A catalytic deracemisation of alcohols†

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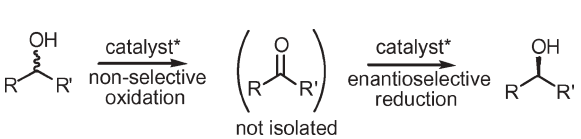
Racemic alcohols have been converted into enantiomerically enriched alcohols with up to 99% ee in a one-pot oxidation/reduction procedure.

Deracemisation is usually thermodynamically disfavoured because of the entropy cost of converting two enantiomers into a single enantiomer.[1] We have developed a strategy to overcome this thermodynamic problem for the deracemisation of alcohols. The process involves the non-selective oxidation of an alcohol into an achiral ketone by transfer hydrogenation, followed by asymmetric reduction back into an enantiomerically enriched alcohol by direct hydrogenation, according to Scheme 1. In some cases, catalysts are known to be highly selective for direct hydrogenation but to be poorly selective for transfer hydrogenation.[2] In a recent report from Nishibayashi and co-workers, they achieve a successful deracemisation by oxidation of the alcohol by acetone using one ruthenium catalyst and reduction by adding a second catalyst and a huge excess of isopropanol.[3]

In order to achieve oxidation of an alcohol by transfer hydrogenation, it is conventional to use a large excess of the acceptor ketone, such as acetone, in order to drive the equilibrium towards complete oxidation of the alcohol.[4,5] We chose to use cyclohexanone as the acceptor ketone, since it is known to be a stronger oxidant than similar acyclic ketones,[6] thereby reducing the need for a large excess.

Our initial studies demonstrated that the use of the preformed Noyori complex $RuCl_2$[(*R*)-BINAP][(*R*,*R*)-DPEN][7] proved to be unsatisfactory, since unwanted aldol reactions were found to occur during the oxidation process. The use of the ruthenium hydride complex $Ru(PPh_3)_4H_2$ in the presence of the ligands (*R*)-BINAP **1** and (*R*,*R*)-DPEN **3** led to clean oxidation of the alcohol into ketone, which was reduced back to alcohol with a reasonable level of enantioselectivity.[8] However, we recognized that the enantioselectivity was being compromised by the presence of achiral triphenylphosphine in the reaction mixture and our attention turned to the use of commercially available, phosphine-free ruthenium complexes as catalyst precursors.



Scheme 1 Deracemisation by an oxidation/reduction sequence.

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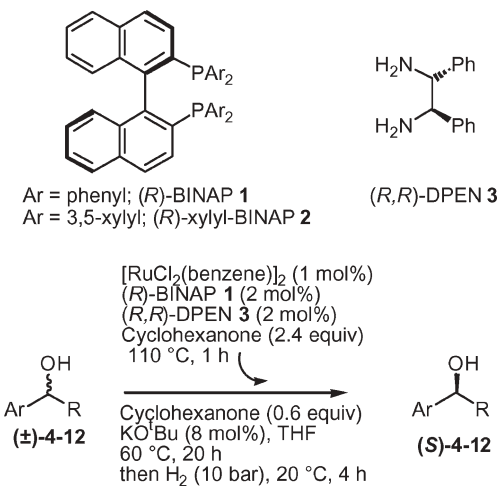
Preliminary screening experiments led to the development of the following reaction procedure, as shown in Scheme 2. $[RuCl_2(benzene)]_2$ (1 mol%), (*R*)-BINAP **1** (2 mol%) and (*R*,*R*)-DPEN **3** (2 mol%) were heated in cyclohexanone at 110 °C for 1 h in order to effect complexation. The racemic alcohol, solvent (THF) and potassium *tert*-butoxide were added and the reaction mixture was heated at 60 °C for 20 h, resulting in oxidation of the alcohol into the corresponding ketone by transfer hydrogenation. Pressurisation of the reaction mixture with hydrogen reduced the ketone back into the alcohol with a good level of enantioselectivity for most of the alcohols examined (Table 1). The enantiomeric excess of products was established by analysis of the chiral HPLC traces.[9]

The alcohol **11** containing a chlorophenyl group was reduced more slowly and with a lower enantiomeric excess. It has previously been observed that aryl chlorides can react with ruthenium complexes, which may explain the lack of success with this substrate.[10] In the case of the formation of the product **5** where the R group is propyl (C_3H_7), the starting alcohol was the corresponding alkene (R is $CH_2CH{=}CH_2$). Under the reaction conditions, the allyl alcohol was isomerised into the saturated ketone prior to reduction.

$[RuCl_2(cymene)]_2$ was treated with (*R*)-BINAP in d^8-toluene at 60 °C in the presence of an additive (DMF, DMSO, THF or cyclohexanone) to enhance ligand exchange. The ^{31}P {^1H} NMR spectra showed signals at δ 24.3 (d, J = 61.8 Hz) and 40.7 (d, J = 61.8 Hz), assigned to [RuCl[(*R*)-BINAP](*p*-cymene)]Cl[11] along with minor unidentified species. Addition of (*R*,*R*)-DPEN and further heating provided a new signal at δ 46.8 (s) assigned to $RuCl_2$[(*R*)-BINAP][(*R*,*R*)-DPEN].[12] Using cyclohexanone as the

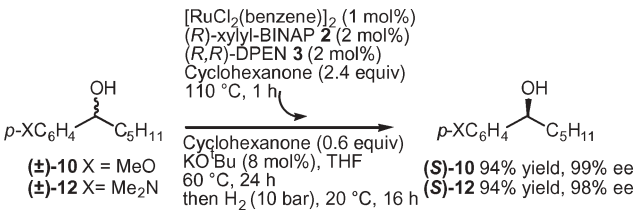


Scheme 2 General procedure for the deracemisation of alcohols.

