Highly Selective Reduction of $\alpha$, $\beta$-Unsaturated Aldehydes and Ketones under Ambient Conditions using Tetraalkylphosphonium-based Ionic Liquids

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An efficient and green protocol for highly selective reduction of $\alpha$, $\beta$-unsaturated aldehydes and ketones at room temperature is described in a range of ionic liquids, in the absence of noble metal catalysts, by using NaBH$_4$ as reducing agent. Most notably, using $[\text{P}_{4}\text{Et$_3$$_4}$][\text{Ni(CN)$_3$}]$ ionic liquid, in absence of organic solvent, within 10 min, 97% conversion of cinnamaldehyde was achieved with 100% selectivity towards cinnamyl alcohol. The ionic liquid was easily recycled without any noticeable decline in activity. The reduction protocol was further extended to a variety of $\alpha$, $\beta$-unsaturated aldehydes and ketones.

Introduction

The selective hydrogenation of $\alpha$, $\beta$-unsaturated aldehydes and ketones is of high importance in the fine chemical industry especially in the production of pharmaceuticals, fragrances and flavours. Chemo selective hydrogenation of $\alpha$, $\beta$-unsaturated aldehydes and ketones has been extensively studied, especially using noble metal based catalysts with molecular hydrogen. However, hydrogenation utilizing petroleum-derived H$_2$ is neither entirely green nor economic because it requires high pressure H$_2$, costly reactor equipment and precious metal based catalysts, which increases process costs. From the range of metal catalysts studied; palladium, rhodium and copper based catalysts have shown higher selectivity towards the reduction of the C=C group; while, ruthenium, platinum and nickel catalysts have shown higher selectivity for reduction of the carbonyl group. Also, it can be difficult to prevent the formation of the fully saturated alcohol formed further by subsequent reduction of unsaturated alcohol.

In current industrial practice, the reduction of $\alpha$, $\beta$-unsaturated aldehydes and ketones is performed either under high hydrogen pressures using supported metal based catalysts or by hydrogen transfer reaction using alcohol as hydride donor. High pressure hydrogenation shows lower selectivity since C=C double bond reduction is thermodynamically favoured over carbonyl bond reduction; while hydrogen transfer produces by-products and has lower atom-efficiency besides producing ketone along with the desired unsaturated alcohol. Another attractive alternative for reduction of aldehydes and ketones is by using sodium borohydride, NaBH$_4$, as reducing agent, owing to its ready availability, high stability and easy downstream work-up. Although the use of NaBH$_4$ is known over seven decades, the reaction rates are often low, leading to the use of a stoichiometric excess of NaBH$_4$. In this context, the development of efficient chemoselective methods for reduction of aldehydes and ketones continues to be desirable. The key parameters sought are the use of mild reaction conditions and high selectivity to the desired product. In continuation to our interest in chemoselective reductions, in this study, we have investigated the reduction of $\alpha$, $\beta$-unsaturated aldehydes and ketones, using cinnamaldehyde as the model substrate under ambient conditions (temperature 20 $\degree$C, atmospheric pressure), in a range of ionic liquids, by using sodium borohydride as reducing agent. The selective hydrogenation of cinnamaldehyde at the C=O group produces cinnamyl alcohol; an important building block in organic and pharmaceutical synthesis. The selective reduction of cinnamaldehyde at the C=C double bond produces hydrocinnamaldehyde, which has a floral odour that gives cinnamon its flavour and is widely used in perfumery.

Ionic liquids have been extensively studied as solvents for a wide range of chemical reactions over the years. This interest is due to the diverse physical properties of these liquids and their tunability. Physical properties that can be tailored to suit the requirements of a process include; viscosity, solubility, melting point, density and hydrophobicity of the ionic liquid. A wide range of reactions has been performed in ionic liquids.
including hydrogenations,\(^6\) coupling reactions,\(^7\) epoxidations,\(^8\) hydroformylation,\(^9\) carbonylation,\(^10\) polymerization,\(^11\) biocatalysis,\(^12\) electrochemistry,\(^13\) synthesis of 5-(hydroxymethyl)furfural\(^14\) and alkylations.\(^15\) Ionic liquids have also been used as nanosynthetic templates to stabilize the metal nanoparticles on the basis of the ionic charge and supramolecular network.\(^16\) Metal nanoparticles stabilized in ionic liquids can then be used as catalysts.

