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Review Article

Asymmetric Hydrogenation as Ideal Green Chemistry

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We should be proud of being chemists. Chemistry is more than a science of observing and understanding Nature. It is characterized by the capability of generating high values from almost nothing. Therefore, synthesis is not merely an intellectual challenge but also a practical technology for the survival of our species. Man-made substances and materials determine the quality of life. In fact, throughout the history of humankind, chemistry has been essential to the prosperity of society [1]. Its significance is ever increasing.

In 2003, the National Academy of Engineering in the US characterized the 20th century as "A Century of Innovation" and selected 20 greatest technologies that decisively changed our lives during that period [2]. The first was electrification, which was followed by the automobile, airplane, water supply and distribution, electronics, radio and television, agricultural mechanization, computers, telephony, air conditioning and refrigeration, highways, spacecraft, internet, imaging, household appliances, health technologies, petroleum and petrochemical technologies laser and fiber optics, nuclear technologies, and high-performance materials. Without these innovations, we could not have developed the affluent, civilized societies we live in today. This list shows that the field of chemistry has contributed enormously to our lives by inventing new artificial materials and substances. Naturally occurring substances are important but not enough to sustain society. However, chemical manufacturing, like all other science-based technologies, is double-edged. Its benefit is clear but, currently, our environments are heavily polluted by various man-made chemical compounds. All the people in the world must co-operate to keep planet earth clean.

Thus, Green Chemistry, namely environmentally benign chemistry, is crucial for the survival of human beings [1]. It is a creative, prosperous, and responsible science. The essential aspects of Green Chemistry are the use of safe starting materials, renewable resources, and safe solvents, minimum production of wastes, and conservation of energy resources. Promoting this science is a serious task. In this context, catalysis is important because it is the only rational, general means to produce important compounds in a cost-effective, energy-saving, and environmentally benign manner. The world maket of catalysts is ca. 12B USD, and the chemical production through catalysis is estimated to be 1.2-6.0T USD. Therefore, chemists must develop practical catalytic processes using heterogeneous, homogeneous, and biological catalysts.

Since long before the significance of Green Chemistry became apparent, I have pursued hydrogenation, the ultimate Green Technology. Hydrogen is a clean and abundant resource and has unlimited applicability to basic and applied science, technology, and industry at large. In particular, asymmetric hydrogenation has been my long-life research theme. The recent progress in this filed has totally changed the way to prepare significant chiral compounds including pharmaceuticals, agrochemicals, flavors, and fragrances. In this regard, BINAP chemistry has played a key role [3, 4]. Described below is a novel way to efficiently saturate carbonyl compounds with high enantioselectivity.

In nature, ethanol is oxidized to acetaldehyde using alcohol dehydrogenase and nicotinamide adenine dinucleotide (NAD) as a cofactor (Fig. 1). Acetaldehyde is further oxidized to acetic acid. Actually, the alcohol/aldehyde conversion is reversible; acetaldehyde is reduced by using the same enzyme and NADH, a reduced form of NAD, as a cofactor. Such enzymatic reactions are very selective and stereospecific. This reduction uses only two hydrogen atoms in a large NADH molecule with a molecular weight of 665. Organic synthesis needs cheaper, readily available cofactors. 2-Propanol is among the most convenient hydrogen donors, because it is stable, easy to handle (bp 82^{o}C), nontoxic, inexpensive and dissolves many organic compounds. It is small alcohol with a molecular weight of 60, but two hydrogen atoms out of eight can be used. Numerous attempts have been made to achieve an asymmetric Meerwein-Ponndorf-Verley reaction of ketones, but without great success.