Table 1 Results of ruthenium catalysed deracemisation

Alcohol	Ar	R	Yield[a] (%)	ee (%)
4	C_6H_5	C_2H_5	87	83
5[b]	C_6H_5	C_3H_7	82	87
6	C_6H_5	C_4H_9	92	86
7	2-Naphthyl	C_5H_{11}	95	82
8	*m*-MeC_6H_4	C_5H_{11}	97	90
9	*p*-$MeOC_6H_4$	CH_3	89	79
10	*p*-$MeOC_6H_4$	C_5H_{11}	94	88
11	*m*-ClC_6H_4	C_5H_{11}	26	57
12	*p*-$Me_2NC_6H_4$	C_5H_{11}	96	92

[a] Isolated yields after column chromatography or distillation. [b] The starting alcohol was $PhCH(OH)CH_2CH{=}CH_2$.

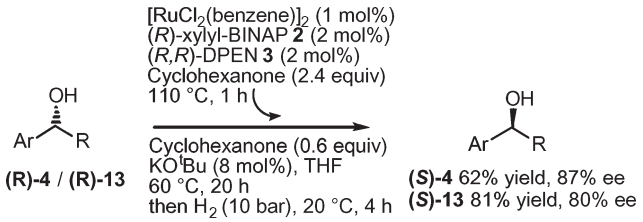


Scheme 3 Higher selectivity obtained using xylyl-BINAP **2**.

additive provided a sample without any significant impurities, whilst the other additives led to spectra which contained signals suggesting the formation of other $RuCl_2$[(*R*)-BINAP](L) species. Essentially the same observations were made using $[RuCl_2(benzene)]_2$ although the exchange reactions were slightly faster. It is not clear why the catalyst prepared *in situ* was more effective than the use of preformed complex. Several other bidentate phosphine ligands were examined for their ability to achieve deracemisation. Under the standard reaction conditions, (*S*)-Phanephos[13] and (*S*)-xylyl-Phanephos[14] reduced catalytic activity dramatically in the reduction step and were not investigated further. (*R*)-Synphos[15] was comparable to (*R*)-BINAP in terms of selectivity and yield when applied to the deracemisation of 1-phenylpropanol (78% ee, 100% conversion). As expected, the use of the other enantiomers of ligands, (*S*)-BINAP and (*S*,*S*)-DPEN, led to the selective formation of the other enantiomer of alcohol. Xylyl-BINAP **2**[16] has been shown to be more selective than BINAP **1** in some reactions,[17] and we found that this ligand provided very high enantioselectivity in the deracemisation of alcohols **10** and **12**, as shown in Scheme 3. The bulkier ligand required a longer reaction time in order to achieve the complete reduction back into the alcohol, but provided 99% ee and 98% ee in the deracemisation process.

Since these reactions proceed *via* an achiral ketone, the opportunity for stereoinversion exists. Thus, one enantiomer of a starting alcohol can be converted into the opposite enantiomer by the same oxidation/reduction sequence employed for deracemisation reactions. These reactions were performed using xylyl-BINAP **2** as the diphosphine ligand, and led to an overall stereoinversion of substrates **4** and **13** (Scheme 4). The lower isolated yields in these cases are a consequence of incomplete reduction.

In summary, we have developed a procedure for the deracemisation of alcohols using a non-biological system that provides up to 99% enantiomeric excess. The process operates using a ruthenium catalysed oxidation of a racemic alcohol by



Scheme 4 Stereoinversion of enantiomerically enriched alcohols.

non-selective transfer hydrogenation followed by an enantioselective direct hydrogenation back into the regenerated enantiomerically enriched alcohol.

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9 A Chiralcel OD-H® column was used for alcohol **4** (3 : 97 isopropanol–hexane, 14.7 min (*R*), 16.7 min (*S*), alcohol **5** (3 : 97 isopropanol–hexane, 14.1 min (*R*), 15.6 min (*S*), alcohol **6** (3 : 97 isopropanol–hexane, 18.8 min (*R*), 21.0 min (*S*), alcohol **7** (2 : 98 isopropanol–hexane, 30.1 min (*S*), 35.5 min (*R*), alcohol **8** (2 : 98 isopropanol–hexane, 11.6 min (*R*), 13.3 min (*S*), alcohol **11** (2 : 98 isopropanol–hexane, 14.4 min (*S*), 16.4 min (*R*). A Chiralcel OB-H® column was used for alcohol **9** (10 : 90 isopropanol–hexane, 18.0 min (*S*), 24.4 min (*R*), alcohol **10** (5 : 95 isopropanol–hexane, 22.7 min (*S*), 27.0 min (*R*), alcohol **12** (5 : 95 isopropanol–hexane, 25.0 min (*R*), 31.4 min (*S*), alcohol **13** (5 : 95 isopropanol–hexane, 19.6 min (*S*), 23.2 min (*R*). The flow rate was 1 mL min^{-1} in all cases. Further details, including comparison of specific rotation with literature values are included in the ESI†.
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