Nanoparticle Catalysis

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A Rhodium Nanoparticle–Lewis Acidic Ionic Liquid Catalyst for the Chemoselective Reduction of Heteroarenes

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Abstract: *We describe a catalytic system composed of rhodium nanoparticles immobilized in a Lewis acidic ionic liquid. The combined system catalyzes the hydrogenation of quinolines, pyridines, benzofurans, and furan to access the corresponding heterocycles, important molecules present in fine chemicals, agrochemicals, and pharmaceuticals. The catalyst is highly selective, acting only on the heteroaromatic ring, and not interfering with other reducible functional groups.*

Catalytic hydrogenation reactions of specific functional groups, such as carbonyl, alkene, alkyne, imine, and nitro, are very important in synthetic chemistry.[1] The direct hydrogenation of heteroarenes is particularly challenging owing to their high stability and the ability of heteroatoms to deactivate catalysts.[2] Nevertheless, the hydrogenated products of heteroarenes are commonly encountered in fine chemicals, agrochemicals, and pharmaceuticals. In particular, quinolines are an important class of compound for accessing tetrahydroquinoline products that are widely found in drug molecules (Figure 1).[3]

Homogeneous pre-catalysts mainly based on Ru, Rh, and Ir have been used for the direct hydrogenation of quinoline. Unfortunately, they tend to require harsh reaction conditions or the presence of a stoichiometric amount of co-catalyst, which hinders reuse.[4]

In contrast, heterogeneous catalysts appear to be much more versatile for quinoline hydrogenation as they can be recycled and reused.[5] Numerous heterogeneous catalysts based on Pt, Ni, Au, and Pd have been reported in recent years.[6] Supported Rh nanoparticles (NPs) immobilized on Al_2O_3, rare earth oxides, and aluminum oxyhydroxide were also found to hydrogenate quinoline.[7] However, the complete conversion of quinoline substrates requires harsh reaction conditions, that is, up to 200 °C and 50 bar H_2. Therefore, selective heterogeneous catalysts that operate under less forcing conditions would be useful (Scheme 1).

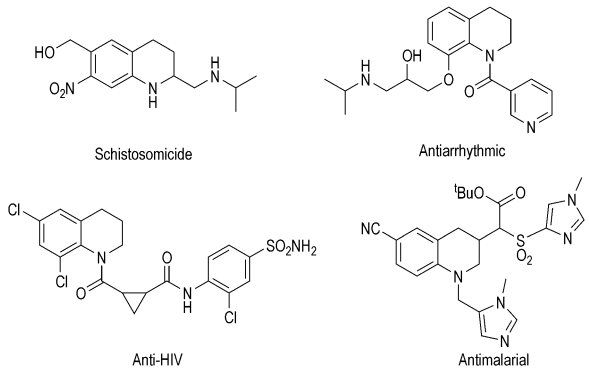
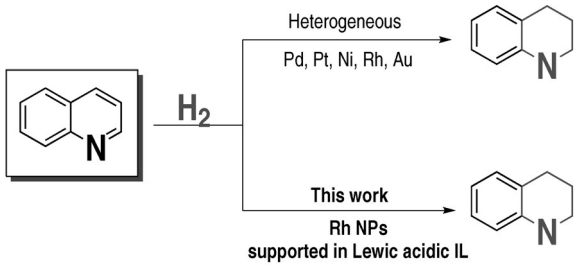


Figure 1. Examples of pharmaceuticals containing the tetrahydroquinoline unit.



Scheme 1. Different heterogeneous catalysts employed for the hydrogenation of quinoline.

The nature of the solid-support material plays a critical role in the hydrogenation reaction and, in this respect, we appreciated that ionic liquids (ILs) may not only act as a support and stabilizer for the NPs, providing rotational freedom and access to the entire NP surface, but also that they can actively participate in the reaction, similar to an active solid support.[8] Notably, ILs that are catalytically active in their own right have been shown to work cooperatively with dispersed metal NPs, allowing tandem reactions to be performed in a single pot.[9] We hypothesized that the heteroatoms (Lewis bases) in heteroarenes would coordinate to Lewis acidic ILs, activating the substrate and facilitating hydrogenation of the ring under mild reaction conditions when combined with a suitable catalyst. Herein, we describe a catalytic system composed of Rh NPs dispersed in

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a chlorozincate-[bmim][BF_4] (bmim = the 1-butyl-3-methylimidazolium cation) IL medium, which selectively hydrogenates heteroarenes under mild conditions.