Hardacre et al. have reported selective hydrogenation of cinnamaldehyde and citral using 10% Pd/C as a catalyst, in a range of ionic liquids and organic solvents.\(^17\) In presence of ionic liquids, selectivity was higher towards the reduction of the C=C group. For instance, after 240 min the selectivity towards hydrocinnamaldehyde in the presence of different ionic liquids was ~97% vs-φ-vis 79–85% in organic solvents. However, the reactions in ionic liquid were found to proceed slower than in organic solvents. At 5 bar H\(_2\) and 30°C in toluene, dioxane, and cyclohexane, 100% conversion of cinnamaldehyde is obtained in 45 min, compared to 240 min in 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl) amide ([C\(_4\)Mim][NTf\(_2\)]) ionic liquid.

Behrens et al. prepared Pt–Sn nanoparticles in methyltriocetylarnonium bis(trifluoromethylsulfonyl) imide ([OMA][NTf\(_2\)]) ionic liquid and studied the hydrogenation of cinnamaldehyde.\(^18\) Using monometallic Pt nanoparticles in the ionic liquid at 10 bar H\(_2\) pressure and 80°C after 22 h just 9% conversion was achieved with 100% selectivity to hydrocinnamaldehyde. However, using bimetallic Pt/Sn nanoparticles in a 3:1 ratio, after 22 h under the same conditions, the conversion had increased up to 84% and the reaction was 80% selective to cinnamyl alcohol. In the monometallic system, the cinnamaldehyde preferentially adsorbs to Pt by π complexing to the C=C bond and yields the reduction of the C=C bond. While in the bimetallic system, the Pt has been alloyed with Sn, which results in lowering of the binding energy of C=C bond. Hence the C=O bond undergoes reduction to give cinnamyl alcohol product.

Virtanen et al. have reported selective reduction of C=C double bond in the hydrogenation of cinnamaldehyde to hydrocinnamaldehyde using supported ionic liquid catalysts (SILCs) using two different ionic liquids, 1-butyl-3-methylimidazolium hexafluorophosphate ([C\(_4\)Mim][PF\(_6\)]) and N-butyl-4-methylpyridinium tetrafluoroborate ([C\(_4\)M4Py][BF\(_4\)]); in presence of palladium particles on active carbon cloth.\(^19\) Amongst the two SILCA catalysts, the system containing [C\(_4\)M4Py][BF\(_4\)] ionic liquid showed higher reaction rate but slightly lower selectivity to hydrocinnamaldehyde (81%). The SILCA catalyst containing [C\(_4\)Mim][PF\(_6\)] displayed higher selectivity to hydrocinnamaldehyde (84%) but showed poor activity. The activity was significantly lower than the catalyst system even in the absence of ionic liquid. The lower activity has been attributed to a lower value for the hydrogen adsorption coefficient for [C\(_4\)Mim][PF\(_6\)] ionic liquid hence the poorer solubility of hydrogen.

Herein, we report the selective hydrogenation of α, β-unsaturated aldehydes in a range of ionic liquids, in the absence of noble metals at room temperature (20°C). Ionic liquids can be easily recovered and reused without any loss of activity. The selective reduction of cinnamaldehyde to cinnamyl alcohol was chosen as a model reaction to optimise the reaction conditions. The reaction scheme and the range of products expected for cinnamaldehyde hydrogenation is given in Figure 1.

![Figure 1. Reaction pathway for reduction of cinnamaldehyde to various products.](image1)