Our general strategy for asymmetric synthesis is to use chiral molecular catalysts consisting of a metallic element and surrounding chiral ligand [5]. It has been considered that the active metal center generates

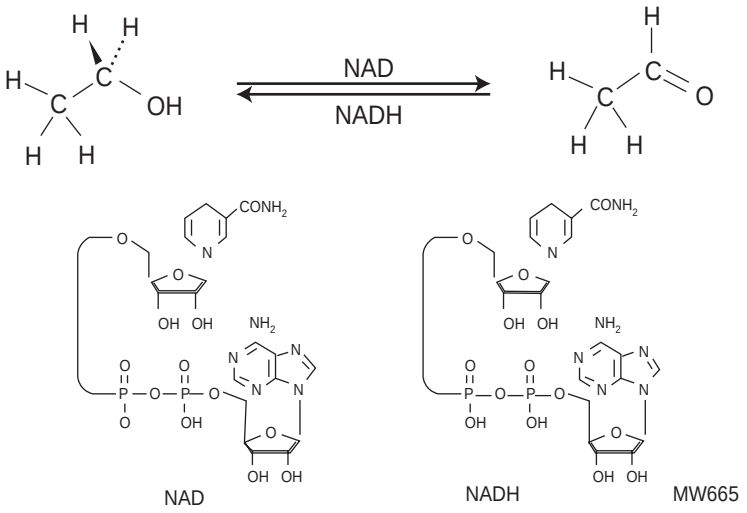


Fig. 1: *In vivo redox processes*

reactivity, while the attached auxiliary controls stereoselectivity. In fact, however, in truly efficient asymmetric catalysis, the metal and ligand strongly interplay with each other to result in high reactivity and selectivity. All of the electronic and steric details cooperate in generating the sufficient chemical functions [6].

We have developed the chiral ethanolamine-and N-tosylated ethylenediamine-Ru complexes shown in Fig. 2. Most notably, the presence of an NH end in the ligands is crucial for catalytic activity. The chiral catalysts in 2-propanol containing a small amount of KOH, or other strong bases, effect asymmetric transfer hydrogenation of various prochiral aromatic ketones or aldehydes and aklynyl ketones to give the corresponding chiral alcohols with high enantiomeric excess' [7]. Thus 2-propanol is a much better cofactor than NADH in asymmetric carbonyl reduction. Furthermore, certain racemic benzylic and allylic alcohols can be efficiently resolved with the same Ru catalyst using acetone as a hydrogen acceptor. Hence, acetone can be a much efficient cofactor than NAD.

The mechanism of transition metal-catalyzed transfer hydrogenation using 2-propanol has long been thought to involve a metal 2-propoxide intermediate which undergoes β-elimination of acetone to give a metal hydride. The hydride would then react with a ketone to form a metal alkoxide, whose ligand exchange with 2-propanol completes the catalytic cycle. The key phenomenon of this conventional mechanism is the interaction between the metallic species and oxygen atoms of the hydrogen donor and hydrogen acceptor. However, such a mechanism does not operate in the asymmetric transfer hydrogenation shown in Fig. 2.

The role of strong bases is unique; they do not facilitate Ru alkoxide formation. As shown in Fig. 3, when the orange-colored octahedral ethylenedimine/cymene-RuCl complex is treated with one equivalent of KOH in aqueous dichloromethane, a purple-colored amido Ru complex is formed by elimination of HCl [8]. The X-ray analysis indicates that the Ru complex has a formal 16e configuration with a square-planar structure. The amido-Ru bond, 1.897 Å, is much shorter than the

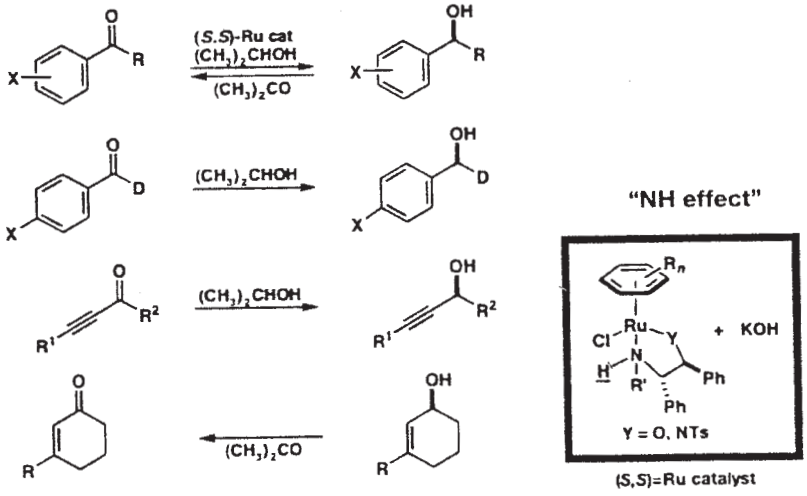


Fig.2: *Ruthenium-catalyzed asymmetric transfer hydrogenation using 2-propanol and dehydrogenation using acetone*