The Rh NPs were prepared by the thermal decomposition of $Rh_6(CO)_{16}$ in which the metal is in the zero oxidation state.[10] This approach avoids salt impurities and affords Rh NPs of various sizes depending on the nature of the IL anion. Specifically, in uniform [bmim][BF_4], Rh NPs with an average diameter of <4 nm were obtained. As well as characterization by high-resolution transmission electron microscopy (HR-TEM), high-angle annular dark-field scanning transmission electron microscopy and energy dispersive X-ray (HAADF-STEM-EDX) elemental mapping of the Rh NPs were also performed to determine the particle size, uniformity, and their nature (Figure 2). The Rh NPs were found to be stable in the IL without any further stabilizers or surfactants, a feature observed by others.[11]

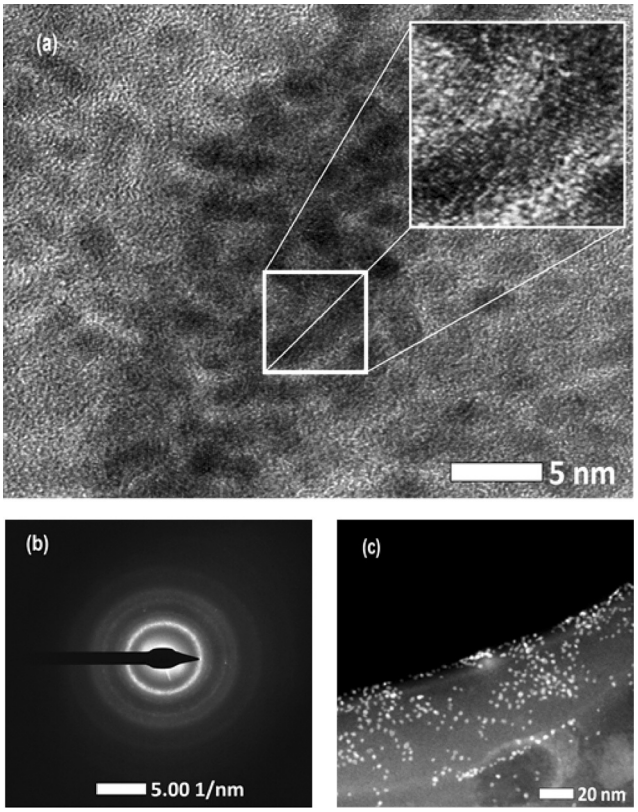


Figure 2. Characterization of the Rh NPs dispersed in [bmim][BF_4]: a) HR-TEM micrograph with enlarged portion showing arrangement of crystal fringes (in inset); b) electron diffraction pattern; and c) HAADF STEM image (in white coloured spots) in lacey carbon-coated copper (amorphous carbon in darker shade) TEM grid showing Z-contrast.

As mentioned above, the second active component of the catalytic system is the Lewis acidic chlorozincate IL. The Lewis acidity of chlorometallate ILs arises from the presence of polynuclear anions, $M_xCl_y^{n-}$, whose nature is dependent upon the metal incorporated, the IL cation, and the ratio of metal chloride to organic salt employed.[12] As reported previously, chlorozincates afford one of the most Lewis acidic ILs and, advantageously, are less sensitive to decomposition than other acidic ILs.[13] The Lewis acidity of ILs may be quantified using approaches applied to solid-state catalysts, for example, using probe molecules such as pyridine combined with vibrational spectroscopy.[14] We applied a similar technique, but based on a nitrile-functionalized IL probe molecule [1-(3-cyanopropyl)-3-methylimidazolium bis(trifluoromethylsulphonyl)imide;[14] Supporting Information, Figure S1], to establish the acidity of chlorozincate ILs. The change in the IR frequencies of the probe molecule is correlated to the Lewis acidity of the solvent, which can be quantified using the Gutmann acceptor number method.[15]

A well-resolved single band at 2251 cm^{-1} corresponds to a probe molecule which remains essentially unchanged in the presence of [bmim]Cl (Figure 3). In the presence of the Lewis

