



Asymmetric Hydrogenation Using H-Cube® Continuous Flow Reactor

INTRODUCTION

Catalytic asymmetric hydrogenation is one of the most efficient and convenient methods for synthesizing optically active compounds, e.g. amino acids, chiral amines, and itaconic acids, which are widely used in the pharmaceutical and fine chemical industries. Chiral phosphorus ligands, such as novel phosphine-phosphoramidite and phosphine-phosphite (P-OP) ligands have been widely applied for asymmetric hydrogenation. Unsymmetrical hybrid phosphine-phosphoramidite compounds have recently emerged as a new class of chiral ligand for highly efficient asymmetric catalysis. Due to the different phosphorus binding sites, this type of ligand can offer a unique electronic environment around the central metal, which results in significantly improved enantioselectivities in some cases. The immobilization of the catalyst can be carried out on natural and mesoporous Al_2O_3 in the presence of phosphotungstic acid (PTA). Phosphotungstic acid is a heteropoly acid that provides high stability to the catalysts and prevents leaching in the asymmetric reduction of different substrates in heterogeneous batch and high throughput microfluidic-based flow reactors.

At ThalesNano we have performed asymmetric hydrogenation on the H-Cube® flow hydrogenation system using solid-supported Rh catalysts bearing chiral phosphorus ligands. The catalyst $\text{PTA}/\text{Al}_2\text{O}_3/[\text{Rh}(\text{COD})(\text{chiral ligand})]$ (the structure of these chiral ligands can be seen in Figure 1.) was tested in the chiral hydrogenation of (*Z*)- α -acetamidocinnamic acid methyl ester (Figure 2.).

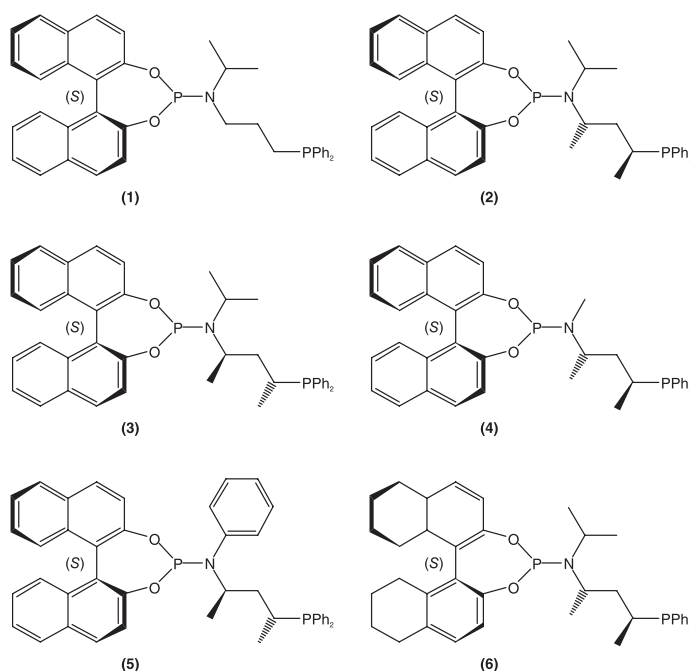
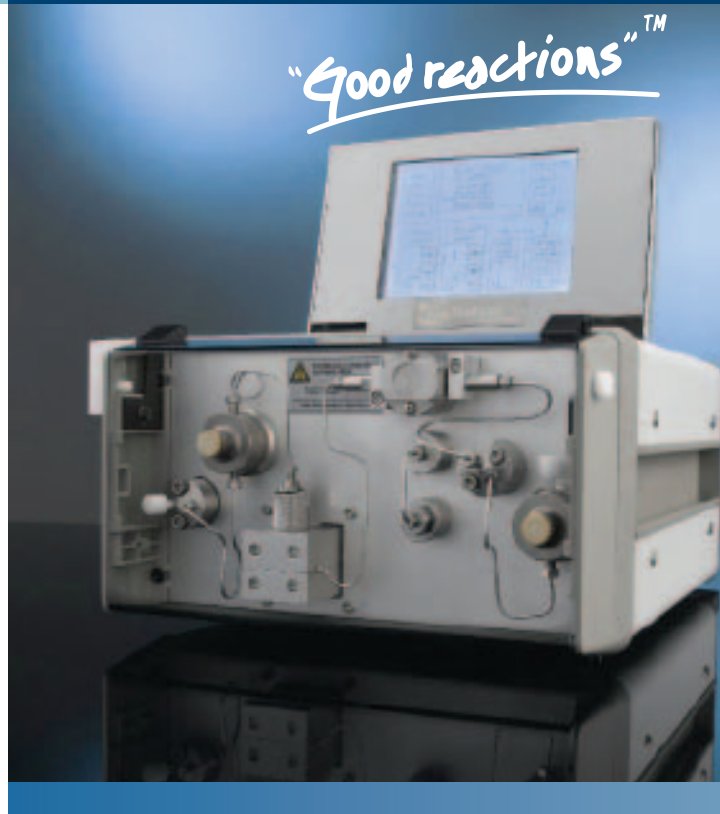


