reactions.<sup>15</sup> In this contribution, we wish to report the development of Ni(0)/NHC complexes associated to a secondary alkoxide as the hydrogen source which catalyze the transfer hydrogenation of the C=N bond to give amines in high yields.

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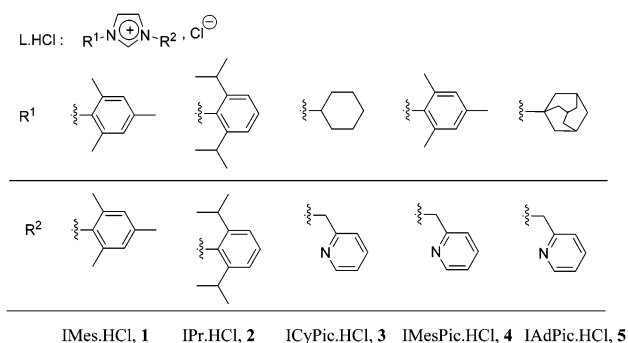
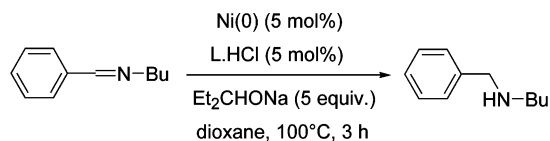
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Chart 1. Imidazolium Salts

Table 1. Reduction of Butyl(1-phenylmethylidene)amine Using Ni(0) with Various Carbene Precursors<sup>a</sup>

entry	ligand L	yield (%) <sup>b</sup>	entry	ligand L	yield (%) <sup>b</sup>
1	none	0	4	ICyPic (3)	86
2	IMes (1)	97	5	IMesPic (4)	15
3	IPr (2)	4	6	IAdPic (5)	5

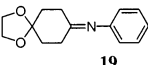
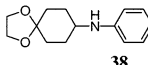
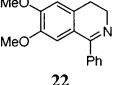
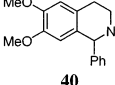
<sup>a</sup> Reaction conditions: 10 mmol of butyl(1-phenylmethylidene)amine, 0.5 mmol of Ni(0), 0.5 mmol of imidazolium chloride, 50 mmol of Et<sub>2</sub>CHONa, 12 mL of dioxane, 100 °C, 3 h. <sup>b</sup> Isolated yields (average of two runs).

In optimization studies, we selected as the model reaction the reduction of the butyl(1-phenylmethylidene)amine to benzylbutylamine in the presence of Ni(0)/NHC catalysts using Et<sub>2</sub>CHONa as the hydrogen donor. In an effort to select the most effective imidazolium salt, a series of 1,3-disubstituted imidazolium chlorides (Chart 1) were used in the test reaction.

The results, given in Table 1, show the influence of the nature of R1 and R2 groups on catalyst activity. The use of IMes (1)<sup>16</sup> or the bidentate ligand ICyPic (3) led to highly efficient transfer hydrogenation reactions (entries 2 and 4). Substitution of IMes with the more electron-donating and bulkier IPr resulted in a dramatic decrease in activity (entry 3). The same trend was also observed with bidentate pincer carbenes 3–5. The reduced steric demand of the ICyPic (3) system, compared to IMesPic (4) (entry 5) and IAdPic (5) (entry 6), affords a catalyst with higher activity in transfer hydrogenation reactions.

The reaction rates also proved to be influenced by the identity of the base used in the reaction. The role of the alkoxide is 3-fold: (i) it deprotonates the imidazolium chloride to form the free carbene ligand which can coordinate to nickel, (ii) it activates sodium hydride used for the in situ reduction of Ni(acac)<sub>2</sub> into Ni(0), and (iii) possessing a β-hydrogen, it acts as a hydrogen donor. The highest activity was achieved with Et<sub>2</sub>CHONa as the base (see the Supporting Information). The base typically used in transfer hydrogenation reactions, *i*-PrONa, led only to a moderately active catalyst. Other secondary alkoxides resulted in lower yields. Further optimization experiments showed that the use of 5 equiv