### Results and Discussion

#### Cinnamaldehyde reduction

A typical reaction composition time profile for the hydrogenation of cinnamaldehyde in [P\(_6\),6,6,6,6,14][N(CN)\(_3\)] ionic liquid is shown in Figure 2. Table 1 summarises additional results of the hydrogenation of cinnamaldehyde in a range of ionic liquids giving the product selectivity and conversions after 40 min. In all cases, cinnamyl alcohol was the major product and the balance was made up of hydrocinnamyl alcohol. The reactions...
in the presence of ionic liquids had a dramatically enhanced rate than when the reaction was conducted in the absence of ionic liquid. For example, in the absence of ionic liquid (blank) after 40 min the conversion was just 5% (Entry 1), while in the presence of ionic liquids the conversion was 83% and selectivity towards cinnamyl alcohol was 97% (Entry 2). This reaction was further improved by allowing the ionic liquid and the substrate to equilibrate for 1 h before addition of NaBH₄ (Entry 3). The cinnamaldehyde conversion was increased to 97% and the cinnamyl alcohol selectivity to 99%. The observed reaction rate enhancement may be attributed to the increased mass transfers of cinnamaldehyde from organic phase and BH₄⁻ from aqueous phase to the ionic liquid phase. Sodium borohydride is known to be a nucleophilic reagent, which is an efficient source of nucleophilic BH₄⁻. It is likely that the ionically charged supramolecular network of ionic liquids greatly accelerates the nucleophilic substitution (SN₂) reaction not only by enhancing the hydride transfer from aqueous phase, but also increasing the stability of hydride anion. Further mechanistic studies are required to understand the influence of presence of ionic liquid structure on the stability and diffusivity of hydride ions. In a separate experiment, the presence of Co in the ionic liquid was found to further increase the conversion and reaction rate, but resulted in a drop in the selectivity. For example after 40 min, with [P₆₆₆₆][Co(N(CN))₄] the conversion of cinnamylaldehyde increased to 97% from 83% for [P₆₆₆₆][N(CN)] in the absence of Co. The selectivity decreased from 97% for [P₆₆₆₆][N(CN)] to 84% in the presence of Co. In literature, the use of additives, such as Co(II), Zn(II), Pd(II), Rh(III) halides along with sodium borohydride is known to reduce functional groups such as nitriles, amides and olefins, which are inert to NaBH₄ alone.20 The effect of Co loading in the ionic liquid was also investigated. In the [P₆₆₆₆][Co(N(CN))₄] ionic liquid there is around 4% Co, this was reduced to 2% in the [P₆₆₆₆][Co(N(CN))₄]: 2[P₆₆₆₆][N(CN)] ionic liquid. It was found that there was only a slight drop in conversion and selectivity compared to the ionic liquid with 4% Co. In the case of the Co containing ionic liquid as the reaction progresses, acetol formation was observed and confirmed by GC-MS. The formation of the acetol results in the reduced selectivity of the Co ionic liquids. Both [P₆₆₆₆][NTf₂] and [C₆CNmin][FeCl₄] ionic liquids performed poorly in the reduction of cinnamaldehyde (Entries 6 and 7), after 40 min the conversions were 25% and 11% respectively, with cinnamyl alcohol as the major product.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ionic liquid</th>
<th>Conversion (%)</th>
<th>Selectivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>blank</td>
<td>5</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>[P₆₆₆₆][N(CN)]</td>
<td>83</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>[P₆₆₆₆][N(CN)]</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>[P₆₆₆₆][Co(N(CN))₄]</td>
<td>97</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>[P₆₆₆₆][Co(N(CN))₄]: 2[P₆₆₆₆][N(CN)]</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>[P₆₆₆₆][NTf₂]</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>[C₆CNmin][FeCl₄]</td>
<td>11</td>
<td>85</td>
</tr>
</tbody>
</table>

Reactions conditions: Cinnamaldehyde 3.97 mmol, dibutyl ether 15 ml, deionized water 1.3 ml, [P₆₆₆₆][N(CN)] 0.5 ml, NaBH₄ 3.97 mmol, temperature 20°C, reaction time 40 min. Cinnamaldehyde and ionic liquid were stirred for 1 hr before addition of NaBH₄.

The hydrogenation of cinnamaldehyde was also investigated in [P₆₆₆₆][N(CN)] in the absence of dibutyl ether solvent. In the absence of solvent the results were significantly enhanced. After just 10 min the conversion was 97% with 100% selectivity towards cinnamyl alcohol (Figure 4). To the best of
our knowledge, such high selectivities at room temperature, without using noble metal catalysts, are unprecedented in literature and hold high significance for speciality and fine chemical industry.

Reusability study
The reusability of the \([\text{P}6,6,6,14]\)[N(CN)2] ionic liquid was established by carrying out 4 runs of cinnamaldehyde reduction (Table 2). For each recycle experiment, fresh feed of cinnamaldehyde and NaBH4 was added to the reaction mixture, at the end of reaction on complete conversion of cinnamaldehyde. In the reusability study, the ionic liquid was not isolated from the reaction mixture. This method for recycle study was adopted to avoid any loss of ionic liquid due to attrition since very small amount of ionic liquid was used in the reduction experiments. As shown in Figure 4, the 1st recycle run, showed significant enhancement in reaction rate, as compared to the fresh cycle. This improvement was ought to be the outcome of an increased liquid-liquid mass transfer from organic phase into the ionic liquid phase. This was validated by performing a control experiment, wherein organic phase containing cinnamaldehyde was pre-mixed with ionic liquid and stirred for 1 hour to equilibrate before addition of NaBH4. This showed significant increase in reaction rate for cinnamaldehyde reduction. In all recycle experiments, selectivity to cinnamyl alcohol stayed consistently in the range of 96–99%. \([\text{P}6,6,6,14]\)[N(CN)2] ionic liquid showed excellent reusability with high selectivity to cinnamyl alcohol.