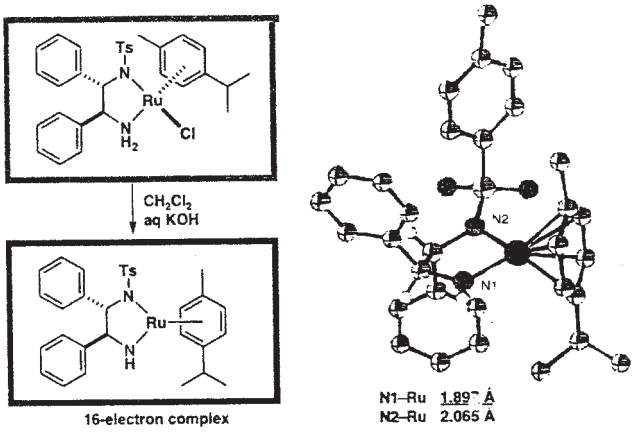


Fig. 3: *Formation of a chiral Ru amide catalyst from an amino Ru chloride*

normal amino-Ru dative bonds, 2.1 Å, because of the partial double-bond character caused by the electron release from the nitrogen to the electron-deficient Ru atom. The purple complex reverts back to the orange RuCl complex by adding ammonium chloride. Thus a strong base is necessary to remove HCl from the amino RuCl. Because of the characteristic bonding scheme, the amido-Ru complex dehydrogenates 2-propanol and many other secondary and primary alcohols to give a yellow-orange Ru hydride complex, as seen in Fig. 4. The chirality of the RuH complex originates from the *S, S* configuration of the chiral diamine ligand. The two phenyl groups, oriented to the equatorial direction, form a skewed five-membered chelate ring, determining the δ conformation, which in turn defines the *R* configuration of the newly formed Ru stereogenic center. Most importantly, this hydride formation occurs without any alkaline base. The 18e Ru species reverts back to the 16e Ru amide through the action of acetone.

The Ru amide and hydride complexes equally act as catalysts for asymmetric transfer hydrogenation of prochiral ketnoes using 2-propanol. The reaction occurs cleanly under neutral conditions without any base

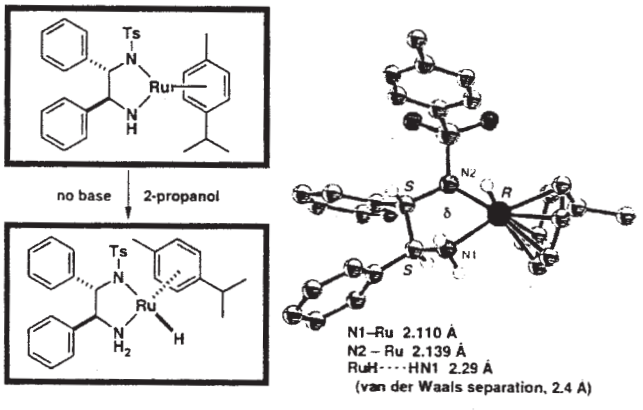


Fig. 4: *Formation of a reducing Ru hydride complex*

(Fig. 5). The Ru amide complex dehydrogenates a secondary alcohol to form the Ru species. The 18e Ru complex delivers two hydrogen atoms to a ketone directly to give an alcohol and the 16e Ru amide catalyst, which is a resting state in the catalytic cycle. Thus the mechanism of the Ru catalyzed transfer hydrogenation is remarkably simple. A kinetic study using deuterated 2-propanol and acetone suggests that it involves only two Ru components shown in Fig. 5. No other complexes that limit the turnover rate are involved. Under such conditions, dehydrogenation of 2-propanol is the turnover-limiting step and reduction of acetone is easier. A small isotope effect, k_H/k_D = 1.5, is seen when 2-propanol is replaced by the 2-deuterio compound. Furthermore, because of the chirality of the Ru catalyst, the enantiofaces of an aromatic ketone substrate are clearly differentiated.

