A novel ruthenium catalysed deracemisation of alcohols

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The deracemisation of alcohols has been achieved with 65–75% ee using a non-selective ruthenium catalysed oxidation to give an intermediate ketone followed by an enantioselective hydrogenation.

The preparation of enantiomerically pure alcohols has been an important synthetic target for decades. Enantioselective reactions involving addition of carbon nucleophiles to aldehydes have been a widely used approach,[1] along with the conversion of ketones into alcohols by hydrogenation, transfer hydrogenation and hydride addition.[2] The preparation of enantiomerically enriched alcohols has also been achieved by kinetic resolution and dynamic kinetic resolution strategies.[3]

Herein, we report the development of a novel deracemisation strategy for the conversion of a racemic alcohol into an enantiomerically enriched alcohol using a catalyst (Scheme 1).

Whilst several catalysts have been reported for the racemisation of alcohols,[4] the reverse process is more demanding, since deracemisation is thermodynamically disfavoured. The conversion of two enantiomers of a compound into a single enantiomer requires a decrease in entropy. It therefore follows that a catalyst will be unable to deracemise a compound unless energy can be provided from some other source.

The Noyori catalyst **2** (Fig. 1) is well known for its ability to reduce ketones with high enantioselectivity by direct hydrogenation.[5] Interestingly, this catalyst has been reported to be rather non-selective in the corresponding reduction achieved with transfer hydrogenation (Scheme 2).[6]

We considered the possibility of using catalyst **2** for the oxidation of a racemic alcohol into a ketone by non-selective hydrogen transfer, followed by *in situ* enantioselective reduction

Scheme 1 Deracemisation of alcohol **1**

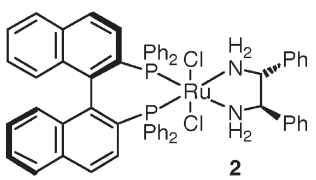

Fig. 1 The Noyori hydrogenation catalyst.

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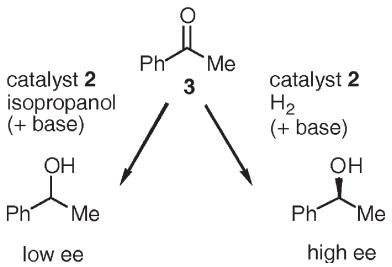


Scheme 2 Noyori catalyst **2** in transfer and direct hydrogenation.

back to the alcohol by direct hydrogenation using the same catalyst.

Preliminary experiments using Noyori catalyst **2** to oxidise phenethyl alcohol **1** into acetophenone **3** were performed using acetone as the oxidant and required the use of base, but were unsuccessful due to the competing aldol reaction of the acetone employed.

We therefore decided to use a combination of ruthenium hydride complex **4** in the presence of (*R*)-BINAP **5** and (*R,R*)-DPEN **6**, with the expectation that the dihydride analogue of the Noyori complex would be formed *in situ* (Fig. 2). It is known that ruthenium hydride complexes do not require the addition of base in order to function as transfer hydrogenation catalysts.[7]

We were encouraged to find that oxidation of phenethyl alcohol **1** occured readily upon treatment with ten equivalents of acetone, using the ruthenium hydride/BINAP/DPEN combination after heating in toluene at 60 °C for 4 h. As expected, this oxidation process gave essentially no kinetic resolution, providing a reaction mixture containing acetophenone **3** in the presence of the ruthenium catalyst and ligands. Pressurisation of this mixture with hydrogen (10 bar) led to a reduction of the acetophenone **3** back into phenethyl alcohol **1** after heating at 45 °C for 16 h. However, phenethyl alcohol **1** was recovered with the (*S*)-enantiomer predominating at 55% ee.

In developing this transformation, we chose to employ cyclohexanone as the oxidant rather than acetone, because cyclohexanone is the more powerful oxidant, and therefore requires fewer equivalents in order to drive the equilibrium forwards.[8] It is important to drive the equilibrium as far towards

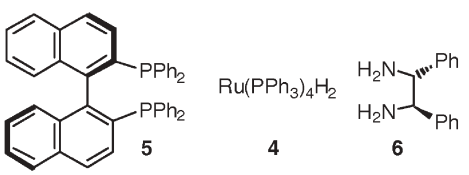
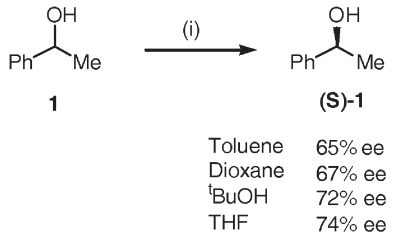


Fig. 2 The components for an *in situ* dihydride complex.



