Efficient Ruthenium-catalysed Transfer Hydrogenation of Ketones by Propan-2-ol

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In the presence of the co-catalyst NaOH (2.4 mol%), $RuCl_2(PPh_3)_3$ (0.1 mol%) catalyses efficient transfer hydrogenation of both aliphatic and aromatic ketones by propan-2-ol with rates up to 900 turnovers per hour at 82 °C; no hydrogenation occurs in the absence of sodium hydroxide.

We have recently developed a mild procedure for the aerobic oxidation of alcohols by the use of the triple catalytic system $RuCl(OAc)(PPh_3)_3$–hydroquinone (HQ)–Co(salophen) [eqn. (1); salophen = *N,N'-o*-phenylenebis(salicylideneaminato)].[1] This reaction involves a multistep electron transfer,[1,2] the initial step being a dehydrogenation of the alcohol by the ruthenium catalyst.

$$RCH_2OH + \tfrac{1}{2}O_2 \rightarrow RCHO + H_2O \qquad (1)$$

Conditions: 20 °C; cat. $RuCl(OAc)(PPh_3)_3$; cat. HQ; cat. Co(salophen)

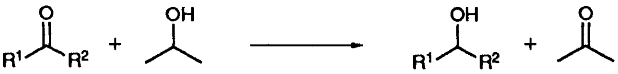
The ability of ruthenium complexes to dehydrogenate alcohols and deliver the hydrides to a ketone[3] or an α,β-unsaturated ketone has made them useful as transfer hydrogenation catalysts.[4] Most such ruthenium-catalysed transfer hydrogenations of ketones described so far, however, require elevated temperature (150–200 °C).

Recently, Cole-Hamilton and coworkers[5] reported that base is required in the $RuH_2(N_2)(PPh_3)_3$-catalysed thermal production (150 °C) of hydrogen from different alcoholic substrates.[5] The role of the base, as rationalized by the authors, is to generate a more nucleophilic alkoxide ion, which would rapidly attack the ruthenium complex responsible for dehydrogenation.

In the light of this observation, we decided to study the effect of base in hydrogen transfer catalysis using the complex $RuCl_2(PPh_3)_3$. Herein we report a remarkable activity of base in the ruthenium-catalysed hydrogen transfer from propan-2-ol to various ketones at 82 °C (Scheme 1).

When a solution of cyclohexanone in propan-2-ol was treated with $RuCl_2(PPh_3)_3$ (0.10 mol%) at 82 °C, no formation of cyclohexanol was observed according to GC analysis. However, the addition of sodium hydroxide (2.4 mol%)† triggers the transfer hydrogenation and in one hour an 89% conversion to cyclohexanol was observed, which corresponds to 890 turnovers per hour.‡ It is interesting that the initial turnover rate measured during the first 15 min was 1800 h^{-1}. This is a dramatic improvement of previously reported $RuCl_2(PPh_3)_3$-catalysed transfer hydrogenations which were run under neutral conditions. Full conversion was observed if the acetone formed was distilled from the reaction mixture.

The analogous reaction [$RuCl_2(PPh_3)_3$, NaOH] in boiling MeOH failed to afford any noticeable production of cyclohexanol, while in refluxing ethanol the catalytic activity had completely ceased after 28% conversion (4 h). This observation is in accord with the fact that the aldehyde formed from dehydrogenation of the primary alcohol deactivates the ruthenium catalyst *via* decarbonylation. In particular decarbonylation from a formyl complex (methanol case) is expected to be facile. With propan-2-ol decarbonylation cannot occur and, therefore, the catalyst lifetime is long.

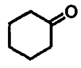
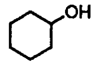
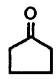
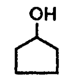
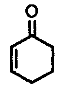
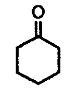
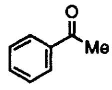
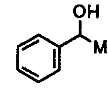
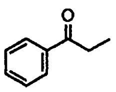
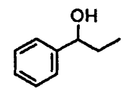


Scheme 1 *Reagents*: 0.1 mol% $RuCl_2(PPh_3)_3$; 2.4 mol% NaOH

As Table 1 summarizes, in refluxing propan-2-ol (82 °C) the present catalytic system efficiently reduces both five- and six-membered cyclic ketones as well as alkyl aryl ketones with a turnover rate of 500–900 h^{-1}. Propiophenone is an exception, for which a relatively low turnover rate, 189 h^{-1}, was obtained.

