

New Advances in Asymmetric Hydrogenation of Ketones

Carlisle J. E. D'Souza

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Chiral compounds are very useful as pharmaceuticals, animal health products, agrochemicals, flavors and fragrances, due to the chirality of the receptors in living organisms that interact with these compounds.¹ Chiral drugs accounted for \$7 billion of pharmaceutical research and development in 2002 and this number is expected to rise to \$9.5 billion in 2005.² Ryoji Noyori's ruthenium(II) BINAP asymmetric hydrogenation catalysts³ helped him earn a share of the 2001 Nobel Prize with William Knowles and Barry Sharpless. These homogeneous catalysts are particularly useful for the asymmetric hydrogenation of ketones and provide good chemoselectivity, enantioselectivity and turnover numbers while requiring mild conditions and allowing high substrate-catalyst ratio.⁴ On the other hand, heterogeneous catalysts incorporate the advantages of easier catalyst-product separation and ability to be stored and used for long periods of time. To optimize asymmetric hydrogenation for industrial applications, systems that incorporate both sets of these advantages need to be designed. There are several ways to go about this such as modifying metal surfaces with chiral modifiers, tethering homogeneous catalysts onto various supports and incorporating homogeneous catalysts into organic and inorganic polymers.

Nanoparticles are rapidly increasing in popularity as catalyst supports due to their large surface area and ready dispersibility in most solvents.⁵ Lin and coworkers tethered a ruthenium(II) BINAP catalyst to magnetite (Fe_3O_4) nanoparticles (via a phosphonic acid substituent on the BINAP ligand) in order to catalyze the asymmetric hydrogenation of aromatic ketones to chiral alcohols.⁶ The results showed yields and enantiomeric excesses comparable to those of the homogeneous catalyst. Furthermore, after the reaction was completed the reaction flask was placed on a permanent magnet and the product was decanted off, free from ruthenium and magnetite contamination (Figure 1). These heterogenized catalysts could be recycled up to 15 times without significant (>2%) loss in enantioselectivity.

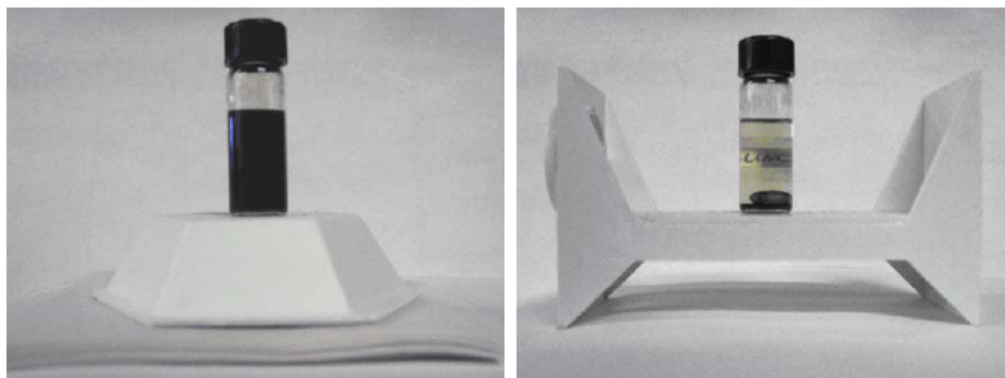


Figure 1: Reaction mixture for the asymmetric hydrogenation of 1-acetonaphnone using a Ru (II) BINAP catalyst supported on magnetic nanoparticles (left) and the same reaction mixture after sitting on a permanent magnet for 5 minutes (right).⁶

In addition to magnetite nanoparticles, Lin and coworkers also incorporated this phosphonated-BINAP catalyst into the synthesis of a zirconium phosphonate material.⁷ This hybrid chiral material was highly porous and offered a large surface area for catalyst-substrate interaction, resulting in asymmetric ketone hydrogenation yields and enantioselectivities similar to those of the homogeneous catalyst. Furthermore, as the catalyst is incorporated into the material, less than 0.2% ruthenium leached into the product.

Fan and coworkers synthesized dendrimer-like poly(ether) polymers through a condensation reaction between phenyl-alcoholic monomers and amine-substituted BINAP ruthenium(II) complexes.⁸ These dendronized complexes asymmetrically hydrogenated aromatic ketones with enantioselectivities of up to 96% ee.