A detailed ab initio MO and DFT study indicates that the transfer hydrogenation takes plece via a six-membered pericyclic mechanism (Fig. 6) [9]. The reducing Ru species having an NH ligand acts as a 1,4-dipole, which fits well with the carbonyl dipole. Thus the hydride on Ru and the proton on N are simultaneously delivered to the C=O function. Most significantly, neither alcohol oxygen nor ketone oxygen touches the Ru center of the catalyst during the reaction. This view has been confirmed by a theoretical study on the model reaction of formaldehyde and a simplified Ru hydride. In the calculated pericyclic transition state (TS) the C=O group is hydrogen-bonded to NH, while a hydride is migrating

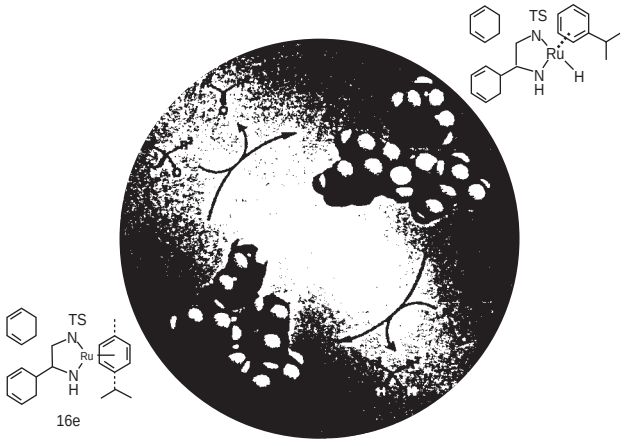


Fig. 5: *Asymmetric transfer hydrogenation of simple ketones*

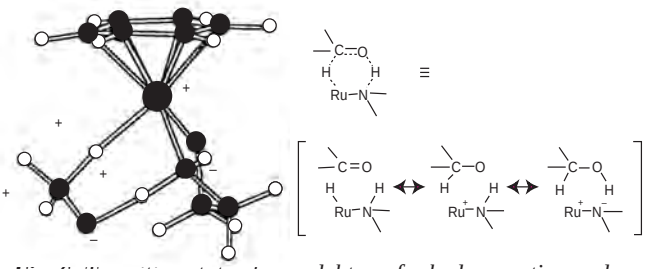


Fig. 6: *Transition state of a model transfer hydrogenation and its reverse process*

from Ru to the C=O carbon center. This is also the TS of dehydrogenation of methanol by the Ru amide complex. The forward and reverse reactions take place via low energy barriers, the activation energies being only 7 to 8 kcal/mol, respectively.

2-Propanol is a better reducing agent than NADH for transfer hydrogenation in laboratory organic synthesis. However, a major problem of this chemical process is its reversibility. Because 2-propanol is a formal adduct of H_2 and acetone, the starting and product systems are similar. The asymmetric reaction starts with 2-propanol and a prochiral ketone ends with a chiral secondary alcohol and acetone. Therefore, the chiral efficiency is highly dependent on the substrate structures and reaction conditions. The redox potentials of the ketones and alcohols are very important. Furthermore, the ketone concentration relative to 2-propanol must be low in order to shift the equilibrium to the product side. The ee value tends to decrease as the conversion increases because of the contamination of the reverse process.

This problem can be solved by using formic acid as a hydrogen donor, because formic acid is formally an adduct of H_2 and the very stable CO_2[7]. In fact, the reaction proceeds irreversibly under truly kinetic control, since oxidation of alcohols with CO_2 is impossible (Fig. 7). The reaction is achievable in a formic acid-triethylamine mixture with a high substrate concentration. In 2-propanol, certain ketones such as 4-methoxyacetophenone are unable to hydrogenate with high enantioselectivity. This modified process is practical on an industrial scale.

