

## Solvent Effects and Effect of Additives in the Asymmetric Reduction of a Key Statin Intermediate

Initial studies on the selective asymmetric hydrogenation of the carbonyl group of a key statin intermediate were complicated by byproduct formation. It was eventually realized that the ruthenium BINAP catalysts have acidic properties which cause reactions with solvents (eg methanol and ethyl acetate) to occur. When 0.5 moles of triethylamine were added with methanol as solvent, a high syn/anti ratio of products was obtained and a quantitative conversion occurred in 100 minutes. If 1 mole of the amine was added, however, the reaction slowed and 2 moles caused the reaction to almost stop.

A catalyst derived by treating the RuBINAP with triethylamine was prepared and this gave good results in methanol, but surprisingly not in isopropanol or 96%aq ethanol.

If triethylamine was replaced by sodium acetate then the same effects were observed. 1 mole of NaOAc gave good results but 1.5 slowed the reaction and 2 moles stopped it altogether. Best results were eventually obtained under the conditions shown below (V I Tararov et al. *Adv Synth Catal.*, 2006, 348, 2633-2644). The work was supported by the company Ratiopharm so maybe this process may have applications in the synthesis of statins (eg atorvastatin) for the generic market.