Table 2. Ni(0)/IMes-Catalyzed Transfer Hydrogenation of Imines with Et<sub>2</sub>CHONa<sup>a</sup>

entry	substrate	product	time (h) <sup>b</sup>	yield (%) <sup>c</sup>
1	PhCH=N-Bu, 6	PhCH <sub>2</sub> NH-Bu, 25	3	97
2	PhCH=NCH <sub>2</sub> CH <sub>2</sub> Ph, 7	PhCH <sub>2</sub> NHCH <sub>2</sub> CH <sub>2</sub> Ph, 26	4	99
3	Ph-N=C(Et) <sub>2</sub> , 8	Ph-NHCH(Et) <sub>2</sub> , 27	7	85
4	PhC(Me)=N-Ph, 9	PhCH(Me)NH-Ph, 28	1.5	89
5	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> -N=C-C <sub>7</sub> H <sub>13</sub> , 10	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> -NH-C-C <sub>7</sub> H <sub>13</sub> , 29	6	87
6	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> -N=C-C <sub>6</sub> H <sub>10</sub> , 11	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> -NH-C-C <sub>6</sub> H <sub>10</sub> , 30	3	89
7	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> -N=C-C <sub>5</sub> H <sub>8</sub> , 12	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> -NH-C-C <sub>5</sub> H <sub>8</sub> , 31	4	90
8	<i>m</i> -Me-C <sub>6</sub> H <sub>4</sub> -N=C-C <sub>5</sub> H <sub>8</sub> , 13	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> -NH-C-C <sub>5</sub> H <sub>8</sub> , 32	6	87
9	<i>o</i> -Me-C <sub>6</sub> H <sub>4</sub> -N=C-C <sub>5</sub> H <sub>8</sub> , 14	<i>o</i> -Me-C <sub>6</sub> H <sub>4</sub> -NH-C-C <sub>5</sub> H <sub>8</sub> , 33	15	65
10	2-Nap-C(Me)=N-Ph, 15	2-Nap-CH(Me)NH-Ph, 34	7	94
11	<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> -N=CPH <sub>2</sub> , 16	<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> -NHCHPh <sub>2</sub> , 35	9	86
12	<i>p</i> -OMe-C <sub>6</sub> H <sub>4</sub> -N=C(Me)CH <sub>2</sub> CH <sub>2</sub> CH=CMMe <sub>2</sub> , 17	<i>p</i> -OMe-C <sub>6</sub> H <sub>4</sub> -NHCH(Me)CH <sub>2</sub> CH <sub>2</sub> CH=CMMe <sub>2</sub> , 36	6	80
13	C <sub>6</sub> H <sub>5</sub> CH=N-C <sub>6</sub> H <sub>4</sub> - <i>m</i> -CF <sub>3</sub> , 18	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NH-C <sub>6</sub> H <sub>4</sub> - <i>m</i> -CF <sub>3</sub> , 37	3.5	89
14			6	87
15	<i>p</i> -NC-C <sub>6</sub> H <sub>4</sub> -C(Me)=N-C <sub>6</sub> H <sub>4</sub> - <i>p</i> -OMe, 20	<i>p</i> -NC-C <sub>6</sub> H <sub>4</sub> -CH(Me)NH-C <sub>6</sub> H <sub>4</sub> - <i>p</i> -OMe, 39	15	0
16	PhC(Me)=N-C <sub>6</sub> H <sub>4</sub> - <i>p</i> -Cl, 21	PhCH(Me)NH-C <sub>6</sub> H <sub>5</sub> , 28	1	94
17			7	84
18	<i>c</i> -C <sub>6</sub> H <sub>10</sub> =N-C-C <sub>6</sub> H <sub>11</sub> , 23	<i>c</i> -C <sub>6</sub> H <sub>11</sub> -NH-C-C <sub>6</sub> H <sub>11</sub> , 41	36	78
19	C <sub>6</sub> H <sub>5</sub> -CH=N-CH <sub>2</sub> -2-Py, 24	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub> -N-CH <sub>2</sub> -2-Py, 42	15	0

<sup>a</sup> Reaction conditions: 10 mmol of imine, 0.5 mmol of Ni(0), 0.5 mmol of IMes·HCl (1), 50 mmol of Et<sub>2</sub>CHONa, 12 mL of dioxane, 100 °C. <sup>b</sup> Determined by GC analysis. <sup>c</sup> Yields are of isolated and purified products.

of Et<sub>2</sub>CHONa relative to the starting imine was more effective for the transfer hydrogenation reaction.