Thus, the "atom economy" of transfer hydrogenation is greatly improved in going from the use of NADH (Fig. 1) to 2-propanol (Fig. 2) and to formic acid with a molecular weight of 46 (Fig. 7). Although H_2 is obviously an ideal reducing agent (100% atom economy), the chiral RuCl complexes could not be used as catalysts. However,

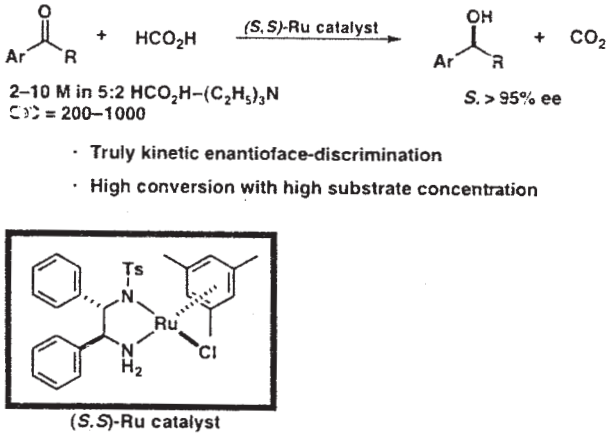


Fig. 7: *Irreversible asymmetric transfer hydrogenation using formic acid*

we have long thought that transfer hydrogenation and hydrogenation are mechanistically linked, because both reactions commonly involve a metal hydride intermediate. As shown in Fig. 9 (X = Cl), the chiral amino RuCl complex eliminates HCl in the presence of a strong base to form the Ru amide, which effects transfer hydrogenation in 2-propanol. Unfortunately, under such basic conditions, H_2 gas cannot be used a s a reducing agent. However, Fig. 9 also suggests the possibility of a reaction using the same catalyst and H_2, simply by switching the conditions from basic to slightly acidic. The ionization of the Ru-X bond forms the 16e cationic Ru species (solvate), which reversibly accommodates H_2.

Subsequent deprotonation of the η^2-H_2 Ru complex gives the same Ru that hydrogenates a ketonic substrate. The Ru amide cannot be protonated by pure alcohols, but is protonated under such slightly acidic conditions to give back the amino Ru complex.

The key is the efficient generation of the cationic Ru species and the acidity of the reaction medium. This attractive possibility has been tested by using 4-chromanone and the RuCl as a catalyst (Fig. 10) [10]. In 2-propanol, the ketone is inert to hydrogenation. However, the increase in the dielectric constant of the alcohol media facilitates the ionization of the Ru-Cl bond to genrate a cationic amino Ru complex. In fact, hydrogenation starts to occur in going from 2-propanol to ethanol to methanol, giving (*S*)-4-chromanol in high ee. The presence of one equivalent of tetrabutylammonium chloride suppresses the hydrogenation.

Increasing the reaction temperature from 30 to 60^0 C gives the *S* alcohol in 99% and in 97% ee. Thus, our mechanism based scenario is valid. However, the RuCl is not ideal because the ionization remains insufficient. Obviously, the Ru triflate in methanol is an ideal catalyst (Fig. 11). Thus a 2.4-kg scale hydrogenation of 4-chromanone affords the *S* alcohol in 98% ee. Various base-sensitive ketones can be smoothly hydrogenated with this new method.