Ding and coworkers synthesized ligand-metal-ligand chiral polymers that produced (*R*)-chiral alcohols with up to 98% ee.⁹ The system was based off replacing the traditional BINAP and DPEN ligands in Noyori's catalyst with linked ligands that could bind two metal centers and therefore propagate a polymer chain (Figure 2). The authors also observed less than 0.1 ppm ruthenium leaching into the organic product.

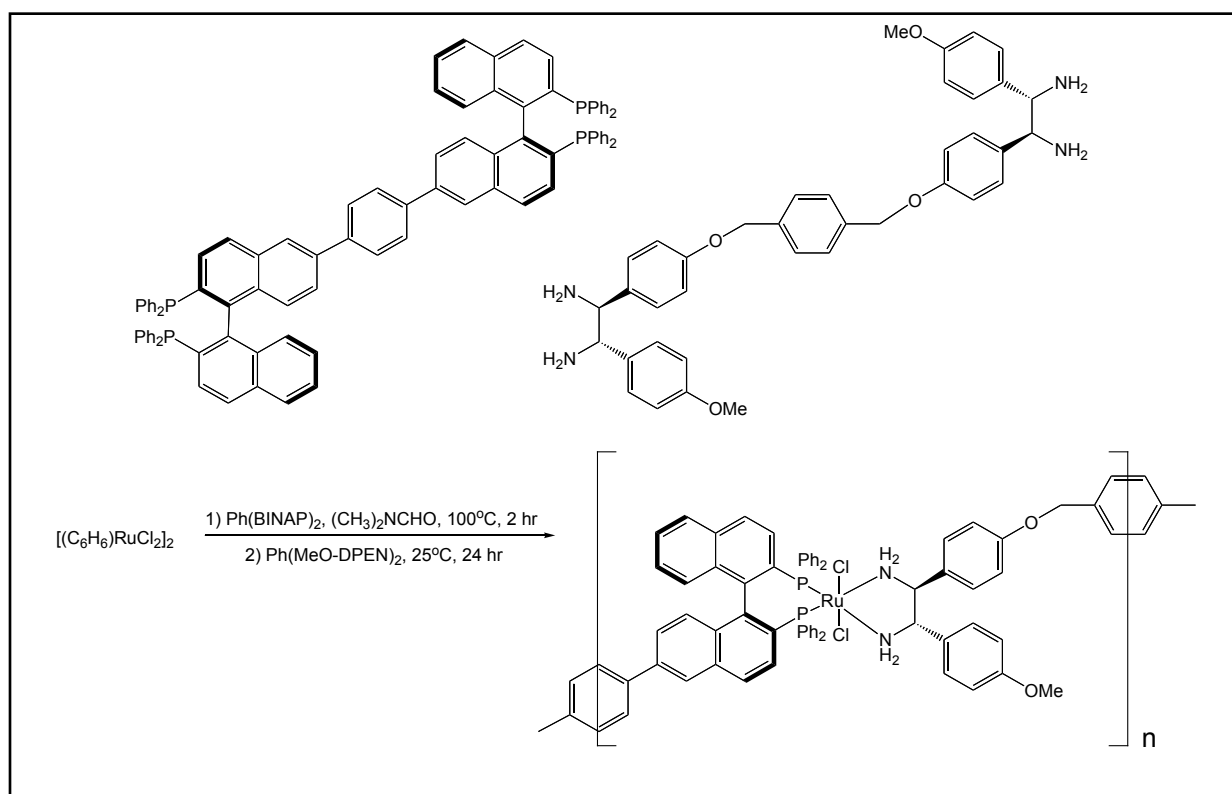


Figure 2: Example of the synthesis of a ligand-metal-ligand chiral polymer.⁹

All these heterogenized systems, unlike most heterogeneous catalysts, offer enantioselectivities comparable to their homogeneous counterparts while avoiding the homogeneous problems of leaching, difficult catalyst-product separation and the inability to

reuse the catalyst, thus illustrating methods of improving asymmetric hydrogenation catalysts to boost their industrial viability.

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