The hydrogenation of prochiral ketones, aldehydes, and imines to yield single enantiomer chiral products has been a challenging problem for many years. The ability to specify a single enantiomer product is the stepping-stone in synthetic chemistry for producing enantiomerically pure pharmaceuticals, agricultural chemicals, and fragrances.\textsuperscript{1,2}

The principle that a chiral transition metal-based catalyst could transfer chirality to a nonchiral substrate was first demonstrated in 1968 by William Knowles,\textsuperscript{3} when he showed that a chiral rhodium complex could catalyze the asymmetric hydrogenation of phenylacrylic acid. Knowles used chiral phosphine ligands in a modified version of Wilkinson's catalyst (Figure 1). While the catalyst only produced modest enantioselectivity, it was the harbinger for the coming revolution in synthetic organic and organometallic chemistry. Since that time, several different technologies have also emerged for the reduction of carbonyl groups, the two most prevalent being catalytic metal hydride reduction and transfer hydrogenation.\textsuperscript{1,2,4,5}

Transfer hydrogenation is defined as the reaction of multiple bonds in functional groups, such as ketones, aldehydes, and imines, that is aided by a hydrogen donor (usually an alcohol) and promoted with an inorganic base. Chiral ancillaries enable asymmetric reductions.\textsuperscript{1,4}

Transfer hydrogenation has significant benefits over conventional catalytic metal hydride reductions. It avoids the use of molecular hydrogen and the special handling concerns involved. Since the solvent is the same as the hydrogen source, there is an intrinsic simplicity to the catalytic system. The alcohols usually used for transfer hydrogenation, such as 2-propanol are also non-toxic, stable, easy to handle, inexpensive, and environmentally friendly.\textsuperscript{1,2,4} The only real disadvantage to this system is the inherent reversibility, since the desired alcohol or amine is the kinetic product, whereas the ketone substrate is the thermodynamic product.\textsuperscript{4,6} The textbook mechanism for transfer hydrogenation is shown in Figure 2.\textsuperscript{4,7}
Recently several new catalysts have emerged that do not seem to follow this mechanism. Noyori, Casey, Oro, etc. do not observe reaction intermediates like those illustrated in Figure 2. There is a pronounced ligand effect observed in these new catalysts, a dependence on a ligand supplied proton source, either NH, NH₂, or OH, for the catalytic cycle to proceed. An example of this phenomenon is Noyori’s transfer hydrogenation reaction that is shown in Figure 3. Other examples work through a similar concerted mechanism, but take advantage of the inherent natural chirality of amino acids to effect asymmetric catalysis, such as the one studied by Oro. Mechanistic, computational, and kinetic studies have led to the proposed mechanism (Figure 4) for the transfer hydrogenation observed by Noyori, and others.

The proposed mechanism proceeds through a six-membered transition state, but neither the ketone nor the alcohol are directly coordinated to the metal center at any time during the reaction. The proton from the attached amine ligand is transferred to the oxygen end of the ketone and the hydride from the metal is transferred to the carbon. The key to the mechanism is that both of these hydrogen transfers are believed to occur in a concerted manner, which is why there are not any ketone or alkoxide intermediates observed during the reaction. The proposed transition state is shown in Figure 5.

Transfer hydrogenation is a complementary method to catalytic hydrogenation, as well as stoichiometric and catalytic metal hydride reduction, because it is selective for C=X groups such as ketones and imines. These systems are also tolerant of a wide range
of functional groups, such as nitro, sulfones, sulfides, esters, alkenes, alkynes, aryl chlorides and cyanides, and furan and thiophene ring systems. There is enormous potential for such a general system, that has strong selectivity, yet is quite gentle.4.18

References


6. Faller, J.; Lavoie, A. “Catalysts for the Asymmetric Transfer Hydrogenation of Ketones Derived from L-Prolinamide and (p-CymeneRuCl₂)₂ or (Cp*RhCl₂)₂,” Organometallics 2001, 20, 5245-5247.


