Pursuing practical elegance in chemical synthesis

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In the 21st century, the field of chemistry will face more than just academic challenges. Indeed, our ability to devise straightforward and practical chemical syntheses is indispensable to the survival of our species.

Chemistry is not merely a science of making observations in order to better understand Nature. Our science is creative and productive, generating substances of very high value from almost nothing. Our health and daily lives rely largely on man-made substances that are produced in a step-by-step process from inexpensive fossil resources or biomass-based feedstocks. Because of the ever-increasing significance of this endeavour, chemists must pursue "Practical Elegance":[1] that is chemical synthesis must be intellectually logical and technically truly efficient. Toward this goal, a range of scientific principles and technological tools must be explored. Our solutions must fall within the boundary conditions of our planet: they must be safe, environmentally benign, and reasonable in terms of cost, resources, and energy. Without attention to what is now called "green chemistry",[2] chemical manufacturing will be unsustainable in this century.

Synthesis experts can now prepare any complex organic compounds desired as long as they are sufficiently stable and their structural formulae can be drawn. This amazing state-of-the-art capability is most effectively utilized in the fine chemical, agrochemical, and pharmaceutical industries.[3] Certain pharmaceuticals, known as blockbusters, currently have annual sales exceeding 10 billion US dollars. On the other hand, the synthetic efficiency is highly dependent on the compounds' biological or physiological activities or commercial values, and not purely on their scientific/technical effectiveness. Thus, at present only high-added value compounds can be prepared with sufficient practicality, and we need to extend more broadly the utility of chemical synthesis. In fact, the current standards of chemical technology must be much improved so as to minimize the energy needed to transform substances and also to reduce the burden on the environment. Many existing chemical processes, though beneficial, produce unwanted waste along with the target products, and inefficient recovery of solvents is an environmental problem. Every reaction in multi-step synthesis should proceed with a high atom-economy (a term coined by B. M. Trost), and the overall synthesis must be accomplished with a low E-factor (a term coined by R. Sheldon). As such, chemists today are asked to develop "perfect chemical reactions"[4] that proceed with 100% yield and 100% selectivity without forming any waste products. Molecular catalysis, together with traditional heterogeneous catalysis, significantly contributes to the realization of this goal. The following are some limited efforts that have been made in our laboratories along this line.

Solving a solvent problem by use of supercritical CO_2

We should avoid or minimize the use of harmful solvents such as chlorinated hydrocarbons. One question that has been raised is, why do we perform synthetic reactions or catalysis in a liquid solution? The answer is that the reactants dissolve in solvents to achieve homogeneity and facilitate mass transport and molecular collisions. In the liquid phase, molecules are packed densely to form a solvent sphere as illustrated in Fig. 1. In order to realize an intermolecular reaction between the pink and blue

Ryoji Noyori (b. 1938, Japan) was educated at Kyoto University and became an Instructor in Hitosi Nozaki's group at the same university in 1963. He was appointed Associate Professor at Nagoya University in 1968, spent a postdoctoral year at Harvard with E. J. Corey in 1969–1970 and, shortly after returning to Nagoya, was promoted to Professor in 1972. In 2003, he was appointed President of RIKEN and also University Professor at Nagoya. Noyori is an Honorary Fellow of the Royal Society of Chemistry, a Member of the Japan Academy and the Pontifical Academy of Sciences, and a Foreign Member of the National Academy of Sciences, USA, and the Russian Academy of Sciences. His research has long focused on the fundamentals and applications of molecular catalysis based on organometallic chemistry, particularly asymmetric catalysis and what is now known as "green" chemistry. In 2001, he shared the Nobel Prize in Chemistry with W. S. Knowles and K. B. Sharpless.
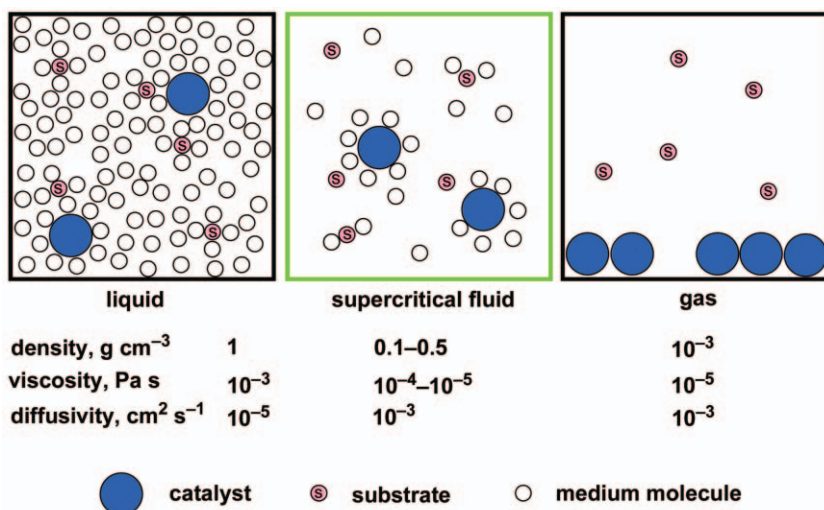
Fig. 1 Phases of catalytic reaction.