Screening experiments revealed also that best results were obtained in ethereal solvents (such as dioxane, DME, and THF). The highest catalytic activity was achieved in refluxing dioxane (97% yield in 3 h, Table 1, entry 2). Reactions run in THF or DME required longer reaction times (7–11 h). Finally, modification of the solvent/base system had dramatic effects. The Ni(0)/IMes or Ni(0)/ICyPic complexes were inactive when Et<sub>2</sub>CHOH was used as solvent or when Et<sub>2</sub>CHOH was associated to a base such as NaOH or KOH.

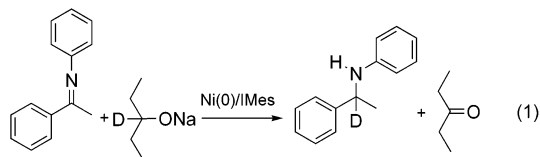
Since the complex Ni(0)/IMes displayed the highest activity of the complexes tested, it was investigated as a catalyst for hydrogen transfer from Et<sub>2</sub>CHONa to a number of imines.<sup>17</sup> The scope of the reaction is shown in Table 2. As indicated, except in one case (entry 15), the reduction of aldimines and ketimines proceeds rapidly in good to excellent yields under the general conditions previously outlined. Aldimines (entries 1, 2, and 13), however, reacted faster than ketimines. This is also the normal order of reactivity for the reduction of imines with hydride reagents.<sup>18</sup>

(16) IMes·HCl (1) is commercially available from Strem Chemicals.

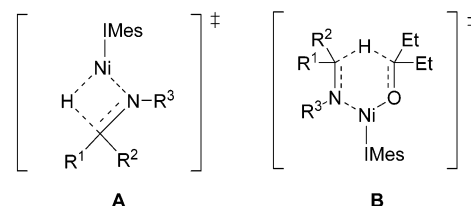
*N*-aryl imines prepared from small aliphatic cyclic and acyclic ketones (cyclopentanone, cyclohexanone, and diethyl ketone, entries 3 and 6–9) were most reactive while cycloheptylidene(4-methylphenyl)amine (**10**) (entry 5) reacted somewhat slower. Steric hindrance at the reaction center slowed the imine reduction (compare entries 7–9), this being an indication of coordination between the substrate and the Ni(0)/IMes catalyst along the reaction course. Carbon–carbon multiple bonds (entry 12) and trifluoromethyl groups (entry 13) are well-tolerated, and the Ni-catalyzed transfer hydrogenation can be performed in the presence of acid-sensitive functional groups such as ketals (entry 14). The method was also found useful in the reduction, producing 1-aryl-substituted tetrahydroquinolines (entry 17) and dialkylamines (entry 18). With chloroimine **21** (entry 16), the imine and the carbon–chlorine functions are both reduced. Complete reduction of compound **21** was achieved in 1 h. Sampling reveals that the dechlorinated imine **9** is the major intermediate (95% after 20 min). This observation is in agreement with our previous results on Ni(0)/NHC-mediated dehalogenation.<sup>15a</sup>

The variations of the substrates described in Table 2 were used to elucidate the mechanism of the reaction. While the presence of one or two methoxy groups on the aromatic ring had no influence on the reactivity of the imine, a strong decrease of the rate was observed with 4-(phenylethanimidoyl)benzotrile **20** (entry 15). We assume that the imine nitrogen binding with the Ni(0)/IMes complex is strongly inhibited by the cyano group. An independent run performed with butyl(1-phenylmethylidene)amine (**6**) and 1 mol equiv of benzotrile supports this hypothesis, and the observed conversion of the starting imine was significantly reduced (5% after 3 h). It is therefore no surprise that transfer hydrogenation of the pyridyl imine **24** (entry 19) was similarly unsuccessful, due to the pyridyl nitrogen poisoning of the catalyst. Extended reaction times or higher catalyst loadings (10 or 20 mol %) do not change yields significantly. These results clearly indicate that coordination of the imine to nickel comes into the rate expression.