Scheme 3 Conditions (i) $Ru(PPh_3)_4H_2$ (2 mol%), (R)-BINAP (2 mol%), (R,R)-DPEN (2 mol%), cyclohexanone (2 equiv.), solvent, 60 °C, 4 h. Then pressurisation with H_2 (10 bar), 45 °C, 16 h.

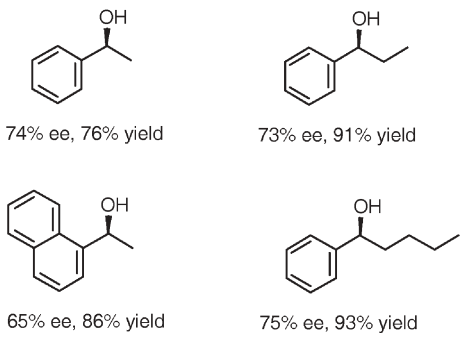


Fig. 3 Alcohols successfully deracemised.

the ketone as possible, since any racemic alcohol remaining at this stage will compromise the enantioselectivity of the alcohol recovered at the end of the reaction.

As shown in Scheme 3, repeating the reaction using only two equivalents of cyclohexanone in place of ten equivalents of acetone provided the recovered alcohol with 65% ee. Changing the solvent from toluene provided slightly higher enantioselectivity in the case of dioxane, *tert*-butanol and THF.

Application of this deracemisation procedure to other alcohols was also successful. For the other alcohols, we chose to use three equivalents of cyclohexanone, simply to ensure that the initial oxidation to ketone was essentially driven to completion. The alcohols shown in Fig. 3 were recovered in good yields and good enantioselectivities, using THF as the solvent. Phenethyl alcohol was isolated by column chromatography, whilst the other alcohols were isolated by distillation.[9] Enantiomeric excess was determined by HPLC or GC.[10]

The isolated yields were consistently good, and whilst the enantiomeric excesses were good, they are lower than those obtained by direct hydrogenation of the ketone with the pre-formed Noyori catalyst **2**.[4] Analysis of the ^1H NMR spectrum of a combination of ruthenium hydride complex **4** with (*R*)-BINAP **5** and (*R,R*)-DPEN **6** in C_6D_6 revealed several peaks in the hydride region, suggesting that several hydride complexes were present. However, when we used this combination in a simple hydrogenation of acetophenone **3** we were able to obtain phenethyl alcohol with 80% ee, somewhat higher than that obtained in the deracemisation procedure. Ruthenium catalyst **4** by itself was a very poor catalyst for direct hydrogenation, as was a combination of catalyst **4** with (*R*)-BINAP, providing less than 5% conversion of ketone into alcohol. Catalyst **4** in combination with (*R,R*)-DPEN provided a 12% conversion with a modest 27% ee.

It seems reasonable to suggest that there is more than one ruthenium hydride species present in the reaction mixture, but that the Ru/BINAP/DPEN complex is the most reactive and the most selective during the reduction process.

In summary, we have developed a procedure for deracemisation of alcohols based on the Noyori catalyst. The reactions depend on a non-selective oxidation step followed by a selective hydrogenation step. Studies are now in progress to understand the nature of the catalyst more fully.

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9 A representative experimental procedure is as follows: 1-phenyl-1-pentanol (328 mg, 2 mmol), $Ru(PPh_3)_4H_2$ **4** (46 mg, 0.04 mmol), (*R*)-BINAP **5** (25 mg, 0.04 mmol), (*R,R*)-DPEN **6** (8.4 mg, 0.04 mmol) and cyclohexanone (588 mg, 6 mmol) were heated at 60 °C in THF (2 mL) for 4 h. After pressurisation with hydrogen (10 bar), heating was continued at 40 °C for 16 h. After removal of solvent under reduced pressure, the alcohol was re-isolated by Kugelrohr distillation (304 mg, 93% yield, 75% ee).
10 The enantiomeric excess of 1-phenylethanol was determined using chiral GC (Supelco BETA-DEX 110, 60 m × 0.25 mm). 1-Phenylpropanol and 1-phenylpentanol were anaylsed by HPLC using a Daicel Chiracel OD-H column (hexane : isopropanol, 97 : 3), and α-methyl-1-naphthalene methanol with a Daicel Chiracel OB-H column (hexane : isopropanol, 90 : 10).