molecules, the solvent molecules must be removed or the shell structure reorganized. Certain chemical reactions occur very rapidly in gas phase due to the high molecular mobility and the lack of interaction between the solvent and reactants. Unfortunately, however, many organic compounds are not volatile enough to occur in gas phase. Then we noticed the utility of supercritical fluids for synthetic reactions. These fluids have the beneficial effects of both liquid and gas phases, because their physical properties, such as density, viscosity, and diffusivity, are intermediate between the two.

We became interested in CO_2 from both a scientific and a technical point of view. CO_2 has a critical temperature of 31 °C and a critical pressure of 73 atm (Fig. 2).[5] When CO_2 is heated above 31 °C, it cannot liquefy, even if a high pressure is applied, but instead forms a supercritical state, $scCO_2$. The physical properties vary dramatically near the critical point under the influence of pressure and temperature. In addition, since CO_2 interacts only weakly with reactants under such an environment, some unique molecular clustering may take place locally. Furthermore, CO_2 has several technical benefits: it is nontoxic, nonflammable, and very cheap. It can be separated easily from the reaction system without leaving harmful residue. In fact, as shown in Fig. 2, we observed an eminent catalytic efficiency in the hydrogenation of $scCO_2$ catalyzed by a Ru

complex, where CO_2 acts as both the reactant and reaction medium. Since the reaction of H_2 with CO_2 giving formic acid is endothermic, the presence of triethylamine is needed to stabilize the product. In the presence of methanol, formic acid is further converted to methyl formate by dehydration. When triethylamine is replaced by

dimethylamine, DMF is formed with a very high turnover number (TON). The excellent efficiency is ascribed to the very high solubility of H_2 in $scCO_2$ and the high reactivity of the Ru catalyst under such conditions. Thus $scCO_2$ has clear advantages as a reaction medium.[6,7] Although pure CO_2 can dissolve only nonpolar substances, the solubility is greatly enhanced by addition of certain protic or fluorinated "entrainers".

"Green" oxidation with aqueous hydrogen peroxide

Although oxidation is a fundamental reaction in the chemical industry, it is still among the most problematic processes. Many textbook methods are unacceptable because of the low atom-economy. Furthermore, conventional heavy metal oxidants form toxic wastes and known organic stoichiometric oxidants are usually very expensive. Nitric acid, the most conventional industrial oxidant, is inexpensive but unavoidably forms various nitrogen oxides, including N_2O which has a strong greenhouse effect and also causes catalytic stratospheric ozone destruction as well as acid
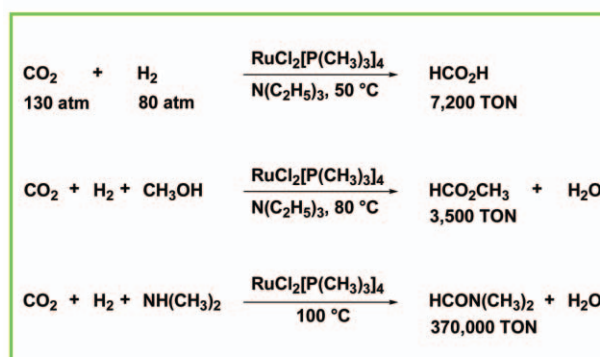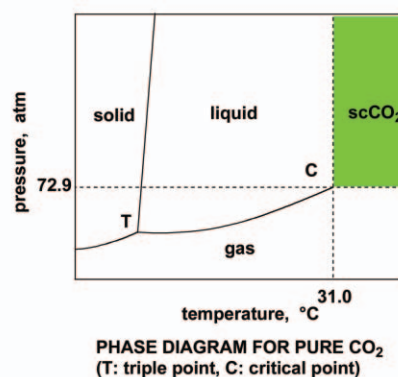

Fig. 2 Phase diagram of CO_2 and hydrogenation in the supercritical phase.