Hydrogenation of acetophenone using the (*S, S*)-RuOTf catalyst in methanol containing a trace amount of TfOH forms (*S*)-1-phenylethanol in 96% ee (Fig. 12) [11]. The same *S, S* catalyzes transfer hydrogenation of acetophenone in 2-propanol containing $KOC(CH_3)_3$, giving the same *S* alcohol in the same ee. Thus, in going from basic to acidic conditions, the hydrogen source can be switched from 2-propanol to hydrogen gas. Both the asymmetric hydrogenation and transfer hydrogenation proceed via a common Ru intermediate. This observation indicates that the sterically congested *Re* TS is favoured over the less crowded *Si* TS. This is due to the presence of the CH/π attraction between the cymene CH and the

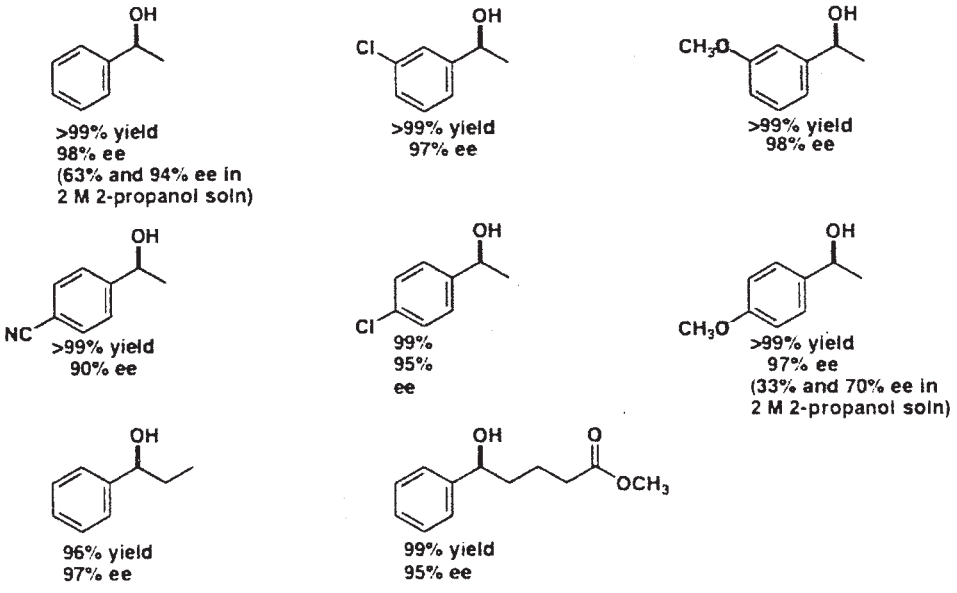


Fig. 8: *Examples of asymmetric transfer hydrogenation using formic acid*

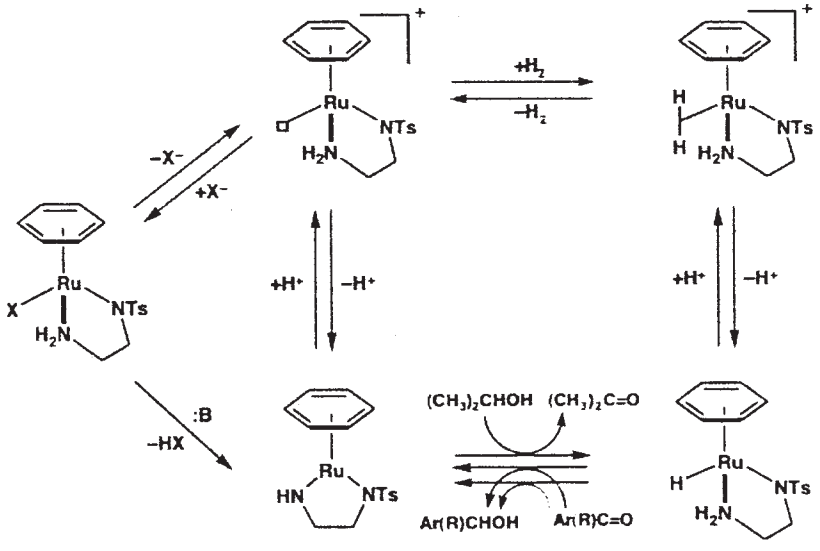
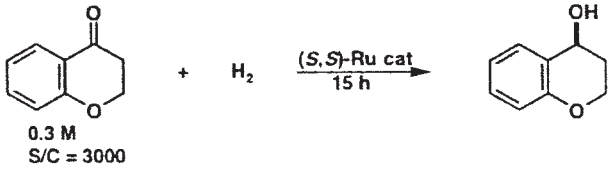
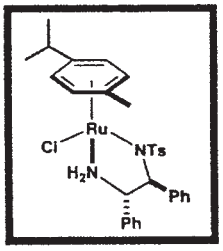


