

Utilization of Chiral-at-Metal Complexes for Asymmetric Catalysis

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In 1992 the Food and Drug Administration issued a policy which stressed the importance of enantiomerically pure drugs, and in 2003 six of the top ten best selling pharmaceutical drugs were marketed as single enantiomers.¹ Methods to obtain enantiomerically pure products include the use of compounds drawn from a chiral pool, resolution of racemic products, and asymmetric synthesis. Synthesis from a chiral pool, which is a stock of available enantiopure starting material, suffers from the fact that a suitable substrate may not be available. Sulfoxides, for example, used in anti-ulcer drugs are not readily obtainable from a chiral pool. Although chiral resolutions are often employed in industrial processes, the maximum 50% yield is a drawback. Finally, asymmetric synthesis can be carried out in two ways, either by stoichiometric auxiliaries or by means of asymmetric catalysis.² Asymmetric catalysis is not limited by low yields, availability of materials constituting a chiral pool, or the need for stoichiometric reagents.

Asymmetric catalysis has historically relied upon chiral ligands to produce a chiral environment, but recently a new approach has been explored: the use of achiral ligands to produce catalytically-active chiral-at-metal complexes.^{3,4,5} The key features of any asymmetric metal catalyst include the ability to catalyze the desired reaction, as well as induction of chirality into the products.⁶ The first criterion is fulfilled by allowing coordination sites on the metal center to be accessible to the substrate during the catalytic transformation. The second criterion is satisfied by transferring stereochemical information to the products from the chiral environment surrounding the metal.⁶ For transition metal catalysts containing chiral ligands, whether the enantioselectivity stems from the chiral ligand, or rather through the chirality engendered at the metal by the ligands remains unclear. Described below are three examples of chiral-at-metal catalysts which incorporate inexpensive achiral ligands, thus avoiding the use of more costly chiral ligands.

The catalytic hydrosilylation of ketones to optically active secondary alcohols was pioneered by Nishiyama through rhodium bis(oxazolonyl)pyridine (pybox) complexes.⁷ The reaction has proven successful because of the relatively mild conditions employed.⁸ Gladysz has shown that hydrosilylation of ketones can be catalyzed by a dinuclear system containing a chiral rhodium complex bound to a catalytically active rhodium center (Figure 1).³ This rhodium-rhenium catalyst yielded hydrosilylated acetophenone with an enantiomeric excess (ee) of 63%.⁴ Studies of the hydrosilylation mechanism by a chiral diphosphine rhodium complex provided insights into the Gladysz system.⁹ The enantioselective step is the coordination of the ketone to the hydrido(silyl)Rh(III)(diphosphine) intermediate such that the more sterically demanding group is positioned away from the congested region around the metal (Figure 2).⁹ Insertion followed by reductive elimination yields the optically active silyl ether, which is further converted to the optically active alcohol.

