Direct and Transfer Hydrogenation of Ketones and Imines with a Ruthenium N-Heterocyclic Carbene Complex

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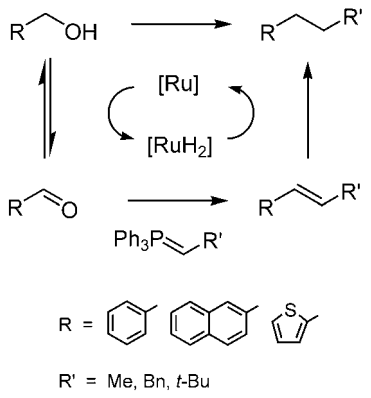
Abstract: The dihydride ruthenium N-heterocyclic carbene complex $Ru(IMes)(PPh_3)_2CO(H)_2$ (**1**) (IMes = 1,3-dimesityl-1,3-dihydro-2*H*-imidazol-2-ylidene) is an efficient catalyst for both direct hydrogenation and transfer hydrogenation of ketones and imines, in the absence of base.

Keywords: homogeneous catalysis; N-heterocyclic carbenes; ruthenium; transfer hydrogenation

The ability of transition metal catalysts to add or remove hydrogen from organic substrates by either direct or transfer hydrogenation processes is a valuable synthetic tool.[1] Ruthenium complexes have a long pedigree as catalysts for hydrogen transfer reactions,[2] including several recent examples of ruthenium N-heterocyclic carbene complexes.[3] We have previously exploited the ruthenium complex $Ru(IMes)(PPh_3)_2CO(H)_2$ (**1**) (IMes = 1,3-dimesityl-1,3-dihydro-2*H*-imidazol-2-ylidene) for an indirect Wittig reaction on alcohols (Scheme 1), where the catalyst is able to remove hydrogen from the alcohol substrate and then return it to the intermediate alkene.[4]

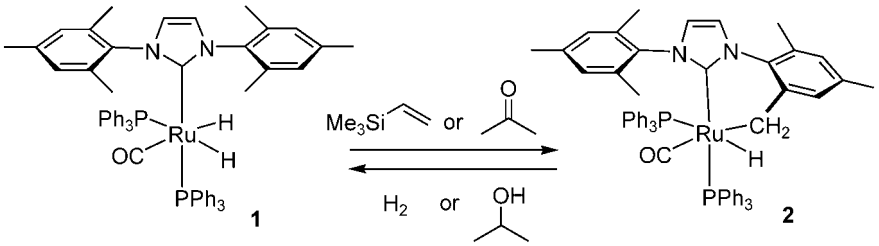


Scheme 1. Indirect Wittig reaction of alcohols.

In our efforts to improve both the reaction conditions and scope of this indirect Wittig reaction we have now investigated the individual hydrogenation/dehydrogenation processes occurring within the overall transformation. Herein we report the further synthetic applications we have established for this catalyst.

Crucial to the success of our complex for both direct and transfer hydrogenation reactions is a reversible C–H bond activation process. Complex **1** undergoes a facile dehydrogenation reaction in the presence of an alkene resulting in C–H activation of one of the mesityl groups of the coordinated carbene ligand, producing $Ru(IMes')(PPh_3)_2CO(H)$ (**2**) (Scheme 2). This process occurs at room temperature and is fully reversible under an atmosphere of H_2 over several days.[5]

We have now shown that dehydrogenation of complex **1** may also be achieved by the addition of a ketone such as cyclohexanone or acetone at 50 °C. The original complex can be restored by the addition of 2-propanol to **2** at 50 °C. Since complex **1** can be regenerated with either hydrogen or with an alcohol, this suggested that it might be equally successful as both a direct hydrogenation and a transfer hydrogenation catalyst. Morris and co-workers have recently published a comprehensive study which highlighted just how few catalyst systems have been established which are able to perform both roles.[6]



Scheme 2. Reversible dehydrogenation/hydrogenation of complex **1**.