Fig. 9: *Transfer hydrogenation/hydrogenation network. The ligand structures are simplified*





solvent	P_{H_2}	*T*, °C	additive	% yield	% ee
$(CH_3)_2CHOH$	10	30	—	0	—
C_2H_5OH	10	30	—	7	93
CH_3OH	10	30	—	34	97
CH_3OH	10	30	$(n\text{-}C_4H_9)_4NCl$	6	92
CH_3OH	50	60	—	99	97

Fig. 10: *Asymmetric hydrogenation of 4-chromanone with a chiral Ru chloride*

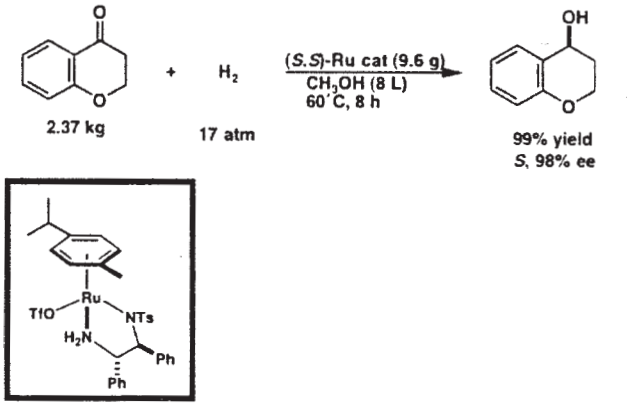


Fig. 11: *Asymmetric hydrogenation of 4-chromatione with a chiral Ru triflate*

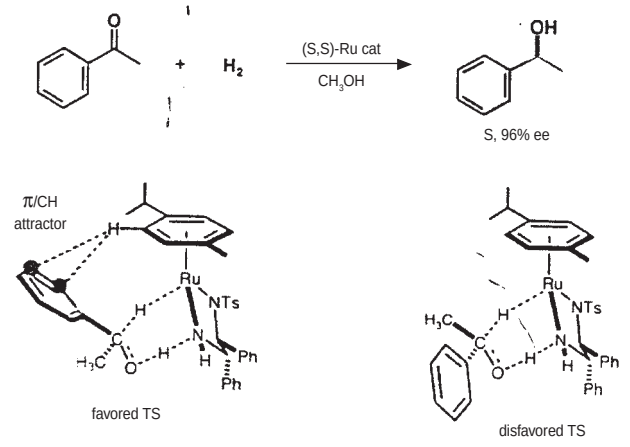


Fig. 12: *Origin of enantioselection in asymmetric reduction of acetophenone*

phenyl ring of aceto-phenone, as substantiated by theoretical calculations (Fig. 12) [9]. The electron flow from the cymene ligand to the phenyl ring via the Ru-H-C linkage increases the acidity of the cymene C(Sp^2)H and the electron density of the ortho and meta carbons in the reacting acetophenone substrate. Thus enantioselection is obtained by such electronic attraction rather than steric repulsion. These TS structures are suggested by X-ray crystallographic analysis of the reducing RuH species (Fig. 4) and a DFT calculation on the model reaction system.

This asymmetric hydrogenation of simple ketones is performed under slightly acidic conditions. Similar efficient asymmetric hydrogenation is also achievable under basic conditions using BINAP/1,2-diamine-Ru complexes, as illustrated in Fig. 13. [3, 4] A series of aromatic, hetero-aromatic, and olefinic ketones, can be employed. The general reaction is productive and rapid.