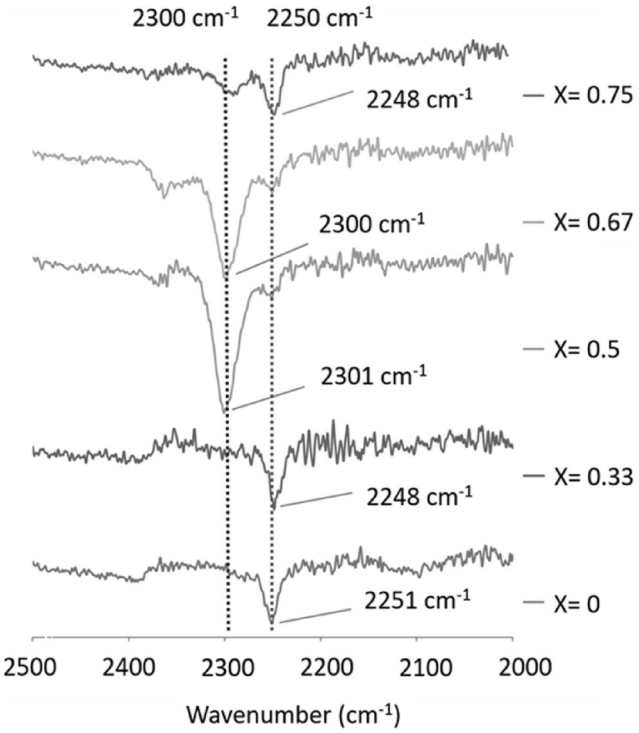


Figure 3. FT-IR spectra highlighting the probe molecule nitrile stretch in [bmim]Cl-$\chi ZnCl_2$ ILs where χ is the effective mole fraction of $ZnCl_2$ (the corresponding shifts of the probe molecule nitrile stretch are shown in Table S1).

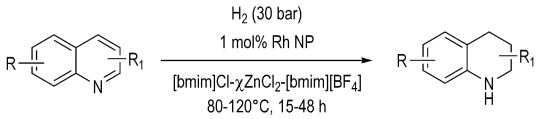
acid, the peak shifts to 2300 cm^{-1}, consistent with the coordination of a nitrile group to Lewis acid sites. The maximum acidity was observed with 0.5 and 0.67 mole fraction of $ZnCl_2$. Speciation of chlorozincates has been investigated by a wide range of techniques,[15b,16] and the Raman spectrum (Supporting Information, Figure S2) of the sample with 0.67 mole fraction of $ZnCl_2$ indicates that $Zn_2Cl_6^{2-}$, $Zn_3Cl_8^{2-}$, and $Zn_4Cl_{10}^{2-}$ are present in the IL.[15b,17]

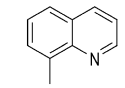
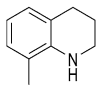
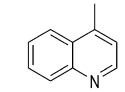
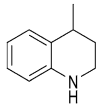
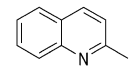
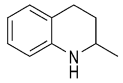
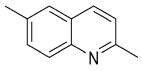
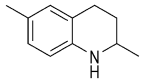
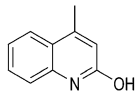
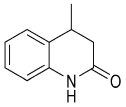
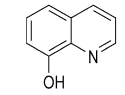
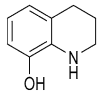
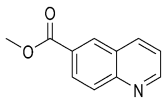
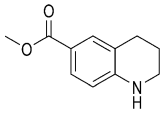
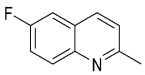
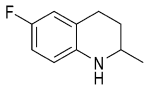
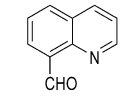
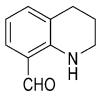
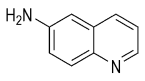
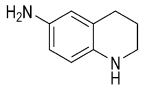
Consequently, the Lewis acidic chlorozincate,[bmim]Cl-$\chi ZnCl_2$, where $\chi = 0.67$ was added to the Rh NP-[bmim][BF_4] solution and the system evaluated in the hydrogenation of quinoline and other heteroaromatic substrates. At a catalyst loading of 1 mol% (based on Rh) reduction of the hetero-

aromatic ring of quinoline was observed under 30 bars of H_2 at 80 °C, affording 1,2,3,4-tetrahydroquinoline in 95% yield. Reduction of the aromatic ring was not observed. The chlorozincate IL itself is not effective for quinoline hydrogenation, but using the Rh NP–[bmim][BF_4] solution in the absence of the chlorozincate IL results in a lower conversion under the same conditions.