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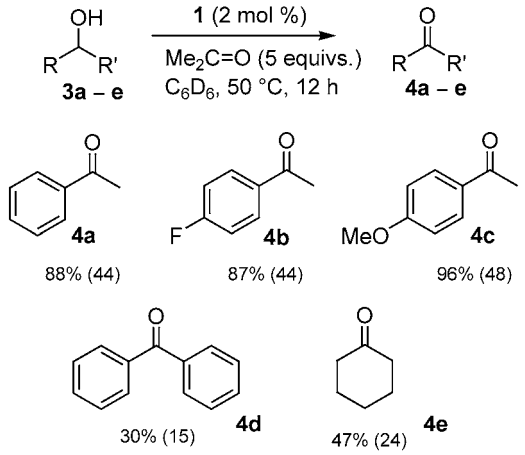
The first requirement of our one-pot Wittig reaction is the oxidation of an alcohol to an aldehyde or ketone. We investigated the oxidation of a series of secondary alcohols into ketones by transfer hydrogenation using acetone as the hydrogen acceptor and in the absence of base, unlike most other catalytic systems (Scheme 3).[7] Reactions were performed at 50 °C in resealable NMR tubes under argon using 2 mol % of catalyst **1** and 5 equivalents of acetone. The reaction progress was followed by ^{1}H NMR spectroscopy for 12 hours.

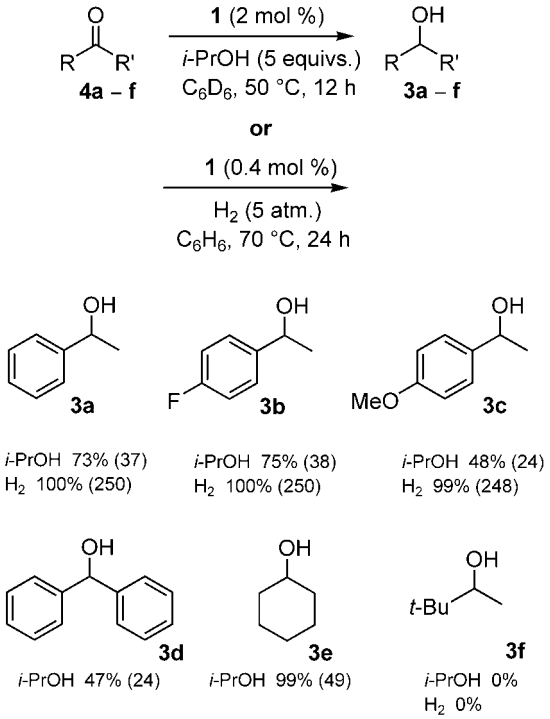
Significant conversions were noted for simple aromatic systems, however, the extent of oxidation was limited by the attainment of an equilibrium position based on the relative oxidation potentials of the product ketone and acetone.[8] Figure 1 shows similar reaction profiles for most substrates, indicating maximum conversion is typically reached between 3–6 hours.[9] The lower reaction rate and hence conversion observed for benzophenone **4d** was more likely due to steric reasons.



Scheme 3. Alcohol oxidation by transfer hydrogenation with acetone. Numbers in brackets are turnover numbers (TON).

The reverse reaction, the reduction of ketones to alcohols *via* transfer hydrogenation was also achieved with complex **1** in the absence of base (Scheme 4). Under the same reaction conditions as above but using 2-propanol as the hydrogen donor, reactions were followed by ^{1}H NMR spectroscopy for 12 hours.

As was found for alcohol oxidation, several of the substrates had reached their maximum conversion much sooner than 12 hours.[10] For example, 4-fluoroacetophenone **4b** is readily reduced to the corresponding alcohol



Scheme 4. Ketone reduction by transfer hydrogenation with 2-propanol and direct hydrogenation. Numbers in brackets are turnover numbers (TON).