The chiral Ru chemistry has displayed a range of nonclassical aspects not seen in conventional orgnic and organometallic chemistry. Designing a practical catalyst is an integrated molecular approach. The desired molecular function emerges by combing various steric

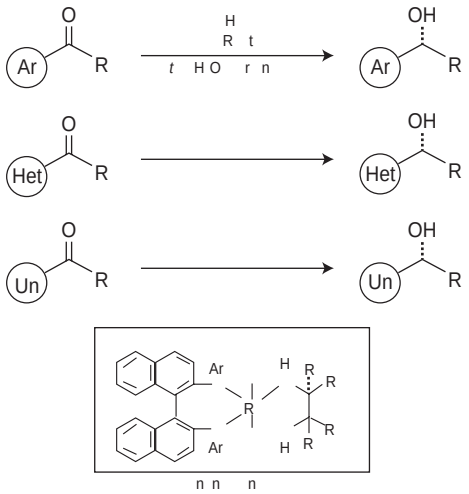


Fig. 13: *General asymmetric hydrogenation of simple ketones*

and electronic properties together with appropriate reaction parameters. We have observed the presence of an effective hydrogenation/transfer hydrogenation network. The ketone reductions involve a non-classical metal-ligand bifunctional mechanism rather than the conventional metal alkoxide pathway. Thus, the C=O bond is directly saturated with an 18e metal hydride without substrate-metal interaction. The Ru center delivers a hydride to the C=O carbon, and the nitrogen ligand simultaneoulsy delivers a proton to the C=O oxygen, Chiral recognition occurs on a moleular surface of a coordinatively saturated 18e complex in place of an unsaturated molecular template. The CH/π attraction is the major cause of enantioselection.

What is the significance of these hydrogenation process in modern chemistry? Over a half century, selective reduction of ketones has heavily relied on chemsitry of boron hydrides or organoboranes. For example, $NaBH_4$ is generally used for C=O reduction and allows for preferential reduction of C=O linkage over an olefinic or acetylenic linkage. Seletrides are excellent reagents of diastereoselective reduction of cyclic and certain acyclic ketones. Enantioselective reduction of simple ketones has been achieved with a stoichiometric DIP chloride or Alpine-borane reagent and the CBS asymmetric hydroboration using diborane or catecolborane. These reductions are convenient, but produce large amounts of boron containing waste. Obviously they do not meet with the requirements of the new century's environment-friendly chemistry. We no longer need such boron reagents, because all these selective reactions are achievable by using clean H_2 gas.

The above described is an ideal chemistry from a scientific viewpoint. However, Green Chemistry is not a clear-cut matter of scientific or technical expertise, but rather a complex social issue. Science is destined to be

involved in society in our age, and researchers should not stay in their traditional ivory towers and research laboratories. Researchers must strongly affect public opinion and governmental policies toward contructing a sustainable society in the 21st century. We must take up responsibility for the sake of the current and future genrations [1].

References

1. R Noyori *Chem Commun* (2005) 1807-1811
2. G Constable and B Somerville *A Century of Innovation* Joseph Henry Press 2003
3. R Noyori and T Ohkuma *Angew Chem Int* Ed **40** (2001) 40-73
4. R Noyori *Angew Chem Int* Ed **41** (2002) 2008-2022
5. R Noyori in *Asymmetric Catalysis in Organic Synthesis* Wiley (1994) Chapter 2
6. R Noyori, M Kitamura and T Ohkum *Proc Nat Acad Sci USA* **101** (2004) 5356-5362
7. (a) R Noyori and S Hashiguchi *Acc Chem Res* **30** (1997) 97-102 (b)T Ikariya, K Murata and R Noyori *Org Biomol Chem* **4** (2006) 393-406
8. KJ Haak, S Hashiguchi, A Fujii, T Ikariya and R Noyori Angew *Chem Int Ed Engl* **36** (1997) 285-288
9. R Noyori, M Yamakawa and S Hashiguchi *J Org Chem* **66** (2001) 7931-7944
10. T Ohkuma, N Utsumi, K Tsutsumi, K Murata, CA Sandoval and R Noyori *J Am Chem Soc* **128** (2006) 8724-8725
11. CA Sandoval, T Ohkuma, N Utsumi K, Tsutsumi K Murata and R Noyori *Chemistry–An Asian Journal* **1-2** (2006) 102-110