By deuterium labeling of the donor alkoxide and using phenyl(1-phenylethylidene)amine (**9**) as the acceptor, we demonstrate that Et<sub>2</sub>CHONa is the main hydrogen donor in hydrogen transfer reactions catalyzed by the Ni(0)/IMes/Et<sub>2</sub>CHONa combination. From the <sup>1</sup>H NMR and GC-MS analyses, the actual content of D atoms in phenyl(1-phenylethyl)amine (**28**) could be estimated to be superior to 90% of the theoretical content (eq 1).



The deuterium isotope effect for the catalytic hydrogen transfer of phenyl(1-phenylethylidene)amine (**9**) was also determined. The initial rate was measured (between 0 and 1 h) for both the deuterated<sup>19</sup> and the



**Figure 1.** Proposed transition states for Ni(0)/NHC catalyzed transfer hydrogenation of imines.

nondeuterated sodium pentane 3-alkoxide of in the transfer hydrogenation of imine **9** to amine **28**. The initial rate using nondeuterated sodium pentane 3-alkoxide was  $k_{\text{obs}} = (1.7 \pm 0.2) \times 10^{-6} \text{ mol s}^{-1}$ , and for the sodium 3-deuteriopentane 3-alkoxide  $k_{\text{obs}} = (4.4 \pm 0.2) \times 10^{-7} \text{ mol s}^{-1}$ . The deuterium isotope effect of the reaction was therefore  $k_{\text{H/D}} = 3.9 \pm 0.2$ . This result suggests that the elimination of the hydrogen in Et<sub>2</sub>CHONa or  $\beta$ -elimination from a nickel alkoxide to give a nickel hydride is the rate-determining step of the Ni(0)/IMes-catalyzed transfer hydrogenation reaction.

While a detailed reaction mechanism still remains to be established, it has been demonstrated that, in the presence of transition metals, the transfer hydrogenation occurs via a metal hydride which undergoes hydride transfer with a coordinated imine (Figure 1, transition state A).<sup>1</sup> However, a hydrogen transfer between the alkoxide and the imine occurring via metal alkoxides through the six-membered transition state B classically depicted for Meerwein–Ponndorf–Verley reductions could also be considered.

In summary, we have demonstrated that the association of nucleophilic *N*-heterocyclic carbenes with Ni(0) affords active catalysts in transfer hydrogenation. The Ni(0)/IMes complex is particularly effective in hydrogen transfer from Et<sub>2</sub>CHONa with imines and compares favorably with Rh, Ru, or Ir complexes described in the literature. The Ni(0)/IMes catalyst was shown to be tolerant of sterically hindered substrates. Since Ni(0) coordination to the C=N double bond is the most likely route for these hydrogen transfer reactions, we intend to develop an asymmetric reduction process in the presence of a chiral alkoxide and/or NHC ligand.

**Supporting Information Available:** Text giving the experimental procedures and characterization data for compounds **24**–**41**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) In a typical catalytic run, a 50 mL Schlenk tube was loaded with degreased NaH (36.05 mmol), Ni(acac)<sub>2</sub> (0.35 mmol), IMes·HCl (**1**; 0.35 mmol), and 8 mL of dioxane, and the mixture was heated at 100 °C. A solution of pentan-3-ol (35 mmol) in 4 mL of dioxane was then added dropwise, and the mixture was further heated for 1/2 h. The imine (7 mmol) in 4 mL of dioxane was then added dropwise, and the reaction was monitored by GC. After consumption of the starting material, the reaction mixture was cooled to room temperature and adsorbed onto silica. Purification was achieved by silica gel chromatography.

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