The scope of the catalyst was explored under optimized reaction conditions (Table 1). Different substituted quinoline derivatives react smoothly, leading to isolated yields of up to 85%. Quinolines with both electron-donating and -withdrawing substituents on the aromatic ring react well, and only reduction of the heteroarene ring was observed. Moreover, fluoro-substituted quinoline gave the corresponding product in 73% yield (Table 1, entry 8). Notably, reductive dehalogenation was not observed. The reaction may also be performed on a multigram scale with longer reaction times leading to similar yields. The functional group tolerance of the catalyst was studied using some particularly challenging substrates with different functional groups grafted onto different parts of the quinoline structure. Remarkably, without further optimization, ester-, hydroxy-, amine-, and aldehyde-substituted quinolines react well, providing the corresponding product in good to excellent yield. Hydrogenation takes place chemoselectively even in the presence of an aldehyde group, which is known to be much more reactive towards reduction.[18] In all of the reactions, reduction of the functional group was not observed, demonstrating the excellent chemoselectivity of the catalyst. To our knowledge, this chemoselectivity is unparalleled among other homogeneous and heterogeneous catalysts.

Table 1: Rh NP/[bmim]Cl-$\chi ZnCl_2$-[bmim][BF_4] ($\chi = 0.67$) catalyzed hydrogenation of quinolines.[a]



Entry	Substrates	Products	Yield[b] [%]
1			85
2			73
3			71
4			82
5			70
6			78
7			65
8			73
9			72
10			60[c]

[a] Reaction conditions: substrate (1.0 mmol), catalyst (1 mol%), H_2 (30 bar), 80–120 °C, 15–48 h. [b] Isolated yield. [c] GC yield.

The recyclability of the catalyst system was explored using quinoline as the substrate (5.0 mmol) with a 48 hour reaction time under the optimized conditions. After reaction, the product was extracted with ethyl acetate and the IL layer was charged with further substrate and the hydrogenation reaction repeated. The catalyst could be recycled multiple times with only a slight decrease in activity (Figure 4), and could be easily compensated by increasing the reaction time or adding a small amount of fresh catalyst.

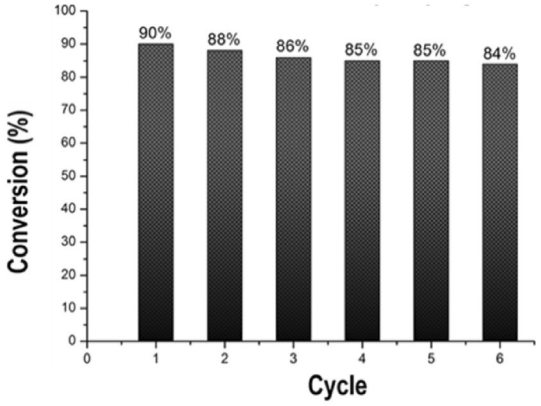
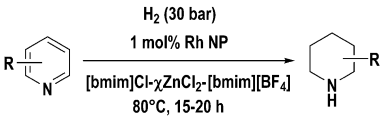


Figure 4. Recycling of the Rh NP/[bmim]Cl-$\chi ZnCl_2$-[bmim][BF_4] catalyst, where $\chi = 0.67$, catalyst in the hydrogenation of quinoline.

Hydrogenation of pyridine derivatives is also important in the chemical and pharmaceutical industries.[19] The resulting functionalized piperidine derivatives can be used as building blocks and intermediates in the synthesis of natural products and pharmaceuticals. Owing to the aromatic nature of these molecules, hydrogenation often requires harsh reaction conditions.[20] The Rh NPs are able to hydrogenate different pyridine derivatives at 80 °C, with the corresponding piperidine derivatives obtained in excellent yield in 15–20 h- (Table 2).

The Rh NP-chlorozincate IL system was assessed as a catalyst for the hydrogenation of other heteroarenes as well (Table 3). The catalyst also selectively hydrogenates the heteroarene in benzofuran derivatives in high yield, and is completely selective towards the aromatic ring.