Table 2. Reusability of \([\text{P}6,6,6,14]\)[N(CN)2] ionic liquid in the reduction of cinnamaldehyde.

<table>
<thead>
<tr>
<th>Reuse</th>
<th>Cinnamaldehyde Conversion (%</th>
<th>Cinnamyl alcohol Selectivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh IL</td>
<td>89</td>
<td>98</td>
</tr>
<tr>
<td>1st reuse</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>2nd reuse</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>3rd reuse</td>
<td>99</td>
<td>96</td>
</tr>
</tbody>
</table>

Reaction conditions: Cinnamaldehyde 3.97 mmol, dibutyl ether 15 cm³, \([\text{P}6,6,6,14]\)[N(CN)2] 0.5 cm³, NaBH4, 0.15 g in deionized water 1.3 cm³, temp. 20°C, reaction time 1 hr.

Substrate study with \([\text{P}6,6,6,14]\)[N(CN)2] and solvent
The scope of the reduction protocol developed above was further extended to the hydrogenation of other \(\alpha,\beta\)-unsaturated aldehydes and ketones including ketoisophorone, 2-cyclohexen-1-one, citral and trans-4-phenyl-3-buten-2-one using the \([\text{P}6,6,6,14]\)[N(CN)2] ionic liquid (Table 3). Similar, to the

Table 3. Substrate study with various ionic liquids.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Major Product</th>
<th>([\text{P}6,6,6,14])[N(CN)2] + solvent (60 min)</th>
<th>([\text{P}6,6,6,14])[N(CN)2] solvent free (10 min)</th>
<th>([\text{P}6,6,6,14])[Co(N(CN)2)3] solvent free (10 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conv. (%)</td>
<td>Sel. (%)</td>
<td>Conv. (%)</td>
</tr>
<tr>
<td>1</td>
<td>Cinnamaldehyde</td>
<td>Cinnamyl alcohol</td>
<td>89</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>Ketoisophorone</td>
<td>4-hydroxyisophorone</td>
<td>100</td>
<td>97</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>Citral (geraniol &amp; nerol)</td>
<td>geraniol &amp; nerol</td>
<td>86</td>
<td>82</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>2-cyclohexen-1-one</td>
<td>cyclohexanone</td>
<td>100</td>
<td>58</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>Trans-4-phenyl-3-buten-2-one</td>
<td>4-phenyl-2-butanol</td>
<td>41</td>
<td>75</td>
<td>12</td>
</tr>
</tbody>
</table>

*cyclohexanol product
cinnamaldehyde hydrogenation, the reduction of ketoisophorone (Entry 2) was completed within less than 1 hour with 97% selectivity to the alcohol product; 4-hydroxyisophorone. 4-Hydroxyisophorone is a volatile constituent of saffron, a flavour and fragrance in foods and a very useful intermediate in synthesis of various pharmaceuticals.

Ketoisophorone is a difficult molecule to reduce with high selectivity, due to the presence of multiple functionalities in the aromatic ring. In case of citral hydrogenation (Entry 3), after 1 h, 86% conversion was achieved with 82% selectivity towards the unsaturated alcohols, geraniol and nerol. The hydrogenation of 2-cyclohexene-1-one (Entry 4) was complete in 1 h, with 100% conversion achieved, however a mixture of products were obtained. The product mixture consisted of 58% cyclohexanol and 41% cyclohexanone, where both the C=C and C=O bond have undergone reduction. The mixture of cyclohexanol and cyclohexanone is also known as KA oil, Ketone-Alcohol oil, and is the highly useful precursor to adipic acid, which is the monomer for production of nylon. The hydrogenation of trans-4-phenyl-3-buten-2-one, which is a more difficult to reduce ketone, was slower compared to cinnamaldehyde hydrogenation, the reduction of ketoisophorone was completed within less than 1 hour with 97% with [P\textsubscript{6,6,6,14}][N(CN)\textsubscript{2}] ionic liquid resulting in 97% conversion of cinnamaldehyde with 100% selectivity to cinnamyl alcohol. The rate of hydrogenation was greatly enhanced in ionic liquid in the absence of organic solvent. [P\textsubscript{6,6,6,14}][N(CN)\textsubscript{2}] ionic liquid was easily recycled, and upon recycle, it showed increased reaction rates without any noticeable loss of selectivity. Using [P\textsubscript{6,6,6,14}][N(CN)\textsubscript{2}] the method was successfully extended to other of α,β-unsaturated aldehydes and ketones.