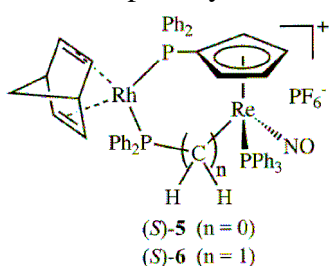


Figure 1: Gladysz hydrosilylation catalyst

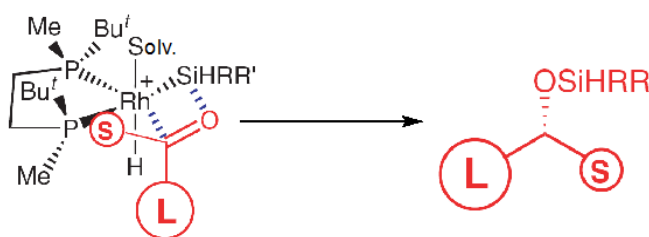


Figure 2: Enantioselective step

The epoxidation of alkenes using O_2 and the hydroxylation of alkanes with H_2O_2 by a bis-phenanthroline ruthenium catalyst (Figure 3) appears to proceed through a ruthenium-dioxo intermediate.^{10,11} Ligand of 2,9-dimethyl-1,10-phenanthroline (dmp) to the ruthenium enforces the *cis* configuration of the Ru-dioxo moieties, which has been demonstrated to increase the oxidizing potential over *trans* Ru-dioxo analogues.¹¹ Oxidation of pro-chiral sulfides to their respective chiral sulfoxides by this catalyst proceeded with relatively low enantiomeric excesses ranging from 7-18% and a selectivity of 9:1 sulfoxide: sulfone.⁴ Enantioselective oxidation of the sulfide to the sulfoxide can be achieved by the use of a vanadium chiral salen complex with a 64% ee.¹² Mechanistic details of $[Ru(O)_2]^{2+}$ oxidation are hampered by the many oxidation states available to ruthenium. A pathway akin to the [3+2] cycloaddition for oxidative cleavage of olefins by RuO_4 (Figure 4) could be applied for the oxidation of sulfides which would proceed through a [3+1] transition state.¹¹

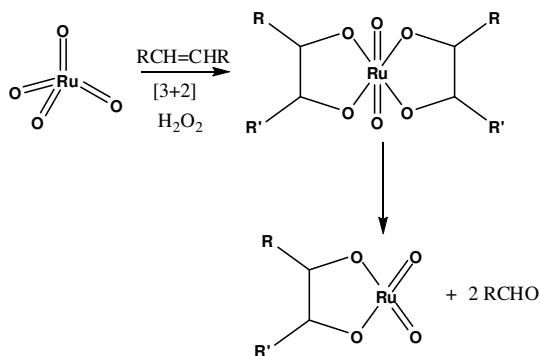
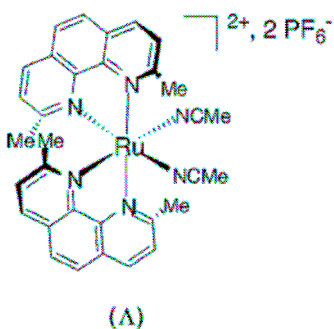


Figure 3: Pre-catalyst for ep(oxidation) **Figure 4: Oxidative cleavage of olefins**

The Noyori asymmetric transfer hydrogenation (ATH) of ketones by ruthenium complexes bearing chiral diamine ligands is known to be highly enantioselective, producing high yields and high enantiomeric excesses of optically active alcohols.¹³ Recently, work on systems similar to these successful catalysts has been attempted with an achiral ligand set (Figure 5).⁵ The enantioselectivity of the reaction is due to a favorable π/CH interaction between the aromatic ring of acetophenone and a hydrogen from the *p*-cymene. Additional stabilization is provided by hydrogen bonding from the N-H group on the ligand to the carbonyl of acetophenone (Figure 6).¹⁴ Both of these stabilizing effects have been confirmed computationally.¹⁵ The hydrogenation of acetophenone by the dinuclear ruthenium complex yielded product with an enantiomeric excess of 26%,⁶ whereas acetophenone reduction by the Noyori catalyst yielded product with a 96% ee.¹⁶

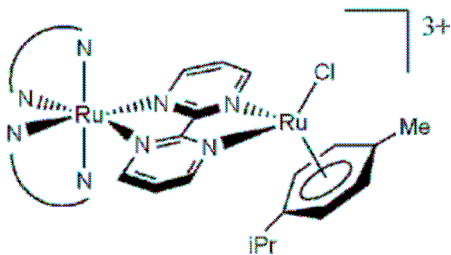


Figure 5: Dinuclear catalyst for ATH
(N-N is bipyridine, or dmp)

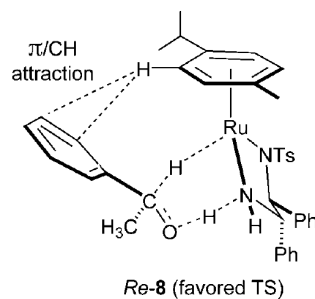


Figure 6: Noyori ATH
transition state

Products from the asymmetric reduction of pro-chiral ketones are chiral alcohols, which are important for carotenoid-derived bioactive terpenes and odorants.¹⁷ Additionally, chiral alcohols are important intermediates in the synthesis of the NK1 receptor antagonist Aprepitant, which is marketed as Emend used to treat vomiting in chemotherapy patients.¹⁸ Chiral sulfoxide groups have been incorporated into anti-ulcer drugs such as Nexium and Losec.² The 25 billion dollars of enantiomerically pure pharmaceuticals sold in 2003 underscores the need to develop increasingly inexpensive and active asymmetric catalysts.¹

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