rain and smog. Molecular oxygen (O_2) is an ideal oxidant, only if (1) the process is controlled safely without over-oxidation or combustion and (2) both O atoms are used for oxidation (100% atom-economy). Aerobic oxidation often uses only one O atom out of two and requires certain reducing agents to capture the extra oxygen (50% atom-economy). Hydrogen peroxide (H_2O_2), produced effectively from H_2 and O_2 in a quantity of 2.4 million metric tons per year, is another attractive oxidant for liquid-phase reactions. It costs less than 0.7 US dollar per kg (as 100% H_2O_2). Since H_2O_2 is viewed as an adduct of an O atom and an H_2O molecule, water is the only theoretical waste product in its use as an oxidant (47% atom-economy). One of the major benefits of H_2O_2 oxidation is the high tunability of the reaction parameters. The oxidation process may further switch to *in situ* or on-site technology using H_2 and O_2 in the future.

This clean oxidant, when coupled with a tungstate complex and a quaternary ammonium hydrogensulfate as an acidic phase-transfer catalyst, oxidizes a variety of organic compounds, as illustrated in Fig. 3.[8] The catalytic system converts primary alcohols to aldehydes and/or carboxylic acids and secondary alcohols to ketones. Olefins are oxidized to epoxides in a high yield with the aid of a phosphonic acid, while sulfides are converted to sulfoxides and then sulfones. Notably, these oxidations take place under organic solvent- and halide-free conditions in an economically, technically, and environmentally satisfying manner. This catalytic system is highly desirable, because it is physiologically harmless and does not cause any unproductive decomposition of H_2O_2. Cyclo-olefins smoothly undergo the oxidative cleavage. The utility of this biphasic oxidation method was best demonstrated by its application to adipic acid synthesis (Fig. 3). Cyclohexene is an attractive C_6 starting material for this purpose, because an excellent technology for selective hydrogenation of benzene to cyclohexene has been established by the Asahi Chemical Industry. When a mixture of cyclohexene, a *ca.* 4 molar equivalent of 30% H_2O_2, and small amounts of Na_2WO_4 and methyl-(trioctyl)ammonium hydrogensulfate is
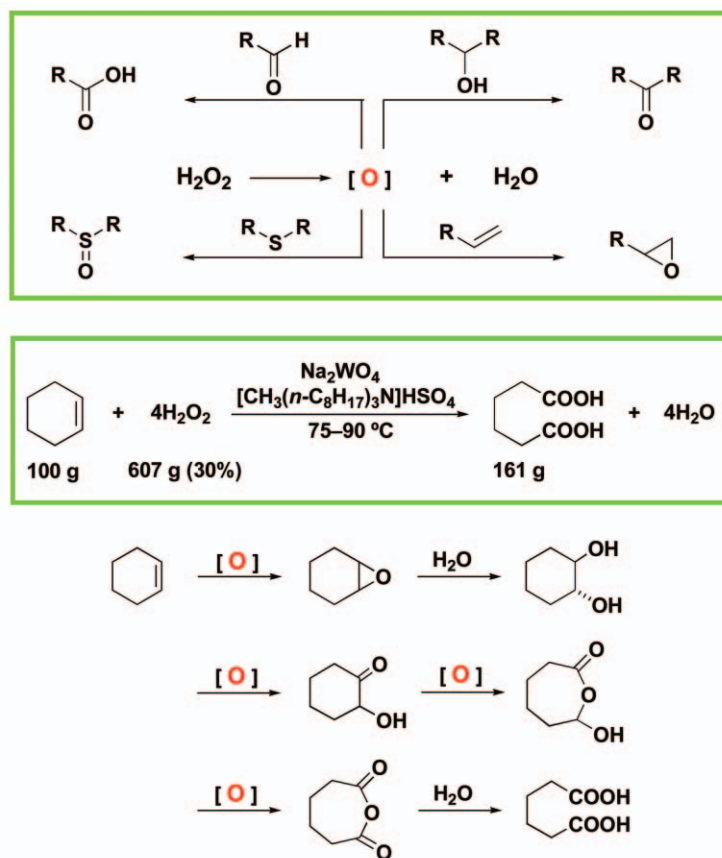

Fig. 3 Green oxidation with aqueous H_2O_2 and the direct conversion of cyclohexene to adipic acid.

stirred at 75–90 °C, adipic acid is directly obtained as shiny, colorless, analytically pure crystals in a high yield. This procedure is much more environmentally benign than is the current oxidation of a cyclohexanol–cyclohexanone mixture with nitric acid.[9]