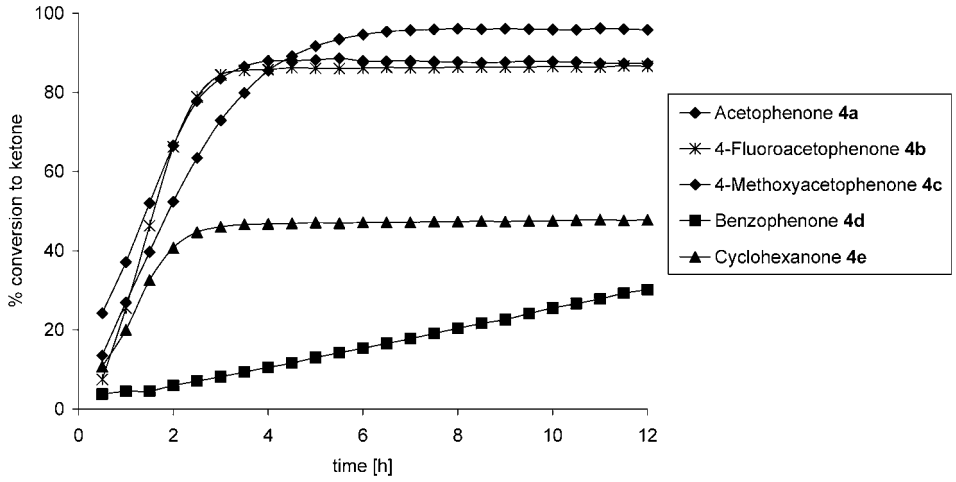
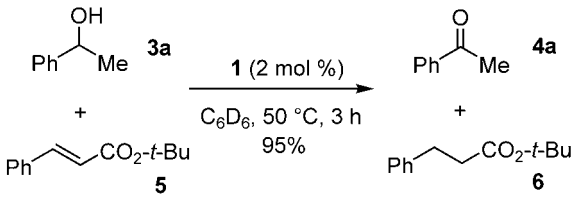
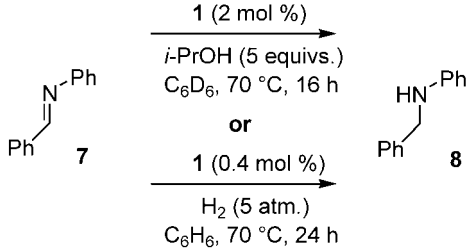


Figure 1. Oxidation of alcohols **3a – e** to ketones **4a**–**e** by transfer hydrogenation with acetone (5 equivs.) catalysed by complex **1** (2 mol %). Reactions were monitored by ^{1}H NMR and conversions are based on integration of the ^{1}H signals.



Scheme 5. Crossover transfer hydrogenation.



Scheme 6. Imine reduction by transfer hydrogenation with 2-propanol and direct hydrogenation.

3b, reaching the equilibrium position of 75% conversion to the alcohol within 4 hours. Cyclohexanone **4e** is completely reduced to cyclohexanol **3e** within 5 hours. However, in the case of the reduction of benzophenone **4d**, the equilibrium position is still not reached after 12 hours.

The direct hydrogenation of ketones was catalysed by complex **1** under 5 atmospheres of H_2 in an autoclave, with significantly lower catalyst loadings than required for transfer hydrogenation (Scheme 4). As was found for transfer hydrogenation, the reduction of pinacolone was unsuccessful. However, both 4-fluoroacetophenone **4b** and 4-methoxyacetophenone **4c** were reduced successfully.

Alcohol oxidation could also be achieved by crossover transfer hydrogenation, using an alkene as the hydrogen acceptor (Scheme 5). Thus, phenethyl alcohol **3a** and *tert*-butyl cinnamate **5** underwent crossover transfer hydrogenation to provide acetophenone **4a** and dihydrocinnamate **6** with 95% conversion in only 3 hours. The success of this reaction was critical for the overall Wittig process and prompted us to look at more simple alkene sources for transfer hydrogenation.