Substrate study with [P\textsubscript{6,6,6,14}][N(CN)\textsubscript{2}]

The reduction of α,β-unsaturated aldehydes and ketones was also investigated in the absence of dibutyl ether. The reactions in the absence of solvent were considerably faster than in the presence of solvent. In the case of cinnamaldehyde reduction, in the absence of solvent, after 10 mins the cinnamaldehyde conversion was 97% compared to 89% conversion after 60 min, in the presence of dibutyl ether, furthermore the selectivity to cinnamyl alcohol was 100%. Also, for all other substrates studied, the reactions proceeded much faster in the absence of dibutyl ether.

Substrate study with [P\textsubscript{6,6,6,14}][Co(N(CN)\textsubscript{2})\textsubscript{2}]

The reduction of α,β-unsaturated aldehydes and ketones was also investigated with [P\textsubscript{6,6,6,14}][Co(N(CN)\textsubscript{2})\textsubscript{2}] ionic liquid in the absence of dibutyl ether. In case of the reduction of cinnamaldehyde, in contrast to using solvent (Table 1, Entry 4), enhanced reaction rate and high selectivity to cinnamyl alcohol (99%) was observed. In the case of ketoisophorone, there was significant increase in selectivity towards 4-hydroxyisophorone, from 82% with [P\textsubscript{6,6,6,14}][N(CN)\textsubscript{2}] to 91% with [P\textsubscript{6,6,6,14}][Co(N(CN)\textsubscript{2})\textsubscript{2}]. Using [P\textsubscript{6,6,6,14}][Co(N(CN)\textsubscript{2})\textsubscript{2}] in the reduction of citral, the conversion was reduced from 62% with [P\textsubscript{6,6,6,14}][N(CN)\textsubscript{2}] to 26% with the Co containing ionic liquid. There was a similar trend in the reduction of 2-cyclohexen-1-one, in which the conversion was reduced from 89% with [P\textsubscript{6,6,6,14}][N(CN)\textsubscript{2}] to 57% with the Co ionic liquid. Interestingly the reverse was observed in the case of trans-4-phenyl-3-buten-2-one, where the conversion increased from 12% with [P\textsubscript{6,6,6,14}][N(CN)\textsubscript{2}] to 20% with the Co ionic liquid, however, there was a slight drop in selectivity from 71% to 64% respectively.

Conclusions

Highly selective hydrogenation protocol for reduction of a range of α,β-unsaturated aldehydes and ketones, has been developed in presence of ionic liquids by using NaBH\textsubscript{4} as reducing agent. Amongst the ionic liquids evaluated, [P\textsubscript{6,6,6,14}][N(CN)\textsubscript{2}] ionic liquid showed the best activity and selectivity for reduction of cinnamaldehyde to cinnamyl alcohol in presence of dibutyl ether as solvent. In the absence of any organic solvent, just using [P\textsubscript{6,6,6,14}][N(CN)\textsubscript{2}] ionic liquid resulted in 97% conversion of cinnamaldehyde with 100% selectivity to cinnamyl alcohol. The rate of hydrogenation was greatly enhanced in ionic liquid in the absence of organic solvent. [P\textsubscript{6,6,6,14}][N(CN)\textsubscript{2}] ionic liquid was easily recycled, and upon recycle, it showed increased reaction rates without any noticeable loss of selectivity. Using [P\textsubscript{6,6,6,14}][N(CN)\textsubscript{2}] the method was successfully extended to other of α,β-unsaturated aldehydes and ketones.

Supporting Information Summary

General information, experimental procedures and characterization data are available in the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** α,β-Uunsaturated aldehydes and ketones · Mild reaction conditions · Reactions in ionic liquid · Selective reduction · Sodium borohydride


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