Figure 1. Chiral phosphine-phosphoramidite ligands

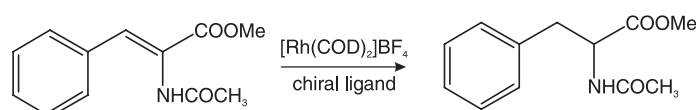


Figure 2. Hydrogenation of (*Z*)- α -acetamido-cinnamic acid methyl ester

The H-Cube® reactor was used for asymmetric hydrogenation under flow conditions. This system provides safe and rapid optimization of the reaction conditions (flow rate, temperature, pressure, solvent, substrate concentration) using only a few mg of substrate.

STANDARD EXPERIMENTAL PROTOCOL

PTA/Al₂O₃/[Rh(COD)(**2**)] was filled into a CatCart® column. The substrate was stirred in the solvent to prepare a 0.05 mol/dm³ solution and the solution was fed into the reactor using a flow rate of 0.1 mL/min at room temperature. The conversions of the hydrogenation reactions of (*Z*)- α -acetamidocinnamic acid methyl ester and the enantiomeric excesses of the product were determined by chiral GC using a Hewlett Packard HP 4890 D, equipped with CHIRASIL-L-VAL column (25 m x 0.25 mm, df = 0.12 μ m), N₂ as carrier gas, a split/split less injector at 250 °C, and an FID at 250 °C. Temperature program: 2 min at 140 °C; 2 °C/min from 140 °C to 180 °C; 40 min at 180 °C. Retention times were 12.3 min for (*R*), 13.2 min for (*S*)-product, and 22.1 min for (*Z*)- α -acetamidocinnamic acid methyl ester. The productivity of a catalyst can be described by the turn over number (or TON) and the catalytic activity by the turn over frequency (TOF), which is the TON per time unit. The results of solvent effects are displayed in Table 1 and the monitoring of catalyst stability over time is detailed in Table 2.

CONCLUSION

We found that high enantioselectivity can be achieved in asymmetric hydrogenation when using the bidentate phosphine-phosphoramidite ligands depicted above. The advantage of these ligands is that there is little or no decomposition in common polar protic solvents. The immobilization of the catalyst can be carried out on Al₂O₃ in the presence of phosphotungstic acid.

Solvent	Conversion (%)	TOF (h ⁻¹)	e.e. (%)
CH₂Cl₂	65.8	15.8	90.9
EtOAc	>99	24.1	99.3
MeOH	>99	24.1	99.4

Reaction conditions: Substrate concentration: 0.05 mol/dm³, temperature: 25 °C, flow rate: 0.1 mL/min, pressure: 1 bar

Table 1. Results of solvent effects in the asymmetric hydrogenation of (*Z*)- α -acetamidocinnamic acid methyl ester with (PTA/Al₂O₃/[Rh(COD)(2**))]**

Reaction time (min)	Conversion (%)	TOF (h ⁻¹)	e.e. (%)
First sample	65.8	25.2	98.5
60	>99	25.2	99.7
120	>99	25.2	99.7
210	92.0	23.2	99.7
240	86.3	21.7	99.7
300	64.5	16.2	99.6
360	69.0	17.4	99.6
540	43.5	11.0	99.6
570	35.5	9.0	99.6
630	39.1	9.9	99.5
700	28.4	7.2	99.5
780	29.5	7.4	99.5

Reaction conditions: Solvent: EtOAc, pressure: 1 bar, substrate concentration 0.05 mol/dm³, temperature: 25 °C, flow rate: 0.1 mL/min

Table 2. The stability of the catalyst over time in the asymmetric hydrogenation of (*Z*)- α -acetamidocinnamic acid methyl ester with (PTA/Al₂O₃/[Rh(COD)(2**))]**

Legal information

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