Unfortunately the use of 1-hexene in the dehydrogenation of phenethyl alcohol **3a**, under the same conditions described above, was found to be problematic. Conversions were limited to ~30% and significant isomerisation of the hexene was also observed. Ruthenium-catalysed isomerisation of alkenes is well known with phosphine hydride complexes[11] and has more recently been observed with ruthenium NHC complexes.[12] Subsequent reactions using 2-hexenes and 3-hexene produced comparable rates of alcohol conversion (*cis*-2-hexene: 28%; *trans*-2-hexene: 22%; *trans*-3-hexene: 25% after 24 hours at 50 °C) and alkene isomerisation.

The reduction of imines to amines *via* transfer hydrogenation has not been studied as thoroughly as the analogous reduction of ketones, however there are an increasing number of transition metal catalysts achieving transfer hydrogenation with 2-propanol[2c,3a,13] or other reducing agents.[14] We found the reduction of imine **7** was achieved quantitatively using 5 equivalents of 2-propanol at 70 °C in 16 hours (Scheme 6). At this temperature some slight degradation of the catalyst **1** into $Ru(PPh_3)_3CO(H)_2$ was found at the end of the reaction. When the same reaction was performed at 50 °C complete conversion was observed after 3 days with no degradation of complex **1**. Complex **1** was also a competent catalyst for the direct hydrogenation of imine **7**, using the same conditions required for ketone hydrogenation. Both the transfer hydrogenation and direct hydrogenation reactions gave complete conversion into the amine **8**. Further imine substrates are currently under investigation.

In summary, the ruthenium carbene complex **1** displays a remarkable range of activity, acting as a catalyst for transfer hydrogenation between alcohols and ketones, alcohols and alkenes, alcohols and imines, all in the absence of base. Complex **1** also catalyses direct hydrogenation of ketones and imines and alkene isomerisation. In the case of transfer hydrogenation between alcohols and ketones it is clear that relevant oxidation potentials will influence the rate of reaction and may impact on our choice of substrate for future Wittig-type applications.

Experimental Section

General Procedure for Ruthenium-Catalysed Transfer Hydrogenation Reactions

Transfer hydrogenation reactions were performed on a small scale in J. Young Teflon capped NMR tubes under an atmosphere of argon. The substrate (0.4–0.5 mmol) was added to $Ru(IMes)(PPh_3)_2CO(H)_2$ (**1**)[5] (2 mol %) dissolved in benzene-d_6 (0.6 mL) at room temperature, followed by addition of the appropriate oxidant/reductant (5 equivalents). Reactions were performed at elevated temperature by heating in an oil bath at the desired temperature or within the NMR spectrometer (Bruker AV 400 MHz or Varian Mercury 400 MHz) for kinetic experiments. ^{1}H NMR spectra were recorded at regular intervals and products were confirmed by comparison with spectral data of authentic samples. The conversion of starting material to product was determined by integration of the product resonances relative to substrate resonances in the ^{1}H NMR spectrum.

General Procedure for Direct Hydrogenation Reactions

Direct hydrogenation reactions were performed in a Parr autoclave charged with 5 atmospheres of H_2. $Ru(IMes)(PPh_3)_2CO(H)_2$ (**1**) (0.4 mol %) and the appropriate substrate

(5 mmol) were dissolved in benzene (dried and degassed) (10 mL) in the reactor vessel before sealing and charging with H_2. The vessel was heated at 70 °C and stirred. After the designated reaction time, the contents of the vessel were allowed to cool before carefully releasing the pressure. The volatiles were removed under vacuum from a 1-mL aliquot of the reaction mixture (passed through a silica plug to remove catalyst) and the residue redissolved in $CDCl_3$. Conversion was determined by examination of the ^{1}H NMR spectrum.

Acknowledgements

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[9] Oxidation of phenethyl alcohol **3a** to acetophenone **4a** was performed on a synthetic scale (1 mmol in a sealed ampoule) with the same catalyst loading but heating at 50 °C for only 4 hours. 90% conversion was observed by ^{1}H NMR after work-up.

[10] Reduction of acetophenone **4a** to phenethyl alcohol **3a** was performed on a synthetic scale (1 mmol) with 70% conversion observed after 6 hours at 50 °C.

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