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TETRAHEDRON: *ASYMMETRY*

Probing subtle ligand effects in the enantioselective transfer hydrogenation of ketones

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Abstract

The rational modification of an established amino-alcohol scaffold has revealed new, highly effective ligands for the enantioselective transfer hydrogenation of acetophenone that affords the product in up to 95% ee.

The catalytic, enantioselective transfer hydrogenation of ketones provides a useful method for obtaining enantiomerically enriched secondary alcohols.[1] In this communication we highlight the significant observations from a programme of research directed towards the discovery of enantioselective catalysts using ligands assembled in situ.[2] We proposed to start with an amino-alcohol **1** and refine its structure under mild conditions to afford modified ligands **2** and **3**. The success of this approach would enable key conclusions to be drawn concerning the use of modified amino-alcohol ligands for enantioselective transfer hydrogenation reactions and a unique ligand synthesis strategy for high-throughput screening (Fig. 1).[3]

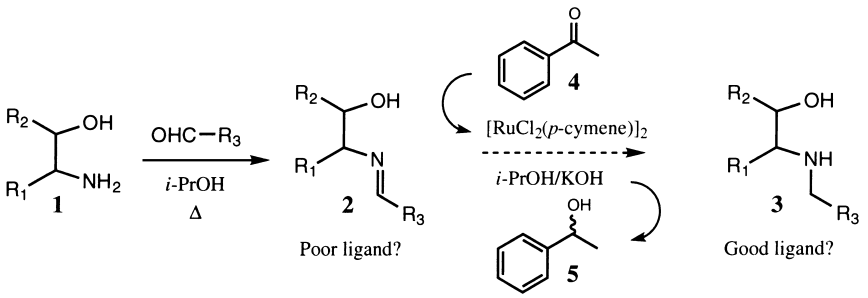

Figure 1. Probing subtle ligand effects using amino-alcohol scaffold

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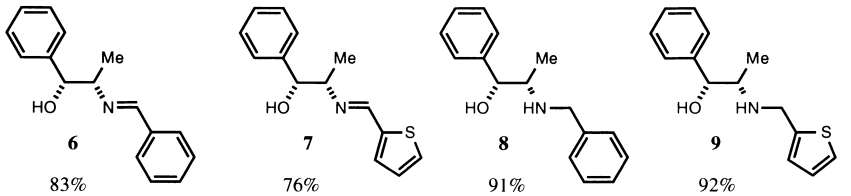
At the outset we established that the imino-alcohols could be formed in quantitative yield in the reaction solvent (*i*-PrOH). The next step was to test the imino-alcohols for any asymmetric induction. The ligands were tested in the enantioselective transfer hydrogenation of acetophenone **4** into 2-phenylethanol **5**.[4] Of the initial imino-alcohols tested (for example, $R_1 = Ph$, *i*-Pr, Bz, $R_2 = H$), only the ligands derived from (1*R*,2*S*)-(–)-norephedrine ($R_1 = Me$, $R_2 = Ph$) afforded significant enantioselectivity (for example, **6** and **7**, Scheme 1). The possibility of the imino-alcohols being reduced in situ to the amino-alcohols was anticipated but our attempts to substantiate this by spectroscopic studies were not conclusive. For the sake of comparison the ligands **8** and **9** were prepared in a separate step by reductive amination using sodium cyanoborohydride.[5]



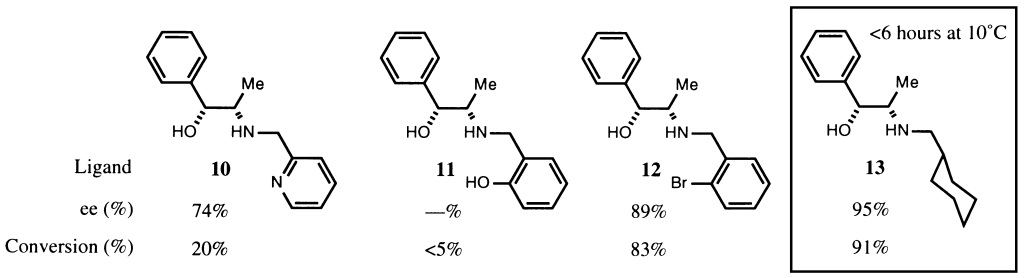
Ligand	**6**	**7**	**8**	**9**
ee (%)	83%	76%	91%	92%
Conversion (%)	96%	92%	95%	92%

Scheme 1.

