Yes! Asymmetric hydrogenation with cheap ligands!

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Yes! Asymmetric hydrogenation with cheap ligands!

The market for chiral intermediates is steadily increasing, fuelled by the growing efficiency in drug development over the past decade. The majority of these intermediates is still produced using classical resolution or, increasingly, using enzymes. Asymmetric catalysis was heralded 30 years ago as a new and most efficient method as it made resolution and racemisation obsolete. Yet the number of processes using asymmetric catalysis is still relatively small. Analysis of this situation revealed that catalyst cost is still a very important factor.

The rhodium-catalysed asymmetric hydrogenation of functionalised olefins, exemplified in Scheme 1, is probably the most well studied transition metal-catalysed reaction in homogeneous catalysis. The catalysts normally used in this reaction contain chiral, enantiomerically pure phosphorus ligands. Until recently it was thought that only using bidentate ligands enantioselectivities higher than 95% could be reached. Within a research co-operation between DSM Fine Chemicals and the University of Groningen the discovery has been made last year that the simple and cheap monodentate phosphoramidite MonoPhos affords excellent enantioselectivities, up to 99%, in the rhodium-catalysed hydrogenation of several dehydroamino acids and their derivatives (1). Simultaneously, two other research groups have also developed monodentate ligands that are effective in this reaction (2). This breakthrough shows that monodentate ligands can be compared with the best of their bidentate counterparts in this reaction.

The beauty of the use of MonoPhos in asymmetric hydrogenation is the low cost of the ligand. The synthesis of MonoPhos is performed in one step and in large scale from the commercially available starting materials BINOL and HMPT (Scheme 2) (3). MonoPhos is a shelf stable compound, resistant to air and moisture and distinguishes itself in this way from a number of phosphine ligands which are often prone to oxidation and form phosphites which tend to hydrolyse in the presence of water.

Apart from the cost of the catalyst, an important economic factor in catalysis is the rate of the reaction expressed as the turnover-frequency of the catalyst. In asymmetric hydrogenation the reaction speed strongly increases with higher pressures, but for a number of catalysts it is known that the enantioselectivity drops strongly with increasing the pressure. We have studied the hydrogenation reaction at a higher hydrogen pressure (Table I)
Table I - Asymmetric hydrogenation of dehydroamino acid derivatives at elevated pressure.
The reaction was performed at room temperature using 5 bar of H₂ [substrate (0.8 mmol, 0.04 M) : Rh(COD)₂BF₄ : MonoPhos = 1 : 0.005 : 0.011], 100% conversion was observed and demonstrated that there is hardly any influence on the enantioselectivity. So, the enantioselectivity is kept at an excellent level whereas the reaction has a much higher turnover-frequency.

For our initial experiments dichloromethane was chosen as a solvent, but we realised that from an environmental point of view chlorinated solvents should be avoided. We were pleased to see that, using Monophos, ethyl acetate is as good as - or better than dichloromethane as a solvent. So ethyl acetate, an environmental benign solvent, is the favourite choice.

DSM Fine Chemicals has patented the invention and its full scope is currently being determined in Groningen and in Geleen.

CHEMICAL BACKGROUND

In the rhodium catalysed asymmetric hydrogenation a functionalised olefin, often an N-acyl or N-benzoyl dehydroamino acid, is converted with hydrogen to the corresponding amino acid derivative. The reaction is important in the fine chemical and pharmaceutical industry for, among other things, the production of non-natural amino acids. During the years it has been shown that also succinic acid derivatives, hydroxy acids, amines and alcohols can successfully be prepared using this asymmetric hydrogenation reaction.

In the last three decades numerous bidentate phosphorus ligands have been synthesised and applied. A significant number of these ligands gives high enantioselectivities for certain substrates, but not for others, whereas some of them connect an excellent selectivity with a broad scope. Several ligands are commercially available.

HISTORICAL BACKGROUND

As stated, a feature of the currently applied rhodium catalysts is the presence of a bidentate ligand. When homogeneous asymmetric hydrogenation was developed, chiral monodentate ligands were applied initially, in analogy with the well known Wilkinson catalyst. However, enantioselectivities were in general disappointing. Due to the work of Kagan et al. (4) it was shown that bidentate ligands afforded superior e.e.’s compared to the monodentate ones and therefore bidentate ligands became the standard. Although a number of bidentate ligands have an excellent performance, their synthesis requires a number of steps which makes the ligands expensive. Therefore, simple monodentate ligands that give excellent enantioselectivities are a breakthrough in this field.

REFERENCES