Metal-catalysed transfer hydrogenation with propan-2-ol is convenient in large-scale synthesis since there is no need to employ a high hydrogen pressure or to use hazardous reducing agents. Furthermore, it is superior to the classical Meerwein–Ponndorf–Verley reduction[6] for which aluminium *iso*-propoxide is required in stoichiometric amounts. Previously an iridium-based system, H_2IrCl_6 (10 mol%), $P(OMe)_3$ (200 mol%) and propan-2-ol, has been used for transfer hydrogenation of cyclohexanone and steroidal ketones.[7] The present ruthenium-based system does not need the excess of phosphite and, furthermore, it operates under relatively mild conditions with a very low amount of catalyst to give a high turnover rate.

Table 1 $RuCl_2(PPh_3)_3$–NaOH-catalysed transfer-hydrogenation of ketones in refluxing propan-2-ol[a]

Catalysts (mol%)				
$RuCl_2(PPh_3)_3$	NaOH	Substrate	Product	Conversion[b] (%) (time)
0.10	2.4			89 (1 h)
0.0	2.4			0 (6 h)
0.10	0.0			0 (6 h)
0.10	2.4			50 (1 h) 60 (4 h)
0.10	2.4			71 (1 h)[c]
0.10	2.4			48 (1 h) 75 (6 h)
0.10	0.0			0 (6 h)
0.10	2.4			18 (1 h) 39 (5 h)

[a] The experiments were run on a 10 mmol scale in 10 ml of propan-2-ol. [b] Unless otherwise noted the conversion is equal to the yield of the product (>99% selectivity). The conversion (yield) was determined by gas chromatography. [c] In this case the selectivity for the product indicated was only 90%, the remaining 10% being cyclohexanol. At a higher conversion the ratio cyclohexanol:cyclohexanone increased.

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† *Typical procedure for catalytic transfer hydrogenation of ketones.* To solid $RuCl_2(PPh_3)_3$ (9.5 mg, 0.01 mmol), after evacuation and purging with argon (× 3), was added degassed propan-2-ol (5 ml) and the mixture heated at 82 °C for 5–10 min under argon. Cyclohexanone (0.98 g, 10.0 mmol) dissolved in degassed propan-2-ol (3 ml) was added dropwise to the refluxing mixture. The resulting grey suspension was stirred for 10 min and then a solution of NaOH (9.5 mg, 0.237 mmol) in propan-2-ol (2 ml) was added dropwise. The grey suspension rapidly turned to a red homogeneous mixture after the addition of base. The mixture was kept at 82 °C for 1 h. GC analysis using an internal standard showed an 89% yield of cyclohexanol.

‡ No condensation products from cyclohexanone or acetone could be detected.

We also tested $RuH_4(PPh)_3$ as catalyst for this transfer hydrogenation in refluxing propan-2-ol. In the absence of base also this catalyst was inactive, but in the presence of catalytic amounts of NaOH it catalysed the transfer hydrogenation of cyclohexanone at almost the same rate as $RuCl_2(PPh_3)_3$.

As this work was in progress a number of articles[8] appeared dealing with enantioselective transfer hydrogenation of alkyl aryl ketones by chiral Ir and Rh complexes bearing bidentate nitrogen-based ligands. Unlike the ruthenium-based process these Ir and Rh catalysts are unreactive towards transfer hydrogenation of dialkyl ketones.

This mild hydrogen transfer with $RuCl_2(PPh_3)_3$ in the presence of NaOH probably proceeds *via* a mechanism similar to that depicted by Cole-Hamilton:[5] (*i*) the attack of *iso*-propoxide ion on the Ru complex to give an anionic species, (*ii*) β-hydrogen elimination from the alkoxide ligand leading to acetone and an anionic ruthenium hydride complex, (*iii*) rapid protonation of the anionic species giving a ruthenium dihydride and, (*iv*) reduction of cyclohexanone by ruthenium dihydride.

Interestingly, bidentate phosphine derivatives which form seven-membered chelated rings with ruthenium(II) show similar catalytic activities for transfer hydrogenation of ketones.[9] We are currently engaged in exploring the utility of this process in enantioselective hydrogen transfer reactions using chiral ruthenium complexes.

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