Asymmetric hydrogenation

Hydrogenation is a core technology in chemical synthesis. Over the last half century, however, selective reduction of a C=O and C=N linkage has relied heavily on the use of metal hydride reagents with a low atom-economy, forming as a side product a large amount of boron, aluminium, or other metallic residue. We have aimed at the replacement of such stoichiometric methods by catalytic processes using a clean, abundant resource, H_2, which proceeds with 100% atom-economy. Furthermore, asymmetric hydrogenation is among the most significant subjects in modern organic synthesis.[10]

This goal is realized only by suitable architectural and functional designing of molecular catalysts as well as careful selection of reaction parameters.[11] H_2, the simplest molecule, can be activated by various transition metal complexes by forming a metal hydride (heterolytic cleavage of H_2 on metal) or a metal dihydride (oxidative addition of H_2 to metal). However, catalytic hydrogenation requires the repeated transfer of a hydride from metal to unsaturated organic compounds with a high TON and turnover frequency (TOF). The catalytic process normally involves several metal-based intermediates that are interconverted without any destructive side reactions or substrate- or product-inhibition. Notably, no universal catalysts exist, because there are numerous classes of unsaturated compounds that affect the reactivity and selectivity. Only so-called "molecular catalysts" can cope with the complexity of this situation, since any molecules, by definition, can be designed and synthesized at will.

We could invent a catalytic system consisting of RuCl$_2$(PAr$_3$)$_2$(ethylenediamine) (**Ru-A** in Fig. 4) and an alkaline base that allows for chemoselective hydrogenation of a C=O function leaving a C=C bond intact.[12] The presence of the NH moiety in the diamine ligand is crucial for a mechanistic reason.[13] We no longer need NaBH$_4$ for converting olefinic ketones to unsaturated alcohols. This hydrogenation involves a "bulky hydride" effecting diastereoselective reduction of various ketones, which otherwise is achieved with stoichiometric Selectride reagents.[12] For example, 4-*tert*-butylcyclohexanone is hydrogenated to give *cis*-4-*tert*-butylcyclohexanol with >98:2 selectivity.

When a suitable chiral diphosphine and a 1,2-diamine are bound to the Ru center, a rapid, productive asymmetric hydrogenation of simple ketones is achievable.[11] Thus the use of RuCl$_2$(binap)(diamine) (**Ru-B** in Fig. 4) or RuH(η^1-BH$_4$)(binap)(diamine) converts a wide variety of aromatic, heteroaromatic, olefinic, and some aliphatic ketones to the chiral alcohols with high enantiomeric purity. In certain cases, the new hydrogenation realized a TON of 2,400,000 and a TOF of 228,000 h^{-1} or 63 s^{-1}. This asymmetric hydrogenation is far superior to the existing asymmetric metal hydride reductions. The utility has been amply demonstrated by the synthesis of intermediates of biologically or physiologically important chiral compounds.

The chiral Ru complexes of type RuCl[(*R*,*R*)- or (*S*,*S*)-[H$_2$NCH(C$_6$H$_5$)-CH(C$_6$H$_5$)NHTs](η^6-arene) can be used for highly enantioselective transfer hydrogenation of C=O and C=N functions using 2-propanol or formic acid as a hydride source.[14] The presence of the NH group in the chiral ligand is crucial for the catalytic activity.

The diamine-free RuX$_2$(binap)(dmf)$_n$ complexes (polymeric; X = halogen) (**Ru-C** in Fig. 4) catalyze hydrogenation of various functionalized ketones with high enantio-face selection to give the corresponding chiral alcohols.[10] Unlike the hydrogenation of simple ketones, this reaction proceeds smoothly under acidic conditions. β-Keto esters are particularly good substrates, where the ester oxygen interacts with the Ru center in the chiral catalyst. Carbapenem antibiotics are now best synthesized *via* a chiral hydroxy ester produced from an α-amidomethylated β-keto ester under dynamic kinetic resolution.[15] In addition, (*R*)-1,2-propanediol formed by the simple asymmetric hydrogenation of acetol is used for the commercial synthesis of levofloxacin, an important antibacterial agent. Furthermore, the BINAP-Ru dihalide and dicarboxylate complexes act as excellent catalysts for asymmetric hydrogenation of a range of functionalized olefins, giving, for instance, anti-inflammatory (*S*)-naproxen and (*R*)-citronellol of high enantiomeric purity (Fig. 4).