Table 2: Rh NP/[bmim]Cl-$\chi ZnCl_2$-[bmim][BF_4] ($\chi = 0.67$) catalyzed hydrogenation of pyridine derivatives.[a]



Entry	Substrates	Products	Yield[b] [%]
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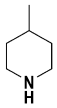
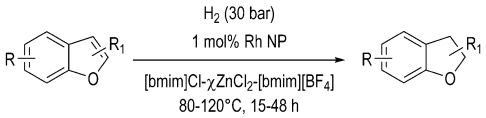
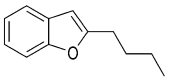
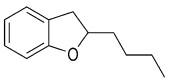
2			60
3			60

[a] Reaction conditions: substrate (1.0 mmol), catalyst (1 mol%), H_2 (30 bar), 80 °C, 15–20 h. [b] GC yield.

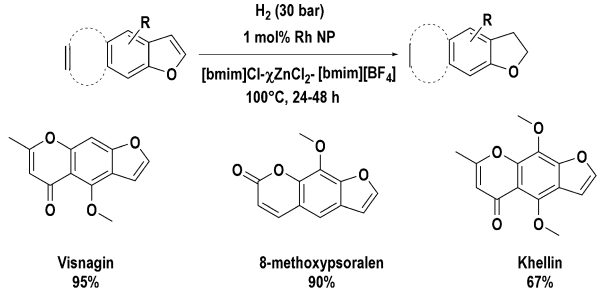
Table 3: Rh NP/[bmim]Cl-$\chi ZnCl_2$-[bmim][BF_4] ($\chi = 0.67$) catalyzed hydrogenation of benzofuran derivatives.[a]



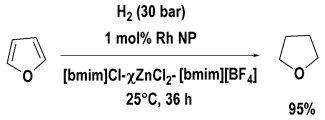
Entry	Substrates	Products	Yield[b] [%]
1			90[c]
2			75

[a] Reaction conditions: substrate (1.0 mmol), catalyst (1 mol%), H_2 (30 bar), 80–120 °C, 15–48 h. [b] Isolated yield. [c] GC yield.

To check the utility of the catalyst in complex molecules, the compounds visnagin, 8-methoxypsoralen, and khellin were studied, and the expected products were obtained in 95–67% yield (Scheme 2). Once again, the catalyst is highly selective and, to our knowledge, such chemoselectivity has not been observed for heterogeneous catalysts. Finally, the catalyst was applied in the hydrogenation of furan molecule at room temperature affording tetrahydrofuran in 95% yield (Scheme 3).



Scheme 2. Rh NP/[bmim]Cl-$\chi ZnCl_2$-[bmim][BF_4] ($\chi = 0.67$) catalyzed hydrogenation of complex molecules. Reaction conditions: substrate (1.0 mmol), catalyst (1 mol%), H_2 (30 bar), 100 °C, 24-48 h. Isolated yields (%).



Scheme 3. Rh NP/[bmim]Cl-$\chi ZnCl_2$-[bmim][BF_4] ($\chi = 0.67$) catalyzed hydrogenation of furan. Reaction conditions: substrate (1.0 mmol), catalyst (1 mol%), H_2 (30 bar), 25 °C, 36 h. GC yield (%).

In summary, we have developed a Rh NP-Lewis acidic IL catalyst for the efficient hydrogenation of various heteroarene derivatives. The catalyst is tolerant to a broad range of substrates and functional groups, allowing the selective hydrogenation of several drug molecules to be achieved. We believe this catalyst could find uses in the sustainable synthesis of highly functionalized molecules, including natural products, and opens the door to catalysts that could extend beyond selective hydrogenation reactions.

Experimental Section

An autoclave with a glass inlay was used to conduct the hydrogenation reactions. The vessel was charged with a stock solution of the Rh NPs in [bmim][BF_4] (0.01 mmol Rh, 1 wt.% in IL) and [bmim]-[Cl]-$\chi(ZnCl_2)$ ionic liquid (0.1 mmol), followed by the substrate (1 mmol) and [bmim][BF_4] (2.0 mL). The autoclave was sealed and purged with H_2, pressurized to 30 bar, and then heated to 80–120 °C. After reaction the heating was stopped and the autoclave cooled to room temperature and the pressure was then released. Excess ethyl acetate (20 mL) was added and the mixture stirred for 48 h. The ethyl acetate layer was separated and analyzed by GC. The final product was purified by column chromatography using ethyl acetate and hexane.

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Keywords: hydrogenation · ionic liquids · Lewis acids · nanoparticle catalysis · quinolines

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