The initial results demonstrated that the imine ligands afforded reasonable levels of enantioselectivity. Previous studies employing diimine ligands had revealed only low enantioselectivities in similar systems (28% ee).[6] We were mindful of the possibility of imine hydrolysis to restore the original amino-alcohol but there was no evidence of this by ^{1}H NMR. It is proposed that even a small amount of amino-alcohol ligand present in the reaction would afford reasonable levels of enantioselectivity in the product. The purified amine analogues **8** and **9** proved to be superior affording high yields of product **5** with very good enantioselectivity (>90% ee). This can be rationalised with reference to the observation by Noyori et al. that the presence of a NH-group leads to higher yields and enantioselectivities.[7] It is worthy of note that using **8** or **9** the enantiopurity of the product **5** does not significantly erode over extended periods of time, unlike other reported systems.[8] Lowering the reaction temperature (to 10°C) afforded product with slightly higher enantioselectivity but this was accompanied by a concomitant reduction in the rate of reaction (for example, using ligand **8** at 10°C, after 4 h, 82% conversion, 94% ee).[9]

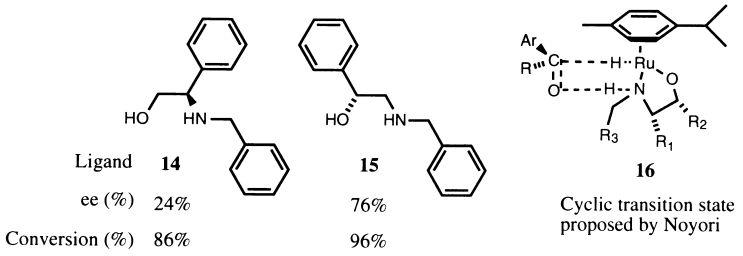
The initial success of the modified amino-alcohol ligands prompted further attempts to fine-tune the structure (Scheme 2). The introduction of an extra coordinating group to the ligand structure was seriously detrimental to the activity of the catalyst (**10** and **11**). This is possibly as a result of the extra ligand blocking a coordination site on the ruthenium.[10] The presence of an *o*-bromo substituent in **12** afforded product with similar enantioselectivity to **8**. The replacement of the phenyl ring with a cyclohexyl ring afforded ligand **13** which, in combination with $[RuCl_2(p\text{-cymene})]_2$, resulted in a highly active, enantioselective catalyst for the reduction of acetophenone **4** to (*R*)-2-phenylethanol **5**.

A striking example of the importance of subtle structural effects is illustrated by comparing the ligands **14** (prepared from (*R*)-(–)-2-phenylglycinol) and **15** (prepared from (*R*)-(+)-styrene oxide).[11]

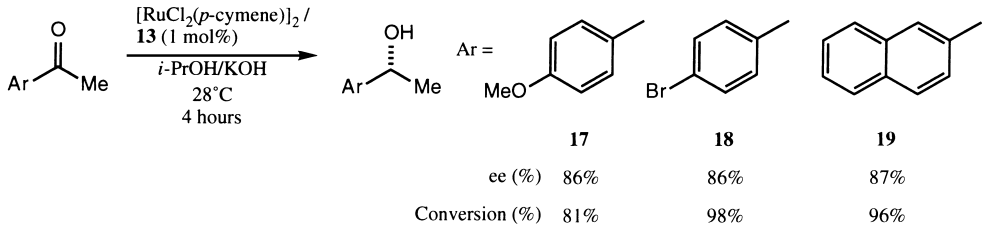


Scheme 2.

The transposition of the phenyl group from the carbon bearing the amino moiety **14** to the carbon bearing the alcohol **15** has a significant beneficial effect on enantioselectivity (Scheme 3). Ligand **15** is essentially ligand **8** without the (*S*)-methyl group and the observation that the enantioselectivity is still relatively high (compared with using **14**) suggests that R_2 assumes a pivotal role in controlling asymmetric induction. It is assumed that the mechanism proceeds via the metal–ligand bifunctional mechanism involving a cyclic transition state of type **16** proposed by Noyori and Yamakawa.[12] Ligand **13** which afforded the highest enantioselectivity in the transfer hydrogenation of acetophenone was tested using ketones **17** to **19**. In each case the enantiopure catalyst showed good activity and produced the product with consistent enantioselectivity (Scheme 4).



Scheme 3.



Scheme 4.

In conclusion, the facile modification of an amino-alcohol scaffold has resulted in the identification of a new enantioselective catalyst for ruthenium promoted transfer hydrogenation of ketones. Using the described catalysts, the enantioselective process is sensitive to minor changes in the ligand design. Future work will focus on refining the general ligand synthesis to be amenable

to true parallel screening. This will allow the rapid optimisation of enantioselectivity for any given substrate.

Acknowledgements

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4. General procedure for enantioselective reduction of ketones: A solution of the ligand (3.3×10^{-5} mol) and [(*p*-cymene)$RuCl_2$]$_2$ (8.3×10^{-6} mol) in dry, degassed IPA (10 ml) was heated to 80°C and allowed to stir for 1 h. The red solution was cooled to room temperature and then KOH was added (0.2 M in IPA, 8.3×10^{-5} mol). After stirring for a further 5 min the reaction was placed in a bath at the desired temperature (0–40°C) and acetophenone (1 M in IPA, 1.67×10^{-3} mol) was added to the mixture. The reaction was allowed to stir and aliquots taken and analysed by chiral GC analysis.
5. All ligands have been satisfactorily characterised (^{1}H, ^{13}C, MS, IR).
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