Thus the recent advances of in this field have totally changed the methods for preparing precious chiral compounds. Asymmetric catalysis is now widely practiced in research laboratories worldwide and also at the industrial level.[16]
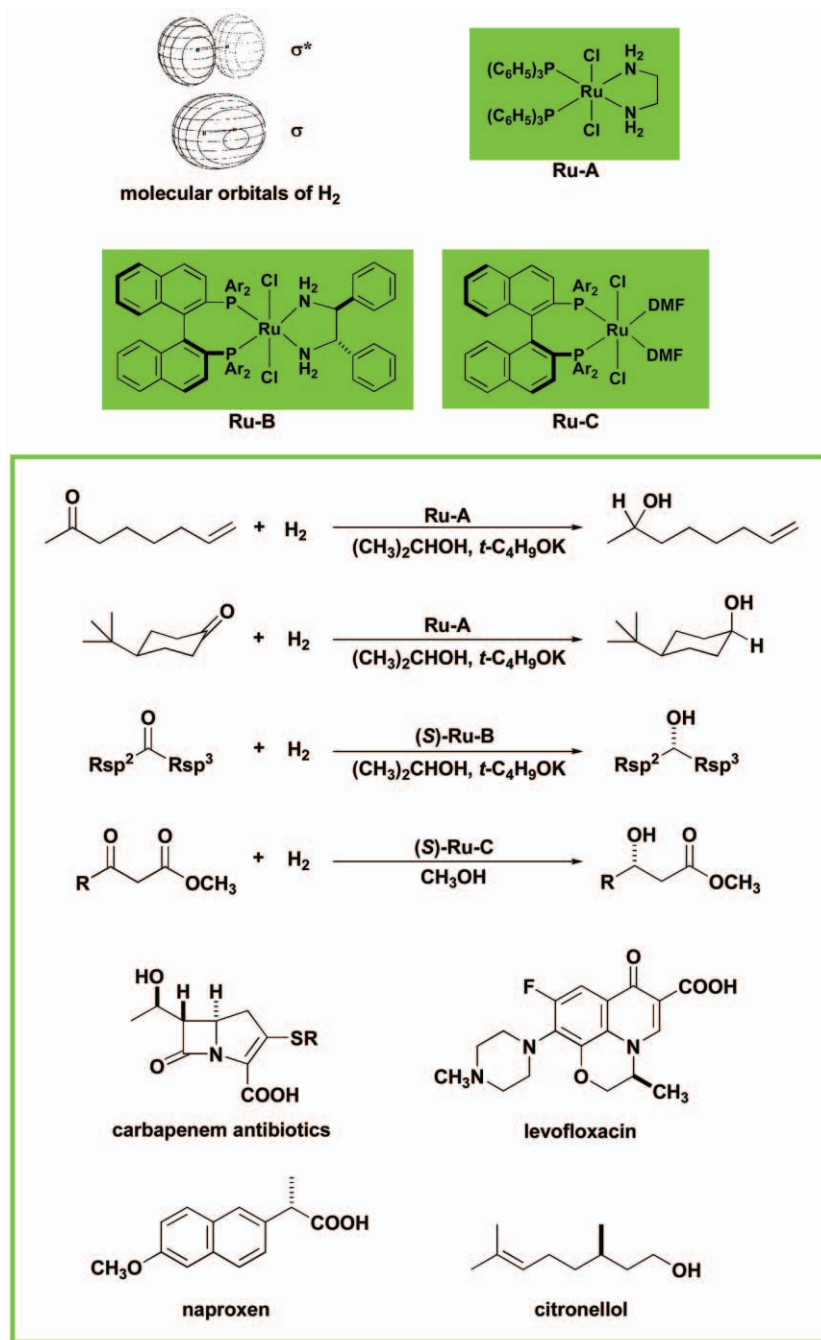

Fig. 4 Chemoselective, diastereoselective, and enantioselective hydrogenation catalyzed by Ru complexes.

Conclusion

Catalysis provides a logical means to produce valued compounds from raw materials in a cost-effective and environmentally friendly manner. Green chemistry is not a mere catch-phrase but an indispensable principle that will sustain our civilized society in the 21st century. I would emphasize that this concept is not a matter of clear-cut scientific or technical expertise but rather a serious, complex social issue. In order to materialize our research goals in the real world, we need a rational, long-term program supported by public understanding, governmental policies, and worldwide cooperation. At both the individual and institutional level, all members of our society must recognize the significance of green chemistry. We must embrace it and take responsibility for the current and future generations.

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